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Non-steroidal anti-inflammatory drugs and risk of mortality in lung cancer
A meta-analysis of 5 prospective cohorts studies

Yifei Chen, Lili Kang, MD, Ying Zhu, MD, Chuanhong Jing, BS*, Yifei Chen, MD, Lili Kang, MD, Ying Zhu, MD

Abstract

Background: Non-steroidal anti-inflammatory drugs (NSAIDs) especially aspirin has been gained increasing attention due to its potential therapy against to lung cancer. Previous investigations have showed different findings in this issue. We studied the safety profile and efficacy of NSAIDs in treating lung cancer.

Method: Embase, Pubmed, and Cochrane Library databases were searched from January 2011 to February 2019. We identified the studies meeting a priori inclusion criteria and it also conducted a secondary review. This meta-analysis of 5 prospective studies was launched to evaluate the effect of NSAIDs for patients with lung cancer on the hazard risk (HR). We used the Random-Effect Model to assess pooled HR and between-study heterogeneity. Application of subgroup analysis, meta-regression, as well as sensitivity analysis was to pinpoint the exact sources of the observed heterogeneity.

Results: 5 Prospective Cohorts Studies, including 6017 patients with lung cancer were recruited in the final meta-analysis. In general, using of NSAIDs especially aspirin is not associated with mortality of lung cancer: pooled hazard ratio (HR) of 0.88 [95% confidence intervals (CI): 0.73–1.05] with low heterogeneity (Q = 6.95; I^2 = 42.4%, P = .139). Egger (P = .665) and Begg (P = 1.000) test also showed little trial error in this meta-analysis.

Conclusion: NSAIDs did not increase the risk of mortality in patients with lung cancer.

Abbreviations: BMI = body mass index, CI = confidence intervals, COX = cyclooxygenase, HR = hazard ratio, MOOSE = Meta-analysis of Observational Studies in Epidemiology, NSAIDs = non-steroidal anti-inflammatory drugs, NSCLC = non-small-cell lung cancer, OR = odds ratio, PCS = prospective cohort study, RR = relative risk.

Keywords: lung Cancer, meta-analysis, nonsteroidal anti-inflammatory drugs

1. Introduction

Lung cancer especially non-small cell lung cancer (NSCLC), which accounts for more than 80% of Lung Neoplasms, is a dominant cause of death in the whole world. The average survival time of patients with advanced lung cancer is 6 to 10 months in performance status 0 to 2 following first-line chemotherapy.[1–3] Over the past few years, nonsteroidal anti-inflammatory drugs, including aspirin, have been regarded as potential chemopreventive agents due to the pathogenesis of inhibiting cyclooxygenase (COX) enzymes, which

may be associated with carcinogenesis.[4] Previous studies showed that NSAIDs, especially aspirin use is related to decreased risk of colorectal carcinomas[5,6] and breast cancer (pooled relative risk (RR): 0.91 95% confidence interval [CI]: 0.83–0.98).[7] In addition, aspirin shows protective effect in gastric and esophageal cancer.[7,8] Searching and collecting the data about patients using daily aspirin versus no aspirin from 8 randomized trials, Rothwell et al launched an analysis, which showed aspirin can reduce risk of deaths from cancer by 20% around.[9] Such a reduction in the death of cancer would be an extremely important achievement.

Previous meta-analysis focus on the association between NSAIDs and the incidence of lung cancer especially NSCLC. An investigation conducted by Oh et al showed that there was no association between aspirin use and lung cancer risk with the pooled odds ratio (OR) 0.86 (95% confidence interval (CI) 0.76–0.98).[10] Xu et al also, performed a meta-analysis which showed aspirin use with a dose of 7 tablets per week can significantly reduce lung cancer risk (pooled OR 0.80, 95%CI: 0.67–0.95), whereas non-aspirin NSAIDs showed no chemopreventive value.[11] Meta-analysis by Jiang et al reported that aspirin do not display protective effect of regular aspirin use on lung cancer risk.[7] However, few investigations concentrated on the clinical profile of NSAIDs using and risk of death in patients with lung cancer. A meta-analysis published in 2016 showed that COX-2 inhibitors increased ORR of advanced NSCLC and had no impact on survival indices.[12] Relationship between other NSAIDs especially aspirin using and risk of death in patients with lung cancer remains unclear.

In this light, we performed a systematic review and meta-analysis to summarize the results of available studies, to synthesize the current evidence for between NSAIDs using and risk of death in patients with lung cancer, and to explore potential bias underlying the contrasting results. And we also hope our work could give support to clinical medicine.

2. Method

The study was performed in accordance with institutional guidelines and was approved by the Committees for the Ethical Review of Research at the Yangzhou University affiliated Jiangdu People's Hospital of Yangzhou City.

