The Effect of Transdermal Testosterone on Mammographic Density in Postmenopausal Women Not Receiving Systemic Estrogen Therapy

Susan R. Davis, Angelica Lindén Hirschberg, Leigh K. Wagner, Imran Lodhi, and Bo von Schoultz

Women's Health Program (S.R.D.), Department of Medicine, Monash Medical School, Alfred Hospital, Commercial Road, Prahran, Victoria 3181 Australia; Karolinska Institute and University Hospital (A.L.H., B.v.S.), SE-141 86 Stockholm, Sweden; and Procter & Gamble Pharmaceuticals (L.K.W., I.L.), Mason, Ohio 45040

Context: Greater mammographic density is associated with increased breast cancer risk and reduced diagnostic mammographic sensitivity and may be seen with estrogen/progestin therapy (EPT). The effects of testosterone therapy on mammographic density in postmenopausal women not on EPT are not known.

Objective: Our objective was to compare effects of two doses of the testosterone transdermal patch (TTP) with placebo in postmenopausal women without concomitant EPT on mammographic density over 52 wk.

Design: We conducted a randomized, double-blind, placebo-controlled, parallel-group, multinational trial.

Patients: Patients included 279 postmenopausal women participating in a testosterone and sexual function study with paired mammograms for baseline and 52 wk/exit.

Interventions: Patients were randomized to placebo, TTP 150 μg/d, or TTP 300 μg/d, stratified by menopause type (natural or surgical).

Main Outcome Measures: Change from baseline to wk 52 in the percentage of dense tissue (PD) on digital mammograms.

Results: A total of 250 women with paired mammograms for study baseline and wk 52 were included in the primary analysis. Mean age was 54.6 yr, baseline body mass index was 27.5 kg/m^2, and 78% were naturally menopausal. There were no baseline differences between groups. Mean changes from baseline ($\pm$SEM) in PD for placebo, TTP 150 μg/d and TTP 300 μg/d were small (0.05 $\pm$ 0.16, 0.06 $\pm$ 0.19, and 0.21 $\pm$ 0.17%) and not significantly different. There were no statistically significant differences from placebo for total dense or nondense area and no significant relationships between hormone levels and PD after adjustment for body mass index.

Conclusion: TTP therapy over 52 wk appears to have no significant effect on digitally quantified absolute or percent dense mammographic area in postmenopausal women not using EPT. **(*J Clin Endocrinol Metab* 94: 4907–4913, 2009)**

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in U.S.A.

doi: 10.1210/jc.2009-1523 Received July 16, 2009. Accepted September 16, 2009.
First Published Online October 22, 2009

Abbreviations: BMI, Body mass index; E+P, estrogen-progestin; NM, naturally menopausal; SM, surgically menopausal; TTP, testosterone transdermal patch.

Mammographic breast density seems to reflect the net influence of hormonal and reproductive factors and its background genetics on the breast during a woman's life span (1–3). Although a breast density increase implies breast epithelial cell proliferation, its major characteristic seems to be tissue remodeling and an increase of stromal proteoglycans (4, 5). Greater mammographic density is associated with increased breast cancer risk (6) but also with reduced diagnostic sensitivity for breast cancer (7). Numerous reports have shown that mammographic breast density is increased in a significant proportion of women using estrogen-progestin (E+P) hormone therapy (6, 7).

In vitro and *in vivo* studies suggest testosterone may serve as a natural endogenous protector of the breast and limit the mitogenic and cancer-promoting effects of estrogen on mammary epithelium (8–12). The effects of exogenous testosterone and breast cancer risk remain unclear. Whereas a retrospective study of women exposed to testosterone, primarily as methyltestosterone, reported an increase in breast cancer risk for current users (13), Jick *et al.* (14) reported no increase in breast cancer risk with the addition of methyltestosterone to either estrogen alone or E+P therapy. Two studies involving a similar number of testosterone users to that studied by Tamimi *et al.* (13) reported no increase in breast cancer risk for current or past users of transdermal testosterone and testosterone pellets (15, 16).

