EUROPEAN UROLOGY ONCOLOGY xxx (xxxx) xxx–xxx

available at www.sciencedirect.com
journal homepage: euoncology.europeanurology.com

European Association of Urology

Nonsurgical Interventions to Prevent Disease Progression in Prostate Cancer Patients on Active Surveillance: A Systematic Review and Meta-analysis

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Article info

Article history:
Received 24 August 2023
Received in Revised form
17 September 2023
Accepted 10 October 2023

Associate Editor:
Elena Castro

Keywords:
Prostate cancer
Active surveillance
5-Alpha reductase inhibitor
Statin
Diet
Exercise
Coffee

Abstract

Context: Active surveillance (AS) is a standard of care for patients with low-risk and selected intermediate-risk prostate cancer (PCa). Nevertheless, there is a lack of summary evidence on how to impact disease trajectory during AS.

Objective: To assess which interventions prevent PCa progression effectively during AS.

Evidence acquisition: We queried PubMed, Scopus, and Web of Science databases to identify studies examining the impact of interventions aimed at slowing disease progression during AS. The primary endpoint was PCa progression, the definition of which must have included pathological upgrading. The secondary endpoint included treatment toxicities.

Evidence synthesis: We identified 22 studies, six randomized controlled trials and 16 observational studies, which analyzed the association between different interventions and PCa progression during AS. The interventions considered in the studies included 5-alpha reductase inhibitors (5-ARIs), statins, diet, exercise, chlormadinone, fexapotide triflutate (FT), enzalutamide, coffee, vitamin D3, and PROSTVAC. We found that administration of 5-ARIs was associated with improved progression-free survival (PFS; hazard ratio: 0.59; 95% confidence interval 0.48–0.72), with no increased toxicity signals. Therapies such as vitamin D3, chlormadinone, FT, and enzalutamide have shown some

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https://doi.org/10.1016/j.euo.2023.10.010

Please cite this article as: A. Matsukawa, T. Yanagisawa, K. Bekku et al., Nonsurgical Interventions to Prevent Disease Progression in Prostate Cancer Patients on Active Surveillance: A Systematic Review and Meta-analysis, Eur Urol Oncol (2023), https://doi.org/10.1016/j.euo.2023.10.010

Vitamin D3
PROSTVAC

efficacy. However, these anticancer drugs have been associated with treatment-related adverse events in up to 88% of patients.

Conclusions: The use of 5-ARIs in PCa patients on AS is associated with longer PFS. However, for the other interventions, it is difficult to draw clear conclusions based on the weak available evidence.

Patient summary: Patients with prostate cancer managed with active surveillance (AS) who are treated with 5-alpha reductase inhibitors have a lower risk of disease progression, with minimal adverse events. Other interventions require more studies to determine their efficacy and safety profile in men on AS.

1. Introduction

Active surveillance (AS) is a standard of care for patients with low-risk and selected favorable intermediate-risk prostate cancer (PCa) [1]. Compared with AS, local radical therapy is associated with an increased risk of long-term, harmful complications such as erectile dysfunction, and gastrointestinal or genitourinary toxicity [2]. Even focal therapy is associated with unnecessary intervention, complications, and costs [3]. Opting to undergo AS allows patients to maintain their health-related quality of life (HRQoL) without compromising survival outcomes. Even though early-stage PCa is associated with favorable outcomes, the most extensive studies on AS to date show that up to 60% of patients ultimately go onto local radical treatment due to disease progression or patient desire [3–5].

In clinical practice, multiple tools, including biomarkers, clinical parameters such as prostate magnetic resonance imaging (MRI), or nomograms, help select appropriate patients and tailor AS intensity [6–8]. However, no interventions have been proved to delay PCa progression, although patients often inquire about the potential benefits of lifestyle changes, diet, and/or specific drugs [9–31]. Despite some studies providing evidence of the efficacy of these different approaches in preventing PCa progression, the absence of summary data does not allow for reliable conclusions. Furthermore, when considering interventions during AS, one needs to take treatment-related adverse events (TRAEs) into consideration as maintaining HRQoL is the differential benefit of AS over radical therapies.

Therefore, we conducted a systematic review and meta-analysis to synthesize the data on strategies for delaying disease progression for patients with PCa undergoing AS. Our goal was to analyze the efficacy as well as the safety of specific interventions; this is expected to provide clarity on the optimal treatment strategy for patients with PCa under AS.

2. Evidence acquisition

Our study protocol is registered with the International Prospective Register of Systemic Reviews database (PROSPERO: CRD42023423971). This meta-analysis adheres to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement and AMSTAR2 checklist [32,33].

2.1. Search strategy

In June 2023, a comprehensive search was conducted using the PubMed, Scopus, and Web of Science databases to identify studies that evaluated oncological outcomes of interventions for patients with PCa undergoing AS. The search terms included the following: "prostate cancer," "active surveillance," and "progression." The detailed search strategy is shown in the Supplementary material. Initial screening based on the titles and abstracts was performed by two investigators to identify eligible studies. Potentially relevant studies were subjected to a full-text review. To find additional studies of interest, manual searches of reference lists of relevant articles were also carried out. Disagreements were settled by consensus with coauthors.

2.2. Study selection

Included studies must have analyzed patients diagnosed with PCa on AS (patients), who had undergone specific nonsurgical interventions aiming at delaying disease progression (interventions), and were compared with those managed with patients on AS without interventions (comparison) to assess the impacts of these interventions on PCa progression (outcome). The primary outcome of interest was PCa progression defined as pathological reclassification. However, studies that include both pathological progression and other criteria for PCa progression, such as prostate-specific antigen (PSA) or clinical progression, were also included in this review, provided that these were analyzed separately. Studies that did not feature original patient data, single-arm studies, reviews, editorial comments, replies to authors, case reports, and articles not written in English were excluded. In instances of duplicate patient cohorts, the most recent publication was selected. References from all included papers were examined with the aim of identifying further pertinent studies. The details of study selection are outlined in the PRISMA flow chart (Fig. 1).

2.3. Data extraction

Data on study design, patient characteristics, AS details, and outcomes were extracted independently by two authors. Subsequently, the number of patients who experienced progression, the result of Kaplan-Meier analysis, the hazard ratios (HRs), and 95% confidence intervals (CIs) from Cox regression models for progression-free survival (PFS) were

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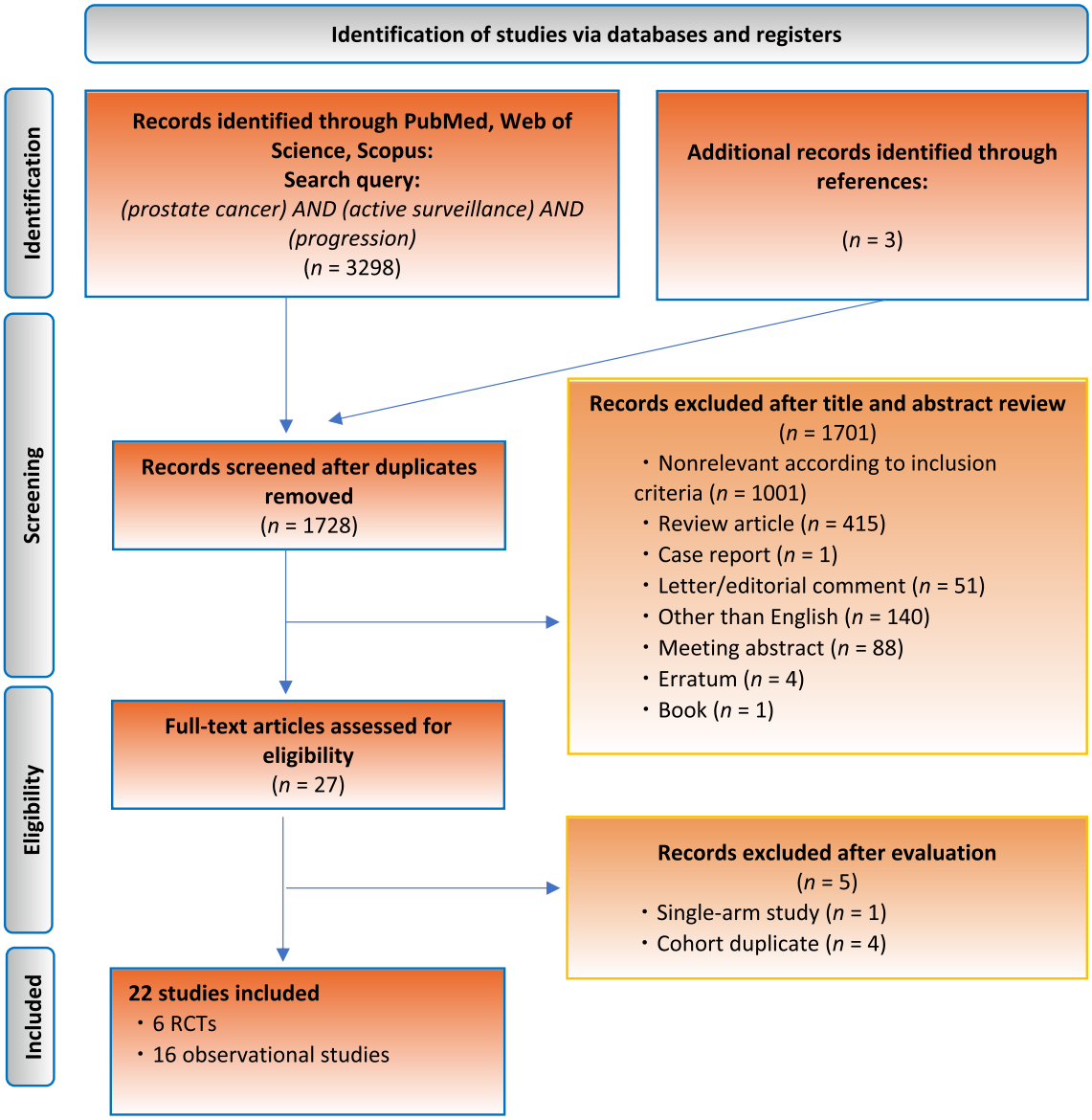

Fig. 1 – The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow chart, detailing the article selection process. RCT = randomized controlled trial.

retrieved. All included studies provided sufficient HR data for the meta-analysis. Studies lacking these data were not considered for the meta-analysis but were included in the systematic review. All discrepancies were resolved by consensus between coauthors. Two authors independently extracted data on studies, patients, and treatment characteristics. The HRs and 95% CIs for oncological outcomes, as well as the absolute numbers of TRAEs and pathological response characteristics, were obtained. The time from randomization to biochemical failure, local relapse, metastasis, or death was determined as the PFS [12]. The synthesis of the study outcomes and certainty assessments are presented in Tables 1–3.

