Association between 5α-reductase inhibitors therapy and incidence, cancer-specific mortality, and progression of prostate cancer: evidence from a meta-analysis

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5α-reductase inhibitors (5-ARI) are widely employed for the treatment of benign prostatic hyperplasia. It has been noted that 5-ARI exhibit the potential to attenuate the risk of prostate cancer, but consistent agreement has not been achieved. Moreover, the effect of 5-ARI on cancer-specific mortality and progression of prostate cancer remains unclear. Therefore, the goal of the current meta-analysis was to elucidate the impact of 5-ARI on the incidence and progression of prostate cancer. We searched for all studies assessing the effect of 5-ARI on risk of prostate cancer in PubMed, Embase, Medline, and Cochrane Library databases. Pooled relative risk (RR) and corresponding 95% confidence intervals (CIs) were accepted to evaluate the association between 5-ARI and the risk of prostate cancer. Synthetic results implied that subjects who accepted 5-ARI compared with the placebo group experienced a distinctly weakened overall incidence of prostate cancer (RR = 0.74; 95% CI: 0.66–0.82; P < 0.001). Subgroup analyses further revealed that 5-ARI reduction of the incidence of prostate cancer was limited to low-grade (Gleason score 2–6; RR = 0.68; 95% CI: 0.57–0.81; P < 0.001) and intermediate-grade tumors (Gleason score 7; RR = 0.81; 95% CI: 0.67–0.97; P = 0.023), but not high-grade tumors (Gleason score >7; RR = 1.19; 95% CI: 0.98–1.43; P = 0.069). The results also showed that 5-ARI treatment did not significantly alter prostate cancer-specific mortality (RR = 1.0; 95% CI: 0.95–1.05; P = 0.916). In addition, it was worth noting that 5-ARI treatment acted in a protective role that presented a dramatic benefit to delay the progression of low-risk tumors (RR = 0.58; 95% CI: 0.43–0.78; P < 0.001).

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5α-reductase inhibitors (5-ARI) are widely recognized as the major route of nonsurgical treatment to relieve symptoms of patients with BPH. Over the past several years, some reports have stated that a history of 5-ARI exposure could affect the risk of prostate cancer. A study by Thompson et al., who recruited 9060 patients with BPH, reported that the overall incidence of prostate cancer was 18.4% (803/4368) and 24.4% (1147/4692) among the finasteride-exposed group and the placebo group, respectively. They further observed that the incidence of low-grade cancer (Gleason score ≤6) of the finasteride-exposed group was dramatically weakened compared with the placebo group (relative risk [RR] = 0.619; 95% confidence interval [CI]: 0.561–0.684). However, patients in the finasteride-exposed group achieved an increase in the incidence of high-grade cancer (Gleason score 7–10) compared with those in the placebo group (RR = 1.258; 95% CI: 1.064–1.488). Andriole et al. reported that the proportion of prostate cancer in the dutasteride-exposed group was 19.9% (659/3305), whereas it was 25.0%
(858/3424) in the placebo group. 5-ARI exposure was not related to the incidence of tumors with Gleason score of 8–10 (RR = 1.581; 95% CI: 0.888–2.814). Zhu et al. reported that the proportion of prostate cancer was 9.8% among the finasteride-exposed group and 18.6% of individuals in the placebo group. They also observed that high-grade cancer (Gleason score 7–10) accounted for 71.4% and 40% of patients with prostate cancer in the finasteride-exposed group and placebo group, respectively. Based on prospective research conducted in the United States in 2014, it was estimated that patients with 5-ARI treatment had 26% and 34% reduction in the incidence of low-grade (Gleason score 2–6) and intermediate-grade tumors (Gleason score 7), respectively, compared with the placebo group. However, the incidence of tumors with Gleason score 8–10 among the 5-ARI group seemed comparable to the placebo group (RR = 0.97; 95% CI: 0.64–1.64).

Likewise, numerous studies were examined to assess 5-ARI exposure in relation to prostate cancer-specific mortality. A cohort study was conducted by Kjellman et al., who stated that for the incidence of nonlocalized prostate cancer, patients in the finasteride-exposed group compared with those in the placebo group might have more than a 14% increase. Interestingly, the RR of cancer-specific mortality of the finasteride-exposed group was 0.93 (95% CI: 0.76–1.14), indicating no substantial connection. The results were similar to another study, which assessed the connection between 5-ARI exposure and prostate cancer-specific mortality, while failing to identify a close link (RR = 0.85; 95% CI: 0.72–1.01).

