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Chemoprevention of Gastrointestinal Cancers: An Umbrella Review of Meta-Analyses of Randomized Controlled Trials and Cohort Studies

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ABSTRACT

Several meta-analyses have investigated the association between chemopreventive agents (CPAs) and the risk of gastrointestinal cancers, but syntheses of the quality of evidence in aggregate are lacking. This umbrella review aimed to assess the quality of evidence from meta-analyses of randomized controlled trials (RCTs) and cohort studies that examine inverse associations between CPAs and the risk of gastrointestinal cancers or any premalignant conditions. Summary effect sizes from random-effects models, between-study heterogeneity, 95% prediction interval, small-study effect, excess significance, and credibility ceilings were devised to classify the credibility of evidence from meta-analyses of cohort studies, whereas the GRADE approach was used for meta-analyses of RCTs. From 20,296 publications, 577 full-text articles were evaluated for eligibility, and 69 articles that provided 194 unique meta-analyses were included. Among meta-analyses of RCTs ($N=93$), 26 reached statistical significance ($p<0.05$). Seven inverse associations were graded as either high quality (celecoxib and colorectal adenomas, ($N=4$)) or moderate (aspirin and colorectal adenomas, ($N=2$) and *H-pylori* eradication and gastric cancer ($N=1$)). Among meta-analyses of cohort studies ($N=101$), 60 reached statistical significance. Four inverse associations were graded as either convincing (antivirals with hepatocellular carcinoma (HCC); $N=1$) or highly suggestive (aspirin with HCC ($N=2$) and colorectal cancer ($N=1$)). This review suggests that the associations with the most consistent empirical evidence were confined to those targeting the well-established risk factors of gastrointestinal cancer progression. Despite the limited established evidence, the inverse associations observed between metformin and colorectal, esophageal, and gastric cancers, as well as between statins and HCC and gastric cancer, merit further research.

Summary

- What is the current knowledge on the topic?
  - Several meta-analyses have investigated the association between chemopreventive agents (CPAs) and the risk of gastrointestinal cancers. While existing evidence suggests that some of these agents may hold promise, the accumulated data remain complex and inconclusive, with studies reporting mixed findings.
- What question did this study address?
  - How credible is the evidence behind the inverse associations between chemopreventive agents (CPAs) and gastrointestinal cancers in meta-analyses of randomized clinical trials (RCTs) and cohort studies?
- What does this study add to our knowledge?
  - Eighty-six statistically significant associations supporting chemopreventive approaches were found from 194 examined associations from meta-analyses of RCTs and cohort studies. Inverse associations between celecoxib and aspirin on colorectal adenomas and *H.pylori* eradication on gastric cancer were supported by good-quality evidence from RCTs. Inverse associations of antivirals with hepatocellular carcinoma (HCC), aspirin with HCC, and colorectal cancer were supported by good-quality evidence from cohort studies. Metformin with colorectal cancer, esophagus cancer, and gastric cancer, and statins with HCC and gastric cancer yielded suggestive evidence.
- How might this change clinical pharmacology or translational science?
  - Overall, the association between several CPAs and gastrointestinal cancers has been extensively studied, but only a few associations with CPAs targeting well-established risk factors are graded as good-quality evidence. Several CPA approaches have demonstrated promising effects in reducing the risk of several gastrointestinal cancers but have fallen short of having established evidence that merits further investigation.

1 | Introduction

Gastrointestinal (GI) cancers account for a significant portion of the global cancer burden, representing about a quarter of all cancer cases and a third of cancer-related deaths [1]. The global economic cost of GI cancers is projected to reach 8.2 trillion dollars between 2020 and 2050 [2]. Given the significant public health and economic implications, there is a pressing need to identify effective strategies for preventing GI cancers. Chemoprevention could be a promising strategy for achieving this objective.

Chemoprevention is the use of natural, synthetic, or biological agents to reverse, suppress, or prevent either the initial phases of carcinogenesis or the progression of premalignant cells to invasive disease [3]. A large body of research has investigated the potential use of various chemopreventive agents (CPAs). While existing evidence suggests that some of these agents may hold promise, the accumulated data remain complex and inconclusive, with studies reporting mixed findings [4]. Over the past few decades, numerous systematic reviews and meta-analyses have been published; these studies have consolidated the clinical efficacy of various chemopreventive approaches and informed future research directions. However, there has been little synthesis of the quality of evidence in an aggregate manner across these studies. Moreover, the strength, precision, and potential influence of bias on these associations need further clarification.

This umbrella review aimed to systematically identify relevant meta-analyses of randomized clinical trials (RCTs) and cohort studies on chemoprevention of GI cancers, summarize the findings, assess the precision of associations and the presence of bias, thereby enabling the grading of evidence using well-defined criteria.

2 | Methods

The study followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline [5] and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) reporting guideline [6]. The protocol of this study was registered with PROSPERO (CRD42024575101).

2.1 | Search Strategy and Selection Criteria

A systematic literature search was conducted in PubMed, the Cochrane Database of Systematic Reviews, and Epistemonikos from database inception until May 2024 using a predefined search strategy (Table S1).

Studies were included if they met the following criteria: (1) systematic reviews with meta-analysis of RCTs or cohort studies investigating the association between the use of CPAs and risk of GI cancers or any premalignant conditions (example, colorectal adenomas), (2) investigated CPAs, such as repurposed drugs, vitamins, antioxidants, or any supplements, at any dose, either alone or in combination. This review did not consider dietary components and plant-derived chemicals. When more than one meta-analysis was available for the same research question (i.e., overlapping meta-analyses), we selected the meta-analysis with the largest data set (Table S2). We excluded (1) meta-analyses of studies with other study designs (e.g., cross-sectional, case–control); (2) meta-analyses published in languages other than English; (3) meta-analyses that directly compared different CPAs; and (4) meta-analyses that provided insufficient or inadequate data for the selection process and/or quantitative synthesis.

Two authors (J.E.C. and S.K.) independently screened titles or abstracts and examined the full text of potentially eligible articles. Discrepancies were resolved by a third reviewer (S.K.V.).

2.2 | Data Extraction

Data were extracted, and the methodological quality of included meta-analyses was assessed using A Measurement Tool to Assess Systematic Reviews (AMSTAR-2) [7] independently by

TABLE 1 | Criteria for credibility of evidence classification in meta-analyses of cohort studies.

