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Five-Alpha Reductase Inhibitor and Breast Cancer Risk in Men: A Systematic Review

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Dear Editor:

The 5-alpha reductase inhibitors (5ARIs), including finasteride and dutasteride, are commonly prescribed to treat benign prostatic hyperplasia (BPH), lower urinary tract symptoms (LUTS), and androgenetic alopecia (AGA). In addition to well-known adverse reactions of 5ARIs such as erectile dysfunction and decreased libido, previous randomized controlled trials (RCTs) in male subjects on the effect of 5ARI for BPH revealed a higher frequency of breast cancer in a finasteride 5 mg group than in a placebo group[1]. However, another large RCT demonstrated a contradictory result[2]; therefore, the relationship between 5ARIs and male breast cancer remains controversial. Therefore, we performed a literature search to acquire all the available evidence regarding the association between 5ARIs and breast cancer risk in men.

We searched PubMed, EMBASE, and The Cochrane Library databases on November 24th, 2015 using the following keywords: "finasteride," "dutasteride," "reductase inhibitor," "breast cancer," "breast carcinoma," "breast tumor," "breast malignancy" or "breast malignancies," and "breast neoplasm." No language restriction was applied, articles were selected by title and abstract, and the full texts were reviewed for eligibility (Fig. 1).

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. Case-con-

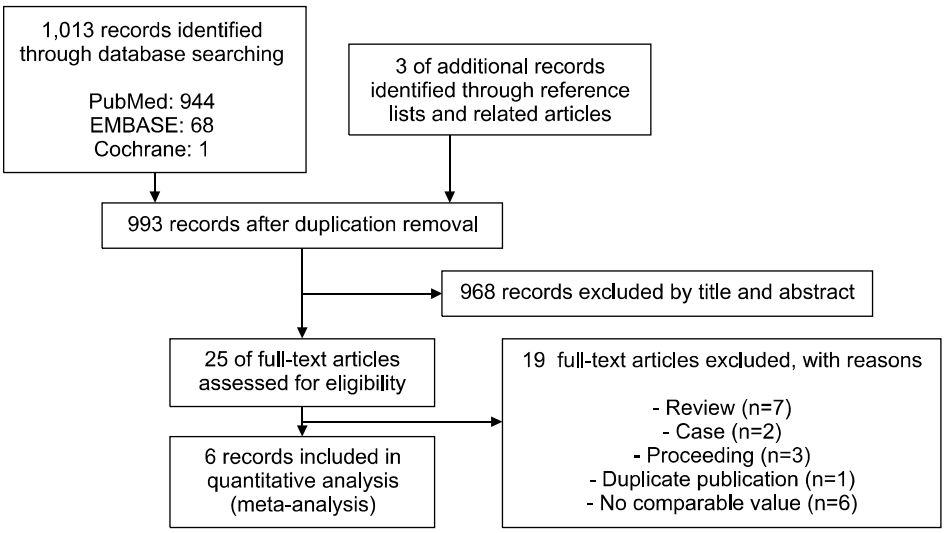

Fig. 1. Flow diagram of study selection (search date: November 24, 2015).

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Table 1. Study characteristics of 6 studies included in the meta-analysis

First author (year)	Study design	Country	Breast cancer patients (n)		Age (yr)	Follow up (yr)	Quality assessment	Study population	Risk of breast cancer (95% confidence interval)
			Exposed to 5ARI	Non-exposed					
McConnell et al.[2] (1998)	RCT	USA	0/1,524	2/1,516	64 (mean)	4	4	BPH patients with moderate to severe symptoms of urinary destruction	Crude RR=0.19 (0.01~4.14)
Thompson et al.[7] (2003)	RCT	USA	1/9,423	1/9,457	At least 55	7	5	Normal population with prophylactic use of 5ARI to prevent prostate cancer	Crude RR=1.00 (0.06~16.04)
McConnell et al.[1] (2003)	RCT	USA	4/1,554	0/1,493	62 (mean)	4.5	5	BPH patients with moderate to severe symptoms	Crude RR=8.64 (0.46~160.46)
Bird et al.[6] (2013)	Case-control	USA	8/339	331/6,780	60 (median)	At least 1	3	Prescription and medical coverage data in the United States IMS LifeLink™ Health Plan claims database	Adjusted rate ratio=0.70 (0.34~1.45) Adjusted to drug exposure, gynecomastia, Klinefelter syndrome, liver damage, obesity, estrogen, orchiectomy, radiation
Duijnhoven et al.[5] (2014)	Case-control	United Kingdom	17/398	381/3,930	71 (mean)	At least 1	3	Data from the United Kingdom Clinical Practice Research Datalink database	Adjusted odds ratio=1.08 (0.62~1.87) Adjusted to history of lymphoma, gynecomastia, testicular cancer, treatment with luteinizing-hormone-releasing hormone-blockers
Robinson et al.[4] (2015)	Cohort	Sweden	9/124,183	90/545,293	69.6 (mean)	Median 6		Data on prescriptions for 5ARI used for LUTS from the Prescribed Drug Register, Patient Register, Cancer Register	Adjusted hazard ratio=0.65 (0.32~1.31) Adjusted to education level, antidiabetic drugs, statins

