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Aspirin use and the risk of prostate cancer: a meta-analysis of 24 epidemiologic studies

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Abstract
Purpose Several epidemiologic studies were performed to clarify the protective effect of regular aspirin use on prostate cancer risk; however, the results remain controversial. Therefore, we conducted this meta-analysis to assess the association between regular aspirin use and risk of prostate cancer.
Methods Electronic databases including PubMed, EMBASE and Cochrane Library were searched between January 1966 and April 2013 to identify eligible studies. Pooled relative ratios (RRs) and 95 % confidence intervals (CIs) were computed to assess the influence of aspirin use on prostate cancer risk. All statistical tests were two-sided.
Results A total of 24 observational studies including 14 case–control studies and 10 cohort studies were eligible for this meta-analysis. Regular aspirin use was associated with reduction in overall and advanced prostate cancer risk (pooled RR 0.86, 95 % CI 0.81–0.92; pooled RR 0.83, 95 % CI 0.75–0.91, respectively). When we restricted our analyses to studies with long-time regular aspirin use (equal or more than 4 years), reverse association became stronger (pooled RR 0.82, 95 % CI 0.72–0.93; pooled RR 0.70, 95 % CI 0.55–0.90, respectively).
Conclusions Our findings suggest that regular, especially long-time regular aspirin use may reduce the risk of overall and advanced prostate cancer. Considering the limitation of included studies, further well-designed large-scaled cohort studies and RCTs are required to draw more definitive conclusions.

Keywords Aspirin · Prostate cancer · Advanced prostate cancer · Meta-analysis · Epidemiologic

Introduction

Prostate cancer is the most commonly diagnosed non-skin cancer and the second leading cause of cancer death in man [1]. Primary prevention of prostate cancer is, therefore, a significant public health issue. The mechanism of prostate carcinogenesis is still not fully understood. Inflammation was proved to have large beneficial effects in colorectal, esophageal and gastric cancer. Recent laboratory and animal studies indicated that inflammation may also influence prostate carcinogenesis through inhibiting the cyclooxygenase (COX) pathway, which is an inducible enzyme that facilitates inflammation by promoting production of prostaglandin [2].

Aspirin is one of the most common used nonsteroid anti-inflammatory drugs (NSAIDs), which was proved having protective effects in colorectal adenoma through inhibiting of COX-2 enzymes, restoring of normal apoptosis and reducing of angiogenesis [3]. Several epidemiologic studies were performed to illuminate the association with prostate cancer. However, the results remain controversial. No significant difference was reported in a meta-analysis

Tian-bao Huang and Yang Yan have contributed equally to this work.

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[4] based on 15 relevant studies [pooled relative ratio (RR) 0.98, 95 % CI 0.95–1.01]. In 2010, Mahmud et al. [5] reported an updated result, a significant inverse association was found in patients who took aspirin regularly [pooled odds ratio (OR) 0.83, 95 % CI 0.77–0.89]. In the more recent meta-analysis [6], 10 % reduction in prostate cancer was reported among regular aspirin users. The protective effect of aspirin use against prostate cancer was suggestive, but not conclusive due to the large heterogeneity between included studies.

Recently, several large-scaled studies [7–9] were published and showed controversial associations between regular aspirin use and risk of prostate cancer. Besides, so far there were no meta-analyses evaluating the association of long-time regular aspirin use on the risk of overall and advanced prostate cancer. We, therefore, conducted this meta-analysis to update these associations.

Methods

Data source and search strategy

Electronic databases including PubMed, EMBASE and Cochrane library were searched between January 1966 and 21 April 2013 to identify eligible studies, using following key words: "aspirin or acetylsalicylic acid or nonsteroidal anti-inflammatory agent or NSAID or analgesics," "prostate or prostatic" and "cancer or carcinoma or neoplasm or neoplasms or tumor". Furthermore, the reference lists of every article retrieved and reviews were manually searched to identify additional eligible studies.

Criteria for inclusion and exclusion

Studies are eligible for inclusion if they meet the following criteria: (1) had to be case–control or cohort studies; (2) evaluated the association between aspirin use and the risk of prostate cancer separated from other NSAIDs; (3) had explicit description of aspirin exposure and (4) provided RRs or ORs and their 95 % CIs or sufficient information to calculate them. Review articles, case reports, letters to the editor and editor comments were excluded.

Date extraction

Eligibility evaluation and data abstraction were carried out independently by 2 investigators (Tian-bao Huang, Yang Yan) according to the meta-analysis of observational studies in epidemiology (MOOSE) guidelines [10], and discrepancies were adjudicated by consensus. For each study, the following data were extracted: first author; year of publication; country; study design; type of controls; sample size; definition of aspirin exposure; RRs or ORs; and their 95 % CIs. Estimates of the association between aspirin use and the risk of advanced prostate cancer were also extracted. When more than one estimate was available, we chose the "most adjusted or multi-adjusted" estimate.

Statistical analysis

Due to the low incidence of prostate cancer, the RR mathematically approximates the OR in case–control studies. To simplify, only pooled RR and its 95 % CI were used as effect of interest to assess the association between aspirin use and the risk of prostate cancer. When data of different duration of use or different intake levels were available, we chose the one with longest duration or highest intake. Regular aspirin use refers to "more than one table per day for at least 4 days per week in a certain period". Long-time regular aspirin use refers to "period of regular aspirin use is more than 4 years". Besides, advanced prostate cancer is defined as "tumor stage $\geq$2c or Gleason score $\geq$ 7". The statistical heterogeneity among studies was evaluated using the Cochrane's Q and I^2 statistics. As for Q statistic, heterogeneity was considered exist for $P < 0.1$. When $P > 0.1$ and $I^2 < 50$ %, the included studies were identified as with acceptable heterogeneity, and fixed-effects model was used. Otherwise, the random-effects model was used.

