

Nonsteroidal anti-inflammatory drugs and prostate cancer: a systematic review of the literature and meta-analysis

Siavash Jafari, MD, MHSc;* Mahyar Etmiran, PharmD, MSc;†‡ Kourosh Afshar, MD, MHSc, FRCSC*

Abstract

Prostate cancer is the most common visceral cancer in men. Many studies have shown that nonsteroidal anti-inflammatory drugs (NSAIDs) may reduce the risk of prostate cancer. We systematically searched all relevant databases (MEDLINE, EMBASE, The Cochrane Collaboration, CINAHL, Database of Abstracts of Review of Effects and ACP Journal Club) to March 2008. We also explored bibliographies of the articles, pertinent journals and conferences. We selected relevant articles according to predefined inclusion criteria by 2 independent reviewers. We used both fixed and random-effect models for meta-analysis. We performed subgroup and sensitivity analysis based on predefined variables. From 962 extracted articles, 20 met the inclusion criteria with a total of 25 768 participants. All the studies had an observational design. There was a statistically significant protective effect for NSAIDs on risk of prostate cancer (odds ratio [OR] 0.92, 95% confidence interval [CI] 0.86–0.97). Subgroup analysis did not show any effect of study design or quality score on the results. There was a small but statistically significant protective effect for acetylsalicylic acid (ASA) (OR 0.95, 95% CI 0.91–1.00). Exposure to non-ASA NSAIDs was associated with a slightly reduced likelihood of prostate cancer (OR 0.92, 95% CI 0.85–1.00). With the available data, we were not able to determine an optimum dosage for NSAIDs. We conclude that taking NSAIDs may reduce the risk of prostate cancer. Nevertheless, the effect is small.

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Résumé

Le cancer de la prostate est le cancer viscéral le plus fréquent chez l'homme. Bon nombre d'études ont montré que les anti-inflammatoires non stéroïdiens (AINS) pouvaient réduire le risque de cancer de la prostate. Notre objectif était de réaliser une revue systématique et une méta-analyse des articles publiés sur les effets des AINS dans la réduction du risque de cancer de la prostate. Toutes les bases de données pertinentes (MEDLINE, EMBASE, Collaboration Cochrane, CINAHL, Database of Abstracts of Review of Effects et ACP Journal Club) ont été systématiquement consultées en mars 2008. On a également examiné la bibliographie des articles dégagés et des revues et conférences pertinentes. Les articles pertinents ont été sélectionnés en fonction de critères d'inclusion prédéfinis par 2 analystes indépendants. Pour la méta-analyse,

on a eu recours à des modèles à effets fixes et à effets aléatoires. Une analyse par sous-groupes et une analyse de sensibilité ont été effectuées à l'aide de variables prédéfinies. Sur les 962 articles dégagés, 20 satisfaisaient aux critères d'inclusion, pour un total de 25 768 sujets. Toutes les études étaient de type observationnel. On a noté un effet protecteur statistiquement significatif sur le risque de cancer de la prostate avec les AINS (rapport de cotes de 0,92; IC à 95 % de 0,86 à 0,97). L'analyse par sous-groupes n'a révélé aucun effet du plan de l'étude ou du score de qualité sur les résultats. On a noté un effet protecteur léger mais tout de même significatif sur le plan statistique avec l'aspirine (RC 0,95; IC à 95 % de 0,91 à 1,00). L'exposition à des AINS autres que l'aspirine a été associée à une probabilité légèrement moindre de cancer de la prostate (RC 0,92, IC à 95 % de 0,85 à 1,00). Les données disponibles ne nous ont pas permis de déterminer la posologie optimale des AINS. Nous avons observé un effet favorable possible associé à la prise d'AINS dans la réduction du risque de cancer de la prostate, mais cet effet est minime.

Introduction

Prostate cancer is the most common malignancy among men in Western countries. Older age, African American race and family history are the 3 well-established and non-modifiable risk factors for prostate cancer. Modifiable lifestyle factors that may affect the risk of prostate cancer include diet, smoking habits, exercise and body size.¹ The development of prostate cancer involves many cellular pathways, which could be targeted for prevention or treatment. For example, chemoprevention using antiandrogens has been shown to reduce the risk of prostate cancer by 25%.² There is evidence that inflammatory pathways may be involved in the development of prostate cancer.³⁻⁶ This has led to the hypothesis that acetylsalicylic acid (ASA) and other nonsteroidal anti-inflammatory drugs (NSAIDs) may reduce the risk of prostate cancer.

