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Brief report

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Incidence of Invasive Breast Cancer in Women Treated with Testosterone Implants: Dayton Prospective Cohort Study, 15-Year Update

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Abstract

Background: Previously published 10-year results (March 2008-2018) from the Dayton prospective breast cancer prevention study showed a 40% reduction in the incidence of invasive breast cancer in women receiving testosterone or testosterone/anastrozole combination implant therapy compared to age-matched Surveillance Epidemiology and End Results (SEER) expected incidence rate. Study subjects on therapy were followed through March 2023.

Methods: 1267 eligible pre and postmenopausal women, accrued between March 2008 - March 2013, treated with subcutaneous testosterone pellets, were prospectively followed for the incidence of invasive breast cancer. All patients were treated at a single practice location. The breast cancer incidence rate was determined by the number of newly diagnosed cases divided by the sum of person-time of therapy (observation) in years. The incidence rates on testosterone therapy were compared with age-specific SEER incidence rates and local (Montgomery County, Ohio) incidence rates.

Results: As of March 1, 2023, a total of 16 eligible patients were diagnosed with invasive breast cancer within 240 days of their last testosterone pellet insert. This equates to an incidence rate of 189/100000 p-y, which is significantly less than the national SEER expected incidence rate of 355/100000. Interestingly, local incidence rates in Montgomery County are higher than US national averages.

Conclusion: The 15-year follow-up data revealed a 47% reduced incidence of invasive breast cancer with long-term testosterone or testosterone/anastrozole implant therapy. Due to the increased incidence of invasive breast cancer in our area, the reduction (benefit) from testosterone therapy may be underestimated using national data/statistics for comparison.

Keywords: Androgens, Testosterone, Breast Cancer Incidence, Prevention, Dayton, Ohio

Introduction

Extensive preclinical [1,2] and clinical [2] evidence supports the beneficial effect of testosterone in breast tissue and breast cancers. Data on the protective role of hormone balance in breast cancer prevention continues to evolve [3,4].

Since 1937, subcutaneous testosterone (T) implants have been used to treat a wide range of hormonal imbalances, including breast cancer. We previously reported the results of our prospective, institutional review board-approved, 10-year cohort study on the reduced incidence of invasive breast cancer in women treated with T or testosterone combined with anastrozole (T+A) implant therapy. Details of the 'Dayton study,' including the STROBE checklist, study design, approval, methods, results, and statistical analysis have been previously published and can be found here [3,4]. Although the study was designed as a 10-year prospective study, patients were followed through year 15, which ended March 1, 2023. All patients were seen at a single practice location and treated by a breast cancer surgeon (RG) with access to all records and data throughout the entire 15-year period.

We again compared our results to national age-specific Surveillance Epidemiology and End Results (SEER) age-matched incidence rates [5]. In addition, we discuss local (Montgomery County) overall and age-adjusted breast cancer incidence rates [6-8] and how they compare to Ohio and national incidence rates.

Materials and Methods

As previously reported, pre- and postmenopausal women who received at least two T pellet implants between March 2008 and March 2013 were included in the analysis (N=1267) [3,4]. Patients were monitored at each visit and followed prospectively for the incidence of invasive breast cancer. The baseline patient demographics were previously published (Table 1) [3].

	N=1267
Postmenopausal	76.8%
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

Table 1: Patient demographics at first T pellet insertion [3].

*I*ndications for the inclusion of aromatase inhibitor (anastrozole) therapy have been previously reported, **Supplement 1** *[4]*.

As previously reported in our 5-year interim analysis and 10-year results [3,4]:

'A custom web-based application using Microsoft Active Server Pages with a MySQL database backend system was developed to prospectively follow and track patients. The 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 patients 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

Statistical methods have been previously described [4]. The incidence rates are reported as the number of newly diagnosed breast cancer cases divided by the cumulative sum of person-years of therapy. The incidence of breast cancer was calculated per 100000 p-y so that our results could be compared with age-adjusted SEER and Montgomery County incidence rates. Details can be found in **Supplement 2**.

Results

As of March 1, 2018, 425 patients remained active and continued to receive T or T + A therapy. The mean age was 60.7 + 8.3 years. As of 1 March 2023, there were 299 patients on therapy with a mean age of 65.4 ± 7.8 years.

As of March 2023, a total of 15 patients who were adherent to therapy had been diagnosed with invasive breast cancer since

March 2008 out of 1267 patients. One patient discontinued therapy for 259 days, received a single pellet implant, and was diagnosed with breast cancer within less than 6 weeks, i.e., nonadherence to therapy[a]. Interestingly, she had received testosterone implants consistently prior to this (14 years), and it was only after an extended absence that her stage 1, low-grade, estrogen receptor (ER) positive cancer was diagnosed. This patient was included in the analysis, patient 16.