2.1. Search strategy

Followed by rules of Meta-analysis of Observational Studies in Epidemiology (MOOSE),[13] we conducted a systematic search in Embase, Pubmed and Cochrane Library databases from January 2011 to February 2019. We aimed to find out the association between NSAIDs using and risk of death in patients with lung cancer. Search strategy is based on subject title, abstract and key words. The Pubmed search syntax is as follow: (("2011/01/01"[Date - Publication]: "3000"[Date - Publication])) AND ((((risk[Title/Abstract] OR risk[MeSH:noexp] OR mortality[Title/Abstract] OR mortality[MeSH:noexp] OR cohort[Title/Abstract]))) AND ((((((((((((((((((((((Acetylsalicylic Acid[Title/Abstract]) OR Acid, Acetylsalicylic[Title/Abstract]) OR 2-(Acetyloxy)benzoic Acid[Title/Abstract]) OR Acylpyrin[Title/Abstract]) OR Aloxiprimum[Title/Abstract]) OR Colfarit[Title/Abstract]) OR Dispril[Title/Abstract]) OR Easprin[Title/Abstract]) OR Ecotrin[Title/Abstract]) OR Endosprin[Title/Abstract]) OR Magnecyl[Title/Abstract]) OR Micristin[Title/Abstract]) OR Polopirin[Title/Abstract]) OR Polopiryna[Title/Abstract]) OR Solprin[Title/Abstract]) OR Solupsan[Title/Abstract]) OR Zorprin[Title/Abstract]) OR Acetysal[Title/Abstract])) OR "Aspirin"[14]) OR (((((((((((((((((((((Anti Inflammatory Agents, Non Steroidal[Title/Abstract]) OR Anti-inflammatory Agents, Non Steroidal[Title/Abstract]) OR Anti-inflammatory Agents, Nonsteroidal[Title/Abstract]) OR Agents, Nonsteroidal Antiinflammatory[Title/Abstract]) OR Nonsteroidal Antiinflammatory Agents[Title/Abstract]) OR Nonsteroidal Anti-Inflammatory Agents[Title/Abstract]) OR Agents, Nonsteroidal Anti-Inflammatory[Title/Abstract]) OR Anti-Inflammatory Agents, Nonsteroidal[Title/Abstract]) OR Nonsteroidal Anti Inflammatory Agents[Title/Abstract]) OR NSAIDs[Title/Abstract]) OR Anti Inflammatory Agents, Nonsteroidal[Title/Abstract]) OR Non-Steroidal Anti-Inflammatory Agents[Title/Abstract]) OR Aspirin-Like Agents[Title/Abstract]) OR Agents, Aspirin-Like[Title/Abstract]) OR Aspirin Like Agents[Title/Abstract]) OR Analgesics, Anti-Inflammatory[Title/Abstract]) OR Analgesics, Anti Inflammatory[Title/Abstract]) OR Anti-Inflammatory Analgesics[Title/Abstract]) OR Anti-Rheumatic Agents, Non-Steroidal[Title/Abstract]) OR Agents, Non-Steroidal Anti-Rheumatic[Title/Abstract]) OR Anti Rheumatic Agents, Non Steroidal[Title/Abstract]) OR Non-Steroidal Anti-Rheumatic Agents[Title/Abstract]) OR Antirheumatic Agents, Non-Steroidal[Title/Abstract]) OR Agents, Non-Steroidal Antirheumatic[Title/Abstract]) OR Antirheumatic Agents, Non Steroidal[Title/Abstract]) OR Non-Steroidal Antirheumatic Agents[Title/Abstract])) OR "Anti-Inflammatory Agents, Non-Steroidal"[14]))) AND (((((((((((((((("Lung Neoplasms"[14]) OR Pulmonary Neoplasms[Title/Abstract]) OR Neoplasms, Lung[Title/Abstract]) OR Lung Neoplasm[Title/Abstract]) OR Neoplasm, Lung[Title/Abstract]) OR Neoplasms, Pulmonary[Title/Abstract]) OR Neoplasm, Pulmonary[Title/Abstract]) OR Pulmonary Neoplasm[Title/Abstract]) OR Lung Cancer[Title/Abstract]) OR Cancer, Lung[Title/Abstract]) OR Cancers, Lung[Title/Abstract]) OR Lung Cancers[Title/Abstract]) OR Pulmonary Cancer[Title/Abstract]) OR Cancer, Pulmonary[Title/Abstract]) OR Cancers, Pulmonary[Title/Abstract]) OR Pulmonary Cancers[Title/Abstract]) OR Cancer of the Lung[Title/Abstract]) OR Cancer of Lung[Title/Abstract])) OR ((((((((((("Carcinoma, Non-Small-Cell Lung "[14]) OR Carcinoma, Non Small Cell Lung[Title/Abstract]) OR Carcinomas, Non-Small-Cell Lung[Title/Abstract]) OR Lung Carcinoma, Non-Small-Cell[Title/Abstract]) OR Lung Carcinomas, Non-Small-Cell[Title/Abstract]) OR Non-Small-Cell Lung Carcinomas[Title/Abstract]) OR Nonsmall Cell Lung Cancer[Title/Abstract]) OR Non-Small-Cell Lung Carcinoma[Title/Abstract]) OR Non Small Cell Lung Carcinoma[Title/Abstract]) OR Carcinoma, Non Small Cell Lung[Title/Abstract]) OR Non-Small Cell Lung Cancer[Title/Abstract]))))). We did not set any restrictions and then conducted a secondary reference review after the search.

2.2. Selection criteria

Two principle investigators reviewed titles, abstracts, and full-texts, respectively. And we ensure all the studies included matched the following criteria:

1. a prospective study,
2. NSAIDs was used in recruited participants,
3. the endpoint is death,
4. the association between NSAIDs using and risk of death in patients with lung cancer by HR with corresponding confidence intervals (CI) or with enough data to calculate the HR and CI.

2.3. Data extraction

We extracted the following data from all selected studies: first author, country of origin, year of publication, sample size, research design, gender, age range, follow-up period, disease outcome, adjustment variables, HR of death with corresponding 95% CI. Two principle investigators calculated the data with a standard extraction rule respectively. All of discrepancies were compared with the related references and discussed by our research team.

2.4. Quality evaluation

We used a well-known standard for evaluation of methodological conducted by Downs and Black score.[13] Other investigators verified the assessment accuracy done by them.