2.4. Risk of bias assessment

Study quality and risk of bias were evaluated using the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool, along with the Risk-of-Bias (ROB version 2) tool, as outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Supplementary Fig. 2 and Supplementary Table 2) [34]. In the case of ROBINS-I, every bias domain and the overall risk of bias were classified as "low," "moderate," "serious," or "critical." The presence of confounders was determined by consensus and a review of the literature. The ROBINS-I and ROB assessments of each study were conducted independently by two authors.

2.5. Statistical analysis

2.5.1. Meta-analysis

Forest plots with HRs were utilized to assess the relationship between interventions and PFS. Studies employing Cox proportion or general logistic regression analyses were deemed ineligible for the meta-analysis. The presence of heterogeneity among the outcomes of included studies in

Table 1 – Basic characteristics of 22 studies analyzing the impact of intervention in prostate cancer treated with active surveillance

Author [Reference]	Name/ registration no.	Years	Study design	Recruitment years	Inclusion criteria	Definition of progression	Surveillance protocol	Trigger for earlier rebiopsy	Study arm treatment	Control arm treatment	Overall *N*	Study arm *N*	Control arm *N*
Pharmacological treatment													
5-Alpha reductase inhibitor													
Finelli et al. [27,28]		2021/ 2011	Retrospective study	1995–2016	PSA <10 ng/ml cT1c-T2a GG 1 Positive core ≤3, 50%	Upgrading Up volume (increased number of cores to ≥3, or any core involvement of >50%)	PSA: every 3 mo for 2 yr (6 mo in stable patients) DRE: every 6 mo Confirmatory biopsy: 12–18 mo Rebiopsy: every 2–3 yr until the patient reached 8 yr of age or refused MRI: performed at clinician's discretion	Rapid PSA velocity Abnormal DRE Discretion of the treating physician	5-ARI	AS	288	85	203
Ashrafi et al. [31]		2021	Retrospective study	2000	GS 3 + 3 or low volume GS 3 + 4 who deferred treatment cT1c/T2a PSA <20 Age 40–80 yr Life expectancy ≥10 yr	Upgrading Up volume (increase in maximum cancer core length ≥4 mm or ≥25%)	PSA: every 6 mo DRE: every year TRUS: every year Biopsy: 2–3 yearly or at any time	Changes in PSA, DRE, and TRUS	5-ARI (finasteride 5 mg or dutasteride 0.5 mg daily)	AS	361	119	242
Kearns et al. [21]	PASS/ NCT000756665	2019	Prospective cohort study	2008–2016	Diagnosed within 5 yr GS ≤3 + 4 Biopsy core ≤34%	Upgrading and/or up volume (biopsy core ≥34%)	PSA: every 3 mo Confirmatory biopsy: 6–12 mo after initial biopsy Rebiopsy: every 24 mo MRI: performed at clinician discretion	(20% occurring either earlier or later than protocol schedule)	5-ARI	AS	1007	107	902
Özkan et al. [17]		2018	Retrospective study	2002–2011	PSA ≤15 ng/ml PSAD ≤0.20 ng/ml/g Clinical stage ≤T2c GS ≤6 Cancer-positive cores ≤3 Not receiving prostate cancer treatment	Upgrading Up volume (percentage of cancer-positive cores)	PSA: every 3–6 mo within the first 2 yr, every 2 yr after 2nd year DRE: every 3–6 mo within the first 2 yr, every 2 yr after 2nd year Biopsy: every year	Increased PSA levels Abnormal DRE	5-ARI	AS	69	29	40
Dai et al. [29]		2018	Retrospective study	2002–2015	NCCN very low, low, favorable intermediate risk	Upgrading	PSA: every 6–12 mo DRE: every 6–12 mo Confirmatory biopsy: within 12 mo Rebiopsy: every 1–2 yr	Increased PSA levels Abnormal MRI Abnormal DRE	5-ARI	AS	371	70	301
Fleshner et al. [26]	REDEEM/ NCT00363311	2012	RCT	2006–2010	48–82 yr cT1c-T2a GS ≤6 Positive core ≤3 PSA ≤11 Diagnosed within 14 mo before screening	Pathological progression: Upgrading Up volume (positive cores ≥4, ≥50%) Therapeutic progression	PSA: every 3 mo for the 1st year, every 6 mo thereafter DRE: 18 mo and 3 yr Biopsy: 18mo and 3 yr	increased PSA levels Adverse change on DRE	Dutasteride	AS	302	147	155

Table 1 (**continued**)

Author [Reference]	Name/ registration no.	Years	Study design	Recruitment years	Inclusion criteria	Definition of progression	Surveillance protocol	Trigger for earlier rebiopsy	Study arm treatment	Control arm treatment	Overall *N*	Study arm *N*	Control arm *N*
Ross et al. [14]		2012	Retrospective study	1994–2010	T1c PSAD <0.15 GS ≤6 Positive core ≤3, ≤50%	Upgrading (Gleason pattern ≥4) Up volume (positive cores ≥3, >50%)	PSA: every 6 mo DRE: every 6 mo Biopsy: every year		5-ARI	AS	587	47	540
Statin													
Nyame et al. [18]		2019	Retrospective study	2005–2015	Favorable and select intermediate risk	Upgrading or up volume	PSA: every 6–12 mo DRE: every 6–12 mo Confirmatory biopsy: within 12 mo Rebiopsy: every 1–2 yr MRI: performed at clinician discretion	Discretion of each provider	Statin use	AS	635	356	279
Jayalath et al. [22]		2018	Prospective cohort study	1995–2016	GS <7 <4 positive cores, <50% involvement of any one core PSA <10.0 ng/dl	Pathological progression: Upgrading GS Up volume (≥4 positive cores, >50% core involvement) Therapeutic progression	PSA: every 3–6 mo DRE: every 3–6 mo Confirmatory biopsy: within 24 mo Rebiopsy: every 2–3 yr	(Patients who did not have a confirmatory biopsy within 24 mo of diagnosis were excluded)	Statin use	AS	797	188	609
Anticancer drugs													
Sugimoto et al. [10]	PROSAS/ UMIN000012284	2022	RCT	2013–2019	Diagnosed PCa by histological exam T1c, N0, M0, GS ≤6, PSA ≤10 Untreated PCa Within 6 mo of starting AS Age ≥65 ECOG PS 0 or 1	Upgrading Stage T2a Metastasis Up volume Onset of difficulty in urination or urinary symptoms requiring invasive treatment Investigator determines that 2nd-line treatment for PCa or BPH is needed	PSA: 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, and 36 mo Testosterone: 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, and 36 mo DRE: 6, 12, 18, 24, 30, and 36 mo Ultrasound: 6, 12, 18, 24, 30, and 36 mo Medical and biochemical examination: 1, 2, 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, and 36 mo Biopsy: 12 and 36 mo		Chlormadinone 50 mg for 3 yr + AS	Placebo + AS	143	71	72
Shore et al. [12]	Study NX03-0040/ NCT01620515	2020	RCT	2012–2018	T1c GG 1; prostate biopsy within previous 6 mo (≥10 cores; single core positive; ≤50% in the single positive core) PSA ≤10 ng/ml and no previous treatments for PCa	Upgrading	PSA: every 6 mo Physical examination: every 12 mo Biopsy: every 18 mo		FT 2.5 mg FT 15 mg Control AS	FT 2.5 mg: 49 FT 15 mg: 48 AS: 49			

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Table 1 (**continued**)

Author [Reference]	Name/ registration no.	Years	Study design	Recruitment years	Inclusion criteria	Definition of progression	Surveillance protocol	Trigger for earlier rebiopsy	Study arm treatment	Control arm treatment	Overall *N*	Study arm *N*	Control arm *N*
Shore et al. [11]	ENACT/ NCT02799745	2022	RCT	2016–2020	≥18 yr old Low or intermediate risk	Pathological progression: Upgrading Up volume (≥15% increased cancer positive cores) Therapeutic progression	PSA: every 3 mo DRE: every 6 mo Biopsy: 12 and 24 mo	Adverse change on DRE Increased PSA levels	Enzalutamide 160 mg for 1 yr	AS	227	114	113
PROSTVAC													
Parsons et al. [37]	NCT02326805	2023	RCT	2014–2017	50% random biopsy cores positive GG 2 cT2a PSA <20 ng/ml (PSA <10 ng/ml if on 5-ARI)	Upgrading	PSA: day 0, 84; 7–14 d after last vaccination; 6 mo DRE: day 0, 7–14 d after last vaccination, 6 mo Biopsy: 7–14 d after last vaccination		PROSTVAC	Empty vector control	154	106	48
Lifestyle modifications													
Diet													
Schenk et al. [13]	PASS/ NCT000756665	2023	prospective cohort study	2008–2013	Adenocarcinoma cT1–2, NX or N0, MX or M0 No previous treatment for prostate cancer ECOG PS 0 or 1	PSA ≥10 ng/ml PSADT <3 yr Upgrading Up volume	PSA: every 3 mo Confirmatory biopsy: 6–12 mo Rebiopsy: every 2 yr MRI: performed at clinician discretion	(20% occurring either earlier or later than protocol schedule)	HEI-2015 score: Low: 43.5–65.7 Medium: 65.8–74.5 High: 74.6–92.7) Mediterranean diet score: Low: 0–3 Medium: 4–5 High: 6–9 DASH diet score: Low: 12–22 Medium: 23–27 High: 28–37	HEI-2015 score: Low: 16 Medium: 18 High: 27 Mediterranean diet score: Low: 21 Medium: 17 High: 23 DASH diet score: Low: 17 Medium: 20 High: 24			
Gregg et al. [23,24]	NCT00490763	2021/ 2019	Prospective cohort study	2006–2012	Very low or low risk	Upgrading	PSA: every 6 mo DRE: every 6 mo Confirmatory biopsy: study entry Rebiopsy: every 1–2 yr		Mediterranean diet score: Low: 0–3 Medium: 4–5 High: 6–9	Low: 141 Medium: 171 High: 98			
						Upgrading Up volume			HEI-2015 score: Low: 34.8–63.3 Medium: 63.3–72.7 High: 72.9–95.1	Low: 137 Med: 137 High: 137			
Parsons et al. [15]	MEAL study/ NCT01238172	2020	RCT	2011–2015	50–80 yr old cT2a or less within 24 mo 70 yr GG <1 70 yr GG ≥2 or less PSA <10	PSA ≥ 10 ng/ml PSADT <3 yr Pathological progression Upgrading (age <70: GG ≤1, age ≥70: GG ≤2) Up volume (positive core ≥25%, ≥50% of any 1 core positive)	PSA: every 3 mo Biopsy: 24 mo	(The urologist or the participants will have the right to secure a biopsy earlier than 24 mo)	MEAL intervention + AS (7 daily vegetable-fruit servings, including at least 2 servings each of cruciferous vegetables and tomatoes)	AS	443	226	217

