

The effects of nonsteroidal anti-inflammatory drugs in the incident and recurrent risk of hepatocellular carcinoma: a meta-analysis

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Background: Recent studies have showed that nonsteroidal anti-inflammatory drugs (NSAIDs) could reduce the risk of several types of cancer. However, epidemiological evidence of the association between NSAIDs intake and the risk of hepatocellular carcinoma (HCC) remains controversial.

Methods: To assess the preventive benefit of NSAIDs in HCC, we simultaneously searched the databases of PubMed, EmBase, Web of Science, and Scopus and screened eligible publications.

Results: A total of twelve articles (published from 2000 to 2017) from five countries were identified by retrieval. We observed a significantly lower risk of HCC incidence among users of NSAIDs than among those who did not use NSAIDs (pooled hazard ratio [HR] value =0.81, 95% confidence interval [CI]: 0.69–0.94). No evidence of publication bias was observed (Begg's test, $P=0.755$; Egger's test, $P=0.564$). However, when stratified according to the categories of NSAIDs, users of non-aspirin NSAIDs (HR =0.81, 95% CI: 0.70–0.94), but not aspirin (HR =0.77, 95% CI: 0.58–1.02), showed a statistically significant reduced HCC incidence. We also found that NSAIDs use significantly reduced the recurrent risk of HCC, with a HR value of 0.79 (95% CI: 0.75–0.84), whereas there was no statistically significant association between NSAIDs use and HCC mortality, with a HR value 0.65 (95% CI: 0.40–1.06).

Conclusion: Taken together, our meta-analysis demonstrates that NSAIDs significantly reduce the incident and recurrent risk of HCC.

Keywords: NSAIDs, aspirin, hepatocellular carcinoma, incidence, recurrence

Introduction

Hepatocellular carcinoma (HCC) is one of the leading causes of cancer-related death worldwide, especially in less developed countries. According to the Global Cancer Statistics of 2012,¹ the yearly burden of HCC is estimated to be 782,500 new cases, resulting in 745,500 deaths. To lower the incidence and mortality of HCC, preventative drugs for HCC need to be explored.

A growing body of convincing evidence demonstrates that host systemic and local inflammation promotes tumorigenesis and tumor progression.^{2–5} More than 70%–90% cases of HCC gradually unfold on the background of chronically inflamed hepatic parenchyma and thus HCC represents one of the pro-inflammatory stimuli-related malignancies.⁶ In addition to the elevated risk of HCC incidence, there is increasing evidence supporting the adverse role of systemic inflammation in the prognosis of HCC.^{7,8}

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The close association between inflammation and tumorigenesis forms the basis of the hypothesis that anti-inflammatory drugs may have antitumor effects. Based on this, recently considerable evidence from experimental and clinical studies indicates that nonsteroidal anti-inflammatory drugs (NSAIDs) could reduce the risk of several types of cancer, including gastric cancer,⁹ prostate cancer,¹⁰ colorectal cancer,¹¹ esophageal cancer,¹² breast cancer,¹³ bladder cancer,¹⁴ and head and neck cancers.¹⁵ The key mechanism of the protective action of NSAIDs is the inhibition of the cyclooxygenase (COX) enzymes, which could catalyze the synthesis of prostaglandins (PGs) in inflammatory processes. Taking into account that HCC is a chronic inflammation-related disease and is characterized by high expression of COX,¹⁶ it is tempting to speculate that NSAIDs may reduce HCC risk. Herein, we used the approach of meta-analysis to summarize all eligible epidemiological evidence for an association between aspirin or non-aspirin NSAIDs use and the incident or recurrent risk of HCC.

Materials and methods

Search strategy and selection criteria

A systematic search through databases of PubMed, EmBase, Web of Science, and Scopus databases until April 2017 was performed by two independent investigators (PQ and JH). Our core search consisted of terms (“nonsteroidal anti-inflammatory drugs” or NSAIDs or aspirin) AND (“hepatocellular carcinoma” or “liver cancer”). Additionally, we retrieved the reference lists of the included publications and related reviews manually. Endnote X7 software (Thomson Corporation, Stamford, CT, USA) was used to analyze and manage references.

Studies that met the following predetermined selection criteria were included: 1) published as an original article in English; 2) designed as an observational study; 3) exposure was use of aspirin or non-aspirin NSAIDs; 4) outcome was the incidence, recurrence, or mortality of HCC; 5) reported hazard ratio (HR), relative risk, or odd ratio value and 95% confidence interval (CI),^{17,18} or provided sufficient data to assess them. We excluded the following studies: 1) those that assessed the effect of NSAIDs on the survival of patients with HCC; 2) those that just provided *P*-value or other conditions wherein effect size and 95% CI could not be estimated; 3) animal studies, reviews, conference abstracts, commentaries, editorials, and duplicate studies.

Data abstraction

Based on the above inclusive and exclusive criteria, two authors (PQ and JH) independently evaluated the retrieved

publications for inclusion and discrepancy was resolved by discussion. Kappa concordance coefficient was then calculated to assess the agreement between the two screeners. We extracted the following data with a standardized data collection protocol: tumor location, first author, publication year, country, study period, duration of follow-up, information source, types of NSAIDs, median age of study population, number of participants, number of cases, HR value (adjusted HR value in preference) and 95% CI, and controlled confounders. The research quality of each included study was assessed by MZ by using the modified Newcastle–Ottawa Scale (NOS) scores. The score ranged from zero to nine and ≥ 7 points was defined as high quality. We adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines for reporting the current meta-analysis. All data were double checked by the first author (PQ).

