1900-2000: Changes In Life Expectancy In The United States

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Life Expectancy

Year	White Men			White Women
	At Birth	At Age 65	At Age 85	At Birth
1900	47	12	4	33
1910	49	–	4	34
Additional Years	28	4	2	35
Percentage Change	60%	33%	50%	106%

Year	White Men			
	At Birth	At Age 65	At Age 85	At Birth
1920	54	–	4	46
1930	60	–	4	47
1940	62	–	4	52
1950	67	13	4	59
1960	67	13	4	61
1970	68	13	5	60
1980	71	14	5	64
1990	73	15	5	65
2000	75	16	6	68
Additional Years	28	4	2	35
Percentage Change	60%	33%	50%	106%

Year	White Women			
	At Birth	At Age 65	At Age 85	At Birth
1900	49	12	4	34
1910	52	–	4	38
1920	66	–	4	45
1930	64	–	4	49
1940	67	–	4	55
1950	72	15	5	63
1960	74	16	5	66
1970	76	17	6	68
1980	78	18	6	73
Additional Years	31	7	3	41
Percentage Change	63%	58%	75%	121%

Year	White Women			
	At Birth	At Age 65	At Age 85	At Birth
1990	80	19	7	74
2000	80	19	7	75
Additional Years	31	7	3	41
Percentage Change	63%	58%	75%	121%

Data Sources: National Vital Statistics Reports, Vol. 50, No.6. Life Expectancy at Birth, by Race and Sex, Selected Years 1929-98.; National Vital Statistics Reports, Vol. 49, No.12.Deaths, Preliminary Data for 2000.;U.S. Census Bureau. P23-190 Current Population Reports: Special Studies. 65+ in the United States.

There is a lot of data that tells us about the quality of life of people throughout time. From forensic records and bone samples of people who live two thousand years ago to the dental records and death records of people who died just yesterday. What does that data tell us about the life expectancy of Adults in the US both from a century ago and today? In this article, we explore that data.

Impacts to Life Expectancy

There are many factors that impact the life expectancy of people and individuals. War, disease, genetics, diet, lifestyle, gender, and health are a few of those. As we explore this data, ask yourself about your own health, wellness, and how they impact your own life expectancy. The short story here is that life expectancy is expanding and people are living longer than they once did. Here is a closer look at that progress.

Men and Life Expectancy

In 1900, the expectation for white men was to live to age 47 and 12 percent of those born in 1900 would make it to age 65. In contrast, an African American man born in 1900 was only expected to live until the age of 33 and of those born in 1900, only 10 percent of them would live to reach age 65. For both white and African American men born in 1900, a mere four percent (for each) would reach age 85.

By 1910 the life expectancy for white men grew by two years and those born in 1910 the expectancy was to live to 49 years of age. For African Americans, that decade saw only a single year improvement in life expectancy. Five percent of African American men born in 1910 would reach age 85, whereas, only four percent of white men born in that year would celebrate their 85th birthday.

In 1920, white men had an expectancy to live to age 54 and African Americans to age 46. In the 1920's several medical breakthroughs occurred. We discovered things like vitamins, vaccines, and the introduction of new medications such as Sulfa – all helped to improve the life expectancy. [1]

At the end of the 1920's (1929) the great depression started. It would last until 1939 when another incident – World War II – would begin. Both of those events caused premature death. Despite all this, life expectancy in the 1930's rose for white men with an expectancy to live until the age of 60. For African American, the life expectancy for men was low – age 47. For African American men born in 1930, a decrease in the data appears – only four percent would reach the age of 85. A drop of one percent.

White men born in 1950 had a life expectancy of 67 – which today is the age of retirement. For African American men born in 1950, the life expectancy was 59 years of age – nearly a full decade earlier than that of white men. I fact, African American males have a life expectancy of age 68

only after the year 2000 and for white men, born in 2000, the life expectancy is age 75. A difference that parallels from 1950-2000.

In part, the jump in life expectancy in 1950 were improvements in medicine, such as the development of the external pacemaker in 1952 and the first successful open heart surgery in 1953. [2]

Read more about the advancements in medicine as a timeline.

Women and Life Expectancy

White women born in 1900 were expected to live until age 49 and of those women born in that decade, 12 percent would live to be age 65 and 4 percent to age 85. For African American women born in 1900, life was short. Their life expectancy was only 34 years and only 11 of those women would make it to age 65 and five percent would turn 85. For those women born in 1910, white women on average lived until age 52 and African American women to age 38. It would not be until the 1950's that African American women would live to reach age 63. In 1950, white women had a life expectancy of 72. For those women born in 1950, 15 percent would reach age 65 and five percent of white women would make it to their 85th birthdays and six percent of African American women would reach age 85. Between 1900 and 1950 only 12 percent of white women would live to reach age 65 and 11 percent of African American women would live to age 65.

By the year 2000, White women had a life expectancy of 80 years and African American woman were expected to live to age 75.

What the data shows us that as technology improves and advancement in medicine and medical procedures improve, the life expectancy of men and women expand. Technological advancements, such as medical alert

systems, have greatly contributed to increased life expectancy. Also, improved elder care found in nursing homes, convalescent homes, memory care facilities and assisted living facilities have all helped to improve the average life expectancy. A good example of this is the Gregor Mendel's genetic experiment in 1866 – the first scientific description of genes and how they work. Today, we understand a fair bit more about genetics but there is much left to learn. As time passes, those people born today, well have a longer life expectancy than that of their parents. It is quite possible that as Americans, we could top the century mark for life expectancy for all men, women, and every heritage that calls the US home. What that means is that we must look to the future to make sure that we have in place the resources to meet our needs as we age. Those include savings, insurance, and a legal framework that helps us to enjoy the later years of our life, whatever our life expectancy should be.

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Since graduating from Harvard with an honors degree in Statistics, Jeff has been creating content in print, online, and on television. Much of his work has been dedicated to informing seniors on how to live better lives.

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REVIEW ARTICLE | Free Access

A systematic review of randomized controlled trials investigating the efficacy and safety of testosterone therapy for female sexual dysfunction in postmenopausal women

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Summary

The clinical sequelae of oestrogen deficiency during menopause are undoubted. However, the pathophysiological role of testosterone during the menopause is less clear. Several randomized, placebo-controlled clinical trials suggest that testosterone therapy improves sexual function in postmenopausal women. Some studies suggest that testosterone therapy has additional effects, which include increased bone mineral density and decreased serum high-density lipoprotein (HDL) cholesterol. Furthermore, the long-term safety profile of testosterone therapy in postmenopausal women is not clear. This article will provide a concise and critical summary of the literature, to guide clinicians treating postmenopausal women.

1 INTRODUCTION

Menopause is the cessation of menstruation and reproductive function, due to reduced ovarian activity. Menopause typically occurs between 45 and 55 years of age.[1]

Reduced circulating levels of oestrogen during menopause transition or perimenopause may cause hot flushes, low mood and symptoms of vulvovaginal atrophy.[2] The hallmark symptoms of menopausal transition/perimenopause are hot flushes and irregular periods, whereas amenorrhoea is required for menopause itself. Women may experience vaginal atrophy and

vaginal dryness mostly in the late menopausal transition and even beyond.[2-4] Some women also experience decreased libido, receptivity and responsiveness, and reduced frequency of sexual thoughts and fantasies during menopause transition and postmenopause. It is estimated that 50%-60% of all postmenopausal women suffer from symptoms of urogenital and sexual dysfunction.[5, 6]

Androgens are natural steroid hormones regulating the development and maintenance of classically male characteristics. However, women also depend on the physiological action of androgens which are thought to include regulation of libido and sexual arousal.[7] Androgens are synthesized in the testes, ovaries and adrenal glands.[8]

It is over 60 years since testosterone therapy was first reported in postmenopausal women.[9] There is currently growing interest in the role of testosterone therapy for the treatment of sexual dysfunction in postmenopausal women; however, prescribing behaviour is highly variable across the UK, which reflects uncertainty about the safety and effectiveness of therapy. This article aims to provide an objective summary of the evidence to date investigating the effectiveness and safety of testosterone replacement for sexual dysfunction in postmenopausal women.

2 MATERIALS AND METHODS

2.1 Search and selection

A search of the electronic databases CENTRAL, EMBASE, MEDLINE and PubMed was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement during July 2018[10] (See Table S1). All studies identified using search terms up until July 2018 were considered for inclusion to the study. Databases were searched using the following terms: “female OR females OR women OR woman,” AND “postmenopausal OR postmenopausal OR postmenopause OR postmenopause OR perimenopausal OR peri-menopausal OR perimenopause OR peri-menopause OR climacteric” AND “testosterone” AND “placebo OR placebos OR random OR randomised OR randomized OR randomly OR randomly allocated.” Identified studies were excluded if the abstracts were not in the English language, or included purely pharmacokinetic outcomes. For studies to be included, subjects were required to be perimenopausal or postmenopausal women presenting with symptoms of sexual dysfunction, dyslipidaemia, impaired memory, decreased bone mineral density or breast symptoms. One study was excluded because all subjects had rheumatoid arthritis.[11]

2.2 Data extraction

Study titles and abstracts were initially screened before full-text review was completed in duplicate by two study investigators (CSL and CNJ). Discrepancies were dealt with by consensus.

A total of 69 studies fulfilled the criteria for inclusion to this systematic review (Figure 1). Data identified for all studies were as follows: date of publication; intervention administered; blinding; randomization; treatment duration; allocation; route of administration and treatment dosage; number of subject participants; design of the study, study references and source of funding.

