Article published online: 2021-06-23

Original Article

Nonsteroidal Anti-inflammatory Drugs and Clinical Outcomes among Men with Prostate Cancer: A Systematic Review and Meta-analysis

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Abstract

Background: Nonsteroidal anti-inflammatory drugs (NSAIDs) have shown properties of inhibiting the progression of prostate cancer (PCa) in preclinical studies. However, epidemiological studies yield mixed results on the effectiveness of NSAIDs in PCa. **Objective:** The objective of this study was to determine the effect of NSAID use on clinical outcomes in PCa using systematic review and meta-analysis. **Methods:** Original articles published until the 1st week of October, 2016, were searched in electronic databases (Medline-Ovid, PubMed, Scopus, The Cochrane Library, and Web of Science) for studies on NSAID use in PCa. The main clinical outcomes for the review were: PCa-specific (PCM) and all-cause mortality (ACM), biochemical recurrence (BCR), and metastases. Meta-analysis was performed to calculate the pooled hazard ratio (pHR) and their 95% confidence interval (95% CI). Heterogeneity between the studies was examined using I^2 statistics. Appropriate subgroup analyses were conducted to explore the reasons for heterogeneity. **Results:** Out of 4216 retrieved citations, 24 observational studies and two randomized controlled studies with a total of 89,436 men with PCa met the inclusion criteria. Overall, any NSAID use was not associated with PCM, ACM, and BCR, with significant heterogeneity. Neither precancer treatment aspirin use (pHR: 1.00, 95% CI: 0.83, 1.19, $P = 0.97$, 5 studies, I^2: 51%) nor postcancer treatment aspirin use (pHR: 0.94, 95% CI: 0.72, 1.23, $P = 0.67$, 8 studies, I^2: 86%) was associated with PCM. Similar findings, that is, no significant association was observed for NSAID use and ACM or BCR overall, and in subgroup by types of NSAID use, and NSAID use following radiation or surgery. **Conclusion:** Although NSAID use was not associated with ACM, PCM, or BCR among men with PCa, significant heterogeneity remained in the included studies even after subgroup analyses.

Keywords: *Aspirin, biochemical recurrence, prostate cancer, prostate cancer-specific mortality*

Introduction

Prostate cancer (PCa) is the second most common nonskin cancer with an estimated 508,345,355 survivors and 1,392,727 incident cases by 2020 as per the World Health Organization's report of 184 countries. PCa accounts for 15% of incident cancer cases diagnosed in men as of 2012 and is the fifth leading cause of death due to cancer in men.[1] Along the global disease burden, the worldwide cost of cancer medications is expected to increase by 11.5% from $107 billion in 2015 to 150 billion by 2020, attributed mainly to newly approved cancer chemotherapy.[2] With advance in the health-care management and focus on the value-based incentive payment models, there are needs to find potentially effective and affordable care among men with PCa.

Nonsteroidal anti-inflammatory drugs (NSAIDs) have been the first line of treatment to relieve pain and fever – two common indicators of majority of diseases. With aspirin being the first NSAID, NSAIDs have seven chemical classes: salicylates, fenamates, para-aminophenol, acetic acid, enolic acid and propionic acid derivatives, and diaryl heterocyclic.[3] Biologically, NSAIDs inhibit development prostanoids by blocking the activity of the cyclooxygenase (COX) enzymes. Blockage of COX enzyme activity leads to a cascade of beneficial reactions inhibiting inflammatory response in cancer. For example, preclinical studies have found that NSAIDs inhibit platelet activation which in turn inhibits the development of aggressive cancers and metastases. Such studies have demonstrated that activated platelet could lead to carcinogenesis via releasing angiogenic factors, forming platelet–tumor cell aggregates, and evading immune surveillance in the blood.[4,5] In addition, NSAIDs could also play a role by inhibiting

How to cite this article: Thakker D, Raval AD, Raval N, Vyas A. Nonsteroidal anti-inflammatory drugs and clinical outcomes among men with prostate cancer: A systematic review and meta-analysis. Indian J Med Paediatr Oncol 2018;39:127-41.

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Access this article online

Website: www.ijmpo.org

DOI: 10.4103/ijmpo.ijmpo_61_17

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cancer-related inflammation such as the infiltration of white blood cells; tumor-associated macrophages (TAMs); cytokines such as interleukin (IL)-1, IL-6, tumor necrosis factor-α; chemokines such as (C-C motif) ligand 2 (CCL2) and CXCL8; acceleration of cell cycle progression and cell proliferation; evasion from apoptosis; and stimulation of tumor angiogenesis.[6,7] Therefore, the NSAID may serve as a novel therapeutic option to manage PCa.

Epidemiological studies on NSAIDs yielded mixed results on the association between NSAIDs and clinical outcomes among men with PCa. Previously Liu *et al.* conducted a systematic review of eight observational studies and found beneficial association of NSAID and PCa-specific mortality (PCM) for certain subgroups using published literature until 2013.[8] However, there still remains the need for future research to explore significant heterogeneity in the pooled study estimates with limited subgroup analyses. In addition, Liu *et al.* did neither examine association between the NSAID use and biochemical recurrence (BCR), metastases, or all-cause mortality (ACM) among men with PCa, nor examine the effect of primary cancer treatment in men with PCa. With available recent publications, there is a need to re-evaluate the impact of NSAIDs and PCa-related outcomes. There have been publications of many studies since the date of search of previous two systematic reviews. Therefore, we carried out a systematic review and meta-analysis to examine the effect of NSAID on the clinical outcomes such as PCM, ACM, BCR, and metastases among men with PCa.

Methods

We followed the standard guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[9] and the Strengthening the Reporting of Observational studies in Epidemiology statement[10] to conduct and report the current systematic review and meta-analysis.

Criteria for study selection

Our systematic review included both prospective randomized controlled trials (RCTs), as well as prospective and retrospective nonrandomized a.k.a observational studies examining the effects of NSAIDs among men with PCa. However, we excluded experimental studies a. k. a cell lines, *in vitro* and animal studies, and studies with shorter duration (≤6 months) of follow-up. The main outcomes of interest for our review were PCM, ACM, BCR, and development of metastases.

Data sources and searches

We searched electronic databases (Medline [Ovid], Scopus, and the Cochrane library) to identify published articles on topic of our interest from the inception of each database to the 2nd week of March 2016. In addition, we also searched the Web of Science (WOS) to identify gray literature related to conference abstracts from the inception of WOS to the 3rd week of July 2016. We searched these databases using keywords such as "Non-steroidal anti-inflammatory drugs," "Aspirin," "prostate neoplasm," and "prostate cancer." We reported the details of search strategy for each database in Appendix 1 with keywords and number of retrieved citations per string. Further, we created a weekly alter for new citations' electronic databases. As of now, we included articles available in weekly search until October 10, 2016. Furthermore, we also scanned through the reference lists of identified studies for additional relevant studies.

Data extraction and quality assessment

Two authors (NR and DT) independently assessed the retrieved articles and gray literature for inclusion of articles in the review. We also checked the agreement for inclusion and exclusion of studies between two authors using the kappa statistic. In case of discrepancies about the inclusion or exclusion between two authors, a third author (ADR) resolved the issues with consensus. Three authors (ADR, NR, and DT) independently extracted information from the included studies using a data extraction template. The data extraction template has information on study design, country of participants, year of publication, sample size, inclusion and exclusion criteria of individual studies, PCa stage and severity-related variables, duration of NSAID use, and type and other baseline characteristics. In addition, we also extracted reported outcomes from each study on BCR, metastases, ACM, and PCM with details on statistical parameters such as number of events, median time to outcomes, unadjusted rates of outcomes, and unadjusted and adjusted hazard ratios (HRs).

