Association of Aspirin Therapy with Risk of Hepatocellular Carcinoma: a systematic review and dose-response analysis of cohort studies with 2.5 million participants

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Original citation & hyperlink:
Wang, S, Yu, Y, Ryan, P, Dang, M, Clark, C, Kontogi, V, Rahmani, J, Kord-Varkaneh, H, Salehisahlabadi, A, Day, AS & Zhang, Y 2020, 'Association of Aspirin Therapy with Risk of Hepatocellular Carcinoma: a systematic review and dose-response analysis of cohort studies with 2.5 million participants', Pharmacological Research, vol. 151, 104585.
https://dx.doi.org/10.1016/j.phrs.2019.104585

DOI 10.1016/j.phrs.2019.104585
ISSN 1043-6618

Publisher: Elsevier

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Abstract

Although aspirin is commonly used for the prevention of cardiovascular disease, evidence from research has shown that these beneficial effects might extend to hepatocellular carcinoma (HCC). This dose-response analysis was performed to investigate the association between aspirin use and risk of HCC. A systematic search was conducted in MEDLINE/PubMed, SCOPUS, Cochrane, and Web of Science databases from inception up to 29th October 2019. DerSimonian and Laird Random-effects model was used to estimate pooled hazard ratios (HRs) from included studies. Overall, eight studies containing 2,604,319 participants evaluating the association between aspirin use and risk of HCC were uncovered and included in the present meta-analysis. Pooled results of included studies showed a significant reduction in risk of HCC in participants who used aspirin (HR 0.59, 95% CI 0.47-0.75, $P_{heterogeneity}$=0.001, I^2=90%). In total, 13636 cases of HCC detected during the follow-up period of these studies. Furthermore, linear dose-response model showed an significant inverse association between aspirin dose and risk of HCC (exp (b) = 0.994, p<0.001), while non-linear dose-response analysis revealed an even more robust association ($Coef_1$=-0.008, p_1=0.04, $Coef_2$=0.033, p_2=0.13). This systematic review and dose-response analysis identified significant inverse relation between aspirin and risk of HCC using both linear and non-linear models.

Keywords: Aspirin; Liver Cancer; Hepatocellular Carcinoma.

1. Introduction:

Liver cancer is the sixth most prevalent cancer globally, with over 840,000 new cases reported in 2018 (1). Indeed, this malignancy remains a highly fatal disease, with European mean age-standardized survival rate at five years sitting at just 12% at present (2). Hepatocellular carcinoma (HCC) is the most common form of liver cancer, comprising approximately 70–85% of the total cases, and represents the third highest cause of cancer-related mortality worldwide (3). Given this considerable incidence rate, the identification of efficacious interventions or programs that could prevent, or indeed attenuate, disease onset and progression is of paramount importance.

Aspirin, one of the most ubiquitously consumed drugs worldwide, has proven benefits in the context of cardiovascular disease (4) and colorectal cancer (5-7), although there exists a paucity of chemoprotective evidence in relation to other cancers. In fact, the evidence has been conflicting at times, with trial data in discordance with observational findings at times. Schreinemachers and Everson initially reported that aspirin was associated with reductions in incidence of overall cancer, as well as breast, trachea, bronchus and lung cancer (8). Concordantly, Tsoi et al reported a significant reduction in cancer of the liver, stomach, colorectal, lung, pancreas, and oesophagus, as well as leukaemia following aspirin use (9). However, an 11-year-long randomised control trial (RCT) of 39,876 US women, reported no beneficial effects associated with aspirin use and all forms of cancer (10). In addition, some evidence exists which suggests that aspirin may be effective only in the prevention of certain types of cancer; for instance, Flossmann et al reported a beneficial effect only for colorectal cancer (11).

Although empirical evidence has demonstrated that aspirin may be chemoprotective in the context of HCC (12-16), equivocality is ever-present. Such inconsistencies may be attributable to varying study designs or follow-up durations, in addition to relatively modest sample sizes, accompanied by wide confidence intervals, which makes consensus difficult to attain. Thus, in the current systematic review and dose-response analysis, we aimed to pool the evidence from cohort studies examining the effects of aspirin use on HCC incidence and to subsequently explore the dose-response if indeed a relationship truly exists.