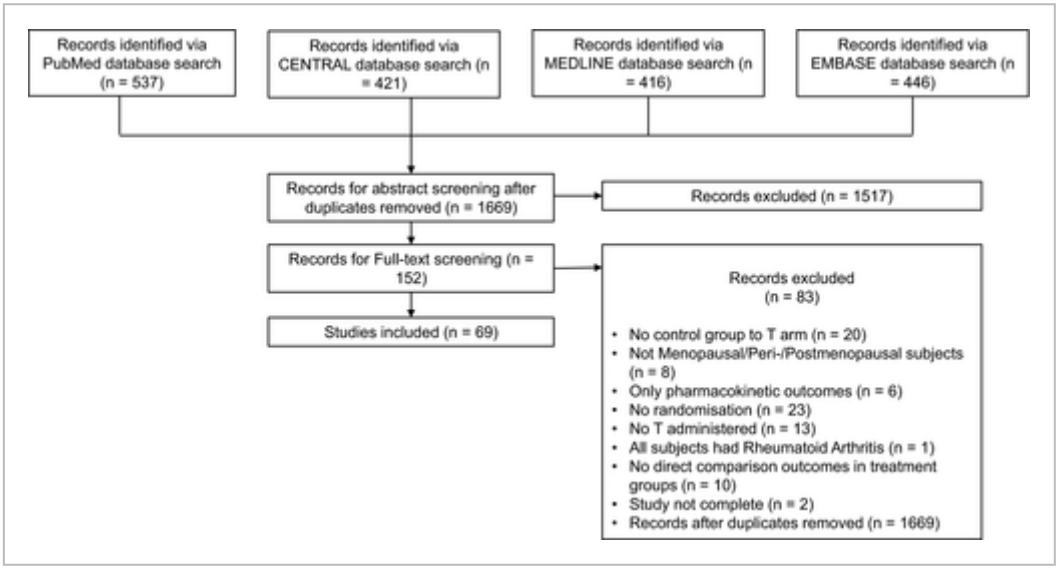

Figure 1

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PRISMA chart summarising search strategy for the systematic review

3 ANDROGENS AND THEIR ROLE IN SEXUAL FUNCTION

Oestrogens are the dominant sex hormones required for female reproductive maturation and activity. However, androgens also play a biological role in women. Further, in premenopausal women, circulating T and E2 have similar picomolar concentrations. The major androgens in the serum of normal cycling women are dehydroepiandrosterone sulphate (DHEAS), dehydroepiandrosterone (DHEA), androstenedione, testosterone and dihydrotestosterone (DHT). Though abundant in the circulation, DHEAS, DHEA and androstenedione may be considered pro-hormones, requiring conversion to testosterone or DHT to express their androgenic effects.12 As testosterone requires conversion to E2 or DHT to express its biological effects, it too can be considered a pro-hormone in males and females.

The ovaries and the adrenal glands are the major sources of androgen synthesis in women. Testosterone is the major ovarian androgen, and dehydroepiandrosterone (DHEA) is the major adrenal androgen.13 Androgen hormones circulate in the blood stream bound to carrier proteins such as sex hormone binding globulin (SHBG) and albumin and corticosteroid binding globulin. Circulating testosterone is highly bound to plasma proteins, with about 66% bound to

SHBG and 33% to albumin. SHBG weakly binds DHEA but not DHEAS.[14-16] Androgens exert biological effects by activating androgen receptors (AR), and indirectly by conversion to oestrogen via aromatization. Androgen receptors are located in several organs of the body, including breast, brain, ovaries, bone, muscle, fat, liver and skin.[17] Moreover, testosterone is known to have multiple anabolic effects on muscles, body fat and bone mineral content in women.[18] Androgens are likely to influence behaviour through organizational or activational effects on the brain, which may be either directly, or indirectly mediated through aromatization to oestrogen.[19] It is also important to recognize that effects of sex hormones on sexual function, sexual thoughts and behaviour may be (at least partially) mediated indirectly through improved vaginal lubrication.[20] Of relevance in men, penile injury following intercourse reduces libido, and circumcision to prevent future penile injury is associated with recovery of libido.[21]

A cross-sectional study of 1423 women between the ages of 18 and 75 suggested total testosterone measured via radioimmunoassay, calculated free testosterone, dehydroepiandrosterone sulphate and androstenedione declined steeply in the early reproductive years and do not vary as a consequence of natural menopause, and the postmenopausal ovary seems to be an ongoing site of testosterone production.[22, 23] It is however important to highlight that there are many limitations using immunoassays to measure testosterone in women; this is due to limited accuracy and sensitivity at low concentrations of total testosterone when compared with mass spectrometry.[24]

Some studies measuring serum androgen levels in premenopausal and menopausal women (whether natural or surgically induced) have failed to demonstrate any consistent relationship between low androgen concentrations and low sexual function. However, other studies have shown associations between androgens and sexual function in women. Davis SR et al reported the results of a community-based study of 1021 randomly recruited healthy women observed a direct association between an endogenous level of DHEAS below the tenth percentile and low sexual responsiveness in women aged 45 years or older. In women aged 18-44 years, concentrations of DHEAS below the tenth percentile were directly associated with low libido, arousal and responsiveness. No associations with androstenedione or total and free testosterone were seen. Wahlin-Jacobsen et al reported that the serum level of free testosterone and androstenedione was statistically significantly correlated with libido in the total cohort of women including 560 healthy women aged 19-65 years. Moreover, a prospective longitudinal study of 3266 women aged 42-52 years reported by Randolph JF et al demonstrated that endogenous testosterone was associated with masturbation frequency, libido and arousal, and DHEAS was positively associated with masturbation frequency and desire.[22, 25-27] Data correlating androgen levels with specific signs or symptoms are unavailable. Consequently, the American Endocrine Society[28] recommends against making the

diagnosis of androgen deficiency in women. In summary, it is accepted that androgens may influence sexual behaviour, but it is unclear whether a reduction in endogenous androgen production contributes to sexual dysfunction during the postmenopause.

The 11-ketotestosterone (11 KT) and 11-ketodihydrotestosterone (11KDHT) are androgen derivatives of the adrenal steroid precursor, 11β-hydroxyandrostenedione (11OHA4). Both 11 KT and 11KDHT are potent agonists of the human androgen receptor (AR). Studies are required to investigate whether levels of 11 KT and 11KDHT are significantly related to sexual function in women during menopause transition.[29]

4 THE DIAGNOSIS AND PREVALENCE OF SEXUAL DYSFUNCTION IN MENOPAUSAL WOMEN

A number of previous studies have investigated the prevalence of sexual dysfunction in menopausal women using structured questionnaires. A prospective observational community-based study of Australian born women aged 45-55 observed that the prevalence of sexual dysfunction using the McCoy Female Sexuality Questionnaire rose from 42% at early menopause to 88% at late menopause defined by hormone testing.[30] Furthermore, cross-sectional studies using the Female Sexual Function Index (FSFI) in postmenopausal, sexually active Malaysian and Thai women suggest that the prevalence of sexual dysfunction is 89.0% and 82%, respectively.[31], [32] The American Psychiatric Associations Diagnostic and Statistical Manual of Mental Disorders (DSM) provides a strict set of diagnostic criteria for sexual dysfunction. The previous edition (DSM-4) classified reduced libido in men or women as a form of hypoactive sexual desire disorder (HSDD). However, the newer DSM-5 classification has split HSDD into gender-specific diagnoses; female sexual interest/arousal disorder is defined as symptoms including absent or significantly reduced interest in sexual activity, sexual thoughts or fantasies, and reduced initiation of sexual activity absent arousal from external sexual/erotic cues.[33] These symptoms need to have persisted for a minimum duration of 6 months, be significant enough to cause distress to the individual, and not be attributable to other mental or physical health conditions. The Women's International Study of Health and Sexuality (WISHeS) analysed the prevalence of sexual symptoms associated with distress in over 3500 women aged 20-70 years in the United States; the prevalence of HSDD was reported as 12%-19% in the United States and 6%-13% in Europe.[34] Therefore, the prevalence of HSDD defined using strict DSM-5 criteria is much lower than the prevalence of sexual dysfunction estimated using the structured questionnaire tools. However, there has been criticism of the DSM-V criteria among experts (McCabe 2016). An alternative classification system for female sexual dysfunction has been produced by the International Society of Sexual Medicine (McCabe 2016) and is summarized in Table [1].[35]

Table 1. Definitions of female sexual dysfunction recommended by International Society of Sexual medicine (ISSM)35 and DSM-V Criteria for comparison33

Sexual dysfunctions	ISSM Definitions	DSM-V Criteria
Hypoactive sexual desire dysfunction	Persistent or recurrent deficiency or absence of sexual or erotic thoughts or fantasies and desire for sexual activity	Split into diagnoses below
Female sexual arousal dysfunction	Persistent or recurrent inability to attain or maintain arousal until completion of the sexual activity, an adequate subjective assessment of her genital response	Lack of or significantly reduced sexual interest/arousal, as manifested by at least three of the following: (a) absent/reduced interest in sexual activity; (b) absent/reduced sexual/erotic thoughts or fantasies; (c) no/reduced initiation of sexual activity and typically unreceptive to partner's attempts to initiate; (d) absent/reduced sexual excitement/pleasure during sexual activity in almost all sexual encounters; (e) absent/reduced sexual interest/arousal in response to any internal or external sexual/erotic cues; (f) absent/reduced genital or nongenital sensations during sexual activity in almost all sexual encounters
Female orgasmic dysfunction	(a) Marked delay in, marked frequency of, or absence of orgasm and/or (b) markedly decreased intensity of orgasmic sensation	Presence of either of following symptoms and experienced on almost all or all occasions of sexual activity: (a) marked delay in, marked infrequency of, or absence of orgasm; (b) markedly reduced intensity of orgasmic sensations
Female	Persistent or recurrent difficulties	Persistent or recurrent difficulties with one (or more) of the

5 EFFECTS OF TESTOSTERONE SUPPLEMENTATION ON SEXUAL FUNCTION

Greenblatt et al in 1950 conducted the first randomized study of testosterone therapy (alone or in combination with oestrogen) in postmenopausal women. Since then, several randomized controlled trials have investigated the effects of testosterone therapy in postmenopausal women with symptoms of sexual dysfunction (Table 2). These trials have utilized different dosing regimens and routes of administration. Some trials have used testosterone replacement alone, whereas others have studied the effects of testosterone therapy during oestrogen replacement. Some studies have included women with age-associated (“natural”) menopause,

whereas others have included women with surgically induced menopause. All studies excluded women with psychological or medical conditions that could impact on their sexual function in keeping with the DSM-4 and DSM-5 diagnostic criteria. Furthermore, most studies were restricted to participants with long-term partners.

