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A Randomized Phase IIb Study of Low-dose Tamoxifen in Chest-irradiated Cancer Survivors at risk for Breast Cancer

Smita Bhatia, MD, MPH[1], **Melanie R Palomares, MD, MS**[2], **Lindsey Hageman, MPH**[1], **Yanjun Chen, MS**[1], **Wendy Landier, PhD, CRNP**[1], **Kandice Smith, RN**[1], **Heidi Umphrey, MD**[3], **Caroline A Reich, MD, PhD**[1], **Kathryn W Zamora, MD, MPH**[1], **Saro H Armenian, DO, MPH**[4], **Therese B Bevers, MD**[5], **Anne Blaes, MD**[6], **Tara Henderson, MD, MPH**[7], **David Hodgson, MD, MPH**[8], **Melissa M Hudson, MD**[9], **Larissa A Korde, MD, MPH**[10], **Susan A Melin, MD**[11], **Sofia D Merajver, MD, PhD**[12], **Linda Overholser, MD**[13], **Sandhya Pruthi, MD**[14], **F Lennie Wong, PhD**[4], **Judy E Garber, MD, MPH**[15]

[1]University of Alabama at Birmingham, Birmingham, AL

[2]Cancer Prevention Movement, Arcadia, CA

[3]MidSouth Imaging, Germantown, TN

[4]City of Hope, Duarte, CA

[5]The University of Texas MD Anderson Cancer Center, Houston, TX

[6]University of Minnesota, Minneapolis, MN

[7]University of Chicago, Chicago, IL

[8]University of Toronto, Toronto, ON

[9]St. Jude Children's Research Hospital, Memphis, TN

[10]Seattle Cancer Care Alliance, Seattle WA

[11]Wake Forest School of Medicine, Winston-Salem, NC

[12]University of Michigan, Ann Arbor, MI

[13]University of Colorado, Denver, CO

Correspondence: S. Bhatia, MD, MPH, Institute for Cancer Outcomes and Survivorship, University of Alabama at Birmingham, 1600 7th Avenue S, Lowder 500, Birmingham, AL 35233; Telephone: (205) 638-2120; Fax: (205) 638-2121; sbhatia@peds.uab.edu.

Author Contributions:

Conception and design: Smita Bhatia, Melanie Palomares

Administrative support: Smita Bhatia, Melanie Palomares, Lindsey Hageman, Kandice Smith

Provision of study materials or patients: Smita Bhatia, Melanie Palomares, Saro H. Armenian, Therese B. Bevers, Anne Blaes, Tara Henderson, David Hodgson, Melissa M. Hudson, Larissa A. Korde, Susan A. Melin, Sofia D. Merajver, Linda Overholser, Sandhya Pruthi, Judy E. Garber

Collection and assembly of data: Lindsey Hageman, Kandice Smith

Data analysis and interpretation: Smita Bhatia, Yanjun Chen, F. Lennie Wong, Lindsey Hageman, Wendy Landier, Heidi Umphrey, Caroline A. Reich, Kathryn W. Zamora

Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

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[14]Mayo Clinic, Rochester, MN

[15]Dana Farber Cancer Institute, Boston, MA

Abstract

Purpose: Low-dose tamoxifen reduces breast cancer risk, but remains untested in chest-irradiated cancer survivors – a population with breast cancer risk comparable to *BRCA* mutation carriers. We hypothesized that low-dose tamoxifen would be safe and efficacious in reducing radiation-related breast cancer risk.

Experimental Design: We conducted an investigator-initiated, randomized, phase IIb, double-blinded, placebo-controlled trial (FDA IND107367) between 2010 and 2016 at 15 US sites. Eligibility included ≥12Gy of chest radiation by age 40y and age at enrollment ≥25y. Patients were randomized 1:1 to low-dose tamoxifen (5mg/day) or identical placebo tablets for 2y. The primary endpoint was mammographic dense area at baseline, 1y and 2y. Insulin growth factor-1 (IGF-1) plays a role in breast carcinogenesis; circulating IGF-1 and IGF-BP3 levels at baseline, 1y and 2y served as secondary endpoints.

Results: Seventy-two participants (low-dose tamoxifen: n=34, placebo: n=38) enrolled at a median age of 43.8y (35-49) were evaluable. They had received chest radiation at a median dose of 30.3 Gy. Compared with the placebo arm, the low-dose tamoxifen arm participants had significantly lower mammographic dense area (P=0.02) and IGF1 levels (P<0.0001), and higher IGFBP-3 levels (P=0.02). There was no difference in toxicity biomarkers (serum bone-specific alkaline phosphatase, lipids, and anti-thrombin III; urine N-telopeptide crosslinks) between the treatment arms. We did not identify any grade 3-4 adverse events related to low-dose tamoxifen.

Conclusions: In this randomized trial in chest-irradiated cancer survivors, we find that low-dose tamoxifen is effective in reducing established biomarkers of breast cancer risk and could serve as a risk-reduction strategy.

INTRODUCTION

Adolescent and young adult females treated with chest radiation for their primary cancer are at risk for breast cancer; the cumulative incidence of radiation-related breast cancer exceeds 35% by age 50.(1) This risk is as high as that observed in *BRCA* mutation carrier.(1) Mortality rates are higher after radiation-related breast cancer than after primary breast cancer.(2) These findings present an urgent yet unmet need to develop breast cancer risk-reduction strategies for radiation-exposed cancer survivors.