2. Materials and methods

2.1. Search Strategy

This systematic review was performed according to the Preferred Reporting Items for Systematic Review and Meta-analysis [PRISMA] Statements(17). A systematic literature search was conducted from inception, without time or language restrictions, in PubMed/MEDLINE (https://www.ncbi.nlm.nih.gov/pubmed), Scopus (https://www.scopus.com), Cochrane library (https://www.cochranelibrary.com/), and Web of Science databases (http://apps.webofknowledge.com) up to 29th October 2019. The Supplementary Table 1 presents the search terms that were used in each database. Furthermore, the reference lists of relevant original and review studies were scrutinized to identify additional studies of relevance.

2.2. Inclusion and exclusion criteria

The following inclusion criteria were considered in this study: 1) Studies which report a retrospective or prospective design; 2) Studies which reported hazard ratio (HR), odds ratio (OR), or risk ratio (RR) for HCC based on aspirin use categories. Review papers, case reports, ecological studies, editorials, non-human studies, *in vitro* research, or letters without sufficient data were excluded from the present review. Furthermore, studies containing patients diagnosed with HCC at baseline were excluded also. In studies that reported multiple timepoints, data from the longest follow-up period was used in the meta-analysis.

2.3. Data extraction and quality assessment

After removal of duplicated studies, screening was conducted by two authors independently based on title and abstract. Full texts of studies were examined by two authors (HKV and AS) and discrepancies between authors were resolved by a senior author (YZ). The following data were extracted from the included studies: first author`, location of study, year of publication, number of participants, number of cases, gender distribution of participants, mean age of participants, aspirin use and dose, length of follow up, fully adjusted model and 95% CIs of liver cancer risk. Finally, two authors evaluated the quality of the included studies independently using the Newcastle-Ottawa Quality Assessment Scale (18).

2.4. Statistical analysis

The results of the included studies were combined by DerSimonian and Laird random effects model (19). Based on the included studies, the aspirin-naïve group was considered as the reference category. The fully adjusted model considered nine models in the combination of results. The subgroup analysis was based on the type of cohort assessed, as each study was run in different populations (*e.g.*, public population or population with liver disease, such as hepatitis or cirrhosis). In addition, Cochran Q test (P heterogeneity) and I^2 statistic were used to evaluate heterogeneity among the included studies, while meta-regression based on the duration of follow-up was applied in order to identify the probable source of detected heterogeneity. Studies which reported sufficient data in terms of number of participants, number of cases, and dosage of aspirin were included in dose-response analysis. Restricted cubic splines with three knots at percentiles 10%, 50%, and 90% of the distribution were applied to linear and non-linear dose-response analysis (20). We calculated the linearity curve of the meta-analysis by testing the null hypothesis that the coefficient of the second spline was equal to zero with GLST. Sensitivity analysis was performed to investigate the effect of each study on the overall analysis. Funnel plots, as well as Begg's and Egger's asymmetry tests were all used in order to detect any publication bias which may have existed. All statistical analyses were conducted by STATA 14.0 software and a p value <0.05 was considered significant.

3. Results

3.1. Literature search

The flow diagram of the search strategy is provided in Figure 1. After removing duplicate studies from the systematic search, 392 articles remained for screening. During title and abstract screening 346 irrelevant studies were excluded and 46 studies included in the full text screening. From these, 38 studies were excluded as they did not meet the predefined inclusion criteria (Supplemental Table 2) and eight studies with 2,604,319 participants were ultimately included (21-28).

3.2. Study characteristics and quality assessment

Included studies were published between 2012 to 2019 (Table 1). All studies were conducted in both males and females, and the mean length of follow-up was 8.9 years. Out of the eight studies, five were conducted in the general population (21, 23, 24, 27, 28), while the remaining three were focused on patients with liver disease(22, 25, 26). One study was conducted in Hong Kong (21), one in Taiwan (22), three in US (23, 27, 28), and the remaining three in South Korea (24-26). Quality assessment of the included articles was performed using NOS scores, in which most articles scored as having high quality (Supplemental Table 3). Three studies achieved a score of eight, while the remainder scored nine. The most commonly detected weakness of the included studies was in adjustment for perceived cofounders.