We utilized the Newcastle Ottawa scale (NOS) tool to examine the risk of bias in included observational studies. The NOS allots up to nine points for the least risk of bias in three domains: (1) selection of study groups (four points); (2) comparability of groups (two points); and (3) ascertainment of exposure and outcomes (three points) for cohort studies. The risk of bias or poor quality was considered as "high" with one or four score total scores, "fair" with a total score of 4–6, and "good" with a total score 7 or more.[11] In addition, we used the Cochrane Risk of Bias assessment tool to evaluate the risk of bias for performance, selection, reporting, and detecting bias domain for RCTs.[12]

Data synthesis and analysis

We computed a pooled hazard ratio (pHR) with 95% confidence interval (CI) for all clinical outcomes reported in the included studies using random-effects models. We used the Cochrane Chi-square (Cochran Q) statistic and the I^2 test to analyze heterogeneity across included studies.[13] In the presence of heterogeneity of pooled estimates, we performed subgroup analyses by study design, countries of studies, cancer stage, primary cancer treatment, types of NSAIDs, timing of NSAID exposures, and potential adjusted confounders. We also determined the presence of publication bias for observational studies using Egger's

method (Kendall's Tau)[14] and using a contour-enhanced funnel plot to determine other causes of publication bias by examining the symmetry of the plot.[15] All the analyses were performed using Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Results

We identified 4219 citations through electronic databases and other resources. Out of the 4219 citations, we removed 875 duplicates with 3344 citations eligible for first-level screening. We excluded 3068 citations in the first pass based on title and abstract and 237 citations in the second level screening based on full-text information. We excluded the following studies: animal models, *in vitro* studies, reviews, RCTs on interventions other than NSAIDs, RCTs or observational studies on NSAID use in noncancer population, and studies assessing the risk of PCa with the use of NSAIDs. Finally, a total of 26 studies (39 references) met inclusion criteria for our review. Figure 1 depicts the study selection process as per the PRISMA framework from the retrieved citations.

Characteristics of included studies

Table 1 describes the general characteristics of included studies published between 2001 and 2016. We identified 24 observational studies and two randomized controlled studies with a total pooled cohort of 89,436 men with PCa. The included studies had a total of 69,247 men from 20 retrospective cohort studies,[16-33,40,41] 13,855 men from two prospective cohort studies,[34,35] 1619 men from one case cohort study[36] and 4715 men from one nested case–control study,[37] and 300 men from two prospective randomized controlled studies.[38,39] Seventeen studies were carried out in the United States,[16-18,20,21,26-28,31-35,38-40,41] three in the United Kingdom (UK),[22,29,37] two in Canada,[24,36] one each in Belgium,[19] Greece,[30] Finland,[41] and Norway.[25] The sample size of the study cohort ranged between 74[27] and 11,779.[29] With respect to types of NSAID use, 23 of the included studies reported aspirin as the NSAID, one of the each studies reported Exisulind and Ketorolac, and two studies did not specify the type of NSAIDs. The proportion of men with NSAID use ranged from 9.7%[30] to 66%.[18] All the included studies had at least 1 year of median follow-up period with a maximum median duration of 9.25 years in a study.[32]

Seven of the included studies restricted their study cohort to localized PCa[18,20,24,28,29,31,32] and one study included men with advance PCa,[27] whereas the rest of studies did not restrict their cohort based on PCa stage. Six studies included men with PCa treated with radiation therapy (RT),[16,23,24,27,31,33] five studies restricted the study cohort to men with PCa treated with radical prostatectomy (RP),[18-20,26,38] one study had men with active surveillance,[32] and the rest of the included men were diagnosed with PCa without restricting them to any primary PCa treatment such as RP/RT.

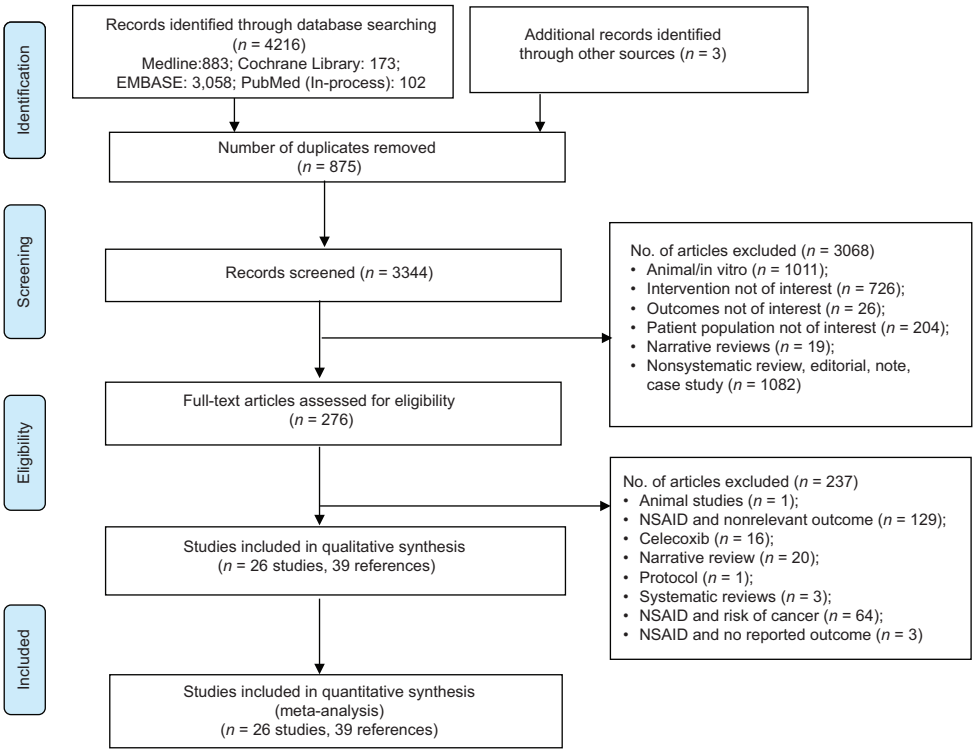

Figure 1: Systematic review and meta-analyses flow chart for study selection for the systematic review on nonsteroidal anti-inflammatory drugs and clinical outcomes in men with prostate cancer. RCT: Randomized Controlled Trials

Table 1: Study characteristics of included studies

Study name	Study design	Time frame	Study sample	Types of NSAID	Number of NSAID users	Percentage of NSAID users	Follow-up (median, IQR), in years	Stage of cancer
Radical prostatectomy								
Goluboff, 2001, US	RCT	2000-2001	94	Exisulind	47	50	1	Any PCa
Forget, 2011, Belgium	RCS	1993-2006	1111	Ketorolac	278	25	3.16 (1.33-5.75)	Any PCa
Mondul, 2011, US	RCS	1993-2006	2399	ASA	1584	66	7	Localized PCa
Kontraros, 2013, Greece	RCS	1999-2010	588	ASA	74	13	μ: 3.4 (SD: 2.6)	Any PCa
Ishak-Howard, 2014, US	RCS	1999-2009	539	ASA	270	50	μ: 7.9 (SD: 4.7)	Any PCa
Zaorsky, 2015, US	RCS	1991-2008	189	ASA	60	32	4.17 (0.28, 17.8)	Localized PCa
Radiation therapy								
Zaorsky, 2011, US	RCS	1989-2006	2051	ASA	743	36	6.3 (1.5-19.9)	Localized PCa
Caon, 2014, Canada	RCS	2000-2007	3851	ASA	917	24	8.0	Localized PCa
Jacobs, 2014b, US	RCS	2005-2008	74	ASA	41	55	4.63	Advanced PCa
Choe, 2010, US	RCS	1988-2005	662	ASA	196	30	4.08	Any PCa
Osborn, 2016, US	RCS	2003-2010	469	ASA	147	31	5.08 (2.42-6.83)	Any PCa
Active surveillance								
Agarwal, 2015, US	RCS	1994-2000	102	NSAIDs	51	50	9.25 (6.1-12.2)	Localized PCa
Any prostate cancer treatment								
Ratansinghe, 2004, US	PCS	1971-1992	9,869	ASA	3934	40		Any PCa
D'Amico, 2008, US	RCT	1995-2001	206	ASA	86	42	8.2 (7.0-9.5)	Any PCa
Choe, 2012, US	RCS	-	5955	ASA	1817	31	5.83	Any PCa
Dhillon, 2012, US	PCS	1990-2005	3986	ASA	1586	40	μ: 8.4	Any PCa
Cardwell, 2013[a], UK	NCCS	1998-2006	4715	ASA	1982	42	μ: 6.0	Any PCa
Daugherty, 2013, US	RCS	1993-2009	3857	ASA	-	-	5	Any PCa
Flahavan, 2013, UK	RCS	2001-2006	2936	ASA	1131	39	5.5	Any PCa
Grytli, 2014, Norway	RCS	2004-2009	3561	ASA	1149	32	3.25	Any PCa
Stock, 2008[b], Canada	Case-Cohort	1990-1999	1619	ASA + others NSAIDs	419	26	-	Any PCa
Veitonmaki, 2015, Finland	RCS	1996-2012	6537	ASA + others NSAIDs	NSAID: 5,591; ASA: 637	NSAID: 86%; ASA: 10	7.5	Any PCa
Katz, 2010, US	RCS	1990-2003	7042	NSAIDs	1830	26	4 (0-16)	Any PCa
Jacob, 2014C-1, US	RCS	1992-2010	8427	ASA	4827	57	μ: 9.3	Localized PCa
Jacobs, 2014-C2, US	RCS	1992-2010	7118	ASA	4151	58	μ: 8.4	Localized PCa
Assayag, 2015, UK	RCS	1996-2012	11,779	ASA	4147	35	μ: 5.4 (SD: 2.9)	Localized PCa