Credibility of evidence	Classification criteria
Convincing (Class-I)	– Number of cases > 1000 – $p < 10^{-6}$ – Heterogeneity (I^2) < 50% – Largest component study reporting a statistically significant result ($p < 0.05$) – 95% prediction interval excluding the null – Absence of small-study effects – Absence of excess significance bias – Survived 10% credibility ceiling test
Highly Suggestive (Class-II)	– Number of cases > 1000 – $p < 10^{-6}$ – Largest component study reporting a statistically significant result ($p < 0.05$)
Suggestive (Class-III)	– Number of cases > 1000 – $p < 10^{-3}$
Weak (Class-IV)	– $p < 0.05$
Non-significant	– $p > 0.05$

two authors (J.E.C. and S.S.G) and checked by a third author (S.K.V.). For each eligible meta-analysis, we abstracted data at the meta-analysis level (Table S2). Disagreements were resolved by consensus.

2.3 | Statistical Analysis

For each association, we recalculated the pooled summary estimates and corresponding 95% CIs with *p*-values using the DerSimonian and Laird random-effects model. Heterogeneity was assessed with the I^2 statistics. The evidence for small-study effects was evaluated using the Egger test. For meta-analyses of cohort studies, we estimated the 95% prediction interval [8], assessed excess significant bias [9], and performed the credibility ceiling test using a 10% ceiling value [10]. Detailed descriptions of these tests are provided in Table S2 in the Supplement. All statistical analyses were conducted using Stata software, version 16.0 (StataCorp LLC). All tests were conducted at a significance level of 2-sided $p = 0.05$, except for the Egger and excess significance tests, which used a 2-sided $p = 0.10$ significance level.

2.4 | Summary of Evidence

For meta-analyses of RCTs, we evaluated the certainty of evidence for each association using the Grading of Recommendation, Assessment, Development and Evaluations (GRADE) framework, which classified evidence as very low, low, moderate, or high [11]. For meta-analyses of cohort studies, we have applied several criteria to grade the credibility of evidence and classified it as conclusive (class I), highly suggestive (class II), suggestive (class III), or weak (class IV) (Table 1). Statistically significant associations demonstrating an overall risk reduction of at least 25% (i.e., risk ratio (RR) ≤ 0.75) can be considered meaningful from a public health perspective, given that the outcome of interest is the risk of cancer [12], and here such associations have been listed as promising approaches.

2.5 | Sensitivity and Subgroup Analyses

We performed sensitivity analyses for associations initially graded as having high or moderate quality evidence (for RCTs), or class I or II evidence (for cohort studies). These analyses included excluding small studies (< 25th percentile) [13], excluding primary studies with low quality or high risk of bias, as well as applying the Hartung-Knapp-Sidik-Jonkman approach for meta-analyses with fewer than five studies [14].

3 | Results

Overall, we identified a total of 20,296 publications, evaluated 577 eligible full-text articles (2.84%), and finally included 69 articles (11.96%) describing 194 unique associations (i.e., meta-analyses) (Figure S1). One hundred thirty-seven articles (23.74%) were excluded because of overlap characteristics (Table S3).

3.1 | Findings From Meta-Analyses of RCTs

Thirty-four eligible articles (Table S4) describing 93 unique associations for 6 GI cancers (Figure 1) were included. Characteristics of included associations are given in Table S4. The median number of studies per association was three (interquartile range [IQR]: 2.5–5). The methodological quality of the meta-analyses assessed using AMSTAR-2 varied, with 22 rated as high quality, 7 as moderate, 4 as low, and 60 as critically low quality (Table S4).

Twenty-six [15–29] of 93 associations (27.96%) achieved statistical significance ($p < 0.05$). Summaries of all statistically significant and nonsignificant associations are presented in Tables S5 and S6, respectively. Among 26 statistically significant associations, 8 meta-analyses were initially graded as moderate to high-quality evidence (Table 2). The inverse associations ($N = 4$) between the use of celecoxib on colorectal adenomas in a population with a previous history of colorectal

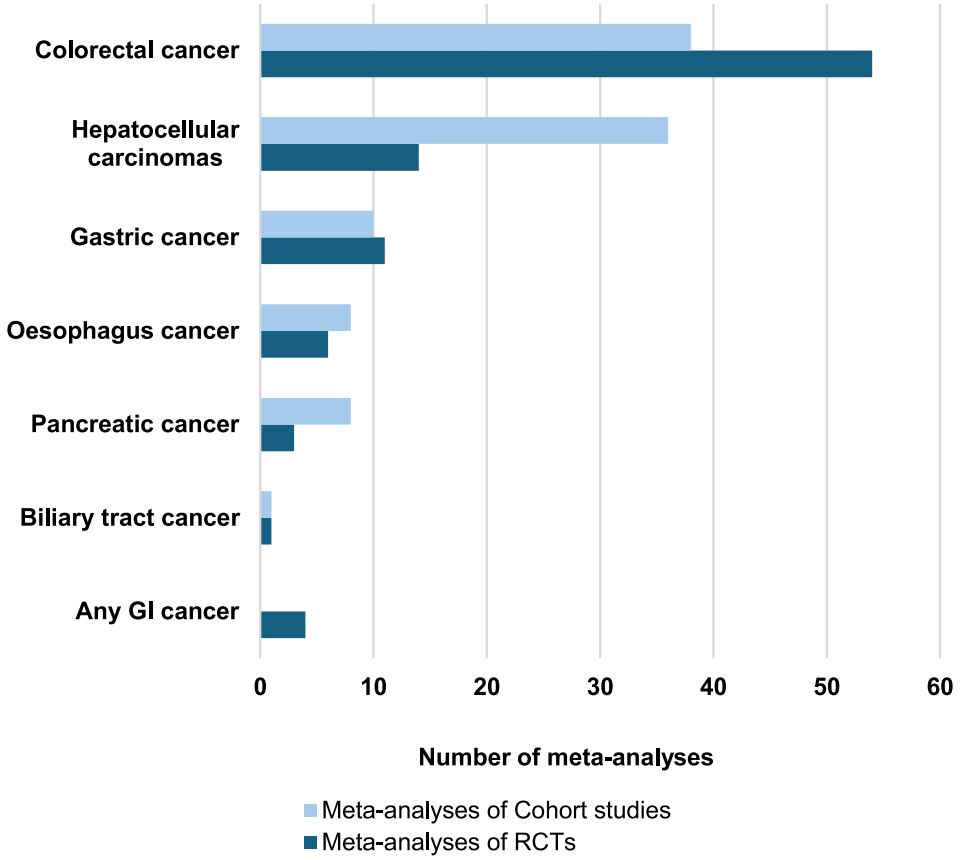

FIGURE 1 | This figure illustrates the distribution of meta-analyses investigating different gastrointestinal (GI) cancers in published literature.

adenomas were supported by high-quality evidence [18]. Moderate-quality evidence supported the following inverse associations: aspirin use with colorectal adenomas ($N=2$) [17, 19], selenium supplementation with HCC ($N=1$) [20], and *Helicobacter pylori* (*H. pylori*) eradication therapy with gastric cancer ($N=1$) [27]. The association between selenium supplementation with HCC was downgraded to low quality after sensitivity analysis excluded trials with a high risk of bias (Table S7). Associations graded as high or moderate quality of evidence in both main and sensitivity analyses were provided in Table 2. We also identified 13 additional promising chemoprevention approaches in the main analysis: colorectal adenoma recurrence ($N=3$; difluoromethylornithine with sulindac, berberine, and calcium supplement), advanced colorectal adenoma recurrence ($N=2$; low and high-dose aspirin), HCC incidence and recurrence ($N=5$; antivirals, selenium and vitamin K2), gastric cancer ($N=2$; *H. pylori* eradication), any GI cancer ($N=1$; selenium) (Table 2).