3.3. Main results of the analysis

Eight studies with 2,604,319 participants included in this dose-response analysis (21-28), the results of which were combined by DerSimonian and Laird random effects model. The combined results suggested a significant reduction in the risk of liver cancer in participants who used aspirin (HR 0.59, 95% CI 0.47-0.75, $P_{heterogeneity}$=0.001, I^2=90%) (Fig. 2). There was a significant heterogeneity between results of included studies, but this heterogeneity refers to amount of effect size and all studies show reverse relation. In addition to that, all studies independently demonstrated a reduction in the risk of liver cancer. Four studies with total of 2,168,012 participants were included in the dose-response analysis (21, 22, 24, 27). The linear dose-response model showed a significant inverse association between aspirin dose and risk of liver cancer (exp (b) = 0.994, p<0.001) (Fig. 3). Furthermore, the non-linear dose-response analysis revealed a comparable association ($Coef_1$=-0.008, p_1=0.04, $Coef_2$=0.033, p_2=0.13) (Fig. 4). Non-linear graph shows aspirin to have effective at doses up to around 100 mg per day, after which higher doses do not confer a further significant effect on HCC incidence.

3.4. Sub-grouped analysis and meta-regression

Results of the subgroup analyses and meta-regression are summarized in Supplemental Figure 1. We stratified studies based on type of population (*i.e.*, general population or population with liver disease, such

as hepatitis or cirrhosis). Subgroup analyses did not show a significant difference in risk of liver cancer (heterogeneity between groups p=0.29) between general populations (HR 0.60, 95% CI 0.56-0.63) and populations with liver disease (HR 0.66, 95% CI 0.55-0.80). Additionally, meta-regression based on the duration of follow-up was not significant for HCC either (coef = -0.0120072, p=0.51).

3.5. Publication bias and Sensitivity analysis

Funnel plot, Begg's rank correlation test, and Egger's regression asymmetry test were used to detect publication bias; however, the funnel plots did not reveal any asymmetry between the studies (Fig 5). Furthermore, Begg's and Egger's regression tests were not found to be significant either (p=0.21 and p=0.99, respectively). Finally, sensitivity analysis did not show any significant differences beyond the limits of 95% CI between calculated combined results (Supplemental Fig 2).

4. Discussion

Liver cancer is the sixth most prevalent cancer globally and the third most common cause of cancer-related death (3), with incidence and mortality rates ever-increasing (29). In vitro studies suggest that NSAIDs, such as aspirin, have preventive and therapeutic benefits for liver cancer (30, 31). Furthermore, human studies have yielded promising associations with aspirin use and the risk of liver cancer (32, 33). However, as of yet, no systematic compilation and dose-response analysis of available evidence has been performed. The principal findings of this study were that a significant reduction in risk of liver cancer was evident in participants who consumed aspirin. Moreover, linear and non-linear dose-response models showed a significant inverse association between aspirin dose and risk of liver cancer, with largely diminished returns at doses greater than 100 mg per day.

The chemoprotective influence of aspirin has been documented in epidemiological evidence since the early 1980's, with more contemporary evidence from the Physician's Health Study (34), the Women's Health Study (10), the UK Transient Ischaemic Attack Aspirin Trial (11), the British Doctors Aspirin Trial (11), and the Colorectal Adenoma/carcinoma Prevention Programme (35). In a recent benefit-harm

investigation which documented the impact of taking aspirin for 10 years, the authors reported absolute reductions in incidence of cancer from 0.76% in women to 2.51% in men (36). In the present study, included articles were contemporary, all being published between 2012 to 2019, and utilized an equitable split of both genders with an appropriately long mean follow-up (~9 years). Five out of eight studies were conducted in the general population (21, 23, 24, 27, 28) while the others included patients with liver disease (22, 25, 26). One study was conducted in Hong Kong (21), one in Taiwan (22), three in US (23, 27, 28), and three in South Korea (24-26).