The risk of radiation-related breast cancer is lower in survivors who also received ovarian radiation.(3) These findings suggest a role for endogenous estrogens in radiation-related breast carcinogenesis, making tamoxifen a viable risk-reducing option for pre- and post-menopausal cancer survivors.(4) While effective in reducing the risk of primary breast cancer, the possibility of severe adverse events (AEs), such as venous thromboembolism and endometrial cancer, have contributed to the low uptake of tamoxifen at 20mg/d.(4) Low-dose tamoxifen (5mg/d) appears to retain the efficacy in reducing breast cancer risk, but with a

safer AE profile.(5) These findings make low-dose tamoxifen an attractive breast cancer risk-reducing strategy for chest-irradiated cancer survivors.

Radiation-related breast cancer has a latency of 8-10y after exposure, necessitating use of a biomarker as a surrogate endpoint for assessing efficacy of breast cancer prevention. Mammographic density(6) and serum Insulin Growth Factors (IGF-1 and IGF-BP3)(7) are established biomarkers of breast cancer risk. We hypothesized that tamoxifen at a dose of 5mg/d for 2y would be an efficacious and safe option for reducing mammographic dense area and serum IGF-1 levels and increasing IGFBP-3 levels, in young female cancer survivors at risk for radiation-related breast cancer.

PATIENTS AND METHODS

Study Participants

We conducted a multi-center, investigator-initiated, randomized phase IIb, double-blinded, placebo-controlled trial of tamoxifen 5mg/d *vs.* placebo administered for 2y (FDA IND 107367; NCT01196936; protocol in Appendix).

Study Design

Women who were ≥25yo at enrollment, with a history of chest radiation at ≥12Gy at age ≤40 for a primary cancer, and were off-therapy for ≥6mo, were eligible. Patients with a prior history of breast cancer or ductal carcinoma *in situ* in both breasts, and those with baseline mammographic dense area <25% were excluded (eligibility in Appendix Table A1). The trial was conducted in accordance with the Declaration of Helsinki, and approval was received from institutional review boards at all participating sites. Participants provided written informed consent and enrolled between October 2010 and September 2016; last patient follow-up occurred in November 2019.

Eligible participants were randomized 1:1 in a double-blinded fashion by an Interactive Web Response System (Sharp Clinical Services; Allentown, PA) using block-stratified randomization, with menopausal status (pre-menopausal; post-menopausal), chest radiation dose (1200-2599cGy; ≥2600cGy) and age at radiation (<18y; 18-40y) as stratification factors and a block size of 4. Sharp Clinical Services provided 5mg tamoxifen and identical placebo tablets.

Study Intervention

Women received low-dose tamoxifen or placebo daily for 2y. After a screening visit, research staff enrolled participants and provided them the study drug every 90d. Mammograms and collection of a morning fasting blood and urine sample occurred at baseline (t0), 1y (t1) and 2y (t2). Participants, treating clinicians, and research staff were masked to treatment assignments.

Study End Points

Mammographic dense area was the primary endpoint. Participating sites submitted de-identified mammograms for study participants. Three study radiologists evaluated every

mammogram independently on Mammography Quality Standards Act-certified monitors, and determined breast density by visually estimating the proportion of dense breast tissue (fibroglandular tissue) to nondense tissue (fatty tissue) to the nearest 5%. The percentage given was based on the 4th edition of the ACR BI-RADS Atlas. The radiologists were masked to study arm assignment and study timepoint. Concordance among the three radiologists was 0.89 (95%CI, 0.87-0.92).

Serum IGF-1 and IGFBP-3 levels were measured using chemiluminescent immunoassay (ARUP laboratories, Salt Lake City, UT).

Safety and tolerability

Safety endpoints included serum bone-specific alkaline phosphatase (BSAP: marker of bone formation), urine N-telopeptide crosslinks (NTX: marker of bone resorption), serum anti-thrombin III levels [AT-III: for thrombophilic propensity), and fasting serum lipid panel. Participating sites reported AEs (graded using Common Terminology Criteria for Adverse Events), and likely attribution to study drug. Study participants returned their pill kits every 90d for calculation of adherence rates using pill count. Patient-reported symptoms were recorded every 90d. Voluntary withdrawals were tabulated at study end.

Statistical analysis

We provide details regarding sample size and power calculations in Appendix Table A2. Assuming a Type I error=0.05, 2-sided test, 10% attrition between annual visits, and correlation=0.8 between measurements, we projected that a sample size of 115/arm would provide 80% power to detect an effect size of 0.25 at t2.(8, 9) Slower than expected accrual, and financial constraints of supporting study drug costs necessitated an interim analysis for futility; results showed a separation of the two arms. Sample size was adjusted using the between-measurement correlation (r=0.95; lower 95%CI=0.9) obtained from the interim data. Assuming an annual attrition rate of 10%, r=.95 (r=0.9), n=31/arm (n=59/arm) would be needed to detect an effect size of 0.25 at t2 with 80% power and a type I error=0.05 (Table A2). We performed all analyses using SAS version 9.4.

Efficacy

Mammographic dense area: Using an intention-to-treat analysis, we examined the efficacy of low-dose tamoxifen in reducing mammographic dense area by applying the linear mixed effects (LME) model for normally distributed data. All patients with a minimum of baseline (t0) mammographic data were included. Mammographic dense area data from each breast was square root transformed to normality. We used an average of the left and right mammographic dense area as the dependent variable (given between breast r=0.99). Random effects were assumed for the intercept (to account for within-person correlations) and for the three radiologists. We treated time as a categorical variable using two indicator variables, and examined the treatment arm*time interaction to determine the efficacy of low-dose tamoxifen. We adjusted the analysis for baseline mammographic dense area. We considered low-dose tamoxifen to be efficacious if the 2-df test was significant, or if mammographic dense area was lower at t2 alone for low-dose tamoxifen group when compared to the placebo group. The two-sided significance level was set at .05.