3.2 | Findings From Meta-Analyses of Cohort Studies

Forty-two articles describing 101 unique associations for six GI cancers (Figure 1) were included. The characteristics of included associations were provided in Table S8 in the Supplement. The median number of studies per association was 5 (IQR: 3–10). The details of adjustment for potential confounding variables in the included meta-analyses are reported in Table S8. According to AMSTAR-2, three meta-analyses met the moderate-quality level, 16 had low quality, and the majority, 82 meta-analyses, were deemed to be of critically low quality (Table S8).

Sixty [16, 21, 30–55] of the 101 associations (59.41%) were statistically significant ($p<0.05$) (Table S9). The forty-one (40.59%) non-significant associations are presented in Table S10 in the Supplement. Of the 77 of the 101 associations that provided sufficient data to reperform the meta-analysis, only 12 (15.58%) reached statistical significance at $p<10^{-6}$. Among 77 associations, 40 (51.95%) demonstrated large heterogeneity ($I^2>50\%$). The 95% prediction intervals excluded the null value for 11 associations (14.29%). Small-study effects were found in 17 associations (22.08%). The effect sizes of the largest study were statistically significant at $p\leq0.05$ for 43 associations (55.84%). Twenty-five associations (32.47%) passed the 10% credibility ceiling test. Excess significance bias was identified for only five associations, as the necessary data was unavailable to perform this test for the majority of the examined associations.

Among the 42 statistically significant associations evaluated for credibility [16, 21, 30, 31, 33–42, 44–50, 52–54], one association was found to have convincing evidence [47], three had highly suggestive evidence [44, 52], and eight had suggestive evidence (Table 3) [30, 31, 34, 38, 45, 47, 48, 53]. The inverse association between interferon-based antiviral treatment for chronic hepatitis C (CHC) (sustained virological response (SVR) vs. non-SVR) and risk of HCC ranked as convincing [47]. Our review found highly suggestive evidence ($N=3$) that

TABLE 2 | Findings of statistically significant associations in meta-analyses of randomized controlled trials.

Author, year	Cancer types	Outcome	Population	Intervention	Comparator	Studies per association	No. of participants	Cases	Follow-up	Effect size (RR/OR/HR) (95% CI)	I^2 (%)	AMSTAR	CE[a]
Associations with high or moderate quality of evidence in both primary and sensitivity analyses													
Veettil et al. [18]	CRC	Recurrence of any colorectal adenomas	History of colorectal adenomas	Celecoxib at any dose (400–800 mg/day)	Placebo	3	3463	1437	1–3 years	0.67 (0.62–0.72)	0.00	Moderate	High
Veettil et al. [18]	CRC	Recurrence of any colorectal adenomas	History of colorectal adenomas	Celecoxib (400 mg/day)	Placebo	3	2862	1224	1–3 years	0.69 (0.64–0.75)	0.00	Moderate	High
Veettil et al. [18]	CRC	Recurrence of advanced adenomas	History of colorectal adenomas	Celecoxib at any dose (400–800 mg/day)	Placebo	3	3457	291	1–3 years	0.42 (0.34–0.53)	0.00	Moderate	High
Veettil et al. [18]	CRC	Recurrence of advanced adenomas	History of colorectal adenomas	Celecoxib (400 mg/day)	Placebo	3	2856	256	1–3 years	0.45 (0.35–0.58)	0.00	Moderate	High
Ma et al. [19]	CRC	Recurrence of any colorectal adenomas	History of CRC or adenomas	Low-dose aspirin (80–160 mg/day)	Placebo	4	1383	NR	1–4 years	0.79 (0.69–0.90)	0.00	Critically low	Moderate
Veettil et al. [17]	CRC	Recurrence of advanced adenomas	History of CRC or adenomas	Any dose of aspirin (80–325 mg/day)	Placebo	5	2950	253	2–4 years	0.70 (0.55–0.88)	0.00	Moderate	Moderate
Ford et al. [27]	Gastric cancer	Incidence of gastric cancer	Healthy asymptomatic *H. pylori*-infected individuals	*H. pylori* eradication therapy	Placebo	7	8323	193	4–22 years	0.54 (0.40–0.72)	0.00	High	Moderate

(Continues)

TABLE 2 | (Continued)

Author, year	Cancer types	Outcome	Population	Intervention	Comparator	Studies per association	No. of participants	Cases	Follow-up	Effect size (RR/OR/HR) (95% CI)	I^2 (%)	AMSTAR	CE[a]
Statistically significant associations demonstrating a risk reduction of ≥ 25%													
Veettil et al. [17]	CRC	Recurrence of advanced adenomas	History of CRC or adenomas	Low-dose aspirin (80–160 mg/day)	Placebo	3	1178	91	2–4 years	0.66 (0.44–0.99)	0.00	Moderate	Low
Veettil et al. [17]	CRC	Recurrence of advanced adenomas	History of CRC or adenomas	High-dose aspirin (300–325 mg/day)	Placebo	4	2218	216	2–4 years	0.73 (0.56–0.94)	0.00	Moderate	Low
Veettil et al. [15]	CRC	Recurrence of any adenomas	History of CRC or adenomas	Calcium supplement with elemental dose ≥ 1600 mg/day	Placebo	2	447	121	3 years	0.74 (0.56–0.97)	0.00	High	Very low
Fang et al. [23]	CRC	1-year recurrence of colorectal adenoma	History of colorectal adenomas	Berberine supplement at any dose (0.3–0.6 g/day)	Placebo	3	1066	322	1 year	0.57 (0.35–0.93)	45.30	Critically low	Low
Yang et al. [24]	CRC	Recurrence of any colorectal adenomas	History of colorectal adenomas	DFMO + sulindac	Placebo	3	677	78	3 years	0.24 (0.14–0.41)	4.00	Critically low	Low
Bjelakovic et al. [20]	HCC	Incidence of HCC	High-risk population[b]	Selenium supplement	Placebo	4	9798	177	NR	0.56 (0.42–0.76)	0	High	Moderate
Singal et al. [16]	HCC	Incidence of HCC	Patients with chronic HCV cirrhosis	IFNs alone or with RBV	Placebo	4	347	75	Median: 37–103 months	0.30 (0.14–0.63)	40.70	Critically low	Low
Zhang et al. [21]	HCC	Recurrence of HCC	Patients after curative resection or ablation of HBV-related primary HCC	Nucleos(t)ide analogues[c]	Placebo	2	304	NR	NR	0.71 (0.58–0.85)	0.00	Critically low	Very low