2.5. Statistical analysis

The relationship in these studies were measured with HR and all the results were reported by HR. In this analysis, we used death as referent group and the final confounder set for all of studies. The estimations about pooled of risk was calculated with random-effect model due to heterogeneity. The I^2 statistics and the

Cochrane Q statistics in which significance level is $P < .10$ were used to estimate the heterogeneity of HR among studies. Because the characteristics in research design, adjustment of confounding and populations were not consistent among studies, we then conducted sensitivity analysis and to find out the proper explanation for heterogeneity. Finally, we conducted cumulative meta-analysis to figure out the strong evidence over time.

In sensitivity analysis, we investigated effect of every single study on risk factors by delete 1 study in turn. Trial error was evaluated by Egger test and Begg test. We also conducted the Egger funnel plots and Begg funnel plot in visual inspection and plotted log HRs against their SEs.[15]

We explored potential sources of heterogeneity via subgroup analysis by study population, sample type, country of origin, follow-up duration, and year of publication. A meta-regression model fitted with co-variables including study population, sample type, country of origin, follow-up duration, and year of publication was analyzed to explore potential sources of heterogeneity. To assess the influence of new studies on overall effects, we performed cumulative meta-analysis according to the year of publication for individual studies.

Analysis above were performed by STATA version 14.1 for mac (Stata Corp LP, College Station, TX). We defined value of $P < .05$ as statistically significant.

3. Results

3.1. Literature search

We first retrieved 351 abstracts from Embase, Pubmed, and Cochrane databases (301 from Embase and 71 from Pubmed while 21 duplicates were removed). Most of these papers were excluded after reviewing title and abstracts due to not matching research criteria. There are 3 investigations not providing the data of hazard risk.[16–18] And 2 studies do not give 95% CI.[19,20] After full-text reviewing, we include 5 articles for meta-analysis.[8,21–24] We also presented a flow chart to show our selection (Fig. 1).
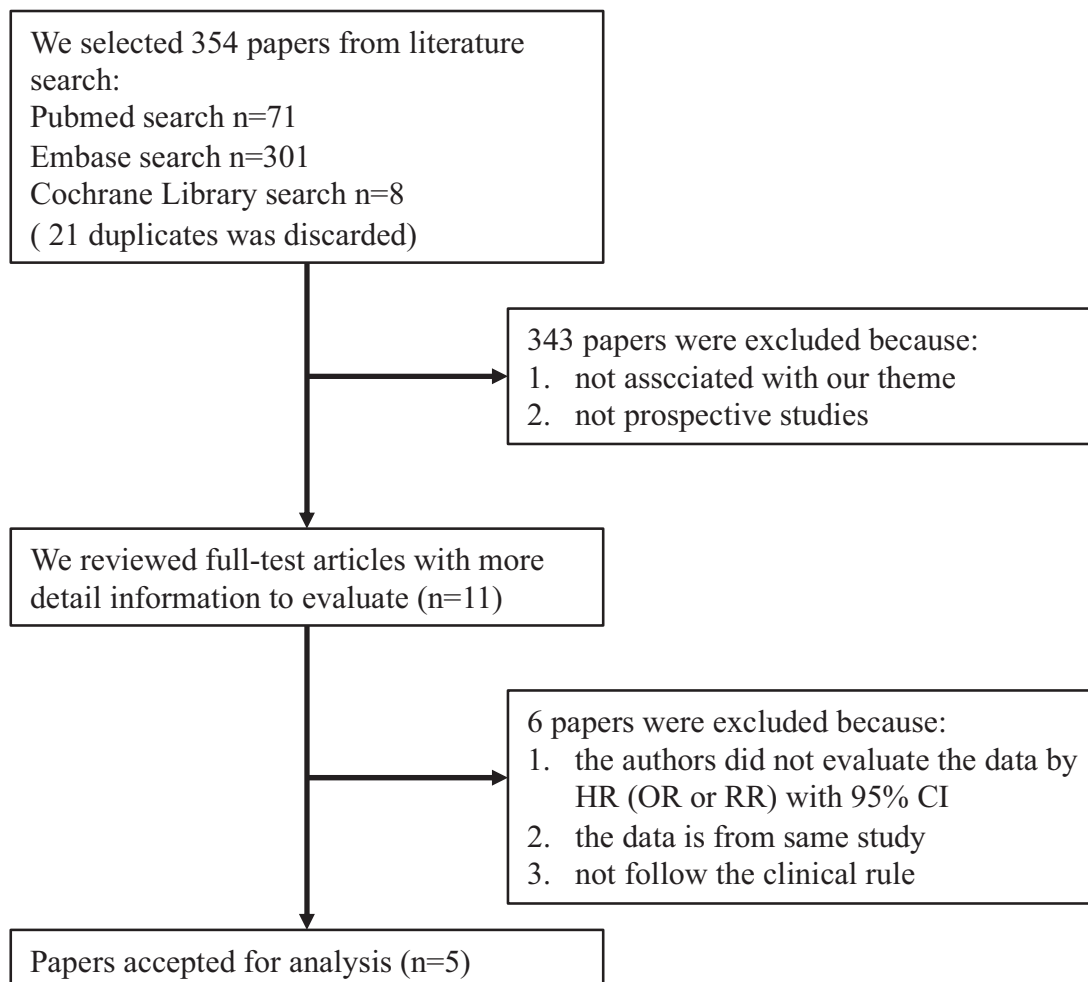
We selected 354 papers from literature search:
Pubmed search n=71
Embase search n=301
Cochrane Library search n=8
(21 duplicates was discarded)

343 papers were excluded because:
1. not asscciated with our theme
2. not prospective studies

We reviewed full-test articles with more detail information to evaluate (n=11)

6 papers were excluded because:
1. the authors did not evaluate the data by HR (OR or RR) with 95% CI
2. the data is from same study
3. not follow the clinical rule

Papers accepted for analysis (n=5)

Figure 1. Flow chart of study selection.