The primary objective of this meta-analysis was to assess the effect of NSAIDs on the incidence of prostate cancer, using a systematic review of all available studies and meta-analytic techniques when appropriate. The primary study question in this review is, Do NSAIDs reduce the risk of

prostate cancer? Secondary questions include the following: In the case that a protective effect is observed, does this benefit differ among NSAID and ASA users? Is the effect dose-dependent?

Methods

We searched all relevant databases to March 2008 and identified one systematic review.⁷ However, since the publication of this review, other observational studies have been published that warrant a more up-to-date systematic review.

Search protocol

We identified relevant studies and abstracts by searching MEDLINE (1966 to March 2008); CINHALL (1982 to March 2008), ACP Journal Club (1991 to March 2008), Database of Abstracts of Reviews of Effects (1990 to March 2008), and The Cochrane Collaboration Controlled Trials Register for studies published before March 2008. The following search terms were used: "prostate," "prostate cancer," "prostate neoplasm," "prostate carcinoma," "aspirin," "anti-inflammatory drugs," "NSAIDs," "NSAID," "Cyclooxygenase II inhibitors," "Cox-2 inhibitor," "Celecoxib," "ibuprofen," "naproxen," "diclofenac sodium," "mefenamic acid," "indometacine" and "piroxicam."

We combined the sensitive strategies of the Cochrane handbook for systematic reviews of interventions⁸ to search relevant studies in MEDLINE and EMBASE. Retrieved studies were assessed for any text words or medical subject headings for NSAIDs therapy that have not been used. We also incorporated any new terms that were identified into the search strategy.

In addition, we screened the bibliographies of identified publications for further citations. We also hand searched the reference lists of retrieved studies, journals related to prostate, cancer, epidemiology, and abstracts and books of cancer and urology conferences.

Study inclusion

Figure 1 illustrates the process we used for inclusion and exclusion of literature. Studies were eligible if they were randomized controlled trials, case-control, nested case-control, cohort or cross-sectional studies. We included studies if they met the following criteria: 1) exposure to NSAIDs (defined as any nonsteroidal medication that can reduce production of prostaglandins and thromboxane) was explicitly stated, 2) relative risks (RRs) or odds ratios (ORs) were provided or could be estimated from provided data, and 3) diagnosis of prostate cancer was made based on histological diagnosis or through an established tumour registry database.

We used a standard data extraction form to record the extracted information. We included all studies evaluating the effects of NSAIDs and/or ASA, with any duration or dosage. After the elimination of irrelevant articles (e.g., basic science, animals studies or case reports), 2 authors (S.J. and K.A.) independently reviewed the extracted papers. Discrepancies were settled by discussion among all authors.

Methodological quality of included studies

Two reviewers (S.J. and K.A.) independently assessed the study quality according to modified criteria previously used by Lichtenstein and colleagues.⁹ These criteria include an explicit statement of the research question, a description of cases and controls selection, definition of ASA or NSAID exposure, information on data collection, analytic methods and sample size. We generated an overall quality score (0 to 10) and ranked the studies. Two independent reviewers scored the study quality in a blinded manner to ensure unbiased review.

Data abstraction

We abstracted data onto structured forms designed to capture relevant information in a concise, focused fashion. Age was recorded as the range, mean, standard deviation and/or median (whichever available). Study name, population of study, year of study and publication, study design, sample size, type of drug, duration and dosage of use, adjustments, and method of diagnosis of prostate cancer were recorded.