One patient was diagnosed with breast cancer within the first 240 days following her initial T pellet insertion and, per protocol, was excluded from analysis. Another patient who was off therapy for more than 240 days (352 days) prior to diagnosis was excluded from the analysis per protocol. Both patients also had stage 1, ER-positive breast cancer.

The total person-time for eligible patients was 8464 years, which translates to a breast cancer incidence (BCI) of 189/100000 p-y (N=16). The age-adjusted SEER expected BCI rate was 355/100000 p-y, and the number of expected cases was 30.

These results represent a BCI reduction of 47% compared to the national SEER data. If all 18 diagnosed patients were included, the BCI rate would be 213/100000 p-y, which is still a 40% reduction in the incidence of invasive breast cancer. The results are summarized in Table 2. The difference in the confidence intervals between the Dayton BCI and the expected age-adjusted SEER BCI was statistically significant.

	BCI	P value
Dayton (15 adherent [a] patients)	177.2 (99.2, 292.2)	P = 0.004
Dayton (16 eligible patients)	189.0 (108.0, 307.0)	P = 0.008
Dayton (18 total patients)	212.6 (126.0, 336.1)	P = 0.028
SEER expected (30 patients)	355.1 (239.1, 505.9)	

Table 2: *Observed Dayton and expected SEER invasive breast cancer incidence (BCI) (95% confidence interval) (P values of Dayton BCI compared to expected SEER BCI)*

Patient data and tumor characteristics

The breast cancer patient data and tumor characteristics are described in Table 3**.** *The mean age at first pellet insertion was 53.4 + 6.9 (39.7-67.6) years. The mean age at diagnosis was 61.2 + 8.4 (43.4–70.9) years. The mean baseline BMI of the patients diagnosed with invasive breast cancer was 29.0 ± 6.0 (19.2–39.3), which was greater than the mean cohort baseline BMI of 26.3 ± 5.5 (16.5–53.2) (P = 0.057).*

*A total of 14/16 (87.5%) of the tumors were ER positive, and 13/16 (81%) were progesterone receptor (PR) positive. Interestingly, only 1/16 (6.25%) tumors were human epidermal growth factor 2 (HER2)-positive, which is lower than the expected rate of 22% [*9]. Ten of 16 patients were stage 1 at the time of diagnosis. Eight of 11 patients diagnosed in the last ten years have continued T or T + A implant therapy following diagnosis.

Table 3.

Patient data and tumor characteristics

*Patient data and tumor characteristics of eligible patients per protocol. Fifteen patients treated with T or T + A implants diagnosed with invasive breast cancer (IBC) from March 2008 to March 2023 within 240 days of receiving therapy were adherent to therapy. Non-adherent patients had more than 240 days between implants, i.e., Patient 16**

Patient	Age at 1st TT (years)	Age at IBC diagnosis (years)	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 diagnosis
1	46.2	49.3	19.2	TAH FSH 4.6	Y	Mammo	206	T1b, N0 (1) Gd 2 IDC	ER+, PR+ Her 2 -	
2	55	59.2	33.3	Post	Y	Palpable	123	T3, N2 (3) Gd 3 IDC	ER-, PR- Her 2 -	
3	67.6	70.2	24.7	TAH BSO	Y	Mammo	151	T1b, N0 (1) Gd 1 IDC	ER+, PR+ Her 2 –	
4	48.9	55.5	24.4	TAH	Y	Mammo	146	T1b, N1a (2) Gd 2 ILC	ER+, PR- Her 2 -	
5	56.2	60.6	28.8	TAH BSO	Y	Mammo	51	T1 N0 (1) Gd 2 IDC	ER+, PR+ Her 2 -	
6	50	55.2	28.7	Post	N	Mammo	54	T1a N0 (1) 1.2 mm IDC	ER-, PR+ Her 2 -	T T+AI
7	58	61.5	39.3	TAH BSO	N	Palpable	50	T2 N1a (2) Gd 3 IDC	ER+ PR+ Her 2 -	T + AI BRCA 2 pos.
8	39.7	43.4	23.2	Pre	N	Palpable	15	T1c N0 (1) Gd 2 IDC	ER+ PR+ Her 2-	
9	44	51	23.5	Pre	N	Mammo	92	Clinical T2 N0 (2A) Gd 3 IDC	ER+ PR+ Her 2 +	T + AI
10	59	70.9	32.9	Post	Y	Mammo MRI	24	T1b N0 (1) Gd 1 IDC	ER+ PR+ Her 2 -	T + AI
11	58.8	68.7	37.8	TAH BSO	Y	Mammo	90	T1 N0 (1) Gd 2 IDC H/O DCIS	ER+ PR+ Her 2 -	T + AI
12	47.4	60.6	36.5	TAH BSO	Y	Palpable	30	T2 NX Gd 1,2 ILC	ER+ PR+ Her 2 -	
13	57.3	69.2	27.8	TAH BSO	N	Mammo	74	T1a, NX (1) Gd 1 tubular IDC	ER+ PR+ Her 2 -	T alone T+AI
14	56.6	67.3	33.6	Post	N	CXR Palpable Untreated	160 d	Stage (4) Gd 2 IDC	ER+ PR- Her 2 -	T + AI (death sepsis)
15	55.5	67	23.2	Post	N	Mammo	72 d	T1 N0 (1) Gd 1 IDC	ER+ PR+ Her 2 -	T + AI
16	54	69.5	27.4	Post	N	Mammo	**Non-adherent** 259 d interval between implants – 51 d	T1 N0 (1) Gd1 ILC	ER+ PR+ Her 2 -	