Serum IGF-1 and IGFBP-3 levels: By applying LME models, we examined the treatment arm*time interaction to determine the efficacy of low-dose tamoxifen in reducing IGF-1 levels, increasing IGFBP-3 levels, adjusting for baseline levels. We considered low-dose tamoxifen to be efficacious if the 2-df test was significant, or if the levels differed at t2 alone, when compared to placebo. Two-sided significance level was set at .05.

Safety and tolerability of low-dose tamoxifen

Adverse events: AEs were graded as not present (grade 0), mild (grade 1), moderate (grade 2), serious (grade 3), life-threatening (grade 4) or fatal (grade 5). We dichotomized AEs (grade ≤2 *vs.* ≥3) and examined the difference in proportion of AEs by treatment group. Cholesterol (total, HDL, LDL), triglycerides, AT-III, BSAP and NTX were treated as continuous variables. We used generalized LME model with random intercepts, and used treatment arm*time interaction to assess the effect of low-dose tamoxifen on these measurements.

Patient-reported symptoms: We scored patient-reported symptoms on a 5-point Likert-type scale (0 to 4), and compared the proportion of patients with moderate-to-severe symptoms between treatment groups.

RESULTS

Patient Characteristics

We enrolled 116 women and randomized 84; 23 were ineligible at screening and nine declined to participate after providing informed consent. A central review identified mammographic dense area to be <25% for 11 patients; one patient withdrew after randomization (before study start), yielding 72 participants at t0 (low-dose tamoxifen: n=34; placebo: n=38) (Figure 1). Most patients (86%) carried a history of Hodgkin lymphoma. Median age at primary cancer diagnosis was 21.5y (IQR, 16-29), and at enrollment was 43.8y (35-49). Median dose of chest radiation was 30.3Gy (21-37.3). Forty-four participants (61%) were pre-menopausal at trial enrollment. Baseline patient characteristics were comparable between treatment groups (Table 1).

Biologic endpoints

Mammographic dense area: The 2-df test was significant (P=0.02). The mean mammographic dense area was lower among participants on the low-dose tamoxifen arm at t1 (low-dose tamoxifen: 44.9 *vs.* placebo: 47.8; mammographic dense area$_{\text{tamoxifen-placebo}}$: −2.9, 95%CI, −3.35 to −2.47, P=0.02) and at t2 (low-dose tamoxifen: 43.7 *vs.* placebo: 46.8; mammographic dense area$_{\text{tamoxifen-placebo}}$: −3.13, 95%CI, −3.57 to −2.68, P=0.03) (Table 2, Figure 2A). This represented a 10.2% relative reduction from t0 to t2 in the low-dose tamoxifen arm and 4.4% in the placebo arm.

IGF1 levels: The 2-df test was significant (P<0.0001), as were study arm differences at t1 (Least Square Means [LSMeans]: low-dose tamoxifen: 133.95 *vs.* placebo: 168.48; IGF1$_{\text{tamoxifen-placebo}}$: −34.53, 95%CI, −45.8 to −23.3, P<0.0001) and at t2 (LSMeans: 144.55 *vs.* 162.53; IGF1$_{\text{tamoxifen-placebo}}$: −16.99 95%CI, −29.41 to −4.56, P=0.008) (Table 2,

Figure 2B). The decline in IGF-1 levels on the low-dose tamoxifen arm were steeper among post-menopausal women (Table A3).

IGFBP-3 levels: The 2-df test was significant (P=0.02) as were study arm differences at t2 (LSMeans: low-dose tamoxifen: 4727.0 *vs.* placebo: 4293.6; $IGF\text{-}BP3_{tamoxifen\text{-}placebo}$: −433.4, 95%CI, 79.8 to 787.1, P=0.02) (Table 2, Figure 2C).

Safety and Tolerability

Biomarkers of toxicity: Lipids, AT-III, BSAP and NTX levels were comparable between the arms at baseline (Appendix Table A4). Treatment arm*time interaction was not significant indicating no difference in these markers between the low-dose tamoxifen and placebo arms (Table 2).

Adverse events: We did not find a statistically significant difference in AEs between study arms (grades 1-2: low-dose tamoxifen: 18% vs. placebo: 18%, P=1.0; grades 3-4: 12% vs. 18%, P=0.5) (Table 3). Breast cancer developed in one participant on the low-dose tamoxifen arm and in three participants on the placebo arm. None of the AEs was attributable to low-dose tamoxifen.

Patient-reported symptoms: There was no difference in the prevalence of patient-reported symptoms between the treatment groups, with the exception of myalgias (low-dose tamoxifen: 21% vs. placebo: 3%, p=0.02) and fatigue (low-dose tamoxifen: 29% vs. placebo: 8%, p=0.03) (Table 3).

Voluntary withdrawals and adherence to low-dose tamoxifen: Voluntary withdrawals did not differ between the two arms (low-dose tamoxifen: 26.5% vs. placebo: 31.6%, P=0.60). Median adherence rates over 2y were comparable (low-dose tamoxifen: 97.5% vs. placebo: 96.7%, P=0.9).

DISCUSSION

In this phase IIb randomized, double-blinded, placebo-controlled trial of chest-irradiated cancer survivors, low-dose tamoxifen (5mg/d for 2y) resulted in a 10.2% reduction in mammographic dense area compared with 4.4% reduction in the placebo arm. We observed statistically significant changes in serum IGF-1 and IGF-BP3 levels. Importantly, low-dose tamoxifen was well tolerated and without any serious AEs.