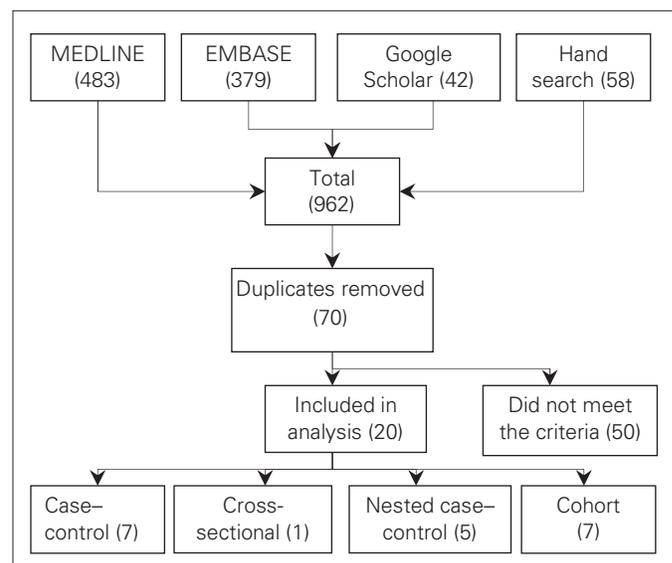


Fig. 1. Literature inclusion and exclusion process.

Analysis

We extracted the number of prostate cancer events in NSAID/ASA users and controls, and calculated the pooled fixed and random effect estimates of the odds ratio for risk of prostate cancer. We performed Cochran Q test and estimated I^2 index to test for heterogeneity across studies. We did subgroup analyses based on several predefined variables such as study type and drugs categories (ASA v. NSAIDs). We conducted Duval & Tweedie's¹⁰ trim and fill method to test for possibility of publication bias.

Results

Characteristics of included studies

No randomized controlled trial was identified. Twenty observational studies with a total of 25 768 participants were included.^{11–30} Characteristics of these studies are presented in Table 1. One study was published in a conference proceeding in 2002, and published again with a smaller sample size in 2005.²¹ We included the more recent study. Study populations varied in their age and in the stage of

Table 1. Characteristics of studies included in the meta-analysis

Study; year	Site	Design	Total cases	Mean/ range of age, yr	Outcome of interest	OR	95% CI	Drug type	Study period	Source of data
Norrish et al. ²⁴ ; 1998	Europe	CC	317	70	PC	0.88	0.64–1.20	N & A	1996	Questionnaire
Neugut, et al. ²³ ; 1998	USA	CC	319	69	PC	1.60	0.82–3.11	ASA	1984–1986	Records
Nelson and Harris ²² ; 2000	USA	CC	417	64	PC	0.34	0.23–0.58	N & A	1992–1995	Interview
Irani et al. ¹⁵ ; 2002	France	CC	639	66.8	PC	0.80	0.64–0.99	N & A	1999–2000	Interview
Menezes et al. ²¹ ; 2005	USA	CC	1029	67.1	PC	1.05	0.89–1.25	ASA	1982–1998	Questionnaire
Bosetti et al. ¹¹ ; 2006	Europe	CC	1261	46–74	PC	1.10	0.81–1.50	ASA	1991–2002	Interview
Liu et al. ¹⁹ ; 2006	USA	CC	506	—	PC	0.67	0.52–0.87	N & A	2001–2004	Interview
Sørensen et al. ²⁹ ; 2003	Europe	NCC	324	—	PC	1.30	1.20–1.50	NSAID	1989–1995	Database
Rodríguez and Gonzalez-Perez ¹³ ; 2004	UK	NCC	2185	50–79	PC	0.93	0.71–1.21	N & A	1995–2001	Database
Mahmud et al. ²⁰ ; 2006	Canada	CS	1299	63	PC	0.71	0.48–1.03	NSAID	1999–2003	Interview
Dasgupta et al. ¹² ; 2006	Canada	NCC	2025	73	PC	0.71	0.58–0.86	N & A	1999–2002	Database
Langman et al. ¹⁷ ; 2000	UK	NCC	1813	—	PC	1.34	1.09–1.64	NSAID	1993–1995	Database
Perron et al. ²⁶ ; 2003	Canada	NCC	2221	75.7	PC	1.14	0.83–1.57	N & A	1993–1996	Database
Schreinemachers and Everson ²⁸ ; 1994	USA	Cohort	123	65	PC	0.95	0.66–1.35	ASA	1971–1987	Interview
Paganini-Hill et al. ²⁵ ; 1989	USA	Cohort	149	73	PC	0.90	0.63–1.30	ASA	1981–1988	Questionnaire
Habel et al. ¹⁴ ; 2002	USA	Cohort	2574	18–84	PC	0.76	0.60–0.98	ASA	1964–1996	Questionnaire
Leitzmann et al. ¹⁸ ; 2002	USA	Cohort	2479	40–75	PC	1.05	0.96–1.14	ASA	1986–1996	Questionnaire
Roberts et al. ²⁷ ; 2002	USA	Cohort	91	64	PC	0.45	0.28–0.73	NSAID	1990–1996	Interview
Jacobs et al. ¹⁶ ; 2005	USA	Cohort	4853	—	PC	0.95	0.86–1.05	N & A	1992–1993	Questionnaire
Platz et al. ³⁰	USA	Cohort	1244	—	PC	0.71	0.49–1.02	N & A	1980–2004	Database