Table 1

Characteristics of 5 prospective studies of NSAIDs using and risk of death in patients with lung cancer.

Authors	Year	Country	Population	Follow-up Years	Subjects	Age	Kinds of NSAIDs	Outcome	Design	Quality
Veitonmaki, T.	2016	United States	Lung Cancer	10	113	59.0 (55–67)	NSAIDs	Death	PCS	13
Lee, B. M.	2016	United States	NSCLC	5	1637	64.7 (65–89)	NSAIDs	Death	PCS	14
Mc Menamin, U. C.	2015	England	Lung Cancer	5	3635	N/A	aspirin	Death	PCS	15
Gulyás, M.	2015	Sweden	NSCLC	5	316	N/A	celecoxib	Death	PCS	14
Sörenson, S.	2013	Sweden	NSCLC	5	316	N/A	celecoxib	Death	PCS	13

NSCLC=non-small cell lung cancer, PCS=Prospective cohort study.

3.2. Study characteristics

The 5 prospective studies were published from January 2011 to February 2019, and the basic characteristics were showed (Table 1). Among all of studies, 2 were conducted in United States,[21,25] others were launched in England[22] and Sweden,[23,24] respectively. Follow-up years of these studies range from 5 to 10 years. The population of 3 studies were NSCLC patients[21,23,24] and other 2 investigations were conducted in patients with all kinds of lung cancer.[22,25] The size of study cohorts varied from 113 to 3635 participants (total 7115). The endpoint of all of participants was death. Per Downs and Black score assessment, mean quality scores for 5 cohort studies was 13.8 (range from 11 to 15).

3.3. NSAIDs using and risk of death in patients with lung cancer

We presented adjusted HRs as follow (Table 2). Among 5 selected studies, 1 study conducted by Veitonmaki et al showed that NSAIDs increase the mortality for lung cancer,[25] while other investigations showed no impact[21–24] or reduce the mortality for lung cancer.[26] The HR for the relationship ranging from 0.64 to 1.61 among all 6 studies.

Among the meta-analysis of all studies included, NSAIDs using in patients with lung cancer was not related to increased risk of mortality: pooled HR was 0.88 (95% CI: 0.73–1.05) with low heterogeneity (Q=6.95; P=.139; I^2=42.4%). The forest plots were as follow (Fig. 2).

Next, we divided included studies by country of origin, study population and time of publication to probe the potential sources of heterogeneity in the aspirin taking on mortality. In NSCLC patient subgroup, aspirin taking was associated with a 22% (HR=0.78, 95% CI: 0.64–0.94, I^2=0%) decrease of over-all mortality, while no significant association between NSAIDs using and risk of death was demonstrated in patients with all kinds of lung cancer (HR=1.05, 95% CI: 0.71–1.56, I^2=33.2%) (Fig. 3). Furthermore, pooled HR from studies performed in the US

(HR=1.01, 95% CI: 0.52–1.96, I^2=62.5%) was not statistically significant while studies conducted in other countries showed a 13% lower risk of death in patients who take NSAIDs (HR=0.87, 95% CI: 0.68–1.11, I^2=45.7%). As all included studies in this meta-analysis have been published within 5 years, we checked whether the year of publication affected the pooled HR by cumulative analysis (Fig. 4). The results showed that the NSAIDs effect remained stable after the addition of more recent studies. This finding was further supported by our meta-regression for publication year (P=.490). Fitting other variates, including country of origin, follow-up years, sample types, and population into the meta-regression model did not indicate additional sources of heterogeneity (Table 3).

Considering the low study numbers in each subgroup, we carried out a sensitivity analysis to search for studies with the most prominent difference compared to the others (Fig. 5). Exclude 1 study just recruiting men for analysis (23), pooled HR was 0.86 (95% CI: 0.72–1.02) with low heterogeneity (Q=5.05; P=.169; I^2=40.5%). Further exclusion of any single study did not change the pooled HR.

The funnel plot showed obvious asymmetry, indicating the presence of small trial error (Fig. 6). Application of trim-and-fill model suggested that trial error is low. Nonetheless, statistics using the Egger (P=.665) and Begg (P=1.000) regression tests did not show significant bias in publication (Fig. 7a and b).

4. Discussion

In this meta-analysis of 5 prospective cohorts with totally 6017 participants, we showed that NSAIDs using are not associated with overall mortality in patients with lung cancer. Those who takes NSAIDs were at 12% lower risk to die. This is a new finding compare to existing clinical practice.