Statistical analysis

We estimated the incident risk of HCC in users of any NSAIDs, aspirin, and non-aspirin NSAIDs compared with nonusers, respectively. With the eligible studies, we uniformly used a random-effects model to calculate the pooled HR value and 95% CI. Heterogeneity across studies was estimated by *Q* value and *I*² statistic. *I*² values of 25%, 50%, and 75% correspond to cutoff points of low, moderate, and high degrees of heterogeneity, respectively. A study was considered to demonstrate statistically substantial heterogeneity provided $P < 0.1$ in *Q* statistic or $I^2 > 50\%$; otherwise, there was no significant heterogeneity. Based on the factors that might bring in potential heterogeneity, we subsequently performed subgroup analyses and meta-regression to seek the potential source of heterogeneity.

We also did influence analyses to evaluate whether any single study could markedly affect the pooled results. We compared the pooled HR values calculated by using a fixed-effects model with that calculated by using a random-effects model. Then, publication bias was determined by Begg’s funnel plot and Egger’s test. Finally, the Galbraith plot was studied to detect potential outliers, which might bias the results. We considered a statistically significant difference to be present if a bilateral *P*-value was < 0.05 .

Results

The flow chart of the literature retrieval and screening process is shown in Figure 1. Of the total 1,059 citations, 43 full text articles were assessed and 31 were further excluded. Thus, we finally included 12 publications in this meta-analysis.

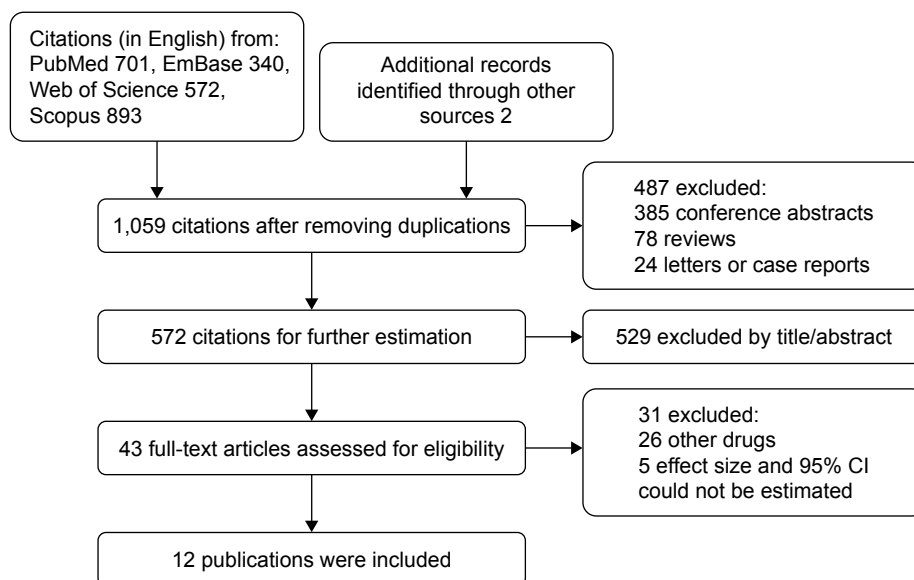


Figure 1 Flow chart of search strategy and study selection.
Abbreviation: CI, confidence interval.

Agreement between the two investigators on which studies were to be included was good ($\kappa = 0.917$).

Article characteristics

The main characteristics of the twelve articles, seven of which were published after 2013, are summarized in Table 1. Five of the publications were performed in western countries and others were from Asia. Seven, four, and one were cohort, case-control, and nested case-control studies, respectively. The mean (or median) follow-up time (reported) ranged from 2.1 to 17.0 years. Nine publications controlled potential confounders and reported adjusted HR values. The assessment of study quality scores from the NOS scale demonstrated that the median score was 8 with a range from 6 to 9, and 91.6% of the studies were high quality.

Effects of NSAIDs on HCC incidence

Seven articles with eleven studies estimated the risk of HCC incidence in individuals with NSAIDs intake compared with unexposed persons. Among five, three studies were available to estimate the associations between use of aspirin, non-aspirin NSAIDs, and risk of HCC incidence, respectively. The remaining three studies failed to distinguish aspirin from non-aspirin NSAIDs. A random-effects model was used to pool the included studies which were stratified according to the categories of NSAIDs. As shown in Figure 2A, on the whole, NSAIDs use significantly reduced the incident risk of HCC, with a HR value 0.81 (95% CI: 0.69–0.94) and a moderate degree of between-study heterogeneity ($I^2=66.6%$,

$P<0.001$). The stratified analysis showed that non-aspirin NSAIDs (HR =0.81, 95% CI: 0.70–0.94), but not aspirin (HR =0.77, 95% CI: 0.58–1.02), significantly reduced HCC incidence and was identified as potential antitumor drugs.

Effects of NSAIDs on HCC recurrence and mortality

Accumulating evidence suggests that postoperative recurrence of HCC may arise from de novo tumor in the remnant liver. By summarizing eight relevant studies with a random-effects model, we subsequently analyzed the effects of NSAIDs on HCC recurrence. We demonstrated that NSAIDs use significantly reduced the recurrent risk of HCC, with a HR value 0.79 (95% CI: 0.75–0.84) and a low degree of between-study heterogeneity (Figure 2B; $I^2=0%$, $P=0.460$). In addition, two studies reported the association between NSAIDs and HCC mortality, and the pooled HR value was 0.65 (95% CI: 0.40–1.06).

