Review

Analysis of Data From Breast Diseases Treated With 5-Alpha Reductase Inhibitors for Benign Prostatic Hyperplasia

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Abstract

Objective: 5-alpha reductase inhibitors (5ARIs) decrease the androgen levels in vivo and are currently used for the treatment of benign prostatic hyperplasia (BPH) in men. However, these inhibitors can also increase the risk of gynecomastia, breast tenderness, and breast cancer. Hence, we did a systematic review and meta-analysis to evaluate the rate of breast-related diseases in men treated with 5ARIs. **Materials and Methods:** PubMed, Embase, Cochrane, and CNKI databases were searched for randomized controlled trials using 5ARIs in patients with BPH. Data were analyzed by using Cochrane Collaboration review manager program and Stata 12.0 software. **Results:** In total, 14 studies were included in the meta-analysis. Gynecomastia was significantly more common with 5ARIs treatment when compared with placebo (3.30% vs. 1.84%; $P < .00001$) or alpha blockers (ABs) monotherapy (2.33% vs. 1.00%; $P = .0009$). Both dutasteride (2.03% vs. 0.90%; $P < .00001$) and finasteride (4.08% vs. 2.43%; $P < .00001$) are associated with significantly higher risk of gynecomastia than placebo. Risk for breast tenderness was elevated in 5ARIs users (0.83% vs. 0.25%; $P = .01$) or in users having combination therapy with ABs (2.48% vs. 0.58%; $P < .0001$). Finasteride is associated with significantly higher risk of breast tenderness than placebo (0.80% vs. 0.25%; $P = .02$). **Conclusion:** In male patients with BPH, 5ARIs have significantly increased the risk of gynecomastia and breast tenderness but may be not to the breast cancer. In addition, combination therapy is significantly associated with higher risk of breast tenderness compared to single ABs monotherapy.

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Introduction

Five pharmacologic classes of drugs (alone or in combination) are available for treating lower urinary tract symptoms/benign prostatic hyperplasia (LUTS/BPH), including alpha blockers (ABs), 5-alpha reductase inhibitors (5ARIs), antimuscarinics, β3-adrenoceptor agonists, and phosphodiesterase type 5 inhibitors (Figure 1).[1-3] Medical treatment is mainly based on the use of 5ARIs (finasteride, 1 or 5 mg and dutasteride, 0.5 mg) and ABs.[4] 5ARIs are also used to treat androgenic alopecia.[5] However, use of these medications has often been associated with further worsening of sexual functions and breast problems. Both of these diseases are related to the hormone disruption caused by 5ARIs.

By inhibiting the activity of 5-alpha reductase and blocking the conversion of testosterone to dihydro-testosterone (the more potent androgen), 5ARIs reduce the overall "androgenicity" in the tissues. Thus, it appears to increase the risk of sexual dysfunction, including ejaculatory dysfunction (odds ratio [OR], 2.73; $P < .0001$), hypoactive sexual desire (OR, 1.54; $P < .0001$), and erectile dysfunction (OR, 1.47; $P < .0001$).[6,7] There is also mounting evidence to suggest that certain individuals may be more sensitive to the fertility effects of 5-alpha reductase inhibition and the use of finasteride leads to infertility in few men, including decrease in ejaculation volume and sperm counts.[8,9] In addition, cases were reported and clinical trials have shown that 5ARIs (finasteride and dutasteride) treatment of BPH may be associated with male breast issues, which included gynecomastia, breast tenderness, and breast cancer.[10,11] In an observational cohort of 14,772 male patients who used finasteride treatment for BPH, after follow-up

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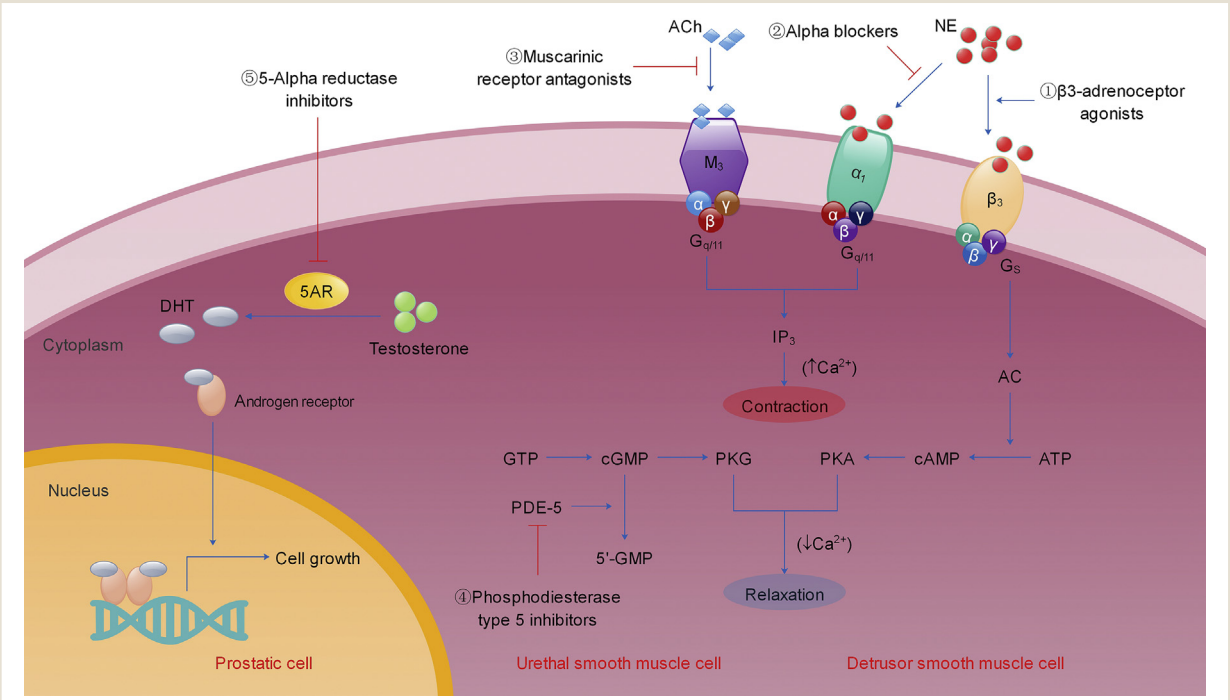
Figure 1 Schematic Diagram Depicting Mode of Action of 5 Drugs Currently Used for Lower Urinary Tract Symptoms/Benign Prostatic Hyperplasia



Abbreviations: AC = adenylate cyclase; Ach = acetylcholine; 5AR = 5-alpha reductase; ATP = adenosine triphosphate; cAMP = cyclic adenosine monophosphate; cGMP = cyclic guanosine monophosphate; DHT = dihydrotestosterone; 5'-GMP = 5'-guanosine monophosphate; GTP = guanosine triphosphate; IP_3 = inositol 1,4,5-triphosphate; NE = norepinephrine; PDE-5 = phosphodiesterase type-5; PKA = protein kinase A; PKG = protein kinase G.

