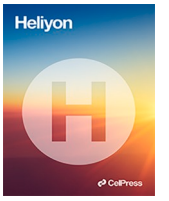
Heliyon 10 (2024) e23203

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Review article

The relationship between nonsteroidal anti-inflammatory drugs and cancer incidence: An umbrella review

Puze Wang [a,1], Bo Chen [a,1], Yin Huang [a], Jin Li [a], Dehong Cao [a], Zeyu Chen [a], Jinze Li [a], Biao Ran [a], Jiahao Yang [a], Ruyi Wang [a,b], Qiang Wei [a,**], Qiang Dong [a,***], Liangren Liu [a,2,*]

[a] Department of Urology, West China Hospital, Sichuan University, Chengdu, China
[b] Department of Urology, Hospital of Chengdu University, Chengdu, China

ARTICLE INFO

Keywords:
NSAIDs
Cancer
Umbrella review
Systematic review
Meta-analysis

ABSTRACT

Several clinical and preclinical studies have shown that nonsteroidal anti-inflammatory drugs (NSAIDs), particularly aspirin, reduce the incidence of various cancer types. However, there is still a lack of literature evaluating the overall association between multiple cancer morbidities and NSAIDs. Thus, we conducted an umbrella review to evaluate the quality of evidence, validity, and biases of the existing systematic reviews and meta-analyses on the relationships between NSAIDS and multiple tumor incidence outcomes. We found that NSAIDs might be associated with a decreased risk of several cancers, including the central nervous system, breast, esophageal, gastric, head and neck, hepatocellular, cholangiocarcinoma, colorectal, endometrial, lung, ovary, prostate, and pancreatic cancers, but regular intake of any dose of non-aspirin NSAIDs (NA-NSAIDs) could increase the incidence of kidney cancer. However, most of included studies are evaluated as low quality according to our evidence assessment. Furthermore, due to the potential side effects, such as hemorrhage, digestive symptoms and peptic ulcer, it is still not recommend to use NSAIDs regularly to prevent cancers.

1. Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are a group of compounds with unrelated chemical structures and different mechanisms. More than 100 of them have been studied, many of which have been approved for clinical application. They have been used worldwide for treating cardiovascular events, rheumatic immune diseases, and other painful conditions, owing to their potent anti-inflammatory, analgesic, and antipyretic activities [1]. Among the causes of death worldwide, cancer accounts for a large proportion at all income levels, according to the Cancer Mondial Database, especially in developing countries [2]. Data from the United States Cancer Statistics (USCS) reveal approximately one in every five deaths was due to cancer, and nearly 600 patients had cancer for

* Corresponding author. Department of Urology, West China Hospital, Sichuan University, Chengdu, China.
** Corresponding author.
*** Corresponding author.
E-mail addresses: weiqiang933@126.com (Q. Wei), dqiang888@163.com (Q. Dong), liuliangren@scu.edu.cn (L. Liu).
[1] These authors contributed equally as co-first author.
[2] Main research field includes prostate diseases and andrology.

https://doi.org/10.1016/j.heliyon.2023.e23203
Received 24 June 2023; Received in revised form 28 November 2023; Accepted 29 November 2023
Available online 12 January 2024

every 100,000 people in 2019 [3]. Owing to this increasing burden, topics related to the prevention and treatment of cancers have received much attention globally.

Several clinical and preclinical studies have detected that NSAIDs, especially aspirin, can reduce the incidence of various types of cancer as they decrease the level of inflammatory mediators around cancer cells [4–8]. However, several studies have reported that NSAIDs have no significant advantage in reducing the morbidity of some cancer types [9,10]. Although the associations between NSAID intake and various cancer incidences have been assessed in an increasing number of studies, including many systematic reviews and meta-analyses of diverse quality, there is still a lack of comprehensive literature evaluating the overall connection between multiple cancer morbidities and NSAIDs. In addition, the dose-response relationship between NSAID intake and cancer risk remains inconsistent in studies with different exposures. To comprehensively evaluate the quality of evidence, possible biases, and validity of the associations between different types of NSAIDs and diverse cancer outcomes, we conducted an umbrella review of the evidence according to existing systematic reviews and meta-analyses.

2. LITERATURE and methods

2.1. Literature search

Systematic reviews and meta-analyses in databases, including PubMed, Embase, Web of Science, and the Cochrane Database of Systematic Reviews, were searched using the following strategies: (Non-steroidal anti-inflammatory drugs OR Nonsteroidal anti-inflammatory drugs OR Nonsteroidal anti-inflammatory agents OR Nonsteroidal anti-inflammatory analgesics OR NSAIDs OR NSAID OR NSAIAS OR NSAIA) AND (systematic review OR meta-analysis). The 2020 Sign Guidance was also referenced in the literature search [11,12]. Two independent investigators (PZW and YH) screened titles and abstracts and selected eligible articles through a full-text review. A third investigator (LRL) resolved discrepancies between the two investigators during the selection process. Our study is registered on PROSPERO (Number: CRD42023417591).

2.2. Umbrella review methods

After excluding studies inconsistent with our criteria, existing data from systematic reviews and meta-analyses were searched and evaluated by referring to umbrella methods [13,14]. We also excluded systematic reviews without meta-analyses because of a lack of data on the analysis of different NSAID doses in participants.

2.3. Eligibility criteria

In our review, NSAIDs were defined as a group of drugs that can inhibit cyclooxygenase (COX) to prevent arachidonic acid (AA) from transforming into prostanoids. We included systematic reviews with meta-analyses published in English that evaluated overall NSAIDs and individual drugs. Other categories of studies (cohort studies, case-control studies, randomized controlled trials [RCTs], nonrandomized controlled trials [NRCTs], reviews, case reports, and letters) were excluded. The baseline characteristics of the participants were not used as screening criteria. If a meta-analysis reported the incidence of two or more cancers, we extracted the data for each outcome separately. For studies with similar cancer outcomes, we selected a larger number of participants. We excluded analyses that only reported the total cancer incidence because the cancer data could not be extracted separately through subgroup analysis. Meta-analyses involving animals and laboratories were also excluded.

2.4. Data extraction

PZW and BC independently extracted the following data from included studies: 1) name of the first author, 2) year of publication, 3) category of exposure (categories of NSAIDs), 4) outcome, 5) the number of included studies, 6) the number of participants in each study, 7) study design (case-control, cohort, RCT, and NRCT), 8) follow-up time, 9) type of comparisons (highest versus lowest, any versus never, and increment or reduction of any dose of NSAIDs), 10) the estimated summary effect (RR, relative risk; OR, odds ratio) and corresponding 95 % confidence intervals (CIs), and 11) journal name. If the meta-analyses reported various doses of NSAIDs (low-, medium-, or high-dose), we chose the data of the groups with higher-dose intakes.

2.5. Data analysis

We extracted related data and estimated the summary effect with the 95 % CI reported in each meta-analysis, if available [11]. If an article included meta-analyses of both cohort and case-control studies and the analysis was performed separately without an overall outcome, we extracted the data by study design. The I^2 test and Cochran's Q test were performed to estimate the heterogeneity among the studies, and Egger's test was performed to calculate the publication bias in every study [15]. Statistical significance was set at $P < 0.10$ for Egger's test and test for heterogeneity. For other tests, a $P < 0.05$ was regarded as significant. In addition, if meta-analyses presented dose-response relationships, we extracted the associations as much as possible.

2.6. Assessment of methodological quality of included studies and quality of evidence

AMSTAR was used to evaluate the methodological quality of the included articles using 11 items, which has been reported as a valid standard for assessing the quality of systematic reviews and meta-analyses [16–18]. In addition, we evaluated the strength of the evidence for each outcome presented in the umbrella review using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) classification system. The evidence classifications were divided into "high," "moderate," "low," and "very low" quality to make recommendations [19].

3. Results

3.1. Characteristics of meta-analyses

A flowchart of the literature screening and selection procedures is shown in Fig. 1. We identified 7691 articles, and finally, 80 meta-analyses were conducted based on the criteria above. Twenty unique cancer outcomes were extracted from the eligible studies. Because of the large number of meta-analyses that evaluated aspirin separately, subgroup analyses of aspirin NSAIDs and non-aspirin NSAIDs (NA-NSAIDs) were also conducted. The associations between NSAID intake and cancer incidence are shown in Table 1. Table 2 shows the related information for aspirin NSAIDs and NA-NSAIDs.

3.2. Associations between total NSAIDs and cancer incidence

3.2.1. Significant associations

In total, 36 independent meta-analyses presented the relationship between NSAIDs without classification and cancer rates, including 14 unique cancer outcomes. A secondary study involving 38 primary articles revealed that NSAIDs may decrease the risk of breast cancer without a linear relationship [20]. Overall, NSAID use could reduce the incidence of central nervous system (CNS) tumors, accompanied by a significant dose-response relationship. This meta-analysis demonstrated that increasing the cumulative 100 defined daily doses of NSAIDs resulted in a 5 % decrease in CNS tumor risk (RR = 0.95, 95 % CI = 0.92–0.98, P = 0.003), and the proportion reached 6 % after increasing the duration of NSAID intake by 2 years (RR = 0.94, 95 % CI = 0.92–0.98, P = 0.001). However, the results did not show a positive association with meningiomas [21]. Another meta-analysis found that the risk of esophageal squamous cell carcinoma (ESCC) was significantly decreased by 52 % in patients exposed to NSAIDs compared to that in controls [22]. In addition, a meta-analysis reported that the incidence of ESCC could be slightly lower when NSAIDs were used once or more daily than when used less than once, and no difference was found after comparing two groups with different duration categories and methods of obtaining exposure data. In addition, NSAIDs are positively associated with the prevention of gastric cancer without a clear linear association, especially in non-cardiac gastric tumors [23]. Furthermore, NSAID use could be associated with a significantly lower incidence of oropharyngeal, laryngeal, and other head and neck cancers. A dose-relationship meta-analysis reported that an increase of 2 prescriptions/week of NSAIDs resulted in a 4 % decrease in head and neck cancer risk with statistical significance (RR = 0.96, 95 % CI = 0.94–0.99, P < 0.001) [24]. The highest dose of NSAID consumption also correlated with a lower risk of both incidence