Despite several publications addressing the link between 5-ARI and risk of prostate cancer, consistent agreement was not achieved. Thus, the present meta-analysis was performed to investigate the influence of 5-ARI on risk of prostate cancer.

MATERIALS AND METHODS
This meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Supplementary Table 1). Search strategy
The eligible documents were sourced from PubMed, Embase, Medline, and the Cochrane Library databases from the inception to July 2018. Only studies published in English involving human participants were considered in the present meta-analysis. For the search, the following terms were used: (5-alpha-reductase inhibitors) OR (finasteride) OR (dutasteride) OR (5-ARI) AND (prostate cancer) OR (prostate tumor) OR (prostate carcinoma) OR (prostatic neoplasms). In addition, the references of relevant studies were reviewed to expand the search.

Selection criteria
Any available studies that described 5-ARI exposure on risk of prostate cancer were included in the present meta-analysis. Studies were included when they provided information about the effect of 5-ARI on prostate cancer risk or cancer-specific mortality or progression of prostate cancer and reported RR estimates or odds ratios (ORs) with 95% CI or sufficient data to calculate them. In addition, reviews, congress reports, letters, abstract, editorials, case reports, and commentaries did not meet the criteria.

Data extraction and quality assessment
Relevant information was extracted according to a specially designed form by two authors. The methodological quality of nonrandomized studies was dependent on the Newcastle–Ottawa Scale (NOS). Cochrane’s risk of bias assessment tool was adopted to evaluate the quality of randomized controlled trial (RCT) studies.

Statistical analyses
The pooled RR and its 95% CI were employed to evaluate the connection between 5-ARI exposure and risk of prostate cancer. \( P < 0.05 \) indicated statistical significance. Heterogeneity was assessed according to the Cochrane Q statistic and \( I^2 \) statistics. The fixed effects model was adopted when significant statistical heterogeneity was free (\( I^2 < 50\% \); \( P > 0.10 \)). Otherwise, a random effects model was employed. In addition, sensitivity analysis and subgroup analyses were employed to detect the potential source of heterogeneity. STATA 12.0 was applied in the meta-analysis (Stata Corp., College Station, TX, USA).

RESULTS

Literature search
The steps are depicted in Figure 1. In the initial screening, 1265 citations were identified. After eliminating studies that did not meet the inclusion criteria, 17 studies were analyzed.

Study characteristics
Table 1 illustrates the relevant detailed information of included publications. Ten studies focused on the incidence of prostate cancer among 605 970 participants. Six studies assessed the cancer-specific mortality of prostate cancer among 236 320 participants. Two studies evaluated the progression of prostate cancer among 590 participants.

Quality assessment
The outcomes of the quality assessment of the cohort and case–control studies are depicted in Supplementary Table 2, and the outcomes of methodological quality in the RCT are depicted in Supplementary Figure 1 and 2.

5-ARI and incidence of prostate cancer
As shown in Figure 2, the pooled RR for incidence of prostate cancer in patients with 5-ARI exposure as compared with the control group was 0.74 (95% CI: 0.66–0.82, \( P < 0.001 \); heterogeneity: \( I^2 = 73.8\% \), \( P < 0.001 \)), indicating a protective effect of 5-ARI treatment on overall incidence of prostate cancer.

Subgroup analyses
To further evaluate the effect of 5-ARI treatment on the incidence of prostate cancer, subgroup analyses were performed based on tumor grade, study design, intervention drug, ethnicity, and...
### Table 1: Characteristics of studies included in the meta-analysis