of the original reports, there were 46 cases of gynecomastia, 10 cases of breast disorder, and 2 cases of mastalgia.[12] 5ARIs caused breast problems not only in BPH but also in androgenetic alopecia. In a randomized, active, and placebo-controlled treatment study of male androgenetic alopecia, each treatment group (finasteride 1 mg/day dose and dutasteride 0.5 mg/day and 0.1 mg/day dose groups) has 1 patient who developed breast enlargement, whereas in dutasteride 0.1 mg/day and 0.02 mg/day dose groups, each group also has 1 patient who developed breast tenderness.[13] Although most cases described have a regimen of 5 mg/day of oral finasteride, Ferrando et al reported 4 patients who developed gynecomastia with 1 mg/day dose.[14] A recent registry-based cohort study shows an increased risk of breast cancer among finasteride users (Incidence rate ratio, 1.44; 95% confidence interval [CI], 1.11-1.88) compared with non-users.[15] Owing to demasculinization induced in the treatment of male BPH by finasteride and dutasteride, new drugs such as episteride (a kind of 5-alpha reductase selective inhibitor) seem to effectively solve this problem. However, further research and observation are still needed owing to a lack of clinical trials.[16,17]

To date, except for a big case-control analysis in the United Kingdom, no major observational studies and systematic evaluation of real-world data associating the use of 5ARIs with male breast disease have been performed.[18] In addition, more and more clinical trials reported the use of 5ARIs to treat BPH or androgenetic alopecia, which might cause male breast disease. Thus, a systematic evaluation of real-world data is an invaluable tool to assess this important association. We have collected all the randomized controlled trials (RCTs) that reported breast disease, to conduct a meta-analysis and examine a proposed association between the use of 5ARIs and the risk of breast disease, as well as during alpha blocker(s) treatment of BPH. The aim of our study is to provide a systematic review and meta-analysis of the available randomized clinical trials, which report the impact of medical treatments for LUTS owing to BPH on gynecomastia, breast tenderness, and breast cancer.

Materials and Methods

Systematic Literature Search

An extensive Pubmed, Embase, Cochrane and CNKI database search was performed using the following words ("dutasteride" [MeSH Terms] OR "dutasteride" [All Fields]) OR ("finasteride" [MeSH Terms] OR "finasteride" [All Fields]) OR ("episteride" [MeSH Terms] OR "episteride" [All Fields]) AND ("prostatic hyperplasia" [MeSH Terms] OR ("prostatic" [All Fields] AND "hyperplasia" [All Fields]) OR "prostatic hyperplasia" [All Fields] OR ("benign" [All Fields] AND "prostatic" [All Fields] AND "hyperplasia" [All Fields]) OR "benign prostatic hyperplasia" [All Fields]). The search was done with the available data from January 1, 1969 to November 1, 2018 and was restricted to placebo-controlled RCTs and humans.

Selection of Studies

Three reviewers (Q.F., P.C., and N.D.) have independently screened the title, abstract, and keywords of each article retrieved.

Full-text papers were screened for further assessment if the information given suggested that the study met the inclusion but not the exclusion criteria. Identification of relevant studies was performed independently by 2 of the authors (Q.F., P.C.) and conflicts were resolved by the third investigator (N.D.). Randomized controlled trials were required to meet the following inclusion criteria: (1) any studies on the treatment of LUTS or BPH with 5-alpha reductase inhibitors; (2) they were RCTs, with at least 3 months duration; (3) the overall occurrence of breast disease has been detailed; and (4) the full text of the study could be accessed. If the mentioned inclusion criteria were not met, the studies were excluded from the analysis.

Bias Assessment

The methodological quality of included studies was appraised with the Cochrane Collaboration bias appraisal tool. In particular, the following factors were evaluated: (1) Adequate sequence generation; (2) Allocation concealment; (3) Blinding of participants and personnel; (4) Blinding of outcome assessment; (5) Incomplete outcome data addressed; (6) Free of selective reporting; and (7) Free of other bias. Each question was answered with "low risk", "high risk," or "unclear," and 3 reviewers (Q.F., P.C., and N.D.) have assessed the validity of each trial independently. Where differences in opinion existed, they were resolved through open discussions.

Statistical Analysis

Meta-analysis was conducted using Cochrane Collaboration review manager software (RevMan [Computer program] Version 5.3.3 Copenhagen: the Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Heterogeneity among studies was assessed using the Q test and the I^2 index statistic. If $P > .1$ and $I^2 < 50\%$, the variation between studies was considered to be homogeneous, then the fixed effect model was adopted. If $P < .1$ and $I^2 > 50\%$, there was significant heterogeneity between studies, and the random effects model was used. Summary effect was calculated as relative risk (RR) for rate variable, together with their 95% confidence intervals (CIs). The publication bias of meta-analysis was performed by using Stata 12.0 software (StataCorp, College Station, TX). The Begg and Egger methods were used to assess publication bias. Funnel plots were drawn. If publication bias was indicated, we further evaluated the number of missing studies in a meta-analysis by the application of the trim and fill method and recalculated the pooled risks estimate with the addition of those missing studies.[19] Publication bias was considered insignificant when the P value was more than .05.

Results

Study Characteristics

The systematic review flow chart is summarized in Figure 2. Pubmed, Embase, Cochrane, and CNKI database searches retrieved 465, 383, 390, and 196 records, respectively. All the records were screened, and 1434 papers were excluded because they were not relevant for the purpose of the present study. The remaining 128 papers were evaluated in full-text form. We have also excluded studies without RCTs (n = 2) as well as review papers (n = 2), retrospective studies (n = 2), duplicate publications (n = 10), and open-label extension studies (n = 3) having no data on breast disease (n = 95). Finally, we obtained 14 RCTs involving more than 50,000 patients. No further RCTs were published during the preparation of this manuscript. The publication dates ranged from 1996 to 2018. Table 1 summarizes the RCTs included in the present review. An independent author has judged each risk of bias item for all the included studies (Table 2).

Risk of Bias

As described in Table 2, most of the included studies did not describe their methods of randomization. Thus, it had unclear bias risk for the assessment of adequate sequence generation. One study[22] stratified participants according to their center practice. Only one study[33] showed a method of allocation concealment, whereas others did not describe their approach. One study[30] was designed as an open label trial. The risk of bias from incomplete outcome data was assessed and found to be low (14 studies). We gave positive judgment for all the included studies in the assessment of other biases, as we could not detect any risks.

Risk of Gynecomastia, Breast Tenderness, and Breast Cancer (5ARIS Versus Placebo)

There were 7 RCTs of 5ARIs involving 37,851 patients with BPH who had a cumulative effect on mammary gland hyperplasia after 6 months. Heterogeneity test values obtained using fixed-effect model analysis are as follows: $P = .21$; $I^2 = 28\%$. Meta-analysis results: 3.30% versus 1.84%; RR, 1.79; $P < .00001$. The results show that the incidence of gynecomastia was significantly higher in the 5ARIs than placebo (Figure 3A). The sub-group analysis shows that the incidence of gynecomastia in dutasteride and finasteride was significantly higher than that in the placebo group (dutasteride compared with placebo [2.03% vs. 0.90%; RR, 2.25; $P < .00001$] and finasteride compared with placebo [4.08% vs. 2.43%; RR, 1.69; $P < .00001$]).

