

Aspirin use is not associated with the risk or prognosis of bladder cancer: a case-control study and meta-analytic assessment

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Research

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Abstract

Background

Aspirin, widely used for the prevention of cardiovascular disease, could reduce the risk of many types of cancer, including colorectal, breast, and pancreatic cancer. Concerns have also been linked to bladder cancer (BCa), but relevant studies on the effects of aspirin on the occurrence or prognosis of BCa are inconsistent or even controversial. Meanwhile, existing studies focusing on Chinese populations are relatively uncommon, especially for Northeast China. Therefore, this study aims to assess the association of aspirin use with the occurrence and prognosis of BCa in Northeast China.

Methods

First, we investigated the association between aspirin use and BCa risk in a retrospective cohort study including 1087 patients with BCa from 2002 to 2019 and 1100 healthy persons in the same period as controls. Subsequently, we quantitatively combined the results with those from the published literature evaluating aspirin intake and its effects on the occurrence and prognosis of BCa by meta-analysis after searching the PubMed, Embase, Cochrane Library, and Google Scholar databases up to March 1, 2020.

Results

The results of our case-control study demonstrated that the regular use of aspirin was not associated with a reduced incidence of BCa (OR = 1.17, $p = 0.311$). Stratified analyses of sex showed that aspirin intake did not lead to a lower risk of BCa in male patients (OR = 1.25, $p = 0.230$) or in female patients (OR = 0.90, $p = 0.744$). Significant correlations were not found in the age subgroup analysis dividing age into younger or greater than 65, with a pooled OR estimate of 1.25 ($p = 0.230$) and 0.899 ($p = 0.744$). In 230 patients who relapsed from the 1087 BCa patients above, no significant relationship was found in the aspirin group (RR = 1.19, $p = 0.360$), and the sex stratification resulted in the same conclusion; however, in people younger than 68, aspirin seemed to have protective effects (RR = 0.60, $p = 0.030$). In addition, we performed a meta-analysis after searching several databases, and 10 articles involving 12441 BCa cases met the eligibility criteria, contributing to the analysis of aspirin intake and the incidence of BCa. The combined results indicated that aspirin intake was not associated with the occurrence of BCa (OR = 1.03, $p = 0.221$). In the subgroup analysis, aspirin intake did not reduce the risk of BCa in male patients (OR = 1.08, $p = 0.163$), female patients (OR = 0.92, $p = 0.441$), Asian patients (OR = 1.07; $p = 0.088$), European patients (OR = 1.12, $p = 0.390$), or North American patients (OR = 0.99, $p = 0.839$). At the same time, the study type did not influence the lack of a connection between aspirin intake and the risk of BCa in the cohort study (OR = 1.05; $p = 0.176$) and case-control study (OR = 1.01; $p = 0.797$). To explore the impact of aspirin intake on the prognosis of patients with BCa, 8 articles involving 3250 BCa cases were eligible. The combined results showed that patients with aspirin intake did not have a significantly lower risk of BCa recurrence than those without aspirin intake (HR = 0.94, $p = 0.718$), and a consistent conclusion was also reached for overall survival (HR = 1.04, $p = 0.879$) and cancer-specific survival (HR = 0.98, $p = 0.980$) by subgroup analysis.

Conclusions

Both our retrospective study and literature meta-analysis suggested a lack of a relevant association between the use of aspirin and the risk and prognosis of BCa. Thus, additional long-term follow-up prospective research is warranted to clarify the association of aspirin with BCa incidence and prognosis.

Background

Bladder cancer (BCa) is the 11th most common cancer in the world. The global age-standardized incidence rate per 100,000 persons/year is 2.2 for women and 9.0 for men [1, 2]. According to the National Cancer Institute, the estimated numbers of new BCa cases and deaths in the USA alone (2014) will be 74,690 and 15,580, respectively [3, 4]. In China, the incidence and mortality rates have increased gradually in the past few years. According to the NCCR of China 2015 annual report, the overall incidence of BCa was 7.68/10⁵[5, 6]. Among patients with superficial or non-muscle invasive tumors after transurethral resection or perfusion therapy, 70% would experience recurrence, and 10–20% would show progression to muscle-invasive tumors [7, 8]. Due to the unfavorable prognosis of muscle-invasive cancer, the treatment involves multiple modalities, including radical surgery, radiotherapy, and chemotherapy. However, nearly half of these patients develop metastases and die within 3 years [7, 9]. The occurrence or recurrence of BCa is a molecular biological change or process that is influenced by occupational factors, non-occupational factors, and genomics and proteomics factors [10]. Other non-occupational factors, including cigarette smoking [11], drinking water used for washing or cleaning drinking water used for washing or cleaning [12], the consumption of substances with nitrate and nitrite content [13], alcohol consumption[14], and special drug intake[15, 16], have also been associated with BCa but are less well established. Therefore, early detection strategies and prognosis monitoring are extremely important for reducing mortality from BCa.

Aspirin, a typical non-steroidal anti-inflammatory drug, has been widely used for pain, fever and cardiovascular disease [17, 18]. In recent years, a large number of studies have suggested that aspirin has a potential preventive effect in several types of cancers [18–20]. The antitumor activity of aspirin is thought to be based mainly on 2 different mechanisms. First, aspirin may interfere with carcinogenesis by inhibiting the target of cyclooxygenase (COX), which is produced in response to inflammation and leads to angiogenesis and reduced apoptosis. As one of two isoforms, the level of COX-2 may not only increase the malignant stemness properties of BCa cells but also be related to high-grade and advanced-stage BCa patients [21, 22]. Second, aspirin plays roles in promoting apoptosis or inhibiting the proliferation of tumor cells by interfering with the pathway independent of COX-2 as an anticancer agent. Aspirin inhibits the growth of PI3K mutant breast cancer by activating AMPK and inhibiting mTORC1 signaling independent of COX-2 and IKK- β /NF- κ B[23]. Furthermore, aspirin inhibited the proliferation of neuroblastoma cells, upregulated p21Waf1 and regulated Rb1 to promote differentiation through a Cox-independent mechanism [24].

Since aspirin has obvious preventive effects on other tumors, its role in BCa has also received attention. The findings about the impact of aspirin intake and the incidence and mortality of BCa have been inconclusive. Moreover, there are few studies on the relationship between aspirin intake and BCa in mainland China, especially in Northeast China. To explore whether the use of aspirin is associated with an altered risk of BCa, we conducted a case–control analysis by enrolling 1087 patients with BCa. To avoid bias from single-center study results, we further completed a meta-analysis of eligible literature by searching electronic journals or databases for documents before March 1, 2020 to investigate the connection between aspirin intake and the incidence and prognosis of BCa, which helps to further determine whether the use of aspirin has a preventive effect on BCa and provides a basis for further exploration of the role of aspirin in the future.