Table 2. Summary of systematic review of testosterone therapy in peri- and postmenopausal women

Author and date	Number of subjects	Study design	Findings	Industry funding
Raghunandan C, 20106	75	RCT Postmenopausal 3 study arms: Twice weekly—Topical. E; E + T (1 mg); Placebo (KY Jelly) 12 wk	McCoy improvement: E: 42% E + T: 147% Placebo: 18.6% $P < 0.01$	None stated
Nathorst-Boos J, 200636	53	RCT, crossover study Postmenopausal aged 50-65 EP + 10 mg testosterone gel EP + placebo gel 3 mo	McCoy Questionnaire: "significantly improved ($P < 0.001$) for testosterone vs placebo"	Yes

For studies to be included, subjects were required to be perimenopausal or postmenopausal women presenting with symptoms of sexual dysfunction, dyslipidaemia, impaired memory, decreased bone mineral density or breast symptoms. BISF-W, brief index of sexual functioning for women; CSFQ-F-C, changes in sexual functioning questionnaire; FSFI, female sexual function index; McCoy, McCoy female sexuality questionnaire; PFSF, profile of female sexual function; PGWB,

psychological general well-being scale; SAL, sexual activity log; SSEs, satisfying sexual episodes; SSSS, Sabbatsberg sexual self-rating scale; WHQ, women's health questionnaire.

Drugs: APO, apoprotein; AR, androgen receptor; AUC, area under curve; BISF-W, brief index of sexual functioning for women; BMD, bone mineral density; BMI, body mass index; CEE, conjugated equine oestrogens; CES-D, centre for epidemiological studies depression scale; CSFQ, changes of sexual functioning questionnaire; DHEA, dehydroepiandrostenedione; E, oestrogen; E2, oestradiol; EE, esterified oestrogens; EP, oestrogen-progestogen; EPT, oestrogen-progestin therapy; ER, oestrogen receptor; FAI, free androgen index; FFM, free fat mass; FM, Total body fat mass; FNA, fine needle aspirate; HAM-D, Hamilton rating for depression; HDL, high-density lipoprotein; HOMA, homeostatic model assessment; hs-CRP, high-sensitivity C-reactive protein; ICA, internal carotid artery; IGFBG-1, insulin-like growth factor binding globulin-1; IL, interleukin; IM, intra-muscular; ISLT, international shopping list test; LDL, low-density lipoprotein; LPA, lipoprotein A; MCA, middle cerebral artery; MP, medroxyprogesterone acetate; MT, methyltestosterone; NA, norethisterone acetate; P, progesterone; PGWB, psychological general well-being index; PI, pulsatility index; PR, progesterone receptor; Q-Les-Q, quality of life enjoyment and satisfaction questionnaire; RBMT, Rivermead behavioural memory test; SIQ, sexual interest questionnaire; SRS, Sabbatsberg revised sexual self-rating scale; T, testosterone; TFS, tape/film scale; TNF-A, tumour necrosis factor-A; TTP, transdermal testosterone patch; VCAM-1, vascular cell adhesion molecule-1; VPA, vaginal pulse amplitude; WAIS-R, wechsler adult intelligence scale-revised.

Most trials measured sexual function using validated symptom scores. Some authors[6], [36], [37] have used the modified McCoy's sex scale[38] which covers sexual experience and responsiveness during the last 30 days and contains seven items (eg, "Are you satisfied with your present frequency of sexual activity?" "How enjoyable is sex for you?" and "How often do you have an orgasm during sex?"). Some studies[39], [40] used the female sexual function index (FSFI), which is a standardized questionnaire used to assess sexual function among postmenopausal women, and is an anonymous patient-based self-reported instrument.[41] Other authors[42]-[48] have used the following validated scales: Sexual Activity Log; Profile of Female Sexual Function; Personal Distress Scale. The result of testosterone administration in postmenopausal women has also been summarized in a recent Cochrane review.[49]

5.1 Transdermal testosterone administration

Several placebo-controlled double-blind studies have investigated whether testosterone improves sexual function in postmenopausal women taking oestrogen with or without progestin therapy. Most studies have investigated the effects of transdermal testosterone therapy. Three of the largest published studies randomized postmenopausal women with surgically induced menopause to daily dermal patch administration of placebo or 300 μg testosterone for 24 weeks of duration.[42], [44], [45] All women included in these trials had received oestrogen supplementation for at least 3 months before randomization. Simon et al[44]

observed that in 562 women, testosterone administration significantly increased the frequency of total satisfying sexual activity (as measured by the SAL) from 2.82 to 4.92 episodes per 4 weeks, when compared with an increase from 2.94 to 3.92 episodes per 4 weeks in the placebo group ($P = 0.0003$). Libido was also increased significantly during testosterone supplementation when compared with placebo. Buster et al[42] observed in 533 women that testosterone increased total satisfying sexual activity when compared with placebo (1.56 episodes vs with 0.73 episodes per 4 weeks), and improved libido. Braunstein et al[45] randomized 447 women to one of 3 different daily doses of testosterone supplementation (150, 300 or 450 μg) or placebo; subjects receiving the 300 μg testosterone dose reached total serum testosterone levels of 91 ng/dL by week 24 and experienced a statistically significant increase in libido from baseline when compared with placebo (67% vs 48%; $P = 0.05$) and in frequency of satisfying sexual activity (79% vs 43%; $P = 0.049$); these results are concordant with similar smaller studies.[46], [50] However, it is important to note the placebo response was substantial. No significant changes in libido or satisfying sexual activity were observed during 150-μg/d or 450-μg/d testosterone supplementation reaching total serum testosterone concentrations of 44.5 and 122.5 ng/dL, respectively, when compared with placebo in postmenopausal women. Shifren et al[47] studied the effects of testosterone patch in 549 women with natural menopause who were taking a stable dose of oral oestrogen (with or without progestin). Participants were randomized to placebo or transdermal testosterone patch (300 μg/d) twice weekly for 24 weeks. They were then followed up to measure a change from baseline in the number of satisfying sexual events using the SAL. Women allocated to testosterone reported a significantly greater increase in sexual events measured using SAL during testosterone when compared with placebo (placebo, 0.5 ± 0.23; testosterone, 2.1 ± 0.28, $P < 0.0001$ vs placebo). The largest RCT performed to date randomized 814 women with menopause (natural or surgical) and HSDD to placebo or testosterone patch at the doses 150 μg or 300 μg per day over a 24-week period.[48] Participants randomized to the 300 μg group, but not the 150 μg group reported significantly greater Satisfying Sexual Events (SSEs) over a 4-week period when compared with participants in the placebo group (episodes per 4 weeks: placebo, 0.7; 150 μg testosterone, 1.2, $P = 0.11$ vs placebo; 300 μg testosterone, 2.1, $P < 0.001$ vs placebo). Though not reported, it would be interesting to determine whether the effects of testosterone differed between women with a natural or surgical menopause.

Panay et al[43] conducted a 6-month placebo-controlled, double-blind trial (the ADORE study). They randomized 272 women to transdermal testosterone patch (TTP; 300 μg/d) or placebo, and used the SAL to measure satisfying sexual episodes as their primary end-point. Increases in Significant Sexual Events (SSEs; $P = 0.0089$), libido $P = 0.0007$ and reduced personal distress ($P = 0.0024$) were observed following 6 months of TTP administration when compared with placebo in menopausal women. In summary, several studies suggest transdermal testosterone increase sexual activity. Collectively, these multiple randomized placebo-controlled studies

suggest that testosterone therapy significantly improves symptoms of sexual dysfunction in women with natural or surgical menopause. These conclusions are in keeping with two recent systematic reviews of the literature.[18], [49] However, it is important to consider that symptoms of sexual dysfunction do not have a clear relationship with low level of circulating testosterone. Therefore, questions remain as to whether testosterone administration in postmenopausal women exerts pharmacological or physiological actions. It is also important to consider to what extent any effects of androgens on sexual function are attributable to aromatization to oestrogens. For instance in men, aromatase inhibition prevents testosterone administration from improving libido in GnRH agonist-induced hypogonadism.[51] Finally, it would be helpful to specifically investigate whether the testosterone therapy improves sexual function in postmenopausal women whose serum oestradiol levels are replete (eg, serum E2 levels 300-600 pmol/L) during HRT; this would suggest that testosterone is not simply acting to supplement bodily oestrogen exposure (via aromatization).

5.2 Other routes of testosterone administration

Recent clinical trials have investigated the administration of nontransdermal application of testosterone in postmenopausal women. Urogenital topical application was investigated in 75 menopausal women (natural or surgical), who were randomized to placebo, oestrogen only or oestrogen with testosterone over a 12-week period.[6] McCoy Sexuality scores increased in all treatment groups, but were highest in the oestrogen with testosterone group (Percentage improvement in McCoy Sexuality score: placebo, 18.6; oestrogen only, 42.4, $P < 0.05$ vs placebo; oestrogen with testosterone, 147, $P < 0.01$ vs placebo). This implies that effects of sex hormones on sexual function may be partially mediated indirectly through improved vaginal lubrication.[20] Studies are needed to delineate the relative importance of vulvovaginal vs cerebral effects of sex steroids in sexual function in postmenopausal women. Similar increase in McCoy Sexuality score was observed in a 2002 study of 50 surgically menopausal women[52]; enjoyment of sex, satisfaction with frequency of sexual activity, interest in sex and total score all increased significantly with testosterone compared to placebo, as well as studies in 2006[36] and 2007.[37]

Tungmunsakulchai et al[40] investigated the effects of twice weekly administration of either oral placebo or testosterone undecanoate 40 mg in combination with oral oestrogen in a randomized double-blind study. Sexual function was significantly higher in the testosterone group when compared with placebo (FSFI scores: placebo, 28.6 ± 3.6; testosterone, 25.3 ± 6.7, $P = 0.04$ vs placebo).

Lobo et al[53] performed a double-blind randomized trial of 221 postmenopausal women receiving either oral combined esterified oestrogens/methyltestosterone or oral esterified oestrogens alone; changes in levels of sexual interest or desire as rated on the Sexual Interest

Questionnaire were investigated. Treatment with the combination of esterified oestrogens and methyltestosterone significantly increased the concentration of bioavailable testosterone and suppressed SHBG. Scores measuring sexual interest or desire and frequency of desire increased from baseline with combination treatment and were significantly greater than those achieved with esterified oestrogens alone. Treatment with the combination was well tolerated.