In a study examining the effects of the addition of transdermal testosterone to continuous combined oral E+P therapy, mammographic density did not increase beyond those assigned to placebo after 6 months treatment (17). The effects of exogenous testosterone on mammographic density in postmenopausal women not using concurrent systemic estrogen are not known.

The Aphrodite study was a 52-wk, randomized, double-blind, placebo-controlled, parallel-group, multinational, multicenter trial designed to evaluate the efficacy and safety of two doses (150 or 300 μg/d testosterone) of the transdermal testosterone patch (TTP) in naturally menopausal (NM) or surgically menopausal (SM) women with hypoactive sexual desire disorder who were not receiving systemic estrogen or E+P therapy. The doses used approximate half or the full estimated production of testosterone per day in premenopausal women (18). The results of the study have been reported elsewhere (19). Here we report the results of the mammographic breast density analysis from the study.

Patients and Methods

Study design

Recruitment to the Aphrodite study has been described in detail (19). Briefly, the key inclusion criteria were SM women between the ages of 20 and 70 yr and NM women between the ages of 40 and 70 yr in a stable relationship with partner present more than 50% of the time, SHBG higher than 12 nmol/liter, and in general good health. The relevant exclusion criteria were the use of systemic estrogen or E+P in the preceding 3 months or any androgen use in the previous 3 months (7 months for testosterone implants), history of breast cancer or any estrogen-dependent neoplasia, diabetes, cardiovascular disease, or other serious medical conditions. Women had to have a clinically acceptable bilateral mammogram (if age 40 yr or older) within the preceding 12 months or have a bilateral mammogram undertaken as part of recruitment screening. Previous mammograms were not digitized. Only patients who had both wk −4 and wk 52/exit mammograms performed as part of the study were sent for digitization and provided data for this analysis.

Mammograms were performed at screening (wk −4) and again at wk 52 or study exit (if withdrawal was not before 24 wk) to assess eligibility and the effect of the TTP on breast density after 1 yr of treatment.

Data handling and digitization methods

All eligible paired mammograms were mailed directly from the sites to Synarc, Inc.(San Francisco, CA), along with computer image transmittal forms. Upon receipt of the mammograms, Synarc logged receipt of the images and digitized the images (12 bits per pixel with a pixel spacing of 50 μm) with a Lumisys LS100 scanner (Lumisys, Eastman Kodak Co., Rochester, NY). The patient number, study visit, and body side were provided to identify the image.

Breast density endpoints and measurement methods

All mammograms were read by trained observers in a standard fashion. Mammograms for each patient were read in sets (baseline and after baseline), and the order of presentation was randomized. The observers were blinded to patient treatment assignment and study visit. The left craniocaudal view was selected for measurement. If paired evaluable images were not available for the left craniocaudal view, paired images for the right breast were measured.

Using the digital images, the total area of the breast appearing on the mammogram and the area of dense tissue were measured by the observers. The breast area measurements were checked to ensure that values were within scientifically valid ranges for the endpoints. If a value was not within the logical range, it was remeasured. A subsample of 5% of the mammogram images was randomly selected and reread to assess intra-reader reliability and showed an intraclass correlation coefficient of more than 0.92. The percentage of dense tissue was calculated as the number (in square millimeters) representing the dense breast area divided by the number (in square millimeters) representing the total breast area ($\times$ 100%). Nondense area was additionally calculated as the total breast area minus the dense breast area.

Populations for analyses

Paired mammograms from 279 patients were available. Of these patients, nine had mammogram dates in the breast density dataset that were considerably different from the dates in the clinical database and were considered unevaluable. Of the remaining 270 patients with evaluable data, 20 did not complete 52 wk treatment. This resulted in a primary analysis population

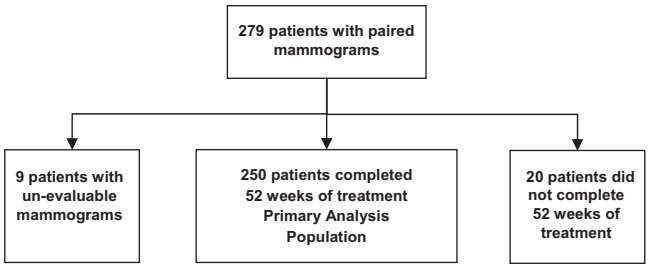

FIG. 1. Patient disposition.

of 250 patients who completed 52 wk treatment and the secondary analysis population of 270 patients (Fig. 1).