[a]Cardwell *et al.* had a total of 453 cases and 1619 men in the subcohort, [b]Stock *et al.* had 1184 cases and 3531 controls of which 617 cases and 1365 controls used any NSAID, [c]Other NSAID use includes the use of diclofenac, naproxen, indomethacin, and ibuprofen. IQR - Interquartile range; NCCS - Nested case-control study; NSAIDs - Nonsteroidal anti-inflammatory drugs; PCa - Prostate cancer; PCS - Prospective cohort study; RCS - Retrospective cohort study; RCT - Randomized controlled trial; ASA - Aspirin

Characteristics of men with prostate cancer

Table 2 describes the demographic, comorbidity, and lifestyle characteristics of men among the included studies by NSAID use. Majority of the included studies had 60–66 years of median or mean age of men with PCa. Five of the included studies had 1%–2% of cohort with African-American race distributed evenly between NSAID users and nonusers,[18,26,27,29,38] whereas one study[33] included only African-American men with PCa. Eleven studies reported the status of chronic conditions.[17,20,22-24,28-30,33,37,39] Five studies reported significant greater rate scores of Charlson Comorbidity Index or Adult Comorbidity Score-27 among NSAID users as compared to nonusers,[20,22,24,30,39] whereas six studies reported greater rates of difference in types of chronic conditions, specifically diabetes, heart disease, and hypertension among NSAID users as compared to nonusers.[17,23,24,27,29,37] With regard to lifestyle characteristics, eight studies reported body mass index of the study cohort and majority of the studies had greater proportions of overweight or obese men in both NSAID users and nonusers.[17,18,26,27,29,35-37] Six studies reported had the smoking status of study cohort and out of those all the studies had more than one-third of past or current smokers across NSAID users and nonusers.[17,18,22,27,36,37]

Table 3 describes PCa-related clinical and cancer-related treatment characteristics by NSAID use. Fourteen studies reported the status of prostate-specific antigen (PSA) levels[16,18-20,23,25,26,28,29,31,35,36,38,39] and those studies did

Table 2: Demographic, comorbidity, and lifestyle characteristics of study population by nonsteroidal anti-inflammatory drugs use among the included studies

Study name	Study groups	Age (years)	Race/ ethnicity (%)	Comorbidities (%)	BMI (kg/m^2)	Smoking (%)
Radical prostatectomy						
Mondul, 2011, US	Overall	µ: 56.9	W: 92.5 AA: 02	-	µ: 26.5	C: 1; P: 30
Zaorsky, 2015, US	NSAID-users	M: 65 (51, 80)	-	ACE-27 score: 0: 20	-	-
	Nonusers	M: 61 (43, 77)		ACE-27 score: 0: 33		
Ishak-Howard, 2014, US	Overall	µ: 65 (9)	W: 97; AA: 2.4	-	BMI >25: 73%	-
Goluboff, 2001, US	NSAID-users	µ: 68	W: 92; AA: 4	-	-	-
	Nonusers	µ: 66	W: 90; AA: 4			
Forget, 2011, Belgium	Overall	µ: 65 (7)	-	-	-	-
Kontraros, 2013, Greece	Overall	µ: 65 (6)	-	DM: 18	-	-
Radiation therapy						
Zaorsky, 2011, US	Overall	M: 69 (36, 86)	-	-	-	-
Caon, 2014, Canada	No-statin/no ASA	µ: 71	-	CCI 0: 73	-	-
	Statin/no ASA	µ: 71		CCI 0: 51		
	ASA/statin	µ: 72		CCI 0: 62		
	Statin + ASA	µ: 72		CCI 0: 40		
Jacobs, 2014b, US	NSAID-users	M: 70 (53, 86)	-	-	-	-
	Nonusers	M: 66 (49, 84)				
Choe, 2010, US	NSAID-users	M: 70 (42, 83)	-	-	-	-
	Nonusers	M: 68 (44, 83)				
Osborn, 2016, US	NSAID users	M: 69	AA: 100	-	-	-
	Nonusers	M: 68	AA: 100			
Active surveillance						
Agarwal, 2015, US	NSAID-users	70 (68,73)	-	-	-	-
	Nonusers					
D'Amico, 2008, US	Overall	M: 72.5 (49-82)	-	ACE-27 score: severe: 3	-	-
Choe, 2012, US	NSAID-users	66 (42, 86)	-	-	-	
	Nonusers	63 (39, 85)				
Dhillon, 2012, US	NSAID-users	µ: 70 (7)	-	-	µ: 26 (4)	-
	Nonusers	µ: 68 (8)			µ: 26 (3)	
Cardwell, 2013, UK	Case	>60: 99	-	MI: 11; DM: 12	µ: 26 (4)	C: 19; P: 34
	Control	>60: 99		MI: 10; DM: 11	µ: 26 (4)	C: 14; P: 34
Daugherty, 2013, US	NSAID-users	-	-	-	-	-
	Nonusers					
Flahavan, 2013, UK	NSAID-users	µ: 72 (6)	-	CCI: 11 (6)	-	C: 14; P: 20
	Nonusers	µ: 70 (7)		CCI: 7 (6)		c: 18; P: 18
Grytli, 2014, Norway	NSAID-users	µ: 76 (8)	-	-	-	-
	Nonusers					
Stock, 2008[a], Canada	Sub-cohort	µ: 67	-	-	>25: 55	P/C: 60
	Case	µ: 68			>25: 55	P/C: 64
Veitonmaki, 2015, Finland	NSAID never	µ: 67	-	CCI-0: 58	-	-
	NSAID ever	µ: 67		CCI-0:59		
	ASA ever	µ: 68		CCI-0: 31		
Katz, 2010, US	NSAID-users	µ: 64 (8)	-	HTN: 49; HF: 28	>25: 74	C: 7
	Nonusers			HTN: 38; HF: 16	>25: 71	C: 11

Contd...

Table 2: Contd...

Study name	Study groups	Age (years)	Race/ ethnicity (%)	Comorbidities (%)	BMI (kg/m^2)	Smoking (%)
Radical prostatectomy						
Jacob, 2014 C-1, US	NSAID user-OD	<75: 68	W: 98; AA: 1	DM: 13; CVD: 37	μ: 26.4	C: 5; P: 61
	NSAID-use LT OD	<75: 73	W: 98%; AA: 1	DM: 9; CVD: 11	μ: 26.3	C: 5; P: 59
		<75: 70		DM: 9; CVD: 12	μ: 26.2	C: 5; P: 57
	Nonusers		W: 97; AA: 2			
Jacobs, 2014-C2, US	NSAID user-OD	<75: 69.9	W: 99; AA: 1	DM: 14; CVD: 44	μ: 26	C: 3; P: 63
	NSAID-use LT OD	<75: 72.4	W: 97; AA: 1	DM: 9; CVD: 15	μ: 26	C: 3; P: 60
		<75: 71.4	W: 97; AA: 2	DM: 12; CVD: 17	μ: 26	C: 4; P: 59
	Nonusers					
Assayag, 2015, UK	NSAID-users	μ: 74 (8)	W: 69; AA: 1	HTN: 63; HF: 16; MI: 8	>30: 16	-
	Nonusers	μ: 70 (7)	W: 67; AA: 1	HTN: 36; HF: 6; MI: 1	>30: 10	

μ - mean; M - median; AA - African-American; ASA - Aspirin; BMI - Body mass index; CCI - Charlson Comorbidity Score; COPD - Chronic obstructive pulmonary disease; CVD - Cardiovascular disease; DM - Diabetes mellitus; HF - Heart failure; HTN - Hypertension; LT - Less than; MI - Myocardial infarction; NSAID - Nonsteroidal anti-inflammatory drugs; OD - Once daily; UK - United kingdom; US - United states; W - Whites; ACS - Adult Comorbidity Score-27; C/P - Current smoker or past smoker

Table 3: Prostate cancer and its treatment-related characteristics among the included studies