Exploration of heterogeneity

The meta-analysis on the association between NSAIDs and HCC incidence included eleven studies (more than ten) and produced substantial heterogeneity ($P<0.10$). To explore the source of the heterogeneity, we subsequently performed subgroup and meta-regression analyses (Table 2). We analyzed the factors that might cause potential heterogeneity and there were no less than two studies in each subgroup. The covariates included NSAIDs categories (aspirin, non-aspirin, mixed NSAIDs), information source

Table 1 Baseline characteristics for studies included in meta-analysis

Study	Area	Design	Study period	Follow-up (years)	Information source	Drug type	Definition of user	Median age	Total size	Cases size	Adjusted variables	NOS
HCC incidence												
Coogan et al ¹⁹	America	CC	1977–1998	–	Questionnaire	NSAIDs	Regular use ≥ 1 y	50–70	5,833	51	Age, sex, interview year, center, race, religion, smoking, family education, drinking	7
Chiu et al ²⁰	Taiwan	CC	1996–2008	NR	Database	Aspirin, NSAIDs	≥ 1 prescription ^a	66.08/65.92	1,166	1,166	None	6
Jacobs et al ²¹	America	Cohort	1992–2008	Up to 16	Questionnaire	Aspirin	Regular use	60	58,848/41,291	70/48	Age, sex, race, education, smoking, BMI, physical activity, heart disease, stroke	8
Sahasrabudde et al ²²	America	Cohort	1995–2008	17	Questionnaire	Aspirin, non-aspirin NSAIDs	Any use	62.8	260,555/39,949	199/51	Age, sex, race, BMI, smoking, drinking, diabetes	8
Petrick et al ²³	America	Cohort	1985–2010	11.9	Questionnaire	Aspirin, non-aspirin NSAIDs	Any use	≥ 40	477,470/606,663	315/364	Age, sex, race, cohort, BMI, smoking, drinking, diabetes	8
Yang et al ²⁴	UK	CC	1988–2011	NR	Database	Aspirin, non-aspirin NSAIDs	≥ 2 prescriptions	67.2/67.0	4,640	1,195	BMI, smoking, alcohol disorders, HBV, HCV, diabetes, other NSAIDs, antidiabetic medications, statins	7
Kim et al ²⁵	Korea	Nested CC	2002–2013	NR	Database	Aspirin	Any use	≥ 40	1,374	229	None	7
HCC recurrence												
Wu et al ²⁶	Taiwan	Cohort	2003–2010	2.23	Database	NSAIDs	Any use	54.5	2,452/2,117	939/932	Age, sex, resection extent, liver cirrhosis, diabetes, use of statins, metformin	9
Yeh et al ²⁷	Taiwan	Cohort	1997–2010	2.9	Database	Aspirin, non-aspirin NSAIDs	Any use	58.3	9,811/5,763	7,229	Age, sex, HBV, HCV, cirrhosis, diabetes, hypertension, statins, metformin	8
Takami et al ²⁸	Japan	CC	2008–2011	NR	Database	Non-aspirin NSAIDs	15 mg daily	69.5/70.7	1111/113	62/64	None	7
Lee et al ²⁹	Taiwan	Cohort	1997–2011	3.5 4.3	Database	Aspirin, non-aspirin NSAIDs	Any use	62.3/62.2	442/1,786 728/1,482	215/906 404/717	Age, sex, liver cirrhosis, diabetes, coronary artery disease, cerebral vascular accidents, peptic ulcers, and use of nucleoside analogs, statins, metformin	9
HCC mortality												
Jacobs et al ²¹	America	Cohort	1992–2008	Up to 16	Questionnaire	Aspirin	Regular use	60	58,848/41,291	70/48	Age, sex, race, education, smoking, BMI, physical activity, heart disease, stroke	8
Li et al ³⁰	China	Cohort	2008–2013	2.1	Database	Aspirin	Full dose use	67.2/66.0	92	46	Age, gender, total bilirubin and GGT levels, PLT, cirrhosis, tumor size and number, tumor vascular invasion, treatment	8

Note: ^aOne or more NSAIDs prescription(s) recorded from the database or questionnaire.

Abbreviations: NSAIDs, nonsteroidal anti-inflammatory drugs; HCC, hepatocellular carcinoma; CC, case-control; RCT, randomized clinical trial; NR, not reported; BMI, body mass index; HBV, hepatitis B virus; HCV, hepatitis C virus; NOS, Newcastle–Ottawa Scale; GGT, gamma-glutamyl transferase; PLT, platelet count.