Table 1 (**continued**)

Author [Reference]	Name/ registration no.	Years	Study design	Recruitment years	Inclusion criteria	Definition of progression	Surveillance protocol	Trigger for earlier rebiopsy	Study arm treatment	Control arm treatment	Overall *N*	Study arm *N*	Control arm *N*
Vandersluis et al. [9]		2016	Prospective cohort study	Sunnybrook 2010–2011 Royal Marsden Hospital 2013	GS ≤6 cT1c or T2a GS 7 (4 + 3) Age ≥ 70, small proportion of Gleason 4	Sunnybrook: upgrading Royal Marsden: upgrading or PSADT <3 yr, PSA velocity >2.0 ng/ml/yr			Diet score: high scores to food (such as fish, tomato products, cruciferous vegetables, soy products, red grapes and/or red wine, and berries) that are believed to prevent prostate cancer, and low scores to foods (such as milk products, fast food, and red meat) that are believed to promote prostate cancer	Sunnybrook 131 Royal Marsden Hospital 106			
Exercise													
Brassetti et al. [30]		2021	Retrospective study	2006–2019	>10 yr life expectancy GG 1 ≤2 positive cores T1c-T2a PSA ≤10 PSAD <0.2	Upgrading Up volume (≥2 positive cores) Clinical upstaging	PSA: every 3 mo Visit: every 6 mo Biopsy: 12, 48, and 84 mo		PASE: Sedentary (PASE ≤65) Moderately active (65 < PASE < 125) Active (PASE ≥125)	85			
Papadopoulos et al. [16]		2019	Retrospective study	2001–2016	PSA <10 ≤cT2a GS ≤6 Age ≤75 yr	Upgrading Up volume			Physical activity strata (MET-min/wk): Inactive (<210) Insufficiently active (210–500) Active (500–1000) Highly active (>1000)	Total: 421 Inactive: 126 Insufficiently active: 45 Active: 84 Highly active: 166			
Vandersluis et al. [9]		2016	Prospective cohort study	Sunnybrook 2010–2011 Royal Marsden Hospital 2013	GS ≤6 cT1c or T2a GS 7 (4 + 3), age ≥70 yr, small proportion of Gleason 4	Sunnybrook: upgrading Royal Marsden: upgrading or PSADT <3 yr, PSA velocity >2.0 ng/ml/yr			Total physical activity	Sunnybrook 131 Royal Marsden Hospital 106			
Coffee													
Gregg et al. [25]	NCT00490763	2019	Prospective cohort study	2006–2012	Biopsy no more than 6 mo before enrollment of ≥10 cores GS 3 + 3 in one core (tumor focus, <3.0 mm) or GS 3 + 4 in one core (tumor focus, <2.0 mm) PSA had to be <4 ng/ml or adjusted for volume	Upgrading	PSA: every 6 mo DRE: every 6 mo Confirmatory biopsy: study entry Rebiopsy: every 1–2 yr		Coffee: 0 cups/d <1 cup/d 1–1.9 cups/d 2–3.9 cups/d ≥4 cups/d	0 cups/d: 74 <1 cup/d: 85 1–1.9 cups/d: 87 2–3.9 cups/d: 106 ≥4 cups/d: 59			

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Table 1 (continued)

Author [Reference]	Name/ registration no.	Years	Study design	Recruitment years	Inclusion criteria	Definition of progression	Surveillance protocol	Trigger for earlier rebiopsy	Study arm treatment	Control arm treatment	Overall N	Study arm N	Control arm N
Vitamin D3													
Marshall et al. [19]	NCT01045109	2012	Open-label clinical trial	2010–2011	GS ≤6 PSA ≤10, cT1c or cT2a	Upgrading Up volume	PSA: every 2 mo for 1 yr Biopsy: after completing vitamin D3		Vitamin D3 soft gels (4000 IU) for 1 yr	AS	71	52	19

5-ARI = 5-alpha reductase inhibitor; AS = active surveillance; BPH = benign prostatic hyperplasia; DASH = Dietary Approaches to Stop Hypertension; DRE = digital rectal examination; ECOG = Eastern Cooperative Oncology Group; FT = fezapotide triflutate; GG = Gleason group; GS = Gleason score; HEI = Health Eating Index; MET = metabolic equivalent; MRI = magnetic resonance imaging; NCCN = National Comprehensive Cancer Network; PASE = Physical Activity Scale for Elderly; PCa = prostate cancer; PS = performance status; PSA = prostate-specific antigen; PSAD = prostate-specific antigen density; PSADT = prostate-specific antigen doubling time; RCT = randomized controlled trial; TRUS = transrectal ultrasound.

this meta-analysis was evaluated using Cochrane's Q test. In instances of significant heterogeneity ($p < 0.05$ in the Cochrane's Q test), we tried to investigate and explain the heterogeneity [35,36]. We used a fixed-effect model to compute pooled HR. To evaluate the presence of publication bias, funnel plots were used (Supplementary Fig. 2). We did not conduct the Egger's test because the number of included studies was limited. All analyses were carried out with R version 4.3.0 (R Foundation for Statistical Computing, Vienna, Austria), and the statistical significance level was set at $p < 0.05$.

3. Evidence synthesis

3.1. Study selection and characteristics

The search string is presented in Figure 1. Following the application of our inclusion and exclusion criteria, a total of 22 studies (six randomized controlled trials [RCTs] and 16 observational studies) published between 2011 and 2023 were finally selected. The patient characteristics and their outcomes across the included studies are shown in Tables 1–3. The geographical breakdown of the studies showed 18 from North America, two from Europe, and one each from Turkey and Japan. Table 1 showed varied definitions of disease progression across studies, all including pathological reclassification, with some also containing factors such as tumor volume, treatment intervention, PSA velocity, and PSA doubling time [9–31,37]. The median follow-up period ranged from 271 d to 8 yr. Most studies regularly measured PSA every 3–6 mo and performed confirmatory biopsies 1–3 yr after diagnosis or after study enrollment as part of their surveillance protocols. Of the studies included, 12 performed digital rectal examination (DRE) every 3–12 mo. While no studies incorporated MRI scans into their protocols, three studies performed MRI at the discretion of the attending physician. Six studies allowed biopsy timing adjustment based on PSA trends, DRE findings, or the discretion of the physician [17,18,26,28,29,31].

3.1.1. Pharmacological treatment

3.1.1.1. 5-Alpha reductase inhibitors. A total of seven studies, comprising 2985 participants, investigated the impact of 5-alpha reductase inhibitors (5-ARIs) on PCa progression in patients on AS [14,17,21,26–29,31]. This included one RCT, one prospective cohort study, and five retrospective studies. While Finelli et al. [27,28] focused strictly on low-risk patients only, others included both low- and intermediate-risk patients. Three studies highlighted a statistically significant reduction in the risk of PCa progression in patients receiving 5-ARI treatment [26–28,31]. Only the REDEEM study discussed safety, demonstrating no statistical difference in the occurrence of any TRAEs of all grades between the 5-ARI and placebo groups (23% vs 15%, $p = 0.1$), including any serious event (15% vs 15%, $p = 1$). Notably, the incidence of sexual adverse events or breast disorders seems higher in the 5-ARI group than in the placebo group (24% vs 15%).

Table 2 – Patients and treatment characteristics of 22 studies analyzing the impact of intervention in prostate cancer treated with active surveillance

Author (year) [reference]	Age (yr)	PSA (ng/ml)	*c*T stage, *n* (%)	Gleason score, *n* (%)	Positive cores, *n* (%)	Follow-up
Pharmacological treatment						
5-Alpha reductase inhibitor						
Finelli et al (2011/2021) [27,28]	Mean ± SD Study arm: 65.0 ± 6.4 Control arm: 63.9 ± 7.8	Median (IQR) Study arm: 4.9 (3.9–7.6) Control arm: 4.9 (3.3–6.8)			Study arm: 1: 60 (70.6) 2: 16 (18.8) 3: 9 (10.6) Control arm: 1: 148 (72.4) 2: 42 (20.7) 3: 14 (6.9)	Month, median (IQR) Study arm: 98 (59–99) Control arm: 69 (33–104)
Ashrafi et al (2021) [31]	Median (IQR) Study arm: 63 (58–68) Control arm: 61 (56–68)	Median (IQR) Study arm: 4.8 (3.5–6.8) Control arm: 4.8 (3.6–6.2)	Study arm: T1c: 101 (86) T2a: 16 (14) Control arm: T1c: 216 (90) T2a: 22 (9)	Study arm: 3 + 3: 105 (88) 3 + 4: 12 (10) 4 + 3: 2 (1.7) Control arm: 3 + 3: 211 (88) 3 + 4: 27 (11) 4 + 3: 3 (1.2)		Year, median (range) Study arm: 6.0 (2.4–17.2) Control arm: 5.5 (2.0–15.5)
Kearns et al (2019) [21]	Mean ± SD Study arm: 65 ± 7 Control arm: 62 ± 7	Median (IQR) Study arm: 5.0 (3.6–7.0) Control arm: 4.8 (3.6–6.3)	Study arm: T1a-T1c: 93 (87) T2a-T2c: 14 (13) Control arm: T1a-T1c: 803 (89) T2a-T2c: 99 (11)	Study arm: 3 + 3: 97 (91) 3 + 4: 10 (9) Control arm: 3 + 3: 847 (94) 3 + 4: 55 (6)	Study arm: 8 (8–17) Control arm: 8 (8–17)	Median (IQR) 3.6 (2.2–5.4)
Özkan et al (2018) [17]	Mean ± SD Study arm: 66.5 ± 6.1 Control arm: 67.7 ± 8.9	Median (IQR) Study arm: 5.37 (4.3–6.5) Control arm: 5.15 (4.0–7.1)				Month, median (IQR) Study arm: 39 (23–45) Control arm: 23.5 (17–37.5)
Dai et al (2018) [29]	Mean ± SD Study arm: 66 ± 7 Control arm: 64 ± 7	Mean ± SD Study arm: 6.43 ± 4.90 Control arm: 5.52 ± 3.36	Study arm: T1: 63 (90) T2: 7 (19) Control arm: T1: 269 (89) T2: 32 (11)	Study arm: 3 + 3: 67 (96) 3 + 4: 3 (4) Control arm: 3 + 3: 267 (89) 3 + 4: 34 (11)	Study arm: 1 (IQR 1–2) Control arm: 1 (IQR 1–2)	Month, median (IQR) Study arm: 57 (45–75) Control arm: 44 (30–82)
Fleshner et al (2012) [26]	Mean (SD; range) Study arm: 65.1 (7.14; 48–80) Control arm: 65.0 (7.56; 48–81)	Mean (SD; range) Study arm: 5.6 (2.52; 0.4–11.0) Control arm: 5.8 (2.60; 0.3–10.3)		Study arm: 5: 0 6: 147 (100) Control arm: 5: 1 (1) 6: 154 (99)	Study arm: 10.0% (range 5.3–33.3) Control arm: 10.0% (range 4.5–40)	Days, median (range) Study arm: 1092 (1–1183) Control arm: 987 (1–1143)