Study ID	Study groups	Prostate tumor characteristics				Prostate Cancer Therapy			
		PSA level (ng/ml)	Gleason Score	Tumor stage	NCCN risk categories	ADT (%)	RP (%)	RT (%)	AW/WW (%)
Radical prostatectomy									
Mondul, 2011, US	Overall	μ: 6.7	>7: 6.3%	T2/3a: 29%	-	None	All	None	None
Zaorsky, 2015, US	NSAID-users	M: 0.67	>7: 4%	T2/3: 32%	M/H: 32%	-	All	-	None
	Nonusers	M: 0.50	>7: 11%	T2/3: 68%	M/H: 66%				
Ishak-Howard, 2014, US	Overall	μ: 2.1	>7: 17%	T2/3: 90%	-	-	All	-	None
Goluboff, 2001, US	NSAID-users	μ: 2.2	μ: 6.6	-	M/H: 22%	-	All	-	None
	Nonusers	μ: 2.7	μ: 6.5		M/H: 27%				
Forget, 2011, Belgium	Overall	>10: 38%	>7: 24%	T2/3: 100%	-	-	All	-	None
Kontraros, 2013, Greece	Overall	M: 7.6	>7: 51%	-	-	-	-	All	None
Radiation therapy									
Zaorsky, 2011, US	Overall	>10: 30%	>7: 26%	T2/3: 42%	M/H: 56%	None	None	All	None
Caon, 2014, Canada	No-statin/no ASA	-	-	-	M/H: 84%	71%	None	All	None
	Statin/no ASA				M/H: 73%	61%			
	ASA/Statin				M/H: 84%	63%			
	Statin + ASA				M/H: 81%	59%			
Jacobs, 2014b, US	NSAID-users	μ: 49	> 7: 77%	T2c/3b: 44%	-	96%	-	All	None
	Nonusers	μ: 40	7: 62%			86%			
				T2c/3b: 48%					
Choe, 2010, US	NSAID-users	M: 8.1	> 7: 10%	T3: 4%	M/H: 62%	44%	-	All	None
	Nonusers	M: 8.5	>7: 9%	T3: 7%	M/H: 62%	40%			
Osborn, 2016, US	NSAID-users	-	-	-	M/H: 78%	39%	-	All	-
	Nonusers				M/H: 72%	39%			
Any prostate cancer treatment									
D'Amico, 2008, US	Overall	>10: 61%	> 7: 15%	T2: 52%		NR			
Choe, 2012, US	NSAID-users	M: 5.9	> 7: 7%	T3: 2%	M/H: 58%	11%	63%	37%	00%
	Nonusers	M: 6.0	> 7: 8%	T3: 3%	M/H: 58%	08%	70%	30%	00%

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Table 3: Contd...

Study ID	Study groups	Prostate tumor characteristics				Prostate Cancer Therapy			
		PSA level (ng/ml)	Gleason Score	Tumor stage	NCCN risk categories	ADT (%)	RP (%)	RT (%)	AW/WW (%)
Dhillon, 2012, US	NSAID-users	M: 7.2	>7: 7%	T3: 3%		7%	44%	39%	4%
	Nonusers	M: 7.2	>7: 7%	T3: 4%		7%	50%	33%	4%
Cardwell, 2013, UK	Case	-	>7: 54%	-	-	82%	2.4%	21%	
	Control		>7: 73%			59%	7.6%	21%	
Flahavan, 2013, UK	NSAID-users	-	>7: 16%	T3: 13%	-	48%	3.6%	39%	-
	Nonusers		> 7: 16%	T3: 13%		43%	7.4%	38%	
Grytli, 2014, Norway	Overall	>10: 92%	>7: 53%	T2/3: 86%	H: 100%	70%	-	-	
Stock, 2008, Canada	Sub-cohort	>10: 61%	-	T3/4: 8%	-	32%	41%	59%	
	Case	>10: 84%		T3/4: 23%		32%	17%	83%	
Veitonmaki, 2015, Finland	NSAID never	-	>7: 40%	-	-	42%	22%	35%	19.2%
	NSAID ever		> 7: 42%			41%	26%	37%	17.3%
	Aspirin ever		> 7: 41%			44%	18%	39%	17.6%
Katz, 2010, US	NSAID-users	-	-	-	-	15%			
	Nonusers					15%			
Jacobs, 2014-C1, US	NSAID user-OD	-	-	T3/4: 3%	-	-	30%	40%	12%
				T3/4: 3%			38%	32%	10%
	NSAID-use LT OD			T3/T4: 3%			34%	33%	12%
	Nonusers								
Jacobs, 2014-C2, US	NSAID user-OD	-	-	T3/4: 3%	-	-	34%	39%	11%
				T3/4: 2%			37%	34%	11%
	NSAID-use LT OD			T3/4: 3%			37%	34%	11%
	Nonusers								
Assayag, 2015, UK	NSAID users	>10: 46%	>7: 45%	-	-	62%	38%	52%	
	Nonuser	>10: 42%	>7: 46%			56%	47%	62%	

μ - mean; M - median; AA - African-American; ASA - Aspirin; M/H - Medium- or high-risk prostate cancer; NCCN - National Cancer Comprehensive Network; LT - Less than; MI - Myocardial infarction; NSAIDs - Nonsteroidal anti-inflammatory drugs; OD - Once daily; PSA - Prostate-specific antigen

not find significant difference in PSA levels between NSAID users and nonusers. Sixteen studies reported Gleason score,[16,18-20,22,25,26,28-31,35,37,38,21,29,39] of which two studies included >50% of men with Gleason score >7. Thirteen studies reported tumor stage,[16,18-20,22,25-28,30,35,36,39] of which two studies[20,36] had significant differences in the proportion of men with T2/3 stages among NSAID users and nonusers. Nine studies[16,20,21,24,25,31,33,38,39] reported the National Comprehensive Cancer Network scores of which one study[20] had significant difference in medium- and high-risk PCa among NSAID users and nonusers. Fifteen studies reported androgen deprivation therapy (ADT)[16-18,21,22,24,25,27-31,35-37] of which two studies[18,31] did not have any men with ADT users among NSAIDs users and no users.

Quality assessment of included studies

We used NOS tool to determine the quality of the included observational studies and the Cochrane risk of bias tool for RCT. Twenty-four of the included observational studies had a fair or good quality as per the NOS scale and two of the included observational studies had low risk for selection, performance bias, and unclear risk for reporting bias. Details on each of the three domains for risk of bias selection, ascertainment of exposure and outcomes, and comparability for observational studies are provided in Appendix 1.1-1.3 and the risk of bias table for RCT are provided in Appendix 1.4. Out of the 24 observational studies, ten utilized single institutional data,[18-21,23,26,28,31-33] seven utilized survey or prospective cohort data,[16,17,27,30,34,35,40] and six studies utilized cancer registry-linked electronic medical records or administrative claim databases.[22,24,25,29,36,37] The coding algorithms for PCa were not defined with their diagnostic accuracy in single institutional data. With respect to exposure of interest, five studies[20,28,29,31,33] reported the use of NSAID postcancer or postcancer therapy, five studies[22,24,28,34,40] reported the precancer period or precancer treatment period NSAID exposure, and rest of the studies measured NSAID at any time during the study period. Except one study,[27] all other observational studies conducted multivariable regression analysis controlling for the potential confounders while examining association

between NSAID use and clinical outcomes. However, only Fourteen studies[18,19,22-26,28,29,31,33,35,41] controlled for co-medications.

Nonsteroidal anti-inflammatory drug use and clinical outcomes

We conducted meta-analyses of the included studies to evaluate the association between NSAID use and several clinical outcomes in men with PCa. Due to the presence of significant heterogeneity in the pooled estimates, we performed several subgroup analyses by types of NSAIDs, pre-, post- or any NSAID use, and type of PCa treatment.

Prostate cancer-specific mortality

Eleven studies reported the association between NSAID use and PCM,[16,22,24,25,28-30,33,35,36,40] of which three studies found an inverse relationship between aspirin use and PCM,[16,25,33] while two studies found an increased risk of PCM associated with aspirin use,[29,30] whereas rest of the six studies did not find any association between NSAID use and PCM.