ASA = acetylsalicylic acid; CC = case-control; CI = confidence interval; CS = cross-sectional; OR = odds ratio; N & A = NSAIDs and ASA; NCC = nested case-control; NSAID; nonsteroidal anti-inflammatory drug; PC = prostate cancer.

their prostate cancer. Sources of data were identified for only 20 studies: 14 from interviews and 6 from databases or medical records. Factors adjusted for varied among the studies and included age, education, ethnic origin, family history of prostate cancer, diet, body mass index, height and weight.

Figure 2 presents the funnel plot of pooled data using the trim and fill method (RevMan-5 Cochrane Collaboration). Although analysis revealed no evidence in favour of publication bias, the funnel plot shows that the majority of

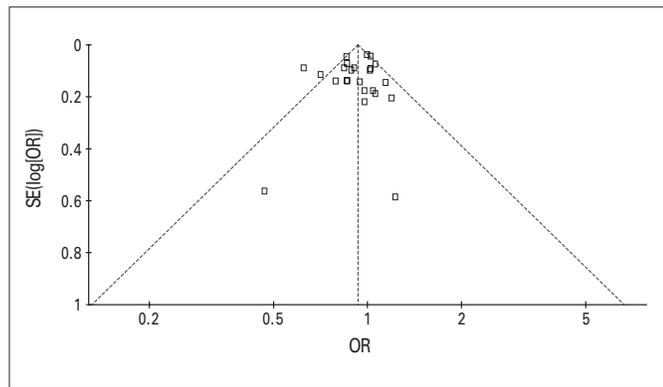


Fig. 2. Funnel plot of pooled data using trim and fill technique. OR = odds ratio; SE = standard error.

studies are grouped in the upper part. This is consistent with lack of small studies favouring positive effect of NSAIDs/ASA in preventing prostate cancer. All results are estimates from random effect model.

Pooled OR for prostate cancer in patients exposed to NSAIDs is 0.92 (95% CI 0.86–0.97). The test of heterogeneity was positive ($I^2 = 56\%$, $df = 23$; $p < 0.001$) (Fig. 3).

The type of study did not affect the findings. Studies were divided into 2 main types of case–control and cohort. Analysis of 13 case–control studies revealed a summary 0.91 (95% CI 0.84–0.99). The summary OR for 7 cohort studies was 0.94 (95% CI 0.86–1.02). Analysis of 15 high-quality studies (quality score $\geq 7/10$) revealed a pooled OR of 0.96 (95% CI 0.91–1.01). There was no significant difference in effect size based on the quality scores (Table 2). When we analyzed data from the 13 studies that used questionnaires to capture exposure data compared with studies that used large administrative database, a small protective effect was seen among the questionnaire studies (OR 0.93, 95% CI 0.88–0.98) compared with database studies (OR 1.04, 95% CI 0.93–1.16).

We also analyzed studies with separate data for ASA and non-ASA NSAIDs (Fig. 4 and Fig. 5). Sixteen studies reported the effect of ASA exposure. Results of our analysis reveal a pooled OR of 0.95 (95% CI 0.91–1.00).