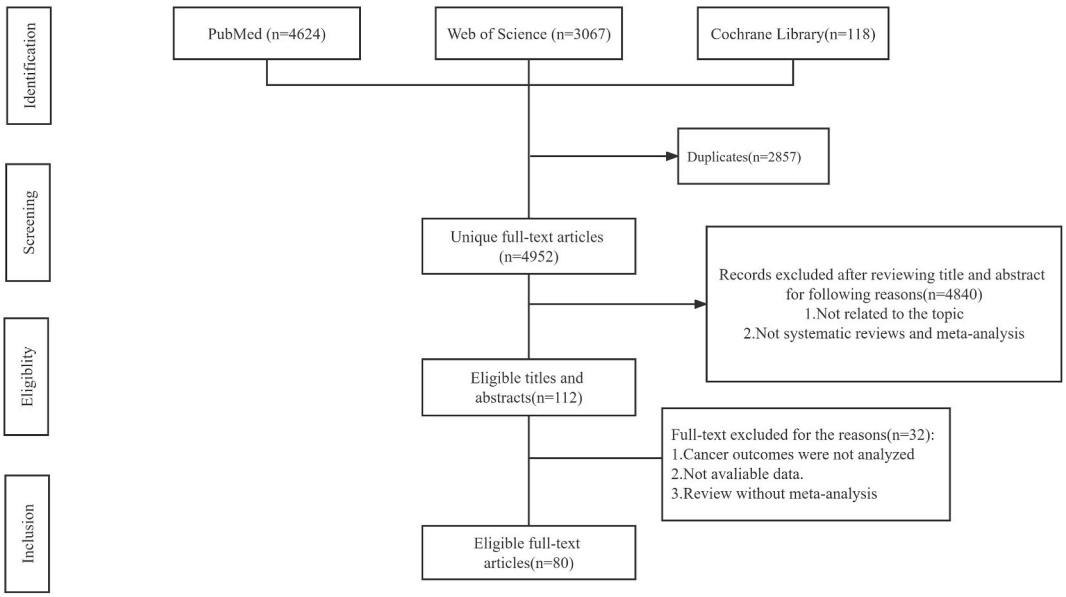


Fig. 1. Flowchart of the systematic search and selection process.

Table 1
Associations between overall NSAIDs and cancer outcomes.

Outcome	Study	No. of cases/ total	MA metric	Estimates	95%CI	No. of studies	Cohort	Case-control	Effects model	I^2; *Q* test *P* value	Egger test *P* value
Significant associations											
Breast cancer	Takkouche, B, 2009	87,421/ 2,625,742	RR	0.88	0.84–0.93	38	22	16	Random	82 %; <0.001	0.34
CNS cancer	Zhang T,2017	19,394/ 667,085	RR	0.89	0.81–0.95	12	4	8	Random	55.8 %; 0.000	0.001
Esophageal cancer	Sun, 2011	1103/NA	OR	0.58	0.47–0.72	7	0	7	Fixed	0 %, 0.57	0.90
Gastric cancer	Tian, 2010	3215/ 548,267	RR	0.76	0.70–0.82	15	4	11	Fixed	38.6 %, NA	0.01
Head and neck cancer	Shi, 2017	12,637/ 653,828	RR	0.84	0.76–0.93	11	4	7	Random	70.5 %, 0.000	0.245
Liver cancer	Pang, 2017	3225/ 809,886	HR	0.81	0.69–0.94	7	3	4	Random	66.6 %, <0.001	0.564
Prostate cancer	Shang, 2018	123,384/ 379,057	RR	0.89	0.81–0.98	17	7	10	Random	94.00 %, 0.000	0.185
Skin cancer	Muranushi, 2014	6004/ 198,009	RR	0.82	0.71–0.94	8	3	5	Random	64.5 %, 0.003	0.25
Non-significant associations											
Pancreatic cancer	Zhang, 2015	2298/ 45,877	OR	0.97	0.86–1.10	5	1	4	Random	0.0 %; 0.451	0.413
Cholangiocarcinoma	Lapumnuaypol, K,. 2019	NA/ 9,200,653	OR	0.79	0.28–2.21	2	1	1	Random	57.0 %; 0.13	NA
Colon cancer	Harewood, 2021	8003/ 681,830	NA	0.83	0.65–1.06	3	3	0	Random	64.4 %; 0.06	NA
Melanoma	Li, 2013	90,343/ 930,659	RR	1.00	0.93–1.07	11	6	5	Random	17.5 %; 0.272	NA
Non-Hodgkin's lymphoma	Bernatsky, S, 2007	5794/ 40,501	OR	0.93	0.74–1.14	7	1	6	Random	NA	NA
Lung cancer	Xu, 2012	3635/ 52,913	OR	0.8	0.63–1.03	6	0	6	Random	94 %, <0.001	NA

MA, meta-analysis; CI, confidence interval; RR, relative risk; NA, not available; OR, odds ratio; NHL, non-Hodgkin lymphoma; CNS, central nervous system.

and recurrence of hepatocellular carcinoma than did the lowest dose of NSAID intake [25].

A meta-analysis involving 123,384 patients found that NSAID intake decreased the risk of prostate cancer by 11 % with apparent heterogeneity, but long-term NSAID use (>5 years rather than >4 years) reduced morbidity (RR = 0.882, 95 % CI = 0.785–0.991, P = 0.035, I^2 = 27.40 %). In addition, subgroup analysis revealed that studies performed in North America and Europe demonstrated a stronger association than those performed in other continents did; however, the risk of advanced prostate cancer or prostate cancer with a Gleason score ≥7 did not decrease after NSAID use [26]. Finally, the overall use of NSAIDs was associated with an 18 % decreased risk of squamous cell carcinoma (SCC) of the skin compared to that of never using them, with the analysis showing significant heterogeneity [27]. The relationship between overall NSAID use and non-SCC skin cancers did not show a positive result in other studies.

3.2.2. Non-significant associations

No significant association was observed between NSAIDs and the risk of pancreatic cancer [28], cholangiocarcinoma [29], colorectal cancer [30], melanoma [31], non-Hodgkin's lymphoma (NHL) [32], or lung cancer [33].

3.3. Associations between aspirin use and cancer incidence

3.3.1. Significant associations

Aspirin intake was associated with a 6 % decrease in the overall risk of breast cancer without a linear relationship [34]. However, a subgroup analysis based on different hormone receptor statuses revealed that aspirin could only decrease the incidence of breast cancer in patients with estrogen receptor (ER)- or progesterone receptor (PR)-positive and in situ cancers. In addition, another subgroup analysis observed that a regular dose of aspirin (325 mg) and a duration of use >3 years were significantly associated with a decreased risk. In addition, aspirin can decrease the risk of cholangiocarcinoma, except in the ampulla of Vater cancer [29]. A meta-analysis also reported that the highest aspirin intake was associated with a 26 % decreased risk of colorectal cancer compared with that of the lowest intake [35]. Dose-response analysis revealed that aspirin use and colorectal cancer risk had a nonlinear relationship in that every 75 mg/d increase in consumption was related to a 10 % decrease in risk. In addition, there was also a nonlinear relationship between colorectal cancer incidence and the frequency of aspirin use, in that greater aspirin use per week

Table 2
Associations between Aspirin, NA-NSAIDS and cancer outcomes.

Outcome	Study	No. of cases/total	MA metric	Estimates	95%CI	No. of studies	Cohort	Case-control	Effects model	I^2; Q test P value	Egger test P value
Aspirin											
Significant associations											
Digestive system cancer incidence	Bosetti C, 2020	211,318/NA	RR	0.73	0.69–0.78	113	37	76	Random	86.0 %; <0.001	NA
Breast cancer	Ma, 2021	99,769/2,060,592	RR	0.94	0.91–0.97	42	27	15	Random	67.0 %; <0.001	0.016
Cholangiocarcinoma	Lapumnuaypol, 2019	NA/9,200,653	OR	0.56	0.32–0.96	5	1	4	Random	98.0 %; 0.00	0.42
Colorectal cancer	Ye,2013	18,750/NA	RR	0.74	0.64–0.83	12	12	0	Fixed	0.0 %; 0.545	0.119
Endometrial cancer	Zhang, 2016	11,998/485,290	RR	0.93	0.88–0.99	12	6	6	Random	0.0 %; 0.550	0.125
Esophageal cancer	Sivarasan N, 2013	2969/238,644	OR	0.671	0.526–0.856	9	1	8	Random	75.0 %; NA	0.05
Gastric cancer	Win TT, 2020	NA	OR	0.64	0.54–0.76	21	10	11	Random	96.0 %; <0.001	NA
Liver cancer	Wang, 2022	41,953+NA/3,305,888	OR	0.54	0.44–0.66	18	16	2	Random	96.0 %; <0.001	0.501
Lung cancer	Friederike, 2016	15,572/1,736,915	RR	0.87	0.79–0.95	20	7	10	Random	74.4 %; <0.001	0.0001
Ovary cancer	Zhang, 2016	15,163/499,950	RR	0.89	0.83–0.96	22	8	14	Random	22.5 %; 0.168	0.004
Prostate cancer	Shang, 2018	2,788,562/107,524,011 (+NA)	RR	0.93	0.89–0.96	34(1cross-section)	17	16	Random	79.5 %; 0.00	0.537
Pancreatic cancer	Bosetti C, 2020	12,193/NA	RR	0.78	0.68–0.89	15	7	8	Random	84.0 %; <0.001	0.216
Non-significant associations											
Bladder cancer	Zhang, 2013	8422/800,139	RR	1.02	0.91–1.14	11	6	5	NA	48.7 %; 0.035	0.686
CNS cancer	Liu, 2014	8704/442,933	RR	1.01	0.84–1.21	7[a](1RCT)	2	4	Random	78.8 %; <0.001	0.644
Head and neck cancer	Tang, 2016	13,827/362,307	OR	0.93	0.79–1.10	10	2	8	Random	60.5 %; 0.002	0.255
Kidney cancer	Choueiri, T, 2014	6665/345,554	RR	1.10	0.95–1.28	13	5	8	Random	65.5 %; <0.001	0.86
Melanoma	Li, 2013	NA/434,908	RR	0.97	0.86–1.08	10(1RCT)	5	4	Random	66.8 %; 0.001	0.672
Skin cancer	Muranushi, 2014	4663/120,278	RR	0.88	0.75–1.03	6	3	3	Random	63.7 %; 0.017	0.854
NA-NSAIDS											
Significant associations											
CNS cancer	Zhang, 2017	NA	RR	0.86	0.78–0.94	10	NA	NA	Random	54.9 %; 0.001	1.000
Colorectal cancer	Tomic, T, 2019	NA/1,286,773	OR	0.74	0.67–0.81	23	10	13	Random	75.9 %; <0.001	0.08
Esophageal cancer	Sun, 2011	877/NA	OR	0.55	0.42–0.72	5	0	5	Random	2.2 %; 0.39	1.000
Gastric cancer	Tian, 2010	NA	RR	0.81	0.74–0.90	6	NA	NA	Fixed	33.7 %; NA	0.134
Kidney cancer	Toni K, 2013	2230/303,067	RR	1.25	1.06–1.46	5	2	3	Random	27.3 %; 0.24	0.41