(Continues)

TABLE 2 | (Continued)

Author, year	Cancer types	Outcome	Population	Intervention	Comparator	Studies per association	No. of participants	Cases	Follow-up	Effect size (RR/OR/HR) (95% CI)	I^2 (%)	AMSTAR	CE[a]
Riaz et al. [28]	HCC	2-year HCC tumor recurrence	History of HCC	Vitamin K2 at any dose (45 or 90 mg/day)	Placebo	5	754	106	2 years	0.66 (0.47–0.91)	26.00	Critically low	Very low
Riaz et al. [28]	HCC	3-year HCC tumor recurrence	History of HCC	Vitamin K2 at any dose (45 or 90 mg/day)	Placebo	5	754	120	3 years	0.71 (0.58–0.85)	0.00	Critically low	Very low
Khan et al. [22]	Gastric cancer	Incidence of metachronous gastric cancer	Post-resection early-stage GC patients with *H. pylori* infection	*H. pylori* eradication therapy	Placebo	4	2658	155	3–6 years	0.47 (0.33–0.67)	0.00	Critically low	Low
Chen et al. [26]	Gastric cancer	Incidence of gastric cancer	*H. pylori* -infected patients with NAG or AG	*H. pylori* eradication therapy	Placebo	6	2662	12	2–9 years	0.28 (0.08–0.95)	0.00	Critically low	Very low
Bjelakovic et al. [20]	Any types of GI cancers	Incidence of all GI cancers[d]	General population + high-risk population[b]	Selenium supplement	Placebo	5	11,110	265	7–7.4 years	0.59 (0.46–0.75)	0.00	High	Low

Abbreviations: AG, Atrophic gastritis; AMSTAR-2, A Measurement Tool to Assess Systematic Reviews; CE, credibility evidence; CI, confidence Interval; CRC, colorectal cancer; DFMO, difluoromethylornithine; ES, effect size; GI, gastrointestinal; HBV, hepatitis B virus; HCC, hepatocellular carcinomas; HCV, hepatitis C virus; *H. pylori*, *Helicobacter pylori*; HR, hazard ratio; IFN, interferon; NAG, non-atrophic gastritis; NR, not reported; OR, odds ratio; RBV, ribavirin; RR, risk ratio.

[a]Associations that were graded as having high, moderate, low, and very low quality of evidence based on the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) assessment.

[b]High-risk populations including populations with premalignant conditions, or populations living in areas with high incidence of GI cancers.

[c]Lamivudine (with adefovir or entecavir rescue) and adefovir.

[d]All GI cancers, including esophageal, gastric, small intestine, colorectal, pancreatic, liver, and biliary tract cancers.

TABLE 3 | Findings of Statistically Significant Associations in Meta-analyses of Cohort Studies.

Author, year	Cancer types	Outcome	Population	Intervention	Comparator	Studies per association	Follow-up	Effect size (RR/OR/HR) (95% CI)	No. of participants	Cases	*p*	I^2 (%)	Largest study effect size (95% CI)	PI (95% CI)	SSE/ESB	10% CCT, 95% CI	AMSTAR	CE[a]
Associations with convincing or highly suggestive quality of evidence in both primary and sensitivity analyses																		
Bang and Song [47]	HCC	Incidence of HCC	Patients with chronic hepatitis C	Received antiviral treatment (IFNs alone or with RBV) and achieved SVR	Received antiviral treatment (IFNs alone or with RBV) but not achieve SVR	34	2.1 (median) to 10 years (mean)	0.20 (0.16–0.25)	27,452	> 1000	2.62×10^{-49}	40.30	0.13 (0.11–0.15)	0.10–0.41	No/NP	0.20–0.42	Critically low	1
Wang et al. [52]	HCC	Incidence of HCC	Patients with chronic liver disease	Any dose of aspirin	Not using aspirin	13	NR	0.68 (0.60–0.77)	338,446	19,539	1.79×10^{-9}	87.20	0.81 (0.80–0.82)	0.44–1.04	Yes/NA[f]	0.75–0.95	Critically low	2
Wang et al. [52]	HCC	Incidence of HCC	HBV-infected population	Aspirin	Not using aspirin	7	NR	0.75 (0.68–0.83)	299,767	18,103	3.54×10^{-9}	62.80	0.81 (0.80–0.82)	0.58–0.97	Yes/NA[f]	0.67–0.92	Critically low	2
Ye et al. [44]	CRC	Incidence of CRC	General population	Highest frequency of aspirin use	Lowest frequency of aspirin use	10	3–24 years	0.81 (0.76–0.87)	NR	> 1000	3.35×10^{-10}	0.00	0.86 (0.79–0.94)	0.75–0.88	Yes/NA[f]	0.71–0.91	Critically low	2
Statistically significant associations demonstrating a risk reduction of ≥ 25%																		
Wang et al. [30]	CRC	Incidence of CRC	General population	Regular aspirin use (≥ 2 times per week)	Not using aspirin	18	NR	0.85 (0.78–0.92)	3,536,448	127,291	9.63×10^{-5}	92.20	0.76 (0.74–0.79)	0.61–1.19	No/Yes	0.89–0.99	Critically low	3
Wang and Shi [53]	CRC	Incidence of CRC	DM patients	Metformin	Not using metformin	22	NR	0.67 (0.57–0.79)	NR	> 1000	1.96×10^{-6}	88.60	0.50 (0.45–0.56)	0.32–1.40	No/NA[f]	0.85–0.98	Critically low	3
Ye et al. [44]	CRC	Incidence of CRC	General population	Highest dose of aspirin use	Lowest dose of aspirin use	5	3–24 years	0.75 (0.66–0.85)	NR	371	1.01×10^{-5}	0.00	0.72 (0.56–0.93)	0.61–0.92	No/NA[f]	0.66–0.96	Critically low	4
Ye et al. [44]	CRC	Incidence of CRC	General population	Highest duration of aspirin use	Lowest duration of aspirin use	10	3–24 years	0.75 (0.67–0.84)	NR	977	4.14×10^{-7}	31.10	0.90 (0.80–1.10)	0.58–0.97	Yes/NA[f]	0.76–0.94	Critically low	4
Ye et al. [44]	Colon cancer	Incidence of colon cancer	General population	Highest duration of aspirin use	Lowest duration of aspirin use	2	3–24 years	0.67[b] (0.44–0.91)	NR	NR	NA	NR	NA	NA	NA/NA[f]	NA	Critically low	NA[g]
Ye et al. [44]	Rectal cancer	Incidence of rectal cancer	General population	Highest frequency of aspirin use	Lowest frequency of aspirin use	5	3–24 years	0.74[b] (0.64–0.83)	NR	NR	NA	NR	NA	NA	NA/NA[f]	NA	Critically low	NA[g]