RCT: randomized controlled trial, BPH: benign prostatic hyperplasia, RR: relative risk, 5ARI: 5-alpha reductase inhibitor, LUTS: lower urinary tract symptoms.

trol studies, cohort studies, and RCTs on 5ARIs and breast cancer risk were included. Case reports or reviews were excluded. Two authors (HSP and JSP) independently extracted the data and any discrepancies were discussed to reach consensus. The quality of included studies was evaluated using a modification of a previously reported scoring system[3]. Details are as follows: study design—cohort studies or RCTs (2), population-based case control studies (1); exposure assessment—pill counts (2), personal recall or assignment to 5ARI group during trial (1), pharmacy database or not stated (0); breast cancer diagnosis—histopathological confirmation (2), personal recall or breast cancer diagnosis report (1), insurance database or not stated (0); confounder adjustment—additional adjustment for more than 2 confounders (2), adjustment for 2 confounders (1), no adjustment or not stated (0). A total score of 5 to 8 was considered high quality and 1 to 4 was considered low quality. All analyses were performed using Comprehensive Meta-Analysis software, version 3 (Biostat, Englewood, NJ, USA).

The search process was summarized in a PRISMA flow diagram (Fig. 1) and our analysis included six studies (137,421 subjects exposed to 5ARI and 568,469 control subjects), and their characteristics are summarized in Table 1[1,2,4-7]. All studies presented data from male populations only. The three RCTs included finasteride 5 mg only[1,2,7], the two case-control studies included finasteride 5 mg or dutasteride[5,6], and the single cohort study included finasteride (dosage not mentioned) or dutasteride[4]. While some researchers planned to include finasteride 1 mg, no study subjects were prescribed the medicine at this dose[5]; other researchers purposely excluded finasteride 1 mg because of its different indication and lower dose[6]. Although the cohort study did not clarify dosage in the methodology, the authors mentioned that prescriptions for 5ARIs used for the treatment of LUTS were extracted from a drug register[4]. The included studies were too heterogeneous to pool for a meta-analysis and only systematic review was done. Three RCTs reported number of breast cancer patients in 5ARI-exposed and non-exposed groups, and crude relative risk was calculated. The RCTs demonstrated variable risks, but the risks were not significant as 95% confidence interval contained 1. The rest two case-control and one cohort studies also revealed insignificant adjusted risk variables.

Breast cancer in men is rare with incidence in general population of 1/100,000 man-years. Its risk factors include breast carcinoma history among female relatives, BRCA1 or 2 mutations, Klinefelter syndrome, altered estrogen to testosterone balance, obesity, testicular diseases, and prostate cancer[8]. Association of male breast cancer and 5ARI use had been mostly investigated focusing on sex hormonal imbalance, because 5ARI inhibits the conversion of testosterone to dihydrotestosterone and decreases androgen activity. Previous studies have suggested that 5ARI therapy increases estrogen levels because estrogen is partly produced by the conversion of testosterone to estradiol and subsequently increases breast cancer risk, in the same manner that Klinefelter syndrome patients with increased estrogen-to-testosterone ratios are more likely to develop breast cancer[8,9]. This speculation is supported by 50 global case reports of male breast cancer in BPH patients who received 5ARI treatment[8]. Consequently, 5ARI product labeling has been updated to include breast cancer case reports.

However, in the present comprehensive search, we could not find evidence that 5ARIs increase breast cancer in male populations. Our finding is supported by studies in which 5ARIs did not increase estrogen[10], contrary to the previous hypothesis[8,9]. Amory et al.[10] reported that both dutasteride and finasteride 5 mg transiently increased testosterone after 2 months of treatment but did not alter estradiol levels over a year of treatment in healthy men. In accordance with these findings, Robinson et al.[4] hypothesized that 5ARI had no effect on breast cancer risk but that BPH itself may be implicated.

Our study has certain strengths that we performed a broad search without language restriction using multiple databases, with a manual review and the inclusion of additional articles[1,2,7]. However, our study also has limitations. The analysis included only a small number of studies, some of which were of low quality. This low number may be partly attributable to the rarity of male breast cancer, which makes it a difficult disease to study. Additionally, the selected studies addressed the effect of finasteride 5mg or dutasteride for BPH or LUTS, but none included finasteride 1 mg for AGA. However, it can present useful information to dermatologists, because they often prescribe dutasteride for AGA.

We did not find evidence of increased breast cancer risk in male populations exposed to 5ARI. However, large-scale studies of high quality are required to confirm these findings. Further studies on the effects of 5ARI on the endocrine milieu will also promote understanding of breast cancer risk in 5ARI-exposed male populations.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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