There is an agreement that platelets play an important role in the progression of cancer.[27,28] Aspirin, a commonly prescribed anti-platelet agent, after cancer diagnosis has been associated with a reduction in the risk of cancer-specific mortality or

Table 2

Overview of multivariable relationships of NSAIDs using and risk of death in patients with lung cancer.

| Authors	Year	Adjusted HR (95% CI)	Adjusted covariate
Veitonmaki, T.	2016	1.61 (0.71–3.65)	age, randomization group, use of cholesterol-lowering medication, antihypertensive medication, antidiabetic medication
Lee, B. M.	2016	0.79 (0.62–1.01)	age, gender, BMI, Type of surgery (thoracoscopy vs thoracotomy)
Mc Menamin, U. C.	2015	0.96 (0.85–1.09)	cancer treatments and comorbid-ities did not materially alter risk estimates
Gulyás, M.	2015	0.96 (0.60–1.54)	none
Sörenson, S.	2013	0.64 (0.43–0.95)	none

BMI=body mass index, HR=hazard risk.
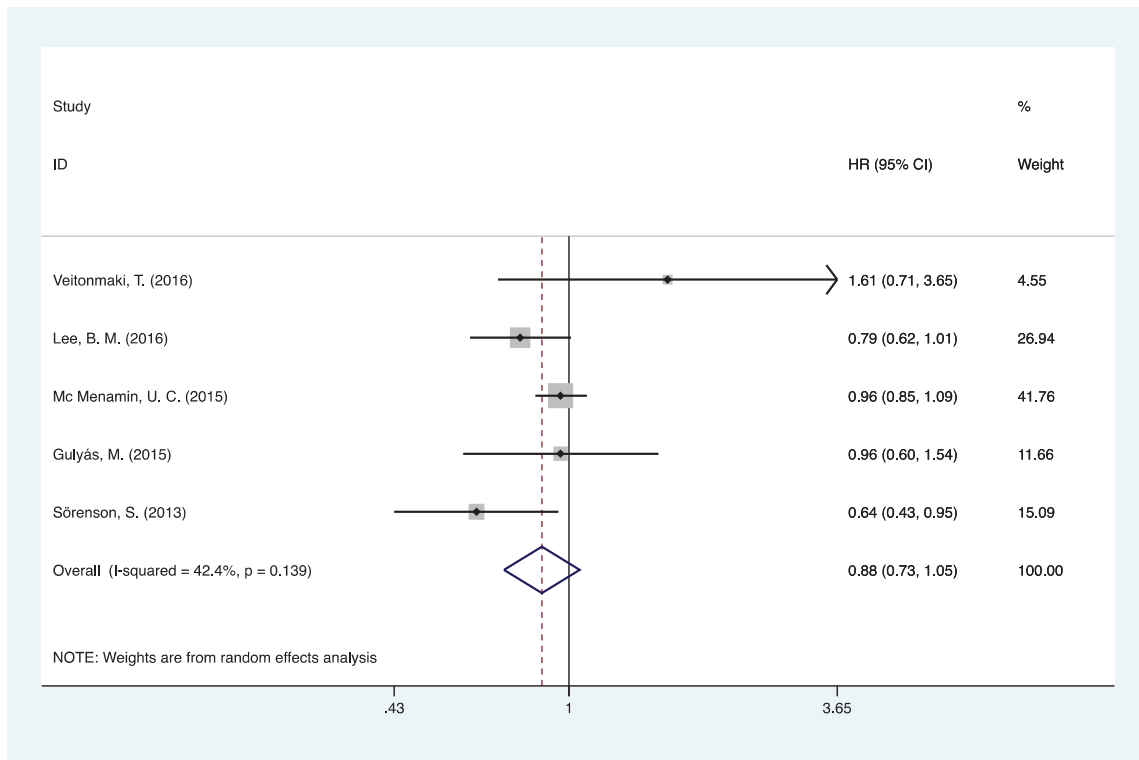
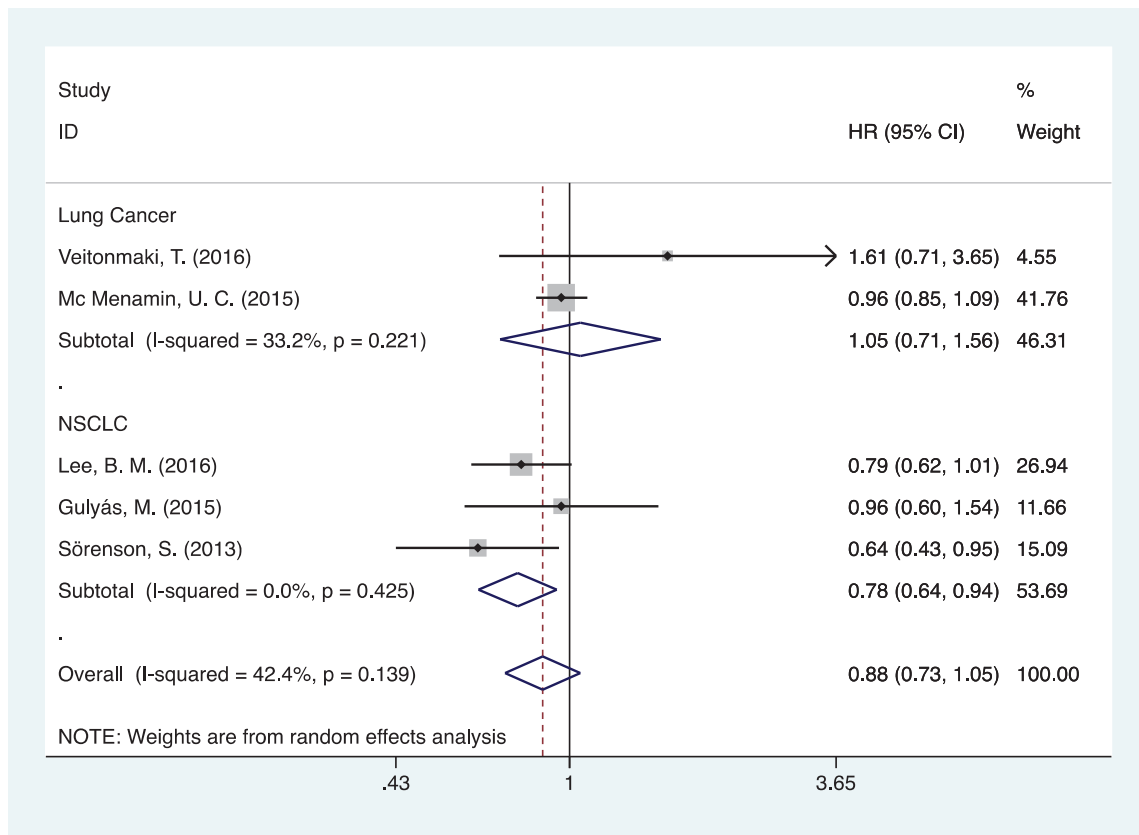**Figure 2.** Forest plot (random-effects model) of NSAIDs using and risk of death in patients of lung cancer.

