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Association Between 5α-Reductase Inhibitors and Prostate Cancer Mortality
A Systematic Review and Meta-analysis

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IMPORTANCE Recently, several large, high-quality analyses have shown opposing results regarding the association between 5α-reductase inhibitor (5-ARI) use and prostate cancer (PCa) mortality.

OBJECTIVE To systematically evaluate the current evidence regarding 5-ARI use and PCa mortality.

DATA SOURCES A literature search began in and was conducted through August 2022 using PubMed/Medline, Embase, and Web of Science databases.

STUDY SELECTION Studies were deemed eligible if they included male patients of any age who were 5-ARI users and were compared with those who were nonusers if they analyzed PCa mortality in randomized clinical trials and prospective or retrospective cohort studies.

DATA EXTRACTION AND SYNTHESIS This study was reported in accordance with Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline. Adjusted hazard ratios (HRs) were extracted from published articles. Data analysis was performed in August 2022.

MAIN OUTCOMES AND MEASURES The primary outcome was PCa mortality among 5-ARI users vs nonusers. The inverse variance method with adjusted HRs and random-effect models were used to determine the association between 5-ARI use and PCa mortality. Two subgroup analyses were performed to assess the effect of 2 main confounders: prostate-specific antigen level and PCa diagnosis at baseline.

RESULTS Among 1200 unique records screened, 11 studies met the inclusion criteria. A total of 3 243 575 patients were included: 138 477 users of 5-ARI and 3 105 098 nonusers. There was no statistically significant association between 5-ARI use and PCa mortality (adjusted HR, 1.04; 95% CI, 0.80-1.35; *P* = .79). No significant association was found when the analysis was restricted to studies that excluded patients with a diagnosis of PCa at baseline (adjusted HR, 1.00; 95% CI, 0.60-1.67; *P* = .99) or the analysis was restricted to prostate-specific antigen–adjusted studies (adjusted HR, 0.76; 95% CI, 0.57-1.03; *P* = .08).

CONCLUSIONS AND RELEVANCE This systematic review and meta-analysis, which draws on 2 decades of epidemiologic literature and includes more than 3 million patients, found no statistically significant association between 5-ARI use and PCa mortality but provides important data to inform clinical care.

Supplemental content

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The development of 5α-reductase inhibitors (5-ARIs) paved the way 2 decades ago for chemoprophylaxis of prostate cancer (PCa).[1] Two large randomized clinical trials (RCTs; namely, the Prostate Cancer Prevention Trial[2] and the Reduction by Dutasteride of Prostate Cancer Events trial[3]) observed 25% and 23% risk reductions, respectively, in the incidence of PCa among 5-ARI users. However, patients randomly assigned to receive 5-ARIs had an unexpected increased risk of high-grade tumors compared with patients in the placebo group. These findings sparked a controversy about the association between 5-ARI use and PCa mortality and led to a US Food and Drug Administration safety warning in 2011. Two recent high-quality cohort studies have reignited the controversy. In 2019, Sarkar et al[4] reported in a cohort of 80 875 men with stage I to V PCa that 5-ARI use was associated with an increase, unadjusted for prostate-specific antigen (PSA) screening, in PCa-related mortality. In 2022, Björnebo et al[5] found, in a cohort of 349 152 men without a prior diagnosis of PCa, a significant decrease, adjusted for PSA screening, in the risk of PCa mortality. We performed a systematic review and meta-analysis of the literature, with particular focus on determining the direction of the association between 5-ARI use and PCa mortality when key confounders were adjusted.

Key Points

Question Is 5α-reductase inhibitor (5-ARI) use associated with an increased risk of prostate cancer (PCa) mortality?

Findings In this systematic review and meta-analysis that included 138 477 users of 5-ARI and 3 105 098 nonusers, no statistically significant association between 5-ARI use and PCa morality was found (adjusted hazard ratio, 1.04; 95% CI 0.80-1.35; $P = .79$).

Meaning This meta-analysis, which draws on 2 decades of epidemiologic literature and includes more than 3 million patients, provides important data to inform clinical care.

