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RESEARCH ARTICLE



Prostate cancer specific mortality after 5 α -reductase inhibitors medication in benign prostatic hyperplasia patients: systematic review and meta-analysis

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ABSTRACT

Background: Our study was conducted to investigate the effect of 5-ARI on the death rate from prostate cancer by means of an updated meta-analysis using related data.

Methods: We did comprehensive literature searches using the PubMed, Embase, and Cochrane databases through July 2019. We evaluated the risk of bias in such studies using the ROBINS-I tool and analyzed deaths from cancer and deaths from all causes using HR.

Results: The meta-analysis included 11 studies. The pooled overall HRs for cancer-specific deaths between 5-ARI treatment versus non-exposed groups were 0.937 (95% CI: 0.730, 1.201). In the subgroup moderator analysis, the number of patients and additional medication variables were significantly associated with deaths from all causes ($p = 0.022$ and $p = 0.005$, respectively). For detecting the publication bias or small-study effect in the included studies, we performed Begg and Mazumdar's correlation test (0.851 and 0.573) and Egger's regression coefficient test (0.035 and 0.245) and suggested that there was no evidence of publication bias or small-study effect in this meta-analysis.

Conclusions: Our study indicated that exposure to 5-ARI had no close association between the overall death rate or cancer-specific deaths. To confirm these results, well-designed prospective studies with large samples are required.

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Introduction

Prostate cancer is the most common male cancer, with 174,640 newly diagnosed cases in the United States, ranking second in cancer-related deaths in 2019 [1,2]. Currently, the management of prostate cancer mainly focuses on early diagnosis and treatment, but the high incidence of prostate cancer and the unpredictable long-term progression of the disease support the possibility that disease prevention may be a more effective approach [3].

5 α -reductase inhibitor(5-ARI)is a specific inhibitor of 5-ARI that is required to convert testosterone into dihydrotestosterone, which is more strongly involved in prostate-cell proliferation [4,5]. Currently, it has been approved and used to relieve symptoms of benign prostatic hyperplasia (BPH) and to treat male

pattern baldness, but the long-term effects on the prostate are still ambiguous [3]. In addition to these known effects, there are various studies indicating that 5-ARI may affect the progression, incidence, and cancer-specific deaths from prostate cancer.

To find out whether 5-ARI medication for BPH affects the incidence of prostate cancer, we looked at various studies, including ones that compare the finasteride-exposed group and the placebo group, others that compared the dutasteride-exposed group and the placebo group. In the study of Thompson et al., the finasteride-exposed group showed a 6.0% lower overall incidence of prostate cancer than did the placebo group. The finasteride-exposed group showed a low incidence of low-grade cancer whose Gleason score was 6 or less (relative risk[RR] = 0.619;

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95% confidence interval [CI] 0.561–0.684), and the incidence of high-grade cancer whose Gleason score was 7–10 increased ($RR = 1.258$; 95% CI, 1.064–1.488) [3]. Zhu et al.'s study also showed an 8.8% lower proportion of prostate cancer in the finasteride-exposed group than in the placebo group. In addition, the ratio of high-grade cancer whose Gleason score was 7–10 was 71.4% in the finasteride-exposed group and 40% in the placebo group [6]. Andriole et al., who studied the effect of dutasteride on prostate cancer, reported a 5.1% lower proportion of prostate cancer in the dutasteride-exposed group than in the placebo group, and found that the incidence of high-grade cancer whose Gleason score was 8–10 was not related to 5-ARI exposure [7]. In a prospective study by Preston et al., the incidence of low-grade and intermediate-grade tumors whose Gleason score was 2–7 was significantly decreased by 8% in the 5-ARI exposed group, and the incidence of high-grade tumors whose Gleason score was 8–10 didn't show any significant difference [8].

In addition, studies on the association between 5-ARI exposure and deaths from prostate cancer were also conducted. LM Luo et al. reported an insignificant association between 5-ARI exposure and deaths from prostate cancer ($RR = 1.0$; 95% CI 0.95–1.05; $p = 0.916$) [9]. Kjellman et al. reported that 5-ARI exposure was not associated with deaths from prostate cancer when compared to the group exposed to alpha-adrenergic blocker (adjusted subdistribution hazard ratio = 0.85; 95% CI, 0.72–1.01) [10].

5-ARI may be able to reduce the risk of prostate cancer, but opinions are divided, and the effects on death rate and progression of prostate cancer, in particular, are not yet clearly established. Therefore, we did this study to investigate the effect of 5-ARI on deaths from prostate cancer by means of a meta-analysis using related data.

Materials and methods

We did this systematic review and meta-analysis using the standard Preferred Reporting Items for Systematic Reviews and Meta-Analyses statements [11].