Figure 3. Forest plot (random-effects model) of NSAIDs using and risk of death in different population.
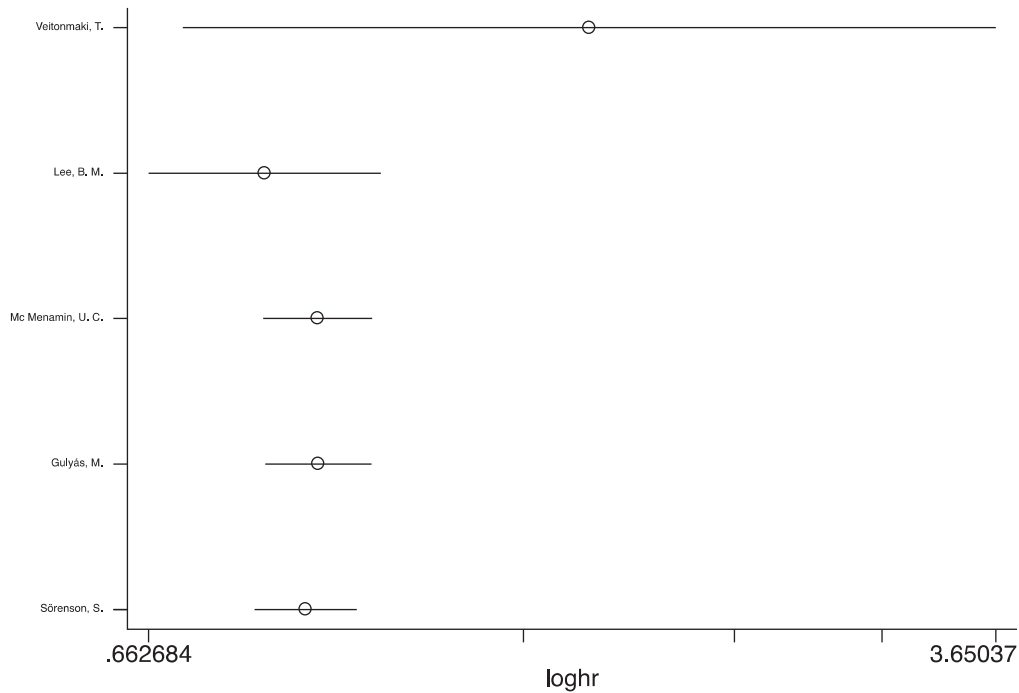
Figure 4. Cumulative analysis of NSAIDs using and risk of death in patients with lung cancer.

recurrence in colorectal,[29,30] breast[31,32] and prostate cancer[33] cohorts. However, few investigations have studied the influence of NASIDs on the progression of lung cancer. And several investigations about NASIDs and lung cancer mortality showed different results. A investigation conducted by Veitonmaki et al showed that lung cancer mortality was increased for NSAID users (HR = 1.61, 95%CI: 0.71–3.65).[8] Other 3 investigations showed no association between NASIDs and lung cancer mortality.[21–23] Sörenson et al reported that NSAIDs could decrease the mortality in patients with NSCLC (HR = 0.64, 95% CI: 0.43–0.95, P = .028).

Regarding these conflicting results concerning the NASIDs using in patients with lung cancer, a comprehensive summarization of current evidence is warranted. To the best of our knowledge, no systematic review or meta-analysis exploring the association between NASIDs using and lung cancer mortality has been published so far. In this light, we pooled the NASIDs effects on clinical outcomes from all available studies, and found NASIDs using is not associated with lung cancer mortality as well as no trace of trial error was indicated. Also, the result of pooled

HR appears robust given the absence of significant heterogeneity. The vast disagreement among studies may attribute to various aspects especially patient population (All kinds of lung cancer and NSCLC). Spectacularly, only studies conducted in USA exhibited a significant heterogeneity. In spite, studies published after the year 2015 did suggest a positive correlation between NASIDs using and lung cancer mortality. This finding is constant with our cumulative analysis that showed a progressive increasing in the pooled HR with the addition of more recent studies. This discrepancy may be resulted from different followed-up durations. However, this notion was not supported by our meta-regression for publication time. In addition, Yi[12] and Zhao[34] also launched meta-analysis about the relationship between NASIDs and lung cancer. They found that NASIDs have a good effect on patients with lung cancer. Anti inflammation and tumor drug development has seen some great advances in recent years, several investigations shows that anti inflammation therapy and new tumor drug could control the tumor.[35–37]

For controversy of some investigations, we make explanations as well. Intricate confounding possibly by population, clinical

Table 3

Stratified analyses of pooled hazard risks of NASIDs using and lung cancer mortality.