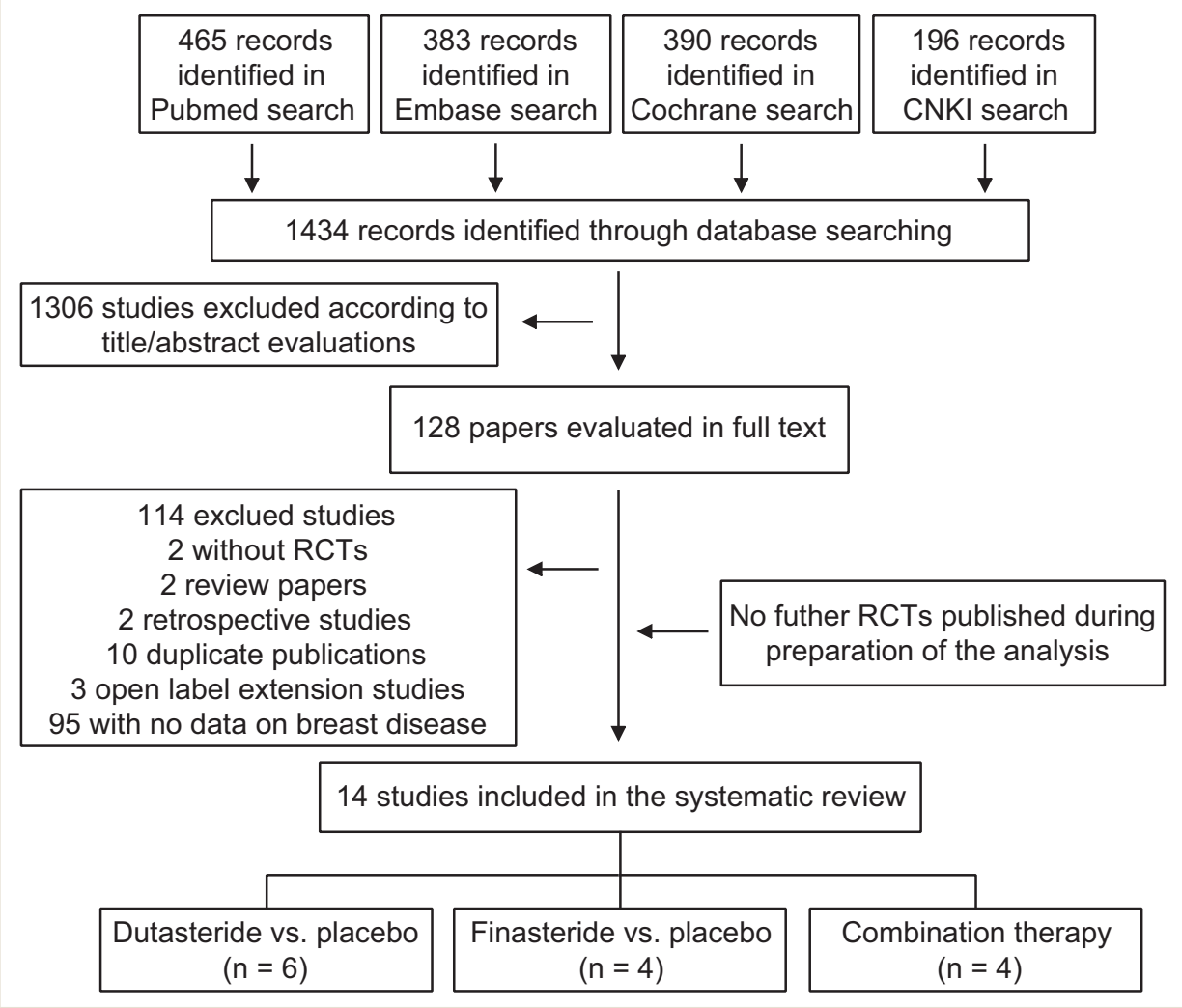
There were 4 RCTs of 5ARIs involving 4798 patients with BPH, which had a cumulative effect on breast tenderness after 3 months. Heterogeneity test values obtained using fixed-effect model analysis are as follows: $P = 1.00$, $I^2 = 0\%$; Meta-analysis results, 0.83% versus 0.25%; RR, 2.85; $P = .01$. These results show that the incidence of breast tenderness is significantly higher in the patients who had 5ARIs than those with placebo (Figure 3B). The subgroup analysis shows that the incidence of breast tenderness in the finasteride treatment group was significantly higher than the placebo group (0.80% vs. 0.25%; RR, 2.85; $P = .02$).

Two studies including 23,425 patients (11,715 in the finasteride group and 11,710 in the placebo group) were included in the analysis. Heterogeneity test values obtained using fixed-effect model analysis are as follows: $P = .26$; $I^2 = 25\%$. According to the analysis, no difference between finasteride treatment and placebo to the risk of breast cancer was found (0.034% vs. 0.026%; RR, 1.23; $P = .76$) (Figure 3C).

Risk of Gynecomastia and Combination (5ARIs Plus ABs) Therapy

Three studies including 4587 patients (2314 in the combination group and 2273 in the ABs group) were included in the analysis. Heterogeneity was not found among the trials that evaluated gynecomastia ($P = .87$; $I^2 = 0\%$). According to the analysis, no difference between the combination therapy and the treatment with ABs to the

Figure 2 PRISMA Flow Diagram



Abbreviations: PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT = Randomized controlled trial.

risk of gynecomastia was identified (1.64% vs. 0.97%; RR, 1.68; $P = .05$) (Figure 4A).

Four studies including 4681 patients (2344 in the combination group and 2337 in the 5ARIs group) were included in the analysis. Heterogeneity was not found among the trials that evaluated gynecomastia ($P = .80$; $I^2 = 0\%$). According to the analysis, no difference between the combination therapy and the treatment of 5ARIs to the risk of gynecomastia was found (1.62% vs. 2.23%; RR, 0.73; $P = .14$) (Figure 4B).

Three studies including 4422 patients (2231 in the 5ARIs group and 2191 in the ABs group) were included in the analysis. Heterogeneity was not found among the trials that evaluated gynecomastia ($P = .96$; $I^2 = 0\%$). According to the analysis, the 5ARIs therapy was found to be associated with an increased risk of gynecomastia compared with monotherapy with ABs (2.33% vs. 1.00%; RR, 2.29; $P = .0009$) (Figure 4C).

Risk of Breast Tenderness and Combination (5ARIs Plus ABs) Therapy

Three studies including 3787 patients (1897 in the combination group and 1890 in the ABs group) were included in the analysis. Heterogeneity was not found among the trials that evaluated breast tenderness ($P = .58$; $I^2 = 0\%$). According to the analysis, the overall prevalence of breast tenderness is significantly higher in the combination treatment group than the ABs group (2.48% vs. 0.58%; RR, 3.97; $P < .0001$) (Figure 5A).