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 (20 mm–50 mm), 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)*

Patients excluded per protocol include patients that had IBC diagnosed 'less than 240 days after first implant' or 'greater than 240 days following their last implant'.

Patient	Age at 1st TT	Age at IBC diagnosis	BMI 1st TT	Meno Status 1st TT	Prior E use	Detection	IBC (Stage) Type	Receptor status	Motive of exclusion	Continued TT post diagnosis
17	52.1	52.9	19.2	Pre OCP	OCP Current	Mammo	T1c, N0 (1) Gd 1 IDC	ER+, PR+ Her 2 -	IBC diagnosis within 240 days after 1st Implant	T +AI x 5y Current T
18	50	54.4	20.5	TAH	No	Mammo	T1a, N0 (1) Gd 2 IDC	ER+ PR- Her 2 +	> 240 days (352d) after last implant	T + AI

Discussion

Our 15-year results support the beneficial effect of T or T + A delivered by subcutaneous implants on the long-term incidence of invasive breast cancer. We demonstrated a 47% reduction in the incidence of invasive breast cancer compared to the national SEER expected incidence rates. Patients were neither at an increased risk nor decreased risk for breast cancer based on confounding variables including family history, body mass index (BMI), hormonal, and reproductive factors.

Testosterone implants actively inhibit the growth of invasive breast cancer tumors [2]. When nonadherent patients stop therapy for more than 8 months, tumors may develop or progress. Even with the inclusion of ineligible patients, there was still a significant reduction in BCI compared to the national data. In addition, most tumors from patients diagnosed while receiving T therapy exhibit favorable histologic and immunohistochemical characteristics, i.e., being ER positive, PR positive, and HER2 negative. Notably, HER2 positive tumors are more aggressive and are associated with a worse prognosis [9].

A limitation of the Dayton study was a lack of a control group from the onset. Our data represents 'real world' results from a clinical practice where women suffering from symptoms of hormone deficiency received T therapy. There was no standard or controlled dosing, which is expected in a clinical practice where individual patients are treated and dosing is adjusted based on symptom response and side effects.

Another limitation of the interpretation of the results was the inability to assess the individual contribution of T (alone) versus the aromatase inhibitor (T + A) on the reduced incidence of breast cancer. Most patients were treated with T implants alone for symptoms of hormone deficiency. A minority of patients were treated with anastrozole in combination with T for symptoms of excess estrogen. Both T and the aromatase inhibitor (AI) could have contributed to the reduced incidence of invasive breast cancer: T directly by its antiproliferative effect at the androgen receptor and anastrozole, indirectly, by preventing conversion to stimulatory estradiol, maintaining a protective balance of T to estradiol in breast tissue [1,2]. We were unable to draw any conclusions about the difference in invasive breast cancer between T alone and T + AI, as patients were selected for AI therapy based on symptoms, which changed throughout the study period with age, lifestyle, weight,

and menopausal status. Although oral anastrozole alone has been shown to reduce the incidence of invasive breast cancer in 'high-risk' women [10], it is difficult to compare patient populations. The indication for T therapy in our patient population was NOT breast cancer prevention but rather as therapy for hormone deficiency symptoms and to improve health and quality of life [11]. It has previously been shown that T implants reduce the risk of breast cancer from conventional estrogen/progestin therapy, further supporting our results [12]. In future studies, utilizing a larger population will allow for a more precise differentiation of the effects of T and AI on reducing the incidence of invasive breast cancer. Additionally, it would be valuable to investigate whether a synergistic interaction between the two drugs could further reduce this incidence.

Despite these limitations, the Dayton study represents the first to demonstrate the effect of T and/or T + AI in the prevention of invasive breast cancer in women over a 15-year period. As one of the few studies with such an extended follow-up, it contributes essential knowledge and lays the groundwork for future research aimed at enhancing invasive breast cancer prevention strategies. Our prospective study involving 1267 patients can provide meaningful insights, although this may be considered a medium sample size for a real-world study. It is crucial to assess whether the population is sufficiently diverse in terms of demographics, age, genetic background, and environmental factors to ensure broader applicability of the results.