Sherwin et al studied 10 premenopausal 43 surgical menopause who received either oestradiol 8.5 mg and testosterone 150 mg, oestradiol 8.5 mg, testosterone 150 mg or placebo 1 mol/L in a randomized control trial. They concluded that a combined oestrogen androgen therapy can enhance the quality of life for both naturally and surgically postmenopausal women and increase sexual arousal and libido. A randomized double-blind trial by Watts et al investigated 66 surgically menopausal women received either oral esterified oestrogens (1.25 mg), or esterified oestrogens (1.25 mg) combined with methyltestosterone (2.5 mg) daily for 2 years. Menopausal symptoms of somatic origin (hot flushes, vaginal dryness and insomnia) were improved significantly by both treatments. Also, both treatment regimens prevented bone loss at the spine and hip.[53-55] However, there was no significant difference in somatic symptoms between the treatment groups.

In another double-blinded randomized study by Huang et al,[56] 71 menopausal women who previously underwent hysterectomy with or without oophorectomy received a standardized transdermal oestrogen regimen during the 12-week run-in period, and were then randomized to receive weekly IM injections of placebo, or 3, 6.25, 12.5 or 25 mg testosterone enanthate for 24 weeks. Dose-dependent improvements in several domains of sexual function, lean body mass, chest-press power and loaded stair-climb power were observed, with the greatest improvements at the highest dose. Furthermore, a double-blind randomized study by Dobs and colleagues, with 40 naturally and surgically menopausal women, observed significant increases in upper and lower body strength with testosterone compared to placebo.[57] Whilst the majority of studies observed testosterone significantly increased sexual arousal/interest,[39, 42, 52, 57, 58] frequency of orgasms[13, 39, 57] and frequency of sexual activity[13, 47, 52] when compared to placebo, some suggest no significant difference between the treatment groups.[39, 58-61] In conclusion, most but not all studies suggest that testosterone improves symptoms of sexual dysfunction regardless of the route of administration. Further studies are required to investigate whether the observed effects of testosterone administration on sexual function are truly dose dependent.

6 NONSEXUAL EFFECTS OF TESTOSTERONE THERAPY

Testosterone therapy is anticipated to cause symptoms of androgen excess such as excess body hair (hirsutism) and acne. Accordingly, clinical trials reported that the most common adverse effects associated with testosterone therapy were skin reactions, unwanted hair

growth, acne and vaginal bleeding; however, most were mild and rarely resulted in withdrawal from the study.[18], [44], [46], [50], [52], [57], [62]-[65] Furthermore, two published studies observed no significant difference in adverse effects between treatment groups.[66], [67]

6.1 Breast cancer risk

Exogenous sex steroids may stimulate the growth of sex-hormone dependent tissues, most notably breast tissue in women,[68], [69] so it is relevant to consider whether testosterone therapy increases the risk of breast cancer. The only published long-term investigation of testosterone therapy in postmenopausal women has been conducted by the product's manufacturer.[62] They performed an open-label, uncontrolled safety and tolerability trial of transdermal testosterone (daily dose, 300 μg) in over 900 women with surgical menopause and HSDD, for up to 4 years of duration. Three cases of invasive breast cancer during 4 years of TTP administration; however, the authors concluded that this was not inconsistent with background rates for women in the same age-group. The randomized controlled trial by Davis et al[48] over 24 weeks observed 4 cases of breast cancer in the testosterone group when compared with no cases in the placebo group. However, the same authors performed a follow-up study suggesting that 1 year of TTP therapy had no significant effect on digitally quantified absolute or per cent dense mammographic area in postmenopausal women when compared with placebo[70]; these data are concordant with results of a study by Hofling et al of 6 months TTP administration in 99 postmenopausal women.[71] Furthermore, Hofling et al also observed no significant increase in breast cell proliferative activity with testosterone compared to placebo.[72]

6.2 Endometrial effects

Testosterone promotes endometrial atrophy when given without concomitant oestrogen. Davis et al[48] investigated endometrial findings in 814 women randomly assigned to receive a patch delivering 150 or 300 μg of testosterone per day or placebo. They observed that endometrial bleeding was reported more frequently on the 300 g/d dose testosterone (10.6%) compared with 150 g/d testosterone (2.7%) or placebo (2.6%). Endometrial bleeding was accompanied at the highest dose by endometrial atrophy.[48] It is therefore important to provide concurrent continuous or cyclic progestin therapy to nonhysterectomized women administered combined oestrogen and testosterone treatment as per normal practice.

6.3 Dyslipidaemia

Whilst many studies have suggested that testosterone administration may cause lipid disarrangements such as reduced high-density lipoprotein (HDL)[18], [49], [55], [57], [65], [73]-[76] and an increase in low-density lipoprotein (LDL),[18], [49] some indicate no change in LDL,[73], [74], [76] a decrease in LDL[75] or no significant change in lipid profile at all with testosterone.[77]-[79] Studies

seem inconsistent regarding total cholesterol with some observing no change with testosterone compared to placebo,[73], [74], [78] whilst others observed a decrease.[55], [57], [75], [76] A similar pattern of inconsistency in the literature is observed with the effects of testosterone on triglycerides; some studies observe a decrease,[55], [57], [75], [76] whereas others observe no change with testosterone.[78] The authors of a 2011 study failed to observe any significant increase in haematocrit, or adverse changes in glycemic markers or lipid profile following up to 4 years of TTP therapy.[62] Further, long-term studies are required to investigate the potential effects of testosterone supplementation on risks of malignancy and cardiovascular disease in postmenopausal women. However, the available evidence allows us to speculate that any effects of testosterone therapy on serum lipids are likely to be minor, which is of relevance when discussing therapeutic options with patients.

6.4 Bone mineral density

The Women's Health Initiative Observational Study of 93 676 postmenopausal women aged 50-79 years investigated hip fracture risk in relation to the circulating level of testosterone. They observed higher circulating levels of serum SHBG is associated with an increased risk of subsequent hip fracture and high endogenous testosterone with a decreased risk, independent of each other, serum oestradiol concentration and other recognized risk factors.[80]

The reported effects of testosterone on bone of naturally postmenopausal women are heterogeneous. Elraiyah et al[18] conducted a systematic review and meta-analysis, which included 35 randomized trials, four of which reported on bone densitometry during combined testosterone and oestrogen therapy, and compared it to oestrogen alone. They concluded that testosterone had no significant effect on bone mineral density (BMD) in any tested site concordant with a study by Garnett et al in 1992.[81] However, Miller et al[82] observed BMD of the hip increased significantly with testosterone compared to HRT alone, whilst a study by Barrett-Connor et al[67] observed an increase in BMD both at the hip and lumbar spine with testosterone treatment when compared to placebo. Further, a 1995 study by Davis et al[13] on 34 postmenopausal women with oestradiol alone, or oestradiol plus testosterone implants observed BMD increased significantly for total body, at vertebrae L1-L4 and the trochanter with testosterone compared to oestradiol alone. In addition, whilst Miller et al[82] observed no difference in bone biochemical markers (Ntx, Dpd or BSAP) between treatment groups, another observed markers of bone formation (IGF-1 and P1CP) were significantly higher with testosterone compared to placebo.[83] No trials have reported long-term fracture rates during testosterone therapy in postmenopausal women. In summary, early data suggest that testosterone may have some beneficial effects of increasing BMD at specific locations in the body, but further longer-term studies are required to provide more conclusive evidence.

6.5 Cardiovascular effects

Exogenous testosterone increases haematocrit, so it is important to consider if the risk of thromboembolic and cardiovascular disease is altered during therapy.[84] Some recent studies have shown an increased risk of cardiovascular events in men treated with testosterone.[85-87] However, other studies data did not provide any evidence of an association between testosterone and cardiovascular events.[88-90] Testosterone-containing medicines are licensed in the European Union (EU) for the treatment of male hypogonadism. There is limited experience on the safety and efficacy of the use of these medicines in patients over 65 years of age, and the use of testosterone to boost these levels in healthy older men is not authorized in the EU. In the United States (US), the US Food and Drug Administration (FDA) cautions that prescription testosterone are approved only for men who have low testosterone levels caused by certain medical conditions. The safety and benefit of these medications have not been established for the treatment of low testosterone levels due to ageing.[91, 92] There is no specific evidence about the cardiovascular effect in women treated with testosterone. The randomized control trials comparing testosterone therapy in women with placebo have not observed any significant differences in event rates for any cardiovascular disease outcomes, including venous thromboembolic events in short-term trials. Furthermore, adverse cardio-metabolic changes have not been frequent during short-term observations (12-24 months) in women treated with testosterone.[28] Data suggest that the testosterone transdermal patch improves exercise tolerance, muscle strength and insulin resistance without side effects in elderly female patients with stable chronic heart failure. In a double-blind, randomized, placebo-controlled study in women with heart failure, testosterone therapy (the TTP releasing 300 μg/d) was associated with significant functional improvements assessed by peak oxygen consumption, distance walked over the 6-minute walking test, muscle strength and insulin resistance compared with placebo. Moreover, a systematic review of testosterone therapy on cardiovascular outcomes in postmenopausal women was conducted by Spoletini et al 2014; they observed a favourable effect of testosterone therapy in postmenopausal women, such as high-density lipoprotein cholesterol, total cholesterol, body fat mass and triglycerides.[93-97] In addition, a study by Kocoska-Maras et al in 2009[98] observed testosterone counteracts the oestrogen induced rise in high-sensitivity C-Reactive Protein (hs-CRP) but had no effects on other inflammatory markers of cardiovascular disease, such as Interleukin-6, Tumour Necrosis Factor-Alpha and Homocysteine. In contrast, a 2014 study[99] observed no significant difference in hs-CRP levels between testosterone and placebo treatments. Studies appear to agree that testosterone has no significant effect on systolic and diastolic blood pressure compared to placebo.[83, 99] Testosterone has also been observed to significantly increase fibrinogen levels with testosterone compared to placebo.[76] In summary, despite many studies being conducted on this topic, the long-term cardiovascular consequences of testosterone therapy remain unclear.[28]

6.6 Anthropometric measurements

Studies seem to agree that testosterone has no significant effect on BMI compared to placebo,[73], [83] but are inconclusive when it comes to body composition. A 2006 study by Zang et al on 63 postmenopausal women[77] observed no significant difference in body fat with testosterone compared to other treatment groups, similar with a study by Davis et al,[79] whilst a 2005 study[83] observed lean body mass significantly increased, consistent with another study[57] indicating significant increases in lean body mass of the legs, arms and trunk. A study by Duarte et al[73] observed visceral fat significantly increased with testosterone by 11% vs placebo, in direct contrast with a 2014 study stating no difference in both abdominal and visceral fat volumes between treatment groups.[99] One study observed free fat mass increased[100] when given testosterone vs placebo, but others observed no change in fat mass[73], [77] with one indicating a decrease in % fat tissue with testosterone.[57] Overall, whilst studies agree that testosterone has no effect on BMI, there is no consensus on its effects on fat mass in the absence of long-term large scale trials.