Two studies including 3067 patients (1528 in the combination group and 1539 in the 5ARIs group) were included in the analysis. Heterogeneity was not found among the trials that evaluated breast tenderness ($P = .38$; $I^2 = 0\%$). According to the analysis, no difference between the combination therapy and the treatment of 5ARIs to the risk of breast tenderness was observed (2.62% vs. 1.95%; RR, 1.34; $P = .22$) (Figure 5B).

Table 1 Characteristics of the Studies Included in the Meta-analysis

Reference	Group	n	Gyn	BTe	BCa	Age, y	Duration, mos	TPV, cm^3	tPSA, ng/mL	Baseline IPSS	Baseline Qmax, mL/s
Dutasteride vs. placebo											
Toren et al, 2013[20]	D	792	19	N	N	62.65 ± 6.68	48	53.19 ± 12.18	5.97 ± 2.23	4.35 ± 2.23	13.56 ± 5.64
	P	825	6	N	N	63.65 ± 6.68	48	52.50 ± 11.21	6.04 ± 2.15	4.35 ± 2.23	13.60 ± 6.16
Na et al, 2012[21]	D	126	1	N	N	65.83 ± 7.71	6	48.19 ± 27.70	3.33 ± 1.89	18.01 ± 5.32	11.43 ± 4.83
	P	127	0	N	N	66.88 ± 8.16	6	42.29 ± 16.52	3.14 ± 1.87	18.61 ± 5.48	12.01 ± 5.43
Andriole et al, 2010[22]	D	4105	76	N	N	62.80 ± 6.04	48	45.70 ± 18.20	5.90 ± 1.97	8.70 ± 5.70	N
	P	4126	43	N	N	62.70 ± 6.08	48	45.70 ± 18.78	5.90 ± 2.00	8.60 ± 5.62	N
Bepple et al, 2009[23]	D	29	N	1	N	66.00 ± 8.00	3	55.00 ± 24.00	1.70 ± 1.50	23.00 ± 5.00	10.00 ± 3.00
	P	27	N	0	N	66.00 ± 8.00	3	64.00 ± 30.00	3.50 ± 2.60	24.00 ± 6.00	10.00 ± 3.00
Roehrborn et al, 2002[24]	D	2167	50	N	N	66.50 ± 7.60	24	54.90 ± 23.90	4.00 ± 2.10	17.00 ± 6.00	10.10 ± 3.50
	P	2158	16	N	N	66.10 ± 7.40	24	54.00 ± 21.90	4.00 ± 2.10	17.10 ± 6.10	10.40 ± 3.60
Finasteride vs. placebo											
Lowe et al, 2003[25]	F'	552	N	2	N	64	12	47.90 ± 2.48	N	13.40 ± 5.60	11.00 ± 0.28
	F	547	N	1	N	64	12	50.20 ± 2.14	N	12.80 ± 0.39	11.20 ± 0.30
	P	558	N	0	N	64	12	47.60 ± 2.11	N	13.10 ± 0.39	11.40 ± 0.31
Thompson et al, 2003[26]	F	9423	426	N	1	≥ 55.00	84	N	< 3.00	N	N
	P	9457	261	N	1	≥ 55.00	84	N	< 3.00	N	N
McConnell et al, 2003[27]	F	768	17	N	3	62.60 ± 7.30	54	36.90 ± 20.60	2.40 ± 2.10	17.60 ± 5.90	10.50 ± 2.50
	P	737	5	N	0	62.50 ± 7.50	54	35.20 ± 18.80	2.30 ± 2.00	16.80 ± 5.90	10.50 ± 2.60
McConnell et al, 1998[28]	F	1524	35	17	0	64.00 ± 6.00	48	54.00 ± 25.00	2.80 ± 2.10	15.00 ± 6.00	11.00 ± 4.00
	P	1516	18	6	2	64.00 ± 7.00	48	55.00 ± 26.00	2.80 ± 2.10	15.00 ± 6.00	11.00 ± 4.00
Gormley et al, 1992[29]	F'	298	N	2	N	64.00 ± 7.00	12	60.90 ± 34.30	3.80 ± 7.20	10.60 ± 5.70[a]	9.20 ± 3.40
	F	297	N	1	N	64.00 ± 6.67	12	58.60 ± 30.50	3.60 ± 4.20	10.20 ± 5.50[a]	9.60 ± 3.70
	P	300	N	0	N	64.00 ± 6.17	12	61.00 ± 36.50	4.10 ± 4.80	9.80 ± 5.30[a]	9.60 ± 3.50

Table 1 Continued

Reference	Group	n	Gyn	BTe	BCa	Age, y	Duration, mos	TPV, cm^3	tPSA, ng/mL	Baseline IPSS	Baseline Qmax, mL/s
Combination therapy											
Roehrborn et al, 2015[30]	C	369	N	7	N	66.30 ± 7.78	24	51.00 ± 18.17	3.90 ± 2.00	13.20 ± 4.06	N
	T	373	N	0	N	66.20 ± 7.34	24	52.60 ± 19.57	3.70 ± 1.91	12.90 ± 3.95	N
Chung et al, 2012[31]	C	1421	25	38	N	66.10 ± 7.00	48	55.60 ± 23.94	4.00 ± 2.05	16.40 ± 6.19	10.90 ± 3.56
	D	1433	34	30	N	66.10 ± 7.02	48	55.00 ± 23.12	3.90 ± 2.07	16.20 ± 5.93	10.70 ± 3.53
	T	1405	14	11	N	66.20 ± 6.93	48	56.50 ± 24.54	4.10 ± 2.09	16.30 ± 6.03	10.70 ± 3.64
Jing et al, 2010[32]	C'	30	0	N	N	N	12	50.00 ± 12.00	N	22.50 ± 4.90	11.00 ± 2.00
	F	30	1	N	N	N	12	51.00 ± 14.00	N	22.80 ± 5.40	11.00 ± 3.00
	T	30	0	N	N	N	12	51.00 ± 13.00	N	21.90 ± 5.30	12.00 ± 3.00
Chung et al, 2009[33]	C	107	1	2	N	66.60 ± 7.64	48	47.70 ± 18.71	4.00 ± 2.12	17.70 ± 7.21	11.20 ± 4.15
	D	106	0	0	N	66.00 ± 6.20	48	48.80 ± 16.91	4.30 ± 2.15	17.80 ± 6.60	9.80 ± 3.88
	T	112	0	0	N	67.50 ± 7.33	48	48.10 ± 20.53	4.00 ± 2.12	17.80 ± 6.53	10.60 ± 4.05
McConnell et al, 2003[27]	C''	786	12	N	1	62.70 ± 7.10	54	36.40 ± 19.20	2.30 ± 1.90	16.80 ± 5.80	10.60 ± 2.50
	F	768	17	N	3	62.60 ± 7.30	54	36.90 ± 20.60	2.40 ± 2.10	17.60 ± 5.90	10.50 ± 2.50
	D'	756	8	N	0	62.70 ± 7.20	54	36.90 ± 21.60	2.40 ± 2.10	17.00 ± 5.80	10.30 ± 2.50