Search strategy

We did comprehensive literature searches of the PubMed, Embase, and Cochrane databases through July 2019 using the Medical Subject Headings terms and text keywords. The search terms included 'steroid 5 alpha reductase inhibitor' and 'finasteride' or 'dutasteride' and 'prostate cancer'. Search terms were

grouped according to the Boolean operators OR and AND. The searches were not restricted in terms of language or study type. Two authors (HY Lee and JH Kim) independently reviewed the titles and abstracts according to inclusion and exclusion criteria. When our opinions were divided, we reached a consensus via mutual discussions.

Study selection

Study inclusion criteria were as follows:

1. the study population comprised patients who were diagnosed with BPH or prostate cancer;
2. interventions included administration of 5-ARI;
3. comparisons were specified for non-exposed 5-ARI treatment,
4. outcomes were hazard ratio (HR) for deaths from cancer and from all causes.

For overlapped studies from the same cohort, we selected the latest and most appropriate outcomes in strict discussions by all investigators. Two of us (JJ Park, HY Lee) independently screened the titles and abstracts of all articles using predefined inclusion criteria. The full-text articles were examined independently by two of us (SR Shim and JH Kim) to decide whether they met the inclusion criteria. Final included articles were chosen by means of all investigators' discussion. We carefully cross-checked all references and data for each included study to ensure that no overlapping data were present and to maintain the integrity of the meta-analysis.

Meta-analysis assessment of outcome findings and statistical analysis

The HR along with their 95% confidence intervals (CIs) were used for deaths from cancer and from all causes. We used the random-effects model to obtain pooled overall HR and 95% CIs for outcomes and meta-regression analysis for each moderator [12].

To examine potential moderators, we did meta-ANOVA or meta-regression analysis for each moderator. We analyzed the variability in the effect sizes caused by differences between the categorical moderators [e.g. types of 5-ARI (finasteride vs. finasteride or dutasteride vs. not-mentioned), study design (RCT vs. cohort), claim data (yes vs. no), medication after prostate-cancer diagnosis (yes vs. no), and additional medication (yes vs. no)] with a weighted meta-analytic analogue to the analysis of tau-common

variance. For continuous moderators (e.g. number of patients, age, study duration, and follow-up years), we used a restricted maximum likelihood (REML) estimator of the variance of the true effects. A two-sided $p \leq 0.05$ or lack of a null value ($HR = 1$) within the 95% was considered to be significant. We did the above-mentioned analyses with R software 3.6.0 (R Foundation for Statistical Computing).

We evaluated statistical heterogeneity by the Cochran's Q test and the I^2 statistic. Either a Cochran's Q statistic $p < 0.1$ or an I^2 statistic $> 50\%$ indicated the existence of significant heterogeneity between studies. However, a non-significant χ^2 test result ($p \geq 0.1$) or an I^2 statistic $\leq 50\%$ indicated a lack of evidence for heterogeneity but did not necessarily imply homogeneity, because there may have been insufficient statistical power to detect heterogeneity. So, we used a random-effects model for analysis.

Assessment of methodological quality

We evaluated risk of bias for the included studies using the ROBINS-I tool. We rated the bias due to a confounding domain based on whether a matched control group had been set and whether the hazard ratio had been adjusted. If the matched control group had been used and adjusted HR was reported, we evaluated it as low. If the matched control group had been used and HR was unadjusted, or if an unmatched control had been used but adjusted HR was reported, we rated it as moderate. If an unmatched control group had been used and HR wasn't reported, we evaluated it as serious. If there was no control group, we rated it critical. We rated bias due to selection of participants by whether participants' cancer risk and PSA value were mentioned. We evaluated this domain as Low if participants' PSA value and cancer risk were displayed, as moderate if PSA value was not displayed, and Serious if there was no description of selection. We rated bias involving classification of intervention as low, because all the included studies involved 5-ARI. We rated bias due to deviations from the intended intervention by whether single/multi-center or claims data were considered. We evaluated this domain as low for a study using single-center data, and as moderate for a study using multi-center data or claims data. We evaluated bias due to missing data as low if claims data were used, as moderate if claims data were not used but there was a description of the follow-up method, and as serious if there was no such mention. We evaluated bias due to measurement of outcomes as low when HR

was calculated and median follow-up was presented, and as moderate when HR was not calculated but the survival rate and follow-up period were presented. If neither HR, survival rate, nor follow-up period was presented, we evaluated it as serious. We considered selection bias of the reported results to be low if all HRs, survival rates, and causes of death were presented, and as moderate if HR was not presented. If neither HR nor survival rate was presented, we rated it as serious.

Publication bias

The funnel plot explains the publication bias using the standard error as the measure of study size and MD measures of treatment effect. In the absence of publication bias, the studies will be distributed symmetrically about the combined effect size. In addition, we conducted a Begg & Mazumdar rank correlation test and Egger linear regression method test for publication biases [13].

Results

Study selection

The initial search identified 1413 articles from different electronic databases (PubMed, 145; Cochrane, 22; Embase, 1246). Excluding the duplicated studies left 1394 studies. After screening the titles and abstracts, we eliminated 1380 studies, because they were not related to this topic. Upon more detailed review, we found 14 studies to be eligible for randomized controlled studies. Of these, three were further excluded because they lacked data about deaths, and one that was a review paper. Finally, 11 studies met our selection criteria for qualitative assessment (Figure 1).