Stratified analysis	Pooled HR (95% CI)	Heterogenety	Meta regression (*P* value)
Country			.490
USA	1.01 (0.52–1.96)	Q = 2.67, P = .102, I^2 = 62.5%	
Non-USA	0.87 (0.68–1.11)	Q = 3.68, P = .159, I^2 = 45.7%	
Public year			.490
Before 2015	0.87 (0.68–1.11)	Q = 3.68, P = .159, I^2 = 45.7%	
After 2015	1.01 (0.52–1.96)	Q = 2.67, P = .102, I^2 = 62.5%	
Population			.125
Lung cancer	1.05 (0.71–1.56)	Q = 1.50, P = .221, I^2 = 33.2%	
NSCLC	0.78 (0.64–0.94)	Q = 1.71, P = .425 I^2 = 0%	

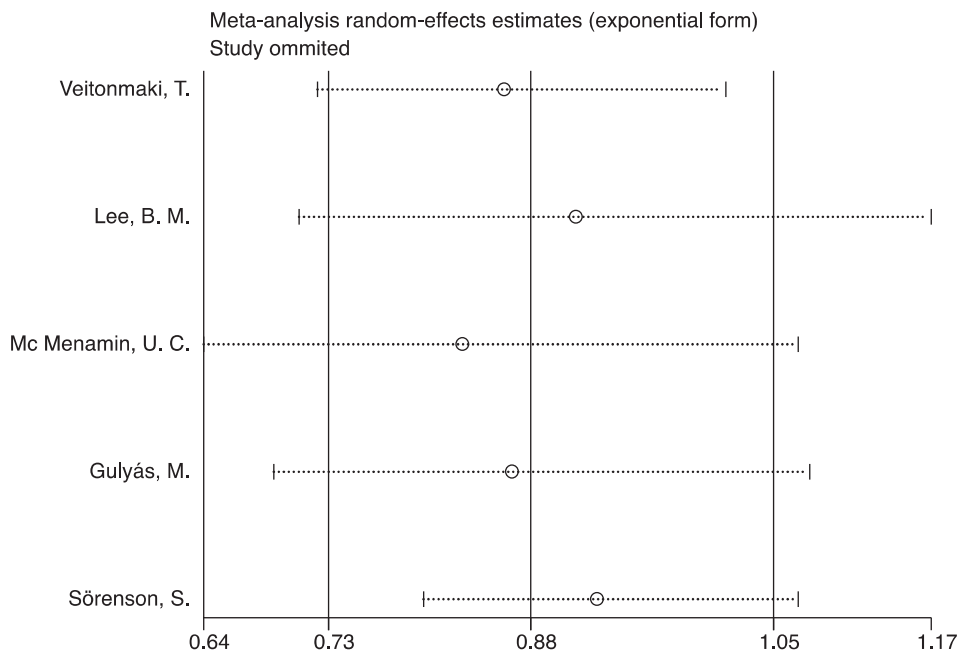Meta-analysis random-effects estimates (exponential form)
Study ommited

Figure 5. Sensitivity analysis of NSAIDs using and risk of death in patients with lung cancer.

features and traditional risk factors, may lead to spurious relationships between NSAIDs using and risk of death in patients with lung cancer in some studies. For example, study conducted by Veitonmaki et al just recruit men into their analysis,[25] this may contribute to the bias of the study.

To further elucidate the potential sources of heterogeneity, we carried out a sensitivity analysis, which indicated that omission of any individual studies did not significantly change the pooled effect, suggesting the consistency of our results. Taken these together with the limited subgroup study numbers, as well as the
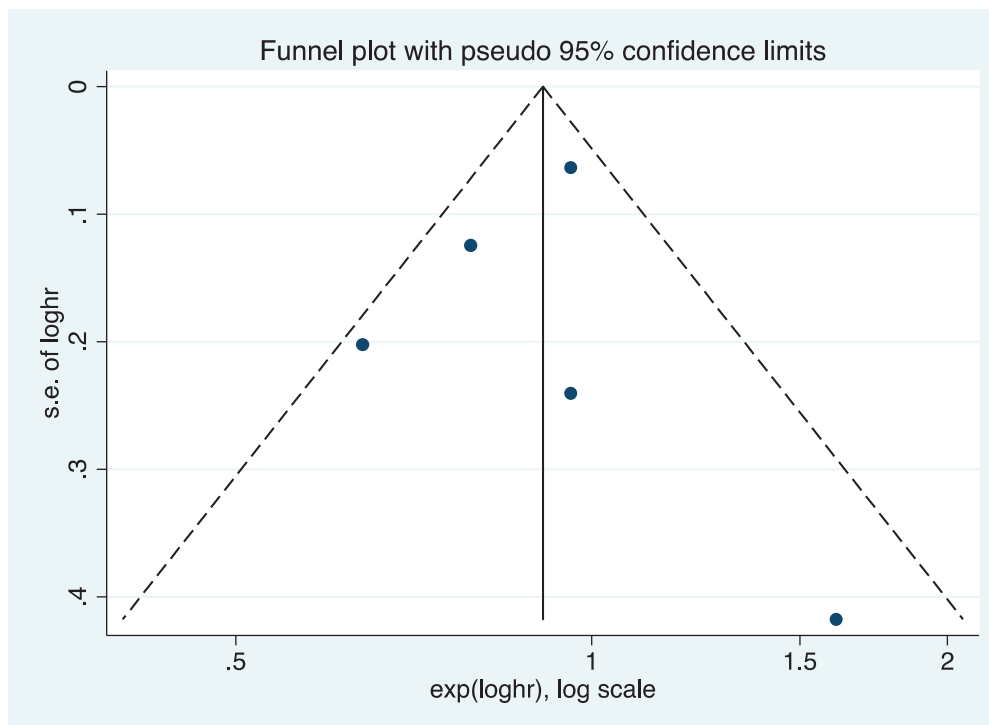
Funnel plot with pseudo 95% confidence limits