Overall, any type of NSAID use was not associated with the risk of PCM (pHR: 0.95; 95% CI: 0.79, 1.05; $P = 0.19$; $I^2 = 62\%$) with significant heterogeneity [Figure 2]. In the subgroup analyses by timing of aspirin use, we found that aspirin use, irrespective of prior to or following PCa diagnosis, was not associated with PCM (pHR: 0.95; 95% CI: 0.77, 1.16; $P = 0.60$; studies = 11, $I^2 = 88\%$). Furthermore, aspirin use prior to PCa diagnosis or primary treatment was not significantly associated with PCM (pHR: 1.00; 95% CI: 0.83, 1.19; $P = 0.97$; studies = 5; $I^2 = 51\%$), and so was for ever (pHR: 1.34; 95% CI: 0.71, 2.51; $P = 0.36$; studies = 2; $I^2 = 97\%$) or postdiagnosis or postcancer aspirin use (pHR: 0.94; 95% CI: 0.72, 1.23; $P = 0.67$; studies = 8; $I^2 = 86\%$). In contrast, postdiagnosis or post-treatment NSAID use was associated with 2.5 times increased risk of PCM (pHR: 2.50; 95% CI: 1.75, 3.57; $P < 0.0001$; studies = 1). However, one study reported a nonsignificant association between precancer diagnosis NSAID use and PCM (pHR: 1.03; 95% CI: 0.79, 1.34; $P = 0.83$).

Nine studies reported the association between NSAID use and PCM among men who had RP, RT, or other therapies.[16,22,25,28-30,35,36,40] In this subgroup, NSAID use was not significantly associated with PCM (pHR: 1.02; 95% CI: 0.79, 1.30; $P = 0.90$; studies = 10; $I^2 = 91\%$). Among men with PCa who had RT as the primary treatment, NSAID use was not significantly associated with PCM (pHR: 0.91; 95% CI: 0.65, 1.27; $P = 0.58$). Two studies[16,29] which controlled for time of NSAID exposure using time-dependent NSAID use reported a lower though nonsignificant risk of PCM due to NSAID use (pHR: 0.84; 95% CI: 0.25, 2.76; $P = 0.77$; studies = 2; $I^2 = 91\%$).

Three studies reported the risk of PCM by NSAID dose.[22,28,36] As compared to nonusers, either high-dose or low-dose NSAID was associated with 5% reduction in the PCM, though the association was not significant.

Nonsteroidal anti-inflammatory drug use and all-cause mortality

Three studies reported ACM as an outcome.[17,22,29] NSAID use was not associated with ACM in the pooled analysis with significant heterogeneity (pHR: 0.82; 95% CI: 0.54, 1.24; $P = 0.19$; $I^2 = 73\%$) [Figure 3]. To find the cause of heterogeneity, leave-one-out sensitivity analysis was performed which did not alter the study finding.

Nonsteroidal anti-inflammatory drug use and biochemical recurrence

The hazard of BCR was reported in five studies.[16,19,20,23,26] Overall, NSAID use was not significantly associated with reducing the hazards of BCR using random-effects model (pHR: 0.82, 95% CI: 0.54, 1.24, $P = 0.34$, 5 studies, I^2: 73%) with significant heterogeneity. We carried out subgroup analyses to explore the possible reasons of heterogeneity. NSAID use in men who had RP (pHR: 0.79, 95% CI: 0.45, 1.38, $P = 0.41$, 3 studies, I^2: 69%) or RT (pHR: 0.85, 95% CI: 0.35, 2.03, $P = 0.71$, 2 studies, I^2: 88%) was not significantly associated with reducing the risk of BCR [Figure 4].

Nonsteroidal anti-inflammatory drug use and metastases

Two studies[16,27] examined the hazards of metastases with the use of NSAID. Both the studies found a beneficial effect of NSAID in the univariate analysis and did not have a sufficient sample size to conduct multivariable analyses.

Discussion

Our review aimed to generate evidence on the effects of NSAIDs on cancer prognosis among men with PCa. We found 24 observational studies and two RCTs examining the impact of NSAIDs on different cancer prognostic outcomes. We found that NSAID use was not associated with BCR, metastases, ACM, and PCM in pooled estimates with significant heterogeneity. To account for heterogeneity, we conducted various subgroup analyses and observed significant findings across those subgroup analyses which reduced the heterogeneity in some cases.

First, as majority of the included studies used aspirin as the main NSAID class, we did a subgroup analysis by types of NSAID as aspirin users and nonaspirin NSAID. We did not find any conclusive evidence on the beneficial effect of NSAIDs and PCM. Our findings are also similar to a previous systematic review by Elwood *et al.* examining the association between NSAID and PCM. Elwood *et al.* found no association between NSAID and PCM in a pooled estimate of nine studies with significant heterogeneity. However, in that study, they observed a significant association with omission of one study.[29] This difference in our findings could be due to negative or no association observed in the newer additional studies included in our review.

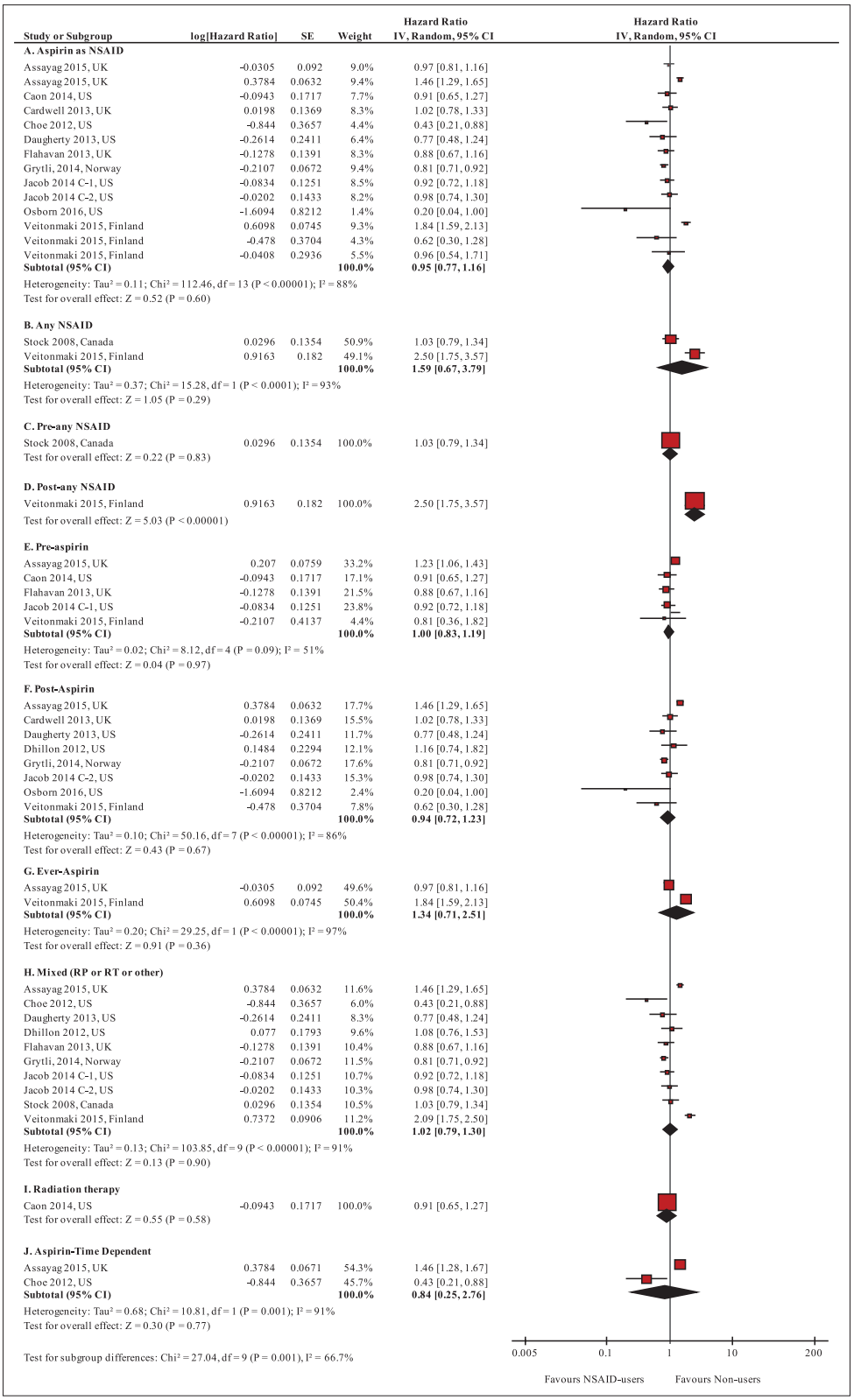

Figure 2: Forest plot of comparison: Nonsteroidal anti-inflammatory drug users versus nonusers for prostate cancer-specific mortality