Breast cancer risk-reduction strategies in other high risk populations include surgical and pharmacologic interventions.(10) Prophylactic bilateral mastectomy is associated with a 90-95% reduction in risk of familial breast cancer(11); however, not all women are comfortable with this option(12). Although bilateral oophorectomy confers a 50-70% reduction in breast cancer risk if performed under age 45, the associated osteoporosis, dyslipidemia, and cardiovascular disease are deterrents, unless the patient is also at increased risk of ovarian cancer.(13) A synergistic effect between radiation and estrogen exposure in mammary carcinoma models(14) and the partial protection afforded to women from radiation-related breast cancer after ovarian radiation(3), suggests that estrogen plays a role

in the etiology of radiation-related breast cancer, supporting investigation of an estrogen-blocking intervention as a prevention strategy. While the US Preventive Services Task Force(4) and the American Society of Clinical Oncology(15) recommend SERMs or AIs for women at high risk for breast cancer, they do not include chest-irradiated women in this recommendation, because of insufficient evidence.

The only FDA-approved option for breast cancer chemoprevention in premenopausal women is tamoxifen. Tamoxifen results in decreased incidence of radiation-induced rodent mammary carcinoma.(16) In clinical trials enrolling women at elevated risk of breast cancer based on the Gail Model, 20mg/d of tamoxifen given for 5y decreased the incidence of breast cancer by ~50%.(17) However, tamoxifen at 20mg/d is associated with uterine malignancies, stroke, venous thromboembolism, and vasomotor/gynecological symptoms, contributing to its limited use for breast cancer prevention.(4) These concerns prompted studies exploring tamoxifen at 5mg/d, which demonstrated breast cancer risk-reduction without AEs.(5, 18) These studies provided us with the rationale for selecting tamoxifen at 5mg/d for a mixed population of pre- and post-menopausal chest-irradiated women. Indeed, we found that biomarkers of toxicity (BSAP, NTX, ATIII and lipid profile) were not different between the low-dose tamoxifen and placebo arms, nor was the prevalence of patient-reported symptoms with the exception of a higher prevalence of myalgias and fatigue in the low-dose tamoxifen arm. Four patients developed breast cancer, one on the low-dose tamoxifen arm and three on the placebo arm. Given the younger age of the study population (median age ~44y), one would expect a lower prevalence of AEs; however, this population is uniquely vulnerable to radiation-related severe/life-threatening adverse events such as second cancers, stroke, cardiomyopathy, and cardiovascular disease.(19) Nonetheless, the burden of treatment-related morbidity should have been comparable between the placebo and low-dose tamoxifen arms, allowing us to evaluate the additional impact of low-dose tamoxifen on AEs.

Mammographic dense area is a biologically plausible surrogate endpoint with a strong association with breast cancer.(6, 20, 21) Tamoxifen is associated with decreases in mammographic dense area after 1-2y of treatment.(22) These observations informed a 2y timepoint for the mammographic dense area as an efficacy endpoint in our trial. The absolute reduction in mammographic dense area of 5.1% after 2y of low-dose tamoxifen in our trial is comparable to the reduction (7.9%) with 20mg/d of tamoxifen for 18 months in the IBIS trial.(22)

IGF-1 (potent mitogen) binds to IGF-1 receptor, triggering a signaling cascade leading to proliferative and anti-apoptotic events in the mammary gland, playing an important role in breast carcinogenesis.(7) Similar to a previous low-dose tamoxifen trial in women with intra-epithelial neoplasia or a 5y Gail risk ≥1.3%,(23), our trial found a decline in serum IGF-1 and increase in the IGF-BP3 levels, providing further support for the potential efficacy of low-dose tamoxifen in chest-irradiated women at risk for breast cancer. We noted that the decline in IGF-1 levels on the low-dose tamoxifen arm was steeper among the post-menopausal women, as previously observed in breast cancer patients receiving adjuvant tamoxifen therapy.(24)

While the initial desired sample size was 230 participants, financial constraints and a slow accrual necessitated an interim analysis with a recalculation of the required sample size ranging between 62 and 118. Main reasons for the slow accrual included inability to travel to the site every 6mo as mandated by the trial (55%), lack of desire to participate in a placebo-controlled trial (39%). If low-dose tamoxifen were to become an accepted risk-reduction strategy for chest-irradiated female cancer survivors, the major deterrents (frequent travel to study site; participation in a placebo-controlled trial) would be obviated. A larger sample would have allowed analyses of subgroups that benefited most from low-dose tamoxifen. Nonetheless, in this first chemoprevention trial for young chest-irradiated cancer survivors, we provide evidence that 2y of low-dose tamoxifen significantly reduces mammographic dense area, and that the drug dosing of 5mg/d is safe and well tolerated. Radiation-related breast cancer is the most prevalent second cancer in survivors of AYA cancer;(25) low-dose tamoxifen could serve as an attractive option because of ease of administration, low cost, and a favorable safety profile, good tolerability and high adherence.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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STATEMENT OF TRANSLATIONAL RELEVANCE

Young females treated with chest radiation for their primary cancer are at increased risk for breast cancer; this risk is as high as that observed in *BRCA* mutation carriers. Estrogen plays a role in the etiology of radiation-related breast cancer, supporting investigation of an estrogen-blocking intervention as a prevention strategy. Low-dose tamoxifen reduces breast cancer risk in high-risk populations with minimal side effects, but has not been tested in chest-irradiated cancer survivors. In an investigator-initiated randomized, phase IIb, double-blinded, placebo-controlled trial, we show that low-dose tamoxifen taken daily for 2y was efficacious in reducing mammographic dense area and IGF-1 levels, and increasing IGFBP-3 levels, when compared with placebo. There were no grade 3-4 toxicities attributable to low-dose tamoxifen. Low-dose tamoxifen can serve as an attractive chemoprevention option in chest irradiated cancer survivors because of its ease of dissemination and favorable safety profile.