Materials And Methods

Retrospective Study

Study population

This study was approved by the institutional review committee of the Second Affiliated Hospital of Dalian Medical University and included 1087 patients with BCa, including 993 males and 194 females, who underwent surgery from January 2002 to January 2019. Among them, the average age was 68 years old, ranging from 49 to 84 years old, and 230 patients experienced recurrence of BCa. The control group consisted of 1100 healthy people of similar age without any history of cancer. Sex, age, pathological stage, pathological grade, pathological lymph node status, distant metastasis, recurrence, and type of surgery were extracted from clinical and pathological data.

Inclusion and exclusion criteria

The inclusion criteria included the following: (1). All patients with BCa were confirmed by pathological biopsy or surgical biopsy, and pathological features, including stage, grade, lymph node metastasis and distant metastasis, were clear. (2). No previous medical history or self-report of other urinary system diseases, including cystitis, kidney stones and kidney cancer. (3). Aspirin users were defined as those who used drugs twice or more weekly for 1 month or more. Non-users are subjects who had never used the drug or had used it < 1 month so far. The indication for the use of aspirin (i.e., analgesic or cardiovascular disease, cerebrovascular disease prevention) was also recorded [25–27]. (4). Patients were stratified according to aspirin intake for most (50% or more) of the interval between diagnosis and the date of the first tumor recurrence or last follow-up. (5). Recurrence is defined as visual and/or biopsy evidence of a tumor confirmed by cystoscopy or urine cytology.

The exclusion criteria were as follows: (1). Unable to obtain accurate medication records, demographic data and patient characteristics. (2). Identification of a history of exposure to carcinogens. (3). Patients on clopidogrel, warfarin, or statins alone or in combination with other fibrin clotting inhibitors. (4). Aspirin use was contraindicated.

Statistical analysis

SPSS version 13.0 (SPSS Inc., Chicago, USA) was used for analysis. The associations between aspirin intake and clinicopathological parameters were evaluated by the chi-square test. Continuous data and frequency data were analyzed by Fisher's exact test. Adjusted odds ratios (ORs) or relative risks (RRs) and the corresponding 95% confidence intervals (CIs) were calculated by binomial logistic regression analysis for the occurrence or relapse of BCa in association with aspirin intake. After SPSS analysis, the p value of the above parameters was obtained. A p value less than 0.05 was considered statistically significant.

Meta-analysis

Search Strategy

The study retrieved articles from the PubMed, Embase, Cochrane Library, and Google Scholar databases published before March 1, 2020, to identify relevant studies evaluating aspirin intake and its effects on the occurrence and prognosis of BCa using the following medical subject headings that include all spelling variations: "bladder cancer" and "aspirin", "occurrence", "risk" and "prognosis", "survival" and "recurrence". Without national and linguistic restrictions, after reviewing the duplicate data, the two reviewers independently screened the titles and abstracts, excluding articles that were not associated with our research, reviews, and related animal experiments and maximizing data quality.

Selection Criteria

Studies satisfying the following criteria were included in our analysis: (1) the histologic type of the tumors was urothelial carcinoma of the bladder by histologic or pathologic examination; (2) the association between aspirin intake and the risk of BCa or prognosis of patients with BCa was investigated; and (3) sufficiency of data for the calculations of OR/RR/hazard ratio (HR), 95% CI and P value. Accordingly, the following exclusion criteria were applied: (1) studies in the form of reviews, letters to the editor, commentaries, or case reports that lacked original data; (2) molecular biology research that explored the impact of aspirin on cancer cell lines and animal models; and (3) studies in which the HR/OR/RR and its standard error could not be collected based on the given information.

Data extraction

After the full-text evaluation, the two authors extracted the data separately for further qualitative and quantitative analysis to increase the authenticity of the data. For the selected articles, we extracted data from each study, including the first author, publication time, region, type of study, number of participants, median age, follow-up, HR/OR/RR, and adjustment factors.

Statistical analysis

The Stata 12.0 statistical software package (StataCorp, College Station, TX, USA) was used for all data analyses. We calculated the OR/RR/HR with a 95% CI for dichotomous outcomes. The Q test was used to qualitatively assess the statistical heterogeneity and judge the p-value. The I^2 value in the I^2 test describes the proportion of the total variation due to heterogeneity rather than sampling errors, and $I^2 > 50\%$ or $p < 0.05$ indicates a high degree of heterogeneity. In these cases, the random-effects model was used; otherwise, there was no heterogeneity, and the fixed-effects model was used. The potential bias was assessed by a funnel plot and Egger's test, and when the funnel plot was symmetrically distributed, there was no significant bias. Conversely, if the funnel plot exhibits skewness and asymmetry, this indicated bias.

Results

Retrospective Study

Association of aspirin intake and risk of bladder cancer

A total of 1087 patients with BCa and 1100 controls were recruited into our study. Among the controls and the cases identified as BCa, the patients who used aspirin accounted for 8.92% of the total number of patients with BCa and 7.72% of the control group. The analysis showed that the regular use of aspirin was not associated with a reduced incidence of BCa (OR = 1.17, 95% CI = 0.863–1.59, $p = 0.311$). Moreover, we performed subgroup analyses stratified by sex, we found that there was no correlation between aspirin intake and the risk of BCa in male patients (OR = 1.25, 95% CI = 0.866–1.81, $p = 0.230$) and female patients (OR = 0.90, 95% CI = 0.473–1.71, $p = 0.744$). We also found that there was no correlation between aspirin intake and the risk of BCa in patients 65 years or younger (OR = 1.25, 95% CI = 0.87–1.81, $p = 0.230$) and patients over 65 years (OR = 0.90, 95% CI = 0.47–1.71, $p = 0.744$).

Aspirin intake and clinicopathological characteristics of bladder cancer

A total of 1087 patients with newly developed BCa were identified from 2002 to January 2019 and divided into the aspirin group and the non-aspirin group. Their characteristics, including sex, age, pathological stage, pathological grade, pathological lymph node status, distant metastasis, recurrence, and type of surgery, are displayed in Table 1.

Of these patients, the male to female ratio was 893:194, and there were 529 patients aged 68 or greater. There were 343 patients (31.6%) with pathologic stage T₂-T₄ and 629 patients (62.1%) with high grade G2 to G3. Positive lymph nodes were present in 72 patients (6.7%), and distant metastasis was present in 32 patients (3%). All patients had a definite type of surgery, and 823 underwent TURBT (75.7%), 31 underwent partial resection (2.9%), and 233 underwent radical prostatectomy (21.4%). Among them, 230 patients (21.2%) experienced relapsed. Notably, an obvious association was identified between age only and the risk of BCa ($p = 0.002$).