| Study          | Study design  | Country       | Study group (n) | Control group (n) | Mean age (year) | Study exposed | Control exposed | Follow-up period | Variable adjustment                                                                 | RR (95% CI)                                                                 |
|----------------|---------------|---------------|-----------------|-------------------|-----------------|---------------|-----------------|------------------|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------|
| Preston et al. | Cohort study  | America       | 2878            | 35 180            | 66.1            | 62.6          | 5-ARI           | Non-5-ARI         | 14 years                                                              | Age, time period, smoking history, race, family history of prostate cancer     | Overall: 0.77 (0.65–0.91); low-grade (Gleason 2–6): 0.74 (0.57–0.95); Gleason 7: 0.67 (0.49–0.91); high-grade (Gleason 8–10): 0.97 (0.64–1.46) |
| Liang et al.   | Case–control  | China         | 1489            | 4331              | 72.5            | 72.6          | Dutasteride     | Non-5-ARI         | 1996–2009                                                | Age and occupation                                                               | Overall: 0.74 (0.27–2.04)                                                         |
| Robinson et al.| Case–control  | Sweden        | 26 736          | 133,671           | 69.3            | 69.3          | 5-ARI           | Non-5-ARI         | 2007–2009                                                | Comorbidity, PSA, socioeconomic factors assessed by family status            | Overall: 0.89 (0.84–0.94); low-grade (Gleason 2–6): 0.88 (0.80–0.96); Gleason 7: 0.85 (0.77–0.94); high-grade (Gleason 8–10): 1.01 (0.90–1.13) |
| Andriole et al.| RCT           | –             | 2167            | 2158              | 66.5            | 66            | Dutasteride     | Non-5-ARI         | 2 years                                                   | Age, race, PSA                                                                  | Overall: 0.49 (0.31–0.77)                                                         |
| Andriole et al.| RCT           | –             | 4105            | 4126              | 62.8            | 62.7          | Dutasteride     | Non-5-ARI         | 4 years                                                   | NA                                                                              |                                                                                  |
| Wallerstedt et al. | Cohort study  | Sweden       | 23 442          | 329 672           | 69              | 60            | 5-ARI           | Non-5-ARI         | 8 years                                                   | PSA, age, family history                                                        |                                                                                  |
| Murtola et al. | Cohort study  | Sweden        | 1754            | 21 566            | 55–67           | 55–67         | Finasteride     | Non-5-ARI         | 1996–2004                                                | Age, PSA, family history of prostate cancer, et.al                            | Overall: 0.74 (0.65–0.81); Gleason ≤6: 0.728 (0.650–0.814); Gleason 7: 0.925 (0.765–1.117); Gleason 8–10: 1.581 (0.888–2.814) |
| Thompson et al.| RCT           | –             | 4368            | 4692              | ≥55             | ≥55           | Finasteride     | Non-5-ARI         | 7 years                                                   | NA                                                                              | Overall: 0.87 (0.63–1.19); Gleason ≤6: 0.59 (0.38–0.91); Gleason 7: 1.33 (0.77–2.30) |
| Roehrborn et al.| RCT           | –             | 1623            | 1611              | ≥50             | ≥50           | Dutasteride     | Tamsulosin       | 4 years                                                   | Age, PSA, prostate volume, IPSS, and body mass index                        | Overall: 0.752 (0.694–0.814); Gleason ≤6: 0.619 (0.561–0.684); Gleason 7–10: 1.258 (1.064–1.488) |
| Zhu et al.     | Cohort study  | China         | 214             | 188               | 74              | 74            | Finasteride     | Nonusers          | 7 years                                                   | NA                                                                              |                                                                                  |
| Murtola et al. | Cohort study  | Finland       | 908             | 3301              | 67              | 70            | 5-ARI           | Non-5-ARI         | 7.5 years                                                | Age, tumor Gleason grade and stage, PSA, et al                                | Overal: 0.53 (0.32–0.87); Gleason ≤6: 0.251 (0.104–0.609); Gleason 7–10: 1.79 (1.10–2.91) |
| Thompson et al.| RCT           | –             | 9423            | 9457              | ≥55             | ≥55           | Finasteride     | Non-5-ARI         | 10 years                                                | Cancer grade, age at diagnosis, race, family history of prostate cancer        | Overall: 0.94 (0.72–1.24)                                                        |
| Kjellman et al.| Cohort study  | Denmark       | 199             | 2806              | 73.9            | 73.6          | Finasteride     | Non-5-ARI         | 3.7 years                                                | Treatment and localized/ nonlocalized cancer stage                            | Overall: 0.93 (0.76–1.14)                                                        |
| Preston et al. | Cohort study  | America       | 2878            | 35,180            | 66.1            | 62.6          | 5-ARI           | Non-5-ARI         | 14 years                                                | Age, time period, smoking history, race, family history of prostate cancer, et al | Overall: 0.99 (0.58–1.69)                                                        |
| Azoulay et al. | Cohort study  | England       | 574             | 13,318            | 76.2            | 71.9          | 5-ARI           | Non-5-ARI         | 12 years                                                | Age, year of diagnosis, ethnicity, alcohol use, smoking status, et al        | 0.86 (0.69–1.06)                                                               |
| Walner et al.  | Cohort study  | America       | 25 388          | 149 507           | 72.4            | 72.3          | 5-ARI           | Non-5-ARI         | 3 years                                                   | Age, BPH initiation year, race, region, Charlson score, and comorbidities     | 0.85 (0.72–1.01)                                                               |
| Fleshner et al.| RCT           | North America | 147             | 155               | 65.1            | 65            | Dutasteride     | Non-5-ARI         | 3 years                                                   | NA                                                                              | 0.62 (0.43–0.89)                                                               |
| Finelli et al. | Cohort study  | Canada        | 70              | 218               | 65.6            | 63.8          | 5-ARI           | Non-5-ARI         | 38.5 months                                              | NA                                                                              | 0.506 (0.301–0.852)                                                           |