(Continues)

TABLE 3 | (Continued)

Author, year	Cancer types	Outcome	Population	Intervention	Comparator	Studies per association	Follow-up	Effect size (RR/OR/HR) (95% CI)	No. of participants	Cases	*p*	I^2 (%)	Largest study effect size (95% CI)	PI (95% CI)	SSE/ESB	10% CCT, 95% CI	AMSTAR	CE[a]
Ye et al. [44]	Rectal cancer	Incidence of rectal cancer	General population	Highest duration of aspirin use	Lowest duration of aspirin use	2	3–24 years	0.54[b] (0.20–0.88)	NR	NR	NA	NR	NA	NA	NA/NA[f]	NA	Critically low	NA[g]
Yi et al. [38]	HCC	Incidence of HCC	Patients with chronic liver disease	Low-dose aspirin (100 mg/day)	Not using aspirin	10	3.1–4.8 years	0.56 (0.44–0.72)	122,095	4929	5.94×10^{-6}	85.40	0.78 (0.64–0.95)	0.24–1.31	Yes/NA[f]	0.65–0.91	Low	3
Bang and Song [47]	HCC	Incidence of HCC	Patients with chronic hepatitis C	Antiviral treatment: IFNs alone or with RBV	No treatment	22	Mean: 32 months to 10 years	0.42 (0.29–0.61)	15,411	1625	4.51×10^{-6}	87.60	0.28 (0.20–0.40)	0.08–2.30	No/NA[f]	0.51–0.92	Critically low	3
Zeng et al. [31]	HCC	Incidence of HCC	Overall population[c]	Statins	Not using statins	10	Mean: 24–79.6 months	0.52 (0.37–0.72)	1,774,476	13,142	9.64×10^{-5}	97.70	0.97 (0.93–1.02)	0.14–1.86	Yes/NA[f]	0.80–1.01	Critically low	3
Li et al. [48]	HCC	Incidence of HCC	DM patients	Metformin	Not using metformin	15	NR	0.60 (0.50–0.73)	NR	>1000	1.73×10^{-7}	97.40	0.99 (0.99–1.00)	0.30–1.22	Yes/NA[f]	0.74–0.98	Critically low	3
Wang et al. [40]	HCC	Incidence of HCC	General population	Aspirin	Not using aspirin	5	4–26 years	0.62 (0.47–0.82)	2,591,272	12,743	1.01×10^{-3}	93.60	0.49 (0.45–0.53)	0.21–1.81	No/NA[f]	0.67–0.97	Critically low	4
Li et al. [49]	HCC	Recurrence of HCC	Patients after HCC resection or TACE	Aspirin	Not using aspirin	4	2.9–4.2 years	0.75 (0.60–0.93)	18,431	NR	1.03×10^{-2}	33.90	0.70 (0.58–0.85)	0.35–1.57	No/NA[f]	0.62–1.02	Critically low	4
Zhang et al. [21]	HCC	Recurrence of HCC	Patients after curative HBV-related HCC resection or ablation	NAs	No treatment	11	NR	0.75 (0.61–0.93)	2288	NR	8.25×10^{-3}	58.20	0.56 (0.47–0.67)	0.41–1.39	No/NA[f]	0.75–1.01	Critically low	4
Lok et al. [37]	HCC	Incidence of HCC	Patients with chronic HBV infection	Any antiviral treatment	No treatment	7	35–114 months	0.53 (0.35–0.79)	4970	NR	2.18×10^{-3}	48.30	0.26 (0.13–0.55)	0.18–1.55	No/NA[f]	0.46–1.03	Low	4
Lok et al. [37]	HCC	Incidence of HCC	Patients with chronic HBV infection and compensated cirrhosis	Lamivudine	No treatment	4	35–114 months	0.61 (0.39–0.96)	2953	NR	3.24×10^{-2}	49.80	0.59 (0.41–0.84)	0.11–3.35	No/NA[f]	0.45–1.18	Low	4
Singal et al. [16]	HCC	Incidence of HCC	Patients with HCV cirrhosis	IFN alone or with RBV	No treatment	16	Median: 32–96 months	0.46 (0.34–0.61)	4353	868	6.44×10^{-8}	71.20	0.66 (0.49–0.88)	0.16–1.27	No/Yes	0.53–0.84	Critically low	4

(Continues)

TABLE 3 | (Continued)