Methods

The systematic review and meta-analysis was conducted in line with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline (PROSPERO registration: CRD42022356865). Data analysis was performed in August 2022. The primary outcome was PCa mortality among 5-ARI users vs nonusers. The risk of bias (RoB) was assessed using the Cochrane RoB tool for randomized trials, and the Newcastle-Ottawa Scale was used for nonrandomized studies. The inverse variance method with adjusted hazard ratios (HRs) and random-effect models were used to determine the association between 5-ARI use and PCa mortality. Two subgroup analyses were performed to assess the effect of 2 main confounders: PSA level and PCa diagnosis at baseline. Statistical significance was set at $P < .05$.

Results

Among 1200 unique records screened, 11 studies[4-14] met our inclusion criteria (**Table**). One study was an RCT, and 10

Table. Study Characteristics

Source	Country	Years of data	Study design	PCa diagnosis at baseline	Total No. of 5-ARI users	Duration of 5-ARI use[a]	Total No. of nonusers	Follow-up, y[a]
Ørsted et al,[6] 2011	Denmark	1980-2006	Cohort study	No	51 219	NR	2 390 075	NR
Kjellman et al,[7] 2013	Denmark	1989-2006	Cohort study	Yes	199	168 d (range, 28-2731 d)	2806	3.7 (range, 0-15.9)
Azoulay et al,[8] 2015	UK	1999-2012	Cohort study	Yes	574	12.8 mo (range, 28 d to 12.6 y)	13 318	4.5 (3.1)
Wallner et al,[9] 2016	US	1992-2007	Cohort study	No	25 388	2.2 (2.1) y	149 507	4.0 (3.1) vs 3.0 (2.6) (5-ARI users vs nonusers)
Goodman et al,[10] 2019	US	1994-2014	RCT	No	9423	Median, 7 y	9457	18.4 (IQR, 14.4-18.7) for placebo group; 18.4 (IQR, 17.3-18.7) for finasteride group
Sarkar et al,[4] 2019	US	2001-2015	Cohort study	Yes	8587	4.8 y (IQR, 26.0-7.80 y)	72 288	5.9 (IQR, 3.50-8.80)
Van Rompay et al,[11] 2019	US	1995-2014	Cohort study	No	4571	Median, 14.5 mo	1677	4.1 (5.1) vs 6.3 (8.0) (5-ARI users vs nonusers)
Kumar et al,[12] 2019	US	2008-2015	Cohort study	Yes	2373	2.5 y (IQR, 1.4-3.7 y)	27 940	3.7 (IQR, 2.3-5.3)
Bonde Miranda et al,[13] 2020	Sweden	2007-2016	Cohort study	Yes	4854	NR	72 130	5.3 (2.7) vs 6.7 (3.0) (5-ARI users vs nonusers)
Björnebo et al,[5] 2022	Sweden	2007-2018	Cohort study	No	26 190	Median, 4.5 y	322 962	8.2
Vaselkiv et al,[14] 2022	US	1996-2017	Cohort study	No	5099	Mean, 4 y	32 938	NR

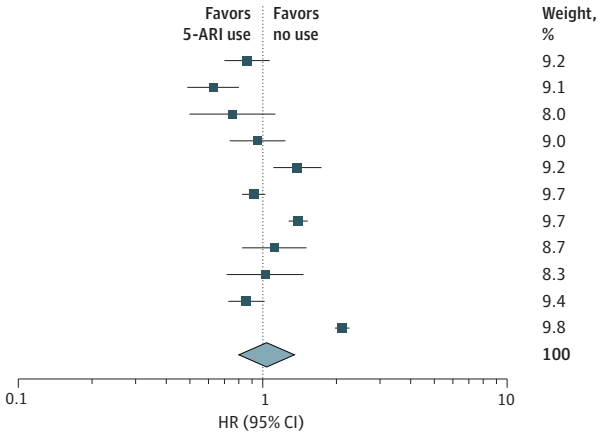
Abbreviations: NR, not reported; PCa, prostate cancer; RCT, randomized clinical trial; 5-ARI, 5α-reductase inhibitor.