5-ARI: 5α-reductase inhibitors; RR: relative risk; CI: confidence interval; PSA: prostate-specific antigen; IPSS: International Prostate Symptom Score; BPH: benign prostatic hyperplasia; NA: not available; RCT: randomized controlled trial; –: not available
duration of treatment (Table 2). In the subgroup analysis stratified by tumor grade, the incidence of low-grade (Gleason score 2–6) and intermediate-grade prostate cancer was reduced by 32.0% and 19.1% among the 5-ARI group, respectively. However, no obvious influence was observed in the risk of high-grade tumors (Gleason score 8–10; RR = 1.19; 95% CI: 0.98–1.43; P = 0.069). In terms of study design, the pooled results of the cohort studies (RR = 0.64; 95% CI: 0.47–0.89; P = 0.008) and case–control studies (RR = 0.89; 95% CI: 0.84–0.94; P = 0.001) as well as RCTs (RR = 0.75; 95% CI: 0.71–0.79; P < 0.001) indicated that the incidence of prostate cancer was found to be dramatically decreased among the 5-ARI group. In terms of drug categories, a significant effect was noted in finasteride (RR = 0.75; 95% CI: 0.70–0.81; P < 0.001) as well as dutasteride (RR = 0.75; 95% CI: 0.68–0.81; P < 0.001). In terms of ethnicity, a beneficial effect of 5-ARI was seen in mixed ethnicity (RR = 0.74, 95% CI: 0.69–0.80; P < 0.001) and Asian ethnicity (RR = 0.57; 95% CI: 0.36–0.89; P = 0.013), but not in Caucasians (RR = 0.72; 95% CI: 0.49–1.06; P = 0.093). In terms of 5-ARI treatment duration, a stronger link was obtained in groups with a treatment duration of 5–10 years (RR = 0.54; 95% CI: 0.33–0.89; P = 0.014) and >10 years (RR = 0.49; 95% CI: 0.31–0.77; P = 0.002) when compared with treatment duration <5 years (RR = 0.79; 95% CI: 0.68–0.92; P = 0.003).

Sensitivity analysis

We drew sensitivity analyses to estimate the impact of each study on the pooled RR. Marked changes were absent in the pooled RR, with a range from 0.72 (95% CI: 0.63–0.82; P < 0.001) to 0.76 (95% CI: 0.69–0.84; P < 0.001) (Table 3 and Supplementary Figure 3). Sensitivity analyses were also adopted for the studies that included the prostate-specific antigen (PSA) variable. The pooled RR ranged from 0.57 (95% CI: 0.37–0.88; P < 0.001) to 0.73 (95% CI: 0.56–0.95; P = 0.009) (Supplementary Table 3), indicating that the results were not dominated by any one study.

Publication bias

Significant publication bias was absent according to Begg’s test (P>|z| = 0.474; z-value is a statistic to evaluate the existence of “publication bias” by determining whether the correlation between the standardized effect scale and variance is statistically significant) as shown in Supplementary Figure 4.

5-ARI and cancer-specific mortality of prostate cancer

Six studies focused on the cancer-specific mortality of prostate cancer.16–18,29–31 The pooled RR for cancer-specific mortality of prostate cancer in patients with 5-ARI exposure as compared with the control group was 1.0 (95% CI: 0.95–1.05; P = 0.016; Supplementary Figure 5), revealing that 5-ARI treatment was not closely related to the cancer-specific mortality of prostate cancer.