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Ross et al (2012) [14]	Study arm: Median 66 (range 54–79) Mean 66 (SD 5.6) Control arm: Median 65 (range 45–82) Mean 65 (SD 5.8)	Study arm: Median 5.6 (range 1.5–11.9) Mean 5.7 (SD 2.2) Control arm: Median 4.4 (range 0.2–19.0) Mean 4.6 (SD 2.3)			Study arm: Median 1 (range 1–2) Mean 1.1 (SD 0.3) Control arm: Median 1 (range 1–2) Mean 1.2 (SD 0.4)	Years Study arm: Median 4.2 (range 1.0–10.6) Mean 4.8 (SD 3.0) Control arm: Median 2.0 (range 0–12.1) Mean 2.6 (SD 2.1)
Statin						
Nyame et al (2019) [18]	Median (IQR) Study arm: 66.7 (62.5–71.3) Control arm: 63.3 (58.8–68.5)	Median (IQR) Study arm: 5.1 (3.8–6.8) Control arm: 5.2 (3.8–6.9)		Study arm: GS 3 + 3: 313 (87.9) GS 3 + 4: 38 (10.7) GS 4 + 3: 5 (1.4) Control arm: GS 3 + 3: 244 (87.5) GS 3 + 4: 29 (10.4) GS 4 + 3: 6 (2.1)		Median (IQR) Study arm: 58.3 (34.5–86.2) Control arm: 5.2 (3.8–6.9)
Jayalath et al (2018) [22]	Median (IQR) Study arm: 65 (61–69) Control arm: 62 (57–67)	Median (IQR) Study arm: 4.9 (3.2–6.5) Control arm: 4.9 (3.7–6.4)		Study arm: 1: 403 (66.2) 2: 150 (24.6) 3: 56 (9.2) Control arm: 1: 115 (61.2) 2: 53 (28.2) 3: 20 (10.6)		Median (IQR) Study arm: 43 (15–78) Control arm: 40 (15–83)
Anticancer drugs						
Sugimoto et al (2022) [10]	Median (IQR) Study arm:70.0 (67.0–75.0) Control arm: 71.0 (67.0–74.5)		Study arm: T1c: 71 (100) Control arm: T1c: 72 (100)	Study arm: 5: 5 (7.0) 6: 66 (93.0) Control arm: 5: 3 (4.3) 6: 69 (95.8)	Study arm: 12 (10–12) Control arm: 12 (10–16)	Years Study arm: 3 Control arm: 3
Shore et al (2020) [12]	Mean ± SD FT 2.5 mg: 64.0 ± 7.1 FT 15 mg: 64.4 ± 7.7 AS: 62.6 ± 7.0	Mean ± SD FT 2.5 mg: 4.7 ± 2.3 FT 15 mg: 4.2 ± 1.9 AS: 4.3 ± 1.9			% of positive core FT 2.5 mg: 9.5 ± 8.8 FT 15 mg: 12.3 ± 12.2 AS: 10.4 ± 11.5	
Shore et al (2022) [11]	Mean ± SD Study arm: 65.2 ± 8.2 Control arm: 66.9 ± 7.3	Median (IQR) Study arm: 5.8 (1–17) Control arm: 5.9 (1–23)	Study arm: T1-T1b: 0 T1c-T2a: 107 (93.9) T2b-T2c: 7 (6.1) Control arm: T1-T1b: 1 (0.9) T1c-T2a: 106 (93.8) T2b-T2c: 6 (5.3)	Study arm: 6: 67 (58.8) 3 + 4: 46 (40.4) Unknown: 1 (0.9) Control arm: 6: 66 (58.4) 3 + 4: 47 (41.6) Unknown: 0	Least square, mean (SE) Study arm: 25.43 (1.61) Control arm: 23.12 (1.58)	Days, median (range) Study arm: 492.5 (1.0–1078.0) Control arm: 270.5 (1.0–806.0)
PROSTVAC						

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Parsons et al (2023) [37]	Mean ± SD Overall: 64 ± 8 Study arm: 65 ± 7 Control arm: 64 ± 8	Mean ± SD Overall: 6.9 ± 3.5 Study arm: 6.9 ± 3.7 Control arm: 6.9 ± 3.2		GG 1 Overall: 102 (66.2) Study arm: 74 (69.8) Control arm: 28 (58.3) GG 2 Overall: 52 (33.8) Study arm: 32 (30.2) Control arm: 20 (41.7)	% positive cores from random biopsy Overall: 19 ± 12 Study arm: 18 ± 12 Control arm: 20 ± 11	
Lifestyle modifications						
Diet						
Schenk et al (2023) [13]	Median (IQR) HEI-2015 score: Low: 64 (60–67) Medium: 64 (60–67) High: 64 (59–67) Mediterranean diet score: Low: 64 (60–67) Medium: 63 (58–68) High: 63 (57–66) DASH diet score: Low: 63 (58–67) Medium: 64 (59–68) High: 63 (58–67)	Median (IQR) HEI-2015 score: Low: 4.7 (3.5–5.9) Medium: 4.7 (3.4–6.3) High: 4.5 (3.5–6.0) Mediterranean diet score: Low: 4.8 (3.6–6.3) Medium: 4.6 (3.6–6.1) High: 4.5 (3.2–5.7) DASH diet score: Low: 4.8 (3.6–6.2) Medium: 4.5 (3.5–6.0) High: 4.6 (3.2–6.0)	*T1* HEI-2015 score: Low: 166 (88) Medium: 171 (91) High: 163 (87) Mediterranean diet score: Low: 184 (89) Medium: 187 (89) High: 129 (87) DASH diet score: Low: 176 (90) Medium: 165 (88) High: 159 (87) *T2* HEI-2015 score: Low: 19 (10) Medium: 17 (9) High: 25 (13) Mediterranean diet score: Low: 22 (11) Medium: 24 (11) High: 19 (13) DASH diet score: Low: 19 (10)	*GG 1* HEI-2015 score: Low: 168 (90) Medium: 173 (92) High: 174 (93) Mediterranean diet score: Low: 189 (92) Medium: 190 (90) High: 136 (93) DASH diet score: Low: 180 (93) Medium: 168 (90) High: 167 (92) *GG 2* HEI-2015 score: Low: 19 (10) Medium: 15 (8) High: 13 (7) Mediterranean diet score: Low: 16 (8) Medium: 20 (10) High: 11 (8) DASH diet score: Low: 14 (7)	% of positive core, mean ± SD HEI-2015 score: Low: 14.5 ± 9.5 Medium: 14.1 ± 9.1 High: 14.1 ± 8.6 Mediterranean diet score: Low: 14.5 ± 9.4 Medium: 14.0 ± 9.0 High: 14.3 ± 8.9 DASH diet score Low: 14.4 ± 9.8 Medium: 14.7 ± 9.3 High: 13.6 ± 7.9	Years, median (IQR) HEI-2015 score: Low: 7.6 (6.3–9.3) Medium: 7.7 (6.6–9.5) High: 8.3 (6.6–9.9) Mediterranean diet score: Low: 7.8 (6.7–9.4) Medium: 8.1 (6.4–9.8) High: 7.7 (6.5–9.5) DASH diet score: Low: 7.9 (6.4–9.4) Medium: 7.7 (6.5–9.4) High: 8.1 (6.4–9.8)

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							Medium: 22 (12)	Medium: 18 (10)	
							High: 24 (13)	High: 15 (8)	
Gregg et al (2019/2021) [23,24]	Mean ± SD	Mean ± SD						GG 1:	Single:
	Low: 62.8 ± 8.5	Low: 4.2 ± 2.7						Low: 129 (91.5)	Low: 106 (75.2)
	Med: 64.9 ± 8.0	Med: 4.0 ± 2.4						Med: 148 (86.6)	Med: 122 (71.4)
	High: 65.8 ± 8.6	High: 4.2 ± 2.8						High: 81 (82.7)	High: 69 (70.4)
								GG 2:	Multiple:
								Low: 12 (8.5)	Low: 35 (24.8)
								Med: 23 (13.5)	Med: 49 (28.7)
								High: 17 (17.4)	High: 29 (29.6)
	Mean ± SD	Mean ± SD		Low	Med	High		GS 6:	
	Low: 62.5 ± 7.8	Low: 4.3 ± 2.3	T1	123 (89.8)	121 (88.3)	117 (85.4)		Low: 125 (91.2)	
	Med: 65.0 ± 8.6	Med: 4.1 ± 2.7	T2a	12 (8.8)	15 (10.9)	18 (13.1)		Med: 121 (88.3)	
	High: 65.7 ± 8.4	High: 4.0 ± 2.7	T2b or T2c	2 (1.5)	1 (0.8)	2 (1.5)		High: 113 (82.5)	
								GS 7:	
								Low: 12 (8.8)	
								Med: 16 (11.7)	
								High: 24 (17.5)	
Parsons et al (2020) [15]	Study arm:	Study arm:	Study arm:						Months, median (IQR)
	Mean 63.7 (SD 6.5)	0–2.5 ng/ml: 25 (11.2%)	T1a: 4 (1.8)						Study arm: 24.1 (22.7–
	Median 64.0 (IQR 59.0–68.0)	2.5–5 ng/ml: 99 (44.2%)	T1b: 1 (0.4)						24.7)
			T1c: 197 (87.6)						Control arm: 24.0 (22.9–
	Control arm:	Control arm:	T2a: 23 (10.2)						24.6)
	Mean 63.5 (SD 6.6)	0–2.5 ng/ml: 30 (13.8%)							
	Median 64.0 (IQR 59.0–68.0)	2.5–5 ng/ml: 98 (45.2%)	Control arm:						
			T1a: 1 (0.5)						
			T1b: 2 (0.9)						
			T1c: 187 (86.2)						
			T2a: 27 (12.4)						