To detect the source of heterogeneity, subgroup analyses based on study design (case–control vs. cohort study, population-based vs. hospital-based case–control study), geographic location (America vs. Europe vs. others) and number of adjusted confounders (equal or more than 5 vs. less than 5) were carried out. It is known that age, race and family history are proved as three major risk factors for prostate cancer [1]. Therefore, we limited the analysis to studies which had adjusted for at least two major factors to eliminate their impact.

Finally, the potential publication bias was evaluated graphically with funnel plots of log risk ratio against the standard error of the included studies. If the funnel plot is asymmetrical, rank correlation method proposed by Begg et al. and linear regression approach suggested by Egger et al. will be used to evaluate the potential publication bias. If the P value is less than 0.05, sensitive analyses will be conducted to explore whether the final effect was strongly influenced by individual studies. All statistical analyses were performed using STATA Statistical Software version 11.0 (Stata Corp., College Station, Texas, USA). All P values are two-tailed.

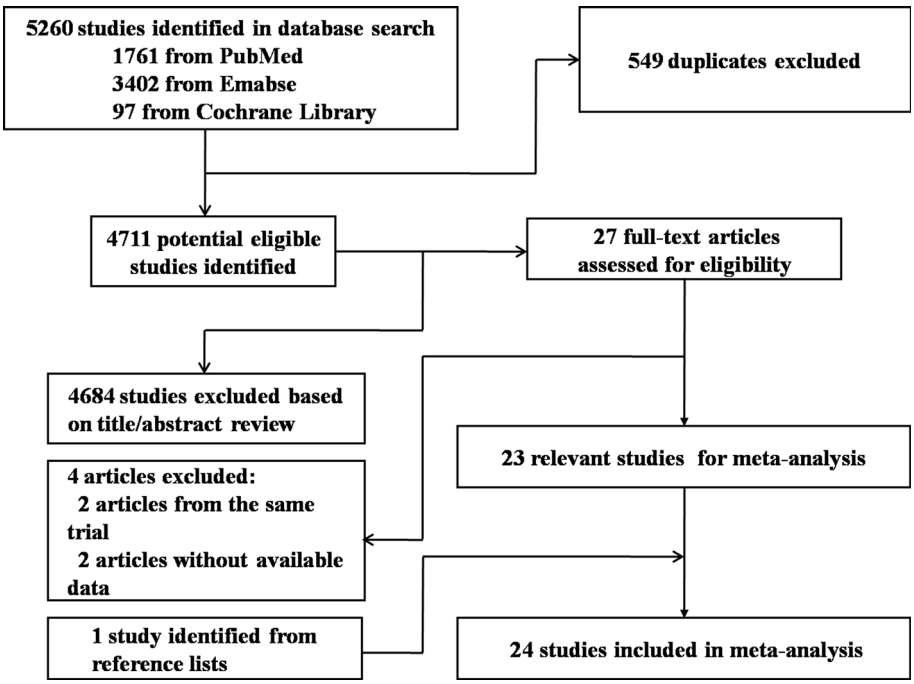

Fig. 1 The detailed steps of the literature search in this meta-analysis

Results

Study characteristics

The detailed steps of our literature search are displayed in Fig. 1. Briefly, one study, which assessed the association between aspirin use and cancer mortality, was excluded [11]. Besides, two another studies [12, 13] were also excluded because two updated reports from the same study populations were published. Finally, a total of 24 observational studies were eligible and included in this meta-analysis.

For simplicity, four nested case–control studies including 14,231 cases and 40,698 controls [14–17] were classified as case–control studies. As a result, 13 case–control studies and nine cohort studies, which assessed the association between aspirin use and overall prostate cancer risk, were included. Among these studies, more than half of the case–control studies were population-based [9, 16–22], whereas the remaining five were hospital-based [14, 15, 23–25]. As to geographic location, 12 studies were carried out in the USA [7, 8, 21–23, 25–31], 3 studies were in Canada [15, 17, 20], 2 studies were in the UK [14, 16] and one each were in New Zealand [18], France [19], Italy [24], Finland [9] and the Netherlands [32]. When it comes to confounding factors, most studies adjusted for age [8, 9, 14, 16, 18, 20–32], race [7, 8, 21–23, 28, 30, 31] and family history of prostate cancer [8, 16, 24, 25, 31] (Table 1).

For advanced prostate cancer, 12 studies including 9,783 cases were used for analysis, which included seven case–control studies including 5,846 cases and 29,053 controls [9, 18, 21, 22, 24, 25, 33] and five cohort studies including 3,937 cases among 272,736 subjects [7, 8, 28, 31, 34]. The detailed characteristics of the studies included are summarized in Table 2.

Overall prostate cancer

For the 22 studies included, nine of them showed protective effects of aspirin use, while the remaining 13 studies did not detect any association of aspirin use on the risk of overall prostate cancer. The pooled estimates data revealed a significant association between regular/any aspirin use and the risk of prostate cancer (pooled RR 0.90, 95 % CI 0.86–0.95) (Fig. 2). Reverse associations were stronger, when we limited our analyses to studies that assessed regular aspirin use versus non-use (pooled RR 0.87, 95 % CI 0.81–0.92). And there were little evidence of heterogeneity ($I^2 = 30.6$ %, P value for heterogeneity = 0.174). The heterogeneity could be subside after stratification by design (case–control study: $I^2 = 0.0$ %, P value for heterogeneity = 0.843; cohort study: $I^2 = 0.0$ %, P value for heterogeneity = 0.427, respectively). Besides, estimated pooled data, which assessed daily aspirin use, showed a deeper reverse association with remarkable heterogeneity (pooled RR 0.82, 95 % CI 0.72–0.93; $I^2 = 53.6$ %, P value for heterogeneity = 0.091) (Supplementary Fig. 1). In addition, a significant reverse association was detected in the association between long-time aspirin use and overall prostate cancer (pooled RR 0.82, 95 % CI 0.72–0.93),