5-ARI and progression of prostate cancer in men under active surveillance

Two studies assessed the progression of low-risk prostate cancer.32,33 The pooled RR for progression of cancer in patients with low-risk prostate cancer receiving 5-ARI as compared with those not receiving 5-ARI was 0.58 (95% CI: 0.43–0.78; P < 0.001; Supplementary Figure 6), demonstrating that a benefit of 5-ARI treatment to delay progression of low-risk prostate cancer existed.

DISCUSSION

The effect of 5-ARI on the risk of prostate cancer has been widely discussed for a long time, but has not reached a unanimous conclusion. The goal of the present meta-analysis was to generate evidence regarding the effect of 5-ARI on risk of prostate cancer. Our results indicated that the incidence of prostate cancer was decreased frequently

Table 2: Subgroup analysis of the association between 5α-reductase inhibitors and incidence of prostate cancer

| Category                  | Subgroup                      | Number of studies | Heterogeneity | RR (95% CI)            | P    |
|---------------------------|-------------------------------|-------------------|---------------|------------------------|------|
| Tumor grade               | Low-grade Gleason score ≤6   | 7                 | 82.9%         | 0.68 (0.57–0.81)       | <0.001|
|                           | Moderate-grade Gleason score=7 | 4                 | 57.3%         | 0.81 (0.67–0.97)       | 0.023|
|                           | High-grade Gleason score 7–108–10 | 7                 | 54.2%         | 1.19 (0.98–1.43)       | 0.069|
| Study design              | Cohort study                  | 4                 | 68.7%         | 0.64 (0.47–0.89)       | 0.008|
|                           | Case–control                  | 2                 | 0             | 0.89 (0.84–0.94)       | 0.001|
|                           | RCT                           | 4                 | 44.8%         | 0.75 (0.71–0.79)       | <0.001|
| Drug categories           | Dutasteride                   | 4                 | 44.5%         | 0.75 (0.68–0.81)       | <0.001|
|                           | Finasteride                   | 3                 | 25.6%         | 0.75 (0.70–0.81)       | <0.001|
| Duration of treatment     | ≤5 years                      | 3                 | 81.3%         | 0.79 (0.68–0.92)       | 0.003|
|                           | 5–10 years                    | 3                 | 76.5%         | 0.54 (0.33–0.89)       | 0.014|
|                           | >10 years                     | 1                 | 76.5%         | 0.54 (0.33–0.89)       | 0.014|
| Race                      | Mixed                         | 5                 | 27.6%         | 0.74 (0.69–0.80)       | <0.001|
|                           | Asian                         | 2                 | 0             | 0.57 (0.36–0.89)       | 0.013|
|                           | Caucasians                    | 3                 | 79.4%         | 0.72 (0.49–1.06)       | 0.093|

RR: relative risk; CI: confidence intervals; –: not available.
among the 5-ARI exposure group (RR = 0.74; 95% CI: 0.66–0.82), implying that 5-ARI treatment has a protective effect on the occurrence of prostate cancer. Subgroup analyses further clarified that 5-ARI treatment could lead to a lower risk of low-grade (Gleason score ≤ 6) and intermediate-grade cancer (Gleason score 7) by 32.0% and 19.1%, respectively, whereas 5-ARI treatment was marginally related to the risk of high-grade cancer (RR = 1.19; 95% CI: 0.98–1.43). Furthermore, we failed to identify a significant link between 5-ARI exposure and prostate cancer-specific mortality (RR = 1.0; 95% CI: 0.95–1.05; P = 0.916). In addition, it was observed that patients with low-risk prostate cancer who accepted 5-ARI compared with the placebo group had remarkably lower progression (RR = 0.58; 95% CI: 0.43–0.78; P < 0.001).