Association of aspirin intake and the recurrence of bladder cancer

Of the 1087 patients, 230 patients experienced recurrence of BCa. Among these patients, there was no significant difference in the number of recurrences between the aspirin group (1.500 ± 0.159 ; $N = 24$) and the non-aspirin group (1.403 ± 0.058 ; $N = 206$). Additionally, we did not find an association between aspirin intake and the recurrence of BCa ($RR = 1.19$; $95\% \text{ CI} = 0.82-1.72$; $p = 0.360$). Stratified analysis by sex showed that there was no correlation between aspirin intake and the recurrence of BCa for both male patients ($RR = 1.12$; $95\% \text{ CI} = 0.75-1.68$; $p = 0.580$) and female patients ($RR = 1.61$; $95\% \text{ CI} = 0.66-3.90$; $p = 0.290$). Furthermore, in exploring whether age affects the related results, stratified analysis by age showed that aspirin intake was significantly associated with the recurrence of BCa in patients who were < 68 years of age ($RR = 0.60$; $95\% \text{ CI} = 0.39-0.94$; $p = 0.030$), indicating that the aspirin group had a 40% lower recurrence rate than the non-aspirin group. However, for patients over 68 years old, the difference was not significant ($RR = 0.87$; $95\% \text{ CI} = 0.50-1.53$; $p = 0.640$).

Meta-analysis

Study Identification and Selection

The selection process for the association of aspirin intake with the risk and prognosis of BCa is presented in Fig. 1. Initially, the database search retrieved 161 relevant publications. After screening the titles, abstracts and full texts of these articles, we excluded duplicate studies and other studies for various reasons (reviews/editorials, animal/molecular biology studies, or not relevant to our analysis). Thus, in the final analysis, we included ten studies about the relation of aspirin intake and risk of BCa and eight studies about the relation of aspirin intake and prognosis of patients with BCa based on the inclusion criteria.

Characteristics of the studies

The characteristics of the ten included trials [28–37] about the relation of aspirin intake and risk of BCa are provided in Table 2. These trials were published between 1989 and 2018. Two results were extracted from each of the two literatures, while the remaining articles contained only one available result. and a total of 13 research results were obtained including this article. Of the thirteen included studies, nine were conducted in the USA [30–33, 35–37], two in China [28] including this study, one in Italy [29], and one [34] in Spain. Among all studies enrolled, seven were cohort studies [28, 30, 32, 36, 37], and six were case-control studies [29, 31, 33–35] containing this study. The sample size of the trials ranged from 839 to 612509, with a total of 12441 patients with BCa. The characteristics of the eight included trials regarding the impact of aspirin intake on the prognosis of patients with BCa are presented in Table 3. The selected studies were published between 2004 and 2018. Seven studies originated from the USA [38–44] and only one was from Italy [45]. The sample size of the trials ranged from 43 to 100139, and the mean/median follow-up durations varied from 31.4 months to over 10 years. Among the eight studies enrolled, four were cohort studies, and four were case-control studies.

Association between aspirin intake and the risk of bladder cancer

Overall analysis

Thirteen studies reported the effect estimates of the association between aspirin intake and the occurrence of BCa. One study reported significant positive associations, and the other twelve studies reported a nonsignificant positive relationship. The fixed-effects model was applied because the test for heterogeneity was not significant ($I^2 = 11.8\%$, $p = 0.326$). We found that patients with aspirin intake did not have a significantly lower risk of BCa than those without aspirin intake (OR = 1.03, 95% CI = 0.98–1.09, $p = 0.221$). This result exhibited a low probability of publication bias, as determined by Egger's test ($p = 0.828$, Figure. 2B).

Subgroup analysis by sex

As a slight degree of heterogeneity was found ($I^2 = 0.0\%$, $p = 0.793$), so a fixed-effects model was used. The results indicated no correlation between aspirin intake and BCa in either the male population (OR = 1.08, 95% CI = 0.97–1.19, $p = 0.163$) or the female population (OR = 0.92, 95% CI = 0.73–1.14, $p = 0.441$). Both Begg's test ($p = 0.851$) and Egger's funnel plot asymmetry test ($p = 0.888$) indicated that there was no significant publication bias (Fig. 3).

Subgroup analysis by research region

Overall, 13 studies were included in this analysis (two were from Asia, two were from Europe and 9 were from North America.). Meta-analysis using a fixed-effects model suggested that aspirin intake had no significant influence on the prevention of BCa in Asian populations (OR = 1.07, 95% CI = 0.99–1.15, $p = 0.088$), European populations (OR = 1.12, 95% CI = 0.87–1.43, $p = 0.390$) and North American populations (OR = 0.99, 95% CI = 0.92–1.07, $p = 0.839$). There was no evidence of significant publication bias by inspection of the funnel plot and formal statistical tests (Egger's test, $p = 0.627$; Begg's test, $p = 0.807$; Fig. 4).

Subgroup analysis by study type

Within 7 cohort studies (Fig. 5), aspirin intake was not linked to a decreased risk of BCa (OR = 1.05, 95% CI = 0.98–1.12, $p = 0.176$). There was no evidence for heterogeneity ($I^2 = 11.8\%$, $p = 0.326$). Moreover, when the data collected from 6 case-control studies [16, 17] were pooled (Fig. 5), there was no statistically significant association between aspirin administration and BCa (OR = 1.01, 95% CI = 0.93–1.10, $p = 0.797$). Begg's test ($p = 0.807$) and Egger's test ($p = 0.627$) showed that the funnel plot distribution was symmetrical and that there was no significant publication bias.

The impact of aspirin intake on the prognosis of patients with bladder cancer

Aspirin intake and the survival of patients with bladder cancer

Among 6 studies including a total of 1502 patients with survival data, 4 studies investigated the relationship between aspirin intake and overall survival (OS) in BCa patients, and 2 studies reported cancer-specific survival (CSS). The random-effects model was used (Fig. 6), as higher heterogeneity was detected among these studies (P -value for heterogeneity < 0.001 ; $I^2 = 66.8\%$). No significantly decreased levels of OS were observed in BCa patients who consumed aspirin compared with the controls, with a combined HR of 1.04 (95% CI = 0.62–1.76, $p = 0.879$). Similarly, aspirin intake had no significant effects on the CSS of BCa patients (HR: 0.98, 95% CI = 0.25–3.92, $p = 0.980$).

Aspirin intake and recurrence of patients with bladder cancer

Six studies that reported the effect estimates of the association between aspirin intake and the recurrence of BCa were included. The random-effects model was applied, as the test for heterogeneity was significant ($I^2 = 71.2\%$, $p = 0.004$). We found that patients with aspirin intake did not have a significantly lower risk of BCa recurrence than those without aspirin intake, as shown in Fig. 3A (HR = 0.94, 95% CI = 0.66–1.34, $p = 0.718$). This result exhibited a low probability of publication bias, as determined by Egger's test ($p = 0.463$, Fig. 6B).