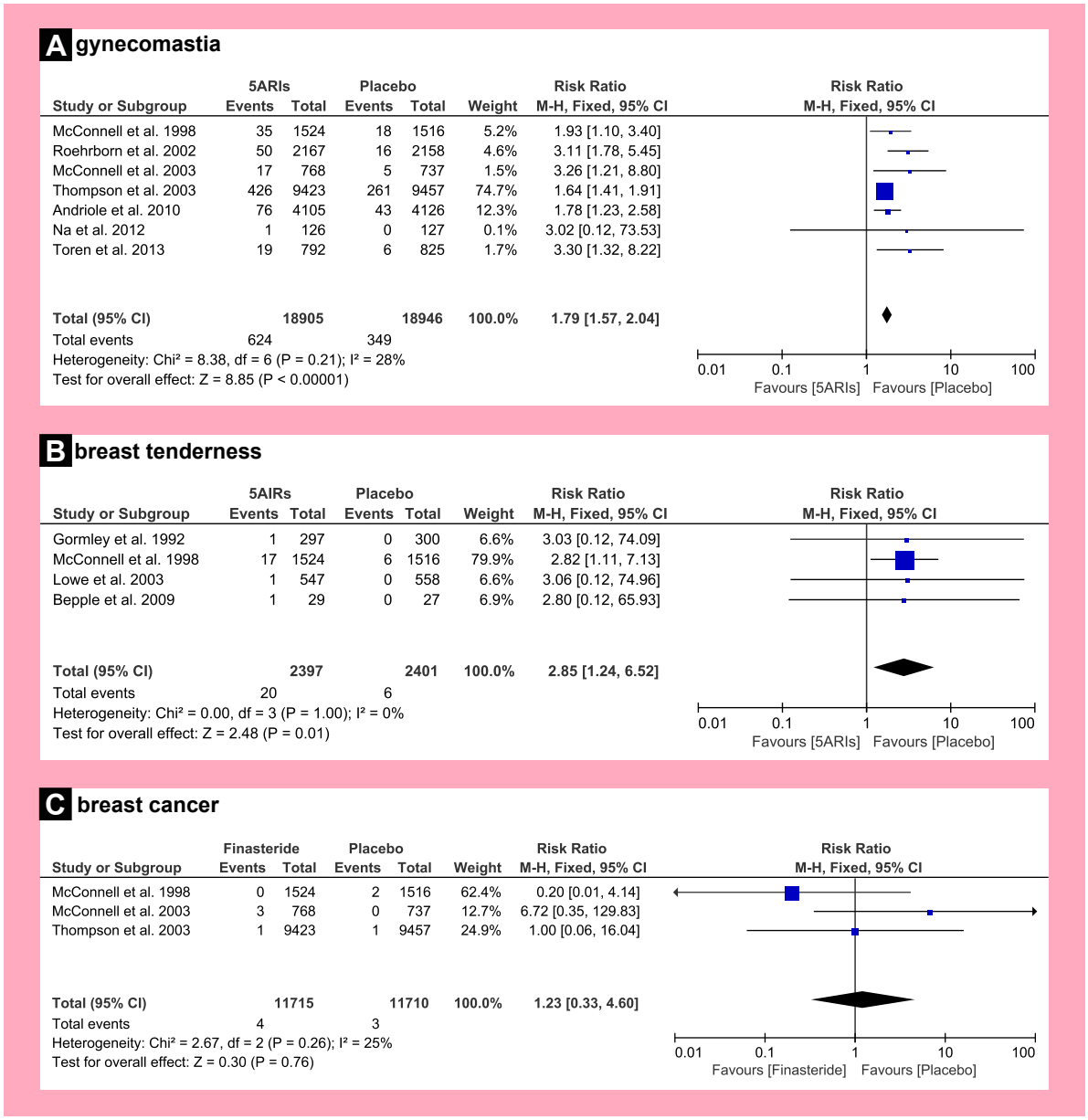
Abbreviations: BCa = breast cancer; BTe = breast tenderness; C = dutasteride 0.5 mg qd plus tamsulosin 0.4 mg qd; C' = finasteride 5 mg qd plus tamsulosin 0.4 mg qd; C'' = finasteride 5 mg qd plus doxazosin 4 mg qd; D = dutasteride 0.5 mg qd; D' = doxazosin 4 mg qd; Gyn = gynecomastia; F = finasteride 5 mg qd; F' = finasteride 1 mg qd; IPSS = International Prostate Symptom Score; N = not reported; P = placebo; qd = daily; Qmax = maximum urinary flow rate; T = tamsulosin 0.4 mg qd; tPSA = total prostate specific antigen; TPV = total prostate volume.
[a]Boyarsky symptom score.

Table 2 Risk of Bias Summary

Study Identification	Adequate Sequence Generation?	Allocation Concealment?	Blinding of Participants and Personnel?	Blinding of Outcome Assessment?	Incomplete Outcome Data Addressed?	Free of Selective Reporting?	Free of Other Bias?
Toren et al, 2013	U	U	L	U	L	L	L
Na et al, 2012	U	U	L	L	L	L	L
Andriole et al, 2010	H	U	L	L	L	L	L
Bepple et al, 2009	U	U	L	L	L	L	L
Roehrborn et al, 2002	U	U	L	L	L	L	L
Lowe et al, 2003	U	U	L	L	L	L	L
Thompson et al, 2003	U	U	U	U	L	L	L
McConnell et al, 2003	U	U	L	L	L	L	L
McConnell et al, 1998	U	U	L	L	L	L	L
Gormley et al, 1992	U	U	L	L	L	L	L
Roehrborn et al, 2015	U	U	H	U	L	L	L
Chung et al, 2012	U	U	L	L	L	L	L
Jing et al, 2010	U	U	U	U	L	L	L
Chung et al, 2009	L	L	L	L	L	L	L

Abbreviations: H = high risk; L = low risk; U = unclear.

Figure 3 Forest Plot Comparing Gynecomastia, Breast Tenderness, and Breast Cancer in Randomized Controlled Trials Evaluating 5ARIs Versus Placebo. A, Gynecomastia Analysis. B, Breast Tenderness Analysis. C, Breast Cancer Analysis