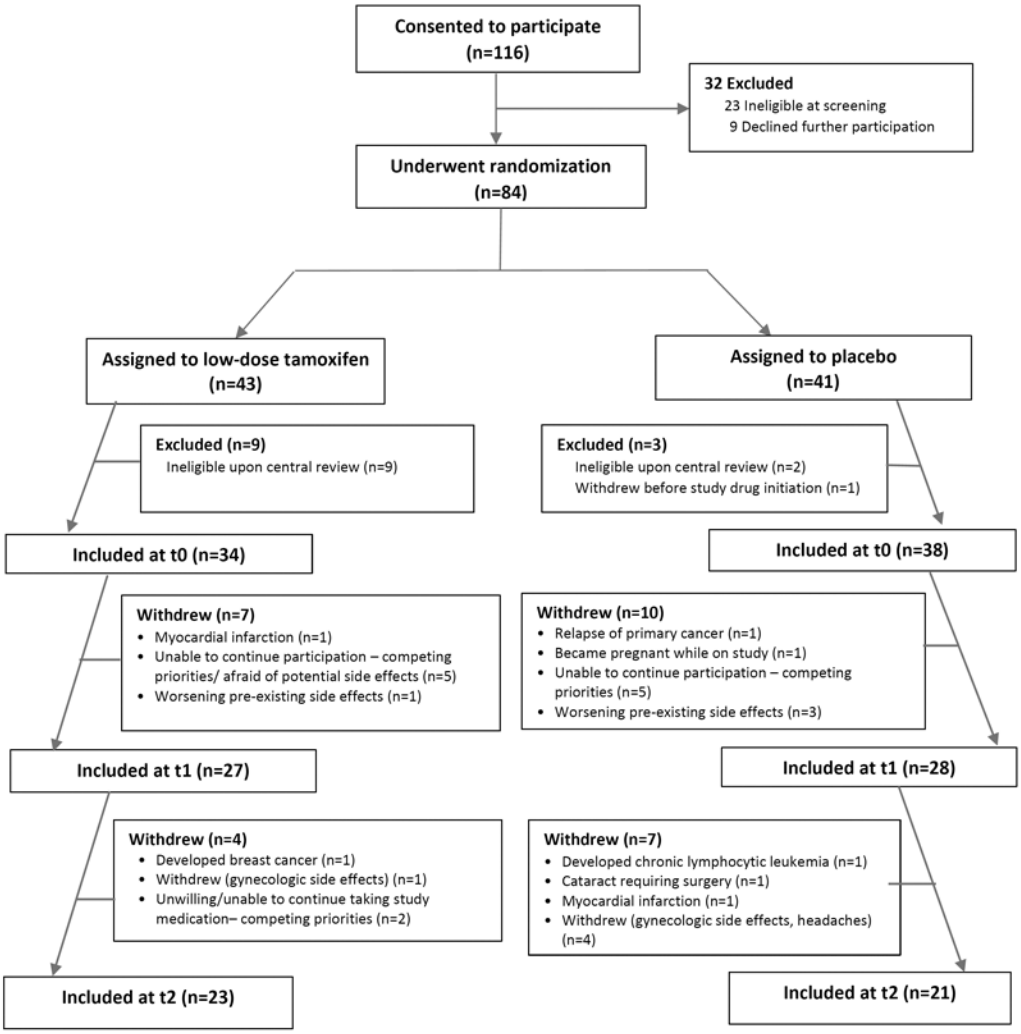

Figure 1:
CONSORT diagram for enrollment of patients on the trial

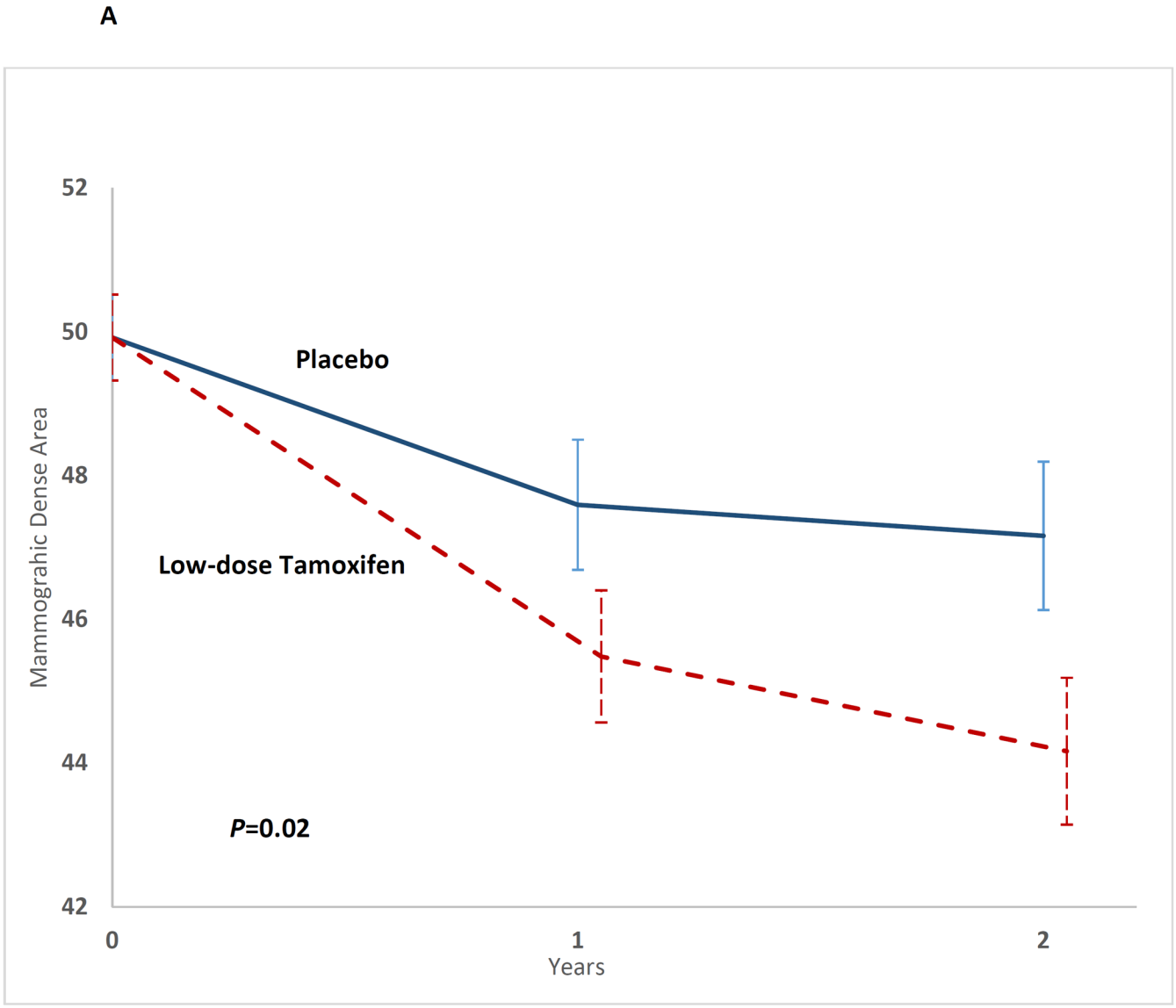

Figure 2A:
Impact of low-dose tamoxifen on mammographic dense area at t1 and t2, shown as mean mammographic