Previous researchers have noted that 5-ARI exposure exhibited a protective role on the incidence of low-grade prostate cancer, but there was no consensus on the impact of the drug on the incidence of high-grade prostate cancer. Based on the two clinical trials, the hazard reduced by 23%–25% after 5-ARI exposure for overall incidence of prostate cancer. In line with these studies, the meta-analysis demonstrated that a protective effect of 5-ARI treatment against overall incidence of prostate cancer was evident. Androgen has the function of maintaining prostate growth and development. In the androgen-free environment, prostate cells will spontaneously undergo apoptosis, while in the normal androgen-level environment, prostate cells can continue to proliferate and differentiate. Androgen has the same effect on hormone-sensitive prostate cancer cells. Individuals who accepted 5-ARI exhibited a dramatically lower level of DHT in their prostate tissue. Imperato-McGinley et al. stated that PSA expression could not be detected among Type II 5α-reductase-free populations. They further observed a significant shrinking in prostate size. It was unexpected that the risk of suffering from prostate cancer was absent among these patients during follow-up. The observation that 5-ARI exhibited advantages in the reduction of prostate cancer incidence may be explained by detection bias. Currently, prostate cancer screening in clinical work is mainly conducted through the serum PSA test. The level of PSA was found to be obviously decreased in subjects who accepted 5-ARI. In theory, patients would experience a significantly weakened probability for biopsy after 5-ARI treatment, and the corresponding result is a lower rate of detection of prostate cancer. Intriguingly, a study by Preston et al. in 2014 reported that the probability of prostate biopsy was 9% in the general population, while it was 24% among individuals after 5-ARI treatment. Similarly, the results were consistent with another study, which indicated that prostate cancer detected by prostate biopsies driven by elevated PSA in the dutasteride group accounted for 28%–29% of cancer, compared with 24% in the placebo group. Therefore, detection bias was not a convincing explanation for the advantages of 5-ARI in the reduction incidence of low-grade and intermediate-grade tumors.

Subgroup analyses demonstrated that 5-ARI treatment exhibited no distinct influence on the hazard of incidence of high-grade prostate cancer (Gleason 7–10/8–10; RR = 1.19; 95% CI: 0.98–1.43). However, it was reported that subjects who accepted 5-ARI treatment exhibited a distinctly higher incidence of higher-grade tumors. A possible explanation for this potential link was that 5-ARI treatment was related to a lower level of DHT, and the morphology of prostate cells induced by this lower level of DHT appeared to be similar to that of high-grade tumors. Previous studies have reported that prostate cancer patients undergo a degree of change in the morphology of cancer cells after androgen deprivation treatment, rendering cancer cells similar to the morphology of high-grade prostate cancer. It was also reported that lower levels of testosterone could be linked to the advanced tumor grades and poor clinical outcomes of prostate cancer when compared with patients with normal testosterone levels. It was also possible that 5-ARI treatment could change the microenvironment in which the tumor grows to a certain extent. This microenvironment change is beneficial to the transformation of low-grade tumors into high-grade tumors. In addition, 5-ARI treatment exhibited a greater impact on the incidence of low-grade malignancies and less of an impact on the incidence of high-grade tumors. Subjects who accepted 5-ARI experienced a relatively decreased incidence of low-grade and intermediate-grade tumors. Therefore, the rate of detection of high-grade tumors in the 5-ARI group will increase, although 5-ARI were not related to high-grade tumors, because it has been suggested that this may be caused by the fact that 5-ARI treatment could shrink the prostate gland and lead to the increased detection sensitivity of prostate cancer. Furthermore, another explanation for the increase in the incidence of high-grade cancer in the 5-ARI treatment group was due to detection bias, rather than the biological characteristics of the tumor. Cohen et al. found that the median prostate volume was 25.1 ml in the 5-ARI treatment group and 33.5 ml in the placebo group. At the final biopsy, the median prostate volume of prostate cancer patients in the 5-ARI treatment group was 24.4 ml, and the placebo group was 31.9 ml. It has been shown that PCa detection rates are higher in smaller prostate glands. The increased risk of high-grade tumors in the 5-ARI treatment group occurred in the early stages of 5-ARI treatment rather than increasing over time, but this does not support the theory that 5-ARI induce high-grade cancer. A possible reason for this situation is that 5-ARI improve the sensitivity of the PSA test in detecting high-grade tumors.