Table 1 Characteristics of studies included in the meta-analysis of aspirin use and risk of prostate cancer

Study	Year	Country	Design	Number of cases/controls or subjects	Definition of aspirin use	RR (95 % CI)	Adjusted factors	Additional comments
Norrish	1998	New Zealand	Case–control study[ac]	317/480	Regular aspirin use versus non-use	0.85 (0.61–1.19)	Age, socioeconomic status, total polyunsaturated fat consumption, a-linolenic acid and ratio of dietary n-6: long-chain n-3 polyunsaturated fatty acids	
					<1/wk low-dose aspirin use (100–150 mg/d) versus non-use or < 1/wk	0.84 (0.59–1.19)		
Neugut	1998	USA	Case–control study[bd]	319/189	Current use versus non-use	1.60 (0.82–3.11)	Age, race, history of coronary heart disease and diabetes	
Irani	2002	France	Case–control study[ac]	639/659	Ever use in the last 5 years versus non-use	0.95 (0.75–1.20)	Crude estimate	
Perron	2003	Canada	case–control study[ad]	2,221/11,105	≥325 mg daily at least 4 years of aspirin use versus non-use	0.72 (0.59–0.88)	Age and recent medical contacts	Duration (+)
					≥80 mg daily at least 8 years of aspirin use versus non-use	0.82 (0.71–0.95)		
García Rodríguez	2004	UK(GPRD)	Nested case–control study [bd]	2,183/10000	Current use versus non-use	0.70 (0.61–0.79)	Age, calendar year, prior BPH history, number of visits to general practitioners, referrals, hospitalizations, and all the variables included in the table using logistic regression	Duration (−),
					300 mg daily more than 1 year versus non-use	0.71 (0.52–0.98)		
Menezes	2006	USA	Case–control study[bc]	1,029/1,029	1 table/wk more than 6 months versus non-regular use	1.05 (0.89–1.25)	Age, family history of prostate cancer and BMI	Frequency RR 0.91 Duration RR 1.17 Table year RR 1.21
Bosetti	2006	Italy	Case–control study[bc]	1,261/1,131	1 table/wk more than 6 months versus non-use	1.10 (0.81–1.50)	Age, study center, education and family history of prostate cancer	Duration (−)
					One table/wk more than 5 years versus non-use	1.17 (0.74–1.90)		
Liu	2006	USA	Case–control study[ad]	506/506	Two tables/wk more than 1 month versus non-use	0.66 (0.51–0.86)	Age, medical institution and ethnicity	Duration (+),$P_{trend} = 0.001$, advanced prostate cancer

Table 1 continued

Study	Year	Country	Design	Number of cases/controls or subjects	Definition of aspirin use	RR (95 % CI)	Adjusted factors	Additional comments
Dasgupta	2006	Canada	Nested case–control study[bd]	2,025/2,150	≥1 prescription more than 4 months versus non-use in 2 years	0.84 (0.74–0.96)	Crude estimate	
					≥1 prescription more than 4 months (without NA-NSAIDs) versus non-use	0.78 (0.66–0.93)		
Salinas	2010	USA	Case–control study[ac]	1,001/942	one table daily more than 3 months versus non-use	0.78 (0.64–0.95)	Age at reference date, race and prostate cancer screening within 8 years before reference date	
					81 mg daily more than 3 months versus non-use	0.71 (0.56–0.90)		
					1 table/wk more than 5 years versus non-use	0.76 (0.61–0.96)		
Murad	2011	UK(PROTECT trial)	Nested case–control study [ac]	1,016/5,043	Any aspirin use versus non-use	1.13 (0.94–1.35)	Age, family history of prostate cancer, any NA-NSAID use and any paracetamol use	
Mahmud	2011	Canada	Nested case–control study [ad]	9,007/35,891	Any aspirin use versus non-use	1.01(0.95–1.07)	Ever visited a urologist 1–11 years prior, SCREENED and volume of family physician visits in the 5 years prior to the index date and when appropriate, for use of other NSAID classes	
					≥5 DDDs per year versus non-use	0.93 (0.84–1.03)		
Veitonmaki	2013	Finland	Case–control study[ad]	24,657/24,657	Any aspirin use versus non-use	0.95 (0.88–1.00)	Age and simultaneous use of other medications	Usage (+, not dose-dependent)
Paganini-Hill	1989	USA	Cohort study[c]	149/5,051	One or more tablets per day versus non-use	0.95 (0.58–1.51)	Age and number of cases	
Schreinemachers	1994	USA (NHANES I)	Cohort study[d]	123/12,688	One or more tablets per month versus non-use	0.95 (0.66–1.35)	Age	
Habel	2002	USA	Cohort study[c]	2,574/91,739	> 6 tablets almost every day for > 1 year versus ≤6 tables/d < 1 year	0.76 (0.60–0.98)	Age, race, birth year, education and number of health checkups	
Platz-	2005	USA	Cohort study[cd]	141/9,748	Ever use versus non-use	0.76 (0.54–1.07)	Calendar year, age and use of the other types of medications	Duration(−)
					Current use versus non-use	0.81 (0.58–1.15)		