Eight studies with a sum total of 2,604,319 participants were included in this dose-response analysis (21-28). Five studies with 2,547,188 participants reported risk of liver cancer based on waist circumference (37-41). Results of the included studies were combined by DerSimonian and Laird random effects model and the combined results suggested a significant reduction in the risk of liver cancer in participants who used aspirin (HR 0.59, 95% CI 0.47-0.75, I^2=90%) (Fig. 2). All studies also showed reduction in the risk of liver cancer independently. A clear inverse dose-response association was uncovered between aspirin dosing and development of liver cancer in both linear and non-linear models. Interestingly, we noted a substantially diminishment in this association once dosage exceeded 100 mg per day, suggesting that higher doses of the drug offered little in the way of additional chemoprotective benefits. Indeed, the analysis suggests that even daily consumption of the low-dose formulation aspirin (81 mg), which is typically prescribed prophylactically to those at risk of occlusive cardiovascular or cerebrovascular events, may achieve the majority of the desired beneficial effects. In addition, although not assessed within this analysis, use of such a dose may maintain a desired degree of safety, at least in those who do not represent a significant hemorrhagic risk.

While there are a range of potential extrahepatic health benefits associated with low-dose aspirin ingestion, we now recognise that such regimens also carry with them a considerable potential for harm, particularly in certain at-risk populations. An important risk associated with sustained use of aspirin is gastrointestinal bleeding, which is of clinical importance in patients with chronic liver disease, where

gastrointestinal bleeding from esophageal varices or portal hypertensive gastropathy are prevalent clinical complications (42). Aspirin-induced bleeding can lead to catastrophic intracranial haemorrhage and therein also increase the risk of suffering from gastric ulceration and bleeding. Furthermore, high doses of the coxib NSAIDs is known to increase the thrombotic cardiovascular risk in a manner which is directly related to dose and age (43).

Strength and limitations

The main strength of this study is the incorporation of an extremely large sample size, consisting of over 2.5 million participants. This provided findings that are generalizable and afforded the opportunity for subsequent dose-response analysis. The current study was found to be free of significant publication bias and is therefore unlikely to be substantially impacted by unpublished studies that returned negative results. The sample size used to generate the evidence reported in this systematic review is large; however, the results do not necessarily provide definitive findings of a causal inference due to the non-randomized design. In fact, as the studies contributing to this meta-analysis were all observational in design, we must consider the possibility of reverse causality and the healthy-person bias; that is to say, could individuals who are innately less prone to liver cancer, or those who are more cognizant of their overall health, be more likely to take aspirin as prophylaxis for other diseases?

In a similar manner, it is indeed worth considering whether significant confounding factors may exist within the compiled studies. For instance, aspirin is commonly prescribed in conjunction with a hypocholesterolemic agent such as a statin, which in itself may reduce the risk of liver cancer in an individual (44). Unfortunately, although the consumption of other potentially chemoprotective agents (including other NSAIDs, statins, and metformin) was recorded and adjusted for in a number of the studies analyzed, several others explicitly outline that concomitant medications could not be assessed or excluded. Therefore, it is recommended that such studies be conducted in order to confirm the veracity of the findings highlighted in this analysis and to control for potential confounders. Furthermore, although the literature

was searched extensively, grey or unpublished literature was not explored to limit the possibility of publication bias.

As aspirin is readily available in over-the-counter formulations, it is possible that the recorded consumption of the medication may have been an underestimated in the included studies. However, as self-reporting was a prominent data collection method utilized in these studies rather than prescription records, it is less likely that underestimation occurred as a result of unrecorded over-the-counter doses. Although this method carries with it a degree of unavoidable recall bias.

Regarding the potential for misclassification bias, the majority of studies included in this analysis utilized the International Classification of Diseases (ICD) 9 or 10, which brings consistency to the classification; although the means of diagnosis was not assessed and potentially differed between cohorts. Finally, as the populations assessed in these studies generally reported a mean age of greater than 60 years, a cohort which may suffer from an array of additional comorbidities, it is important to consider the impact of mortality as a competing risk. Indeed, just one of the eight studies included in this meta-analysis explicitly adjusted for such factors (13), suggesting that this may have impacted somewhat upon the cumulative result.