Comparing our data to national data may underestimate the beneficial effect of testosterone therapy on breast cancer prevention. Montgomery County (Dayton, Ohio) had the highest overall BCI rates in Ohio in 2016-2020 *[6]. Montgomery County also exhibited a significantly greater BCI rate compared to the national US (SEER + NPCR) and Ohio 'Age-Adjusted Incidence Rates' for females aged 50+ and 65+ years (Table 4) [7,8].*

	Age-adjusted incidence rate-cases per 100,000 (95% Confidence Interval) Female, Ages 50+	Age-adjusted incidence rate-cases per 100,000 (95% Confidence Interval) Female, Ages 65+
US (SEER+NPCR) (1)	340.5 (339.9, 341.2)	424.1 (423.0, 425.1)
Ohio (6)	351.8 (348.4, 355.2)	444.4 (438.8, 450.1)
- Montgomery County (6)	394.8 (378.3, 411.8)	500.0 (473.5, 527.7)

Table 4: Invasive Breast Cancer (All Stages^), 2016-2020. All Races – by County [7,8].

Relative to the US (SEER + NPCR) BCI rates, Montgomery County had a 16% higher rate for ages 50+, RR 1.16, 95% (CI 1.11 to 1.20) and an 18% higher rate for ages 65+, RR 1.18, 95% CI (1.12 to 1.24) [7,8]. In addition, surrounding counties where patients are from also have higher overall and age-adjusted BCI rates than the Ohio and US National Rates [6,7,8]. The reason for the increased incidence of breast cancer in Dayton and surrounding counties should be investigated. One consideration is the known contamination of the Great Miami Buried Valley Aquifer, which is the principal (sole) source of drinking water for Montgomery and surrounding counties. See **Supplement 3** *for details.*

Conclusion

The Dayton 15-year follow-up data continue to support a reduced incidence of invasive breast cancer in patients treated with long-term T or T + A pellet implant therapy, corroborating our 5- and 10-year study results. Testosterone implant therapy was shown to be effective for breast cancer prevention even in geographic areas at increased risk, such as Dayton, Ohio.

Our prospective observational study results support preclinical [1] and clinical [2] experimental data demonstrating that testosterone is protective against invasive breast cancer. It is highly unlikely that T or T + A is causative when a patient receiving therapy is diagnosed with breast cancer. It is imperative that physicians understand the relationship between testosterone therapy and breast cancer risk. Further studies comparing T alone or in combination with an aromatase inhibitor, as well as other geographic areas, on the incidence of invasive breast cancer would be beneficial. We are currently investigating the impact of T and T + AI in breast cancer survivors (with or without active disease) on quality of life, recurrence, regression/progression of disease, and survival.

Footnote

[a] *Subcutaneous T implants are sustained release with an average length of clinical efficacy of 96 days in women. The incidence of breast cancer was reported for a predetermined time frame of 240 days post implantation – 2.5 times the average length of clinical efficacy. Patients diagnosed within 240 days of their last pellet*

implant were 'eligible for analysis'. Patients who were adherent to therapy were those who received testosterone pellet implants within the 240-day time frame. Nonadherence indicates >240 days of absence between implant therapies.

Abbreviations

SEER: Surveillance Epidemiology and End Results; BCI: breast cancer incidence; p-y: person-years; T: testosterone; T+A: testosterone combined with anastrozole; ER: estrogen receptor; PR: progesterone receptor; HER-2: human epidermal growth factor 2; AI: aromatase inhibitor

Ethical Guidelines

Ethics approval and consent to participate: Informed written consent was obtained from all participants. This prospective study (Testosterone Implants and Incidence of Breast Cancer-TIBcaP 0108) was approved in March of 2008 by the Atrium Medical Center's Institutional Review Board, One Medical Center Dr., Middletown, Ohio.

Conflict of interest

RG has a patent issued – Pharmaceutical compositions containing testosterone and an aromatase inhibitor. No other COI declared. CD, none declared. IG is employed by bio meds Pharmaceutica, which produces pellet implants. AG is employed by bio meds Pharmaceutica, which produces pellet implants. LPSP is a consultant and speaker for bio meds Pharmaceutica. DGG, none declared.

Author contributions

CD and RG designed the study. RG accrued the data. RG and DGG participated in the collection and analysis of the data. DGG and AP performed the statistical analysis. AP constructed the tables. RG wrote the main ms. CD, IG, DGG, and LPSP contributed to writing the manuscript, and approved the final manuscript and data analysis.

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