Table 1 continued

Study	Year	Country	Design	Number of cases/controls or subjects	Definition of aspirin use	RR (95 % CI)	Adjusted factors	Additional comments
Jacobs	2007	USA (CPS-II Nutrition/ ACS)	Cohort study[c]	5,539/69,810	≥1 tablet per day for more than 5 years versus non-use	0.81 (0.70–0.94)	Age, race, education, smoking, BMI, physical activity level, history of PSA testing, history of colorectal endoscopy, use of NA-NSAIDs, history of heart attack, diabetes, and hypertension	Dose(−,$P_{trend} = 0.75$)
					≥1 tablet per day for less than 5 years versus non-use	1.02 (0.93–1.12)		
Siemes	2008	The Netherlands	Cohort study[c]	150/7,621	Any use versus non-use	1.04 (0.73–1.47)	Age, BMI, CRP level and pack years of smoking	
					Any use more than 1 year versus non-use	0.97 (0.65–1.43)		
Brasky	2010	USA (VITAL)	Cohort study[c]	1,550/34,132	≥four days/wk more than 4 years versus non-use	0.96 (0.83–1.11)	Age, race, education, BMI, multivitamin use, PSA test in the past 3 years, benign prostate biopsy, enlarged prostate, family history of prostate cancer, diabetes, coronary artery disease, osteoarthritis, rheumatoid arthritis, chronic joint pain, chronic headaches and migraines	No association between aspirin use and prostate cancer risk
					1 table/wk more than 1 year versus non-use	0.98 (0.87–1.09)		
Dhillon	2011	USA (HPFS)	Cohort study[c]	4,858/47,271	Current use versus non-use	0.98 (0.91–1.05)	Age, period, family history, ethnic, height, BMI, tomato sauce, vigorous physical activity, smoking, vitamin D, fish, red meat, cholesterol-lowering drugs and total kcal	Frequency(−),$P = 0.15$ usage(+), $P = 0.02$ duration(−),$P = 0.67$
					≥6 tablets per week versus <2 tables per week	0.90 (0.83–0.99)		
					Any use more than 10 years versus non-use	0.99 (0.87–1.12)		

Table 1 continued

Study	Year	Country	Design	Number of cases/controls or subjects	Definition of aspirin use	RR (95 % CI)	Adjusted factors	Additional comments
Shebl	2012	USA (PLCO study)	Cohort study[c]	3,573/29,450	Equal or more than one table per day in last 12 months versus non-use	0.92 (0.85–0.99)	Race, study center, family history of prostate cancer, number of screening exams, and ibuprofen use	Usage (+, $P_{trend} = 0.04$)

BMI body mass index,*PSA* prostate-specific antigen,*NSAIDs* nonsteroidal anti-inflammatory drugs,*NA-NSAIDs* non-aspirin NSAIDs,*CRP* C-reactive protein,*NHS* Nurses' Health Study,*HPFS* health professionals follow-up study,*ProtecT* The prostate testing for cancer and treatment trial,*DDD* WHO's defined daily dose, means the assumed average maintenance dose per day for a drug used for its main indication in adults,*NHANES* National Health and Nutrition Examination Study,*CPS-II Nutrition* Cancer Prevention Study II Nutrition,*ACS* American Cancer Society,*VITAL* vitamins and lifestyle,*PLCO* prostate, lung, colorectal, and ovarian cancer screening trial,*GPRD* general practice research database,*Wk* week, *RR* relative ratios, *CI:* confidence interval

[a] Population-based, [b] hospital-based, [c] by self-questionnaire, [d] by hospital discharge files or database

which, however, with some evidence of heterogeneity ($I^2 = 53.6$ %, P value for heterogeneity = 0.091).

A series of subgroup analyses were carried out to detect the source of heterogeneity (Table 3). The heterogeneity for 13 case–control studies was large ($I^2 = 68.2$ %, P value for heterogeneity = 0.000) and did not subside after stratification by type of control subjects, while no evidence of heterogeneity among nine cohort studies existed ($I^2 = 0.0$ %, P value for heterogeneity = 0.703), indicating that the results of the cohort studies (pooled RR 0.90, 95 % CI 0.86–0.94) were homogeneous. The pooled estimated data in subgroup analyses revealed that geographic location, race and family history of prostate cancer may confuse the assessed association and influence the effect of aspirin use on risk of prostate cancer. It was obvious that the heterogeneity would become weaker when the studies were adjusted for more confounding factors (for equal or more than five:$I^2 = 4.2$ %, P value for heterogeneity = 0.398; for less than five:$I^2 = 61.7$ %, P value for heterogeneity = 0.001). No publication bias was found through Egger's test ($P = 0.169$) or Begg's test ($P = 0.955$) (Fig. 3).

Advanced prostate cancer

A stronger reverse association was detected in the association between aspirin use and the risk of advanced prostate cancer (pooled RR 0.86, 95 % CI 0.78–0.95) (Fig. 4). However, there were some evidence of heterogeneity ($I^2 = 41$ %, P value for heterogeneity = 0.068). When we restricted our analyses to long-time regular usage of aspirin, a 30 % reduction in advanced prostate cancer risk was found with little evidence of heterogeneity ($I^2 = 0.0$ %, P value for heterogeneity = 0.969). In subgroup analysis, a moderate protective rate was obtained in cohort studies with little heterogeneity among studies ($I^2 = 0$ %, P value for heterogeneity = 0.743), which confirmed the protective effect of aspirin use on advanced prostate cancer (Table 4).