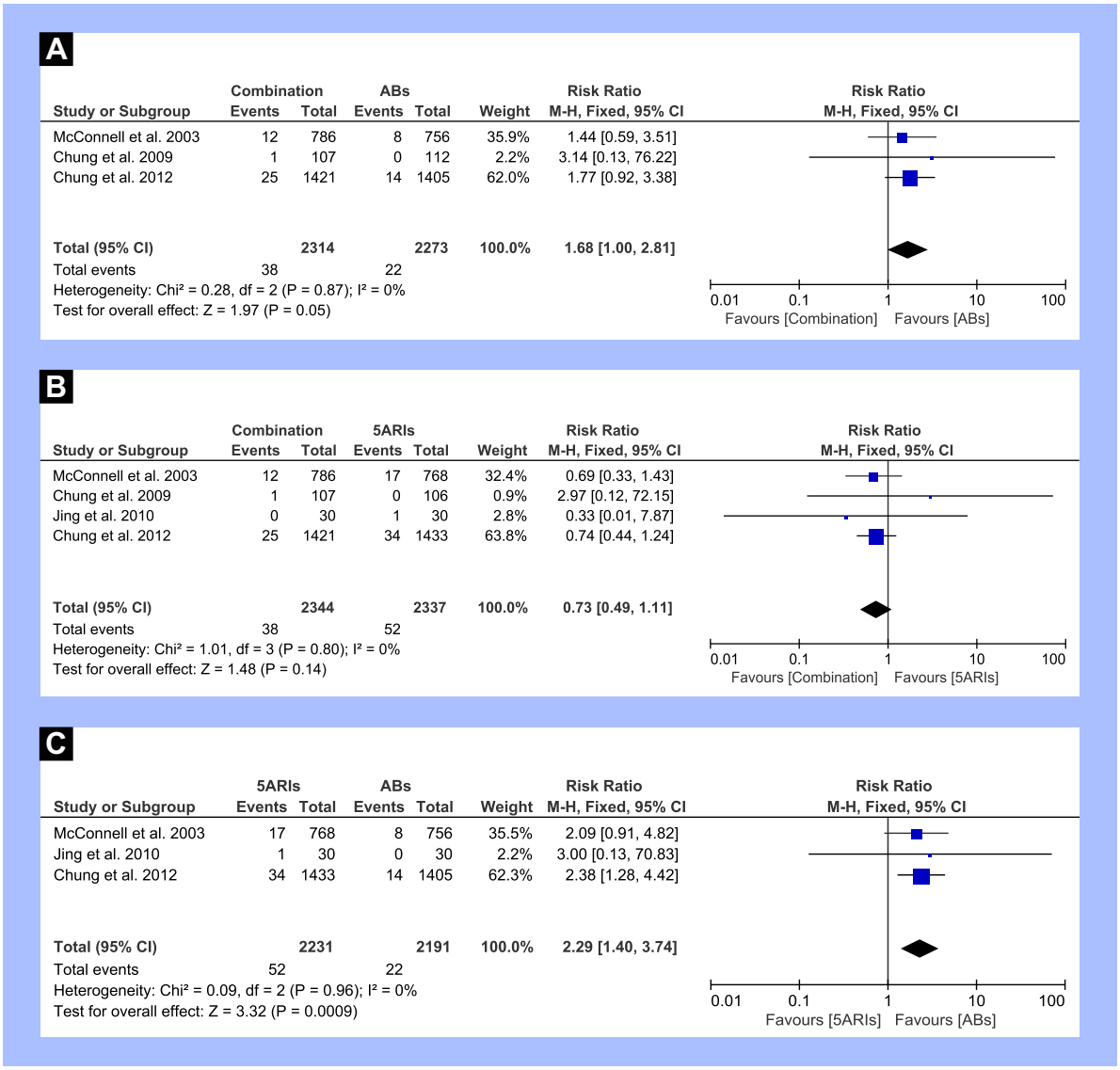


Two studies including 1694 patients (850 in the finasteride group and 844 in the placebo group) were included in the analysis. Heterogeneity was not found among the trials that evaluated breast tenderness ($P = 1.00$; $I^2 = 0\%$). According to the analysis, no difference with finasteride treatment (1 mg and 5 mg groups) to the risk of breast tenderness was found (0.47% vs. 0.24%; RR, 1.99; $P = .43$).

Publication Bias

As shown in figure 6A, the Begg rank correlation test indicated no publication bias ($P = .368$) in our analysis of the data presented in Figure 3A, but the Egger linear regression test indicated possible publication bias for the association ($P = .028$). We used the trim and fill method to recalculate our pooled risk estimate. In the fixed effect model, the point estimation of logrr and 95% CI estimation for the combined effect quantity were 0.573 (0.444-0.703) before the trim and 0.514 (0.390-0.638) after the trim. In the random effects model, the point estimation of logrr and 95% CI estimation for the combined effect quantity were 0.681 (0.459-0.903) before the trim and 0.536 (0.285-0.787) after the trim. The 95% CI before and after the trim was statistically significant, indicating that the results are stable. By adding 4 points, the effect of publication

Figure 4 Forest Plot Comparing Gynecomastia in Randomized Controlled Trials Evaluating Combination Therapy (5ARIs Plus ABs). A, Combination Therapy Versus ABs Analysis. B, Combination Therapy Versus 5ARIs Analysis. C, 5ARIs Versus ABs Analysis



Abbreviations: ABs = alpha blockers; 5ARIs = 5-alpha reductase inhibitors; CI = confidence interval.

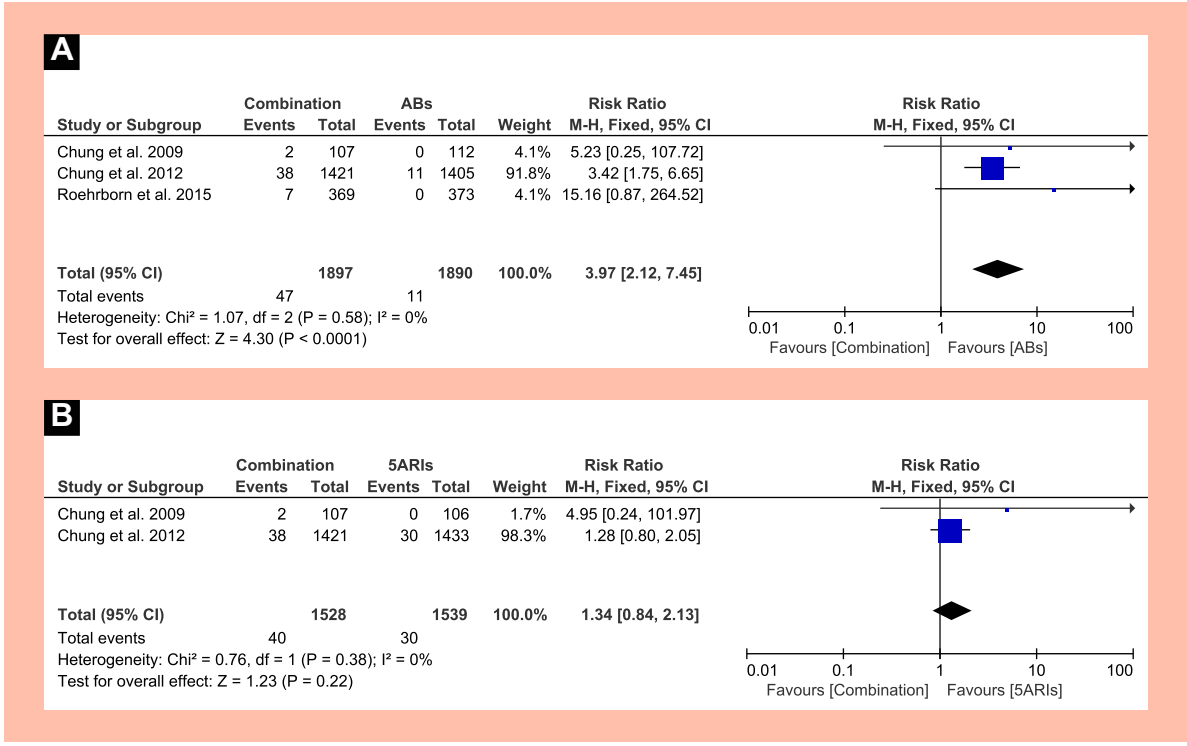
bias was eliminated (Figure 6B). In addition, publication bias was not found in other study data (data not shown).