Author, year	Cancer types	Outcome	Population	Intervention	Comparator	Studies per association	Follow-up	Effect size (RR/OR/HR) (95% CI)	No. of participants	Cases	*p*	I^2 (%)	Largest study effect size (95% CI)	PI (95% CI)	SSE/ESB	10% CCT, 95% CI	AMSTAR	CE[a]
Singal et al. [16]	HCC	Incidence of HCC	Patients with HCV cirrhosis	Received antiviral treatment (IFNs alone or with RBV) and achieved SVR	Received antiviral treatment (IFNs alone or with RBV) but not achieve SVR	12	Median: 25–96 months	0.34 (0.26–0.46)	3194	419	1.22×10^{-12}	0.00	0.49 (0.28–0.86)	0.25–0.48	Yes/Yes	0.22–0.61	Critically low	4
Lui et al. [42]	HCC	Recurrence of HCV-related HCC beyond 1 year after treatment	Adult HCV patients with history of HCC	DAA treatment	No treatment	4	>1 year	0.24 (0.12–0.49)	1775	715	8.13×10^{-5}	74.90	0.11 (0.07–0.18)	0.01–5.16	No/Yes	0.13–0.80	Critically low	4
He et al. [50]	HCC	Incidence of HCC	Patients with cirrhosis	Carvedilol alone at any dose or in combination with other treatments[d]	Not using NSBBs	3	NR	0.66 (0.48–0.89)	107,844	NR	7.60×10^{-3}	8.10	0.61 (0.51–0.73)	0.05–9.37	Yes/NA[f]	0.46–1.45	Low	4
Li et al. [55]	HCC	Incidence of HCC	HBV or HCV-infected patients with diabetes status	Aspirin	Not using aspirin	6	9–15 years	0.75 (0.67–0.83)	NR	NR	7.71×10^{-8}	0.00	0.71 (0.61–0.83)	0.64–0.87	No/NA[f]	0.68–0.95	Critically low	NA[g]
Li et al. [55]	HCC	Incidence of HCC (follow-up ≥5 years)	HBV or HCV-infected patients	Aspirin	Not using aspirin	4	≥5 years	0.70 (0.65–0.76)	99,852	3518	5.45×10^{-20}	0.00	0.69 (0.62–0.76)	0.59–0.83	No/NA[f]	0.57–0.93	Critically low	NA[g]
Zeng et al. [31]	HCC	Incidence of HCC	Patients with hepatitis B	Statins	Not using statins	5	NR	0.53 (0.32–0.88)	152,716	NR	NA	96.70	NA	NA	NA/NA[f]	NA	Critically low	NA[g]
Zeng et al. [31]	HCC	Incidence of HCC	Overall population[c]	Lipophilic statins	Not using statins	3	NR	0.46 (0.37–0.57)	1,083,952	NR	NA	64.00	NA	NA	NA/NA[f]	NA	Critically low	NA[g]
Khajeh et al. [32]	HCC	Recurrence of HCC	Patients after HCC resection or transplantation	Statins	Not using statins	8	NR	0.53 (0.44–0.64)	25,327	>1000	1.17×10^{-11}	37.30	0.51 (0.42–0.62)	0.34–0.82	No/NA[f]	0.41–0.79	Critically low	NA[g]

(Continues)

TABLE 3 | (Continued)

Author, year	Cancer types	Outcome	Population	Intervention	Comparator	Studies per association	Follow-up	Effect size (RR/OR/HR) (95% CI)	No. of participants	Cases	*p*	I^2 (%)	Largest study effect size (95% CI)	PI (95% CI)	SSE/ESB	10% CCT, 95% CI	AMSTAR	CE[a]
He et al. [50]	HCC	Incidence of HCC	Patients with cirrhosis	Nadolol alone at any dose or in combination with other treatments[e]	Not using NSBBs	2	NR	0.73 (0.63–0.86)	107,658	NR	1.59×10^{-4}	0.00	0.74 (0.63–0.87)	NA	NA/NA[f]	0.46–1.08	Low	NA[g]
Chen et al. [45]	Gastric cancer	Incidence of gastric cancer	General population	Statins	Not using statins	25	NR	0.73 (0.63–0.84)	3,504,600	>1000	1.66×10^{-5}	88.80	0.70 (0.65–0.74)	0.39–1.38	No/NA[f]	0.90–1.01	Critically low	3
Lee et al. [39]	Gastric cancer	Incidence of gastric cancer	Asymptomatic *H. pylori*-infected individuals	*H. pylori* eradication therapy	No treatment	8	Mean: 24–121 months	0.57 (0.40–0.82)	35,502	242	2.04×10^{-3}	16.00	0.85 (0.43–1.66)	0.29–1.12	Yes/No	0.48–0.99	Critically low	4
Fan et al. [46]	Gastric cancer	Incidence of metachronous gastric cancer	*H. pylori*-infected patients with early-stage GC treated via endoscopic resection	*H. pylori* eradication therapy	No treatment or failed eradication	10	Mean: 27–79 months	0.43 (0.33–0.57)	2386	211	4.45×10^{-9}	0.00	0.53 (0.32–0.87)	0.31–0.60	No/Yes	0.32–0.77	Critically low	4
Sugano et al. [35]	Gastric cancer	Incidence of gastric cancer	Individuals with gastritis	*H. pylori* eradication therapy	No treatment or failed eradication or both	2	NR	0.22 (0.07–0.71)	1240	21	1.13×10^{-2}	0.00	0.27 (0.07–0.97)	NA	NA/NA[f]	0.04–1.21	Moderate	4
Sugano et al. [35]	Gastric cancer	Incidence of gastric cancer	Individuals with peptic ulcer	*H. pylori* eradication therapy	No treatment or failed eradication or both	3	NR	0.37 (0.21–0.67)	5626	72	9.18×10^{-4}	0.00	0.39 (0.17–0.90)	0.01–16.32	No/Yes	0.17–1.12	Moderate	4
Wang et al. [30]	Gastric cancer	Incidence of gastric cancer	General population	Regular aspirin use (≥2 times per week)	Not using aspirin	10	NR	0.67 (0.52–0.87)	2,378,794	14,933	2.76×10^{-3}	96.20	0.95 (0.89–1.02)	0.26–1.76	No/NP	0.87–0.99	Critically low	4
Wang et al. [30]	Gastric cancer	Incidence of gastric cancer	General population	≥5 years of aspirin use	Not using aspirin	3	≥5 years	0.60 (0.38–0.94)	890,956	6164	2.70×10^{-2}	86.00	NR	0.26–1.39	Yes/NP	NR	Critically low	4
Chen et al. [34]	Esophagus cancer	Incidence of esophagus cancer	DM patients	Metformin	Not using metformin	5	NR	0.53 (0.38–0.75)	5,203,191	>1000	2.62×10^{-4}	31.80	0.68 (0.54–0.85)	0.22–1.28	No/NA[f]	0.37–0.89	Low	3
Alexandre et al. [33]	Esophagus cancer	Incidence of OAC	Patients with BO	Statins	Not using statins	2	NR	0.53 (0.36–0.78)	796	586	1.33×10^{-3}	0.00	0.53 (0.36–0.87)	NA	NA/NA[f]	0.26–1.06	Critically low	4

(Continues)

TABLE 3 | (Continued)

Author, year	Cancer types	Outcome	Population	Intervention	Comparator	Studies per association	Follow-up	Effect size (RR/OR/HR) (95% CI)	No. of participants	Cases	*p*	I^2 (%)	Largest study effect size (95% CI)	PI (95% CI)	SSE/ESB	10% CCT, 95% CI	AMSTAR	CE[a]
Singh et al. [36]	Esophagus cancer	Incidence of OAC	Patients with BO	PPIs	Not using PPIs	5	6–40years	0.31 (0.17–0.57)	NR	198	1.44×10^{-4}	23.70	0.42 (0.18–0.98)	0.07–1.32	No/NA[f]	0.18–0.77	Critically low	4
Zhang et al. [41]	Esophagus cancer	Incidence of OAC	Patients with BO	COX inhibitors	Not using COX inhibitors	6	NR	0.61 (0.49–0.76)	4353	467	9.87×10^{-6}	0.00	0.65 (0.42–0.87)	0.45–0.83	No/NA[f]	0.45–0.88	Critically low	4