Hormone measurements

Serum levels of free and total testosterone and SHBG, bioavailable testosterone, total dihydrotestosterone, free and total estradiol, and estrone were measured by validated methods (Quest Diagnostics, Inc., San Juan Capistrano, CA) (19).

Statistical methods

The primary endpoint was the change from wk −4 (baseline) to wk 52 in the percentage of dense tissue in the breast. An analysis of covariance was used to test for differences between each active dose and placebo in the change from baseline at wk 52 after adjusting for the baseline value, baseline body mass index (BMI), age, and menopausal type (SM or NM). Model assumptions (normality and constant variance) were assessed qualitatively by visual inspection of the residuals. If normality assumptions were severely violated, Koch's nonparametric analysis of covariance was additionally performed. All hypothesis tests were two sided.

Analyses of the secondary endpoints (change from baseline in dense area and nondense area) and analyses using all evaluable patients regardless of their study completion status were conducted using methods similar to that described for the primary endpoint. Additional exploratory analyses of the primary endpoint using the primary analysis population were conducted by menopausal type (SM or NM) using similar methods. Spearman correlations were calculated for the baseline value, wk-52 value, and the change from baseline to wk 52 in percent dense area with baseline, wk 52, and change from baseline in weight and BMI, respectively. A similar analysis was done correlating percent dense with hormone levels.

Results

The participants in this primary analysis population had a mean age of 54.6 yr (range 40–69 yr) with baseline BMI of 27.5 kg /m^2, and 78% were NM (Table 1). Over 60% of the participants had used menopausal hormone therapy at any time before randomization. No significant differences in baseline characteristics between treatment groups were noted. The clinical characteristics of these women

TABLE 1. Patient characteristics

Population	Placebo	TTP 150	TTP 300
Total population			
n	79	79	92
Age (yr)			
Mean (SD)	55.0 (5.5)	54.6 (5.1)	54.4 (5.6)
Range	44.0–69.0	41.0–69.0	40.0–66.0
Race, % Caucasian	89.9	88.6	88.0
Baseline weight [kg (SD)]	73.7 (15.0)	72.0 (16.4)	74.3 (15.3)
Mean BMI [kg/m^2 (SD)]	27.7 (5.4)	27.1 (6.5)	27.7 (4.8)
Current alcohol use [n (%)]	65 (82.3)	63 (79.7)	78 (84.8)
Current tobacco use [n (%)]	9 (11.4)	9 (11.4)	13 (14.1)
NM population			
n	61	64	70
Age (yr)			
Mean (SD)	55.0 (5.1)	55.0 (4.5)	55.7 (4.9)
Range	47.0–69.0	45.0–69.0	43.0–66.0
Hysterectomized (%)	26.2	21.9	20.0
Mean yr since menopause (SD)	8.1 (5.5)	5.7 (3.6)	6.4 (3.4)
Previous androgen use (%)	8.2	9.4	7.1
Previous E+P use (%)	65.6	57.8	68.6
SM population			
n	18	15	22
Age (yr)			
Mean (SD)	54.8 (7.0)	52.5 (7.0)	50.3 (5.8)
Range	44.0–66.0	41.0–69.0	40.0–62.0
Hysterectomized (%)	100	100	100
Mean yr since menopause (SD)	13.0 (10.4)	8.9 (7.0)	9.2 (6.0)
Previous androgen use (%)	22.2	6.7	40.9
Previous E+P use (%)	88.9	86.7	81.8

Years since menopause was computed using oophorectomy date for SM women and last menstrual period date for nonhysterectomized NM women. Hysterectomized NM women are not included due to no clear date for menopause.

did not differ from women in the Aphrodite Study not included in this study (19).