(*continued on next page*)

Table 2 (*continued*)

Outcome	Study	No. of cases/total	MA metric	Estimates	95%CI	No. of studies	Cohort	Case-control	Effects model	I^2; *Q* test *P* value	Egger test *P* value
Skin cancer	Muranushi, 2015	4449+NA/103,363	RR	0.85	0.78–0.94	7(1RCT)	3	3	Random	0.0 %; 0.628	0.548
Non-significant associations											
Bladder cancer	Zhang, 2013	5663/764,146	RR	0.87	0.73–1.05	6	3	3	Random	79.3 %; 0.001	0.118
Breast cancer	María, 2015	NA	RR	1.03	0.99–1.08	10	8	2	Random	43.6 %; NA	0.416
Endometrial cancer	Verdoodt, 2016	3275/389,301	RR	0.94	0.83–1.05	6	6	0	Random	22.4 %; 0.265	0.211
Head and neck cancer	Saka-Herran, 2021	7663/1,217,905	OR	0.92	0.76–1.11	8	3	5	Random	82.0 %; <0.001	NA
Liver cancer	Liu, 2022	NA	HR	0.95	0.80–1.15	4	4	0	Random	56.9 %; 0.073	NA
Lung cancer	Xu, 2012	4066/26,310	OR	0.88	0.67–1.16	5	0	5	Random	93.0 %; <0.001	NA
Melanoma	Li, 2013	5197+NA/431,382	RR	0.98	0.88–1.08	8	4	4	Random	59.1 %; 0.017	0.265
Ovary cancer	Baandrup, 2013	9280/528,403	RR	0.94	0.84–1.06	16	6	10	Random	63.4 %; <0.01	0.91
Pancreatic cancer	Zhang, 2015	981/118,444	RR[c]	1.08	0.89–1.31	3	2	1	Random	0.0 %; 0.676	NA
Prostate cancer	Shang, 2018	NA	RR	1.00	0.91–1.10	15	7	8	Random	94.5 %; 0.000	0.953

NA-NSAIDS, Non-aspirin nonsteroidal anti-inflammatory drugs; MA, meta-analysis; CI, confidence interval; RR, relative risk; NA, not available; OR, odds ratio; CNS, central nervous system.

Table 3
Assessments of AMSTAR scores and GRADE classification for each outcome.

Outcome	Author and year	Category	AMSTAR[a] Score	GRADE[b] quality
Significant associations				
Breast cancer	Takkouche, B, 2009	Overall NSAIDs[d]	8	very low
CNS[c] cancer	Zhang T,2017	Overall NSAIDs	8	low
Esophageal cancer	Sun, 2011	Overall NSAIDs	7	very low
Gastric cancer	Tian, 2010	Overall NSAIDs	9	very low
Head and neck cancer	Shi, 2017	Overall NSAIDs	9	moderate
Liver cancer	Pang, 2017	Overall NSAIDs	9	very low
Prostate cancer	Shang, 2018	Overall NSAIDs	10	very low
Skin cancer	Muranushi, 2014	Overall NSAIDs	7	very low
Digestive system cancer incidence	Bosetti C, 2020	Aspirin	7	very low
Breast cancer	Ma, 2021	Aspirin	9	low
Cholangiocarcinoma	Lapumnuaypol, 2019	Aspirin	9	very low
Colorectal cancer	Ye,2013	Aspirin	8	moderate
Endometrial cancer	Zhang, 2016	Aspirin	9	very low
Esophageal cancer	Sivarasan N, 2013	Aspirin	6	very low
Gastric cancer	Win TT, 2020	Aspirin	9	very low
Hepatocellular carcinoma	Wang, 2022	Aspirin	8	very low
Lung cancer	Friederike, 2016	Aspirin	8	very low
Ovary cancer	Zhang, 2016	Aspirin	9	low
Prostate cancer	Shang, 2018	Aspirin	10	very low
Pancreatic cancer	Bosetti C, 2020	Aspirin	8	very low
CNS cancer	Zhang, 2017	NA-NSAIDs[e]	9	low
Colorectal cancer	Tomic, T, 2019	NA-NSAIDs	9	very low
Esophageal cancer	Sun, 2011	NA-NSAIDs	7	very low
Gastric cancer	Tian, 2010	NA-NSAIDs	9	very low
Kidney cancer	Toni K, 2013	NA-NSAIDs	8	very low
Skin cancer	Muranushi, 2015	NA-NSAIDs	7	low
Non-Significant associations				
Pancreatic cancer	Zhang, 2015	Overall NSAIDs	8	low
Cholangiocarcinoma	Lapumnuaypol, K,. 2019	Overall NSAIDs	9	very low
Colon cancer	Harewood, 2021	Overall NSAIDs	10	very low
Melanoma	Li, 2013	Overall NSAIDs	9	very low
Non-Hodgkin's lymphoma	Bernatsky, S, 2007	Overall NSAIDs	5	very low
Lung cancer	Xu, 2012	Overall NSAIDs	7	very low
Bladder cancer	Zhang, 2013	Aspirin	7	very low
CNS cancer	Liu, 2014	Aspirin	9	low
Head and neck cancer	Tang, 2016	Aspirin	9	very low
Kidney cancer	Choueiri, T, 2014	Aspirin	8	very low
Melanoma	Li, 2013	Aspirin	9	very low
Skin cancer	Muranushi, 2014	Aspirin	9	very low
Bladder cancer	Zhang, 2013	NA-NSAIDs	7	very low
Breast cancer	María, 2015	NA-NSAIDs	7	very low
Endometrial cancer	Verdoodt, 2016	NA-NSAIDs	8	very low
Head and neck cancer	Saka-Herran, 2021	NA-NSAIDs	9	very low
Hepatocellular carcinoma	Liu, 2022	NA-NSAIDs	8	very low
Lung cancer	Xu, 2012	NA-NSAIDs	9	very low
Melanoma	Li, 2013	NA-NSAIDs	9	very low
Ovary cancer	Baandrup, 2013	NA-NSAIDs	6	very low
Pancreatic cancer	Zhang, 2015	NA-NSAIDs	8	very low
Prostate cancer	Shang, 2018	NA-NSAIDs	10	very low

[a] AMSTAR, a measurement tool to assess systematic reviews.
[b] GRADE, Grading of Recommendations Assessment, Development, and Evaluation.
[c] CNS, central nervous system.
[d] NSAIDs: nonsteroidal anti-inflammatory drugs.
[e] NA-NSAIDs:non-aspirin nonsteroidal anti-inflammatory drugs.

correlated with a stronger risk reduction when the frequency of use was under seven times (twice per week: RR = 0.92, 95 % CI = 0.88–0.95; seven times per week: RR = 0.82, 95 % CI = 0.78–0.87; more than seven times per week: RR = 0.82, 95 % CI = 0.78–0.87). For the relationship between colorectal cancer risk and duration of aspirin use, participants with longer aspirin use tended to exhibit stronger risk reduction (5 years: RR = 0.90, 95 % CI = 0.88–0.92; 10 years: RR = 0.82, 95 % CI = 0.78–0.86; 20 years: RR = 0.67, 95 % CI = 0.61–0.73). Moreover, aspirin might have a preventive effect, as the highest aspirin dose intake could decrease the risk of endometrial cancer by 7 % [36]. Subgroup analysis also detected a nonlinear association, where using aspirin twice per week could induce a 3 % decreased risk of endometrial cancer (RR = 0.97; 95 % CI = 0.95–0.99), but there was no significant difference between the duration of aspirin use and the risk of endometrial cancer. Another analysis demonstrated a significant 33 % reduction in esophageal cancer risk with aspirin use [37]. The same study revealed that a higher frequency of aspirin use might provide a greater chemoprevention effect (≤7 tablets/week: OR = 0.808, 95 % CI = 0.677–0.963, P = 0.017; >7 tablets/week: OR = 0.737, 95 % CI =

0.608–0.894, P = 0.002).

Overall, aspirin use was correlated with a lower risk of gastric carcinoma [38]. However, a positive correlation was found only in case-control studies (OR = 0.54, 95 % CI = 0.39–0.74) and not in cohort studies (OR = 0.77, 95 % CI = 0.58–1.02). In addition, a shorter duration (<5 years, OR = 1.01, 95 % CI = 0.72–1.43) of aspirin intake might have a weaker protective effect on gastric cancer than a long duration would (>5 years, OR = 0.67, 95 % CI = 0.34–1.31). However, there was no significant difference between low- and high-dose aspirin intake in reducing gastric cancer risk. In addition, the highest intake of aspirin was associated with a significant reduction in the risk of hepatocellular carcinoma by 46 % [39]. Stronger associations were detected by studies performed in Asia than in Western countries in the subgroup analysis (Asia: OR = 0.53; Western: OR = 0.58). Furthermore, aspirin use has been shown to decrease the risk of lung cancer [40]. A stratified analysis demonstrated that case-control studies showed a more protective relationship than did cohort studies (case-control: RR = 0.74, 95 % CI = 0.60–0.90; cohort: RR = 0.99, 95 % CI = 0.93–1.06). However, an adverse association with small cell lung cancer was found in the cohort studies (RR = 1.31, 95 % CI = 1.08–1.59). Moreover, the highest frequency of aspirin use could result in a decrease in ovarian cancer risk by 11 % in all studies [41] without a dose-response relationship. Another study showed a 7 % risk reduction in prostate cancer risk with aspirin intake [26], especially in advanced cancer, with a Gleason score of >7. Stronger associations were detected in studies performed in North America than in those performed in Europe. In addition, daily usage (≥1 pill/day) was associated with a significantly reduced incidence of prostate cancer (RR = 0.875, 95 % CI = 0.792–0.967), but evidence demonstrated that long-term aspirin intake could not decrease the risk of prostate cancer. Furthermore, regular aspirin intake was correlated with a 22 % lower pancreatic cancer risk than was non-intake [42], and pooled analysis of the same study detected that regular aspirin use might have a protective effect against overall digestive cancer (RR = 0.73, 95 % CI = 0.69–0.78).