We conducted a systematic review of the 11 studies to assess the experimental differences and subject descriptions of 5-ARI in detail (Table 1). All the studies had been conducted in Western countries. The types of 5-ARI were finasteride and dutasteride. The number of patients and the range of the study duration in the quantitative meta-analysis were from 220 to 174,895 and 36 to 240 months, respectively.

Outcome findings

The pooled overall HRs for deaths from cancer between 5-ARI treatment versus the non-exposed group were 0.937 (95% CI: 0.730, 1.201). There was no statistically significant difference between groups. A

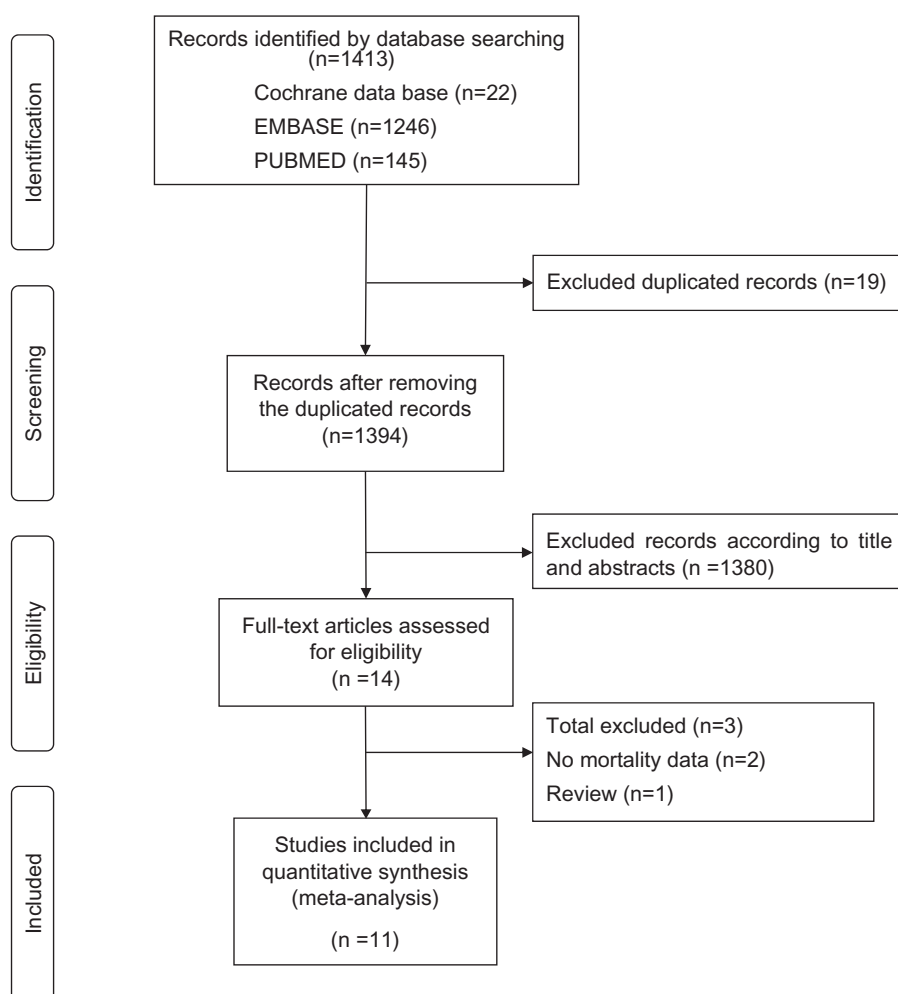


Figure 1. Flow chart.

heterogeneity test produced $p < 0.01$ and the Higgins' I^2 was 90.0%. For evaluation of the types of 5-ARI agents that affect the death rate from cancer, we also conducted subgroup analysis. The HRs were 0.930 (95% CI: 0.759, 1.139) in finasteride, 0.959 (95% CI: 0.673, 1.365) in finasteride or dutasteride, and 0.850 (95% CI: 0.718, 1.007) in no agents' name (Figure 2(a)).

The pooled overall HRs for death from all causes between 5-ARI treatment versus the non-exposed group were 1.021 (95% CI: 0.950, 1.097). There was no statistically significant difference between groups. A heterogeneity test produced $p = 0.04$ and the Higgins' I^2 was 57.0%. In subgroup analysis, the HRs were 1.020 (95% CI: 0.967, 1.076) in finasteride, 1.027 (95% CI: 0.891, 1.185) in finasteride or dutasteride, and 0.930 (95% CI: 0.800, 1.081) in dutasteride (Figure 2(b)).