[a] Data are reported as mean (SD) or median (range or IQR) values in most studies.

Figure. Meta-analysis of the Risk of Prostate Cancer Mortality Among 5-ARI Users vs Nonusers

Study or subgroup	log HR	SE	HR (95% CI)
Azoulay et al,[8] 2015	-0.152	0.1088	0.86 (0.69-1.06)
Björnebo et al,[5] 2022	-0.4709	0.1237	0.62 (0.49-0.80)
Goodman et al,[10] 2019	-0.2893	0.2061	0.75 (0.50-1.12)
Kjellman et al,[7] 2013	-0.0526	0.1338	0.95 (0.73-1.23)
Kumar et al,[12] 2019	0.3221	0.1157	1.38 (1.10-1.73)
Bonde Miranda et al,[13] 2020	-0.0895	0.0556	0.91 (0.82-1.02)
Sarkar et al,[4] 2019	0.3293	0.0461	1.39 (1.27-1.52)
Van Rompay et al,[11] 2019	0.1044	0.1545	1.11 (0.82-1.50)
Vaselkiv et al,[14] 2022	0.0187	0.1843	1.02 (0.71-1.46)
Wallner et al,[9] 2016	-0.1574	0.0873	0.85 (0.72-1.01)
Ørsted et al,[6] 2011	0.7441	0.0348	2.10 (1.97-2.25)
Total (95% CI)			**1.04 (0.80-1.35)**

Heterogeneity: $\tau^2 = 0.19$; $\chi^2 = 313.42$; $df = 10$; $P < .001$; $I^2 = 97\%$
Test for overall effect: $z = 0.27$; $P = .79$



5ARI indicates 5α-reductase inhibitors; HR, hazard ratio.

were registry-based cohort studies. A total of 3 243 575 patients were included: 138 477 users of 5-ARI and 3 105 098 nonusers. The RoB was judged as low for 8 studies and moderate for 2 studies.

There was no statistically significant association between 5-ARI use and PCa mortality (adjusted HR, 1.04; 95% CI, 0.80-1.35; $P = .79$) (**Figure**). The shape of the funnel plots was symmetric, indicating no major publication bias. However, the Cochrane Q ($\tau^2 = 0.19$; $\chi^2 = 313.42$; $df = 10$; $P < .001$) and I^2 (97%) tests revealed significant heterogeneity. Metaregression analysis to explain heterogeneity showed no statistically significant effect of any of the variables assessed (country of research, years of data, PSA screening-adjusted risk estimate, patient age, follow-up duration, diagnosis of PCa at baseline, and duration of 5-ARI use).

No significant association was found when the analysis was restricted to studies that excluded patients with a diagnosis of PCa at baseline (adjusted HR, 1.00; 95% CI, 0.60-1.67; $P = .99$). In 3 studies adjusted for PSA level, the forest plot showed the suggestion of a lower risk of PCa mortality among 5-ARI users, but it did not reach the predefined threshold (adjusted HR, 0.76; 95% CI, 0.57-1.03; $P = .08$).

Discussion

This systematic review and meta-analysis found no statistically significant association between 5-ARI use and PCa mortality. In a subgroup analysis limited to PSA screening-adjusted studies, we found a nonstatistically significant 24% reduction in cancer mortality among 5-ARI users.

Limitations

Limitations include significant heterogeneity, suggesting the potential role of confounding factors that were not accounted for in the individual studies; a risk of misclassification bias, in which 5-ARIs were not used as prescribed; and a lack of long-term data on the risk of metastatic, castration-resistant and fatal PCa.

Conclusions

This systematic review and meta-analysis found no association between 5-ARI use and PCa mortality. This meta-analysis, which draws on 2 decades of epidemiologic literature and includes more than 3 million patients, provides important data to inform clinical care.

ARTICLE INFORMATION

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Author Contributions: Dr Baboudjian had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Baboudjian, Rouprêt, Ploussard.
Acquisition, analysis, or interpretation of data: Baboudjian, Gondran-Tellier, Dariane, Fiard, Fromont, Ploussard.
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