3.3.2. Non-significant associations

There was no relationship between aspirin use and the risk of some cancers, including bladder cancer [43], CNS cancer [44], head and neck cancer [45], melanomas [31], kidney cancer [46], and skin cancer [27].

3.4. Associations between NA-NSAIDs use and cancer incidence

3.4.1. Significant associations

Studies on 16 types of cancer have reported a relationship between NA-NSAID use and cancer incidence. NA-NSAID intake was linearly associated with a lower risk of CNS cancer. A dose-response analysis showed that every 3-prescription increase in NA-NSAID use was associated with a 7 % decrease in CNS tumor risk, and every 2-year increase in the duration of NA-NSAID use decreased CNS tumor incidence by 8 % with statistical significance [21]. Moreover, regular use of NA-NSAIDs was related to a 26 % decreased risk of colorectal cancer in the general population aged forty or older [47], and high-dose NA-NSAIDs had a better protective effect than did low-dose NA-NSAIDs. NA-NSAIDs can also reduce esophageal cancer morbidity [48]. Statistically significant decreased risks (45 %) were detected in the highest NA-NSAID use group without a linear relationship. Furthermore, NA-NSAID intake was correlated with a lower risk of gastric cancer [23]. Regular use of NA-NSAIDs could reduce the incidence of gastric cancer by 19 %. The highest utilization of NA-NSAIDs was also associated with a 15 % decreased risk of skin cancer without a dose-response relationship compared to that in non-users [27]. However, except for cutaneous squamous cell carcinoma, studies involving other types of skin cancers and NA-NSAIDs have not been reported. In addition, regular or any other frequency of NA-NSAID use correlated with a 25 % increased risk of kidney cancer (RR = 1.25, 95 % CI = 1.06–1.46). A stronger association was reported with high-dose and (RR = 1.56, 95 % CI = 1.11–2.19) [46] long duration of intake (RR = 2.92, 95 % CI = 1.71–5.01), especially in the female group (RR = 3.51, 95 % CI = 1.83–6.74).

3.4.2. Non-significant associations

No significant associations were detected between NA-NSAID use and the risk of bladder cancer [43], breast cancer [49], endometrial cancer [50], head and neck cancer [51], hepatocellular carcinoma [52], lung cancer [33], melanoma [31], ovarian cancer [53], pancreatic cancer [28], and prostate cancer [26].

3.5. Heterogeneity of subgroups

Among the studies that analyzed overall NSAID intake, eight meta-analyses reported a Q-test P-value of <0.10. Three meta-analyses reported a low heterogeneity (I^2 < 25 %). Seven meta-analyses reported moderate-to-high levels of heterogeneity (I^2 25%–75 %), and three studies reported high levels of heterogeneity. One meta-analysis did not show the I^2 statistic, and two studies did not report a specific Q-test P-value.

With regard to studies focused on aspirin, a Q-test P-value of <0.10 was reported in 14 meta-analyses and was deficient in two studies. A very high level of heterogeneity (I^2>75 %) was observed in eight meta-analyses. The other eight meta-analyses reported moderate-to-high levels of heterogeneity. Three meta-analyses reported a low heterogeneity.

Among the studies on NA-NSAIDs, nine meta-analyses reported a Q-test P-value of <0.10. Four studies reported a low percentage in the I^2 test, indicating low levels of heterogeneity, and high levels of heterogeneity were found in five studies. Six meta-analyses reported moderate-to-high levels of heterogeneity. Two studies did not report the Q-test P-value in the body text.

3.6. Publication bias of included meta-analyses

With regard to studies focused on overall NSAIDs, seven meta-analyses did not report significant publication bias, and two meta-analyses detected significant publication bias, including those on CNS cancer and gastric cancer. Five studies did not test for publication bias. Among the studies on aspirin, 12 meta-analyses did not report significant publication bias. Significant publication bias was observed in five studies, including overall cancer, breast cancer, esophageal cancer, lung cancer, and ovarian cancer. Two meta-analyses lacked Egger's test for publication bias. In addition, among the studies on NA-NSAIDs, eleven meta-analyses did not detect apparent publication bias, four studies did not conduct tests, and only one study that focused on colorectal cancer reported significant publication bias.

3.7. AMSTAR evaluation of included studies

For studies on overall NSAIDs, the median AMSTAR score was 8.5 (range, 5–10; IQR, 7.5–9), and the median AMSTAR score of studies on aspirin was 9 (range, 7–10; IQR, 8–9); regarding meta-analyses focused on NA-NSAIDs, the median AMSTAR score was 8 (range, 6–10; IQR, 8–9). Detailed AMSTAR evaluations of each outcome are presented in Supplementary Tables S2, S3, and S4.

3.8. GRADE evaluation of included studies

Regarding the quality of evidence for cancer outcomes in different categories of NSAIDs with the GRADE classification, only two cancer outcomes were identified as "moderate," and the vast majority of included articles were rated as "very low" or "low." This is because most of the analyses did not include the characteristics of the excluded primary studies, which is one of the critical domains. Furthermore, potential bias and limited width or breadth could have affected the evaluation of the included studies. The detailed GRADE scores of all types of NSAIDs are presented separately in Supplementary Tables S5, S6, and S7, and the summarized information of the AMSTAR and GRADE evaluation for each outcome is presented in Table 3.

4. Discussion

4.1. Major findings and interpretation

This umbrella review identified 80 meta-analyses with unique outcomes as follows: 37 related to overall NSAIDs, 75 related to aspirin, and 41 related to NA-NSAIDs. Our results revealed that overall NSAID use was associated with a decreased risk of breast, CNS, esophageal, gastric, head and neck, liver, prostate, and skin cancers. Aspirin use was associated with a decreased risk of breast, cholangiocarcinoma, colorectal, endometrial, esophageal, gastric, liver, lung, ovarian, prostate, pancreatic, and digestive system cancers. In addition, NA-NSAID intake might reduce the incidence of CNS, colorectal, esophageal, gastric, and skin cancers but might increase the risk of kidney cancer. Dose-response analyses revealed that increasing the cumulative 100 defined daily doses or duration of overall NSAID use for 2 more years was associated with a 5 % and 6 % decrease in CNS tumor risk, respectively, whereas every 2 prescriptions/week increment of overall NSAID use could decrease the risk of head and neck cancer by 4 %. Furthermore, a dose-response meta-analysis also detected that every three prescription increments or 2-year increments of NA-NSAID intake was related to a reduction in the incidence of CNS tumor risk by 7 % and 8 %, respectively. The summarization of positive outcomes were shown in.

Chronic inflammation is associated with several malignancies. Previous studies reported that approximately 20 % of all cancer cases are characterized by chronic inflammation or autoimmunity in the same location [54]. In addition, low-grade generalized inflammation caused by pathogens or chronic wasting diseases can promote many different cancers, including stomach, prostate, and breast malignancies [55,56]. Successful tumor initiation depends on two main interdependent events: the alteration of genes or signaling pathways involved in tumor regulation and the process of cell growth after malignant transformation. Inflammation can significantly increase the number of macrophages and neutrophils and the levels of reactive oxygen and nitrogen species, which can effectively induce the accumulation of mutations in normal tissues. Furthermore, inflammation can induce the dedifferentiation of epithelial cells into tumor-initiating stem-like cells [57,58]. Moreover, inflammation can affect cancer immunosurveillance or elimination, increasing the probability of tumor cell survival and proliferation [59]. Tumor cells surrounding stromal and inflammatory immune cells form the tumor microenvironment (TME), where cancer cells can conduct tissue repair and regeneration [57,60,61]. In the TME, enhanced expression of inflammation-related indicators has been shown to indicate a higher grade of inflammation induced by primary or metastatic tumors [62,63]. Owing to the important influence of inflammation at all stages of tumorigenesis, agents with anti-inflammatory effects have been widely studied, and epidemiological evidence has demonstrated that NSAIDs have potential advantages in cancer prevention and enhancement of the therapeutic efficacy of cancer drugs (such as cytotoxic agents or targeted agents) [64]. NSAIDs include diverse chemicals with different structures, which can decrease prostaglandins by inhibiting COX enzymes and other signal pathways, including phosphodiesterase (PDE), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), and Akt pathways [65,66].

COX enzymes, also known as prostaglandin-endoperoxide synthases, catalyze the synthesis of prostaglandins (PGs), thromboxane, and prostacyclin by utilizing arachidonic acid [67,68]. COX enzymes have three isomers: COX-1, COX-2, and COX-3. COX-1 is constitutively and universally expressed in many tissues and maintains homeostasis in the internal environment [69]. COX-3 is abundantly expressed in the brain and tumor tissues, with unclear enzyme activity [70]. In contrast, COX-2 expression is limited to inflammatory tissues and is usually overexpressed at the site of inflammation. Previous studies have proven that COX-2 expression is

upregulated in multiple malignancies, including colon and gastric carcinomas [68,71]. COX-2 exerts cancer-promoting effects by increasing the synthesis of PGs, especially PGE_2. Overproduction of PGE_2 can improve the proliferative ability and apoptosis resistance of tumor cells. Moreover, angiogenesis in cancer tissues and the development of the TME are facilitated by PGE_2 accumulation [65]. Therefore, COX-2 inhibition may prevent carcinogenesis. Aspirin and COX-2 selective NSAIDs (COXIBs) can effectively inhibit the activity of COX-2 to reduce the concentration of PGs. Aspirin is a covalent inhibitor that acetylates the catalytic subunits of COX enzymes, resulting in an irreversible loss of function. COXIBS can specifically inhibit the activity of the COX-2 enzyme, and some studies have reported that COXIBs provide more significant protection against cancer than non-selective NSAIDs [66]. In addition, acetaminophen inhibits COX-3, which may protect against cancer [72]. Moreover, owing to the association between COX enzymes and angiogenesis, NSAIDs can delay cancer development by inhibiting the activity of COX isoforms. Studies have shown that ibuprofen and aspirin inhibit angiogenesis in various cancer types, including colorectal, breast, and gastric cancers [66,73–75].