5. Conclusion

In the present meta-analysis, a significant reduction in risk of liver cancer was evident in participants who consumed aspirin. In addition, a significant inverse association between aspirin dose and risk of liver cancer was demonstrated, which displayed diminishing benefits at doses greater than 100 mg per day in non-linear analyses. This may have important clinical ramifications and adds support for the use of daily aspirin as a primary preventive strategy for liver cancer. However, as the studies included in this meta-analysis were all observational in nature, it is now essential that high-quality, large scale RCTs are conducted in order to prove the efficacy of such a regimen in a highly controlled context. Finally, given the potentially injurious side effects of prolonged aspirin use or use in bleed-risk populations, careful monitoring and supervision by clinicians is warranted.

Conflict of interest statement

The authors declare no conflict of interest.

References

1. Liver cancer 2018 [updated 2018/04/24/. Available from: https://www.wcrf.org/dietandcancer/liver-cancer.
2. De Angelis R, Sant M, Coleman MP, Francisci S, Baili P, Pierannunzio D, et al. Cancer survival in Europe 1999–2007 by country and age: results of EUROCARE-5—a population-based study. The lancet oncology. 2014;15(1):23-34.
3. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA: a cancer journal for clinicians. 2011;61(2):69-90.
4. Preventive U. Services Task Force: Aspirin for the prevention of cardiovascular disease: US Preventive Services Task Force recommendation statement. Ann Intern Med. 2009;150(6):396-404.
5. Algra AM, Rothwell PM. Effects of regular aspirin on long-term cancer incidence and metastasis: a systematic comparison of evidence from observational studies versus randomised trials. The lancet oncology. 2012;13(5):518-27.
6. Cole BF, Logan RF, Halabi S, Benamouzig R, Sandler RS, Grainge MJ, et al. Aspirin for the chemoprevention of colorectal adenomas: meta-analysis of the randomized trials. JNCI: Journal of the National Cancer Institute. 2009;101(4):256-66.
7. Rothwell PM, Price JF, Fowkes FGR, Zanchetti A, Roncaglioni MC, Tognoni G, et al. Short-term effects of daily aspirin on cancer incidence, mortality, and non-vascular death: analysis of the time course of risks and benefits in 51 randomised controlled trials. The Lancet. 2012;379(9826):1602-12.
8. Schreinemachers DM, Everson RB. Aspirin use and lung, colon, and breast cancer incidence in a prospective study. Epidemiology. 1994:138-46.
9. Tsoi KK, Ho JM, Chan FC, Sung JJ. Long‐term use of low‐dose aspirin for cancer prevention: A 10‐year population cohort study in Hong Kong. International journal of cancer. 2019;145(1):267-73.
10. Cook NR, Lee I-M, Gaziano JM, Gordon D, Ridker PM, Manson JE, et al. Low-dose aspirin in the primary prevention of cancer: the Women's Health Study: a randomized controlled trial. Jama. 2005;294(1):47-55.
11. Flossmann E, Rothwell PM. Effect of aspirin on long-term risk of colorectal cancer: consistent evidence from randomised and observational studies. The Lancet. 2007;369(9573):1603-13.
12. Simon TG, Ma Y, Ludvigsson JF, Chong DQ, Giovannucci EL, Fuchs CS, et al. Association between aspirin use and risk of hepatocellular carcinoma. JAMA oncology. 2018;4(12):1683-90.
13. Lee T-Y, Hsu Y-C, Tseng H-C, Yu S-H, Lin J-T, Wu M-S, et al. Association of daily aspirin therapy with risk of hepatocellular carcinoma in patients with chronic hepatitis B. JAMA internal medicine. 2019.
14. Hwang IC, Chang J, Kim K, Park SM. Aspirin use and risk of hepatocellular carcinoma in a national cohort study of korean adults. Scientific reports. 2018;8(1):4968.
15. Petrick JL, Sahasrabuddhe VV, Chan AT, Alavanja MC, Beane-Freeman LE, Buring JE, et al. NSAID use and risk of hepatocellular carcinoma and intrahepatic cholangiocarcinoma: the liver cancer pooling project. Cancer Prevention Research. 2015;8(12):1156-62.
16. Sahasrabuddhe VV, Gunja MZ, Graubard BI, Trabert B, Schwartz LM, Park Y, et al. Nonsteroidal anti-inflammatory drug use, chronic liver disease, and hepatocellular carcinoma. JNCI: Journal of the National Cancer Institute. 2012;104(23):1808-14.
17. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Systematic reviews. 2015;4(1):1.

18. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. European journal of epidemiology. 2010;25(9):603-5.
19. Jackson D, White IR, Thompson SG. Extending DerSimonian and Laird's methodology to perform multivariate random effects meta‐analyses. Statistics in medicine. 2010;29(12):1282-97.
20. Harre Jr FE, Lee KL, Pollock BG. Regression models in clinical studies: determining relationships between predictors and response. JNCI: Journal of the National Cancer Institute. 1988;80(15):1198-202.
21. Tsoi KKF, Ho JMW, Chan FCH, Sung JJY. Long-term use of low-dose aspirin for cancer prevention: A 10-year population cohort study in Hong Kong. International Journal of Cancer. 2019.
22. Lee TY, Hsu YC, Tseng HC, Yu SH, Lin JT, Wu MS, et al. Association of Daily Aspirin Therapy With Risk of Hepatocellular Carcinoma in Patients With Chronic Hepatitis B. JAMA Intern Med. 2019.
23. Simon TG, Ma Y, Ludvigsson JF, Chong DQ, Giovannucci EL, Fuchs CS, et al. Association Between Aspirin Use and Risk of Hepatocellular Carcinoma. JAMA Oncol. 2018;4(12):1683-90.
24. Hwang IC, Chang J, Kim K, Park SM. Aspirin Use and Risk of Hepatocellular Carcinoma in a National Cohort Study of Korean Adults. Scientific reports. 2018;8(1):4968.
25. Oh S, Shin S, Lee S, Kim T, Nam S-J, Park J, et al. Aspirin and the risk of hepatocellular carcinoma development in patients with compensated alcoholic cirrhosis. Journal of Hepatology. 2017;66(1):S629-S30.
26. Lee M, Chung GE, Lee JH, Oh S, Nam JY, Chang Y, et al. Antiplatelet therapy and the risk of hepatocellular carcinoma in chronic hepatitis B patients on antiviral treatment. Hepatology. 2017;66(5):1556-69.
27. Petrick JL, Sahasrabuddhe VV, Chan AT, Alavanja MC, Beane-Freeman LE, Buring JE, et al. NSAID Use and Risk of Hepatocellular Carcinoma and Intrahepatic Cholangiocarcinoma: The Liver Cancer Pooling Project. Cancer prevention research (Philadelphia, Pa). 2015;8(12):1156-62.
28. Sahasrabuddhe VV, Gunja MZ, Graubard BI, Trabert B, Schwartz LM, Park Y, et al. Nonsteroidal anti-inflammatory drug use, chronic liver disease, and hepatocellular carcinoma. Journal of the National Cancer Institute. 2012;104(23):1808-14.
29. McGlynn KA, London WT. The global epidemiology of hepatocellular carcinoma: present and future. Clinics in liver disease. 2011;15(2):223-43.
30. FODERÀ D, D'ALESSANDRO N, CUSIMANO A, POMA P, NOTARBARTOLO M, LAMPIASI N, et al. Induction of apoptosis and inhibition of cell growth in human hepatocellular carcinoma cells by COX‐2 inhibitors. Annals of the New York Academy of Sciences. 2004;1028(1):440-9.
31. Leng J, Han C, Demetris AJ, Michalopoulos GK, Wu T. Cyclooxygenase-2 promotes hepatocellular carcinoma cell growth through Akt activation: evidence for Akt inhibition in celecoxib-induced apoptosis. Hepatology. 2003;38(3):756-68.
32. Coogan PF, Rosenberg L, Palmer JR, Strom BL, Zauber AG, Stolley PD, et al. Nonsteroidal anti-inflammatory drugs and risk of digestive cancers at sites other than the large bowel. Cancer Epidemiology and Prevention Biomarkers. 2000;9(1):119-23.
33. Cibere J, Sibley J, Haga M. Rheumatoid arthritis and the risk of malignancy. Arthritis & Rheumatism: Official Journal of the American College of Rheumatology. 1997;40(9):1580-6.
34. Gann PH, Manson JE, Glynn RJ, Buring JE, Hennekens CH. Low-dose aspirin and incidence of colorectal tumors in a randomized trial. JNCI: Journal of the National Cancer Institute. 1993;85(15):1220-4.
35. Burn J, Gerdes A-M, Macrae F, Mecklin J-P, Moeslein G, Olschwang S, et al. Long-term effect of aspirin on cancer risk in carriers of hereditary colorectal cancer: an analysis from the CAPP2 randomised controlled trial. The Lancet. 2011;378(9809):2081-7.
36. Cuzick J, Thorat M, Bosetti C, Brown PH, Burn J, Cook N, et al. Estimates of benefits and harms of prophylactic use of aspirin in the general population. Annals of Oncology. 2014;26(1):47-57.
37. Pang Y, Kartsonaki C, Guo Y, Chen Y, Yang L, Bian Z, et al. Central adiposity in relation to risk of liver cancer in Chinese adults: A prospective study of 0.5 million people. Int J Cancer. 2019.
38. Wei L, Li N, Wang G, Feng X, Lyu Z, Li X, et al. Waist Circumference Might Be a Predictor of Primary Liver Cancer: A Population-Based Cohort Study. Frontiers in oncology. 2018;8:607.
39. Lee J, Yoo SH, Sohn W, Kim HW, Choi YS, Won JH, et al. Obesity and hepatocellular carcinoma in patients receiving entecavir for chronic hepatitis B. Clinical and molecular hepatology. 2016;22(3):339-49.
40. Campbell PT, Newton CC, Freedman ND, Koshiol J, Alavanja MC, Beane Freeman LE, et al. Body Mass Index, Waist Circumference, Diabetes, and Risk of Liver Cancer for U.S. Adults. Cancer Res. 2016;76(20):6076-83.