There has been significant heterogeneity in the pooled estimates even after subgroup analyses, which suggest the variation in the analytic samples among the included studies. Most of the studies had utilized secondary preexisting data and the study was based on a data-driven design approach rather than design-driven data collection approach. For example, there have been great variations on timing of NSAID use as pre/postdiagnosis, or

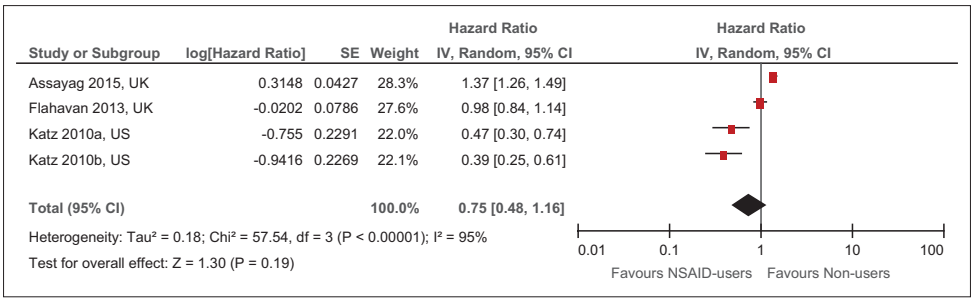

Figure 3: Forest plot of comparison: Nonsteroidal anti-inflammatory drug users versus nonusers for all-cause mortality

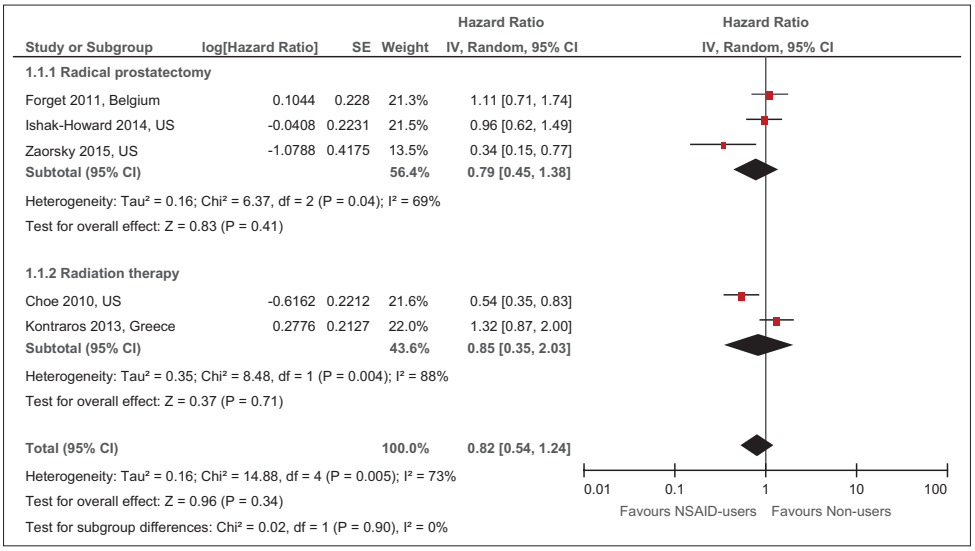

Figure 4: Forest plot of comparison: Nonsteroidal anti-inflammatory drug users versus nonusers for biochemical recurrence

pre/post-treatment NSAID use, or ever use of NSAID. Both pre- and post-diagnosis NSAID could not serve as meaningful treatment to inhibit progression of cancer if men do not adhere to medications or used for symptomatic pain relief. One of the major biases with NSAIDs is bias by treatment indications. NSAID can be used for different indications at different stages of prostate cancer having low or high comorbidity burden. For example, aspirin can be used to prevent primary prevention of heart disease in men with localized PCa as well as to relieve pain in men with metastatic PCa, which have drastically different prognosis.

Second, the timing of aspirin in the postdiagnosis or post-treatment suffers from two major biases: immortal time bias and lag time bias. With respect to immortal time bias, men using NSAID in the follow-up period should be alive until they receive the NSAID postdiagnosis. This leads to misclassification of unexposed person-time as exposed person-time. In addition, if NSAID is initiated few days before death due to palliative pain relief, then there would be very short NSAID exposure time for fatal event. Therefore, such exposure may not provide conclusive findings due to design limitations. Although two studies have controlled for time of NSAID exposure using time-dependent NSAID use, both the studies yielded mixed results on the NSAID use and PCM. Such results may be again due to variation in the population.

Further, we also explored relationship between NSAID and clinical outcomes by high-risk PCa. Again, study findings among those with high-risk PCa had mixed findings. These could be due to effect modification due to hormone therapy use in high-risk PCa with aspirin. A study found that aspirin was associated with abnormal liver function and the serum level of aspirin is also expected to be higher due to low level of testosterone which leads to inhibit the metabolism of aspirin. Eventually, men using NSAID are at risk of abnormal liver function[42] and affect the adherence to hormone therapy in men with PCa. Therefore, the proportion of patients using hormone therapy could serve as a potential confounder for the association between NSAID use and clinical outcomes in men with PCa.

Strengths and limitations of our study findings suggest the need for well-designed observational studies to examine the association between NSAID use and clinical outcomes among homogeneous PCa population, i.e., stage or primary PCa treatment controlling for important covariate including adherence and persistence or duration of NSAID use.