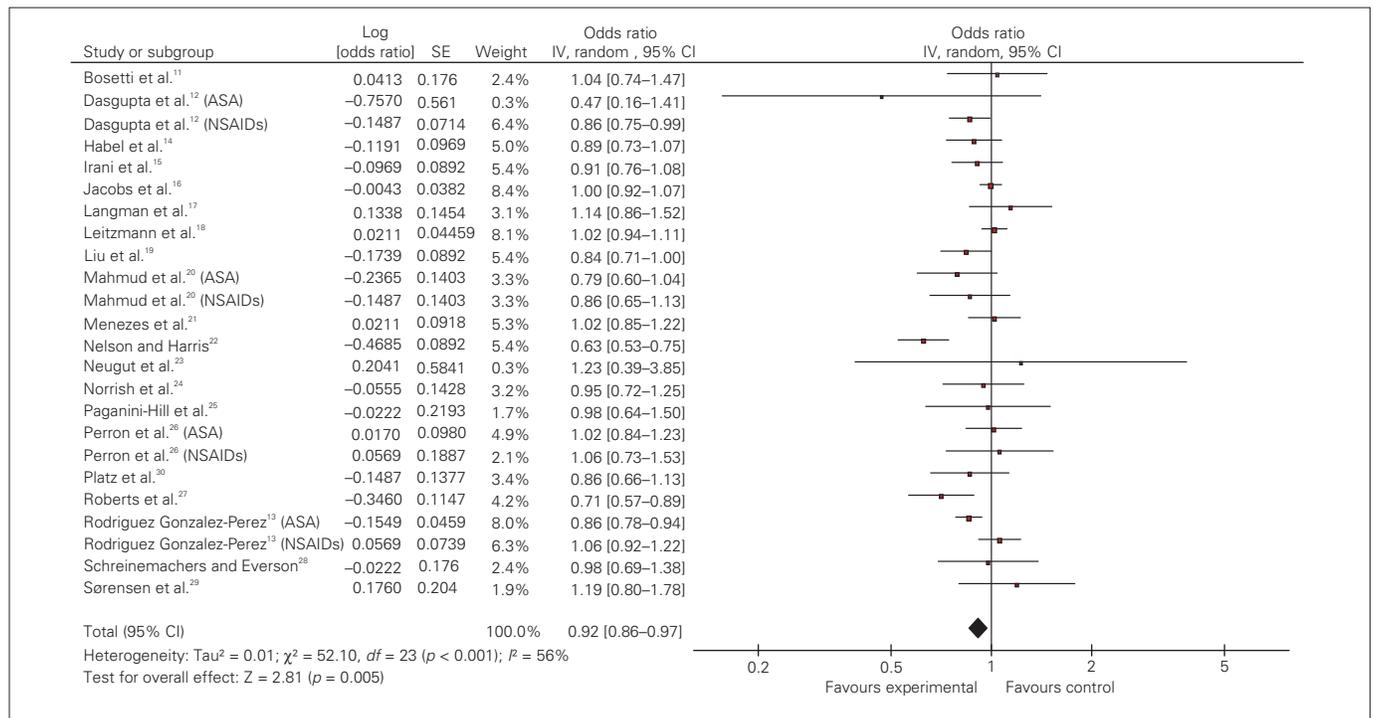


Fig. 3. Effect of nonsteroidal anti-inflammatory drugs (NSAIDs) on prostate cancer risk: random effect model. ASA = acetylsalicylic acid; CI = confidence interval; IV = intravenous; SE = standard error.

Thirteen studies reported the effect of non-ASA NSAIDs with a pooled OR of 0.92 (95% CI 0.85–1.00).

Discussion

The molecular pathogenesis of prostate cancer has been characterized by alterations of genes and proteins involved in proinflammatory pathways.^{31,32} Epidemiological evidence suggests there is a close association between inflammation and prostate cancer.^{3–6} Several studies have demonstrated higher expression of Cyclo-oxygenase 2 (COX-2) in prostate cancer.^{33–36} Studies have revealed the COX-2 dependent and independent mode of action of selective COX-2 inhibitors against prostate cancer.^{37–39} Inflammatory pathway not only may be involved in carcinogenesis, but may also facilitate progression, local invasion, recurrence and metastasis.^{40,41} In a phase II study, Pruthi and colleagues⁴² showed a slowing effect of COX inhibitor celecoxib on the rate of prostate-specific antigen (PSA) rise after biochemical failure of local treatment of prostatic carcinoma. These findings have brought up the possibility of using anti-inflammatory drugs as a means of preventing this disease.