In addition to COX, several other mechanisms explain the association between NSAIDs and cancer incidence. NF-κB is involved in the inflammatory process and tumor tissue development. Aspirin, diclofenac, and sulindac can inhibit the activation of the NF-κB pathway and reduce the risk of carcinogenesis [76–79]. Another pathway, PDK-1/Akt, is upregulated in many types of human cancers [80,81]. Aspirin and some COXIBs (such as celecoxib) can affect Akt signaling and promote apoptosis of cancer cells [82–84]. NSAIDs also affect the MAPK signaling pathway in various types of cancers to enhance their chemopreventive properties [66,85,86]. The β/δ isoform of peroxisome proliferator-activated receptors (PPARs) is reported to be associated with a higher risk of colon cancer, and NSAIDs may have potential cancer-preventing advantages by disrupting the interaction between PPAR-β/δ and its target DNA sequences [87,88]. PDEs, especially PDE5, are closely related to cancer development because of their ability to decrease the levels of cyclic nucleotides that inhibit the development of cancer cells. Studies have shown that PDE5 promotes tumorigenesis in some types of cancer, including lung and breast cancer. Several NSAIDs and derivatives (such as sulindac) can inhibit the expression of PDE5, resulting in higher levels of cyclic guanosine monophosphate (cGMP), a type of cyclic nucleotide that reduces cancer incidence [66,89,90]. In addition, the mammalian target of rapamycin (mTOR), a downstream effector of the Akt signaling pathway, can also be affected by NSAIDs. The mTOR pathway plays a key role in the metabolism of many tumors, including kidney cancer and melanoma [91–93]. Aspirin or some COXIBs can promote the apoptosis of some cancer cell lines or improve the efficacy of radiotherapy and targeted therapy by blocking the mTOR pathway [83,94,95]. In addition, decreasing the expression of mTOR can induce autophagy in cancer cells, resulting in the self-destruction of tumors [96]. Moreover, previous studies have shown that vascular endothelial growth factors (VEGFs) mainly regulate angiogenesis in tumor tissues and affect tumorigenesis and prognosis. Some NSAIDs can regulate the serum level of VEGF, which provides novel strategies for preventing certain cancers, such as breast and cervical cancers [65,97]. Furthermore, the expression of a unique gene known as the NSAID-activated gene (NAG-1) can be upregulated by NSAIDs in numerous malignancies, such as ovarian and pancreatic cancers [98,99]. NAG-1 has antitumorigenic properties in several cancer types, including prostate and colorectal cancers [100–102].

Calcium (Ca^{2+}) can control multiple cellular processes by regulating signaling pathways and Ca^{2+}-associated proteins. Previous studies have reported the inhibition of Ca^{2+}-related proteins in various malignancies [103,104]. NSAIDs such as celecoxib or indomethacin can regulate the level of cellular Ca^{2+} to prevent tumor metastasis or induce apoptosis in cancer cells [105,106]. In addition, as previously mentioned, the TME is extremely important in tumorigenesis and prognosis. The infiltration of various immune cells, such as tumor-linked macrophages and T cells, actively participates in this process. These immune cells can promote the tumorigenic capacity of cancer stem cells, remodel the tumor cell-extracellular matrix, and ultimately support tumorigenesis [107]. Evidence has shown that NSAIDs also regulate the activity of cancer-associated immune cells in TME. For example, low-dose aspirin intake contributes to a low risk of breast cancer in mice with other malignancies undergoing radiotherapy [108]. Additionally, aspirin can increase the levels of lymphocytes in cancer tissues to enhance tumor inhibition [109].

Several types of NSAIDs also play efficient roles against cancer through a unique mechanistic pathway independent of COX [110]. Thus, strategies focused on glycolysis in cancer cells may enhance the efficacy of immunotherapy using immune checkpoint inhibitors [111]. Diclofenac, a monocarboxylate NSAID, can reduce lactate secretion from tumor cells by inhibiting lactate transporters to improve T-cell destruction, which results in increased local antitumor immune reactions. Moreover, this kind of NSAID also has a direct anti-cancer effect because it improves arginase activity and downregulates VGEF expression [112,113].

Tumorigenesis and prognosis induced by the TME are related to carbonic anhydrase (CA). CA is an enzyme that regulates the conversion of carbon dioxide, and some isozymes, such as IX and XII, are overexpressed in tumor tissues and associated with the promotion of tumor cell metastasis [114,115]. Some NSAIDs, including valdecoxib and celecoxib, potently inhibit CA IX and eventually weaken tumor cell invasion and adhesion [66].

Studies have also elucidated the specific mechanisms underlying the cancer-fighting ability of NSAIDs at the genetic level. Previous studies have shown that individual variations in the chemopreventive processes of several malignancies are associated with germline variations, particularly single nucleotide polymorphisms (SNPs). For example, SNP rs1799853 and variant alleles of other genes such as *CYP2C9*, *ODC1*, and *UGT1A6* are involved in aspirin metabolic pathways, and by consuming aspirin, their carriers can eventually decrease their risk of colon cancer [116]. Another study reported that individuals with the SNP rs2965667 variant allele on chromosome 12p12.3 near the microsomal glutathione S-transferase 1 (*MGST1*) gene could also have a protective association between colon cancer risk and regular aspirin or NA-NSAID use [117]. In addition, there is evidence that polymorphisms in or near the *IL16* gene can regulate the secretion of inflammatory cytokines and enhance the chemopreventive effects of NSAIDs in colorectal malignancies [118]. These findings may provide a new perspective on cancer prevention strategies.

Although our study found that NSAIDs have significant tumor-preventive advantages in some types of cancers, their side effects should not be ignored. The use of NSAIDs is often associated with gastrointestinal tract adverse effects, including nausea, vomiting, and epigastric pain, owing to the inhibition of COX enzyme activity. In addition, approximately 38 % of patients who frequently consume

NSAIDs are diagnosed with peptic ulcer [119]. Furthermore, NSAIDs inhibit thromboxane synthesis in platelets and increase the risk of hemorrhage. Studies have also found that NSAIDs can result in new-onset hypertension or aggravation of hypertension-related symptoms [120]. Consequently, for patients with allergies to NSAIDs or who have been diagnosed with diseases such as heart failure, peptic ulcer bleeding, and perforation, the intake of NSAIDs needs to be strictly evaluated and regulated.

4.2. Strengths and limitations

This umbrella review is the latest comprehensive overview of published studies on the relationship between the incidence of multiple cancers and the use of different types of NSAIDs [121]. Standard methods, including AMSTAR and GRADE, were used to assess the methodological quality of the included studies and the strength of their evidence. Two independent investigators conducted a literature review and extracted data to summarize the findings on the morbidity of various cancers. Most meta-analyses did not detect significant publication bias, except for overall cancer and CNS cancer incidence. However, we acknowledge several potential limitations of our umbrella review. First, there were few meta-analyses involving RCTs, so the evidence grade of most studies was considered low or very low quality according to the GRADE classification. Second, the basic demographic characteristics of the patients in every study included were hardly analyzed and adjusted for by the original authors. Therefore, other confounding factors, such as smoking, exercise, and daily meat and vegetable intake, may also affect the association between NSAID use and cancer incidence. Third, when conducting research, most meta-analyses chose “ever used” versus “not used” as the standard measure of NSAID intake; however, the specific definition of “ever NSAID utilization” is different. Due to this diversity, we were unable to summarize the overall dose-response relationship between NSAID use and cancer risk. Finally, only published meta-analyses were included in our umbrella review, which may have resulted in incomplete outcomes. Moreover, owing to the small number of primary meta-analyses, this review did not include a detailed discussion of several recent research directions, including genetic polymorphisms, nanoformulations, and/or the combination of gene therapies and NSAIDs. Therefore, the current evidence does not support the regular use of NSAIDs to prevent cancer before performing general examinations and evaluations in healthy individuals or patients.

5. Conclusions

In this review, we found that NSAID use, especially aspirin intake, was associated with a decreased incidence of a range of cancers and was not significantly associated with harmful effects that increase the risk of other cancers, except for kidney cancer. However, given the side effects of NSAIDs, such as hemorrhage and gastrointestinal reactions, some patients have absolute or relative contraindications. In addition, several outcomes are still controversial because part of included studies are evaluated as low quality based on our evidence assessment. Therefore, it is still too early to recommend that people with no disease regularly consume NSAIDs to prevent cancer. Moreover, because of several possible limitations of our study, more high-quality prospective studies are required to understand better the relationship between NSAID intake and multiple cancer outcomes, such as genetic polymorphisms and nanoformulations.

Data availability statement

Data included in article/supp. material/referenced in article.

Ethics declarations

Review and/or approval by an ethics committee and informed consent was not required for this study because this study based exclusively on published literature.

Consent for publication

Not applicable.

Funding

This study was supported by Natural Science Foundation of China (Grant No. 82000721).

CRediT authorship contribution statement

Puze Wang: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Bo Chen:** Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Yin Huang:** Data curation, Conceptualization. **Jin Li:** Investigation. **Dehong Cao:** Supervision. **Zeyu Chen:** Supervision. **Jinze Li:** Supervision. **Biao Ran:** Supervision. **Jiahao Yang:** Supervision. **Ruyi Wang:** Supervision. **Qiang Wei:** Supervision. **Qiang Dong:** Writing – review & editing, Visualization, Supervision, Conceptualization. **Liangren Liu:** Supervision.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:Puze Wang reports financial support and writing assistance were provided by Natural Science Foundation of China. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

Not applicable.

List of abbreviations

NSAID	Nonsteroidal anti-inflammatory drug
USCS	the United States Cancer Statistics
COX	Cyclooxygenase
AA	Arachidonic acid
RCT	Randomized controlled trial
NRCT	Nonrandomized controlled trial
CI	Confidence interval
GRADE	the Grading of Recommendations, Assessment, Development, and Evaluation
NA-NSAID	Non-aspirin nonsteroidal anti-inflammatory drug
CNS	Central nervous system
SCC	Squamous cell carcinoma
NHL	Non-Hodgkin's lymphoma
ER	Estrogen receptor
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
PG	Prostaglandin
TME	Tumor microenvironment
COXIB	Cyclooxygenase-2 selective nonsteroidal anti-inflammatory drug
PPAR	Peroxisome proliferator-activated receptor
PDE	Phosphodiesterase
cGMP	Cyclic guanosine monophosphate
mTOR	Mammalian target of rapamycin
VEGF	Vascular endothelial growth factors
NAG-1	Nonsteroidal anti-inflammatory drug-activated gene-1
NSAIA	Nonsteroidal anti-inflammatory agent/analgesic
RR	Relative Risk
OR	Odds Ratio
AMSTAR	A Measurement Tool to Assess Systematic Reviews
Ca^{2+}	Calcium
CA	Carbonic anhydrase

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e23203.