Baseline mammographic percent density (mean ± SD) was 28.02 ± 15.8, 27.26 ± 16.7, and 27.91 ± 14.4% for the placebo, TTP 150 μg/d, and TTP 300 μg/d groups, respectively. Baseline weight and BMI were each inversely significantly correlated with the percent dense mammographic area (Spearman correlation coefficients −0.44 and −0.46, respectively; $P < 0.001$) such that overweight women had lower baseline percent density.

The mean changes in percent mammographic density over 52 wk were small (placebo, 0.05 ± 0.16%; TTP 150 μg/d group, 0.06 ± 0.19%; and TTP 300 μg/d group, 0.21 ± 0.17%). The changes in each treatment arm were not statistically significantly different from placebo for percent breast density as well as for dense and nondense area (Fig. 2). For each menopausal type (surgical or natural), no statistically significant changes were seen comparing placebo *vs.* either treatment for percent mammographic density over 52 wk.

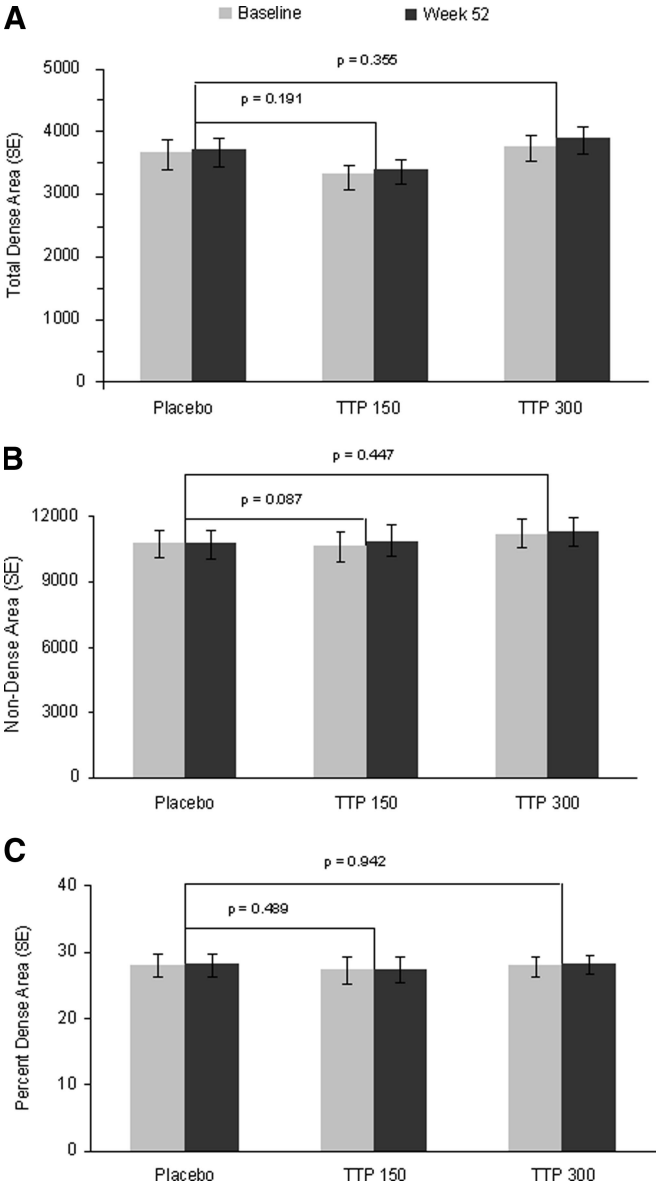

FIG. 2. Dense area (A), nondense area (B), and percent dense area (C) at baseline and wk 52. *P* values are for comparison of change from baseline in testosterone *vs.* change from baseline in placebo.