This meta-analysis attempts to evaluate the effectiveness of NSAIDs in reducing the risk of prostate cancer. Based on

available studies, use of NSAIDs may have a 5% to 8% protective effect against prostate cancer. When ASA and other NSAIDs are analyzed separately, a statistically significant protective effect is still seen. The risk reduction is 5% for ASA and 8% for other NSAIDs. Our results are comparable to those of the meta-analysis by Mahmud and coauthors.⁷ Four studies reported OR for ASA and non-ASA NSAID separately.^{12,13,20,26} These studies posed a challenge to calculate the pooled OR, since they used the same sample for 2 different exposures. To remedy this problem we performed 4 different analyses: excluding these studies, including only ASA or only NSAID data, and including both exposures as if they were from 2 independent samples. The results were similar. The pooled OR varied between 0.93 and 0.95 with very close 95% CI. We have only presented the latter analysis in Figure 3.

There are several potential pitfalls to this meta-analysis. Like any other systematic review, there may be a publication bias which cannot be entirely ruled out based on funnel plot. There is moderate heterogeneity in the results of the included studies, with the lowest for ASA only studies. This may be due to several factors such as study quality, methodological design, tools used to confirm the exposure or the outcome, variations in defining the exposure and background differences in patient

Table 2. Quality score of included papers

Author	Study design	Inclusion/exclusion*	Types of control	Adjustment	Dose/duration of use	Total score
Norrish et al. ²⁴	2	1	2	2	1	8
Neugut, et al. ²³	2	1	1	2	0	7
Nelson and Harris ²²	2	1	1	2	2	8
Irani et al. ¹⁵	2	0	1	2	1	6
Menezes et al. ²¹	2	1	1	2	1	7
Bosetti et al. ¹¹	2	1	1	2	1	7
Liu et al. ¹⁹	2	1	1	2	2	8
Langman et al. ¹⁷	3	0	2	2	1	8
Perron et al. ²⁶	3	1	2	1	2	9
Sørensen et al. ²⁹	3	0	2	1	0	6
Rodríguez and Gonzalez-Perez ¹³	3	1	2	2	2	10
Mahmud et al. ²⁰	1	1	1	2	1	6
Dasgupta et al. ¹²	3	1	1	2	1	8
Schreinemachers and Everson ²⁸	3	1	2	2	0	8
Paganini-Hill et al. ²⁵	3	1	1	1	1	7
Habel et al. ¹⁴	3	1	1	2	2	9
Leitzmann et al. ¹⁸	3	1	1	2	1	8
Roberts et al. ²⁷	3	1	1	2	1	8
Jacobs et al. ¹⁶	3	1	1	2	1	8
Platz et al. ³⁰	3	1	1	2	2	9

*Clearly stated inclusion/exclusion criteria.

populations. Patients exposed to any of the NSAIDs or ASA may differ in several other aspects that are relevant to the risk of the development of prostate cancer or its detection. For instance, results of a recent study showed that the potential protective effect of NSAIDs on prostate cancer may only exist among certain subgroups of men with particular variants of inflammatory response genes *LT4* + *80CC*.¹⁹

We performed subgroup analysis to further explore the

possible factors affecting our analysis based on RRs shown in Figure 3. We evaluated the studies according to their design: case-control versus cohort versus nested case-control. The type of study did not affect the findings significantly. We divided the studies into 2 groups according to their quality score: high quality with a score 7 or more out of 10 and lower quality with a score less than 7. Subgroup analysis revealed no difference between the findings in these