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Vandersluis et al (2016) [9]	Median (range) Sunnybrook: Study arm: 63 (40–81) Control arm: 67 (48–79) Royal Marsden Hospital: Study arm: 64.5 (51–78) Control arm: 68.5 (58–83)	Median (range) Sunnybrook: Study arm: 5.33 (0.30–13.25) Control arm: 5.63 (2.09–14.10) Royal Marsden Hospital: Study arm: 6.25 (0.9–26.6) Control arm: 6.17 (1.5–21.0)	*Sunnybrook* Study arm: <6: 0 (0) 3 + 3: 71 (93) 3 + 4: 5 (7) Unknown: 0 (0) Control arm: <6: 1 (2) 3 + 3: 46 (83) 3 + 4: 7 (13) Unknown: 1 (2) *Royal Marsden Hospital* Study arm: <6: 0 (0) 3 + 3: 73 (96.1) 3 + 4: 3 (3.9) Unknown: 0 (0) Control arm: <6: 1 (3.3) 3 + 3: 28 (93.3) 3 + 4: 1 (3.3) Unknown: 0 (0)		
Exercise					
Brassetti et al (2021) [30]	Total: median 66 (IQR 59–70)	Total: median 5.4 (IQR 4.3–6.8)			Total: 37 (14–53)

Papadopoulos et al (2019) [16]	Inactive: 62.8 ± 6.8 Insufficiently active: 63.1 ± 6.4 Active: 61.3 ± 5.8 Highly active: 61.0 ± 6.7	Inactive: 5.2 ± 2.8 Insufficiently active: 5.4 ± 2.8 Active: 4.8 ± 2.5 Highly active: 4.8 ± 2.4		Inactive: 1.6 ± 0.9 Insufficiently active: 1.6 ± 0.8 Active: 1.6 ± 1.0 Highly active: 1.6 ± 0.9	
Vandersluis et al (2016) [9]	Median (range) Sunnybrook: Study arm: 63 (40–81) Control arm: 67 (48–79) Royal Marsden Hospital: Study arm: 64.5 (51–78) Control arm: 68.5 (58–83)	Median (range) Sunnybrook: Study arm: 5.33 (0.30–13.25) Control arm: 5.63 (2.09–14.10) Royal Marsden Hospital: Study arm: 6.25 (0.9–26.6) Control arm: 6.17 (1.5–21.0)	*Sunnybrook* Study arm: <6: 0 (0) 3 + 3: 71 (93) 3 + 4: 5 (7) Unknown: 0 (0) Control arm: <6: 1 (2) 3 + 3: 46 (83) 3 + 4: 7 (13) Unknown: 1 (2) *Royal Marsden Hospital* Study arm: <6: 0 (0) 3 + 3: 73 (96.1) 3 + 4: 3 (3.9) Unknown: 0 (0) Control arm: <6: 1 (3.3) 3 + 3: 28 (93.3) 3 + 4: 1 (3.3)		

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			Unknown: 0 (0)	
Coffee				
Gregg et al (2019) [25]	Mean ± SD 0 cups/d: 63.3 ± 8.7 <1 cup/d: 64.9 ± 9.2 1–1.9 cups/d: 64.6 ± 8.9 2–3.9 cups/d: 65.1 ± 7.8 ≥4 cups/d: 63.5 ± 7.1	Mean ± SD 0 cups/d: 4.1 ± 2.3 <1 cup/d: 4.4 ± 2.5 1–1.9 cups/d: 4.5 ± 3.1 2–3.9 cups/d: 3.6 ± 2.2 ≥4 cups/d: 4.3 ± 2.8	GS 6: 0 cups/d: 66 (89.2) <1 cup/d: 68 (80.0) 1–1.9 cups/d: 79 (90.8) 2–3.9 cups/d: 96 (90.6) ≥4 cups/d: 49 (83.1) GS 7: 0 cups/d: 8 (10.8) <1 cup/d: 17 (20.0) 1–1.9 cups/d: 8 (9.2) 2–3.9 cups/d: 10 (9.4) ≥4 cups/d: 10 (16.9)	Total: median 36 mo (range 6–126)
Vitamin D3				
Marshall et al (2012) [19]	Mean (range) Study arm: 65 (49–78) Control arm: 66 (50–81)		Study arm: GS 6: 50 (100%) Missing: 2 Control arm: GS 6: 18 (95%) GS 7: 1 (5%)	Study arm: 0: 0 (0) 1: 24 (48) 2: 11 (22) 3: 7 (14) 4: 4 (8) 5: 3 (6) 6: 12 Control arm: 0: 0 (0) 1: 11 (58) 2: 5 (26) 3: 2 (11) 4: 0 (0) 5: 1 (5)

AS = active surveillance; DASH = Dietary Approaches to Stop Hypertension; FT = fezapotide triflutate; GG = Gleason group; GS = Gleason score; HEI = Health Eating Index; IQR = interquartile range; Med = medium; PSA = prostate-specific antigen; SD = standard deviation; SE = standard error.

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Table 3 – Oncological results of 22 studies analyzing the impact of intervention in prostate cancer treated with active surveillance

Author (year) [reference]	Progression, *n* (%)	Kaplan-Meier analysis Log rank	Cox proportional hazard regression, HR (95% CI)	AEs, *n* (%)
Pharmacological treatment				
5-alpha reductase inhibitor				
Finelli et al (2011/2021) [27,28]	Study arm: 24 (28.2) Control arm: 114 (56.2)	$p < 0.001$	5-ARI (no vs yes) Univariate 3.03 (1.72–5.33), $p < 0.001$ Multivariate 3.15 (1.78–5.56), $p < 0.001$	
Ashrafi et al (2021) [31]		Study arm: 5-yr PFS: 77% 10-yr PFS: 41% Control arm: 5-yr PFS: 70% 10-yr PFS: 32% $p = 0.005$	Univariate 0.51 (0.32–0.81), $p = 0.005$ Multivariate 0.50 (0.31–0.81), $p = 0.005$	
Kearns et al (2019) [21]		$p = 0.10$	Univariate 0.63 (0.43–0.94), $p = 0.02$ Multivariate 0.81 (0.55–1.21), $p = 0.31$	
Özkan et al (2018) [17]	Study arm: 10 (34.5) Control arm: 12 (30.0)	$p = 0.4151$	Nonuse of 5-ARI Multivariate 1.93 (0.80–4.69), $p = 0.148$	
Dai et al (2018) [29]	Study arm: 9 (13) Control arm: 43 (14)	Study arm: 3-yr upgrading rate: 7% Control arm: 3-yr upgrading rate: 16% $p = 0.51$	Univariate 0.78 (0.35–1.55), $p = 0.50$ Multivariate 0.80 (0.31–1.80), $p = 0.62$	
Fleshner et al (2012) [26]	Study arm: 54/144 (38) Control arm: 70/145 (36.7)	3-yr PFS Study arm: 54 (38) Control arm:70 (48) $p = 0.009$	HR: 0.62 (0.43–0.89), $p = 0.009$	AEs: Study arm: 122 (83%) Control arm: 135 (87%), $p = 0.34$ Drug-related event: Study arm: 34 (23%) Control arm: 24 (15%), $p = 0.11$ Impotence: Study arm: 13 (9%) Control arm: 14 (9%), $p = 1.00$ Altered (decreased) libido: Study arm: 11 (7%) Control arm: 6 (4%), $p = 0.21$ Ejaculation disorders: Study arm: 8 (5%) Control arm: 2 (1%), $p = 0.06$

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Ross et al (2012) [14]	Study arm: 8 (17.0) Control arm: 169 (31.3) $p = 0.041$		Univariate 0.58 (0.28–1.20), $p = 0.140$ Multivariate 0.55 (0.23–1.28), $p = 0.164$	
Statin				
Nyame et al (2019) [18]		Study arm: 5 yr free from upgrading: 64.5% (58.7–69.7) 10 yr free from upgrading: 56.5% (49.3–63.0) Control arm: 5 yr free from upgrading: 70.0% (63.3–75.7) 10 yr free from upgrading: 58.4% (47.5–67.8) $p > 0.05$	Univariate 0.58 (0.26–1.32), $p = 0.66$ Multivariate 0.39 (0.14–1.57), $p = 0.07$	
Jayalath et al (2018) [22]	Study arm: 51 (27.1) Control arm: 143 (23.5)		Univariate 1.21 (0.84–1.76) Multivariate 1.24 (0.77–1.99)	
Anticancer drugs				
Sugimoto et al (2022) [10]	Study arm: 15 (21.1) Control arm: 32 (44.4)	3 yr persistence rate: Study arm: 75.5% (62.5–84.6) Control arm: 50.1% (36.7–62.2)	HR 0.417 (0.226–0.770), $p = 0.0039$	Incidence of AEs: Study arm: 31 (43.7) Control arm: 9 (12.5) Incidence of severe AEs: Study arm: 4 (5.6), (malignant neoplasm: 2, hepatobiliary disorders: 1, hemato Control arm: 1 (1.4), (malignant neoplasm: 1)