Discussion

Aspirin is a non-steroidal anti-inflammatory drug with a long history. It is suitable for antipyretic and analgesic use and is widely used in the prevention of cardiovascular thrombosis [18]. Recent studies have found that the long-term regular use of aspirin can significantly reduce the incidence of colorectal cancer, gastric cancer, liver cancer and other malignant tumors and improve the survival of patients with its anticancer effects [46–49]. The mechanism of action of aspirin in terms of signaling pathways is as follows. \square Apoptosis-related signaling pathway: NF- κ B dissociates with inhibitor IK-B to enter the nucleus and activates antiapoptotic genes, which inhibits the apoptosis of tumor cells under the stimulation of inflammation and angiopoietin. Aspirin inhibits the activity of IKK by directly acting on it, thus preventing the activation of NF- κ B and reducing the level of NF- κ B [50–52]. Moreover, two important apoptosis-related genes, bcl-2 and Bax, have opposite antiapoptotic functions. By downregulating the expression of bcl-2 and upregulating the level of Bax, aspirin stimulates the death effect factor to increase caspase-3 activity and thereby promote cancer cell apoptosis [53–55]. \square Cell proliferation-related pathway: The P13K/Akt signaling pathway widely exists in cells and is a signal transduction pathway involved in the regulation of cell growth, proliferation and differentiation. Aspirin can irreversibly inhibit cyclooxygenase, thereby inhibiting the production of thromboxane A2 in platelets and inhibiting the P13K/Akt signaling pathway, thereby blocking or alleviating inflammation [56, 57]. Moreover, aspirin can inhibit the mTOR signaling pathway and transcription factors and activate the apoptosis-related proteins caspase-3 and Bim, thereby inhibiting cell proliferation and inducing cell apoptosis [58, 59]. \square Autophagy-related pathway: AMPK not only directly inhibits the mTOR signaling pathway but also regulates the activity of ULK1 through phosphorylation, which is related to activating autophagy. Aspirin inhibits the growth and proliferation of cancer cells by targeting the AMPK pathway to affect autophagy [60–62].

A population-based case-control study analyzed data from 376 BCa cases and 463 controls in New Hampshire and found that aspirin significantly reduced the risk of BCa, especially for tumors containing TP53 mutations (Fortuny J) [33]. Similarly, Castelao J et al illustrated that there was a nonsignificant trend towards increased BCa risk in people with a longer duration of painkillers than in people who do not use painkillers, and regarding the effect of the correlation of different types of analgesics and BCa risk on the direction and strength of the obvious difference, aspirin showed weaker role [35]. However, in a cohort study by Genkinger JM et al [32]. In the USA, there was no association between the frequency and dose of aspirin and BCa risk, which was not altered by known risk factors such as age, smoking or total fluid intake. Furthermore, a population-based cohort study using a database from the Hong Kong Hospital authority tracked 612509 subjects for 14 years, and the results showed that the long-term use of low-dose aspirin is associated with a lower risk of various cancers, including esophageal cancer, pancreatic cancer and stomach cancer, except for bladder, kidney and prostate cancer [28]. To compensate for the lack of related research focusing on the population in Northeast China, we performed a retrospective study to explore the association of aspirin intake and risk of BCa and found that the regular use of aspirin was not associated with a reduced risk of BCa. Moreover, subgroup analyses stratified by sex showed that there was no correlation between aspirin intake and the risk of BCa in male patients and female patients. Although the findings suggested possible relationships between aspirin intake and the risk of cancer at the site of the colon, breast, and liver [46, 48, 49], studies of aspirin use and the risk of BCa have yielded mixed results. Several case-control studies have suggested a

reduced risk of BCa among aspirin users, while other studies have indicated no association. Therefore, we conducted meta-analyses and found that patients with aspirin intake did not have a significantly lower risk of BCa than those without aspirin intake after combining ten included studies with 10000 patients. Subgroup analysis by research region also suggested that aspirin intake had no significant influence on the prevention of BCa in Asian populations, European populations (OR = 1.115, 95% CI = 0.870–1.431, p = 0.390) and North American populations.

Although the antitumor properties of aspirin have attracted increasing attention from scholars, the results regarding the impact of aspirin use on the prognosis of BCa are inconsistent. In terms of the effects of aspirin on tumor recurrence, a case-control study from Italy and a retrospective study from the USA showed a significant association between aspirin and recurrence in patients with BCa (Pastore A, Gee JR) [40, 45]. In the former (Pastore A) [45], the results suggest that long-term aspirin use may reduce the risk of tumor recurrence in patients with NMIBC. In a more detailed analysis, fewer patients with aspirin experienced recurrence, and there were fewer lesions with recurrence. For the latter (Gee JR) [40], the 5-year RFS of aspirin users was 64.3%, which was significantly higher than that of non-aspirin users (26.9%), even after multivariate analysis adjusted for other factors. Considering the effect of aspirin on the survival rate of cancer patients, Lyon TD's study [39] found that daily aspirin significantly improved survival outcomes after radical resection, including CSS, OS and MFS. It has also been observed that patients receiving low-dose aspirin had significantly better outcomes than patients receiving high-dose aspirin and those without aspirin. In contrast, a cohort study from the United States found no significant association between aspirin use and the overall survival of BCa patients [43]. In addition, a prospective study by Singla N et al [44]. showed that the use of aspirin does not affect the survival of patients with any tumors, including CSS, OS, recurrence-free survival and cystectomy-free survival, regardless of the dose (81 or 325 milligrams a day). In response to these mixed findings, we performed a meta-analysis to investigate the impact of aspirin intake on the prognosis of patients with BCa and found that aspirin had no significant effects on the OS and CSS of BCa patients. In addition, patients with aspirin intake did not have a significantly lower risk of BCa recurrence than those without aspirin intake. Until now, available data have not supported a connection between aspirin exposure and the prognosis of BCa despite few prior studies.

Our limitations are as follows: one limitation is that this case-control study is a single-center study, which may lead to certain bias or heterogeneity. To the greatest extent possible to avoid such shortcomings or loopholes, we performed a meta-analysis to investigate the relationship between aspirin intake and the risk and prognosis of BCa. Some included studies did not provide available values of HR, RR or OR from multivariate analysis, so we performed calculations from the univariate data and compared them through formula calculations. The statistical methods we used cannot replace all the research methods, and the conclusions we obtained without correlation are limited to the scope of our research, which may have some statistical errors [63, 64]. Second, we only focused on researching patients who regularly consumed aspirin. Due to the limited available information from clinical data, stratification analysis according to different doses or durations was not conducted. Moreover, other confounding factors affecting the occurrence or prognosis of BCa, including a history of cigarette smoking, alcohol consumption, etc., were not adjusted in our study.

The above factors may influence the results regarding the connection between the risk of BCa and the use of aspirin [10], which will be one of the focuses of our future research. Third, both our case-control study and meta-analysis showed no differences between aspirin intake and the risk and prognosis of BCa. However, previous in vitro studies have shown that aspirin may play a role as a chemopreventive agent in the OH-BBN/BDF BCa model [65], which suggests that there is heterogeneity between human epidemiological experiments and in vitro cell experiments, and the experimental scheme needs to be improved.