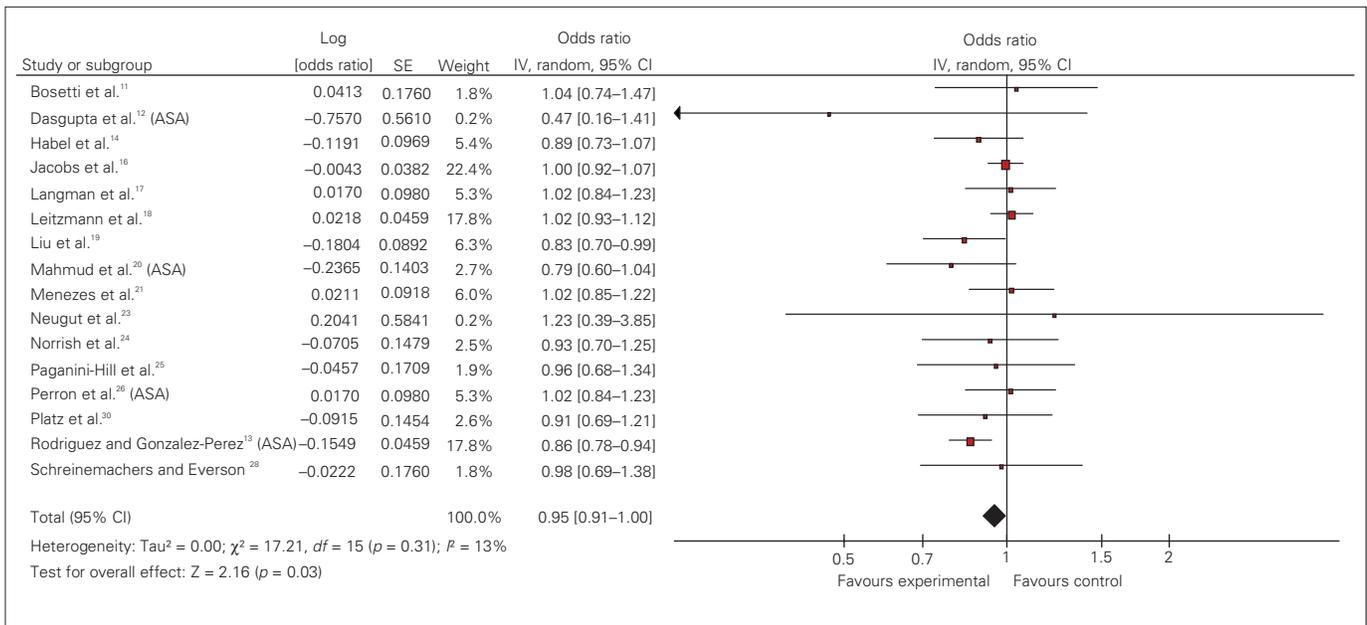


Fig. 4. Effect of acetylsalicylic acid (ASA) on prostate cancer risk: random effect model. CI = confidence interval; IV = intravenous; SE = standard error.

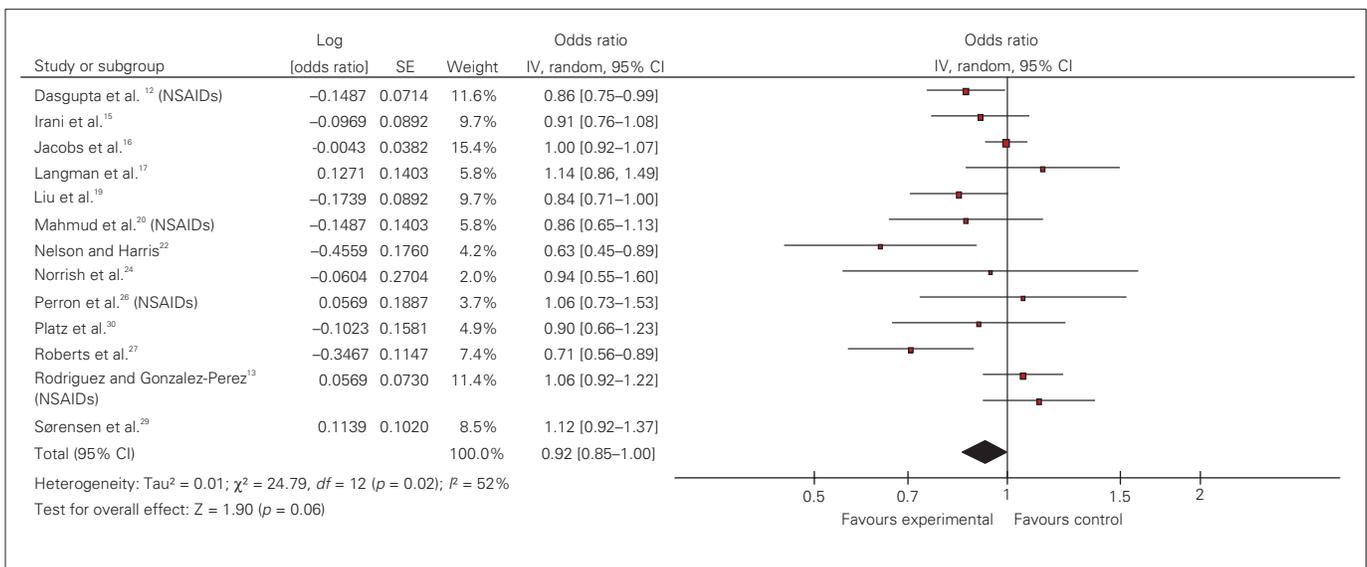


Fig. 5. Effect of non-acetylsalicylic acid nonsteroidal anti-inflammatory drugs (NSAIDs) on prostate cancer risk: random effect model. CI = confidence interval; IV = intravenous; SE = standard error.