The present meta-analysis also stated that 5-ARI treatment was not closely correlated with the cancer-specific mortality of prostate cancer. The findings were in line with some relevant studies, which revealed that neither the hazard of high-grade tumors nor the cancer-specific mortality of prostate cancer were related to 5-ARI treatment. Furthermore, another explanation for the increase in the incidence of high-grade prostate cancer in the 5-ARI treatment group was due to detection bias, rather than the biological characteristics of the tumor. Cohen et al. found that the median prostate volume was 25.1 ml in the 5-ARI treatment group and 33.5 ml in the placebo group. At the final biopsy, the median prostate volume of prostate cancer patients in the 5-ARI treatment group was 24.4 ml, and the placebo group was 31.9 ml. It has been shown that PCa detection rates are higher in smaller prostate glands. The increased risk of high-grade tumors in the 5-ARI treatment group occurred in the early stages of 5-ARI treatment rather than increasing over time, but this does not support the theory that 5-ARI induce high-grade cancer. A possible reason for this situation is that 5-ARI improve the sensitivity of the PSA test in detecting high-grade tumors.

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mortality increases with incidence of high-grade cancer. Intriguingly, the present meta-analysis did not identify any connection between 5-ARI exposure and prostate cancer-specific mortality. Overall, these findings support the notion that 5-ARI exposure was not related to the incidence of high-grade prostate cancer.

Some potential limitations should be acknowledged in this meta-analysis. First, although subgroup analyses and sensitivity analysis were adopted to explore the potential origin, substantial heterogeneity still existed. Second, we did not undertake a dose-response analysis for the effect of 5-ARI on the risk of prostate cancer as a result of the limited data available. Third, the number of included studies that focused on the influence of 5-ARI on cancer-specific mortality and progression of low-risk tumors was limited, especially studies focused on the progression of low-risk tumors. As a result, high-quality, prospective, multicenter studies with long follow-up periods are still needed to confirm our results.

CONCLUSION

Our results indicated that 5-ARI treatment exhibited a protective role on the incidence of low-grade and intermediate-grade prostate cancer, but not high-grade cancer. The results also showed that there was no close link between 5-ARI treatment and prostate cancer-specific mortality. In addition, it is important to note that 5-ARI treatment has a protective role that has a dramatic benefit by delaying the progression of low-risk tumors.

AUTHOR CONTRIBUTIONS

LML and RDY carried out the study design and drafted the manuscript. JMW and SKZ participated in data collection. YZL, ZG Zhu, and QX performed the data analysis. ZG Zhao conceived of the study and revised the manuscript. All authors read and approved the final manuscript.

COMPETING INTERESTS

All authors declared no competing interests.

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Supplementary Information is linked to the online version of the paper on the Asian Journal of Andrology website.

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Supplementary Figure 1: Risk of bias graph: review authors’ judgments about each risk of bias item presented as percentages across all the included studies.

Supplementary Figure 2: Risk of bias summary: review authors’ judgments about each risk of bias item for each included study.
Supplementary Figure 3: Sensitivity analysis after each study was excluded by turns.

Supplementary Figure 4: Begg's test to detect publication bias.

Supplementary Figure 5: Forest plots of meta-analysis of the included studies on the association between 5α-reductase inhibitor therapy and cancer-specific mortality of prostate cancer.

Supplementary Figure 6: Forest plots of meta-analysis of the included studies on the association between 5α-reductase inhibitor therapy and progression of prostate cancer in men on active surveillance.
### Supplementary Table 1: PRISMA Checklist

| Section/topic          | # | Checklist item                                                                                                                                                                                                 | Reported on page # |
|-----------------------|---|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|
| **Title**             | 1 | Identify the report as a systematic review, meta-analysis, or both                                                                                                                                               | 1                 |
| **Abstract**          |   |                                                                                                                                                                                                            | 1                 |
| Structured summary    | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number | 1                 |
| **Introduction**      |   |                                                                                                                                                                                                            | 2                 |
| Rationale             | 3 | Describe the rationale for the review in the context of what is already known.                                                                                                                                  | 2                 |
| Objectives            | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS) | 2                 |
| **Methods**           |   |                                                                                                                                                                                                            | 4                 |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number                                           | No                |
| Eligibility criteria  | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale                                      | 4                 |
| Information sources   | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched                                            | 4                 |
| Search                | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated                                                                                      | 4                 |
| Study selection       | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis)                                                                 | 4                 |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators                                           | 4                 |
| Data items            | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made                                                                              | 4                 |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis | 5                 |
| Summary measures      | 13 | State the principal summary measures (e.g., risk ratio, difference in means)                                                                                                                                     | 5                 |
| Synthesis of results  | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., F) for each meta-analysis                                                                 | 5                 |
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies)                                                                  | 5                 |
| Additional analyses   | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta‐regression), if done, indicating which were prespecified                                                                          | 5                 |
| **Results**           |   |                                                                                                                                                                                                            | 6                 |
| Study selection       | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.                                                                 | 5                 |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.                                                                            | 5                 |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).                                                                                                          | 6                 |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.             | 6                 |
| Synthesis of results  | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency.                                                                                                            | 6                 |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see item 15).                                                                                                                               | 7                 |
| Additional analysis   | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression) (see item 16))                                                                                               | 6                 |
| **Discussion**        |   |                                                                                                                                                                                                            | 7                 |
| Summary of evidence   | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers)                                          | 7-9               |
| Limitations           | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias)                                                            | 9                 |
| Conclusions           | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research                                                                                           | 9                 |
| **Funding**           |   |                                                                                                                                                                                                            | NA                |
| Funding               | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review                                                                       | NA                |