Conclusion And Outlook

Our clinical data studies and meta-analyses did not reveal an effective correlation between aspirin and BCa, but we are not able to deny that there were studies suggesting a protective effect from aspirin. A possible explanation for these inconsistent results might be that clinical cohort studies consider patients or individuals as a whole, while molecular biology experiments, a powerful approach in investigating the relationship between exposure and disease risk, have noted that aspirin has an effect on BCa, primarily at the cellular level. It is key to construct a virtual simulated human microenvironment to explore whether aspirin can prevent or monitor BCa. Although aspirin has been predicted to be protective against a variety of tumors, differences in tumor origin and tissue specificity are bound to influence the results. In the case of BCa, multicenter, large-sample, prospective studies are also needed. Advances in cancer biology clearly indicate that the development of malignant tumors is the result of complex interactions and the integration of gene expression, proteome and metabolome changes, involving genetics, microbes, diet, drugs [66, 67] and other factors such as different living conditions, exposure factors and ethnic differences [68]. In the age of precision oncology, individual cancer treatment should be personalized based on genetic and environmental factors. In addition, aspirin, as a sensitizer, can increase the therapeutic effect of chemotherapy for cancers of the colon and stomach, while there are few studies in the urinary system, which will be a promising research direction. As a continuation of this study, it is necessary to further explore the information of pathological examinations, immune parameters, tumor molecular markers and other aspects from the database. If aspirin's effect on BCa is determined, it would represent an important benefit for the use of NSAIDs and provide a new dimension for BCa treatment, which contributes greatly to the development of human health care.

Declarations

Ethics approval and consent to participate

This study was approved by the institutional review committee of the Second Affiliated Hospital of Dalian Medical University and written informed consent was obtained from each patient or their next of kin.

Consent to publication

Not applicable.

Availability of data and materials

All data generated or analysed during this study are included in this published article [and its supplementary information files].

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Conception and design: Bo Fan and Xiancheng Li

Development of methodology: Huidan Jin and Bo Fan

Acquisition of data (acquired and managed patients, provided facilities, review of literature, etc.): Hong Luo, Zhifei Yun and Man Sun

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): Hong Luo and Bo Fan

Writing, review, and/or revision of the manuscript: Bo Fan ,Hong Luo and Huidan Jin

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): Bo Fan, Mengfan Sun and Man Sun

Study supervision: Zhifei Yun and Rui Zhao

All authors have read and approved the final manuscript.

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Tables

Table1. Association between aspirin intake and clinico-pathological characteristics of BCa in 1087 Chinese patients

	Regular Aspirin use		Total	P Value
	No	Yes		
Gender				0.357
Male	810	83	893	
Female	180	14	194	
Age, years				0.002
Less than 68	523	35	558	
68 or Greater	467	62	529	
Pathologic stage				0.713
Tis-T1	676	68	744	
T2-T4	314	29	343	
Pathologic grade				0.702
G ₁	421	37	458	
G ₂	186	20	206	
G ₃	383	40	423	
Lymph node status				0.938
No	924	91	1015	
N ₁	46	4	50	
N ₂	17	2	19	
N ₃	3	0	3	
Distant metastasis				0.471
M ₀	962	93	1055	
M ₁	28	4	32	
Recurrence				0.365
No	784	73	857	
Yes	206	24	230	
Type of surgery				0.177
TURBT	757	66	823	
Partial cystectomy	27	4	31	
Radical cystectomy	206	27	233	

TURBT: Transurethral resection of bladder tumor

Table2. Main characteristics of individual studies included in the meta-analysis on impact of aspirin intake on risk of BCa.

First author (year)	Region	Study type	Study period	Age	Total number	BCa Cases	Frequency of use	Adjusted HR/RR/OR (95% CI)	Adjustments
Tsoi K KF (2018)	China	Cohort study	2000-2013	67.5	612509	5291	More than 6 moths	1.06 (0.98-1.14)	Age, gender
Guercio V (2017)	Italy	Case control	2003-2014	67	1355	690	At least for a week for more than 6 months	1.21 (0.87-1.68)	Age, gender, education, tobacco smoking, diabetes
Shih C (2013)	USA	Cohort study	2000-2010	50-76	77048	385	1-3 days/week or <4 years	0.86 (0.63-1.17)	Age, gender, race, smoking status, education, family history of bladder cancer, analgesic use
							≥4days/week and ≥4 years	1.16 (0.88-1.53)	Age, gender, race, smoking status, education, family history of bladder cancer, analgesic use
Daugherty SE (2011)	USA	Case control	1995-1997 1993-2001 1994-1998	63.5	508842	2489	>2 times per week	Male: 1.06 (0.95-1.18) Female: 0.92 (0.73-1.18)	Gender, smoking status, stage, grade
Genkinger JM (2007)	USA	Cohort study	1986-2002	40-75	49448	607	≥2 tablets per week	0.99 (0.83-1.18)	Age, smoking status, region, BMI
Fortuny J (2007)	USA	Case control	1997-2000	25-74	839	376	4 times per week during a month or more	0.60 (0.40-0.90)	Ages, sex, grades, stage, Use of tobacco, alcohol
Fortuny J (2006)	Spain	Case control	1997-2000	20-80	1987	958	2 or more times weekly for ≥1 month	1.00 (0.70-1.50)	Ages, gender, region, education, smoking status
Castelao JE (2000)	USA	Case control	1987-1996	58	3028	1514	2 or more times a week for 1 month or longer	0.85 (0.66-1.09)	Ages, gender, race, use of tobacco
Schreinemachers and Everson (1994)	USA	Cohort study	1982-1987	25-74	12668	35	More than 1 time per month	1.06 (0.54-2.09)	Ages, gender, race, education, smoking status, alcohol use, poverty index, BMI, arthritis(ever)
Pagani-Hill (1989)	USA	Cohort study	1981-1988	73	13987	Male :74 Female:22	More than 1 time per day	Male 1.12 (0.63-1.99) Female 0.89 (0.26-3.10)	Ages, gender -

BMI: Body mass index

Table3. Main characteristics of eligible studies collected in the meta-analysis on effect of aspirin intake on prognosis of BCa.