Conclusions

Although we did not find association between NSAID use and clinical outcomes in men with PCa in our systematic review, our study findings highlight the need to consider variation in the population of NSAID users requiring need for better design in future observational studies.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Globocan 2012 – Home. Available from: http://www.globocan.iarc.fr/Default.aspx. [Last accessed on 2016 Jun 04].
2. Global Oncology Trend Report a Review of 2015 and Outlook to 2020. IMS Health; 2016. Available from: http://www.imshealth.com/en/thought-leadership/ims-institute/reports/global-oncology-trend-report-a-review-of-2015-and-outlook-to-2020. [Last accessed on 2016 Jun 04].
3. Thun MJ, Blackard B. Pharmacologic effects of NSAIDs and implications for the risks and benefits of long-term prophylactic use of aspirin to prevent cancer. Recent Results Cancer Res 2009;181:215-21.
4. Goubran HA, Burnouf T, Radosevic M, El-Ekiaby M. The platelet-cancer loop. Eur J Intern Med 2013;24:393-400.
5. Gay LJ, Felding-Habermann B. Contribution of platelets to tumour metastasis. Nat Rev Cancer 2011;11:123-34.
6. Colotta F, Allavena P, Sica A, Garlanda C, Mantovani A. Cancer-related inflammation, the seventh hallmark of cancer: Links to genetic instability. Carcinogenesis 2009;30:1073-81.
7. Kundu JK, Surh YJ. Inflammation: Gearing the Journey to Cancer. Vol. 659. Proceedings 5th International Conference Environmental Mutagens Humam Population ICEMHP; 2008. p. 15-30.
8. Liu Y, Chen JQ, Xie L, Wang J, Li T, He Y, *et al.* Effect of aspirin and other non-steroidal anti-inflammatory drugs on prostate cancer incidence and mortality: A systematic review and meta-analysis. BMC Med 2014;12:55.
9. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. PLoS Med 2009;6:e1000097.
10. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, *et al.* Strengthening the reporting of observational studies in epidemiology (STROBE) statement: Guidelines for reporting observational studies. BMJ 2007;335:806-8.
11. Ottawa Hospital Research Institute. Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. [Last accessed on 2016 Jun 04].
12. Cochrane Handbook for Systematic Reviews of Interventions. Available from: http://www.handbook.cochrane.org/. [Last accessed on 2016 Apr 30].
13. van Houwelingen HC, Arends LR, Stijnen T. Advanced methods in meta-analysis: Multivariate approach and meta-regression. Stat Med 2002;21:589-624.
14. Deeks JJ, Macaskill P, Irwig L. The performance of tests of publication bias and other sample size effects in systematic reviews of diagnostic test accuracy was assessed. J Clin Epidemiol 2005;58:882-93.
15. Peters JL, Sutton AJ, Jones DR, Abrams KR, Rushton L. Contour-enhanced meta-analysis funnel plots help distinguish publication bias from other causes of asymmetry. J Clin Epidemiol 2008;61:991-6.
16. Choe KS, Cowan JE, Chan JM, Carroll PR, D'Amico AV, Liauw SL, *et al.* Aspirin use and the risk of prostate cancer mortality in men treated with prostatectomy or radiotherapy. J Clin Oncol 2012;30:3540-4.
17. Katz MS, Carroll PR, Cowan JE, Chan JM, D'Amico AV. Association of statin and nonsteroidal anti-inflammatory drug use with prostate cancer outcomes: Results from caPSURE. BJU Int 2010;106:627-32.
18. Mondul AM, Han M, Humphreys EB, Meinhold CL, Walsh PC, Platz EA, *et al*. Association of statin use with pathological tumor characteristics and prostate cancer recurrence after surgery. J Urol 2011;185:1268-73.
19. Forget P, Tombal B, Scholtès JL, Nzimbala J, Meulders C, Legrand C, *et al.* Do intraoperative analgesics influence oncological outcomes after radical prostatectomy for prostate cancer? Eur J Anaesthesiol 2011;28:830-5.
20. Zaorsky NG, Li T, Cohen RJ, Horwitz EM, Uzzo RG, Viterbo R, *et al*. Aspirin use decreases the risk of prostate cancer recurrence after post-prostatectomy radiotherapy. J Radiat Oncol 2015;4:193-201.
21. Choe KS, Correa D, Jani AB, Liauw SL. The use of anticoagulants improves biochemical control of localized prostate cancer treated with radiotherapy. Cancer 2010;116:1820-6.
22. Flahavan EM, Bennett K, Sharp L, Barron TI. A cohort study investigating aspirin use and survival in men with prostate cancer. Ann Oncol 2014;25:154-9.
23. Kontraros M, Varkarakis I, Ntoumas K, Deliveliotis C. Pathological characteristics, biochemical recurrence and functional outcome in radical prostatectomy patients on statin therapy. Urol Int 2013;90:263-9.
24. Caon J, Paquette M, Hamm J, Pickles T. Does statin or ASA affect survival when prostate cancer is treated with external beam radiation therapy? Prostate Cancer 2014;2014:184297.
25. Grytli HH, Fagerland MW, Fosså SD, Taskén KA. Association between use of β-blockers and prostate cancer-specific survival: A cohort study of 3561 prostate cancer patients with high-risk or metastatic disease. Eur Urol 2014;65:635-41.
26. Ishak-Howard MB, Okoth LA, Cooney KA. Statin use and the risk of recurrence after radical prostatectomy in a cohort of men with inherited and/or early-onset forms of prostate cancer. Urology 2014;83:1356-61.
27. Jacobs CD, Chun SG, Yan J, Xie XJ, Pistenmaa DA, Hannan R, *et al.* Aspirin improves outcome in high risk prostate cancer patients treated with radiation therapy. Cancer Biol Ther 2014;15:699-706.
28. Jacobs EJ, Newton CC, Stevens VL, Campbell PT, Freedland SJ, Gapstur SM, *et al.* Daily aspirin use and prostate cancer-specific mortality in a large cohort of men with nonmetastatic prostate cancer. J Clin Oncol 2014;32:3716-22.
29. Assayag J, Pollak MN, Azoulay L. The use of aspirin and the risk of mortality in patients with prostate cancer. J Urol 2015;193:1220-5.
30. Veitonmäki T, Murtola TJ, Määttänen L, Taari K, Stenman UH, Tammela TL, *et al.* Use of non-steroidal anti-inflammatory drugs and prostate cancer survival in the Finnish prostate cancer screening trial. Prostate 2015;75:1394-402.
31. Zaorsky NG, Buyyounouski MK, Li T, Horwitz EM. Aspirin and statin nonuse associated with early biochemical failure after prostate radiation therapy. Int J Radiat Oncol Biol Phys

2012;84:e13-7.
32. Agarwal G, Spuches J, Luchey A, Patel T, Pow-Sang J. The effect of NSAID use on disease progression in patients on active surveillance for prostate cancer.Ann Rheum Dis 2015;193:e756.
33. Osborn VW, Chen SC, Weiner J, Schwartz D, Schreiber D. Impact of aspirin on clinical outcomes for African American men with prostate cancer undergoing radiation. Tumori 2016;102:65-70.
34. Ratnasinghe LD, Graubard BI, Kahle L, Tangrea JA, Taylor PR, Hawk E, *et al.* Aspirin use and mortality from cancer in a prospective cohort study. Anticancer Res 2004;24:3177-84.
35. Dhillon PK, Kenfield SA, Stampfer MJ, Giovannucci EL, Chan JM. Aspirin use after a prostate cancer diagnosis and cancer survival in a prospective cohort. Cancer Prev Res (Phila) 2012;5:1223-8.
36. Stock DC, Groome PA, Siemens DR, Rohland SL, Song Z. Effects of non-selective non-steroidal anti-inflammatory drugs on the aggressiveness of prostate cancer. Prostate 2008;68:1655-65.
37. Cardwell CR, Flahavan EM, Hughes CM, Coleman HG, O'Sullivan JM, Powe DG, *et al.* Low-dose aspirin and survival in men with prostate cancer: A study using the UK Clinical Practice Research Datalink. Cancer Causes Control 2014;25:33-43.
38. Goluboff ET, Prager D, Rukstalis D, Giantonio B, Madorsky M, Barken I, *et al.* Safety and efficacy of exisulind for treatment of recurrent prostate cancer after radical prostatectomy. J Urol 2001;166:882-6.
39. D'Amico AV, Chen MH, Renshaw AA, Loffredo B, Kantoff PW. Risk of prostate cancer recurrence in men treated with radiation alone or in conjunction with combined or less than combined androgen suppression therapy. J Clin Oncol 2008;26:2979-83.
40. Daugherty S, Pfeiffer R, Ghazarian A, Izmirlian G, Prorok P, McGlynn K. Frequency of aspirin use and prostate cancer mortality among prostate cancer cases in the control arm of the Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening trial. Cancer Res 2013;73:LB-15.
41. Veitonmäki T, Murtola TJ, Talala K, Taari K, Tammela T, Auvinen A, *et al.* Non-steroidal anti-inflammatory drugs and cancer death in the Finnish prostate cancer screening trial. PLoS One 2016;11:e0153413.
42. D'Amico AV, Kantoff PW, Chen MH. Aspirin and hormone therapy for prostate cancer. N Engl J Med 2007;357:2737-8.

Appendices

Appendix 1: Details on quality of included studies

Appendix 1.1: Risk of bias: Selection in the included studies

Study name	Data source	Type of data	PCa	NOS
Radical prostatectomy				
Mondul, 2011, US	John Hopkins Hospital Database	Single institutional data	1	3
Zaorsky, 2015, US	National Cancer Institute-designated Cancer Center data	Single institutional data	1	3
Ishak-Howard, 2014, US	University of Michigan Prostate Cancer Genetics Project	Single institutional data	1	3
Kontraros, 2013, Greece	Hospital Pitie-Salpetriere	Single institutional data	1	3
Forget, 2011, Belgium	Universite' Catholique de Louvain Center Data	Single institutional data	1	3
Radiation therapy				
Zaorsky, 2012, US	Fox Chase Cancer Center	Single institutional data	1	3
Caon, 2014, Canada	British Columbia Medical Center Data	Cancer registry linked data	2	4
Jacobs, 2014b, US	UT Southwestern Medical Center Data	Single institutional data	2	3
Choe, 2010, US	UT Chicago School of Medicine Data	Single institutional data	1	3
Osborn, 2016, US	New York Harbor Department of Veterans Affairs	Single institutional data	1	3
Active surveillance				
Agarwal, 2015, US	Moffitt Cancer Center Oncology	Single institutional data	1	3
Any prostate cancer treatment				
Ratnasinghe, 2004, US	NHNES-I, II and National Death Index	National survey	3	4
Choe, 2012, US	Prostate Strategic Urologic Research Endeavor Database	Prospective mail survey	1	4
Cardwell, 2013, UK	UK Clinical Practice Research Datalink; Cancer registry	Cancer registry linked data	2	4
Dhillon, 2012, US	Health Professional Follow-up Studies	Prospective mail survey	3	4
Daugherty, 2013, US	Prostate Lung Cancer Screening Trial	Prospective mail survey	1	4
Flahavan, 2013, UK	National Cancer Registry Ireland	Cancer registry linked data	2	4
Grytli, 2014, Norway	Cancer Registry of Norway; Norwegian Prescription database	Cancer registry linked data	2	4
Stock, 2008[1], Canada	Cancer Care and Epidemiology Cancer database	Cancer registry linked data	2	4
Veitonmaki, 2015, Finland	Finnish Prostate Cancer Screening Trial	Prospective clinical trial	1	4
Katz, 2010, US	Cancer of the Prostate Strategic Urologic Research Endeavor	National prospective cohort	3	4
Jacob, 2014 C-1, US	Cancer Prevention Study-II Nutrition Cohort	Prospective mail survey	1	4
Jacobs, 2014-C2, US	Cancer Prevention Study-II Nutrition Cohort	Prospective mail survey	1	4
Assayag, 2015, UK	United Kingdom National Cancer Data Repository and CPRD	Cancer registry linked data	2	4