TABLE 2. Correlations between breast density and BMI and weight at baseline and 52 wk treatment

	BMI (kg/m^2), n = 248	Weight (kg), n = 249
Percent mammographic density at baseline	−0.46[a]	−0.44[a]
Percent mammographic density at wk 52	−0.48[a]	−0.46[a]
Change in percent density from baseline	−0.05	−0.13[a]

BMI and weight are baseline values, wk-52 values, and change from baseline depending on the row.

[a] Spearman correlation is statistically significant ($P < 0.05$).

There were no significant relationships between the change in BMI and change in percent dense area, but we observed a small but statistically significant negative relationship between change in weight and change in percent dense area (Spearman correlation coefficient −0.13, $P < 0.05$) (Table 2).

Serum free testosterone, free estradiol, and estrone were inversely associated with percent dense mammographic area at baseline and wk 52 and total estradiol only at baseline. SHBG was positively associated with percent dense mammographic area at baseline and at wk 52 (Table 3). After adjustment for BMI, there were no significant relationships between any of the hormone levels and percent dense area at baseline, wk 52, or wk 52 change from baseline.

Discussion

Treatment with testosterone at a dose of either 150 or 300 μg/d over 52 wk had no significant effect on digitally quantified absolute or percent dense mammographic area compared with placebo in postmenopausal women not using concurrent estrogen. Furthermore, there were no statistically significant relationships between circulating androgen or estrogen levels and mammographic density after adjusting for BMI over the course of the study.

Mammographic density has been established as a strong and independent risk factor for breast cancer (4, 6). The relationships between endogenous testosterone and breast cancer risk remain unclear (11). Although in one recent study circulating levels of testosterone were associated with breast cancer risk, before and after adjustment for mammographic density (20), the NSABP Cancer Prevention Trial (P-1) did not find an association between

TABLE 3. Correlations between percent mammographic density and circulating hormone levels

	Total T	Free T	SHBG	Total E_2	Free E_2	E_1	DHT
Baseline % density							
n	247	246	250	212	189	214	157
Spearman correlation	−0.02	−0.21[a]	0.27[a]	−0.19[a]	−0.27[a]	−0.17[a]	0.07
Adjusted for BMI	−0.01	−0.08	0.06	−0.00	−0.05	0.01	0.01
wk-52 % density							
n	224	224	224	213	209	216	162
Spearman correlation	−0.04	−0.16[a]	0.32[a]	−0.09	−0.15[a]	−0.14[a]	0.01
Adjusted for BMI	−0.04	−0.06	0.09	0.08	0.06	−0.00	−0.08
wk-52 change from baseline							
n	221	220	224	181	159	183	100
Spearman correlation	0.02	0.04	0.01	−0.01	0.01	−0.07	0.02
Adjusted for BMI	0.01	0.05	−0.01	−0.00	0.01	−0.06	0.02

Percent density data are from evaluable breast density patients with wk-52 data. Hormone levels are baseline values, wk-52 values, and change from baseline depending on the row. n, Number of patients with percent dense and corresponding hormone level data. The n goes down slightly after correlations are adjusted for BMI. Analysis requires no missing BMI values. DHT, Dihydrotestosterone; E_1, estrone; E_2, estradiol.

[a] Spearman correlation is statistically significant ($P < 0.05$).

baseline testosterone levels and the relative risk of developing breast cancer in postmenopausal women (21).

Oral E+P therapy is associated with increased breast cancer risk (22). Furthermore, postmenopausal E+P therapy is associated with an increase in mammographic density on the order of 7% compared with placebo after 1 yr treatment (16). Whether this directly reflects the pathogenesis of the associated increase in breast cancer risk remains unknown. However, tibolone, a synthetic compound with slight androgenic properties, does not increase mammographic density and seems not to increase the risk of breast cancer (23–27). Also, therapeutic interventions that prevent breast cancer will reduce mammographic density (27, 28).