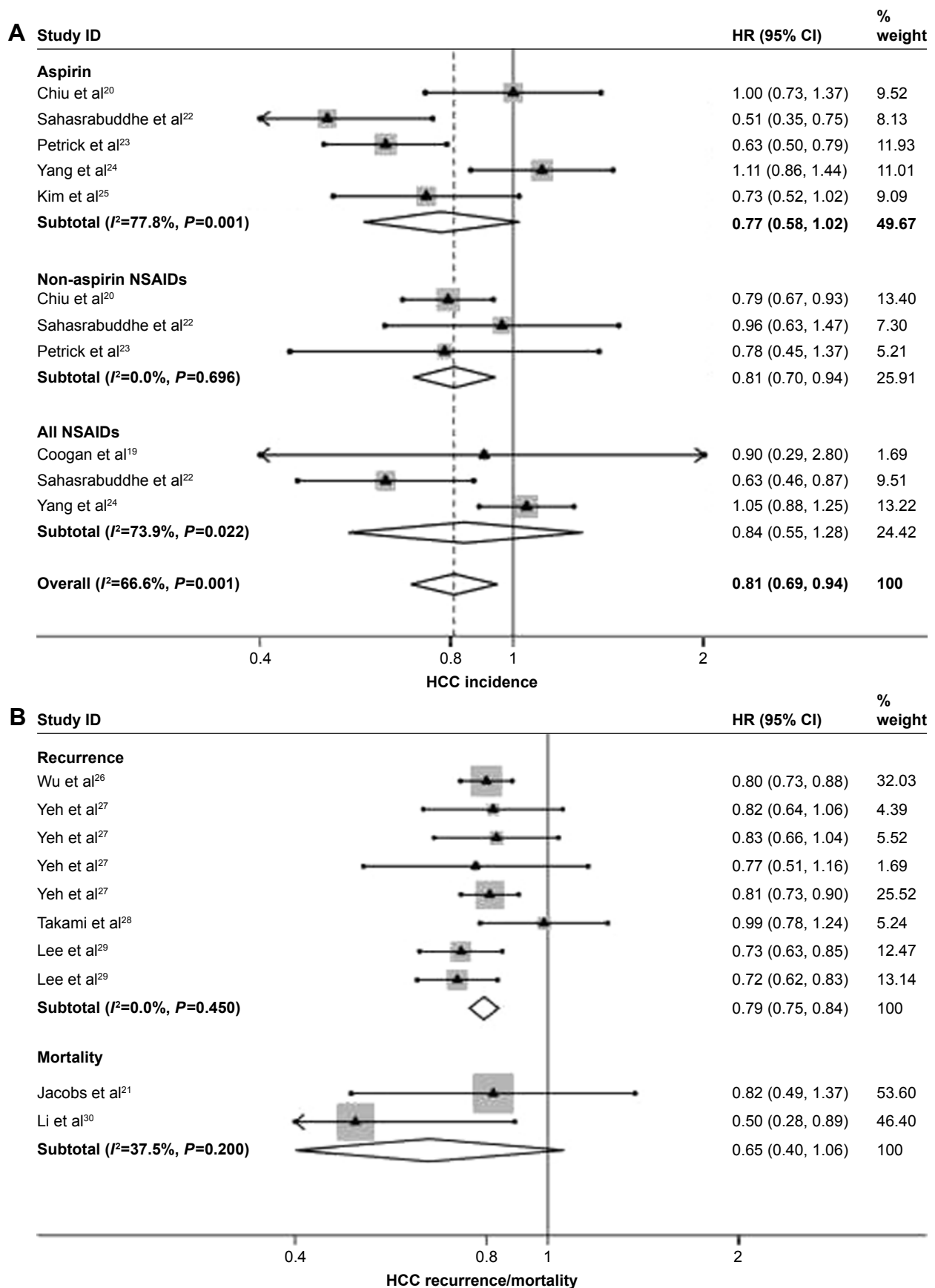


Figure 2 Forest plots of meta-analysis on the use of NSAIDs and risk of HCC incidence (A) and recurrence (B), stratified according to the categories of NSAIDs.

Note: Weights are from random-effects analysis.

Abbreviations: HCC, hepatocellular carcinoma; NSAIDs, nonsteroidal anti-inflammatory drugs; HR, hazard ratio; CI, confidence interval.

Table 2 Subgroup analysis and meta-regression analysis for studies that assessed the preventive effect of NSAIDs use in HCC incident risk

Covariates	Subgroup	No of studies	HR (95% CI)		Heterogeneity		Subgrouped		Meta-regression	
			Random-effects model	Fixed-effects model	P-value	I ²	Q value	P-value	Crude P-value	Adjusted P-value
Overall		11	0.81 (0.69–0.94)	0.83 (0.77–0.90)	0.001	66.6				
NSAIDs categories	Aspirin	5	0.77 (0.58–1.02)	0.78 (0.69–0.89)	0.001	77.8	3.52	0.172	0.647	–
	Non-aspirin	3	0.81 (0.70–0.94)	0.81 (0.70–0.94)	0.696	0				
	All NSAIDs	3	0.84 (0.56–1.28)	0.94 (0.81–1.09)	0.022	73.9				
Information source	Database	5	0.93 (0.79–1.09)	0.92 (0.84–1.02)	0.046	58.8	14.57	<0.001	0.025	1.000
	Questionnaire	6	0.66 (0.56–0.78)	0.66 (0.57–0.76)	0.343	11.3				
Publication year	Before 2013	6	0.76 (0.63–0.93)	0.77 (0.68–0.87)	0.081	49.0	2.89	0.089	0.505	–
	After 2013	5	0.85 (0.66–1.10)	0.89 (0.80–0.99)	0.002	76.8				
Region	Asia	3	0.82 (0.71–0.94)	0.81 (0.71–0.93)	0.344	6.30	0.17	0.685	0.829	–
	America/Europe	8	0.79 (0.63–1.00)	0.84 (0.76–0.93)	<0.001	74.6				
Design	Cohort	5	0.66 (0.55–0.79)	0.65 (0.56–0.76)	0.255	24.9	14.87	<0.001	0.023	0.731
	Others	6	0.93 (0.80–1.08)	0.92 (0.84–1.02)	0.084	48.5				
Adjusted confounders	No	3	0.82 (0.71–0.94)	0.81 (0.71–0.93)	0.344	6.30	0.17	0.685	0.829	–
	Yes	8	0.79 (0.63–1.00)	0.84 (0.76–0.93)	<0.001	74.6				

Note: Bold values indicate statistical significance ($P < 0.05$).