CPRD - Clinical Practice Research Datalink; PCa - Prostate cancer diagnostic criteria were - 1 - diagnosed by clinicians; unclear about the coding manner; 2 - registry-based diagnostic codes; 3 - patient response about their clinical status; NHNE - National Health and Nutritional Examination Survey; NOS - Newcastle Ottawa Scale for Comparability Domain

Appendix 1.2: Risk of bias: drug exposure for clinical outcome assessment in the included studies

Study ID	Types of NSAIDs	Identification	Timing	Dose	NOS
Radical prostatectomy					
Mondul, 2011, US	Any	Survey	Before and After RP	-	3
Zaorsky, 2015, US	ASA	Unclear	On and After RP	-	2
Ishak-Howard, 2014, US	ASA	Self-report	Ever use of ASA	-	3
Kontraros, 2013, Greece	ASA	Unclear	Before and After RP	Reported	3
Forget, 2011, Belgium	Ketorolac	Pharmacy database	Intraoperative	24mg	2
Radiation therapy					
Zaorsky, 2012, US	ASA	Unclear	On and after RT	-	2
Caon, 2014, Canada	ASA	Pharmacy database	Before RT	-	2
Jacobs, 2014b, US	ASA	Database	Anytime	-	2
Choe, 2010, US	ASA	Pharmacy database	Ever	81 mg and 325 mg OD	3
Osborn, 2016, US	ASA	EMR	On or post-RT	-	3

Contd...

Appendix 1.2: Contd...

Study ID	Types of NSAIDs	Identification	Timing	Dose	NOS
Active surveillance					
Agarwal, 2015, US	Any	Database	-	-	
Any prostate cancer treatment					
Ratnasinghe, 2004, US	ASA	Self-report questionnaire	Previous users	-	3
Choe, 2012, US	ASA	Mail survey	Anytime	-	3
Dhillon, 2012, US	ASA	Mail survey	Pre- and post-diagnosis	81 mg/per week	3
Cardwell, 2013, UK	ASA	Pharmacy database	Before and after diagnosis	Low dose	3
Daugherty, 2013, US	ASA	Self-report questionnaire	Prediagnosis	-	3
Flahavan, 2013, UK	ASA	Pharmacy database	Prediagnosis	Dose, duration of ASA	2
Grytli, 2014, Norway	ASA	Pharmacy database	Before and after treatment	-	2
Stock, 2008, Canada	Any	Medical records	Ever	high and low dose	3
Veitonmaki, 2015, Finland	ASA or NSAID	Self-report questionnaire	Ever use of ASA/NSAID	-	3
Katz, 2010, US	Any NSAID	Mail Survey	Ever	-	3
Jacob, 2014 C-1, US	ASA	Self-report questionnaire	Pre- and post-diagnosis	162 mg/day or more	3
Jacobs, 2014-C2, US	ASA	Self-report questionnaire	Pre- and post-diagnosis	162 mg/day or more	3
Assayag, 2015, UK	ASA	Pharmacy database	Postdiagnosis and cumulative		2

CPRD - Clinical Practice Research Datalink; NOS - Newcastle Ottawa Scale for Comparability Domain; OD - Once daily; RP - Radical Prostatectomy; RT - Radiation therapy; ASA - Acetyl salicylic acid

Appendix 1.3: Risk of bias: comparability - adjustment for confounding bias in the included studies

Study ID	PCa Rx/severity	Other Rx	Demographic	Lifestyle/comorbidity	NOS
Mondul, 2011, US	-	ACE, statins	Age, race, history of cancer	BMI, smoking status	2
Zaorsky, 2015, US	GS, PSA, PSM	Warfarin, clopidogrel	-	-	2
Ishak-Howard, 2014, US	GS, PSA, stage	Statins	Age, year	BMI	2
Kontraros, 2013, Greece	GS, PSA, stage, prostate volume, RT	Statins	Age	BMI, diabetes, inflammation	2
Forget, 2011, Belgium	GS, ECE, PSM, LNE	Epidural analgesia, clonidine, sufentanil	-	-	2
Radiation therapy					
Zaorsky, 2012, US	GS, PSA, stage, RT type	Anticoagulant, Statins	-	CVD	2
Caon, 2014, Canada	GS, PSA, stage, ADT	Anticoagulant, Statins	Age	CCI	2
Jacobs, 2014b, US	-	-	-	-	0
Choe, 2010, US	GS, PSA, T-stage, RT dose, IMRT	-	-	-	2
Osborn, 2016, US	NCCN Risk group, ADT	Clopidogrel, warfarin	Age	-	2
Active surveillance					
Agarwal, 2015, US	GS, PSA		Age, follow-up time		2
Any prostate cancer treatment					
Ratnasinghe, 2004, US	-	-	Age, race	BMI, poverty index, education, smoking	1
Choe, 2012, US	PSA, stage, cancer Tx	-	-	-	2
Dhillon, 2012, US	GS, stage, cancer Tx	Vitamin D, Statins	Age, race, height, family history	BMI, tomato sauce, physical activity, smoking, Vitamin D, fish, red meat, smoking, comorbidities (DM, peptic ulcer, COPD, MI, heart disease, cerebrovascular disease)	2

Contd...

Appendix 1.3: Contd...

Study ID	PCa Rx/severity	Other Rx	Demographic	Lifestyle/comorbidity	NOS
Cardwell, 2013[1], UK	Cancer Tx	-			2
Daugherty, 2013, US	GS, stage	-	Age, race	BMI, smoking, heart attack, stroke	2
Flahavan, 2013, UK	GS, tumor size, RT	Statins	Age, year	Smoking status, comorbidity score	2
Grytli, 2014, Norway	GS, PSA, stage, metastases, ADT	Beta-blockers, statins	Age	Performance status	2
Stock, 2008[2], Canada	PSA, stage		-	Smoking status	2
Veitonmaki, 2015, Finland	GS, stage, cancer Tx	Statins, antihypertensive, BHP-Rx, antidiabetic	Age	PSA testing	2
Katz, 2010, US	-	-	Age, race	BMI, comorbid illness, smoking status, visits to cardiologists, endocrinologists, and GPs	2
Jacob, 2014C-1, US	GS, ECE, LNE, Cancer Tx	Statins	Age, race, calendar year	PSA testing, CVD	2
Jacobs, 2014-C2, US	GS, ECE, LNE, Cancer Tx	Statins	Age, race, calendar year	PSA testing, CVD	2
Assayag, 2015, UK	GS, PSA, cancer Tx	Statins, 5-ARI, Antihypertensive, Antidiabetes Rx	Age, race, cohort year	Obesity, smoking, alcohol, socioeconomic status	2

ADT - Androgen deprivation therapy; BHN - Benign hyperprostatic neoplasia; BMI - Body mass index; CCI - Charlson Comorbidity Index; CKD - Chronic kidney disease; CVD - Cardiovascular disease; ECE - Extracapsular extension; GP - General Practitioner; GS - Gleason score; HTN - Hypertension; IMRT - Intensity-modulated radiation therapy; LNE - Lymph node extension; NOS - Newcastle Ottawa Scale for Comparability Domain; NCCN - National Cancer Comprehensive Network; NSAIDs - Nonsteroidal anti-inflammatory drugs; LDL - Low-density lipoprotein; PSA - Prostate-specific antigen; PSM - Positive surgical margin; RP - Radical prostatectomy; RT - Radiation therapy; PCa - Prostate cancer

Appendix 1.4: Risk of bias in the included randomized controlled trials

Risk of bias tool	D'Amico 2008, US	Goluboff 2001, US
Random sequence generation (selection bias)	Low risk	Low risk
Allocation concealment (selection bias)	Low risk	Low-risk
Blinding of participants and personnel (performance bias)	Low risk	Low risk
Blinding of outcome assessment (detection bias)	Unclear risk	Unclear risk
Incomplete outcome data (attrition bias)	Unclear risk	Unclear risk
Selective reporting (reporting bias)	Unclear risk	Unclear risk
Other bias	Low risk	Low risk