References

[1] S. Bacchi, P. Palumbo, A. Sponta, M.F. Coppolino, Clinical pharmacology of non-steroidal anti-inflammatory drugs: a review, Antiinflamm Antiallergy Agents Med Chem 11 (1) (2012) 52–64.
[2] L.A. Torre, R.L. Siegel, E.M. Ward, A. Jemal, Global cancer incidence and mortality rates and trends–an update, Cancer Epidemiol. Biomarkers Prev. 25 (1) (2016 Jan) 16–27.
[3] United States cancer statistics, Data visualizations. https://gis.cdc.gov/Cancer/USCS/DataViz.html, 2021.
[4] Y.I. Cha, R.N. DuBois, NSAIDS and cancer prevention: targets downstream of COX-2, Annu. Rev. Med. 58 (2007) 239–252.
[5] S. Ramos-Inza, A.C. Ruberte, C. Sanmartín, A.K. Sharma, D. Plano, NSAIDS: old acquaintance in the pipeline for cancer treatment and Prevention—Structural modulation, mechanisms of action, and bright future, J. Med. Chem. 64 (22) (2021 Nov 25) 16380–16421.
[6] A.M. Algra, P.M. Rothwell, Effects of regular aspirin on long-term cancer incidence and metastasis: a systematic comparison of evidence from observational studies versus randomised trials, Lancet Oncol. 13 (2012) 518–527.
[7] P.M. Rothwell, 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, Lancet 379 (2012) 1602–1612.

[8] S.M. Crusz, F.R. Balkwill, Inflammation and cancer: advances and new agents, Nat. Rev. Clin. Oncol. 12 (10) (2015 Oct) 584–596.
[9] A. Bens, D. Cronin-Fenton, C. Dehlendorff, M.B. Jensen, B. Ejlertsen, N. Kroman, S. Friis, L. Mellemkjaer, Nonaspirin NSAIDS and contralateral breast cancer risk, Int. J. Cancer 144 (6) (2019 Mar 15) 1243–1250.
[10] B. Li, K.S. Cheung, I.Y. Wong, W.K. Leung, S. Law, Nonaspirin nonsteroidal anti-inflammatory drugs and gastric cancer risk after Helicobacter pylori eradication: a territory-wide study, Cancer 127 (11) (2021 Jun 1) 1805–1815.
[11] Y. Huang, D. Cao, Z. Chen, B. Chen, J. Li, J. Guo, et al., Red and processed meat consumption and cancer outcomes: umbrella review, Food Chem. 356 (2021 Sep 15) 129697.
[12] Scottish intercollegiate guidelines network search filters. https://www.sign.ac.uk/what-we-do/methodology/search-filters/. (Accessed 11 December 2020).
[13] Y. Huang, D. Cao, Z. Chen, B. Chen, J. Li, R. Wang, et al., Iron intake and multiple health outcomes: umbrella review, Crit. Rev. Food Sci. Nutr. (2021 Sep 29) 1–18.
[14] S. Papatheodorou, Umbrella reviews: what they are and why we need them, Eur. J. Epidemiol. 34 (6) (2019) 543–546.
[15] M. Egger, G. Davey Smith, M. Schneider, C. Minder, Bias in meta-analysis detected by a simple, graphical test, Bmj 315 (7109) (1997) 629–634.
[16] R. Poole, O.J. Kennedy, P. Roderick, J.A. Fallowfield, P.C. Hayes, J. Parkes, Coffee consumption and health: umbrella review of meta-analyses of multiple health outcomes, Bmj 359 (2017). Article j5024.
[17] B.J. Shea, L.M. Bouter, J. Peterson, M. Boers, N. Andersson, Z. Ortiz, et al., External validation of a measurement tool to assess systematic reviews (AMSTAR), PLoS One 2 (12) (2007 Dec 26) e1350.
[18] B.J. Shea, C. Hamel, G.A. Wells, et al., AMSTAR is a reliable and valid measurement tool to assess the methodological quality of systematic reviews, J. Clin. Epidemiol. 359 (2009) 1013–1020.
[19] G. Guyatt, A.D. Oxman, E.A. Akl, R. Kunz, G. Vist, J. Brozek, et al., GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables, J. Clin. Epidemiol. 64 (4) (2011) 383–394.
[20] Bahi Takkouche, Carlos Regueira-Méndez, Mahyar Etminan, Breast cancer and use of nonsteroidal anti-inflammatory drugs: a meta-analysis, jnci, Journal of the National Cancer Institute 100 (2008) 1439–1447, 20.
[21] T. Zhang, X. Yang, P. Liu, J. Zhou, J. Luo, H. Wang, et al., Association between nonsteroidal anti-inflammatory drugs use and risk of central nervous system tumors : a dose-response meta analysis, Oncotarget 8 (60) (2017 Oct 11) 102486–102498.
[22] Lei Sun, Shiying Yu, Meta-analysis: non-steroidal anti-inflammatory drug use and the risk of esophageal squamous cell carcinoma, Dis. Esophagus 24 (Issue 8) (2011) 544–549.
[23] W. Tian, Y. Zhao, S. Liu, X. Li, Meta-analysis on the relationship between nonsteroidal anti-inflammatory drug use and gastric cancer, Eur. J. Cancer Prev. 19 (4) (2010 Jul) 288–298.
[24] J. Shi, W. Leng, L. Zhao, C. Xu, J. Wang, X. Chen, et al., Nonsteroidal anti-inflammatory drugs using and risk of head and neck cancer: a dose–response meta analysis of prospective cohort studies, Oncotarget 8 (2017) 99066–99074.
[25] Q. Pang, H. Jin, K. Qu, Z. Man, Y. Wang, S. Yang, et al., The effects of nonsteroidal anti-inflammatory drugs in the incident and recurrent risk of hepatocellular carcinoma: a meta-analysis, OncoTargets Ther. 10 (2017) 4645–4656.
[26] Z. Shang, X. Wang, H. Yan, B. Cui, Q. Wang, J. Wu, et al., Intake of non-steroidal anti-inflammatory drugs and the risk of prostate cancer: a meta-analysis, Front. Oncol. 8 (2018 Oct 23) 437.
[27] C. Muranushi, C.M. Olsen, N. Pandeya, A.C. Green, Aspirin and nonsteroidal anti-inflammatory drugs can prevent cutaneous squamous cell carcinoma: a systematic review and meta-analysis, J. Invest. Dermatol. 135 (4) (2015 Apr) 975–983.
[28] Y.P. Zhang, Y.D. Wan, Y.L. Sun, et al., Aspirin might reduce the incidence of pancreatic cancer: a meta-analysis of observational studies, Sci. Rep. 5 (2015) 15460.
[29] K. Lapumnuaypol, A. Tiu, C. Thongprayoon, K. Wijarnpreecha, P. Ungprasert, M.A. Mao, et al., Effects of aspirin and non-steroidal anti-inflammatory drugs on the risk of cholangiocarcinoma: a meta-analysis, QJM: Int. J. Med. 112 (Issue 6) (June 2019) 421–427.
[30] R. Harewood, R. Disney, J. Kinross, C. von Wagner, A.J. Cross, Medication use and risk of proximal colon cancer: a systematic review of prospective studies with narrative synthesis and meta-analysis, Cancer Causes Control 32 (10) (2021 Oct) 1047–1061.
[31] S. Li, Y. Liu, Z. Zeng, Q. Peng, R. Li, L. Xie, et al., Association between non-steroidal anti-inflammatory drug use and melanoma risk: a meta-analysis of 13 studies, Cancer Causes Control 24 (8) (2013 Aug) 1505–1516.
[32] S. Bernatsky, J.L. Lee, E. Rahme, Non-Hodgkin's lymphoma—meta-analyses of the effects of corticosteroids and non-steroidal anti-inflammatories, Rheumatology 46 (4) (April 2007) 690–694.
[33] J. Xu, Z. Yin, W. Gao, L. Liu, R. Wang, P. Huang, et al., Meta-analysis on the association between nonsteroidal anti-inflammatory drug use and lung cancer risk, Clin. Lung Cancer 13 (1) (2012 Jan) 44–51.
[34] S. Ma, C. Guo, C. Sun, T. Han, H. Zhang, G. Qu, et al., Aspirin use and risk of breast cancer: a meta-analysis of observational studies from 1989 to 2019, Clin. Breast Cancer 21 (6) (2021 Dec) 552–565.
[35] X. Ye, J. Fu, Y. Yang, S. Chen, Dose-risk and duration-risk relationships between aspirin and colorectal cancer: a meta-analysis of published cohort studies, PLoS One 8 (2) (2013) e57578.
[36] D. Zhang, B. Bai, Y. Xi, Y. Zhao, Can aspirin reduce the risk of endometrial cancer?: a systematic review and meta-analysis of observational studies, Int. J. Gynecol. Cancer 26 (6) (2016 Jul) 1111–1120.
[37] N. Sivarasan, G. Smith, Role of aspirin in chemoprevention of esophageal adenocarcinoma: a meta-analysis, J Dig Dis 14 (5) (2013 May) 222–230.
[38] T.T. Win, S.N. Aye, J. Lau Chui Fern, C. Ong Fei, Aspirin and reducing risk of gastric cancer: systematic review and meta-analysis of the observational studies, J Gastrointestin Liver Dis 29 (2) (2020 Jun 3) 191–198.
[39] Y. Wang, M. Wang, C. Liu, W. Wang, J. Shi, S. Dang, Aspirin use and the risk of hepatocellular carcinoma: a meta-analysis, J. Clin. Gastroenterol. 56 (7) (2022 Aug 1) e293–e302.
[40] Friederike Hochmuth, Maximilian Jochem, Peter Schlattmann, Meta-analysis of aspirin use and risk of lung cancer shows notable results, Eur. J. Cancer Prev. 25 (4) (July 2016) 259–268.
[41] D. Zhang, B. Bai, Y. Xi, T. Wang, Y. Zhao, Is aspirin use associated with a decreased risk of ovarian cancer? A systematic review and meta-analysis of observational studies with dose-response analysis, Gynecol. Oncol. 142 (2) (2016 Aug) 368–377.
[42] C. Bosetti, C. Santucci, S. Gallus, M. Martinetti, C. La Vecchia, Aspirin and the risk of colorectal and other digestive tract cancers: an updated meta-analysis through 2019, Ann. Oncol. 31 (5) (2020 May) 558–568.
[43] H. Zhang, D. Jiang, X. Li, Use of nonsteroidal anti-inflammatory drugs and bladder cancer risk: a meta-analysis of epidemiologic studies, PLoS One 8 (7) (2013 Jul 19) e70008.
[44] Y. Liu, Y. Lu, J. Wang, L. Xie, T. Li, Y. He, et al., Association between nonsteroidal anti-inflammatory drug use and brain tumour risk: a meta-analysis, Br. J. Clin. Pharmacol. 78 (1) (2014 Jul) 58–68.
[45] L. Tang, H. Hu, H. Liu, C. Jian, H. Wang, J. Huang, Association of nonsteroidal anti-inflammatory drugs and aspirin use and the risk of head and neck cancers: a meta-analysis of observational studies, Oncotarget 7 (40) (2016 Oct 4) 65196–65207.
[46] T.K. Choueiri, Y. Je, E. Cho, Analgesic use and the risk of kidney cancer: a meta-analysis of epidemiologic studies, Int. J. Cancer 134 (2) (2014 Jan 15) 384–396.
[47] T. Tomić, S. Domínguez-López, R. Barrios-Rodríguez, Non-aspirin non-steroidal anti-inflammatory drugs in prevention of colorectal cancer in people aged 40 or older: a systematic review and meta-analysis, Cancer Epidemiol 58 (2019 Feb) 52–62.
[48] L. Sun, S. Yu, Meta-analysis: non-steroidal anti-inflammatory drug use and the risk of esophageal squamous cell carcinoma, Dis. Esophagus 24 (8) (2011 Nov) 544–549.
[49] M. de Pedro, S. Baeza, M.T. Escudero, T. Dierssen-Sotos, I. Gómez-Acebo, M. Pollán, et al., Effect of COX-2 inhibitors and other non-steroidal inflammatory drugs on breast cancer risk: a meta-analysis, Breast Cancer Res. Treat. 149 (2) (2015 Jan) 525–536.