6.7 Cognitive function

The effects of steroid hormones on human cognition are of considerable interest, particularly during the menopause. A study by Krug et al on 12 postmenopausal women observed testosterone significantly increased divergent thinking, (fantasies and fluency of speech) compared to placebo,[101] but no other aspects of cognitive function were affected. This is in direct contrast to many other studies indicating no change in verbal fluency, or any other measures of cognitive function.[102]-[104] A 2014 study observed testosterone therapy had no effect on cognition after 12 weeks of treatment compared to placebo, but at 26 weeks, the Cogstate International Shopping List Test (ISLT) score significantly increased by 1.57 units vs placebo.[104] One study observed immediate verbal memory to be impaired with testosterone, but no other memory functions were affected.[105] A 2002 study by Wisniewski et al on 26 naturally and surgically postmenopausal women discovered testosterone significantly increased building memory score compared to placebo, despite no other aspects of cognitive function being affected (cube comparison, shape memory or identical pictures).[106] In summary, studies published to date have observed a variety of effects on cognition following testosterone therapy; it is therefore difficult to draw conclusions on the predicted effects of testosterone in postmenopausal women.

6.8 Physical symptoms

A 2002 study by Dobs and colleagues gave esterified oestrogens with or without methyltestosterone to 40 naturally and surgically menopausal women and observed testosterone significantly improved both somatic and vasomotor symptoms compared to oestrogen alone.[57] However, the majority of studies seem to agree testosterone therapy has no significant beneficial effect on suppressing hot flash frequency and severity.[58], [64], [67], [107] A

further study observed no significant improvement in somatic or psychological symptoms with testosterone compared to placebo[58] whilst another observed no significant difference in sweating and vaginal dryness between treatment groups.[67] In summary, most studies suggest that testosterone does not affect menopausal hot flushes and it remains to be determined whether somatic symptoms or vaginal dryness is altered during testosterone therapy.

7 LIMITATIONS OF DATA

Currently, there is limited long-term data evaluating whether testosterone replacement increases the risks of cardiovascular disease, or breast cancer. In view of the controversy regarding the safety of testosterone therapy in older men (albeit when administered at much higher doses),[108] a similarly cautious approach might be appropriate for postmenopausal women with risk factors for cardiovascular disease or breast cancer. It is also important to consider that many of the clinical trials performed to date have been industry funded. It is plausible that reporter bias might have skewed the published literature towards studies supporting the usage of testosterone in postmenopausal women; future, academic-sponsored studies are needed to address this concern. Finally, to fulfil the criteria for HSDD or Female sexual dysfunction, selected study participants were screened to exclude disease comorbidities. It is, therefore, not known whether postmenopausal women with disease comorbidities would also benefit from testosterone therapy. This limits the extent to which published data may reflect everyday clinical practice.

8 CONCLUSION

Sexual dysfunction is a common problem in postmenopausal women, which may profoundly affect quality of life. Endogenous testosterone may influence sexual behaviour in women. However, there is a lack of evidence implicating deficient endogenous testosterone in the evolution of sexual dysfunction in women. Furthermore, there is considerable variation in the prevalence of menopause-related sexual dysfunction, depending on the criteria employed. Several randomized, placebo-controlled clinical trials suggest that testosterone therapy significantly improves sexual function assessed using validated questionnaires, in postmenopausal women with sexual dysfunction or hypoactive sexual desire disorder. The effect size is modest, with approximately one additional satisfactory sexual activity per month. In the short-term, testosterone therapy is generally well tolerated and safe adverse effects predominantly consist of localized skin reactions and cosmetic effects of hyperandrogenaemia. Possible impacts on lipid metabolism, cardiovascular and cancer risk warrant further detailed investigations, although no major safety concerns have been raised to date. In line with the US Endocrine Society Clinical Practice Guidelines, there is currently insufficient evidence regarding general recommendations for testosterone therapy in women.[28] There are also no licensed products in the UK for female administration of testosterone; testosterone preparations

designed to administer much higher doses (to men) must therefore be used. If clinicians are considering offering this treatment to postmenopausal women, it is necessary to provide full counselling on the risks and benefits, particularly the limited effect of testosterone and the lack of long-term safety data. However with these caveats, there is sufficient evidence to recommend testosterone therapy for the minority of postmenopausal women for whom other management strategies have failed.

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CONFLICT OF INTEREST

Nothing to declare.

Supporting Information

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Citing Literature

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Different Forms Of Bioidentical Testosterone

Delivery System of Testosterone	Safety	Use	Cost	Effectiveness	Negatives
Oral bioidentical	Issue with metabolizing in liver, and development of liver tumors	Once daily pill	Bioidentical may not be covered by insurance	Moderate	• Converts into estrone • Mood issues with anger • Not effective for all symptoms of TDS
Oral estratest	Issue with metabolizing in liver, and development of liver tumors	Once daily pill	Covered by insurance	Moderate	• Converts into estrone • Mood issues with anger • Not effective in most patients
Sublingual bioidentical	Low % of people who can absorb under the tongue	One to two times daily	Not covered by insurance; about $100 a month	Minimal	Absorption rate poor
Vaginal	Levels fluctuate extremely over 24 hours	Once time daily	Not covered by insurance; about $100 a month	Good	Fluctuation of levels in bloodstream, cause relief to be intermittent
Creams (transdermal)	Poor response by most patients	Apply every four to six hours	Not covered by insurance; about $100 a month	Minimal	Multiple applications a day, minimal response
Sub-dermal pellets	Safest form	Inserted once every 4-6 months	$400-500 every 4-6 months	Excellent	Side effects of procedure

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RESEARCH ARTICLE Open Access

Incidence of invasive breast cancer in women treated with testosterone implants: a prospective 10-year cohort study

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Abstract

Background: Testosterone implants have been used for over eighty years to treat symptoms of hormone deficiency in pre and postmenopausal women. Evidence supports that androgens are breast protective. However, there is a lack of data on the long-term effect of testosterone therapy on the incidence of invasive breast cancer (IBC). This study was specifically designed to investigate the incidence of IBC in pre and postmenopausal women (presenting with symptoms of androgen deficiency) treated with subcutaneous testosterone implants or testosterone implants combined with anastrozole.

Methods: The 10-year prospective cohort study was approved in March 2008 at which time recruitment was initiated. Recruitment was closed March 2013. Pre and postmenopausal women receiving at least two pellet insertions were eligible for analysis ($N = 1267$). Breast cancer incidence rates were reported as an unadjusted, un-weighted value of newly diagnosed cases divided by the sum of 'person-time of observation' for the at-risk population. Incidence rates on testosterone therapy were compared to age-specific Surveillance Epidemiology and End Results (SEER) incidence rates and historical controls. Bootstrap sampling distributions were constructed to verify comparisons and tests of significance that existed between our results and SEER data.

Results: As of March 2018, a total of 11 (versus 18 expected) cases of IBC were diagnosed in patients within 240-days following their last testosterone insertion equating to an incidence rate of 165/100000 p-y, which is significantly less than the age-matched SEER expected incidence rate of 271/100000 p-y ($p < 0.001$) and historical controls.

Conclusion: Long term therapy with subcutaneous testosterone, or testosterone combined with anastrozole, did not increase the incidence of IBC. Testosterone should be further investigated for hormone therapy and breast cancer prevention.

Keywords: Breast cancer, Incidence, Women, Testosterone, Implants, Prevention

Background

Breast cancer remains the most common cancer in women worldwide and preventive strategies are in their infancy. Although there is cumulative data supporting the protective role of androgens in breast tissue [1–3], the long-term effect of bio-similar testosterone (T) therapy on the incidence of breast cancer has not been previously documented in a prospective study. This is becoming increasingly important as more studies are being published on the benefits of T therapy in pre and post-menopausal women [3–6].

Subcutaneous T implants have been used to treat symptoms of hormone/androgen deficiency in women since 1937 [6, 7]. It has been known for over 70 years that T is anti-proliferative in the breast and inhibits the stimulatory actions of estrogens. Androgens, including subcutaneous T implants, have been successfully used to treat breast cancer [6–12]. However, there has been some concern about T therapy in women, due to some epidemiologic studies reporting

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an association (often misinterpreted as causation) between endogenous T levels and breast cancer risk. T is not an independent variable, and many studies do not adjust for associated higher estradiol levels. Furthermore, epidemiological studies do not address the 'Obesity-Insulin-Testosterone' connection. Obesity and insulin increase inflammation and have direct and indirect causal effects in breast cancer, including increased aromatase activity [13–15]. Insulin stimulates the production of T, which can account for higher T levels 'associated' with breast cancer. In addition, androgen assays lack reliability in the relatively low range of androgens in women, which vary from day to day. Many epidemiologic studies do not measure free bioavailable T levels, which depends on sex hormone binding globulin levels and other endocrine, genetic, and metabolic influences. Also, androgen activity within the mammary cells is not reflected in circulating levels of androgens. Finally, correlation does not imply causation: correlation alone cannot be used as evidence for a cause-and-effect relationship, particularly in view of conflicting studies, and the lack of coherence with biological, preclinical, and clinical evidence.

Testosterone (bio-similar, non-methylated) therapy in women has not been shown to increase the risk of breast cancer and may lower the risk from estrogen-progestin therapy [16–18]. Although the Nurse's Health Study showed an increased risk of breast cancer in 'current users' of oral, methyl-testosterone (the majority of whom were on oral estrogen-progestin therapy), other studies have shown no significant increased risk of breast cancer with methyl-testosterone particularly with esterified estrogens alone (no progestins) [18, 19].