First author (year)	Region	Study type	Study period	Age	Total number	BCa cases	Frequency of use	Reported endpoints	Adjustments
Singla N (2017)	USA	prospective	2006-2012	73/NR	203	99	81 mg vs. 325 mg daily	CSS:3.14 (0.37-26.91) OS:1.91 (0.69-5.27) RFS:1.05(0.64-1.74)	Age,stage,grade, BMI,history of tobacco use,charlson comorbidity score, concomitant CIS,tumor size,tumors number
Lyon TD (2018)	USA	Cohort study	2007-2016	50-59	1061	1061	Low:25, 81or162mg,high:325or650mg	CSS: 0.64 (0.45-0.89) OS: 0.70 (0.53-0.93)	Age, ECOG, BMI, use, stage, pathological node pos, periop blood transfusion
Pastore A (2015)	Italy	case control [method]	2008-2013	62.2	574	574	≥20 mg daily for at least 2 years	RFS: 0.74 [0.452-1.239]	Age, grade, stage, smokers
Lipsky MJ (2013)	USA	Retrospective	2001-2011	68+/-12 73+/-9	224	224	NR	RFS: 2.41(1.08-5.35)	Age, stage, grade, tumor multifocality, tumor recurrence status, concurrent interferon administration
Jacobs EJ (2012)	USA	Cohort study	1997-2008	older than 60 years of age	100139	302	≥1 tablet per day	OS:0.75 (0.48-1.16)	Age, gender, smoking, education, BMI, race, analgesic use, physical activity, history of heart disease, stroke, diabetes, hypertension, cholesterol-lowering use, history of colorectal endoscopy
Ratnasinghe LD (2004)	USA	Cohort study	1982-84, 1986,1987,1992	25-74	22794	40	Any use in the past 30 days or the past 6 months	OS: 3.36 (1.03-10.97)	Gender, race, education, smoking, socioeconomic status, BMI
Boorjian SA (2009)	USA	Retrospective	1990-2006	65 69	907	907	NR	RFS: 0.91(0.751.10)	Age,stage,grade
Gee JR (2009)	USA	Retrospective	1991-2003	72 63	43	43	81 or 325 mg aspirin	RFS:0.179 (0.062-0.516)	Sex, maintenance BCG, presence of CIS, papillary tumor present, pure papillary tumor, current smoker, history of smoking, history of bladder cancer

BMI: Body mass index

ECOG: Eastern Cooperative Oncology Group

BCG: Bacillus Calmette-Guerin

CIS: Carcinoma in situ

Figures

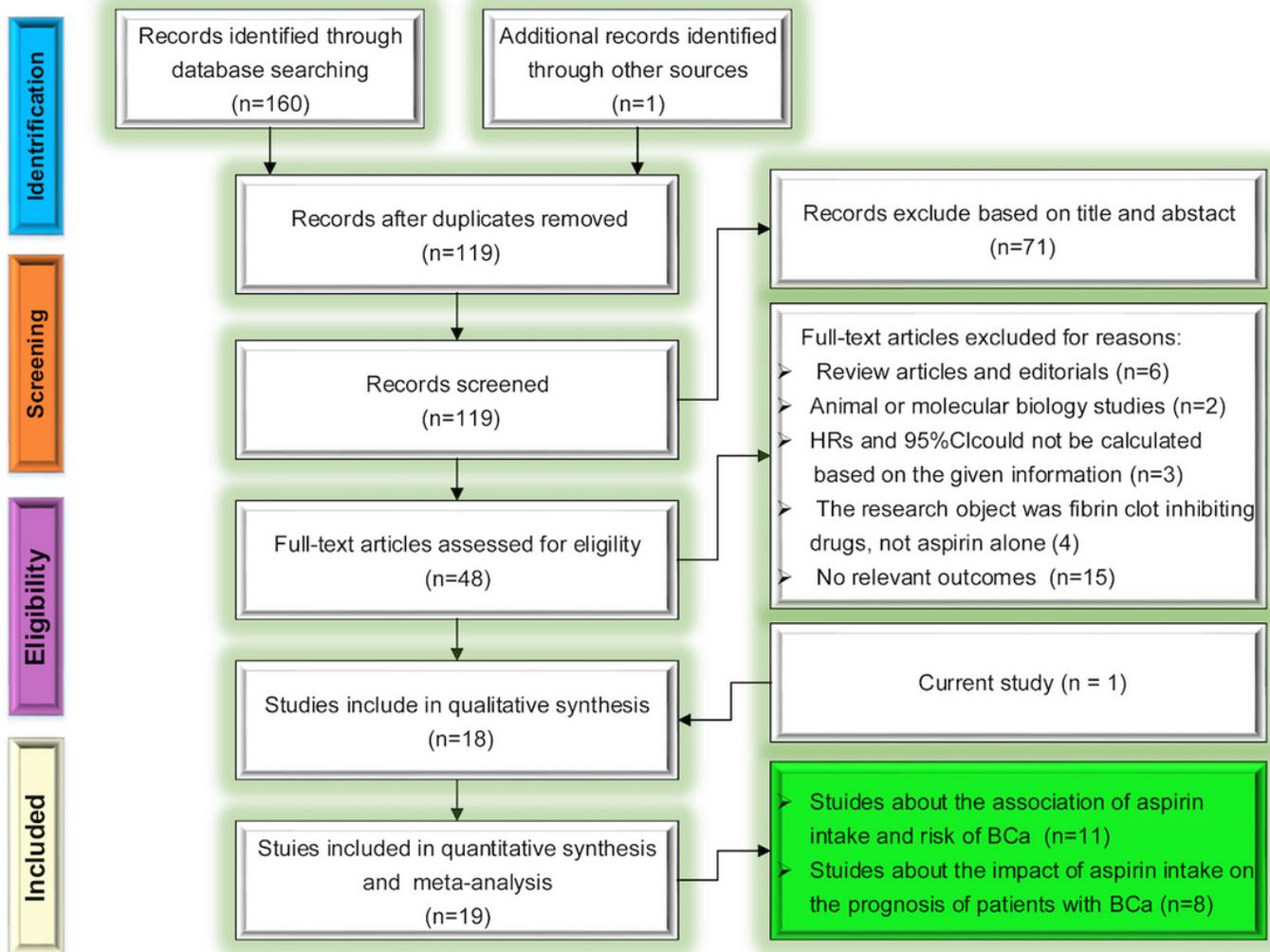


Figure 1

Flow diagram for the selection of articles.