From a clinical perspective, increased breast cell proliferation and increased mammographic density during hormonal treatment should be regarded as basically unwanted and potentially hazardous events. Breast symptoms of soreness and pain are well known to occur in some women during E+P therapy. These symptoms are associated with a change in mammographic density (5, 29). The lack of increase of mammographic density with testosterone therapy in this study is, however, not evidence that testosterone does not alter breast cancer risk. The diagnostic sensitivity of mammography for breast cancer is probably unchanged because radiographic density is not altered by the use of testosterone.

At baseline, the mean percent dense mammographic area was considerably higher than that reported for postmenopausal hormone studies (22), reflecting the relatively young age of the participants and the high prevalence of previous hormone therapy use. Our findings regarding the lack of any relationships between estradiol and testosterone levels and mammographic density after adjustment for BMI are consistent with previous reports that mammographic density appears to be largely independent of circulating endogenous postmenopausal steroid hormone levels and is highly genetically determined (1, 2, 30, 31). In contrast, as demonstrated in this and previous studies, percent mammographic density is influenced by weight and BMI, with greater weight being associated with lower percent breast density, which needs to be taken into account in interpreting the potential influence of mammographic density on breast cancer risk (32, 33). This has led some researchers to recommend that total dense breast area may be a more meaningful risk factor (34).

Strengths of this study are that it was a large randomized controlled trial and included naturally and SM women. One limitation is that we are reporting a secondary outcome that was not the basis of the primary power calculation. However, this study would have been adequately powered to detect a difference between each treatment group and placebo in the change in percentage density of 0.8%, which is considerably less than what is seen with estrogen replacement therapy (17). The other possible limitation is that the study participants, who had mammography before enrollment and hence did not provide data for this analysis, may have been systematically different from the women included in the analysis, potentially limiting the generalizability of the findings.

In conclusion, our results indicate no overall association between transdermal testosterone use by postmenopausal woman not on concurrent estrogen and mammographic density over 52 wk.

Acknowledgments

We acknowledge Cynthia Rodenberg for her contributions to the data analysis.

Address all correspondence and requests for reprints to: Dr. Susan Davis, M.D., Ph.D., Women's Health Program, Department of Medicine, Central and Eastern Clinical School, Monash University, Alfred Hospital, Commercial Road, Prahran, Victoria 3181, Australia. E-mail: susan.davis@med.monash.edu.au.

This research was funded by Procter& Gamble Pharmaceuticals, Mason, OH.

Disclosure Summary: S.D. reports receiving consulting fees from Acrux, AstraZeneca Oncology Australia, Organon, and Procter & Gamble Pharmaceuticals; lecture fees from AstraZeneca Oncology Australia and Organon; and grant support from AstraZeneca Pharmaceuticals, Novartis Oncology Australia, and Procter & Gamble USA. A.L.H. has received consulting fees from Procter & Gamble and lecture fees from Bayer Schering, Pfizer AB, and Novo Nordisk. L.W. and I.L. are employees of Procter & Gamble Pharmaceuticals. B.v.S. has received consulting fees from Procter & Gamble and lecture fees from Wyeth, Organon, and Novo Nordisk.