Abbreviations: HCC, hepatocellular carcinoma; NSAIDs, nonsteroidal anti-inflammatory drugs; HR, hazard ratio; CI, confidence interval.

(database and questionnaire), publication year (before and after 2011), region (Asia and America/Europe), design (cohort and others), and whether the potential confounders were adjusted (yes or no). Among these factors, information source and study design were found to be the potential sources of heterogeneity by subgrouped analysis and univariate meta-regression ($P < 0.05$). However, no independent factor was identified when multivariable meta-regression was performed.

Then, Galbraith's plots identified four outliers as potential sources of heterogeneity (Figure S1). When the meta-analysis was further performed after excluding the four outliers, the heterogeneity nearly disappeared (Figure S2; $I^2 = 0\%$, $P = 0.530$).

Sensitivity analysis and test of publication bias

Afterwards, we carried out a sensitivity analysis to validate our findings. First, we compared the pooled HR values (that were calculated by using a random-effects model) with the estimated effect sizes by using a fixed-effects model (Table 2). There were no significant differences between the two models except that aspirin significantly reduced the risk of HCC when a fixed-effects model was used. Second, we carried out an influence analysis and the results suggested that no study could affect the summary of HCC incidence and recurrence risk estimate (Figure S3).

Eventually, we drew funnel plots for the meta-analysis of HCC incidence and the plots reflected basic symmetry

(Figure 3A and B). Furthermore, no significant publication bias was identified by Begg's test and Egger's test, with a P -value of 0.755 and 0.564, respectively. In addition, there was also no publication bias in the meta-analysis of HCC recurrence (Figure 3C and D; P -value = 0.902 and 0.656, respectively).

Discussion

In the recent decades, there has been great progress in the diagnosis and treatment of HCC. However, to date, diagnosis at early stages of this malignancy is still difficult and the prognosis remains unsatisfactory.³¹ We need to urgently seek several effective strategies for decreasing the risk of HCC incidence and mortality.

Accumulating evidence suggests that systemic inflammatory responses play irreplaceable roles in different stages of tumor progression, such as initiation, promotion, invasion, and metastasis.^{32–34} Tumor could accelerate the inflammatory process, which in turn predisposes to tumor progression via inhibiting apoptosis, promoting angiogenesis and DNA damage.³⁵ Recently, it has been reported that inflammation increases the incident risk of several types of cancer, such as colon cancer, prostate carcinoma, and pancreatic cancer,^{36–38} whereas the possible mechanisms remain unclear. There is no denying that, early in tumorigenesis, inflammatory cells produce numerous cytokines, reactive oxygen species, inflammatory mediators, and eventually provide an attractive environment for tumor formation and angiogenesis.^{39–41} COX-1 and COX-2, which catalyze the