Abbreviations: AMSTAR, A measurement tool to assess systematic reviews; BO, Barrett's Esophagus; CCT, credibility ceiling test; CE, credibility of evidence; CI, confidence Interval; COX, cyclooxygenase; CRC, colorectal cancer; DAAs, direct-acting antivirals; DM, diabetes mellitus; ES, effect size; ESB, excess significance bias; HBV, hepatitis B virus; HCC, hepatocellular carcinomas; HCV, hepatitis C virus; *H. pylori*, *helicobacter pylori*; HR, hazard ratio; NA, not applicable; NAs, nucleos(t)ide analogues; NP, not pertinent (because the number of expected significant studies was larger than the number of observed significant studies); NR, not reported; NSBBs, non-selective beta-blockers; OAC, esophageal adenocarcinoma; OR, odds ratio; PI, prediction interval; PPIs, proton pump inhibitors; RBV, ribavirin; RR, risk ratio; SSE, small study effect; SVR, sustained virologic response; TACE, transarterial chemoembolization.

[a]Associations that were nominally significant (i.e., $p < 0.05$) were graded as having convincing (class 1), highly suggestive (class 2), suggestive (class 3), or weak (class 4) evidence based on the amount of evidence, statistical significance, heterogeneity, small-study effect, excess significance bias, prediction interval, and credibility ceiling test.

[b]Fixed-effect size is used due to insufficient data to reperform meta-analysis using random-effects model.

[c]Overall population includes both general and high-risk populations.

[d]Carvedilol as tested alone or in combination with other treatments such as endoscopic variceal ligation (EVL) and ivabradine.

[e]Nadolol was tested alone or in combination with other treatments such as isosorbide mononitrate (ISMN).

[f]NA, not applicable (due to insufficient data to perform excess significance bias test).

[g]NA, not applicable (due to insufficient to perform the statistical analyses to perform the assessment of credibility of evidence).

aspirin use was inversely associated with the risk of HCC (in patients with chronic liver disease (CLD) [52] and hepatitis B (HBV) [52]) and CRC (high vs. low-frequency use of aspirin) [44]. No associations were downgraded after sensitivity analyses (Table S11).

We also identified 37 additional promising chemoprevention approaches in the main analysis including those with suggestive evidence ($N = 8$): (1) metformin with CRC [53], esophagus cancer [34], and HCC (in patients with diabetes mellitus) [48]; (2) low-dose aspirin (100 mg/day) with HCC in the case of CLD [38], and regular aspirin use with CRC [30]; (3) statins with gastric cancer [45], and HCC [31]; and (4) interferon-based antiviral with HCC (treatment vs. no-treatment) in patients with CHC (Table 3) [47].

3.3 | Comparing Findings From Meta-Analyses of Cohort Studies and Those of RCTs

In total, we identified 18 associations for which findings were available from both meta-analyses of RCTs and cohort studies (Table S12). Statistically significant results favoring CPA were identified in both RCT and cohort data for four outcomes: HCC (antiviral for HCV-related cirrhosis) [16], and HCC recurrence (nucleotide analogues after curative resection or ablation of HBV-related primary HCC) [21], gastric cancer (*H. pylori* eradication therapy in asymptomatic *H. pylori*-cases) [27, 39], metachronous gastric cancer (*H. pylori* eradication therapy in early-stage gastric cancer treated via resection) [22, 46].

4 | Discussion

Findings of our study are important in the context of the current limited empirical evidence supporting chemoprevention strategies. To the best of our knowledge, this is the first umbrella review that provides an overview of the current evidence regarding GI chemoprevention, highlighting both its promising and less conclusive aspects. Overall, the association between several CPAs and GI cancers has been extensively studied, but only a few associations with CPAs are graded as having good-quality evidence.

The associations with the most consistent empirical evidence were confined to interventions that targeted the well-established risk factors of GI cancer progression, for example, antiviral treatment including interferon either alone or in combination with other agents (e.g., ribavirin) for chronic hepatitis infections to prevent HCC [47]. Associations between antiviral therapies and HCC were mostly consistent and frequently of strong magnitude, irrespective of factors like type of viral infection [37, 47], presence of cirrhosis [16, 37], and previous history of HCC [21, 42]. It is anticipated that the risk of HCC would be further reduced by direct-acting antivirals (DAAs) due to their higher SVR rates [56]. Nevertheless, some observational data have raised concerns about the potential association between DAAs and an increased rate of HCC recurrence, as well as the development of *de novo* HCC [57, 58]. A recent meta-analysis of cohort studies found no differences in the risk of developing *de novo* HCC between DAAs and interferon-based therapies [59]. However, the evidence was not conclusive, as the DAA-treated

cohort included a greater proportion of older patients with more advanced liver disease and additional HCC risk factors. Furthermore, the available literature lacks robust evidence on the effects of entecavir or tenofovir disoproxil fumarate, which are currently the recommended first-line treatments for HBV infection in adults [60].

With regards to *H.pylori* eradication to prevent gastric cancer, the evidence was of moderate quality based on a meta-analysis of RCTs [27]. The findings from meta-analyses of cohort studies were also consistent with RCTs [39]. Nonetheless, these meta-analyses were constrained by the paucity of studies from regions outside of Asia, implying that these findings may not be generalizable beyond the Asian populations.