dense area and the corresponding standard error

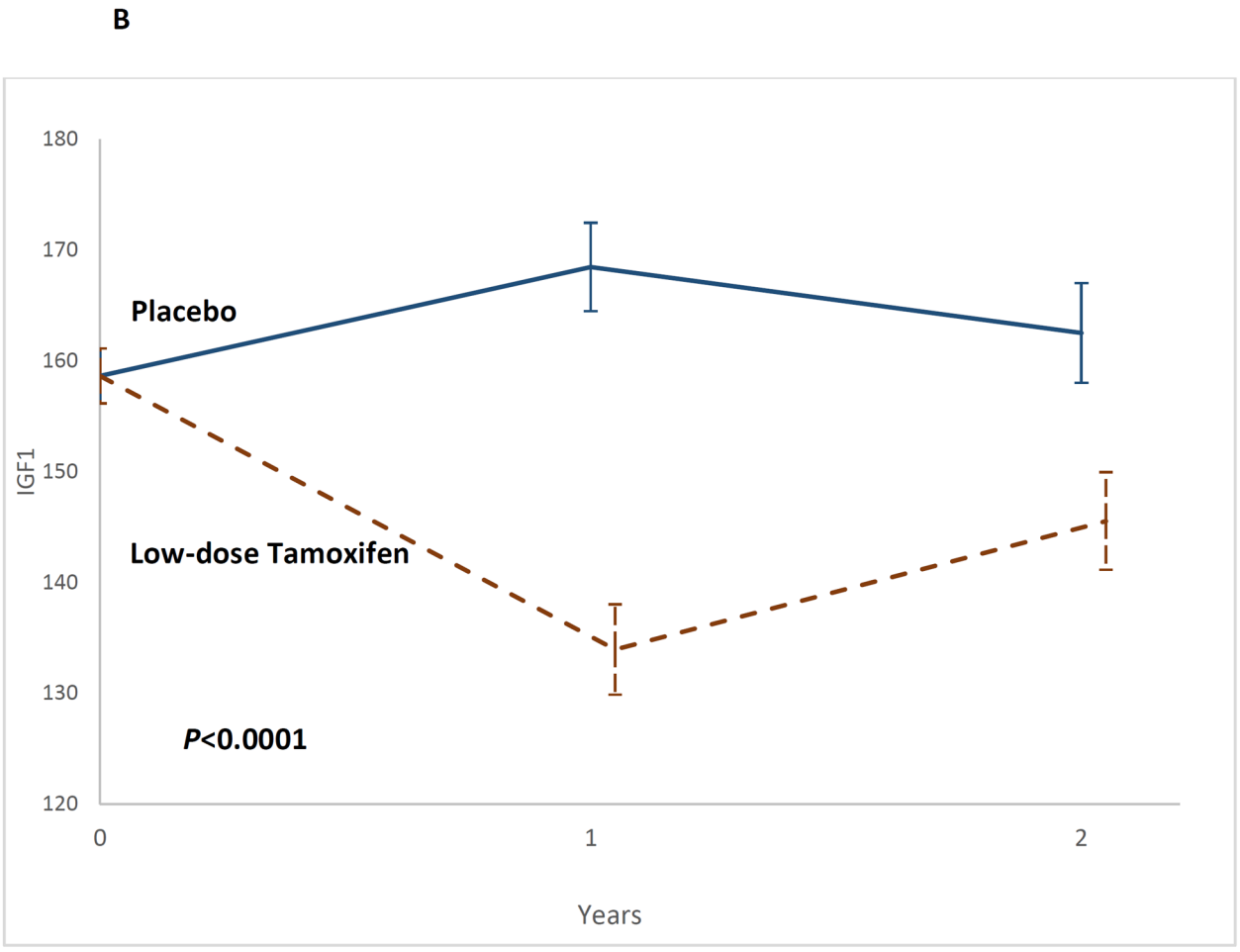

Figure 2B:
Impact of low-dose tamoxifen on serum insulin-like growth factor-1 at t1 and t2, shown as mean IGF-1 levels and the corresponding standard error