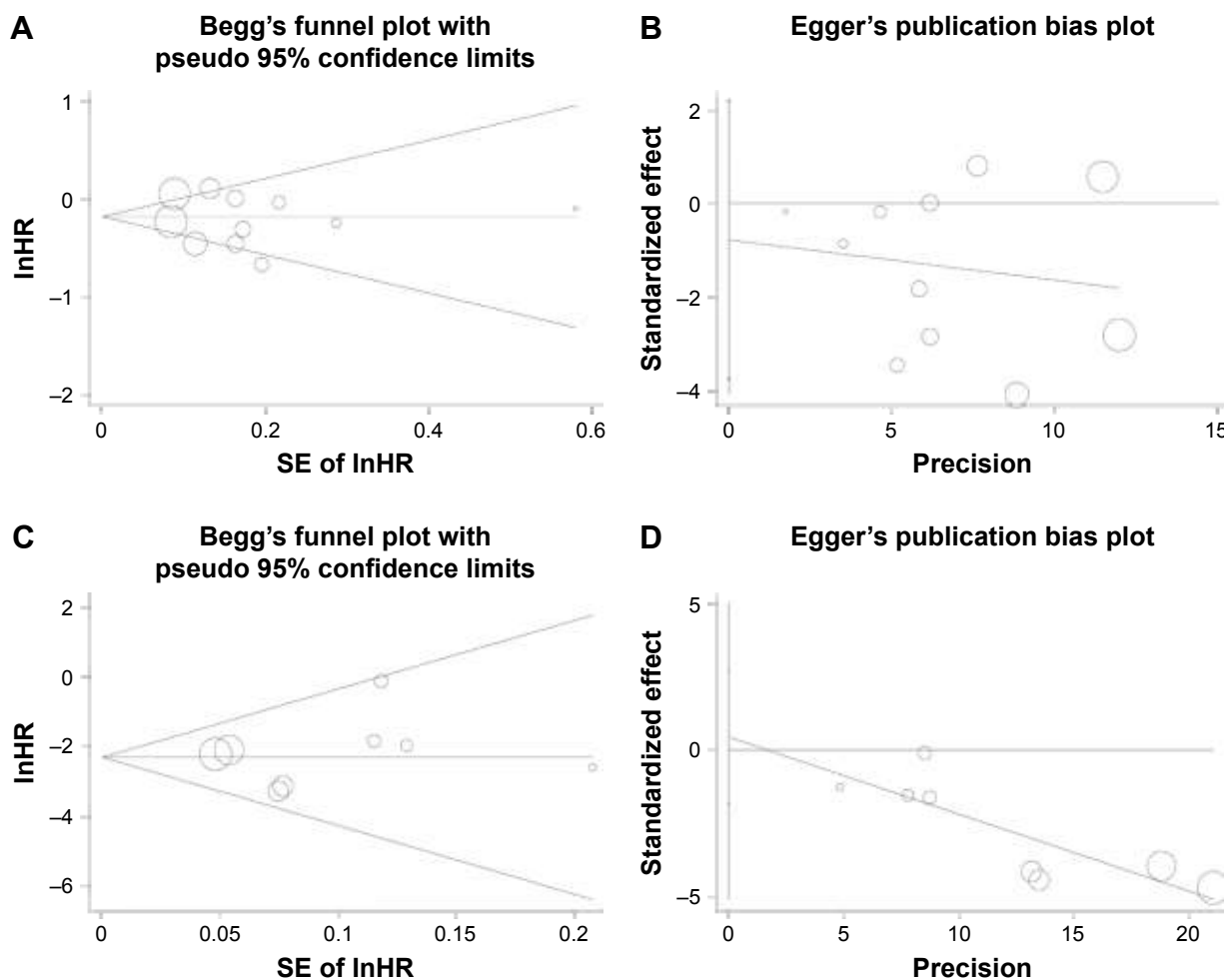


Figure 3 Begg's funnel plots and Egger's funnel plots of studies that assessed the effects of NSAIDs use in risk of HCC incidence (A, B) and recurrence (C, D). **Abbreviations:** HCC, hepatocellular carcinoma; NSAIDs, nonsteroidal anti-inflammatory drugs; HR, hazard ratio.

oxidative conversion of arachidonic acid to PG, are crucial inflammatory mediators.⁴² By increasing PG synthesis and stimulating inflammation processes, COX-1 and COX-2 can promote apoptosis, angiogenesis, and tumorigenesis.

In view of the causal relationship between inflammation response and tumorigenesis, it is postulated that the development of cancer could be inhibited by alleviating inflammation. NSAIDs have been widely used for the prevention and treatment of various diseases by relieving the inflammation process. Recently, several epidemiological studies have indicated that frequent use of NSAIDs significantly reduces the incident risk of several solid cancers, such as prostate cancer,¹⁰ colorectal cancer,¹¹ and breast cancer.¹³ Nevertheless, the antineoplastic mechanism of NSAIDs is not well understood and may be partially related to the inhibition of COX and PG synthesis.⁴³ Aspirin is a strong, irreversible inhibitor of COX-1 and an inhibitor of COX-2 only at higher doses, whereas non-aspirin NSAIDs are nonselective and reversible inhibitors of both COX-1 and COX-2.⁴⁴

It is notable that, as the expression of COX can be induced by various inflammatory cytokines and tumor promoters, the effects of NSAIDs may differ by tissues.⁴⁵ To date, the antitumor effect of NSAIDs in HCC remains controversial.

In our study, we first hypothesized and verified the anti-cancer role of NSAIDs in HCC. We showed that users of NSAIDs experienced a statistically significant lower risk of HCC incidence as well as HCC recurrence than nonusers. When the analysis was stratified by the categories of NSAIDs, non-aspirin NSAIDs were found to be superior to aspirin. This difference may be due to the different pharmacological and toxic mechanisms of NSAIDs. Further basic and clinical studies are still needed to clarify the differences of antitumor effects between aspirin and other NSAIDs. In addition, we found no significant benefit of NSAIDs in reducing the risk of HCC mortality.

Potential mechanisms linking NSAIDs and reduced HCC risk might be manifold. First, the pathogenesis of HCC is strongly related to sustained inflammation. As the

last and the most redoubtable clinical consequence of liver cirrhosis, HCC is developed mainly based on a myriad of pro-inflammatory stimuli and is triggered by well-recognized noxae such as hepatotropic viruses infection, obesity, and alcohol consumption.⁴⁶ Several signaling pathways have been identified to be associated with the inflammation process of HCC, including NF- κ B, JAK-STAT, and MAPK pathways, etc. Second, COX-2 demonstrates high expression in HCC and can promote tumor initiation, differentiation, invasion, and metastasis.^{16,47,48} A meta-analysis with 11 publications further indicates that high expression of COX-2 is associated with decreased survival and worse prognosis in HCC.⁴⁹ In addition, it is suggested that COX-1 plays a similar role, and COX-1 inhibitors may show potential therapeutic implications in HCC.⁵⁰ Third, there is increasing evidence that platelets promote tumor growth, angiogenesis, and metastasis.⁵¹ Meanwhile, tumor patients are often accompanied by thrombocytosis and functional abnormality of platelets. Thus, the protective role of NSAIDs in HCC may be also related to the antiplatelet function.