Moderator analyses

Table 2 provides a subgroup analysis and an overview of the meta-regression and meta-ANOVA analysis

results to identify the moderator effects. There were no statistically significant differences for age, study duration, follow-up years, types of 5-ARI, study design, claims data, or medication after prostate-cancer diagnosis. However, the number of patients and additional medication variables were significantly associated with deaths from all causes ($p = 0.022$ and $p = 0.005$, respectively).

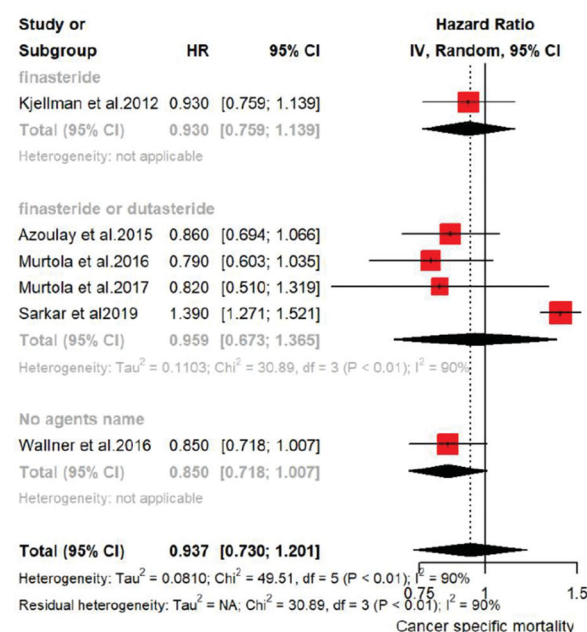
Publication bias

The Funnel plot to detect the publication bias or small-study effect in the included studies is summarized in Figure 3. Individual studies are distributed symmetrically about the combined effect size and toward the top of the graph. The p values of the deaths from cancer and from all causes for Begg and Mazumdar's correlation test (0.851 and 0.573) and for Egger's regression coefficient test (0.035 and 0.245) suggested that there was no evidence of publication bias or small-study effect in this meta-analysis.

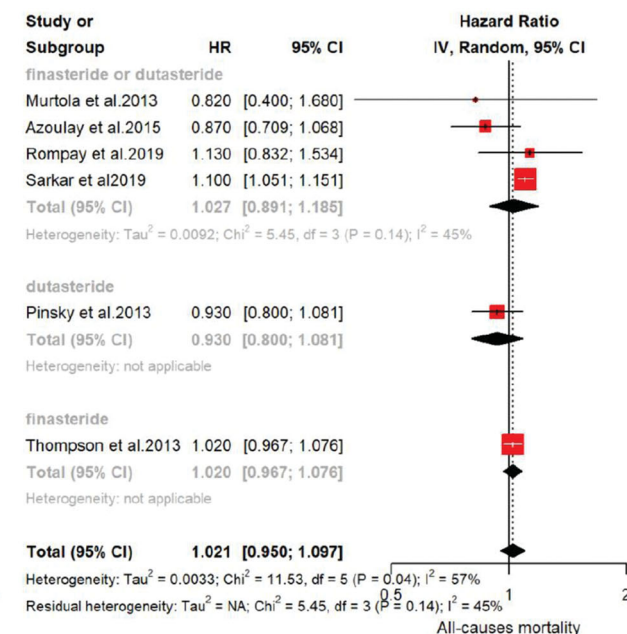
Table 1. Baseline characteristics.

Author	Study period	Area	Number of patients	Actual number of patients	Number of case/control	Kind of 5-ARI	Inclusion criteria	Use of claim data	Study type
Sarkar <i>et al.</i> 2019 [26]	180mo.	Western	80875	80875	8587/72288	finasteride, dutasteride	Patients who were diagnosed as prostate cancer during study period	1	Retrospective cohort
Azoulay <i>et al.</i> 2015	120mo.	Western	13892	13892	574/13318	finasteride, dutasteride	Patients who were diagnosed as prostate cancer during study period	1	Retrospective cohort
Pinsky <i>et al.</i> 2013	36mo	Western	8231	6706	3299/3407	dutasteride	Male who had 1 negative prostate biopsy with PSA 3-10ng/ml (2.5-10ng/ml in under 60years)	0	Prospective cohort
Rompay <i>et al.</i> 2019	240mo.	Western	24012	16248	4571/11677	finasteride, dutasteride	Over 40years male who newly started 5-ARI	1	Retrospective cohort
Wallner <i>et al.</i> 2016 [10]	180mo.	Western	174895	174895	25388/149507	not mentioned	Over 50years male who were prescribed medication for BPH/LUTS	1	Retrospective cohort
Murtola <i>et al.</i> 2017	96mo.	Western	80454	78615	9316/69299	finasteride, dutasteride	Over 55years male who newly started 5-ARI	1	Retrospective cohort
Milonas <i>et al.</i> 2016	36mo.	Western	220	191	85/106	dutasteride	40-80 years male who had suspected prostate cancer due to elevated PSA or abnormal DRE	0	RCT
Murtola <i>et al.</i> 2013	168mo.	Western	1315	1016	115/901	finasteride or dutasteride	Patients who were get radical prostatectomy during study period	0	RCT
Murtola <i>et al.</i> 2016	36mo.	Western	6537	4209	908/3301	finasteride or dutasteride	Patients who were diagnosed as prostate cancer during study period	0	RCT
Thompson <i>et al.</i> 2013 [3]	40mo.	Western	18880	18880	9423/9457	finasteride	Male who had PSA $\leq$ 3ng/ml	0	RCT
Kjellman <i>et al.</i> 2012	204mo.	Western	3791	3005	199/2806	finasteride	Male who were prescribed 5-ARI or a-blocker	1	Retrospective cohort