There is concern that T aromatizes to estradiol, which has a secondary stimulatory effect via the estrogen receptor (ER). Patients with increased aromatase activity may produce excess estrogen resulting in breast tissue proliferation [13–15]. Anastrozole, combined with T in a pellet implant, has been shown to prevent aromatization and provide adequate levels of T without elevating estradiol or increasing recurrence in breast cancer survivors [20]. Testosterone has also been shown to safely relieve side effects of aromatase inhibitor therapy in breast cancer survivors [21–24].

The 'Dayton study' was specifically designed to investigate the long-term incidence of breast cancer in women treated with T for symptoms of hormone deficiency. Early results were reported at year five as an interim analysis [12]. This 10-year analysis reports the incidence of IBC in women treated with subcutaneous T, or testosterone with anastrozole (T + A), combined in the implant, most often without the concurrent use of systemic estrogen or synthetic progestogens.

Methods

Study design, setting, and participants

A 10-year prospective cohort study, investigating the incidence of breast cancer in women treated with subcutaneous T implants, was IRB approved in March of 2008 at which time recruitment was initiated. Recruitment was closed 31 March 2013. Methods, including study design, setting, and participants were previously reported in our 5-year interim analysis published in 2013 [12]:

'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 hormone deficiency or imbalance including hot flashes, sweating, sleep disturbance, heart discomfort, depressive mood, irritability, anxiety, premenstrual 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. No patient was excluded from participation based on age, family history, prior hormone use, oral contraceptive use, endometrial pathology, breast density, increased breast cancer risk, menopausal status or body mass index (BMI). Breast cancer genetic testing was not part of the protocol. Although no patient seen during the enrollment period had a known BRCA mutation per clinical history: per protocol they would have been excluded from this group and followed separately. Mammography and clinical breast exam were not protocol determined. Screening mammograms were recommended but not required prior to enrollment. In addition, benefits and risks of screening mammography were discussed with patients. 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. Patients receiving two or more sets of implants were eligible for analysis (N = 1267). An IRB approved written informed consent was obtained on all patients enrolled in the study. Per protocol, the incidence of breast cancer in our study population was to be compared to historical controls as well as age specific (age matched) Surveillance Epidemiology and End Results (SEER) data. Although a control group was not part of the original IRB approved protocol, it was predetermined (per protocol) that patients receiving only one pellet implant, i.e., three months of therapy, would not be eligible for analysis. Such short-term hormone use would not have a significant impact on the long-term incidence of breast cancer. This group of 119 patients accrued 2008-2009 was followed prospectively through 2013 as an age matched 'pseudo-control' group.

In 2013, the institution (Atrium Hospital, Middletown, Ohio) was sold and disbanded their IRB due to restructuring. All accrued patients continued to be followed. A

second IRB protocol was approved in April 2018 allowing review and publication of collected data (ClinicalTrials.gov NCT03768128).

Therapy: subcutaneous testosterone (T) and testosterone combined with anastrozole implants (T + A)

Subcutaneous implants are composed of non-micronized USP testosterone (T) and stearic acid in a geometric ratio of 20:1, or non-micronized USP T, stearic acid and USP anastrozole in a geometric ratio of 15:1:1. Implants are placed in sealed glass vials and autoclaved for sterility and 'heat fusion'. The sterile implants are inserted into the subcutaneous tissue of the upper gluteal area or lower abdomen through a 5 mm incision using local anesthesia and a disposable trocar kit.

We have previously shown that subcutaneous T therapy alone is able to treat menopausal symptoms in the majority of patients [4]. This is not surprising if one understands basic physiology. T is the major substrate for estradiol in both men and postmenopausal women. The continuous release of T from the implant provides continuous bioavailable T at the cellular level where T has a direct effect via the androgen receptor. In addition, peripheral aromatization of T in fatty tissue and, more importantly, local aromatization at the cellular level, provide adequate and continuous amounts of estradiol at the estrogen receptor. Testosterone implant dosing is weight based with an average starting dose in our study patients of 2–2.5 mg/kg. Patients were evaluated at each visit and T dose was adjusted based on clinical response and side effects. The average interval for T pellet insertion in our study population was 13.8 $\pm$ 3.8 weeks. Serum total T levels were measured using liquid chromatography tandem mass spectrometry (LC/MS-MS) or by electrochemiluminescence immunoassay (ECLIA) standardized via isotope dilution-gas chromatography mass spectrometry. The methodology used depended on the laboratory, which was determined by insurance coverage. Mean serum T level measured 4-weeks post implantation was 299 $\pm$ 107 ng/dl (range 101–633, CV 35.9%). Mean serum T level when symptoms returned (trough) was 171 $\pm$ 73 ng/dl (range 22–461, CV 42.6%), well above endogenous ranges [4, 5]. Doses of T have increased over the past 10 years. More recent data on serum T levels measured one week following implantation demonstrated a mean serum T of 490 $\pm$ 210 ng/dl (CV 42.8%) on an average dose of 198.7 $\pm$ 55.8 mg of T (n = 398). Despite pharmacologic (therapeutic) serum levels, there have been no adverse events attributed to T therapy other than expected androgenic side effects, which are dose dependent and reversible [4, 5]. As previously reported, 85% of patients reported a mild to moderate increase in facial hair, 6% reported a severe increase in facial hair, 11% reported an increase in acne, 50% reported improvement in skin moisture, tone/texture, and fewer wrinkles, and 1% reported perceived voice changes (voice cracking, raspy voice, or deeper voice) [5].

The clinic began using anastrozole, an aromatase inhibitor, combined in the pellet implant in 2008, initially to treat symptoms of hormone deficiency in estrogen receptor positive breast cancer survivors. The amount of anastrozole in each pellet implant is 4 mg combined with 60 mg of T, providing continuous and simultaneous release of both the T and anastrozole. A dose of 4 to 8 mg of anastrozole (1 or 2 T + A implants) has been shown to prevent elevation of estradiol in breast cancer survivors treated with subcutaneous T [20, 25]. Subsequently, beginning in 2010, women who presented with signs or symptoms of excess estrogen (e.g., breast pain, fluid retention, weight gain, anxiety, irritability), obesity, or increased risk for breast cancer, were treated with anastrozole in combination with T. It was 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 benefited from the 'low dose' anastrozole (compared to 1 mg/day oral) delivered subcutaneously with T. T and T + A dosing is based on clinical history and symptoms, response to therapy, weight (BMI), amount of fatty tissue, and laboratory evaluation of hormone levels. There have been no adverse drug events related to subcutaneous anastrozole therapy. The amount of anastrozole released over 100 days is approximately 0.04–0.08 mg per day.

Data analytics, patient follow up

As previously reported in our 5-year interim analysis [12]:

'A custom web-based application using Microsoft Active Server Pages with a MySQL database backend system was developed to prospectively follow and track patients. Date and dose of the first T implant insertion and each subsequent insertion along with patient identifiers were entered. The computer program continuously tracks the number of person-days for patient and calculates a running sum (cumulative total) across the group. The system was programmed to identify women who had not returned for therapy within a pre-set time frame of 240 days, 2.5 times the average interval of insertion/duration of clinical efficacy of 96 days. Weekly 'follow-up' phone calls were made by designated research personnel. Any participant not seen for 240 days was contacted and breast cancer status was documented. All patients no longer receiving therapy, agreed to contact the office in the future for any subsequent diagnosis of breast cancer.'

Approaching study years 5, 7, 9, and 10, additional phone calls were made to patients no longer on T therapy to document breast cancer status.

All abnormal mammograms were followed until biopsy results were available or subsequent imaging demonstrated a Breast Imaging Reporting and Data System assessment of category 1 (negative) or category 2 (benign, non-cancerous). Any self-reported palpable masses were evaluated by clinical breast exam and office ultrasound (RG) followed by radiographic evaluation and biopsy if indicated. All breast cancers were verified by obtaining pathology reports from core biopsies and definitive surgical procedures.

Statistical methods

The incidence rates of invasive breast cancer for the Dayton study are reported as an unadjusted, unweighted value of newly diagnosed cases divided by the sum of person-time of observation of the 'at risk' population. Person-days of observation were calculated from the date of first T pellet insertion for each participant up to the date of cancer registration, the date of death, 240 days after the last pellet insert, or the set date of 31 March 2018, whichever came first. A cumulative total of 'person-days' was calculated for the predetermined 240-day horizon. Person-years (p-y) were calculated by dividing person-days by 365.25. The incidence of breast cancer was calculated per 100,000 p-y so that our results could be compared to age matched SEER breast cancer incidence rates and historical studies.

Unlike pills and topical therapy, subcutaneous implants are long acting (sustained release) and the incidence of breast cancer was reported for predetermined time frame of 240-days post implantation or 2.5 times the average length of clinical efficacy of 96 days [3].

The observed breast cancer incidence rates for the Dayton study patients were compared to the expected (adjusted) SEER breast cancer incidence rates calculated from the age composition of Dayton study patients and the published SEER age-grouped breast cancer incidence rates for two time periods, 2007–2011 and 2011–2015 [Additional file1, Table 1s]. This approach allowed for the possibilities of changing cancer rates over the course of the study and the change in the age composition of our study patients. The 'expected incidence' is a weighted sum of the SEER incidence rates with the weights corresponding to the proportion of the Dayton study patients' person-years (p-y) in each of the SEER age groups.

Classical estimates of the incidence rates and the expected incidence rates, based on the assumption that breast cancer numbers followed a Poisson distribution, were derived. In order to verify the assumptions, bootstrapped estimates of these quantities were calculated. Both bootstrapping and the classical methods were used to assess the significance of these results [26]. For the bootstrapped experiments, 10,000 pseudo-replicates were drawn, and breast cancer incidence rate calculations were repeated. From this ensemble of "replicates" the distributions of incidence were estimated along with expected SEER incidence rates. These were compared to the classical estimates. In addition, asymptotic estimates of the differences between our rates and the expected SEER rates, and the ratios of the SEER rates to our estimated rates were derived. Estimated confidence intervals for Dayton and expected SEER rates and numbers of cancers, and significance tests of difference were performed. All calculations were performed in R [27]; the bootstrapped confidence intervals and tests of statistical significance followed from the R package boot version 1.3–9 [Additional file 1] [27].