Though widely recognized as anti-inflammatory and antitumor agents, NSAIDs still are offset by their complications of major gastrointestinal bleeding and intracranial bleeding even with low-dose usage.^{52,53} Moreover, bleeding risk in HCC patients treated with NSAIDs is also higher than in those not treated with NSAIDs.²⁹ Therefore, the clinical benefit of NSAIDs in an actual clinical setting may be not satisfactory. Although NSAIDs may cause gastrointestinal bleeding and ulcer perforation, several quantitative reviews report that NSAIDs use, long-term (≥ 4 years) and (or) low frequency (1–4.5 times per week) in particular, reduced the risk of gastric cancer (around 26%–33%).^{54–56}

Our analysis embraces several limitations and shortcomings. First, there was substantial heterogeneity in our meta-analysis. In fact, owing to many potential confounders such as population characteristics, year of publication, follow-up time, and so forth, between-study heterogeneity was inevitable in any meta-analysis. By meta-regression analysis, we identified the potential source of heterogeneity: information source and study design. NSAIDs showed better antitumor effects in the subgroup of information source from questionnaire and in the subgroup of cohort study, both of which provide better evidence compared with matched subgroups. To reduce potential confounders and obtain more robust evidence, a generalized worldwide guideline for conducting observational studies of NSAIDs in HCC is needed. Second, the association of NSAIDs and aspirin with HCC risk may be related to the dose, duration,

and frequency of these medicines. However, few included studies reported the effects of different dose or duration of NSAIDs in HCC risk. Further study should focus on the dose–response relationship between NSAIDs and the risk of HCC. Third, when a fixed-effects model was used, aspirin significantly reduced the risk of HCC, unlike the result obtained from the random-effects model. This may be due to the high heterogeneity among the included studies. The significance of aspirin in HCC risk should be further verified through larger, multicentric prospective studies or randomized clinical trials.

In conclusion, our meta-analysis showed that use of NSAIDs significantly reduced the incident and recurrent risk of HCC, but had no effect on HCC mortality. Our results provide significant clinical value in HCC prevention.

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Disclosure

The authors report no conflicts of interest in this work.

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Supplementary materials

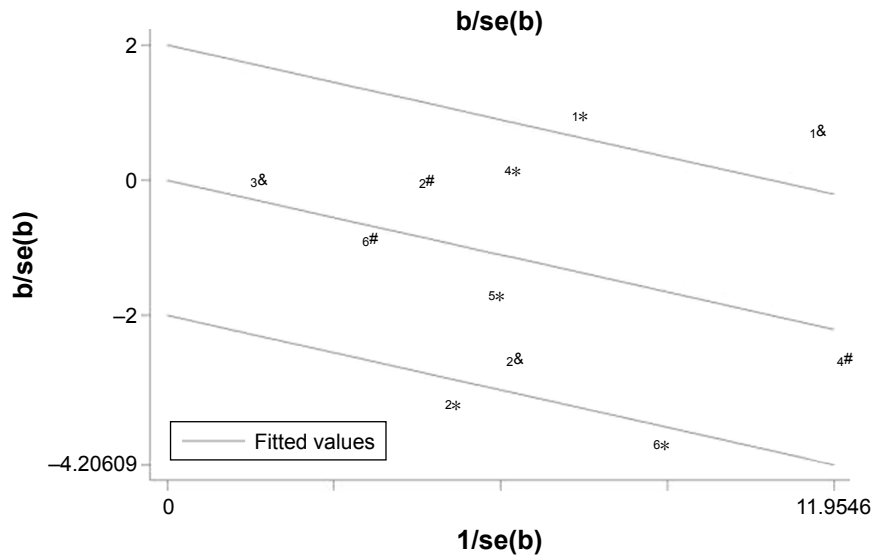


Figure S1 Galbraith's plot of studies that assessed the preventive effect of NSAIDs use in risk of HCC incidence.
Notes: *Aspirin; #non-aspirin NSAIDs; &all NSAIDs.
Abbreviations: HCC, hepatocellular carcinoma; NSAIDs, nonsteroidal anti-inflammatory drugs.