Discussion

We observed 2-fold greater elevation in the risk of gynecomastia for users of 5ARIs alone than the placebo control groups. Sub-group analysis shows that both dutasteride and finasteride increased the risk of gynecomastia. Dutasteride, a more competitive inhibitor of type II or I 5-alpha reductase, is more potent in inhibiting serum testosterone and thus more likely to cause gynecomastia in men than finasteride (Figure 7). Furthermore, in the combined treatment study, taking 5ARIs alone or combined with ABs was also more likely to cause gynecomastia than ABs alone, but no difference between the combination therapy and the treatment with ABs to the risk of gynecomastia was found; it may be because of the lack of included literature. Moreover, the incidence of male gynecomastia was higher in the 5ARIs versus ABs than the 5ARIs versus placebo studies. However, whether this is owing to the difference in the total number of patients involved or possible reduction in the incidence of gynecomastia by ABs is not yet clear. Hence, more research is needed to reassess this possibility in the future.

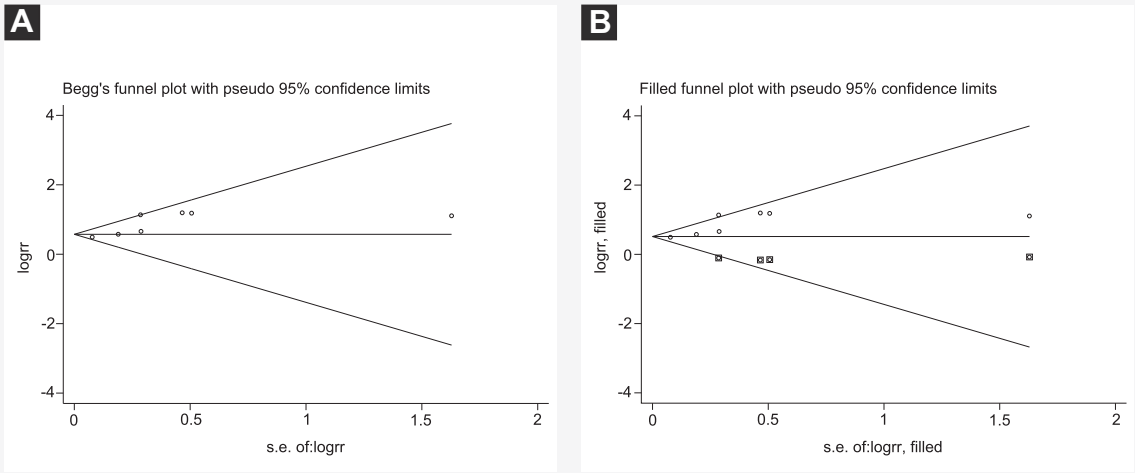
Similar to the results of our study, prior studies have reported an increase in the risk of gynecomastia with the use of 5ARIs (RR, 1.6-3.1).[22,24,26] A retrospective study of 3837 heterosexual male patients, in which physical examination was done, found the prevalence of gynecomastia has increased 3 times more in the patients treated with 5ARIs

Figure 5 Forest Plot Comparing Breast Tenderness in Randomized Controlled Trials Evaluating Combination Therapy (5ARIs Plus ABs). A, Combination Therapy Versus ABs Analysis. B, Combination Therapy Versus 5ARIs Analysis



Abbreviations: ABs = alpha blockers; 5ARIs = 5-alpha reductase inhibitors; CI = confidence interval.

Figure 6 Publication Bias Plot of Studies that Reported Correlation Between 5-Alpha Reductase Inhibitors and Placebo in Patients with Gynecomastia. A, Begg's Test Analysis. B, Trim and Fill Test Analysis



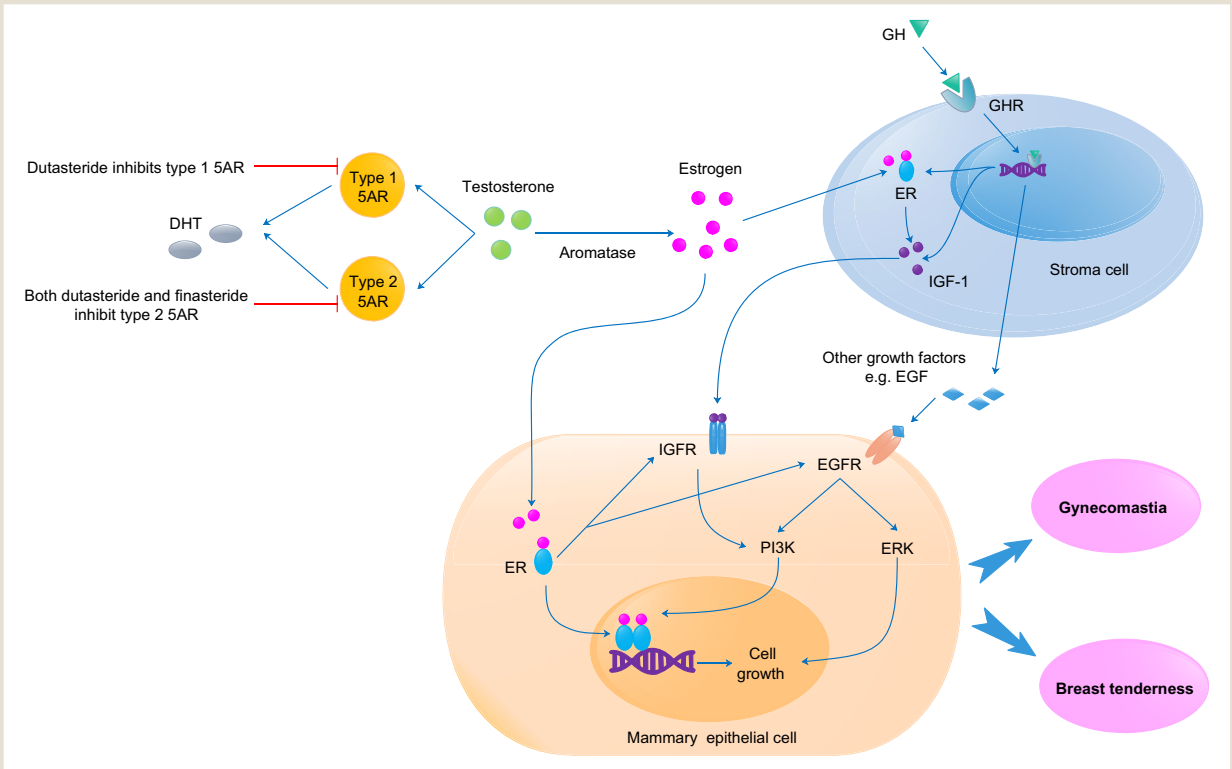
Abbreviation: s.e. = standard error.