Discussion

In this meta-analysis of 24 observational studies, we found that regular aspirin use was associated with reduction in overall and advanced prostate cancer risk (pooled RR 0.86, 95 % CI 0.81–0.92; pooled RR 0.83, 95 % CI 0.75–0.91, respectively). When it comes to long-time regular aspirin use, reverse association became stronger (pooled RR 0.82, 95 % CI 0.72–0.93; pooled RR 0.70, 95 % CI 0.55–0.90, respectively). Previously, there were three systematic reviews [4–6] summarizing the evidence about the association of aspirin use and prostate cancer risk. Of these, a

Table 2 Characteristics of studies included in the meta-analysis of aspirin and risk of advanced prostate cancer (included regional and distant disease)

Study	Year	Country	Design	No of cases/ controls or subjects	Definition of aspirin use	RR(95 % CI)	Adjustment factor	Definition of advanced prostate cancer
Norrish	1998	New Zealand	Case–control study[ac]	192/480	Regular aspirin use versus non-use or < 1/wk	0.71 (0.47–1.08)	Age, socioeconomic status, total polyunsaturated fat consumption, a-linolenic acid and ratio of dietary n-6: long-chain n-3 polyunsaturated fatty acids	Included all cases with evidence of extra-capsular cancer or GS ≥ 7
					Low-dose aspirin use (100-150 mg/d) versus non-use or < 1/wk	0.69 (0.45–1.06)		
Habel	2002	USA	Cohort study[c]	719/91,739	>6 tablets almost every day for >1 year versus ≤6 tables/d < 1 year	0.71 (0.45–1.14)	Age, race, birth year, education and number of health checkups	Regional or distant prostate cancer
Jacobs	2005	USA (CPS-II Nutrition/ ACS)	Cohort study[c]	638/70,144	≥30 pills per month for more than 5 years versus non-use	0.64 (0.39–1.05)	Age, race, diabetes, history of heart attack, history of PSA testing, education, and family history of prostate cancer	Stage III or IV at diagnosis or fatal prostate cancer of unknown stage at diagnosis
Menezes	2006	USA	Case–control study[bc]	513/1,029	1/wk more than 6 months versus non-regular use	1.06 (0.87–1.29)	Age, family history of prostate cancer and BMI	Regional or distant prostate cancer
Mahmud	2006	Canada	Case–control study[ac](in a high-risk population)	289/308	≥1 tablet per day in the last 5 years versus not regular use	0.79 (0.38–1.64)	Age, family history of prostate cancer, history of ischemic heart disease, acetaminophen use, selective COX-2 inhibitors, other NA-NSAIDs and GS	GS ≥ 7 Average core involvement > 50 %: 0.71 (0.32–1.56)
Liu	2006	USA	Case–control study[ad]	506/506	2 tables/wk more than 1 month versus non-use	0.66 (0.51–0.86)	Age, medical institution and ethnicity	GS ≥ 7, stage ≥ T2c and PSA ≥ 10 ng/mL
Bosetti	2006	Italy	Case–control study[bc]	383/1,131	1 table/wk more than 6 months versus non-use	1.31 (0.86–1.99)	Age, study center, education and family history of prostate cancer	GS 7-8 stage III–IV:1.08 (0.60–1.93)
Salinas	2010	USA	Case–control study[ac]	315/942	1 tables daily more than 3 months versus non-use	0.77 (0.58–1.02)	Age at reference date, race and prostate cancer screening within 8 years before reference date	GS ≥ 7 or regional/ distant stage or PSA ≥ 20 ng/mL
					81 mg daily more than 3 months versus non-use	0.71 (0.50–1.01)		
					1 tables/wk more than 5 years versus non-use	0.73 (0.52–1.03)		

Table 2 continued

Study	Year	Country	Design	No of cases/ controls or subjects	Definition of aspirin use	RR(95 % CI)	Adjustment factor	Definition of advanced prostate cancer
Brasky	2010	USA (VITAL)	Cohort study[c]	213/34,132	≥4 days/wk more than 4 years versus non-use	0.72 (0.47–1.09)	Age, race, education, BMI, multivitamin use, PSA test in the past 3 years, benign prostate biopsy, enlarged prostate, family history of prostate cancer, diabetes, coronary artery disease, osteoarthritis, rheumatoid arthritis, chronic joint pain, chronic headaches and migraines	GS ≥ 7
					1 tables/wk more than 1 year versus non-use	0.73 (0.53–1.02)		
Dhillon	2011	USA (HPFS)	Cohort study[c]	808/47,271	Current use versus non-use	0.85 (0.72–1.00)	Age, period, family history, ethnic, height, BMI, tomato sauce, vigorous physical activity, smoking, vitamin D, fish, red meat, cholesterol-lowering drug sand total kcal	Regional prostate cancer (T3b–T4 or N1 and M0) or lethal prostate cancer(M1 or death)
								GS 8–10: 0.74 (0.59–0.91)
Shebl	2012	USA (PLCO study)	Cohort study[c]	1,559/29,450	≥1 table per day in the last 12 months versus non-use	0.88 (0.78–0.99)	Race, study center, family history of prostate cancer, number of screening exams, and ibuprofen use	GS ≥ 7 or stage III or IV
Veitonmaki	2013	Finland	Case–control study[ad]	3,648/24,657	Any aspirin use versus non-use	1.00 (0.82–1.20)	Age and simultaneous use of other medications	Presence of extra-capsular extension and involvement of regional lymph nodes or metastasis

BMI body mass index, *PSA* prostate-specific antigen, *NSAIDs* nonsteroidal anti-inflammatory drugs, *NA-NSAIDs* non-aspirin NSAIDs, *HPFS* health professionals follow-up study, *CPS-II Nutrition* Cancer Prevention Study II Nutrition, *ACS* American Cancer Society, *VITAL* vitamins and lifestyle, *PLCO* prostate, lung, colorectal, and ovarian cancer screening trial, *COX-2* cyclooxygenase-2, *GS* Gleason score, *RR* relative ratios, *CI* confidence interval

[a] Population-based, [b] hospital-based, [c] By self-questionnaire, [d] By hospital discharge files or database