References

1. **Verheus M, Peeters PH, van Noord PA, van der Schouw YT, Grobbee DE, van Gils CH** 2007 No relationship between circulating levels of sex steroids and mammographic breast density: the Prospect-EPIC cohort. Breast Cancer Res 9:R53
2. **Warren R, Skinner J, Sala E, Denton E, Dowsett M, Folkerd E, Healey CS, Dunning A, Doody D, Ponder B, Luben RN, Day NE, Easton D** 2006 Associations among mammographic density, circulating sex hormones, and polymorphisms in sex hormone metabolism genes in postmenopausal women. Cancer Epidemiol Biomarkers Prev 15:1502–1508
3. **Warren R** 2004 Hormones and mammographic breast density. Maturitas 49:67–78
4. **McCormack VA, dos Santos Silva I** 2006 Breast density and parenchymal patterns as markers of breast cancer risk: a meta-analysis. Cancer Epidemiol Biomarkers Prev 15:1159–1169
5. **Harvey JA, Santen RJ, Petroni GR, Bovbjerg VE, Smolkin ME, Sheriff FS, Russo J** 2008 Histologic changes in the breast with menopausal hormone therapy use: correlation with breast density, estrogen receptor, progesterone receptor, and proliferation indices. Menopause 15:67–73
6. **Boyd NF, Rommens JM, Vogt K, Lee V, Hopper JL, Yaffe MJ, Paterson AD** 2005 Mammographic breast density as an intermediate phenotype for breast cancer. Lancet Oncol 6:798–808
7. **Carney PA, Miglioretti DL, Yankaskas BC, Kerlikowske K, Rosenberg R, Rutter CM, Geller BM, Abraham LA, Taplin SH, Dignan M, Cutter G, Ballard-Barbash R** 2003 Individual and combined effects of age, breast density, and hormone replacement therapy use on the accuracy of screening mammography. Ann Intern Med 138:168–175
8. **Hofling M, Hirschberg AL, Skoog L, Tani E, Hägerström T, von Schoultz B** 2007 Testosterone inhibits estrogen/progestogen-induced breast cell proliferation in postmenopausal women. Menopause 14:183–190
9. **Dimitrakakis C, Zhou J, Bondy CA** 2002 Androgens and mammary growth and neoplasia. Fertil Steril 77:S26–S33
10. **Zhou J, Ng S, Adesanya-Famuiya O, Anderson K, Bondy CA** 2000 Testosterone inhibits estrogen-induced mammary epithelial proliferation and suppresses estrogen receptor expression. FASEB J 14: 1725–1730
11. **Somboonporn W, Davis SR** 2004 Testosterone and the breast: therapeutic implications for women. Endocr Rev 25:374–388
12. **Hofling M, Löfgren L, von Schoultz E, Carlström K, Söderqvist G** 2008 Associations between serum testosterone levels, cell proliferation and progesterone receptor content in normal and malignant breast tissue in postmenopausal women. Gynecol Endocrinol 24: 405–410
13. **Tamimi RM, Hankinson SE, Chen WY, Rosner B, Colditz GA** 2006 Combined estrogen and testosterone use and risk of breast cancer in postmenopausal women. Arch Intern Med 166:1483–1489
14. **Jick SS, Hagberg KW, Kaye JA, Jick H** 2009 Postmenopausal estrogen-containing hormone therapy and the risk of breast cancer. Obstet Gynecol 113:74–80
15. **Davis SR, Wolfe R, Farrugia H, Ferdinand A, Bell RJ** 2009 The incidence of invasive breast cancer among women prescribed testosterone for low libido. J Sex Med 6:1850–1856
16. **Dimitrakakis C, Jones R, Liu A, Bondy CA** 2004 Breast cancer incidence in postmenopausal women using testosterone in addition to usual hormone therapy. Menopause 11:531–535
17. **Hofling M, Lundström E, Azavedo E, Svane G, Hirschberg AL, von Schoultz B** 2007 Testosterone addition during menopausal hormone therapy: effects on mammographic breast density. Climacteric 10:155–163
18. **Southren AL, Gordon GG, Tochimoto S** 1968 Further study of factors affecting the metabolic clearance rate of testosterone in man. J Clin Endocrinol Metab 28:1105–1112
19. **Davis SR, Moreau M, Kroll R, Bouchard C, Panay N, Gass M, Braunstein GD, Hirschberg AL, Rodenberg C, Pack S, Koch H, Moufarage A, Studd J; APHRODITE Study Team** 2008 Testosterone for low libido in menopausal women not taking estrogen therapy. N Engl J Med 359:2005–2017
20. **Tamimi RM, Byrne C, Colditz GA, Hankinson SE** 2007 Endogenous hormone levels, mammographic density, and subsequent risk of breast cancer in postmenopausal women. J Natl Cancer Inst 99: 1178–1187
21. **Beattie MS, Costantino JP, Cummings SR, Wickerham DL, Vogel VG, Dowsett M, Folkerd EJ, Willett WC, Wolmark N, Hankinson SE** 2006 Endogenous sex hormones, breast cancer risk, and tamoxifen response: an ancillary study in the NSABP Breast Cancer Prevention Trial (P-1). J Natl Cancer Inst 98:110–115
22. **McTiernan A, Martin CF, Peck JD, Aragaki AK, Chlebowski RT, Pisano ED, Wang CY, Brunner RL, Johnson KC, Manson JE, Lewis CE, Kotchen JM, Hulka BS** 2005 Estrogen-plus-progestin use and mammographic density in postmenopausal women: women's health initiative randomized trial. J Natl Cancer Inst 97:1366–1376
23. **Opatrny L, Dell'Aniello S, Assouline S, Suissa S** 2008 Hormone replacement therapy use and variations in the risk of breast cancer. BJOG 115:169–175; discussion 175
24. **Lundström E, Christow A, Kersemaekers W, Svane G, Azavedo E, Söderqvist G, Mol-Arts M, Barkfeldt J, von Schoultz B** 2002 Effects of tibolone and continuous combined hormone replacement therapy on mammographic breast density. Am J Obstet Gynecol 186:717–722
25. **Cummings SR, Ettinger B, Delmas PD, Kenemans P, Stathopoulos V, Verweij P, Mol-Arts M, Kloosterboer L, Mosca L, Christiansen C, Bilezikian J, Kerzberg EM, Johnson S, Zanchetta J, Grobbee DE, Seifert W, Eastell R** 2008 The effects of tibolone in older postmenopausal women. N Engl J Med 359:697–708
26. **Valdivia I, Ortega D** 2000 Mammographic density in postmenopausal women treated with tibolone, estriol or conventional hormone replacement therapy. Clin Drug Invest 20:101–107
27. **Eilertsen AL, Karssemeijer N, Skaane P, Qvigstad E, Sandset PM** 2008 Differential impact of conventional and low-dose oral hormone therapy, tibolone and raloxifene on mammographic breast density, assessed by an automated quantitative method. BJOG 115: 773–779
28. **Chow CK, Venzon D, Jones EC, Premkumar A, O'Shaughnessy J, Zujewski J** 2000 Effect of tamoxifen on mammographic density. Cancer Epidemiol Biomarkers Prev 9:917–921
29. **Hofling M, Ma L, Sahlin L, Haglund C, Nordling S, von Schoultz B, Cline JM** 2009 Expression of the androgen receptor and syndecan-1