Moher et al.19 NA: not available; PICOS: (P) participants, (I) interventions, (C) comparisons, (O) outcomes, (S) study design.
### Supplementary Table 2: Newcastle–Ottawa Scale assessment of the quality of the cohort and case–control studies

| Study                | Selection | Comparability | Exposure/outcome | Total scores |
|----------------------|-----------|---------------|------------------|--------------|
|                      | 1         | 2             | 3                | 4            | 5       | 6       | 7 | 8 | 9 |
| Preston et al. 2014  | Yes       | Yes           | Yes              | No           | Yes     | No      | Yes | Yes | Yes | 7 |
| Wallerstedt et al. 2018 | Yes   | Yes           | Yes              | No           | No      | Yes     | Yes | Yes | Yes | 7 |
| Murtola et al. 2009  | Yes       | Yes           | Yes              | Yes          | No      | Yes     | Yes | No  | Yes | 7 |
| Zhu et al. 2010      | Yes       | Yes           | Yes              | Yes          | Yes     | Yes     | No  | Yes | Yes | 7 |
| Murtola et al. 2016  | Yes       | Yes           | Yes              | Yes          | Yes     | No      | Yes | Yes | Yes | 8 |
| Kjellman et al. 2013 | Yes       | Yes           | Yes              | Yes          | No      | Yes     | No  | Yes | Yes | 7 |
| Preston et al. 2014  | Yes       | Yes           | Yes              | Yes          | Yes     | Yes     | No  | Yes | Yes | 7 |
| Azoulay et al. 2015  | Yes       | Yes           | No               | Yes          | Yes     | Yes     | Yes | Yes | Yes | 7 |
| Wallner et al. 2016  | Yes       | Yes           | Yes              | Yes          | Yes     | Yes     | Yes | Yes | No  | 8 |
| Finelli et al. 2010  | Yes       | Yes           | Yes              | No           | No      | Yes     | Yes | No  | Yes | 6 |
| Liang et al. 2012    | Yes       | Yes           | Yes              | Yes          | No      | Yes     | No  | Yes | No  | 6 |
| Robinson et al. 2013 | Yes       | Yes           | Yes              | Yes          | Yes     | No      | Yes | No  | Yes | 7 |

1: indicates that the exposed cohort was representative of the population; 2: indicates that the nonexposed cohort was drawn from the same population; 3: indicates that the exposure ascertainment was from secure records or a structured interview; 4: indicates that outcome of interest was not present at start of study; 5: indicates that the cohorts were comparable for age and sex; 6: indicates that the cohorts were comparable on all additional factor(s) reported; 7: indicates that the outcome was assessed from a secure record; 8: indicates that follow-up was long enough for outcomes to occur; 9: indicates that follow-up was complete.

### Supplementary Table 3: Sensitivity analyses for only the studies that included the prostate-specific antigen variable

| Study omitted         | RR (95% CI) for remainders | Heterogeneity |
|-----------------------|-----------------------------|---------------|
| Andriole et al. 2004  | 0.69 (0.50–0.95)            | 79.6          | 0.002         |
| Robinson et al. 2013  | 0.57 (0.39–0.83)            | 68.9          | 0.022         |
| Wallerstedt et al. 2018 | 0.73 (0.56–0.95)           | 73.8          | 0.009         |
| Murtola et al. 2009   | 0.57 (0.37–0.88)            | 85.6          | <0.001        |
| Roehrborn et al. 2011 | 0.65 (0.45–0.94)            | 81.3          | 0.001         |

RR: relative risk; CI: confidence interval