2 groups (Table 3). We acknowledge that using a scoring system in this situation is controversial. The result of our subgroup analysis may have been affected by the inability of the scoring system to probe into areas specific to studies of prostate cancer.

In most studies use of NSAIDs was categorized as frequent, ever used or never used and the exact nature and duration of drug use is largely unknown. Although NSAIDs inhibit COX enzymes, the degree of this effect is variable among different NSAIDs. Furthermore, concurrent use of NSAIDs and ASA is another possibility, as many of these medications are available over the counter. Also, based on available studies, it was not possible to investigate the potential effect of different dosing regimens. Therefore, a clinically meaningful recommendation about the optimal duration and dose of NSAIDs or ASA use to prevent prostate cancer is evasive.

To confirm the exposure, questionnaires were used in some studies and prescription database in others. Recall bias is a well-known weakness of questionnaires. The extent of recall bias is related to characteristics of the exposure of interest and of the respondents.^{43,44} The level of experience of interviewers, reliability of the tool used to obtain data, and the characteristics of interviewees are among the most important factors that can affect the recall bias. On the other hand, medication database may fail to document over-the-counter use. We performed a subgroup analysis to further explore this issue. Studies using interview and/or questionnaires showed a small protective effect for NSAIDs, which was not seen when a database was used.

Meta-analysis of observational studies may suffer from bias in the original studies. Sources of data for studies included in our analysis were from various countries such as

the United States, Canada, New Zealand and France. Background incidence depends on ethnicity and variability of PSA screening programs, which may be different in various countries (screening bias). Confounding by indication may affect the findings. This occurs when the medication used is associated with a condition that may affect the risk of prostate cancer detection. It is possible that users of ASA have a shorter life span than nonusers because of cardiovascular diseases. This may result in a lower chance of being screened and diagnosed with prostate cancer, overestimating the protective effect.⁴⁵ Other types of bias may exist in studies dealing with prostate cancer, such as protopathic bias (when an exposure is influenced by early stages of a disease) and survivor bias (large number of exposed participants who have died from old age). Dissimilarity of study population could be a source of bias in case-control studies. For example, participants selected from referral centres cannot be a true representative of the general population (referral bias). The best way to eliminate bias is a prospective randomized experimental design. But until this type of study is available we are limited to observational studies that should be interpreted with all these limitations in mind.

Conclusion

Results of this meta-analysis reveal that NSAIDs provide some degree of protective effect against prostate cancer. This effect was seen for both ASA and other NSAIDs. Further experimental studies are required to confirm these findings and determine the optimal dosage and duration of NSAIDs.

From the *Department of Urologic Sciences, University of British Columbia, Vancouver, BC, †Centre for Clinical Epidemiology and Evaluation, Vancouver, BC, and the ‡Department of Medicine, University of British Columbia, Vancouver, BC

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Table 3. Results of subgroup analysis

Variable	Total	OR	95% CI
Drug type			
Non-ASA NSAIDs only	12	0.92	0.85–1.00
ASA only	13	0.95	0.91–1.00
Quality of study			
High	15	0.96	0.91–1.01
Low	4	0.92	0.76–1.12
Source of data			
Questionnaire	13	0.93	0.88–0.98
Database	6	1.04	0.93–1.16
Study design			
Case-control	7	0.84	0.67–1.07
Nested case-control	5	1.04	0.76–1.41
Cohort	6	0.89	0.77–1.03

ASA = acetylsalicylic acid; CI = confidence interval; NSAID = nonsteroidal anti-inflammatory drug; OR = odds ratio.

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Correspondence: Dr. Kourosh Afshar, Department of Urologic Sciences, University of British Columbia, Rm. KO-134, 4480 Oak St., Vancouver BC V6H 3V4; fax 604 875-2721; kafshar@cw.bc.ca

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