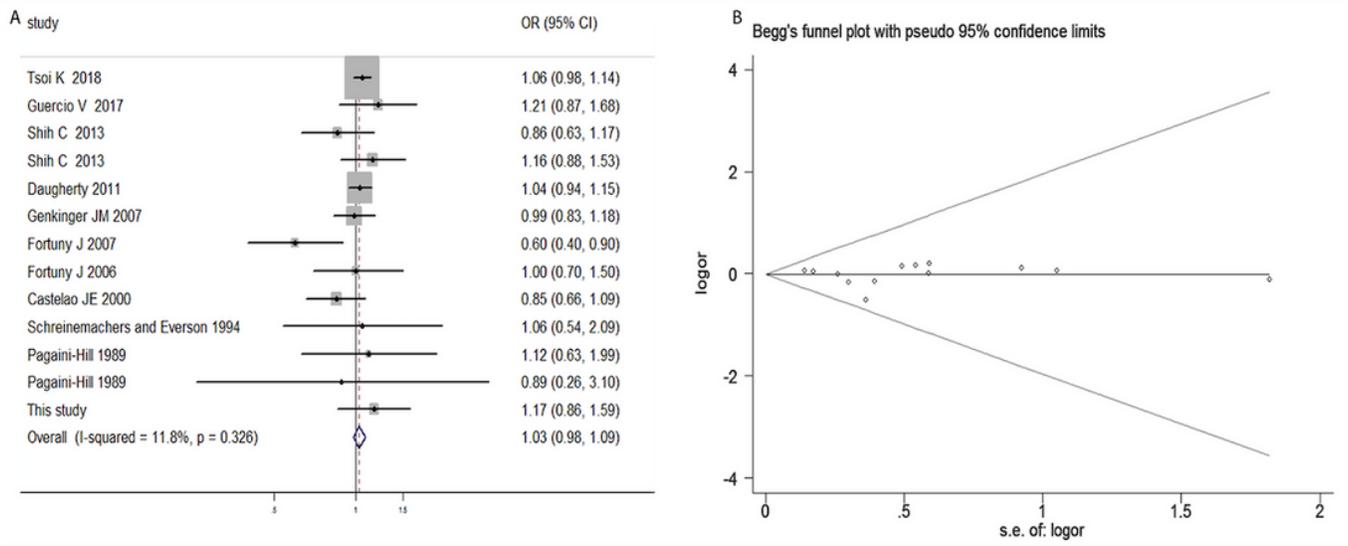


Figure 2

Forest plot (A) and funnel plot (B) showing the relationship between aspirin intake and the risk of bladder cancer in the overall analysis. The x-coordinate scale of solid lines perpendicular to the X-axis is 1. Each horizontal line segment parallel to the X-axis represents a confidence interval of the research results. The wider the confidence interval is, the longer the horizontal line segment. The small square in the middle of the horizontal line represents the position of the point estimate of the OR, and the size represents the weight of the study, which represents the percentage of the results of each study in the overall results. The intersection of the horizontal segment and the solid vertical line indicates that the study results are not statistically significant. Diamonds represent the overall effect of the estimate using the Mantel-Haenszel fixed-effects model. The visual examination of the funnel plot showed no obvious asymmetry, indicating that the publication bias was small and that the effect on the combined effect was negligible.

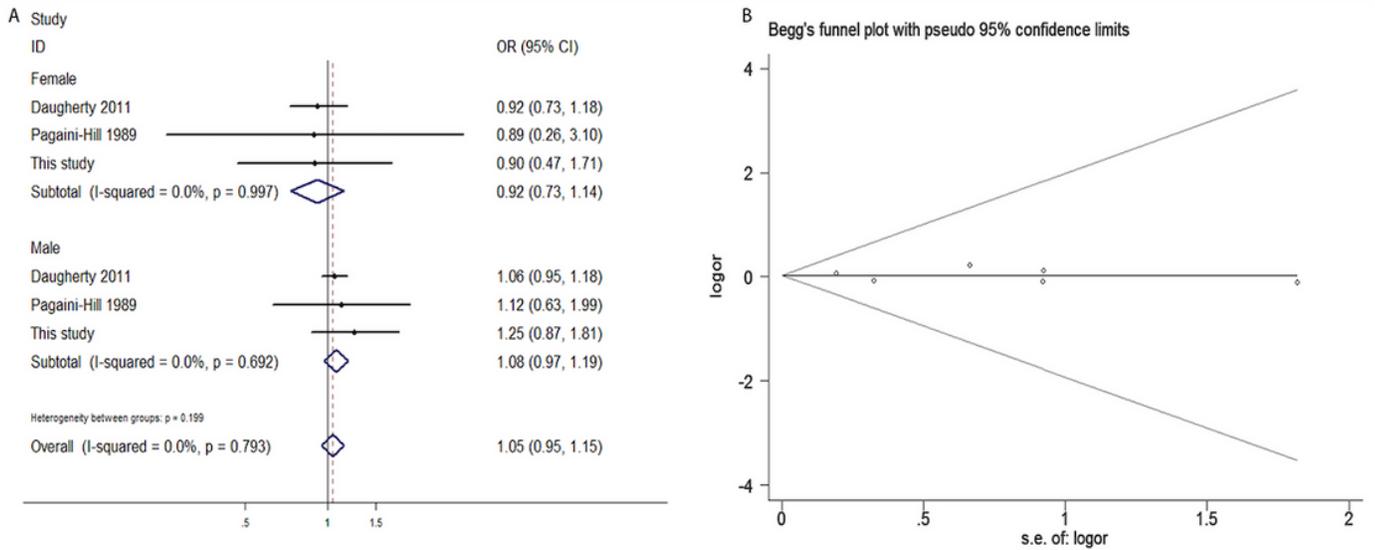


Figure 3

Forest plot (A) and funnel plot showing the association of aspirin intake and the risk of bladder cancer in subgroup analysis by sex. The intersection of the horizontal segment and the solid vertical line indicates that the results are not statistically significant in each subgroup. Diamonds represent the overall effect of the estimate using the Mantel-Haenszel fixed-effects model. The visual examination of the funnel plot showed no obvious asymmetry, indicating that the publication bias was small and that the effect on the combined effect was negligible.