[50] F. Verdoodt, S. Friis, C. Dehlendorff, V. Albieri, S.K. Kjaer, Non-steroidal anti-inflammatory drug use and risk of endometrial cancer: a systematic review and meta-analysis of observational studies, Gynecol. Oncol. 140 (2) (2016 Feb) 352–358.
[51] C. Saka-Herrán, E. Jané-Salas, A. Estrugo-Devesa, J. López-López, Head and neck cancer and non-steroidal anti-inflammatory drugs: systematic review and meta-analysis, Head Neck 43 (5) (2021 May) 1664–1682.
[52] Y. Liu, T. Ren, X. Xu, J. Jin, Association of aspirin and nonaspirin NSAIDS therapy with the incidence risk of hepatocellular carcinoma: a systematic review and meta-analysis on cohort studies, Eur. J. Cancer Prev. 31 (1) (2022 Jan 1) 35–43.
[53] L. Baandrup, M.T. Faber, J. Christensen, A. Jensen, K.K. Andersen, S. Friis, et al., Nonsteroidal anti-inflammatory drugs and risk of ovarian cancer: systematic review and meta-analysis of observational studies, Acta Obstet. Gynecol. Scand. 92 (3) (2013 Mar) 245–255.
[54] S.I. Grivennikov, F.R. Greten, M. Karin, Immunity, inflammation, and cancer, Cell 140 (6) (2010 Mar 19) 883–899.
[55] G. Trinchieri, Cancer and inflammation: an old intuition with rapidly evolving new concepts, Annu. Rev. Immunol. 30 (2012) 677–706.
[56] D.F. Quail, O.C. Olson, P. Bhardwaj, L.A. Walsh, L. Akkari, M.L. Quick, et al., Obesity alters the lung myeloid cell landscape to enhance breast cancer metastasis through IL5 and GM-CSF, Nat. Cell Biol. 19 (8) (2017 Aug) 974–987.
[57] F.R. Greten, S.I. Grivennikov, Inflammation and cancer: triggers, mechanisms, and consequences, Immunity 51 (1) (2019 Jul 16) 27–41.
[58] S. Schwitalla, A.A. Fingerle, P. Cammareri, T. Nebelsiek, S.I. Göktuna, P.K. Ziegler, et al., Intestinal tumorigenesis initiated by dedifferentiation and acquisition of stem-cell-like properties, Cell 152 (1–2) (2013 Jan 17) 25–38.
[59] R.D. Schreiber, L.J. Old, M.J. Smyth, Cancer immunoediting: integrating immunity's roles in cancer suppression and promotion, Science 331 (2011) 1565–1570.
[60] R. Medzhitov, Origin and physiological roles of inflammation, Nature 454 (2008) 428–435.
[61] S.I. Grivennikov, M. Karin, Inflammation and oncogenesis: a vicious connection, Curr. Opin. Genet. Dev. 20 (2010) 65–71.
[62] M. Binnewies, E.W. Roberts, K. Kersten, V. Chan, D.F. Fearon, M. Merad, et al., Understanding the tumor immune microenvironment (TIME) for effective therapy, Nat. Med. 24 (5) (2018 May) 541–550.
[63] S.V. Puram, I. Tirosh, A.S. Parikh, A.P. Patel, K. Yizhak, S. Gillespie, et al., Single-cell transcriptomic analysis of primary and metastatic tumor ecosystems in head and neck cancer, Cell 171 (7) (2017 Dec 14) 1611–1624.e24.
[64] S.M. Crusz, F.R. Balkwill, Inflammation and cancer: advances and new agents, Nat. Rev. Clin. Oncol. 12 (10) (2015 Oct) 584–596.
[65] H. Lai, Y. Liu, J. Wu, J. Cai, H. Jie, Y. Xu, et al., Targeting cancer-related inflammation with non-steroidal anti-inflammatory drugs: perspectives in pharmacogenomics, Front. Pharmacol. 13 (2022 Dec 5) 1078766.
[66] O.R. Kolawole, K. Kashfi, NSAIDS and cancer resolution: new paradigms beyond cyclooxygenase, Int. J. Mol. Sci. 23 (3) (2022 Jan 27) 1432.
[67] H. Yang, Y. Xuefeng, W. Shandong, X. Jianhua, COX-2 in liver fibrosis, Clin. Chim. Acta 506 (2020 Jul) 196–203.
[68] D. Wang, C.S. Cabalag, N.J. Clemons, R.N. DuBois, Cyclooxygenases and prostaglandins in tumor immunology and microenvironment of gastrointestinal cancer, Gastroenterology 161 (6) (2021) 1813–1829.
[69] B. Wang, L. Wu, J. Chen, L. Dong, C. Chen, Z. Wen, et al., Metabolism pathways of arachidonic acids: mechanisms and potential therapeutic targets, Signal Transduct. Targeted Ther. 6 (1) (2021) 94.
[70] E. Oksuz, F. Atalar, G. Tanirverdi, et al., Therapeutic potential of cyclooxygenase-3 inhibitors in the management of glioblastoma, J. Neuro Oncol. 126 (2) (2016) 271–278.
[71] Q.B. Wu, G.P. Sun, Expression of COX-2 and HER-2 in colorectal cancer and their correlation, World J. Gastroenterol. 21 (20) (2015 May 28) 6206–6214.
[72] R. Botting, S.S. Ayoub, COX-3 and the mechanism of action of paracetamol/acetaminophen, Prostaglandins Leukot. Essent. Fatty Acids 72 (2) (2005 Feb) 85–87.
[73] H. Akrami, S. Aminzadeh, H. Fallahi, Inhibitory effect of ibuprofen on tumor survival and angiogenesis in gastric cancer cell, Tumor Biol. 36 (2015) 3237–3243.
[74] X. Dai, J. Yan, X. Fu, Q. Pan, D. Sun, Y. Xu, et al., Aspirin inhibits cancer metastasis and angiogenesis via targeting heparanase, Clin. Cancer Res. 23 (20) (2017 Oct 15) 6267–6278.
[75] M. Yao, W. Zhou, S. Sangha, A. Albert, A.J. Chang, T.C. Liu, et al., Effects of nonselective cyclooxygenase inhibition with low-dose ibuprofen on tumor growth angiogenesis metastasis and survival in a mouse model of colorectal cancer, Clin. Cancer Res. 11 (2005) 1618–1628.
[76] Y. Wu, B.P. Zhou, TNF-alpha/NF-kappaB/Snail pathway in cancer cell migration and invasion, Br. J. Cancer 102 (4) (2010 Feb 16) 639–644.
[77] E. Kopp, S. Ghosh, Inhibition of NF-kappa B by sodium salicylate and aspirin, Science 265 (5174) (1994 Aug 12) 956–959.
[78] M. Cho, J. Gwak, S. Park, J. Won, D.E. Kim, S.S. Yea, Diclofenac attenuates Wnt/beta-catenin signaling in colon cancer cells by activation of NF-kappaB, FEBS Lett. 579 (20) (2005 Aug 15) 4213–4218.
[79] Y. Yamamoto, M.J. Yin, K.M. Lin, R.B. Gaynor, Sulindac inhibits activation of the NF-kappaB pathway, J. Biol. Chem. 274 (38) (1999 Sep 17) 27307–27314.
[80] K. Nakatani, D.A. Thompson, A. Barthel, H. Sakaue, W. Liu, R.J. Weigel, et al., Up-regulation of Akt3 in estrogen receptor-deficient breast cancers and androgen-independent prostate cancer lines, J. Biol. Chem. 274 (31) (1999 Jul 30) 21528–21532.
[81] B.E. Cristiano, J.C. Chan, K.M. Hannan, N.A. Lundie, N.J. Marmy-Conus, I.G. Campbell, et al., A specific role for AKT3 in the genesis of ovarian cancer through modulation of G(2)-M phase transition, Cancer Res. 66 (24) (2006 Dec 15) 11718–11725.
[82] S. Arico, S. Pattingre, C. Bauvy, P. Gane, A. Barbat, P. Codogno, et al., Celecoxib induces apoptosis by inhibiting 3-phosphoinositide-dependent protein kinase-1 activity in the human colon cancer HT-29 cell line, J. Biol. Chem. 277 (31) (2002 Aug 2) 27613–27621.
[83] D. Sun, H. Liu, X. Dai, X. Zheng, J. Yan, R. Wei, et al., Aspirin disrupts the mTOR-Raptor complex and potentiates the anti-cancer activities of sorafenib via mTORC1 inhibition, Cancer Lett. 406 (2017) 105–115.
[84] H. Chen, Q. Qi, N. Wu, Y. Wang, Q. Feng, R. Jin, et al., Aspirin promotes RSL3-induced ferroptosis by suppressing mTOR/SREBP-1/SCD1-mediated lipogenesis in PIK3CA-mutatnt colorectal cancer, Redox Biol. 55 (2022) 102426.
[85] T.I. Kim, S.H. Jin, W.H. Kim, E.H. Kang, K.Y. Choi, H.J. Kim, et al., Prolonged activation of mitogen-activated protein kinases during NSAID-induced apoptosis in HT-29 colon cancer cells, Int. J. Colorectal Dis. 16 (3) (2001 Jun) 167–173.
[86] S. Setia, B. Nehru, S.N. Sanyal, Upregulation of MAPK/Erk and PI3K/Akt pathways in ulcerative colitis-associated colon cancer, Biomed. Pharmacother. 68 (8) (2014 Oct) 1023–1029.
[87] J.M. Peters, T. Aoyama, R.C. Cattley, U. Nobumitsu, T. Hashimoto, F.J. Gonzalez, Role of peroxisome proliferator-activated receptor alpha in altered cell cycle regulation in mouse liver, Carcinogenesis 19 (11) (1998 Nov) 1989–1994.
[88] T.C. He, T.A. Chan, B. Vogelstein, K.W. Kinzler, PPARdelta is an APC-regulated target of nonsteroidal anti-inflammatory drugs, Cell 99 (3) (1999 Oct 29) 335–345.
[89] Y. Yamanaka, T. Mammoto, T. Kirita, M. Mukai, T. Mashimo, M. Sugimura, Y. Kishi, H. Nakamura, Epinephrine inhibits invasion of oral squamous carcinoma cells by modulating intracellular cAMP, Cancer Lett. 176 (2002) 143–148.
[90] M.F. Azevedo, F.R. Faucz, E. Bimpaki, A. Horvath, I. Levy, R.B. de Alexandre, et al., Clinical and molecular genetics of the phosphodiesterases (PDEs) Endocr, Rev 35 (2014) 195–233.
[91] Z. Zou, T. Tao, H. Li, X. Zhu, mTOR signaling pathway and mTOR inhibitors in cancer: progress and challenges, Cell Biosci. 10 (2020) 31.
[92] H.J. Lim, P. Crowe, J.L. Yang, Current clinical regulation of PI3K/PTEN/Akt/mTOR signalling in treatment of human cancer, J. Cancer Res. Clin. Oncol. 141 (2015) 671–689.
[93] C. Di Malta, D. Siciliano, A. Calcagni, J. Monfregola, S. Punzi, N. Pastore, et al., Transcriptional activation of RagD GTPase controls mTORC1 and promotes cancer growth, Science 356 (2017) 1188–1192.
[94] F.V. Din, A. Valanciute, V.P. Houde, D. Zibrova, K.A. Green, K. Sakamoto, et al., Aspirin inhibits mTOR signaling activates amp-activated protein kinase and induces autophagy in colorectal cancer cells, Gastroenterology 142 (2012) 1504–1515.
[95] P. Zhang, D. He, E. Song, M. Jiang, Y. Song, Celecoxib enhances the sensitivity of non-small-cell lung cancer Cells to radiation-induced apoptosis through downregulation of the Akt/mTOR signaling pathway and COX-2 expression, PLoS One 14 (2019) e0223760.