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Shore et al (2020) [12]	18 mo: AS: 41.2% FT 2.5 mg: 16.7% FT 15 mg: 8.8% Pooled FT: 12.9% (AS vs FT 2.5 mg: p = 0.0858, AS vs FT 15 mg: p = 0.0102, AS vs pooled FT: p = 0.0129) 36 mo: AS: 56.3% FT 2.5 mg: 26.9% FT 15 mg: 18.2% Pooled FT: 22.9% (AS vs FT 15 mg: p = 0.0199, AS vs pooled FT: p = 0.0265) 48 mo: AS: 71.4% FT 2.5 mg: 62.5% FT 15 mg: 33.3% Pooled FT: 48.4% (AS vs FT 15 mg: p = 0.0656)			*No FT drug–related AEs* Procedure related: Study arm / Control arm Dysuria 2 (1.7) / 0 (0) Hematochezia 3 (2.6) / 0 (0) Hematospermia 3 (2.6) / 0 (0) Hematuria 7 (6.1) / 0 (0) Penile pain 2 (1.7) / 0 (0) Rectal pain 0 (0) / 1 (2.0) Antibiotic related: Study arm / Control arm Arthralgia 2 (1.7) / 0 (0) Constipation 2 (1.7) / 0 (0) Diarrhea 30 (26.1) / 1 (2.0) Dysgeusia 3 (2.6) / 0 (0) Headache 3 (2.6) / 0 (0) Nausea 10 (8.7) / 0 (0)
Shore et al (2022) [11]	Study arm: 32 (28.1) Control arm: 42 (37.2)	Median Study arm: NR (36.14–NR) mo Control arm: NR (24.67–NR) mo	HR: 0.54 (0.33–0.89), p = 0.02	Study arm: Grade 1 / Grade 2 / Grade ≥3 Control arm: Grade 1 / Grade 2 / Grade ≥3 Any AEs 34 (30.4) / 58 (51.8) / 11 (9.8) / 27 (23.9) / 25 (22.1) / 10 (8.8) Fatigue 49 (43.8) / 11 (9.8) / 2 (1.8) / 3 (2.7) / 1 (0.9) / 0 Gynecomastia 26 (23.2) / 14 (12.5) / 1 (0.9) / 2 (1.8) / 0 / 0 Nipple pain 30 (26.8) / 4 (3.6) / 0 / 0 / 0 / 0 Breast tenderness 25 (22.3) / 4 (3.6) / 0 / 1 (0.9) / 0 / 0 Erectile dysfunction 9 (8.0) / 11 (9.8) / 0 / 2 (1.8) / 0 / 0 Decrease libido 8 (7.1) / 1 (0.9) / 0 / 1 (0.9) / 0 / 0
PROSTVAC				
Parsons et al (2023) [37]	Any GG → GG ≥3 Study arm: 8 (7.6) Control arm: 6 (13.0) p = 0.36 GG 1 → GG ≥2 Study arm: 16 (21.6) Control arm: 11 (40.7) p = 0.08 GG 2 → GG ≥3 Study arm: 4 (12.5) Control arm: 4 (21.1) p = 0.45			Study arm: Grade 1 / Grade2 / Total Control arm: Grade 1 / Grade2 / Total Injection site reaction 30 (28.3) / 65 (61.3) / 95 (89.6) / 18 (37.5) / 27 (56.3) / 45 (93.8) Flu-like symptom 41 (38.7) / 22 (20.8) / 63 (59.4) / 21 (43.8) / 9 (18.8) / 30 (62.5) Fatigue 31 (29.2) / 12 (11.3) / 43 (40.6) / 10 (20.8) / 4 (8.3) / 14 (29.2) Headache 19 (17.9) / 4 (3.8) / 23 (21.7) / 6 (12.5) / 3 (6.3) / 9 (18.8) Dizziness 10 (9.4) / 0 (0) / 10 (9.4) / 0 (0) / 0 (0) / 0 (0) White blood cell decrease 1 (1.0) / 0 (0) / 1 (1.0) / 3 (6.3) / 1 (2.1) / 4 (8.3)

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Lifestyle modifications	
Diet	
Schenk et al (2023) [13]	*Nonadjusted* HEI-2015 score: Low: HR 1.00 Medium: HR 0.81 (0.58–1.13) High: HR 0.87 (0.63–1.20) $p = 0.23$ Mediterranean diet score: Low: HR 1.00 Medium: HR 1.02 (0.75–1.39) High: HR 0.92 (0.65–1.30) $p = 0.71$ DASH diet score: Low: HR 1.00 Medium: HR 0.95 (0.69–1.30) High: HR 0.91 (0.65–1.26) $p = 0.25$ *IPW adjusted* HEI-2015 score: Low: HR 1.00 Medium: HR 0.80 (0.57–1.13) High: HR 0.84 (0.60–1.16) $p = 0.22$ Mediterranean diet score: Low: HR 1.00 Medium: HR 1.03 (0.75–1.41) High: HR 0.86 (0.60–1.24) $p = 0.56$ DASH diet score: Low: HR 1.00 Medium: HR 0.91 (0.66–1.26) High: HR 0.89 (0.63–1.26) $p = 0.24$

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Gregg et al (2019/2021) [23,24]	Low: 24 Medium: 27 High: 12		Univariate: Low vs Med: HR 0.78 (0.47–1.30), $p = 0.95$ Low vs High: HR 0.69 (0.38–1.27), $p = 0.14$ Multivariate: Low vs Med: HR 0.78 (0.47–1.30), $p = 0.77$ Low vs High: HR 0.68 (0.36–1.25), $p = 0.21$
	Low: 29 Medium: 28 High: 19		Univariate: Low vs Med: HR 0.90 (0.53–1.53), $p = 0.70$ Low vs High: HR 0.62 (0.34–1.12), $p = 0.11$ Multivariate: Low vs Med: HR 0.90 (0.52–1.53), $p = 0.69$ Low vs High: HR 0.59 (0.32–1.08), $p = 0.09$
Parsons et al (2020) [15]	Study arm: 124 Control arm: 121	2-yr PFS Study arm: 89.9% (84.4–94.8%) Control arm: 90.2% (84.4–94.8%)	HR: 1.40 (0.79–2.46), $p = 0.24$
Vandersluis et al (2016) [9]	*Multivariate OR* Sunnybrook: Diet score: OR: 0.99 (0.86–1.14), $p = 0.88$ Royal Marsden Hospital: Diet score: OR: 0.89 (0.64–1.23), $p = 0.47$		
Exercise			
Brassetti et al (2021) [30]		Upgrading (%) 2 yr / 5 yr / 10 yr Sedentary: 39 ± 10 / 66 ± 16 / – Moderate: 21 ± 6 / 35 ± 9 / 35 ± 9 Active: 13 ± 8 / 13 ± 8 / – $p = 0.033$	Univariate 0.987 (0.977–0.997), $p = 0.014$ Multivariate 0.987 (0.977–0.998), $p = 0.016$

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Papadopoulos et al (2019) [16]			Univariate: Inactive: HR 1.00 (ref.) Insufficiently active: HR 1.08 (0.53–2.23) Active: HR 0.78 (0.43–1.42) Highly active: HR 1.48 (0.94–2.34) $p = 0.097$ Multivariate: Inactive: HR 1.00 (ref.) Insufficiently active: HR 1.15 (0.51–2.57) Active: HR 0.83 (0.43–1.59) Highly active: HR 1.46 (0.89–2.43) $p = 0.202$	
Vandersluis et al (2016) [9]	*Multivariate OR* Sunnybrook, total PA, MET hours per week: OR: 1.00 (0.99–1.01), $p = 0.62$ Royal Marsden Hospital, total PA, MET hours per week: OR: 1.00 (0.99–1.00), $p = 0.24$			
Coffee				
Gregg et al (2019) [25]		≥4 cups/d vs all others: $p = 0.03$ 0 vs 1–4 cups/d: $p = 0.17$	Univariate 0 cups/d: HR 1.00 (Ref), p = ref. <1 cup/d: HR 0.85 (0.42–1.72), $p = 0.64$ 1–1.9 cups/d: HR 0.52 (0.24–1.14), $p = 0.1$ 2–3.9 cups/d: HR 0.62 (0.31–1.25), $p = 0.18$ ≥4 cups/d: HR 1.32 (0.66–2.65), $p = 1.67$ Multivariate: 0 cups/d: HR 1.00(Ref), p = ref. <1 cup/d: HR 0.83 (0.4–1.71), $p = 0.4$ 1–1.9 cups/d: HR 0.64 (0.29–1.43), $p = 0.29$ 2–3.9 cups/d: HR 0.71 (0.35–1.47), $p = 0.35$ ≥4 cups/d: HR 1.67 (0.81–3.45), $p = 0.16$	
Vitamin D3				
Marshall et al (2012) [19]	Study arm: 15/44 (34%) Control arm: 12/19 (63%) $p = 0.05$			No AEs associated with vitamin D3 were observed

AE = adverse event; 5-ARI = 5-alpha reductase inhibitor; AS = active surveillance; CI = confidence interval; DASH = Dietary Approach to Stop Hypertension; FT = fezapotide triflutate; GG = Gleason group; HEI = Health Eating Index; HR = hazard ratio; Med = medium; MET = metabolic equivalent; NR = not reached; OR = odds ratio; PA = physical activity; PFS = progression-free survival; ref. = reference.

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3.1.1.2. Statin. Two observational studies, comprising 1432 participants, investigated the impact of statins on disease progression in low- and intermediate-risk PCa patients on AS [18,22]. In these studies, statin use was not significantly associated with PFS, and safety was not addressed.

3.1.1.3. Anticancer drugs.

3.1.1.3.1. Chlormadinone. The PROSAS trial [10] recruited 143 low-risk PCa patients with the primary outcome of AS discontinuation, secondary to events such as disease progression, worsening urinary symptoms, or need for secondary prostate treatment for both benign prostatic hyperplasia and/or PCa. Participants were randomly allocated either to a daily regimen of 50 mg chlormadinone for 3 yr or to AS. Chlormadinone significantly reduced the risk of AS discontinuation compared with AS (HR: 0.42; 95% CI: 0.23–0.77; Table 3). This trial focused not only on disease progression, but also on reasons for AS discontinuation. The results suggest that chlormadinone could significantly extend the duration of AS by 58.3%. Disease progression, however, was not individually examined in this trial. All discontinuations in the chlormadinone group were due to pathological progression, compared with 32 out of 35 in the control group. The incidence of any grades of TRAEs and severe TRAEs was observed more frequently in the chlormadinone group than in the placebo group (any grade: 43.7% vs 12.5%; severe: 5.6% vs 1.4%). The most common TRAEs in the chlormadinone group compared with the placebo group were constipation and hepatobiliary disorders (constipation: 22.5% vs 1.4%; hepatobiliary disorder: 9.9% vs 1.4%).