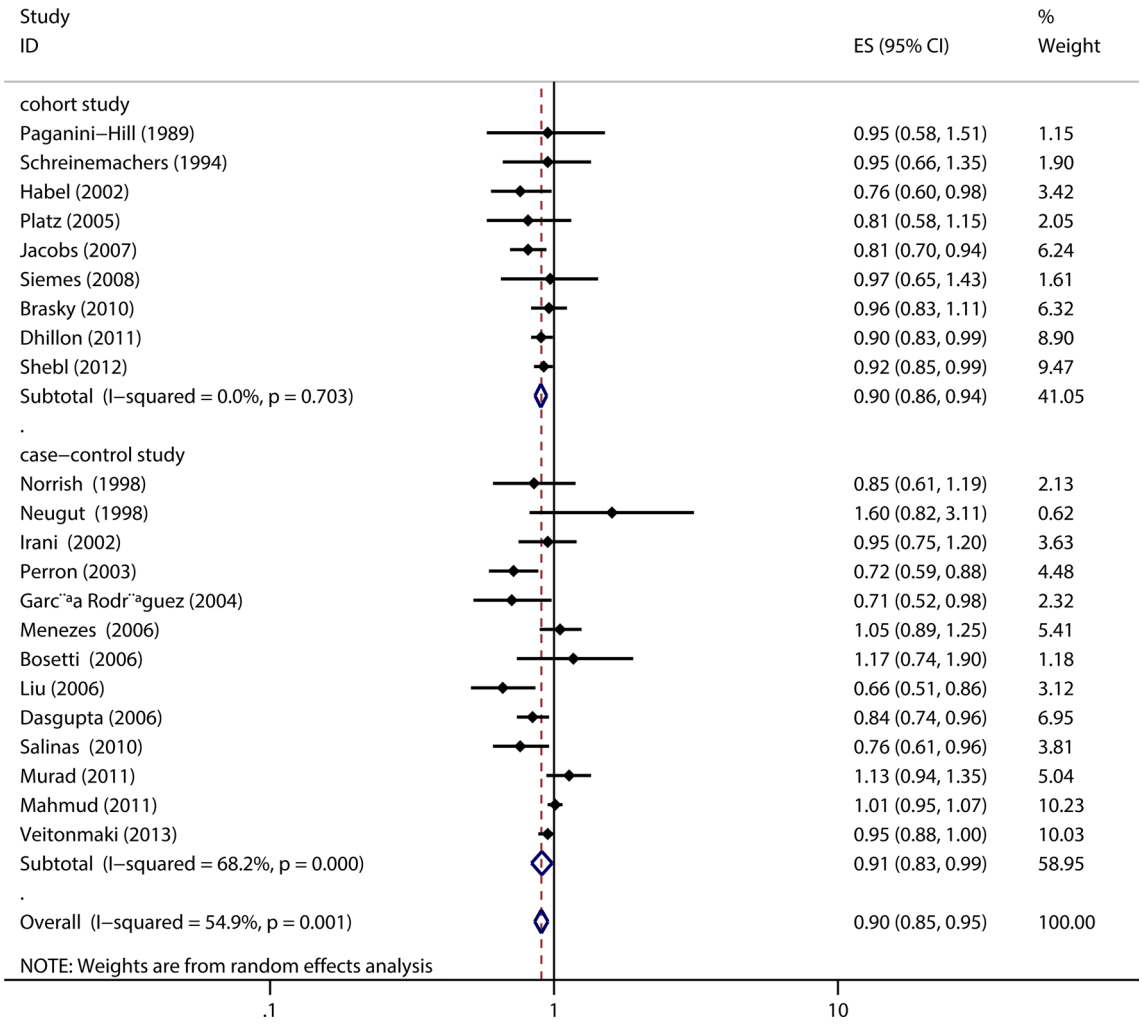

Fig. 2 Forest plot and meta-analysis of the association between any aspirin use and prostate cancer risk. Any aspirin use was associated with a reduction in prostate cancer risk (pooled RR 0.90, 95 % CI 0.85–0.95). Subgroup analysis based on study design obtained a consistent result in cohorts with few heterogeneity. However, some evidence of heterogeneity were detected in case–control studies ($I^2 = 68.2$ %, P for heterogeneity = 0.000)

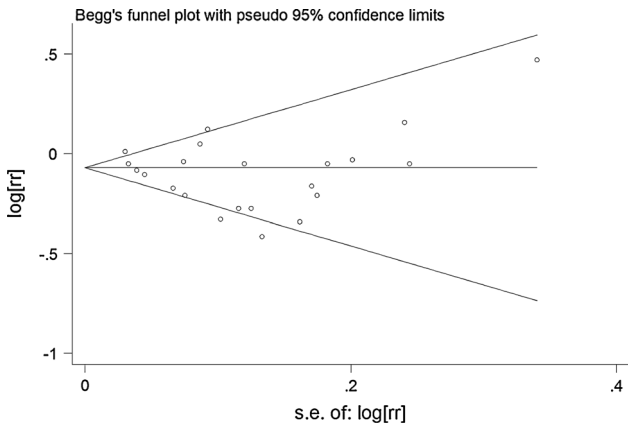

Fig. 3 Begg's funnel plot of any aspirin use and prostate cancer risk

significant inverse association was computed in the meta-analysis conducted by Mahmud et al. [5]. In addition, an updated systematic review, which performed by Bosetti et al., suggested that prostate cancer risk is reduced by 10 % in regular aspirin users, with similar risk reductions reported in both case–control and cohort studies. Recently, several well-designed studies which adjusted more confounding factors were published and reported controversial results. A cohort of 51,529 health professionals aged 40–75 years old was conducted by Dhillon et al. [8] to evaluate the association between long-term aspirin use and the incidence of total, high-grade, regionally advanced and lethal prostate cancer. Any use more than 10 years had no influence with overall prostate cancer risk (pooled RR 0.99; 95 % CI 0.87–1.12). But significantly reverse association