41. Schlesinger S, Aleksandrova K, Pischon T, Fedirko V, Jenab M, Trepo E, et al. Abdominal obesity, weight gain during adulthood and risk of liver and biliary tract cancer in a European cohort. Int J Cancer. 2013;132(3):645-57.
42. Valkhoff VE, Sturkenboom MC, Kuipers EJ. Risk factors for gastrointestinal bleeding associated with low-dose aspirin. Best Practice & Research Clinical Gastroenterology. 2012;26(2):125-40.
43. Derry S, Loke YK. Risk of gastrointestinal haemorrhage with long term use of aspirin: meta-analysis. BMJ (Clinical research ed). 2000;321(7270):1183-7.
44. Kim G, Jang SY, Nam CM, Kang ES. Statin use and the risk of hepatocellular carcinoma in patients at high risk: A nationwide nested case-control study. J Hepatol. 2018;68(3):476-84.

Fig. 1. Flow chart of included studies, including identification, screening, eligibility and the final included sample.

Fig 2. Forest plot of Aspirin usage and risk of Liver Cancer, including eight individual studies and 2,604,319 participants and overall hazard ratios, with respective weightings. Pooled results of included studies showed a significant reduction in risk of HCC in participants who used aspirin (HR 0.59, 95% CI 0.47-0.75, I2=90%).

Fig 3. Linear dose-response relationship between Aspirin usage, in mg/day, and risk of Liver Cancer, presented as hazard ratio, with the associated exponential and p-value. The linear dose-response model showed a significant inverse association between aspirin dose and risk of liver cancer (exp (b) = 0.994, $p<0.001$).

Fig 4. Non- linear dose-response relationship between Aspirin usage, in mg/day, and risk of Liver Cancer, presented as hazard ratio, with the resultant coefficient and p-value. The non-linear dose-response analysis revealed an inverse significant association (Coef=-0.008, p=0.04).

Fig 5. Funnel plots, with pseudo 95% confidence intervals, of Aspirin usage and risk of Liver Cancer, presented with Egger's and Begg's test statistics, respectively