compared with the rest of the samples (9.8% vs. 3.6%; $P = .036$).[34] In a large, United Kingdom population-based electronic medical record database, the risk of gynecomastia was 3 times higher in men who received 5ARIs treatment. Similarly, the risk for gynecomastia was elevated with the 5ARIs users (alone or in combination with ABs) in both the cohorts (incidence rate ratio, 3.55; 95% CI, 3.05-4.14) and case-control analyses (OR, 3.31; 95% CI, 2.66-4.10), whereas the risk was negligible for users of ABs only.[18] Intriguingly, another retrospective analysis reported that dutasteride resulted in significantly more breast complications than finasteride. The incidence of self-reported breast tenderness and/or enlargement was significantly ($P < .01$) greater in the dutasteride group (3.5%) compared with the finasteride group (1.2%).[10] However, the EPICS (Enlarged Prostate International Comparator Study) trial, a multicenter, randomized, double blind, double-dummy, 12-month parallel group study at 138 centers, reported gynecomastia occurrence of 2% in both in the finasteride- and dutasteride-treated patients.[35] Hence, more research is required to distinguish the differences between finasteride and dutasteride in promoting male gynecomastia.

Taking 5ARIs alone increased the risk of breast tenderness, in particular within the finasteride treatment group. However, the risk of breast tenderness with the use of dutasteride is unclear because of the lack of quality in the clinical research done. In combination therapy, 5ARIs combined with ABs are more likely to cause breast tenderness than ABs alone, but no differences were observed between the combination therapy and the treatment of 5ARIs to the risk of breast tenderness in our study. Our analysis shows that breast tenderness is mainly caused by the treatment with 5ARIs. However, RCTs using the combination therapy (5ARIs and ABs) are still lacking, and more clinical studies with a large cohort of patients are needed to clarify this issue.

Gynecomastia is often accompanied by symptoms of breast tenderness, and hence, finding breast tenderness in 5ARIs users is not an unexpected finding. In addition, it might be related to the increased aromatization of testosterone (T), owing to an increase in substrate availability. Subjects treated with 5ARIs show a higher level of total T and calculated free T compared with the rest of the samples.[34] 5ARIs, which inhibit the conversion of T to dihydrotestosterone (DHT), favors the conversion of more T to estrogen under the action of aromatase, and hence leads to the sex hormone imbalance in the body, causing gynecomastia and breast tenderness in men (Figure 6).[36] However, not enough attention is given to the adverse effects of breast enlargement and tenderness in men, and few clinical studies have reported about it. Moreover, clinical trials done so far evaluating the safety of 5ARIs and combination therapy are very recent; hence, it is difficult to detect the side effects of these treatments

Figure 7 Cross-talk Pathways that May Be Active in 5ARIs Treatment Connected to Gynecomastia and Breast Tenderness Development



Abbreviations: 5AR = 5-Alpha reductase; 5ARIs = 5-alpha reductase inhibitors; DHT = dihydrotestosterone; EGF = epidermal growth factor; EGFR = epidermal growth factor receptor; ER = estrogen receptor; ERK = extracellular signal-regulated protein kinase; GH = growth hormone; GHR = growth hormone receptor; IGF-1 = insulin-like growth factor 1; IGFR = insulin-like growth factor receptor; PI3K = phosphatidylinositol 3-kinase.

for long-term use. More importantly, gynecomastia and the breast tenderness are likely precursors for the occurrence of breast cancer in men. Thus, more attention is required to observe the occurrence and progress of these 2 diseases when using 5ARIs for the treatment in men.

Increased numbers of breast cancer cases caused by taking 5ARIs were reported by the Medical Therapy of Prostate Symptoms (MTOPS), Prostate Cancer Prevention Trial (PCPT), and Proscar Long-Term Efficacy and Safety Study (PLESS) trials, and most of the RCT studies are mainly related to finasteride. The discrepancy between the number of breast cancer cases in 3 clinical trials of finasteride suggests that it might be owing to serendipity.[27] However, in the few clinical trials that reported breast cancer development, the incidence of breast cancer was $< 0.3\%$ in men taking 5ARIs.[37] Results of a case-control study from 2001 to 2009 indicated no increase in the risk of breast cancer associated with the use of 5ARIs (3 years or more: RR, 0.75; 95% CI, 0.27-2.10).[38] A cohort study in Sweden also reported no increase in the risk of breast cancer for 5ARIs or ABs users compared with unexposed patients (5ARIs: hazard ratio, 0.74; 95% CI, 0.27-2.03; ABs: hazard ratio, 1.47; 95% CI, 0.73-2.95).[39] More recently, the same group also suggested no increased risk of breast cancer among men using 5ARIs compared with unexposed men (OR, 1.52; 95% CI, 0.61-3.80).[18] Our results are similar to these previous studies. Even then, a causal relationship between long-term use of finasteride and male breast cancer is still unclear. More importantly, we only collected 2 qualified articles on breast cancer for meta-analysis, and only a total of 7 patients had breast cancer. These results did not currently support a strong conclusion of connecting finasteride treatment with an increased risk of breast cancer. Hence, we need more clinical studies to confirm the risk of developing breast cancer with finasteride.[39]

Using 5ARIs undoubtedly increases the risk of gynecomastia and breast tenderness; these are probably preclinical manifestations of breast cancer. A recent case-control study of 74 male cases with breast cancer suggests an increased cancer risk associated with alcohol consumption and gynecomastia.[40] This case study underscores a rare but real possibility of detecting breast cancer in men who have gynecomastia.[41] As mentioned earlier, the relationship between 5ARIs and breast cancer is far from clear, and, based on the existing evidence, finasteride cannot be confirmed to cause breast cancer. However, it cannot be completely ruled out either.[15]

The inhibitory effect of 5-alpha reductase on dutasteride is more obvious than that of finasteride. Moreover, dutasteride has a significantly higher risk of gynecomastia and breast tenderness than finasteride. However, no studies have been reported so far about the carcinogenic effects of dutasteride in breast cancer. Thus, further analysis and testing of this hypothesis is still needed.

Finally, just as for any meta-analysis, the possibility of publication bias is of a concern. In this study, the Egger linear regression test indicated that the *P* value is significant. No publication bias was found for the Begg rank correlation test. However, the Begg test will not give a robust result unless a minimum of 15 to 20 studies are included in a meta-analysis.[42] Thus, we only used the Egger test owing to fewer articles included in this study. Also, the application of the trim and fill method did not change the average effect size, which further suggests that results are not affected by publication bias.

Conclusions

Long-term routine dosage or continuous use of 5ARIs for the treatment of male BPH can increase the risk of gynecomastia and breast tenderness in patients undergoing such treatments. Dutasteride is more likely to cause gynecomastia than finasteride. Our results suggest that there is no increased risk of breast cancer among men using 5ARIs compared with unexposed men. However, owing to the small number of articles included in this study, we need more clinical studies to confirm the risk of developing breast cancer with 5ARIs in the future.

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Disclosure

The authors have stated that they have no conflicts of interest.

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