Table 1 Patient demographics at first T pellet insertion [12]

	N = 1267
Postmenopausal	76.8%
Surgical %	66.2
Natural %	43.8
Pre/perimenopausal	23.2%
Age, mean (SD)	52.1 ± 8.6 y
Family history BCA (1st, 2nd)	29%
Age menarche, mean (SD)	12.8 ± 1.6 y
Age first birth, mean (SD)	24.8 ± 5.2 y
Nulliparous	14.9%
Weight kg, mean (SD)	71.03 ± 15.5 kg
BMI, mean (SD)	26.3 ± 5.5 kg/m^2

Results

Patient demographics, accrual

As of March 2013, 1267 patients had been accrued to the study and were eligible for analysis having received more than one pellet implant. Patient demographics at initial T insertion are listed in Table 1. Characteristics of the study population were similar to women of a comparable age in the United States. Patients were not at an increased or decreased risk for breast cancer based on family history, hormonal, or reproductive factors.

The majority of patients (62%) were accrued to the study within the first year. Over 85% of patients were accrued by study year 2, 90% by year 3, and 96% by year 4 [12]. The mean length of T therapy through March 2018 was 5.3 ± 3.5 y (range 0.7–12.2 y), which included women who received their first T implant prior to study accrual.

407 out of 1267 patients continued to receive therapy March 2017 through March 2018. Current patient demographics are listed in Table 2. The oldest patient was 91.7 years old. The youngest patient was 37.2 years

Table 2 Patient demographics, current users of T therapy

	N = 407
Menopausal status, N (percent)	
Premenopausal	43 (10.6%)
Postmenopausal	364 (89.4%)
Age, mean (SD), (range)	
1st insert	51.7 ± 8.1 y (27.4–80.0)
Current	61.1 ± 8.4 y (37.9–91.7)
Weight, mean (SD)	
1st insert	69.6 ± 15.1 kg
Current	69.8 ± 13.6 kg
Length of T therapy, mean (SD)	9.34 ± 1.71 y
Current T dose, mean (SD)	192 ± 50 mg
Aromatase inhibitor use, N (percent)	
Total	86 (21.1%)
Premenopausal	27 (62.8%)
Postmenopausal	59 (16.2%)

old and has been treated continuously since October 2007 for intractable migraine headaches.

The percent of female patients treated with the combination T + A implant increased from approximately 11% in 2010, to 30% January through July 2011, and to a maximum of 62% December 2012 through March 2013. As women have aged and transitioned into menopause, thus producing less estrogen, fewer women require the addition of the aromatase inhibitor. Currently 21.1% of study patients are treated with anastrozole combined in the implant: 16.2% of postmenopausal patients and 62.8% of premenopausal patients.

Breast cancer incidence

As of March 2018, there have been 11 cases of IBC diagnosed in women within 240 days following their most recent T implant insertion in 6667 p-y of therapy, which translates to an incidence of 165/100000 p-y. The incidence of IBC in women treated with T therapy was significantly less than our previously reported 'control' group incidence of 390/100000 p-y, $P < 0.001$ [12]. No patient was diagnosed with breast cancer within the first 240 days following (their) initial T pellet insertion.

Comparison to SEER data and historical controls

Significantly fewer cases of IBC were diagnosed in our study group compared to the age-matched SEER expected number of IBC cases. At the 240-day designated time period, 11 cases of IBC were diagnosed in our patient population compared to 18 cases expected based on age-matched SEER data [28].

The age-matched SEER incidence rate for IBC was 271/100000 p-y. The calculations are presented in detail in Additional file 1. Asymptotic estimates of Dayton and expected SEER incidence rates (N/100000 P-Y) are shown in Table 3. There was a 39% reduction in the incidence of breast cancer in patients on T therapy compared to the expected age-matched SEER incidence rate ($p < 0.001$). Estimated confidence intervals for Dayton and expected SEER rates and numbers of cancers, and significance tests of difference for whole sample results are presented in Additional file 1, Tables 4 and 5.

In addition, our 10-year incidence rates are lower compared to previous studies using conventional hormonal (estrogen/progestin) regimens including the Adelaide Study, which previously reported a reduced incidence of breast cancer with subcutaneous T used in combination with conventional hormone therapy, Table 4 [17, 29–31].

Abbrev: *T* testosterone, *E* estrogen, *P* progestin, *WHI RCT* Women's Health Initiative Randomized Control Trial, *MWS* Million Woman Study.

Bootstrap results

Bootstrap results confirm a marked reduction in the incidence/distribution of invasive breast cancer at 10-years in T and T + A users (Fig. 1). Estimated confidence intervals for Dayton and expected SEER incidence rates and numbers of cancers, and significance tests of difference for bootstrap results are presented in Additional file 1, Tables 4 and 5.

Breast cancer characteristics

Patient data and tumor characteristics of the 11 women diagnosed with invasive breast cancer are presented in Table 4. Mean age at first insert was 50.97 ± 7.44 y. The mean age at diagnosis was 55.22 ± 7.42 y. The mean length of therapy prior to diagnosis was 4.25 y (range 2.60–6.96 y). Eight of 11 cancers were diagnosed on screening mammography. The three patients that were diagnosed with palpable tumors did have screening mammograms within 1–2 years of diagnosis. Nine of 11 tumors were estrogen receptor (ER) positive. Seven of 11 were stage 1. Of interest, patient 11 was diagnosed with an ER positive tumor while on T / T + A therapy. She received implants containing T (180 mg) plus Letrozole (12 mg) before starting neoadjuvant therapy and there was a 43% reduction in tumor volume within 41 days after implantation *prior* to receiving systemic chemotherapy. The patient continued T + Letrozole throughout chemotherapy and had a complete pathologic response. T also attenuated many side effects of chemotherapy [9]. Three other patients diagnosed with invasive breast cancer have also continued on T implant therapy. As of March 2018, all patients are alive and well with no evidence of disease.

Table 3 Asymptotic estimate of Dayton and expected age-matched SEER incidence rate (per 100,000 p-y), standard deviations (SD), the ratio of the Dayton incidence rate to the SEER and it's SD. See Additional file 1 for the details of the method of calculation

Horizon	Events	P-Y	Dayton incidence	Dayton SD	Seer incidence	Seer SD	Ratio	Ratio SD
240 d	11	6666.6	165.0	49.8	270.5	1.83	0.61	0.18

Ductal carcinoma in situ

From March 2008 through March 2018 three patients enrolled in the study were diagnosed with ductal carcinoma in situ (DCIS) within 240 days of their last pellet insertion. Mean age at the first T pellet insert was 57.74 ± 3.73 years. Mean age at diagnosis of DCIS was 64.44 ± 4.07 years. The incidence of DCIS in our study populations was 45/100000 p-y compared to the SEER expected incidence rate for DCIS of 84/100000 p-y for women age 60–64 [28].

Discussion

Our 10-year analysis of the Dayton study demonstrated a 39% lower incidence of (invasive) breast cancer in T users compared to the 'age-matched' SEER expected incidence. This was not surprising. Although a detailed discussion of the favorable effect of T in the breast is beyond the scope of this paper, it is known that T's direct effect at the androgen receptor (AR) is antiproliferative, proapoptotic, and inhibits ER α and breast cancer growth [1, 3]. Clinical studies in primates and humans support the inhibitory effect of T in the breast [1–3]. We have demonstrated remarkable responses (clinical exam, mammography, ultrasound) of hormone receptor positive tumors to T + aromatase inhibitor implant therapy in the neoadjuvant setting, further confirming the direct beneficial effect of T at the AR [8, 9]. T also improves glycemic control and attenuates the inflammatory process, both of which could have a beneficial effect on the incidence of breast cancer [14, 15, 32, 33].

Table 4 Incidence rates of IBC, comparison to published studies

	Cases per 100,000 p-y	Years Observed
Dayton Study		
T, T + AI	165	10
WHI RCT [29,30]		
Placebo	330	10.7
E alone	260	10.7
E + P	380	5.2
MWS [31]		
Never users	312	14
E alone, E + P	501	14
Adelaide [14]		
T + E, T + E + P	238	5.9
T + E + P	293	5.9

Short-term studies on transdermal T therapy have not shown an increase in the incidence of breast cancer nor did they demonstrate a reduced incidence [3, 16]. Subcutaneous implants provide continuous delivery of therapeutic levels of T and results from T implants may not be applicable to other methods of delivery or lower doses of therapy [4, 5, 24]. Also, patients differ in their ability to aromatize T to estradiol [14, 15]. Caution should be used in treating patients with clinical evidence of increased aromatase activity and consideration should be given to the addition of aromatase inhibitor therapy when indicated.

This prospective study was specifically designed to investigate the incidence of breast cancer in a relatively large sample size. Demographic characteristics of our sample are those of a normal population and are not women at low or high risk for breast cancer. All study patients were followed by a breast surgeon (RG), and the vast majority of women over 40 years of age underwent screening mammography, which could have increased the incidence of detected IBC's. Our study is unique in that most (over 95%) of women were treated with T implants alone without systemic estrogen or progestogens. However, some women did receive estrogen therapy prior to T alone, which could have affected the incidence of IBC. A major strength of our study is that patients were evaluated at each office visit when they received the implants, and there are no missing data on incidence of breast cancer in these patients. Exact doses and intervals of insertion were documented in patient charts allowing for known levels of exposure to the drug therapies, as well as any medical changes, diagnoses, or adverse events. There was no potential for unknown noncompliance to therapy in contrast to other studies using oral or topical formulations where 'use of hormone therapy' is often self-reported from memory or from data on 'filled' prescriptions.