in breast tissue during different hormonal treatments in cynomolgus monkeys. Climacteric 12:72–79

30. **Boyd NF, Stone J, Martin LJ, Jong R, Fishell E, Yaffe M, Hammond G, Minkin S** 2002 The association of breast mitogens with mammographic densities. Br J Cancer 87:876–882
31. **Ursin G, Lillie EO, Lee E, Cockburn M, Schork NJ, Cozen W, Parisky YR, Hamilton AS, Astrahan MA, Mack T** 2009 The relative importance of genetics and environment on mammographic density. Cancer Epidemiol Biomarkers Prev 18:102–112
32. **Caire-Juvera G, Arendell LA, Maskarinec G, Thomson CA, Chen Z** 2008 Associations between mammographic density and body composition in Hispanic and non-Hispanic white women by menopause status. Menopause 15:319–325
33. **Habel LA, Capra AM, Oestreicher N, Greendale GA, Cauley JA, Bromberger J, Crandall CJ, Gold EB, Modugno F, Salane M, Quesenberry C, Sternfeld B** 2007 Mammographic density in a multiethnic cohort. Menopause 14:891–899
34. **Torres-Mejía G, De Stavola B, Allen DS, Pérez-Gavilán JJ, Ferreira JM, Fentiman IS, Dos Santos Silva I** 2005 Mammographic features and subsequent risk of breast cancer: a comparison of qualitative and quantitative evaluations in the Guernsey prospective studies. Cancer Epidemiol Biomarkers Prev 14:1052–1059