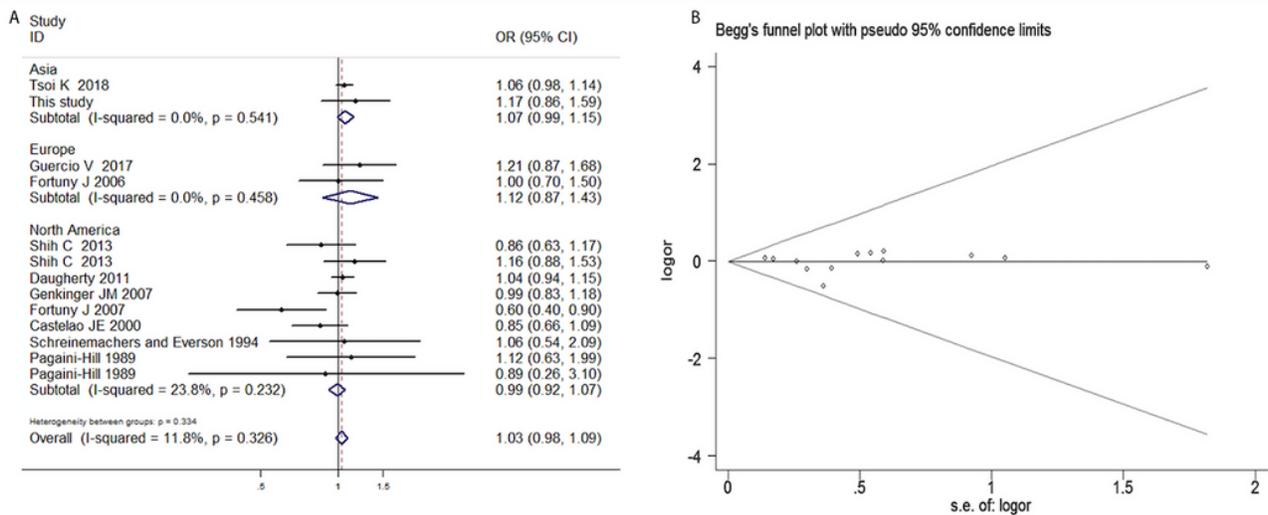


Figure 4

Forest plot (A) and funnel plot showing the association of aspirin intake and the risk of bladder cancer in subgroup analysis by region. The intersection of the horizontal segment and the solid vertical line indicates that the results are not statistically significant in each subgroup. Diamonds represent the overall effect of the estimate using the Mantel-Haenszel fixed-effects model. The visual examination of the funnel plot showed no obvious asymmetry, indicating that the publication bias was small and that the effect on the combined effect was negligible.

Haenszel fixed-effects model. The visual examination of the funnel plot showed no obvious asymmetry, indicating that the publication bias was small and that the effect on the combined effect was negligible.

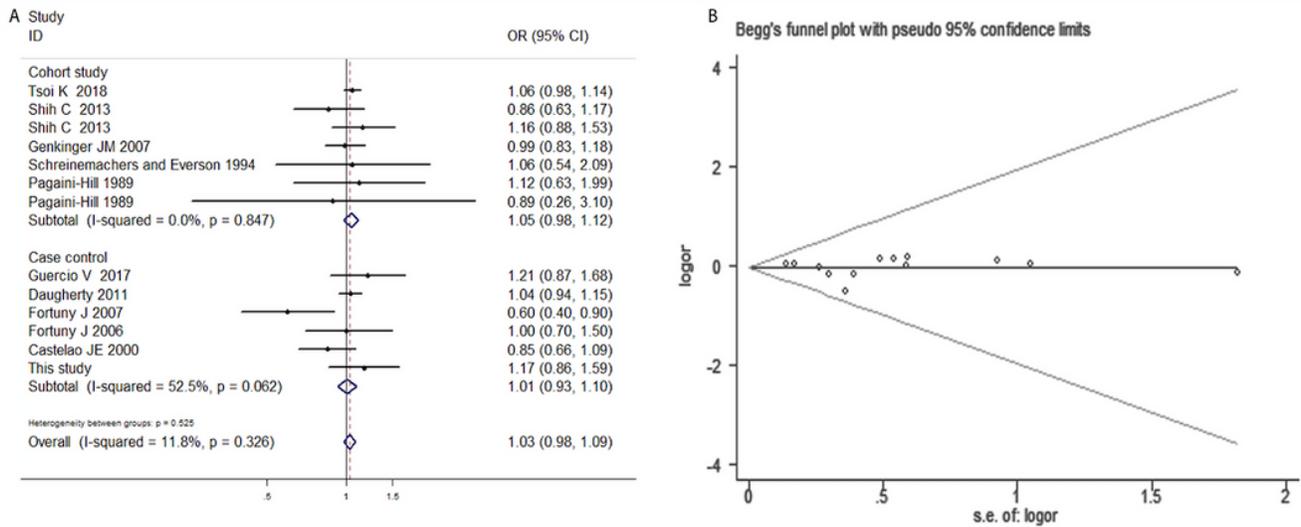


Figure 5

Forest plot (A) and funnel plot showing the association of aspirin intake and the risk of bladder cancer in subgroup analysis by research type. The intersection of the horizontal segment and the solid vertical line indicates that the results are not statistically significant in each subgroup. Diamonds represent the overall effect of the estimate using the Mantel-Haenszel fixed-effects model. The visual examination of the funnel plot showed no obvious asymmetry, indicating that the publication bias was small and that the effect on the combined effect was negligible.

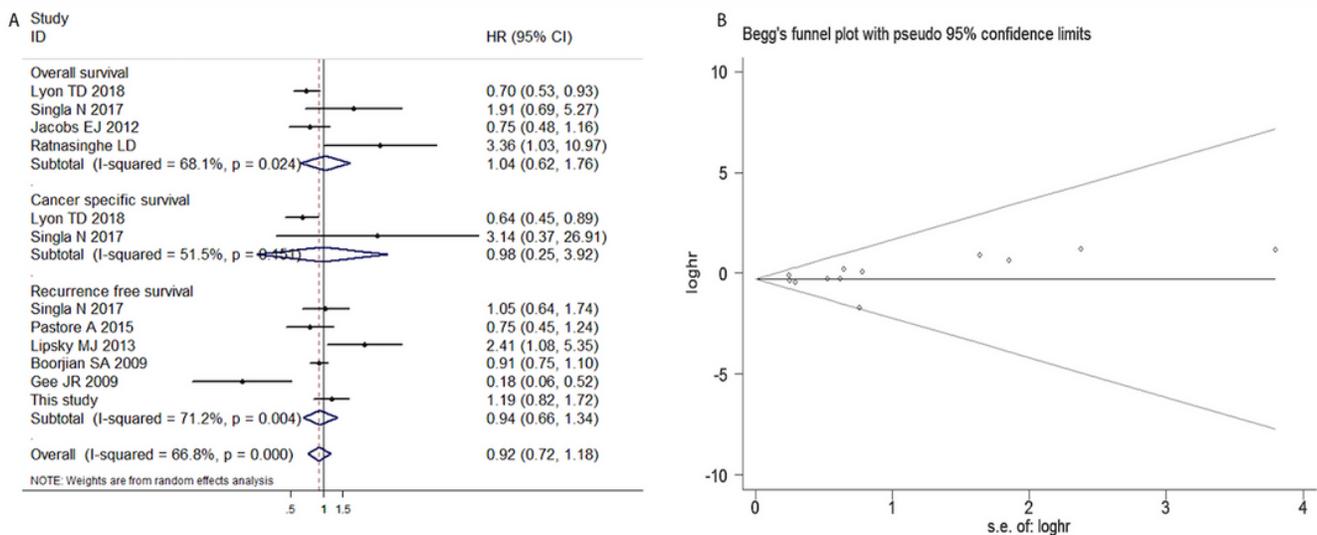


Figure 6

Forest plot (A) and funnel plot (B) showing the relationship between aspirin intake and the prognosis of patients with bladder cancer, which included relapse-free survival, overall survival and cancer-specific survival. The intersection of the horizontal segment and the solid vertical line indicates that the results are not statistically significant in each subgroup. Diamonds represent the overall effect of the estimate using the Mantel-Haenszel random-effects model. The visual examination of the funnel plot showed no obvious asymmetry, indicating that the publication bias was small and that the effect on the combined effect was negligible.