There is some controversy regarding serum levels of T on subcutaneous implant therapy. We have previously published data on 'efficacy and safety', 'intersubject variability in serum levels', as well as detailed rationale supporting the doses of T used (for over ten years) in our patient population [4, 5]. Although (peak) serum T levels, measured one-week post implantation, were in the lower range for endogenous production in men, this has proven inconsequential. Pharmacologic levels in serum do not equate to supra-physiologic levels at the end organ androgen receptor (AR). On the contrary, we have shown that

Table 5 Patient data and tumor characteristics, twelve patients treated with T or T + A implants diagnosed with invasive breast cancer March 2008–March 2018 within 240 days of receiving therapy

Patient	Age at 1st TT Y	Age at IBC dx. Y	BMI 1st TT	Meno Status 1st TT	Prior E use	Detection	N days Last insert prior to dx	IBC (Stage) Type	Receptor status	Continued TT post dx
1	46.2	49.3	19.2	TAH FSH 4.6	Y	Mammo	206 d	T1b, N0 (1) Gd 2 IDC	ER+, PR+ Her 2 -	
2	55.0	59.2	33.3	Post	Y	Palpable	123 d	T3, N2 (3) Gd 3 IDC	ER-, PR- Her 2 -	
3	50.0	52.9	19.2	Pre	OCP Current	Mammo	34 d	T1c, N0 (1) Gd 1 IDC	ER+, PR+ Her 2 -	T + AI x 5y T alone
4	67.6	70.2	24.7	TAH BSO	Y	Mammo	151 d	T1b, N0 (1) Gd 1 IDC	ER+, PR+ Her 2 –	
5	44.9	48.5	21.5	TAH	N	Mammo	48 d[a]	T1c, N0 (1) Gd 1, IDC	ER+, PR- Her 2 -	
6	48.9	55.5	24.4	TAH	Y	Mammo	146 d	T1b, N1a (2) Gd 2 ILC	ER+, PR- Her 2 -	
7	56.2	60.6	28.8	TAH BSO	Y	Mammo	51 d	T1 N0 (1) Gd 2 IDC	ER+, PR+ Her 2 -	
8	50.0	55.2	28.7	Post	N	Mammo	54 d	T1a N0 (1) 1.2 mm IDC	ER-, PR+ Her 2 -	T alone
9	58.0	61.5	39.3	TAH BSO	N	Palpable	50 d	T2 N1 (2) Gd 3 IDC	ER+ PR+ Her 2 -	T + AI Note: tested BRCA 2 pos.
10	39.7	43.4	23.2	Pre	N	Palpable	15 d	T1c N0 (1) Gd 2 IDC	ER+ PR+ Her 2-	
11	44.0	51.0	23.5	Pre	N	Mammo	92 d	Clinical T2 N0 (2A) Gd 3 IDC	ER+ PR+ Her 2 +	T + AI

[a]Patient was diagnosed 48 d after a single pellet insertion following a 23-month lapse in therapy

Abbr: TT testosterone therapy, IBC (invasive breast cancer), Dx. (diagnosis), BMI (Body mass index), E2 (estradiol), OCP (Oral Contraceptive Pill), IDC (Infiltrating ductal carcinoma), ILC (infiltrating lobular carcinoma), T (tumor size), a (< 0.5 cm), b (> 0.5, < 1 cm), c (> 1, < 2 cm), T2 (20mm–50mm), T3 (> 50 mm), N (node status); N0 (no nodes positive), N1a (Single node < 5 mm), N2 (4–9 nodes positive), Gd (tumor grade: 1 low grade, 2 intermediate grade, 3 high grade), ER (estrogen receptor), PR (progesterone receptor), HER2 (human epidermal growth factor 2), T (testosterone implant), T + AI (testosterone combined with an aromatase inhibitor implant), Mammo (mammography)

pharmacologic T levels in serum equate to physiologic (therapeutic) levels at the AR as evidenced by clinical efficacy and the lack of adverse events, other than androgenic cosmetic side effects, which are reversible with lowering the dose [4, 5]. Specifically, our previous published prospective study showed no voice changes on these doses and levels on therapy [34]. In addition, we have shown scalp hair regrowth on T therapy [35]. The clinical necessity of higher (therapeutic effective) serum levels of T can be explained by the significant age-related decline of the adrenal pro-androgens in addition to T, contributing to a marked reduction of bioavailable T at the cellular level. The amount of T released from the implant (and subsequently measured in serum), is replacing T as well as the significant local contribution of DHEA and androstenedione to bioavailable T at the AR [5]. T's effect is dose dependent, and there is no evidence (i.e., drug-concentration in blood studies), or documented safety concerns, supporting the 'opinion' that serum T levels on therapy should remain within endogenous, or 'physiologic' ranges. In point of fact, concentration-response studies on subcutaneous T implants demonstrate the opposite [4, 5, 36]. Most notably, in our patient population, mean serum T level when symptoms returned (trough) was 171 $\pm$ 73 ng/dl, well above endogenous ranges, with significant inter-individual variation (CV 42.6%). In regard to safety, long-term studies on transgender men have shown that even higher (male) doses of T do not increase the risk of cardiovascular events, stroke, or cancer; T therapy also increases insulin sensitivity, as opposed to estrogen therapy in transgender women [32, 37, 38]. No other hormone medication (e.g., insulin, estrogen) is dosed or micromanaged based solely on levels of the active pharmacologic ingredient in serum, but rather on clinical response/beneficial effects versus adverse side effects. Studies showing 'lack of efficacy' may be due to inadequate amounts of T at the AR. Likewise, the breast protective effect demonstrated in our study may not be seen with lower doses of T.

A critique of our study was the use of ECLIA (assay) for measuring T levels in some women. ECLIA is a direct immunoassay without any preceding purification steps, which could result in potential interference from T metabolites.

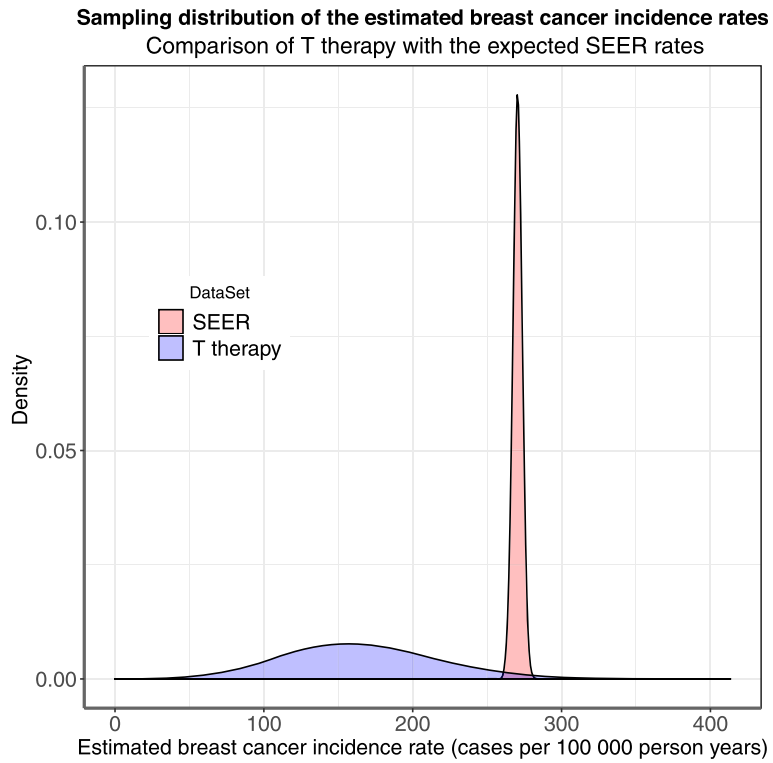

Fig. 1 Bootstrap results confirm a significant reduction in IBC on T therapy

A limitation of the Dayton study was a lack of a matched control group from the onset. However, this study was never designed as a randomized drug trial. Our results represent 'real world' data from a clinical practice where women suffering from symptoms of androgen deficiency received therapy. Another critique of our practice was the use of low dose, subcutaneous anastrozole in some pre/perimenopausal and postmenopausal patients. Our interventions were based on the previously successful use of aromatase inhibitors to treat breast and gynecologic diseases where pathological tissues overexpress aromatase and increase local production of estrogens [13–15]. We have found that low dose anastrozole (0.04–0.08 mg released per day) combined with T delivered subcutaneously effectively treats these conditions without adverse effects or alteration of menstrual cycles [4, 5, 20]. Individual patients were evaluated at each office visit and many women have been treated (alternately) with T or T + A depending on clinical status and symptoms, making it impossible to evaluate the two regimens separately, which remains a major limitation in the interpretation of our results. The potential individual or separate effect of anastrozole on the incidence of IBC remains unknown. However, our earlier results support a protective effect of T, as much of the data was accrued prior to the routine use of anastrozole [12].

Our 10-year results are consistent with preclinical and clinical evidence indicating that androgens have a protective role in the breast and refute the causal interpretation of epidemiologic studies reporting an association of endogenous T levels with IBC. Although subcutaneous T implants have been used (safely) to treat symptoms and diseases, including breast cancer, in women since 1937, there is no FDA approved biosimilar T formulation available for women in the United States. This 'real world' long-term data on subcutaneous implants further supports the safety of T therapy in women.

Conclusion

Our 10-year results demonstrated a 39% reduction in the incidence of IBC in our population compared to the age-matched SEER expected incidence. Long-term subcutaneous T and/or T + A therapy, used to treat symptoms of androgen deficiency in pre and postmenopausal women, did not increase the incidence of invasive breast cancer. Although not novel, testosterone implants should be further investigated for hormone therapy as well as breast cancer prevention. Additional studies, including long-term controlled trials in women treated with testosterone implants alone, and testosterone with anastrozole in a uniform administration, would be optimal to further delineate the effect of T (alone), or T combined with an aromatase inhibitor (when indicated), on the incidence of IBC.

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s12885-019-6457-8.

Additional file 1. Statistical Methods and Results

Abbreviations

DCIS: Ductal carcinoma in situ; ER: Estrogen receptor; IBC: Infiltrating Breast Cancer; p-y: Person-years; SEER: Surveillance Epidemiology and End Results; T + A: Testosterone and anastrozole; T: Testosterone

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Author contributions

CD and RG designed the study. RG collected data. All authors participated in analysis of the data. AY performed the statistical analysis. All authors contributed to writing the manuscript and approved the final manuscript.

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Availability of data and materials

All statistical data and analysis are included in Additional file 1: Statistical Methods and Results. Confidential access to primary data including de-identified spreadsheets will be granted upon reasonable request.

Ethics approval and consent to participate

Informed written consent was obtained from all participants. The prospective study (Testosterone Implants and incidence of breast cancer-TIBcaP 0108) was approved March of 2008 by the Atrium Medical Center's Institutional Review Board, One Medical Center Dr., Middletown, Ohio. In 2018 the Casey Research Foundation IRB board approved a retrospective chart review 'Testosterone implants and the Incidence of Breast Cancer (TIBCaP)', registered with clinicaltrials.gov (NCT03768128).

Consent for publication

not applicable.

Competing interests

CD none declared. AY none declared. RG has a patent issued: Pharmaceutical compositions containing testosterone and an aromatase inhibitor. No financial or other COI declared.

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