3.1.1.3.2. Fexapotide triflutate. Fexapotide triflutate (FT) is a novel molecular agent with proapoptotic effects, administered via an intraprostatic injection. Its application extends to both benign prostatic hyperplasia and low-grade PCa. The NX03-0040 study by Shore et al. [12] exclusively included low-risk PCa patients. The study enrolled 146 patients and divided them into three groups: FT 2.5 mg (n = 49), FT 15 mg (n = 48), and AS alone (n = 49). Progression incidence was significantly lower in FT groups compared with AS (18 mo: AS 41.2% vs FT 15 mg 8.8%, p = 0.01; FT 2.5 mg 16.7%, p = 0.1; pooled FT 12.9%, p = 0.01; Table 3). Although TRAEs were associated with a drug injection (eg, FT group vs AS-alone group: hematuria in 6.1% vs 0%; dysuria in 1.7% vs 0%; and hematospermia in 2.6% vs 0%) and prophylactic antibiotic treatment (eg, FT group vs AS-alone group: diarrhea in 26.1% vs 2.0% and nausea in 8.7% vs 0%), no TRAEs related to FT itself were observed.

3.1.1.3.3. Enzalutamide. In the ENACT trial by Shore et al. [11], 227 low- or intermediate-risk PCa patients were randomized to receive enzalutamide 160 mg for 1 yr or to undergo AS alone. Enzalutamide significantly reduced the risk of PCa progression by 46% compared with AS alone (HR: 0.54; 95% CI: 0.33–0.89; p = 0.02). More TRAEs were observed with enzalutamide (any grades: 92.0% vs 54.9%; severe: 8.0% vs 4.4%). Notably, fatigue (55.4% vs 3.5%) and gynecomastia (36.6% vs 1.8%) were the most commonly reported TRAEs in the enzalutamide group compared with the AS group.

3.1.1.4. PROSTVAC. PROSTVAC, a poxviral vaccine triggering a T-cell immune response against PSA-expressing PCa cells, was studied by Parsons et al. [37] in an RCT compromising 154 low- or intermediate-risk PCa patients on AS. Participants were randomized to the PROSTVAC group (n = 106) or the empty viral vector (EV) group (n = 48). All participants received priming vaccination via a subcutaneous injection of their assigned treatment, followed by six boosters up to day 140. Disease progression rates were comparable between groups. Especially, disease progression from Gleason grade (GG) 1 to GG $\geq$2 was 21.6% in the PROSTVAC group and 40.7% in the EV group (p = 0.08); from GG 2 to GG $\geq$3, it was 12.5% and 21.1%, respectively (p = 0.5). TRAEs were similar across groups (injection site reaction: 89.6% vs 93.8%, p = 0.6; flu-like symptoms: 59.4% vs 62.5%, p = 0.86; fatigue in 40.6% vs 29.2%, p = 0.2; and headaches: 21.7% vs 18.8%, p = 0.8). No TRAEs of grade 3 or above were reported in each group.

3.1.2. Lifestyle modifications

3.1.2.1. Diet. Four studies, comprising one RCT and three observational studies with a total of 1151 participants, examined the impact of diet on PCa progression in patients treated with AS [9,13,15,23,24]. Each study utilized different dietary categorizations and measurements.

Vandersluis et al. [9] used a diet score system in two cohorts. The classification assigning high scores to high-risk food (such as fish, tomato products, cruciferous vegetables, soy products, red grapes and/or red wine, and berries) and low-risk foods (such as milk products, fast food, and red meat). Schenk et al. [13] assessed the dietary patterns based on the Dietary Guidelines for Americans (Healthy Eating Index [HEI]) 2015, alternative Mediterranean diet, and Dietary Approaches to Stop Hypertension. Gregg et al. [23,24] also utilized HEI-2015 and Mediterranean diet (MD) score. This score was derived from nine energy-adjusted food groups, with a higher total score (range: 0–9) indicating increased adherence to the MD. Parsons et al. [15] encouraged the intake of seven daily vegetable-fruit servings (defined as half a cup of raw or cooked vegetables or fruits or 100% vegetable juice) as an intervention. As shown in Table 3, these studies did not provide significant evidence to support dietary interventions in preventing PCa progression. No study reported the safety of these measures.

3.1.2.2. Exercise. The impact of exercise on PCa in patients treated with AS was examined in three observational studies comprising 743 participants. As shown in Table 1, the studies varied in inclusion criteria and their categorization, and measurements of physical activity, complicating a direct comparison [9,16,30].

Vandersluis et al. [9] and Papadopoulos et al. [16] measured physical activity in metabolic equivalents (METs); no significant correlation between physical activity level and disease progression was found. In contrast, Brassetti et al. [30] utilized the Physical Activity Scale for Elderly (PASE) score as a measure of physical activity level in older adults. This study found that the PASE score was the only independent intervention decreasing the risk of progression

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by a very small margin (HR: 0.99; 95% CI: 0.98–0.99; $p = 0.02$; Table 3). No study reported on safety.

3.1.2.3. Coffee. Gregg et al. [25] enrolled 411 patients with PCa on AS to evaluate the association between coffee intake and PCa progression. As shown in Table 3, no significant association with PCa progression was found at various levels of consumption. A nonlinear relationship ($p = 0.01$) indicated that the progression risk did not correspond directly with the amount of coffee consumption. Safety was not assessed in this study.

3.1.2.4. Vitamin D3 supplement. Marshall et al. [19] investigated the impact of vitamin D3 on low-risk PCa progression in AS patients. They compared 4000 IU vitamin D3 orally for a year ($n = 52$) with AS alone ($n = 19$) and found a lower progression rate in the vitamin D3 group (34% vs 63%, $p = 0.05$). No TRAEs were observed.

3.2. Meta-analysis

Our meta-analysis focused on 5-ARIs and statins. These two interventions had a sufficient number of studies available for an analysis. A meta-analysis could not be conducted on the other interventions such as diet and exercise, due to the highly heterogeneous method of evaluation and categorization across studies.

3.2.1. Effect of 5-ARIs

The forest plot (Fig. 2A) reveals that the use of 5-ARIs significantly reduces the risk of PCa progression compared with no intervention (pooled HR: 0.59; 95% CI: 0.48–0.72; $p < 0.001$). Only the study by Fleshner et al. [26] used a broader definition of disease progression, which included therapeutic progression. To address this, we performed a subgroup analysis excluding their study. This subgroup analysis also demonstrated a significant risk reduction of PCa progression with 5-ARI use (pooled HR: 0.58; 95% CI: 0.45–0.73; $p < 0.01$). Cochrane's Q tests revealed no significant heterogeneity among the included studies.

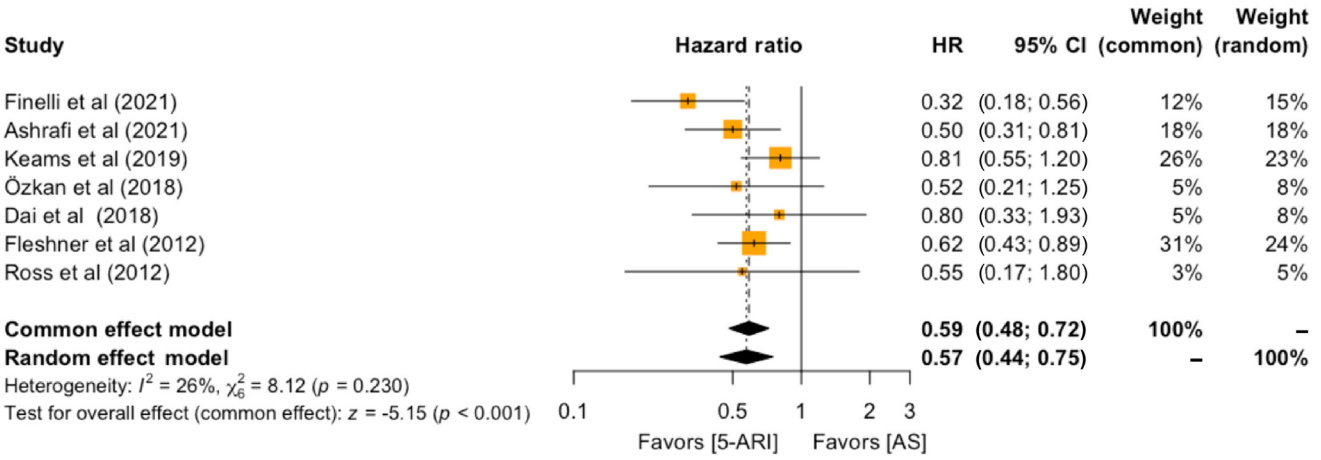
3.2.2. Effect of statin

The forest plot (Fig. 2B) demonstrates no impact of statins on the risk of PCa progression (pooled HR: 1.06; 95% CI: 0.68–1.65; $p = 0.8$) when compared with AS. Cochrane's Q revealed no significant heterogeneity among the included studies.

3.2.3. Risk of bias assessment

The judgments of risk of bias for each domain across all included studies are presented in Supplementary Figure 2 and Supplementary Table 2. Although some RCTs presented concerns in certain domains, two studies demonstrated a low risk across all domains. Despite some observational studies showing a low risk in specific categories, the majority of these studies displayed either moderate or serious

(A)



(B)

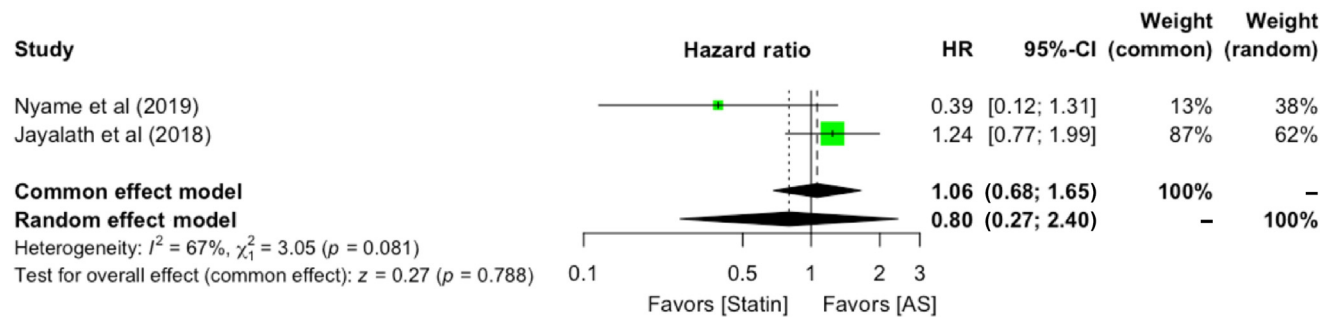


Fig. 2 – Forest plots showing the association between PFS and interventions in patients with prostate cancer under AS: (A) 5-ARI versus AS and (B) statins versus AS. 5-ARI = 5-alpha reductase inhibitor; AS = active surveillance; CI = confidence interval; HR = hazard ratio; PFS = progression-free survival.