Figure 6. Funnel plot of NSAIDs using and risk of death in patients with lung cancer.
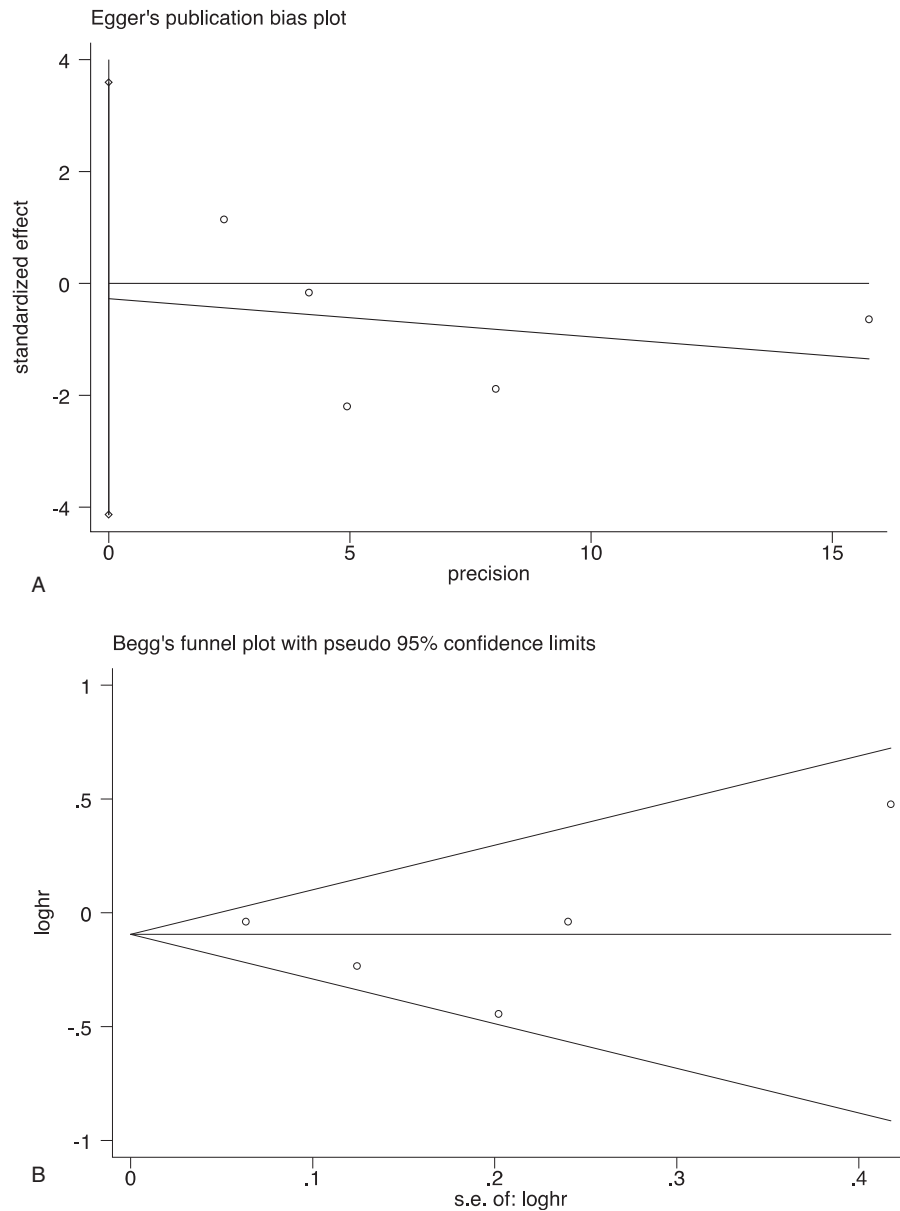
Figure 7. (a) Egger trial error plot (*P* = .665), (b) Begg funnel plot with pseudo 95% confidence limits (*P* = 1.000).

results from trim-and-fill model, more cohort are requested to elucidate of the exact causes of heterogeneity and add more power to our current findings.

Further studies to be performed to find out whether NSAIDs could influence the mortality of lung cancer, and if so, the further mechanisms should be investigated in the future.

4.1. Strength and limitations

Our study demonstrated NSAIDs using have little impact on risk of death in patients with lung cancer. To our knowledge, this is the first meta-analysis that shows a negative correlation between NSAIDs using and risk of death in patients with lung cancer. In this study, we included only prospective cohorts and followed the PRISMA and MOOSE guidelines. Absence of trial error also adds

power to our results. Potential sources of heterogeneity were explored using different methods.

On the other hand, limitation of this meta-analysis is that some studies did not provide HR with 95% CI although some important result was found[16–20] and those studies were not included in our meta-analysis. Firstly, all issues above may result in an underestimation of the relationship between NSAIDs using and risk of death in patients with lung cancer. Secondly, studies we included were not equally designed, so there is heterogeneity in our meta-analysis. Thirdly, the evidence about the association between NSAIDs using and risk of death in patients with lung cancer may be weak, for there were just 5 studies, so further research is still needed. In addition, all studies included were observational studies. It means this can be with unmeasured founding and also difficult to prove causal relationship.

5. Conclusion

In conclusion, the meta-analysis conducted by us displayed NSAIDs using have little impact on survival of patients with lung cancer from several prospective studies.

Author contributions

Data curation: Yifei Chen, Chuanhong Jing.
Formal analysis: Lili Kang.
Resources: Ying Zhu.
Writing – original draft: Yifei Chen, Chuanhong Jing.

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