(A) Cancer specific mortality



(B) All-causes mortality

**Figure 2.** Forest plot diagram showing the effect of 5α-reductase inhibitors on cancer specific mortality and all-causes mortality.**Table 2.** Effects of moderators on cancer specific mortality and all-causes mortality.

Variables	k	Coef.*	Cancer specific mortality				P†	P‡	All-causes mortality					
			HR	95% CI Low	95% CI High				HR	95% CI Low	95% CI High		P†	P‡
No. of patients	6	<0.001	–	<0.001	<0.001	–	0.818	6	<0.001	–	<0.001	<0.001	–	0.022
Age	6	–0.018	–	–0.072	0.036	–	0.516	6	–0.005	–	–0.034	0.025	–	0.757
Study duration (months)	6	0.002	–	–0.001	0.005	–	0.276	6	0.001	–	–0.001	0.002	–	0.215
Follow up (years)	5	0.032	–	–0.134	0.198	–	0.704	5	0.055	–	–0.205	0.315	–	0.679
Types of 5-ARI						0.953	–						0.775	–
Finasteride	1	–	0.930	0.759	1.139			1	–	1.020	0.967	1.076		
Finasteride or Dutasteride	4	–	0.959	0.673	1.365			4	–	1.027	0.891	1.185		
Dutasteride	1	–	0.930	0.800	1.081			1	–	0.930	0.800	1.081		
No agents name	1	–	0.850	0.718	1.007								0.992	–
Study design						0.555	–							
RCT	1	–	0.968	0.739	1.268			2	–	1.019	0.966	1.075		
Cohort	5	–	0.790	0.603	1.035			4	–	1.005	0.882	1.145		
Claim data						0.555	–						0.434	–
Yes	5	–	0.968	0.739	1.268			3	–	1.034	0.884	1.209		
No	1	–	0.790	0.603	1.035			3	–	1.008	0.959	1.060		
Medication after PC diagnosis						0.561	–						0.813	–
Yes	3	–	0.994	0.665	1.486			3	–	0.990	0.810	1.210		
No	3	–	0.878	0.774	0.995			3	–	1.012	0.963	1.064		
Additional medication						0.214	–						0.005	–
Yes	2	–	1.064	0.612	1.849			2	–	0.984	0.918	1.055		
No	4	–	0.873	0.783	0.973			4	–	1.101	1.052	1.151		

k, number of observations. * Regression coefficient. † P-value of meta-ANOVA for categorical moderators. ‡ P-value of random effect meta-regression using restricted maximum likelihood (REML) for continuous moderators.

Methodological quality

We evaluated seven domains in each study using the ROBINS-I tool to assess the risk of bias for included studies. We assessed bias due to a confounding domain according to whether the control group was matched or the HR was adjusted. In this category, one study was evaluated as "Low", six as "Moderate", four as "Serious", and none as "Critical". We rated bias due to selection of participants based on whether

participants' cancer risk and PSA value were mentioned. In this category, six studies were evaluated as "Low", and five as "Moderate". Because all studies were on 5-ARI, bias in classification of intervention was "Low". We rated bias due to deviations from the intended intervention by whether single/multi-center or claims data were used. We evaluated three studies as "Low" and eight as "Moderate". We rated bias due to missing data by whether claims data were used and

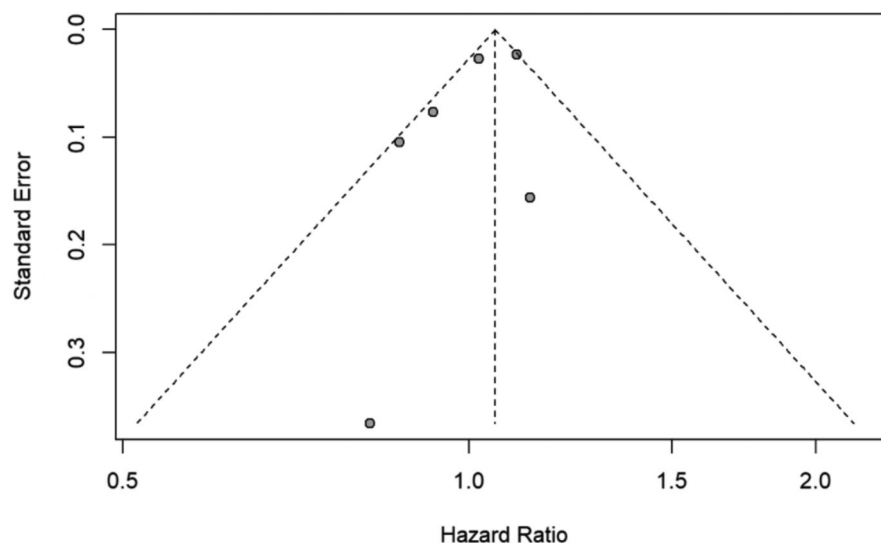


Figure 3. Funnel plots for publication bias.