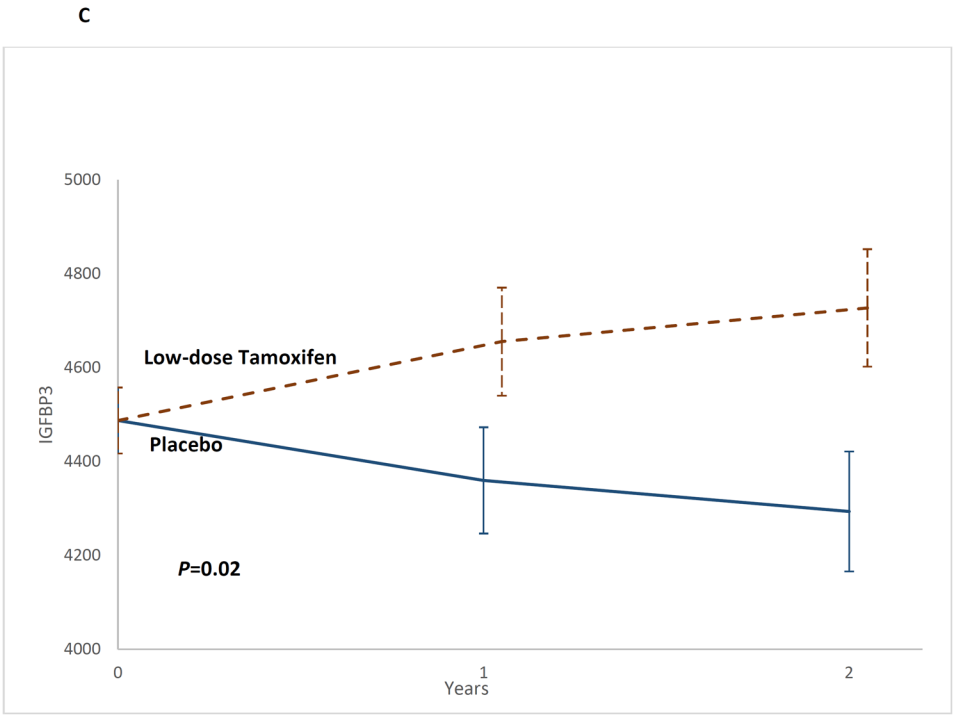

Figure 2C:
Impact of low-dose tamoxifen on serum insulin-like growth factor binding protein-3 at t1 and t2, shown as mean IGF-BP3 levels and the corresponding standard error

Table 1.

Participant Characteristics at Baseline

	Low-dose tamoxifen (n=34)	Placebo (n=38)
Age at study in years		
Median (IQR)	43.7 (34.3 to 48.8)	44.1 (34.6 to 47.0)
Race/ ethnicity (n, %)		
Non-Hispanic whites	27 (79%)	31 (82%)
Body Mass Indexin Kg/m^2		
Median (IQR)	25.0 (21.9 to 29.0)	25.4 (22.1 to 30.8)
Primary Cancer diagnosis (n, %)		
Hodgkin lymphoma	29 (85%)	33 (87%)
Non-Hodgkin lymphoma	5 (15%)	2 (5%)
Other	0 (0%)	3 (8%)
Time between cancer diagnosis and study in years		
Median (IQR)	16.6 (12.5 to 24.8)	17.1 (10.7 to 26.1)
Age at diagnosis of primary cancer in years		
Median (IQR)	23.4 (17.5 to 29.0)	19.9 (15.9 to 28.4)
Dose of radiation to chest for primary cancer in Gy		
Median (IQR)	30.3 (21.0 to 36.6)	29.8 (21.0 to 38.0)
1200-2599 cGy	15 (44.1%)	16 (42.1%)
≥2600 cGy	19 (55.9%)	22 (57.9%)
Radiation field		
Mantle	21 (61.8%)	26 (68.4%)
Mediastinal	4 (11.8%)	3 (7.9%)
Mini-mantle	4 (11.8%)	2 (5.3%)
Other	5 (14.7%)	7 (18.4%)
Pelvic radiation for primary cancer		
Yes (n, %)	4 (12%)	4 (11%)
Alkylating agent exposure (n, %)		
Yes	6 (18%)	5 (14%)
Postmenopausal at study (n, %)		
Yes	13 (38%)	15 (40%)
Age at menarche in years		
Median (IQR)	12 (11 to 14)	13 (12 to 14)
Age at first childbirth in years in years		
Median (IQR) y	28 (27 to 31)	26 (21 to 31)
Family history of breast cancer in first-degree relatives (n, %)		
Yes	12 (35%)	15 (40%)
Baseline estradiol in pg/mL		

	Low-dose tamoxifen (n=34)	Placebo (n=38)
Pre-menopausal	85 (0 to 389)	87 (0-242)
Post-menopausal	14.7 (1.3 to 226)	9.8 (4.6-145)
Baseline Percent Mammographic Breast Dense area		
Median (range)	51.0% (25% to 85%)	50.0% (25% to 95%)
Mean (±SD)	52.6%±18.5%	50.4±20.7%
Baseline Insulin-like growth factor-1 levels (ng/mL)		
Median (range)	166 (82 to 258)	148 (78 to 289)
Mean (±SD)	160.1 (41.0)	156.8 (48.8)
Baseline Insulin-like growth factor binding protein levels (ng/mL)		
Median (range)	4730 (2430 to 6090)	4260 (1990 to 8880)
Mean (±SD)	4601.8 (782.0)	4382.2 (1147.8)

Table 2.