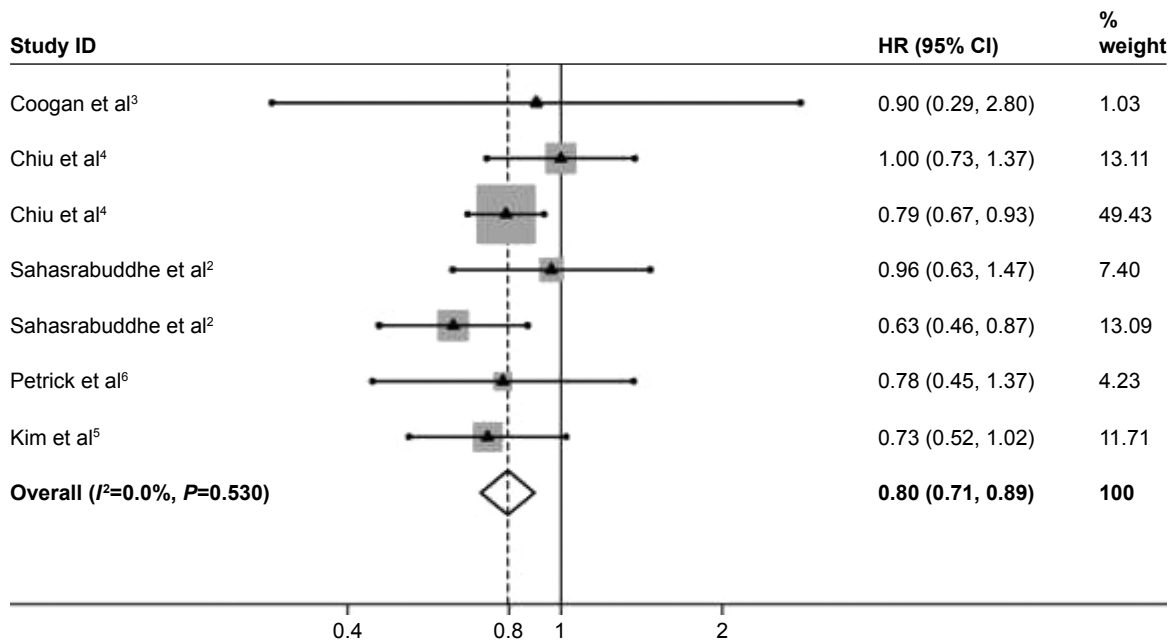


Figure S2 Forest plots of the meta-analysis on the association between NSAIDs and risk of HCC incidence after removal of the outliers of the heterogeneity.
Note: Weights are from random-effects analysis.
Abbreviations: HCC, hepatocellular carcinoma; NSAIDs, nonsteroidal anti-inflammatory drugs; HR, hazard ratio; CI, confidence interval.

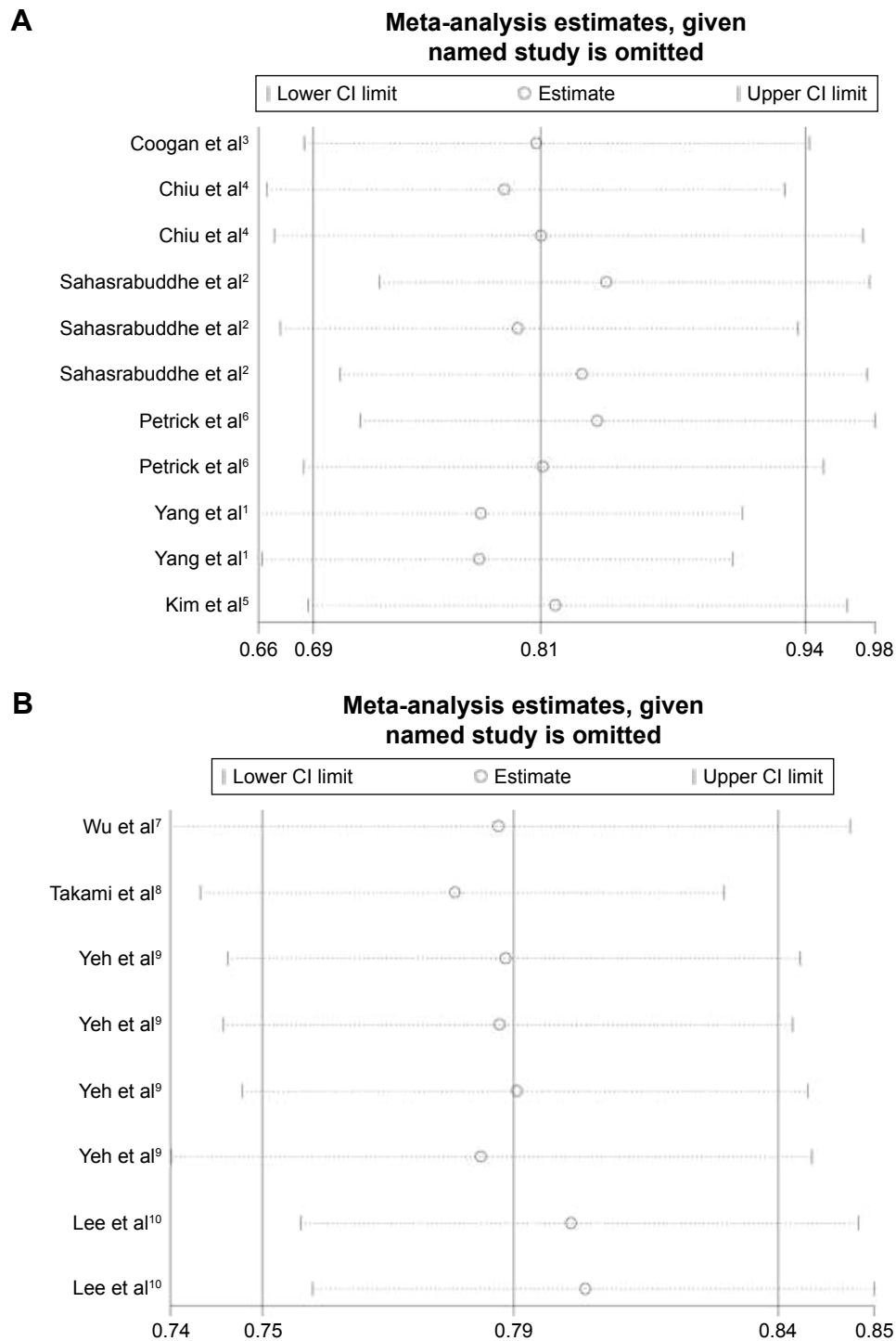


Figure S3 Influence analysis of studies that assessed the effects of NSAIDs use in the risk of HCC incidence (**A**) and recurrence (**B**). **Abbreviations:** HCC, hepatocellular carcinoma; NSAIDs, nonsteroidal anti-inflammatory drugs; CI, confidence interval.

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