follow-up method was mentioned. In this category, six studies were evaluated as "Low", four as "Moderate", and one as "Serious". We rated bias due to measurement of outcomes based on whether HR was calculated and median follow-up was mentioned. In this category, six papers were evaluated as "Low", and five as "Moderate". We assessed bias in selection of the reported results in terms of HR, survival rate, and cause of death. In this category, were evaluated six studies as "Low" and five as "Moderate". Also, given the results of the previous evaluation, we could calculate the overall risk of bias; we found four studies with an overall risk of bias rated as "Low", three as "moderate", and four as "Serious". The evaluation results are plotted in Figure 4 and Table 3.

Discussion

5-ARI, an inhibitor of the 5α -reductase that converts testosterone into a dihydrotestosterone, is a type of medicine that relieves the lower urinary tract symptoms resulting from BPH by reducing the volume of the prostate by means of a hormonal mechanism [9,14]. However, when 5-ARI is used, its side effects should also be considered. In a study comparing finasteride and placebo groups, in the finasteride group, urinary symptoms associated with BPH decreased, but side effects, such as decreased libido and ejaculation volume, caused by 5-ARI were commonly reported [3,4].

5α -reductase is composed of a Type 1 enzyme mainly distributed in the skin and a Type 2 enzyme mainly distributed in the prostate [15]. Finasteride is a specific inhibitor for Type 1 5α -reductase, and

dutasteride is an inhibitor for both Type 1 and Type 2 5α -reductase. The reduction in circulating dihydrotestosterone of these two treatments was 60-70% and 90%, respectively [16,17]. Given these effects, 5-ARI is widely used as a non-surgical method to improve lower urinary tract symptoms in BPH patients [9].

Testosterone is involved in prostate growth and development. Prostate cells induce spontaneous apoptosis in the absence of testosterone, but continue to proliferate and differentiate when there is a normal concentration of testosterone. Since these effects work in the same way in prostate-cancer cells, taking 5-ARI, which is involved in a low concentration of testosterone, is thought to affect the physiology of prostate cancer [18,19]. Therefore, physicians should provide sufficient information about the use of 5-ARI. Factors such as decreased risk of prostate cancer, increased risk of high-grade prostate cancer, risk of side effects, and improvement of urinary symptoms should be compared to decide whether to use drugs according to priority [20,21].

In previous studies on whether 5-ARI affects the grade of prostate cancer, the incidence of high-grade prostate cancer was higher in the finasteride group by 1.3 percent than in the placebo group [3]. There are disagreements on the cause of these differences. Studies have shown that androgen-deprivation therapy causes histological changes that mimic high-grade tumors. There is also evidence that prostate cancer in men with low testosterone levels has a high Gleason score and a poor prognosis, because a decrease in DHT leads to high-grade tumors [22,23]. It is also possible that 5-ARI treatment may cause the microenvironmental changes that can convert low-grade tumors