[96] K.W. Kim, R.W. Mutter, C. Cao, J.M. Albert, M. Freeman, D.E. Hallahan, et al., Autophagy for cancer therapy through inhibition of pro-apoptotic proteins and mammalian target of rapamycin signaling, J. Biol. Chem. 281 (2006) 36883–36890.
[97] J.S. Rader, M.W. Sill, J.H. Beumer, H.A. Lankes, D.M. Benbrook, F. Garcia, et al., A stratified randomized double-blind phase II trial of celecoxib for treating patients with cervical intraepithelial neoplasia: the potential predictive value of VEGF serum levels: an NRG Oncology/Gynecologic Oncology Group study, Gynecol. Oncol. 145 (2) (2017) 291–297.
[98] M. Youns, T. Efferth, J.D. Hoheisel, Transcript profiling identifies novel key players mediating the growth inhibitory effect of NS-398 on human pancreatic cancer cells, Eur. J. Pharmacol. 650 (2011) 170–177.
[99] J.S. Kim, S.J. Baek, T. Sali, T.E. Eling, The conventional nonsteroidal anti-inflammatory drug sulindac sulfide arrests ovarian cancer cell growth via the expression of NAG-1/MIC-1/GDF-15, Mol. Cancer Therapeut. 4 (2005) 487–493.
[100] T. Kawahara, H. Ishiguro, K. Hoshino, J.I. Teranishi, Y. Miyoshi, Y. Kubota, et al., Analysis of NSAID-activated gene 1 expression in prostate cancer, Urol. Int. 84 (2010) 198–202.
[101] S. Wynne, D. Djakiew, NSAID inhibition of prostate cancer cell migration is mediated by nag-1 induction via the p38 MAPK-p75NTR pathway, Mol. Cancer Res. 8 (2010) 1656–1664.
[102] K.S. Kim, S.J. Baek, G.P. Flake, C.D. Loftin, B.F. Calvo, T.E. Eling, Expression and regulation of nonsteroidal anti-inflammatory drug–activated gene (NAG-1) in human and mouse tissue, Gastroenterology 122 (2002).
[103] R. Silvestri, P. Pucci, E. Venalainen, C. Matheou, R. Mather, S. Chandler, et al., T-type calcium channels drive the proliferation of androgen-receptor negative prostate cancer cells, Prostate 79 (2019) 1580–1586.
[104] N.N. Phan, C.Y. Wang, C.F. Chen, Z. Sun, M.D. Lai, Y.C. Lin, Voltage-gated calcium channels: novel targets for cancer therapy, Oncol. Lett. 14 (2017) 2059–2074.
[105] A.J. Johnson, A.L. Hsu, H.P. Lin, X. Song, C.S. Chen, The cyclo-oxygenase-2 inhibitor celecoxib perturbs intracellular calcium by inhibiting endoplasmic reticulum Ca2+-ATPases: a plausible link with its anti-tumour effect and cardiovascular risks, Pt 3Biochem. J 366 (2002) 831–837.
[106] Y.C. Guo, C.M. Chang, W.L. Hsu, S.J. Chiu, Y.T. Tsai, Y.H. Chou, et al., Indomethacin inhibits cancer cell migration via attenuation of cellular calcium mobilization, Molecules 18 (2013) 6584–6596.
[107] K. Dzobo, D.A. Senthebane, C. Dandara, The tumor microenvironment in tumorigenesis and therapy resistance revisited, Cancers 15 (2) (2023 Jan 6) 376.
[108] L. Ma, A. Gonzalez-Junca, Y. Zheng, H. Ouyang, I. Illa-Bochaca, K.C. Horst, et al., Inflammation mediates the development of aggressive breast cancer following radiotherapy, Clin. Cancer Res. 27 (6) (2021 Mar 15) 1778–1791.
[109] Y. Cao, R. Nishihara, Z.R. Qian, M. Song, K. Mima, K. Inamura, et al., Regular aspirin use associates with lower risk of colorectal cancers with low numbers of tumor-infiltrating lymphocytes, Gastroenterology 151 (5) (2016 Nov) 879–892.e4.
[110] K. Fischer, P. Hoffmann, S. Voelkl, N. Meidenbauer, J. Ammer, M. Edinger, et al., Inhibitory effect of tumor cell-derived lactic acid on human T cells, Blood 109 (9) (2007 May 1) 3812–3819.
[111] K. Renner, C. Bruss, A. Schnell, G. Koehl, H.M. Becker, M. Fante, et al., Restricting glycolysis preserves T cell effector functions and augments checkpoint therapy, Cell Rep. 29 (1) (2019 Oct 1) 135–150.e9.
[112] N.T. Sebastian, W.A. Stokes, M. Behera, R. Jiang, D.A. Gutman, Z. Huang, et al., The association of improved overall survival with NSAIDs in non-small cell lung cancer patients receiving immune checkpoint inhibitors, Clin. Lung Cancer 24 (3) (2023 May) 287–294.
[113] P. Pantziarka, V. Sukhatme, G. Bouche, L. Meheus, V.P. Sukhatme, Repurposing drugs in oncology (ReDO)-diclofenac as an anti-cancer agent, Ecancermedicalscience 10 (2016 Jan 11) 610.
[114] P. Hynninen, L. Vaskivuo, J. Saarnio, H. Haapasalo, J. Kivelä, S. Pastoreková, et al., Expression of transmembrane carbonic anhydrases IX and XII in ovarian tumours, Histopathology 49 (6) (2006 Dec) 594–602.
[115] J. Pastorek, S. Pastorekova, Hypoxia-induced carbonic anhydrase IX as a target for cancer therapy: from biology to clinical use, Semin. Cancer Biol. 31 (2015 Apr) 52–64.
[116] H. Sheth, E. Northwood, C.M. Ulrich, D. Scherer, F. Elliott, J.H. Barrett, et al., Interaction between polymorphisms in aspirin metabolic pathways, regular aspirin use and colorectal cancer risk: a case-control study in unselected white European populations, PLoS One 13 (2) (2018 Feb 9) e0192223.
[117] H. Nan, C.M. Hutter, Y. Lin, E.J. Jacobs, C.M. Ulrich, E. White, et al., Association of aspirin and NSAID use with risk of colorectal cancer according to genetic variants, JAMA 313 (11) (2015 Mar 17) 1133–1142.
[118] L. Klampfer, Cytokines, inflammation and colon cancer, Curr. Cancer Drug Targets 11 (4) (2011 May) 451–464.
[119] R. Sohail, M. Mathew, K.K. Patel, S.A. Reddy, Z. Haider, M. Naria, et al., Effects of non-steroidal anti-inflammatory drugs (NSAIDs) and gastroprotective NSAIDs on the gastrointestinal tract: a narrative review, Cureus 15 (4) (2023 Apr 3) e37080.
[120] A. Hervás Angulo, Hypertension emergency as a side-effect of taking NSAIDs, Atención Primaria 34 (5) (2004 Sep 30) 267–268.
[121] Y. Huang, D. Cao, Z. Chen, B. Chen, J. Li, R. Wang, et al., Iron intake and multiple health outcomes: umbrella review, Crit. Rev. Food Sci. Nutr. (2021 Sep 29) 1–18.