Efficacy and Safety of Low dose tamoxifen

Efficacy of low-dose tamoxifen				
Efficacy Endpoints	**Difference between low-dose tamoxifen and placebo**	**95% CI**	**p-value**	**p-value 2df at t1 and t2**
Percent Mammographic Dense area (square root transformed) *				
At t1	−0.21	−0.40 to −0.03	0.02	0.02
At t2	−0.23	−0.44 to −0.03	0.03	
Percent Mammographic Dense area (mean) *				
At t1	−2.9%	−3.35 to −2.47	0.02	0.02
At t2	−3.13%	−3.57 to −2.68	0.03	
Insulin-like Growth Factor-1 (IGF-1) **†				
At t1	−34.53	−45.75 to −23.30	<.0001	<0.0001
At t2	−16.99	−29.41 to −4.56	0.008	
Insulin-like Growth Factor Binding Protein-3 ***‡				
At t1	295.53	−23.52 to 614.59	0.07	0.02
At t2	433.44	79.81 to 787.06	0.02	
Free IGF-1 (IGF-1/IGF-BP3) *100				
At t1	−0.89	−1.15 to −0.64	<.0001	<.0001
At t2	−0.66	−0.95 to −0.38	<.0001	
Safety of low-dose tamoxifen				
Safety Biomarkers	**Difference between low-dose tamoxifen and placebo at t2**	**95% Confidence Interval**	**p-value**	
Lipids				
Total cholesterol	−2.59	−21.30 to 16.10	0.80	
Low-density lipoprotein	−3.23	−18.30 to 11.80	0.70	
High-density lipoprotein	1.13	−6.60 to 8.90	0.80	
Triglycerides	21.51	−14.50 to 57.10	0.20	
Pro-coagulation markers				
Anti-thrombin-III levels	−8.9	−22.90 to 5.20	0.20	
Bone markers				
Bone-specific Alkaline Phosphatase	−0.27	−1.80 to 1.30	0.70	
Urinary N-telopeptide, cross-linked	1.1	−9.00 to 11.20	0.80	

*Adjusted for baseline mammographic dense area

**†Adjusted for baseline IGF-1 levels

***‡Adjusted for baseline IGF-BP3

Table 3:

Adverse events and Patient-reported Symptoms by Study Arm

	Low-dose tamoxifen (n=34)	Placebo (n=38)	P-value*
	N (%)*	N (%)*	
Patient-reported symptoms			
Arthralgia/arthritis	6 (18%)	5 (13%)	0.7458
Back pain	7 (21%)	4 (11%)	0.3288
Myalgias	7 (21%)	1 (3%)	0.0227
Malaise	6 (18%)	5 (13%)	0.7458
Hot flashes	9 (27%)	11 (29%)	1.0000
Night sweats	7 (21%)	6 (16%)	0.7606
Irregular menstruation	9 (27%)	6 (16%)	0.3843
Vaginal discharge	8 (24%)	5 (13%)	0.3593
Vaginal spotting/bleeding	5 (15%)	8 (21%)	0.5512
Breast pain	5 (15%)	3 (8%)	0.4630
Urinary incontinence/frequency/urgency	7 (21%)	10 (26%)	0.5926
Weight gain/ loss	17 (50%)	19 (50%)	1.0000
Insomnia	4 (12%)	7 (18%)	0.5225
Somnolence	9 (27%)	4 (11%)	0.1241
Fatigue	10 (29%)	3 (8%)	0.0296
Irritability	6 (18%)	6 (16%)	1.0000
Memory impairment	6 (18%)	2 (5%)	0.1375
Inability to concentrate	7 (21%)	3 (8%)	0.1748
Restlessness	7 (21%)	4 (11%)	0.3288
Paresthesia	7 (21%)	2 (5%)	0.0746
Mood swings	5 (15%)	4 (11%)	0.7265
Feelings of depression	7 (21%)	8 (21%)	1.0000
Diarrhea	6 (18%)	5 (13%)	0.7458
Constipation	7 (21%)	6 (16%)	0.7606
Heartburn	9 (27%)	7 (18%)	0.5713
Headaches	8 (24%)	6 (16%)	0.5527
Adverse Events**			
Grades 3-4 Adverse Events			
Any grade 3-4 adverse events	4 (12%)	7 (18%)	0.5225
Breast cancer	1 (3%)	3 (8%)	0.6167
Myocardial infarction	2 (6%)	2 (5%)	1.0000
Carotid artery occlusion	1 (3%)	0 (0%)	0.4722
Relapse of primary disease	0	2 (5%)	0.4945
Grades 1-2 Adverse Events			

	Low-dose tamoxifen (n=34)	Placebo (n=38)	P-value*
	N (%)*	N (%)*	
Any grade 1-2 adverse events	6 (18%)	7 (18%)	1.0000
Pregnancy	0	1 (3%)	1.0000
Cataract	2 (6%)	2 (5%)	1.0000
Basal cell carcinoma	0	3 (8%)	0.2418
Endometriosis	0	1 (3%)	1.0000
Thyroid nodules	4 (12%)	0 (0%)	0.0451

*P-value calculated using Fisher's exact test.

**Of note, no episodes of venous thromboembolism, or uterine cancer were observed