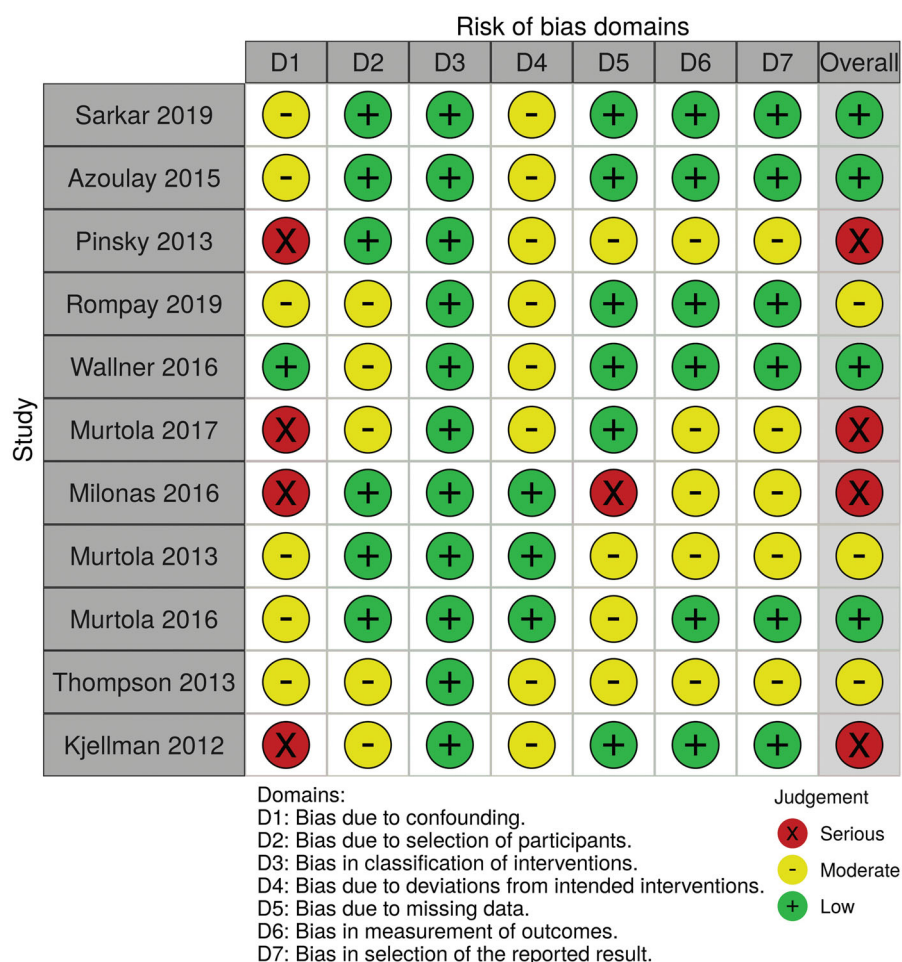


Figure 4. Traffic light plot on Risk of bias.

into high-grade tumors [9]. On the other hand, there is an opinion that finasteride induces selective inhibition of low-grade tumors and thus high-grade tumors are selected [3]. In addition, 5-ARI treatment has a greater effect on the occurrence of low-grade malignancies and less on the occurrence of high-grade tumors [3]. Subjects treated with 5-ARI had less incidence of low-grade and intermediate-grade tumors and an increased detection rate of high-grade tumors [3]. Assuming that 5-ARI has no effect on high-grade tumors, 5-ARI's shrinking of the prostate gland increases the detection sensitivity of prostate cancer [3].

However, various biases can arise in defining the effect of 5-ARI on the incidence of prostate cancer. In clinical practice, screening of prostate cancer mainly relies on increased PSA. Since it is clear that PSA decreases in patients treated with 5-ARI, the probability of a prostate biopsy done because of high PSA decreases, which may act as a bias in estimating the

relationship between 5-ARI and prostate-cancer incidence [9]. In addition, people who need 5-ARI treatment may have higher initial PSA levels than in the general population because of the effect of BPH. Another bias trigger is the prostate volume. Since 5-ARI reduces the volume of the prostate, more prostate tissue is sampled during prostate biopsy; so the probability of a positive biopsy is higher than that of the general population [24,25]. In addition, people who need 5-ARI treatment are likely to have a higher initial prostate volume than is the general population; so this may also act as a bias in estimating the association between 5-ARI and the incidence of prostate cancer.

Our results indicated that the deaths from prostate-cancer (OR = 0.937; 95% CI, 0.730–1.201; $p < 0.01$) and from all causes (OR = 1.021; 95% CI, 0.950–1.097; $p = 0.04$) of the group taking 5-ARI when diagnosed with prostate cancer were not significantly associated with those of the non-exposed group.

Table 3. Assessment of methodological quality.