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overall risk of bias. Funnel plots of each analysis are depicted in Supplementary Figure 3.

3.3. Discussion

In this study, we present a first systematic review and meta-analysis assessing the impact of various interventions on disease progression in patients with PCa managed with AS. We investigated pharmacological treatments (5-ARIs, statins, anticancer drugs such as chlormadinone, FT, enzalutamide, and PROSTVAC) and lifestyle modifications (diet, exercise, coffee intake, and vitamin D3 supplement). There are several important findings of our study. First, we found that 5-ARIs seem to decrease disease progression (defined as reclassification) in patients with PCa managed with AS. Second, we did not find an effect of statins on PCa progression. Third, anticancer drugs, including chlormadinone, FT, and enzalutamide, appeared to prevent disease progression, but due to TRAEs and the paucity of data, no clear conclusions can be made as of now. Fourth, although lifestyle changes such as diet and exercise can enhance overall patient health, the data do not support significant efficacy in preventing PCa progression during AS.

Our meta-analysis confirmed the potential of 5-ARIs for secondary prevention in early-stage PCa patients undergoing AS, suggesting a decrease in the risk of disease progression by 41%. However, it is important to note that disease progression in some studies was defined not only by pathological reclassification, but also by cancer volume increase or physician/-patient choice. We also performed a subgroup analysis that focused exclusively on studies that define progression in terms of pathological progression. This subgroup analysis also demonstrated a significant risk reduction of PCa progression by 42%. Although all the studies we reviewed had a protocol for confirmatory or repeat biopsy, clinical parameters such as PSA and MRI findings were used to trigger biopsy, and there may have been varying conditions set to expedite biopsies in the control group, potentially leading to earlier detection of progression. Conversely, there is a possibility that follow-up biopsies were delayed or abandoned in the 5-ARI group because of the 5-ARI–related PSA decrease. Replanned biopsies of predetermined time points would have unraveled this unknown, but this is unlikely to be attractive to patients enrolling in such a study. Biopsy protocol adherence was not clear in the studies. Therefore, the difference in the definition of disease progression and the timing of biopsies between the two groups, along with the variation in the results, may have influenced the findings. Importantly, the fact that MRI/ultrasound fusion–guided biopsies considered the standard today [38] were not utilized may also have affected the precision of the results. Although Theoret et al. [39] suggested that 5-ARIs can increase the incidence of more aggressive forms of the disease in the context of primary PCa diagnosis, Baboudjian et al. [40] found no impact on PCa mortality; it seems that there is at least no risk of worse oncological outcomes due to the use of 5-ARIs. However, it is essential to note that no definitive conclusion has been reached on this matter. The ongoing RCT, FINESSE trial [41], compares the use of finasteride with AS alone to investigate whether finasteride contributes to extending the duration of AS. Studies besides the REDEEM trial have not consistently addressed potential TRAEs, especially regarding sexual function. As an important objective of AS, this aspect warrants particular attention. Given the significant frequency of sexual adverse events, it is important to underline these adverse events during the shared decision-making process with the patients.

We conducted a meta-analysis of the impact of statins on PCa progression in AS patients using two observational studies [18,22] and found no significant association of statins with disease progression.

While statins have demonstrated anticancer properties across various cancer types [42–45], our findings suggest that they may not possess a chemopreventive potential for men with PCa under AS. Considering anticancer drugs, in both the PROSAS trial [10] and the NX03-0040 study [12], chlormadinone and FT demonstrated the potential to prevent disease progression in patients with low-risk PCa. However, unlike the REDEEM trial, PROSAS trial, and NX03-00400 study, the ENACT trial [11] included nearly half its patients with intermediate-risk PCa. Despite the demonstrated efficacy of chlormadinone and enzalutamide, these led to relatively high rates of adverse events, which make the benefit-risk ratio in patients on AS less attractive. Schweizer et al. [46] in a single-arm study investigated apalutamide in low- and intermediate-risk PCa patients on AS, finding no tumors in 59% of patients after 90 d of treatment in repeated MRI/ultrasound fusion biopsies. Additionally, TRAEs such as fatigue and gynecomastia were observed in 70% of patients. PROSTVAC showed no effect on pathological upgrading and had notable TRAEs. However, given the short observation period after the final vaccination, a longer follow-up may be needed to detect any possible benefit in this patient population.

None of the studies showed a benefit of diet for preventing PCa progression during AS. While these results do not support protective effects from high-quality dietary patterns against disease progression, it is important to note that healthy diet modifications exhibit known protective effects on many chronic diseases and overall mortality. Therefore, adhering to such dietary patterns remains prudent for these men, who are more likely to succumb to other diseases, especially cardiovascular disease, than PCa [3].

We found equivocal evidence that exercise may delay progression of PCa during AS. While Papadopoulos et al. [16] and Vandersluis et al. [9] found no impact of exercise on the prevention of PCa progression via METs, Brassetti et al. [30] demonstrated a positive effect using the PASE metric that combines information on daily work-related and leisure activities, as well as household chores. These different assessment methods may have contributed to the discrepant results. While the effects of exercise on PCa have not yet been determined conclusively, it is known to improve HRQoL in patients with PCa [47]; therefore, it remains a viable recommendation for PCa patients on AS. The impact of coffee consumption on PCa progression under AS remains unclear. Gregg et al. [25] reported that patients with low/moderate coffee intake (up to three cups per day) and AA genotype at rs762551, known as the "fast caffeine metabolizer" genotype, have a lower likelihood of experi-

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encing grade progression than nonconsumers. This study provides intriguing evidence suggesting that genotype may play a role in cancer-related implications of coffee intake. Marshall et al. [19] demonstrated the effectiveness of vitamin D3 supplementation for patients with low-risk PCa on AS. Results from ongoing RCTs such as the Prolaris and ProsD trials are eagerly awaited [48,49]. Therefore, no robust recommendations on coffee or vitamin D3 to delay PCa progression are available currently. Finally, in the lifestyle modifications, we found no strong evidence for preventing disease progression, but their proven benefits to HRQoL and overall health suggest continuing healthy lifestyle, especially as almost all men with low-risk PCa ultimately die from causes other than PCa [3,5].

Our study has several limitations. First, variations in the definitions of progression and the follow-up protocols among studies could cause heterogeneity in the results and their interpretation. Additionally, differing patient backgrounds, such as age, comorbidities, and lifestyle, exist across the included studies. Second, follow-up durations varied among studies; this could impact the assessment of disease progression. Third, due to the scarcity of available studies, our analysis includes both RCTs and observational studies. The observational studies were generally at moderate or serious risk of bias, so their results should be interpreted cautiously. Finally, the reliability of our study is hindered by the inherent uncertainty of a biopsy-based evaluation, which can mislead grading in 20–50% of cases, potentially affecting our assessment of true pathological progression [8,50,51]. Additionally, the selection for AS was not based on the MRI pathway, which has been known to dramatically decrease the risk of misgrading [6]. These limitations highlight the need for cautious interpretation of our findings, and underscore the importance of future studies with large sample sizes and longer follow-up durations to provide more robust evidence regarding the impact of interventions on disease progression in patients under AS.

4. Conclusions

We found that 5-ARIs can delay progression in men with PCa undergoing AS. Certain anticancer drugs, such as chlormadinone, FT, and enzalutamide, demonstrated effectiveness; however, these therapies are associated with significant TRAEs, limiting their use in the setting of AS. We did not observe the marked effectiveness of lifestyle modifications in preventing PCa progression. These findings highlight the importance of continued investigation and personalized approaches to optimize the management of PCa patients on AS.

Author contributions: Akihiro Matsukawa had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Matsukawa, Yanagisawa, Rajwa.
Acquisition of data: Matsukawa, Yanagisawa.
Analysis and interpretation of data: Matsukawa, Yanagisawa.
Drafting of the manuscript: Matsukawa, Yanagisawa.
Critical revision of the manuscript for important intellectual content: Bekku, Parizi, Laukhtina, Klemm, Chiujdea, Mori, Kimura, Miki, Pradere.
Statistical analysis: Matsukawa, Yanagisawa.
Obtaining funding: None.
Administrative, technical, or material support: Rivas, Gandaglia, Kimura, Kasivisvanathan, Ploussard, Cornford.
Supervision: Shariat.
Other: None.

Financial disclosures: Akihiro Matsukawa certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: Takahiro Kimura is a paid consultant/advisor of Astellas, Bayer, Janssen. and Sanofi. Shahrokh F. Shariat received honoraria from Astellas, AstraZeneca, BMS, Ferring, Ipsen, Janssen, MSD, Olympus, Pfizer, Roche, and Takeda; reports a consulting or advisory role for Astellas, AstraZeneca, BMS, Ferring, Ipsen, Janssen, MSD, Olympus, Pfizer, Pierre Fabre, Roche, and Takeda; and reports being in the speakers' bureau of Astellas, Astra Zeneca, Bayer, BMS, Ferring, Ipsen, Janssen, MSD, Olympus, Pfizer, Richard Wolf, Roche, and Takeda. The other authors declare no conflicts of interest associated with this manuscript.

Funding/Support and role of the sponsor: None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euo.2023.10.010.

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Please cite this article as: A. Matsukawa, T. Yanagisawa, K. Bekku et al., Nonsurgical Interventions to Prevent Disease Progression in Prostate Cancer Patients on Active Surveillance: A Systematic Review and Meta-analysis, Eur Urol Oncol (2023), https://doi.org/10.1016/j.euo.2023.10.010