Table 3 Summary risk estimates of the association between aspirin use and the risk of prostate cancer

	Number of studies	Summary RR (95 % CI)	*P* value	Study heterogeneity		
				Q statistic	I^2 value (%)	*P* value
Overall studies	22	0.90 (0.86–0.95)	0.000	46.55	54.9	0.001
Study design						
Case–control study	13	0.91 (0.83–0.99)	0.021	37.72	68.2	0.000
Cohort study	9	0.90 (0.86–0.94)	0.000	5.50	0.0	0.703
Type of control subjects						
Population-based	8	0.90 (0.81–0.99)	0.030	26.45	73.5	0.000
Hospital-based	5	0.95 (0.78–1.15)	0.561	10.38	61.5	0.034
Geographic location						
America	15	0.88 (0.82–0.94)	0.000	37.68	62.8	0.001
Europe	6	0.97 (0.87–1.08)	0.558	7.39	32.3	0.193
Others	1	0.85 (0.61–1.18)	0.340	–	–	–
Regular aspirin use	10	0.86 (0.81–0.92)	0.000	12.88	30.1	0.168
Study design						
Case–control study	4	0.75 (0.66–0.85)	0.000	0.83	0.0	0.843
Cohort study	6	0.90 (0.86–0.94)	0.000	4.91	0.0	0.427
Daily aspirin use	7	0.82 (0.74–0.90)	0.000	10.13	40.8	0.119
≥4 years	2	0.78 (0.69–0.87)	0.000	0.86	0.0	0.353
<4 years	5	0.84 (0.75–0.94)	0.002	5.97	33.0	0.201
Regular aspirin use versus non-use	9	0.87 (0.81–0.92)	0.000	11.5	30.6	0.174
Long-time regular use (≥4 years)	4	0.82 (0.72–0.93)	0.002	6.47	53.6	0.091
Number of adjusted confounders						
Less than 5	14	0.93 (0.86–1.00)	0.052	33.96	61.7	0.001
Equal or more than 5	8	0.89 (0.85–0.94)	0.000	7.31	4.2	0.398
Adjustment for confounders						
Race						
Yes	8	0.86 (0.79–0.94)	0.000	14.81	52.7	0.038
No	14	0.94 (0.87–1.00)	0.052	24.72	47.4	0.025
Family history of prostate cancer						
Yes	5	0.99 (0.90–1.09)	0.850	6.92	42.2	0.140
No	17	0.87 (0.81–0.93)	0.000	38.32	58.2	0.001
Smoking						
Yes	4	0.88 (0.82–0.95)	0.001	1.70	0.00	0.428
No	18	0.91 (0.85–0.96)	0.002	42.07	57.2	0.001
Body mass index						
Yes	5	0.92 (0.85–1.00)	0.041	5.79	30.9	0.216
No	17	0.89 (0.83–0.95)	0.001	40.3	60.3	0.001
Number of three main adjusted factors						
Less than 2	12	0.91 (0.86–0.98)	0.002	19.83	44.5	0.048
Equal or more than 2	10	0.90 (0.82–1.00)	0.057	25.32	64.5	0.003

RR relative risk, *CI* confidence interval, *vs* versus

was observed in high-grade and lethal prostate cancer which associated with higher doses of aspirin (≥6 adult-strength tablets per week). Another large-scaled study [9] carried out in Finland at population level, which suggested a decreased overall prostate cancer risk (OR 0.90, 95 % CI 0.84–0.96) in a dose-dependent fashion.

Table 4 Summary risk estimates of the association between aspirin use and risk of advanced prostate cancer

	Number of studies	Summary RR (95 % CI)	*P* value	Study heterogeneity		
				Q statistic	I^2 value (%)	*P* value
Overall studies	12	0.86 (0.78–0.95)	0.003	18.66	41.0	0.068
Study design						
Case–control study	7	0.88 (0.72–1.07)	0.196	15.38	61.0	0.018
Population-based	5	0.77 (0.62–0.97)	0.028	8.25	51.5	0.083
Cohort study	5	0.85 (0.78–0.92)	0.000	1.96	0.0	0.743
Regular aspirin use	7	0.83 (0.75–0.91)	0.000	3.68	0.0	0.720
Daily aspirin use	4	0.85 (0.77–0.95)	0.003	1.41	0.0	0.704
Regular aspirin use versus non-use	5	0.83 (0.75–0.92)	0.000	3.23	0.0	0.520
Long-time regular aspirin use	4	0.70 (0.55–0.90)	0.006	0.25	0.0	0.969