Bias domain	Bias due to confounding	Bias due to selection of participants	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias due to measurement of outcomes	Bias in selection of the reported results
Evaluation standard for each bias domain	Low : Matched control, adjusted HR Moderate : i) Matched control, unadjusted HR ii) Unmatched control, adjusted HR Serious : Unmatched control, no HR Critical : No control Moderate (Unmatched control, adjusted HR)	Low : Participants' PSA value and cancer risk are displayed. Moderate : PSA value is not displayed Serious : No description of selection	Low : Because all studies are on 5-ARI.	Low : Single center Moderate : Multicenter, claimed data	Low : Claimed data Moderate : Not claimed data, description of the follow up method Serious : Not claimed data, no description of the follow up method	Low : HR is calculated, median follow up period is presented Moderate : Only HR, median follow up period and survival rate are presented Serious : HR, median follow up period and survival rate aren't presented	Low : HR, survival rate and cause of death are presented Moderate : HR isn't presented Serious : HR and survival rate aren't presented
Sarkar 2019	Moderate (Unmatched control, adjusted HR)	Low (Participants' PSA value and cancer risk are displayed)	Low	Moderate (Claimed data)	Low (Claimed data)	Low (HR, median follow up)	Low (HR, survival rate)
Azulay 2015	Moderate (Unmatched control, adjusted HR)	Low (Participants' PSA value and cancer risk are displayed)	Low	Moderate (Claimed data)	Low (Claimed data)	Low (HR, median follow up)	Low (HR, survival rate)
Pinsky 2013	Serious (Unmatched control, no HR)	Low (Participants' PSA value and cancer risk are displayed)	Low	Moderate (PCPT, REDUCE trial data)	Moderate (Not claimed data, description of the follow up method)	Moderate (Survival rate is presented, No HR and median follow up period)	Moderate (survival rate)
Rompay 2019	Moderate (Unmatched control, adjusted HR)	Moderate (PSA value is not displayed)	Low	Moderate (Claimed data)	Low (Claimed data)	Low (HR, median follow up)	Low (HR, survival rate)
Wallner 2016	Low (Matched control, adjusted HR)	Moderate (PSA value is not displayed)	Low	Moderate (Claimed data)	Low (Claimed data)	Low (HR, median follow up)	Low (HR, survival rate)
Murtola 2017	Serious (Unmatched control, Unadjusted HR)	Moderate (PSA value is not displayed)	Low	Moderate (Claimed data)	Low (Claimed data)	Moderate (Only HR)	Low (HR, survival rate)
Milonas 2016	Serious (Unmatched control, no HR)	Low (Participants' PSA value and cancer risk are displayed)	Low	Low (Single center)	Serious (Not claimed data, no description of the follow up method)	Moderate (Only survival rate)	Moderate (survival rate)
Murtola 2013	Moderate (Unmatched control, adjusted HR)	Low (Participants' PSA value and cancer risk are displayed)	Low	Low (Single center)	Moderate (Not claimed data, description of the follow up method)	Moderate (Only HR)	Low (HR, survival rate)
Murtola 2016	Moderate (Unmatched control, adjusted HR)	Low (Participants' PSA value and cancer risk are displayed)	Low	Low (Single center)	Moderate (Not claimed data, description of the follow up method)	Low (HR, median follow up)	Low (HR, survival rate)

(continued)

Table 3. Assessment of methodological quality. Continued.

Bias domain	Bias due to confounding	Bias due to selection of participants	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias due to measurement of outcomes	Bias in selection of the reported results
Thompson 2013	Moderate (Unmatched control, adjusted HR)	Moderate (PSA value is not displayed)	Low	Moderate (PCPT trial data)	Moderate (Not claimed data, description of the follow up method) Low (Claimed data)	Moderate (Only HR)	Low (HR, survival rate)
Kjellman 2012	Serious (Unmatched control, Unadjusted HR)	Moderate (PSA value is not displayed)	Low	Moderate (Claimed data)	Low (Claimed data)	Low (HR, median follow up)	Low (HR, survival rate)

Among the studies included in our meta-analysis, Sarker et al.'s 2019 study [26] had exceptionally high rates of death from cancer and from all causes. Conceivable causes of such high death rates include lead-time bias and misclassification. First, lead-time bias means that if the diagnosis is delayed, the time to death is short; so the death rate for the disease may be overestimated. We set the PSA of 4 ng/ml or more as the standard for elevated PSA to measure the time until prostate biopsy was done. This standard PSA value is higher than that of other included studies. So, in this study, the death rate may have been overestimated because of lead-time bias. On the other hand, in this paper, we calculated the death rate from specific causes using the National Death Index, but as mentioned, the cause of death may have been misclassified; so there may be differences from the actual rate of death from cancer. Considering these points, lower OR values may have been reported than we found in this meta-analysis; so 5-ARI administration and deaths from prostate cancer may have a lower association.

Luo et al.'s study [9] found no significant association between 5-ARI exposure and deaths from prostate cancer, or between 5-ARI exposure and the incidence of high-grade prostate cancer. They explained these two outcomes using the general theory that the death rate from cancer increases with the incidence of high-grade cancer. In other words, that there was no increase in deaths from cancer was associated with the fact that 5-ARI exposure did not show a significant association with the incidence of high-grade prostate cancer [9]. Our findings that 5-ARI exposures are not related to either deaths from all causes or deaths from cancer also support this theory. In addition, we evaluated the methodological quality of each study using the ROBINS-I tool, and analyzed the moderator effect for both deaths from cancer and deaths from all causes of several variables.

We updated the existing studies and did a meta-analysis and methodical review, but there are some limitations. First, we analyzed the moderator effect on deaths from cancer and from all causes for each 5-ARI type, but we did not have enough of the information needed for the meta-analysis to be able to carry out the correlation analysis between 5-ARI dosage and deaths. In addition, the number of studies finally included in the analysis after several steps was small; so there is a need for additional studies. To compensate for these limitations, prospective studies with many more samples should be conducted.

Conclusion

Our study indicated that 5-ARI medication for BPH had no close association between deaths from cancer and deaths from all causes. Also, we confirmed the association between each variable and death rate through moderator analysis. To confirm these results, well-designed prospective studies with larger samples are required.

Author contributions

Study design and conceptualization: JHK; Data extraction and synthesis: HYL; Data-analysis and interpretation: SRS, JHK; Draft the manuscript: JJP; Draft revision: JHK

Disclosure statement

No potential conflict of interest was reported by the author(s).

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