RR relative risk, *CI* confidence interval, *vs* versus

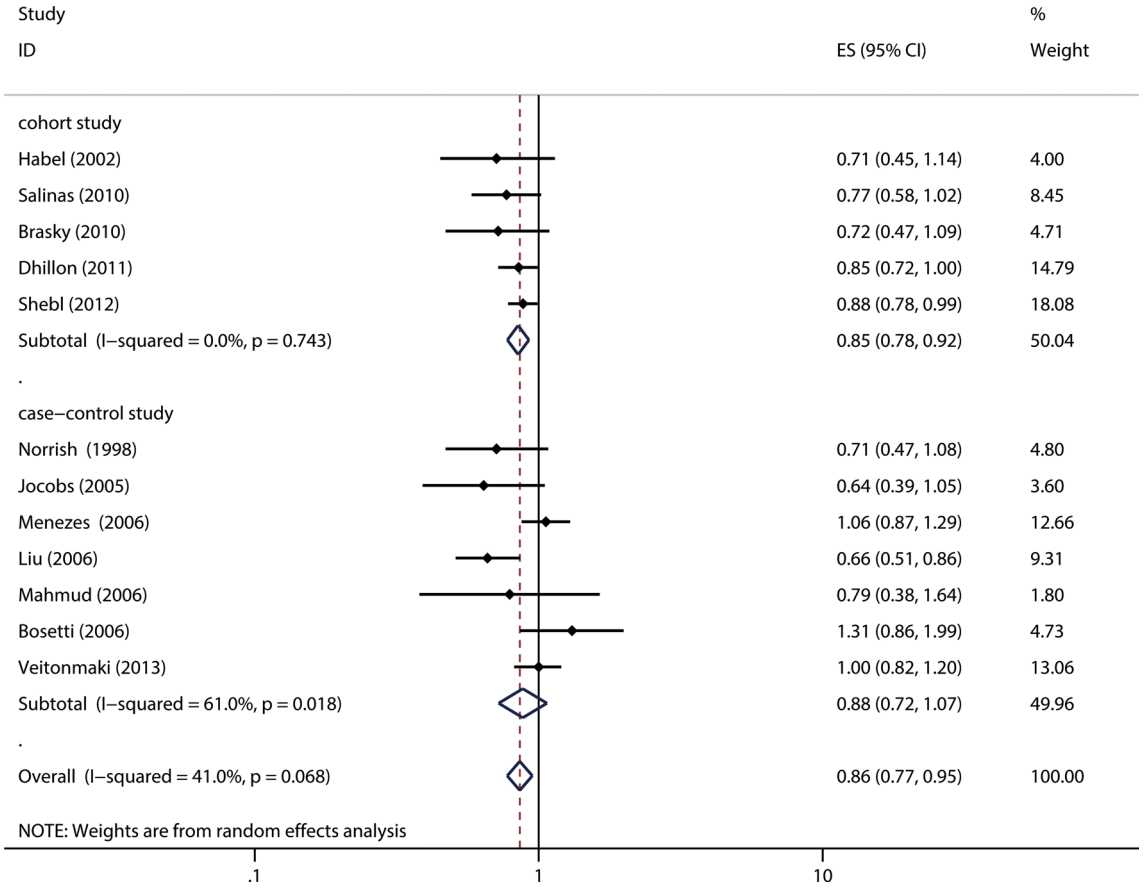

Fig. 4 Forest plot and meta-analysis of the association between any aspirin use and advanced prostate cancer risk. Any aspirin use was associated with a reduction in advanced prostate cancer (pooled RR 0.86, 95 % CI 0.77–0.95). Subgroup analysis based on study design obtained a consistent result in cohorts with few heterogeneity. However, some evidence of heterogeneity were detected in case–control studies ($I^2 = 61.0$ %,*P* for heterogeneity = 0.018)

Several mechanisms were proposed to interpret the protective of aspirin and other NSAIDs on cancers, which included induction of apoptosis via COX-independent pathways, inhibition of cellular proliferation and angiogenesis by up-regulating of tumor suppressor genes [35]. In relation to prostate cancer, inhibition of the COX enzymes

involved in prostaglandin synthesis also played a role in the prevention of prostate cancer. Gupta et al. [36] compared levels of COX-2 mRNA in pair-matched benign and cancer tissue obtained from the same prostate cancer patients and found that COX-2 is over expressed in prostate cancers. Consistent results were obtained from some others studies [37, 38]. However, the influence of prostatitis on prostate cancer risk remains unfathomed.

Several limitations should be taken into account in the present meta-analysis. Firstly, half of included studies were case–control studies, which were susceptible to recall bias and select bias. These kinds of bias might be reduced to a large extent in cohort studies. However, there were still several potential known or unknown confounders, which may influence conclusion drawn from the meta-analysis compiled from these studies. Secondly, our literature search was restricted to the studies published in PubMed, EMBASE and Cochrane Library. It is well known that negative studies were less likely to be published in indexed journals, which may bias our results, though there was no evidence of publication bias basing on either Egger's test or Begg's test. Thirdly, studies included were different in terms of populations, dose and duration of aspirin use, selection of control group and confounders adjusted. Subsequently, subgroup analyses were performed to reduce the considerable heterogeneity. Moderate results were demonstrated when our analyses got rid of the influence of the factors mentioned before. The results also became acceptable with little heterogeneity when we restricted our analyses to regular aspirin use and long-time regular aspirin use. But subgroup analyses and sensitivity analyses were far from removing all the heterogeneity. Finally, it was impossible to clarify the dose–response association because of lack of data. So it is hard to quantitatively assess the aspirin use on prostate cancer risk.

However, subgroup analyses based on several known confounding factors such as age, race and family history of prostate cancer were performed. And moderate results with little heterogeneity were obtained. From this meta-analysis, 10 % reduction in prostate cancer risk and 14–15 % in advanced prostate cancer risk were observed associated with any use of aspirin in overall and cohort studies.

Smoking has not been established as risk factors for prostate cancer, but they are important risk factors for other human cancers and potentially major avoidable factors. Recently, a published large prospective study among Japanese found that smoking was inversely associated with prostate cancer risk among total subjects, but tended to increase the risk of advanced prostate cancer [39]. To evaluate the effect of smoking on prostate cancer risk, subgroup analysis based on smoking was performed. However, no significant heterogeneity between subgroups ($P = 0.244$) was obtained.

In conclusion, the results of this meta-analysis of 24 observational studies provide quantitative evidence that aspirin may reduce the risk of overall and advanced prostate cancer, especially long-time regular aspirin use. Further well-designed large-scaled cohort studies are needed to provide more definitive conclusions.

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Conflict of interest None.

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