Aspirin has long been recognized as a potential CPA, particularly against CRC. One of the biological mechanisms that has been proposed to contribute to aspirin's chemopreventive effect is its potential to inhibit cyclooxygenase-2 (COX-2), an enzyme implicated in promoting inflammation and cell proliferation, and which is frequently overexpressed in colorectal cancer [61, 62]. Our findings from meta-analyses of cohort studies also support the association [44]. In contrast, a most recent meta-analysis of four RCTs found no statistically significant association between low-dose aspirin use (vs. no intervention) and CRC incidence over a 5-to 10-year follow-up period [63], supporting a current recommendation from the US Preventive Services Task Force (USPSTF) [64]. Moreover, there is currently no high-quality evidence to support the effect modification of aspirin in different population groups, such as by age, sex, diabetes status, race, and ethnicity [63]. Notably, no existing recommendations specifically address the use of aspirin for chemoprevention of secondary CRC among patients with previous colorectal neoplasia or CRC, who may already be undergoing routine surveillance colonoscopy. We found moderate quality of evidence from meta-analysis of RCTs for low-dose aspirin in preventing recurrent colorectal neoplasia (reported as advanced or any colorectal adenomas) [17, 19]. Although high-quality evidence supports the use of celecoxib for this purpose [18], concerns over its long-term cardiovascular safety have hampered its clinical adoption. A recent network meta-analysis [65], demonstrated that low-dose aspirin had the most favorable safety profile compared to non-aspirin NSAIDs, and the excess benefit over risk might therefore be favorable for all patients with previous neoplasia, regardless of baseline neoplasia status. Patients without an increased risk of bleeding who are recommended to take low-dose aspirin daily as part of secondary prevention of cardiovascular disease are more likely to experience positive outcomes [64]. Cost-effectiveness analyses that explore the long-term outcomes of aspirin chemoprevention in combination with surveillance colonoscopy at different time intervals in different subgroup populations with varying baseline CRC risks are desirable to further define its potential role in clinical practice.

Our review also identified evidence for the potential effects of aspirin on HCC and gastric cancer. First, with regard to HCC, experimental and clinical evidence indicates that aspirin may hinder the progression of liver disease and HCC development through the prevention of platelet degranulation, modulation of bioactive lipid profiles, and inhibition of the proinflammatory enzyme COX-2 [66]. Notably, an inverse association between aspirin use (around 3–7 years) and HCC risk was observed across patients with chronic viral hepatitis [52], and chronic liver diseases [52]. The presence of cirrhosis appears to be a critical factor that influences the risk of GI bleeding [67]. However, recent observational studies [66, 68] in patients with chronic hepatitis B or C indicated that low-dose aspirin use was not associated with a substantially higher risk of GI bleeding, even among persons with decompensated cirrhosis. Nevertheless, the optimal dose (ranging from 75 to 160 mg) and duration of aspirin needed to achieve maximum clinical benefit without increasing the risk of GI bleeding remains unclear. Moreover, the available evidence suggests that the use of aspirin in conjunction with other drugs (e.g., statins, metformin, antivirals) may yield a synergistic inhibitory effect on the progression of HCC [69]. Further high-quality studies, particularly RCTs, are needed to better understand these issues while accounting for the impact of potential confounding factors. Second, with regard to gastric cancer risk, the available evidence suggests that aspirin's potential to prevent gastric cancer may be attributed to its anti-inflammatory and antiplatelet properties, including the induction of apoptosis and inhibition of angiogenesis [70]. Meta-analysis of cohort studies demonstrated an inverse association with regular use of aspirin [30]; however, the credibility of the evidence was weak. Meanwhile, the meta-analysis of individual patient data from two trials did not corroborate this relationship [30]. Recent meta-analyses of observational studies have suggested that aspirin might confer protective effects against pancreatic cancer [71], and esophageal cancer [72]. However, these beneficial associations were not observed in our review since the analysis was restricted to cohort studies alone.

Obesity and its metabolic complications, including diabetes, have been associated with an increased risk of several cancers, including GI cancers. As a first-line anti-diabetic medication, metformin may indirectly inhibit tumorigenesis by enhancing glycaemic regulation and decreasing circulating insulin levels [73]. Experimental data also indicated that metformin has a direct inhibitory effect on specific signaling pathways responsible for cell proliferation, motility, invasion, and migration [74, 75]. Meta-analyses of cohort studies provided suggestive evidence that metformin was inversely associated with risks of CRC [53], HCC [48], and esophageal cancer [34] in patients with diabetes mellitus. However, evidence from well-designed, high-quality trials was not available to support the observations. The most compelling evidence to date supporting the chemopreventive potential of metformin is derived from a recently conducted clinical trial, which demonstrated the efficacy of low-dose metformin (250 mg per day) in reducing the risk of recurrent colorectal adenomas among Japanese patients who had previously undergone surgical resection of colorectal adenomatous polyps [76]. In addition, a recent umbrella review [77] on metformin and cancer outcomes demonstrated a reduced risk of pancreatic and gastric cancers associated with metformin use, but our review, limited to cohort studies, did not confirm these findings [78, 79]. Given the high prevalence of diabetes and the increased cancer risk associated with that condition, the observed effect of metformin on GI cancers in our review is encouraging.

The available evidence indicates a potential inverse relationship between statin use and the risk of gastric cancer [45], HCC [31], and esophageal adenocarcinoma (among those with Barrett's

esophagus) [33], though the findings are only suggestive and require further investigation. Notably, our findings suggest that the use of statins is associated with a reduced risk of HCC [31], not only among patients with chronic viral hepatitis and cirrhosis, but it could also benefit those with fatty liver disease [80]. Meanwhile, clinicians often express concerns about prescribing statins to patients with chronic liver disease, including fatty liver patients, due to the potential risk of hepatotoxicity. Additional clinical trials should assess the chemoprotective potential of statins among these individuals without a conventional medical indication for statin therapy.

The ideal CPA would be one that is broadly effective, safe, affordable, widely available, and easy to administer. Although the promising agents mentioned above show potential in meeting these criteria, there remains a dearth of high-quality prospective studies, particularly long-term RCTs, that account for the impact of potential confounding factors and identify the optimal dose and appropriate population to target. Future studies should also evaluate the overall impact of these agents on the risk of any cancers collectively, rather than focusing solely on individual cancer types.

While antioxidants and vitamins (such as, vitamins A, C, D, and E, beta-carotene, B-vitamins, folic acid) are commonly believed to play an important role in suppressing cancer progression, our review was unable to identify any clear associations supporting these compounds.

While our umbrella review offers valuable insights, the presence of low-quality evidence limits the ability to draw robust conclusions regarding the chemoprevention of GI cancers for many CPAs. Future research should aim to address the identified gaps, focusing on high-quality study designs and long-term follow-up to strengthen the evidence base. Examining the role of low-dose aspirin in primary colorectal cancer prevention among individuals with high cardiovascular disease risk, as suggested by USPSTF, is a priority. Additionally, determining the optimal doses of aspirin and metformin to reduce the risk of HCC and CRC, respectively, as well as investigating the chemopreventive potential of statins among individuals without a conventional medical indication for statins therapy, are important areas for future research.

4.1 | Limitations

Our review had several limitations. First, the umbrella review focuses only on existing meta-analyses; therefore, CPAs not tested in meta-analysis are not presented in this review. Second, we did not appraise the quality of individual primary studies because this was beyond the scope of the review. Additionally, we did not perform the credibility assessment for some analyses because the data needed for predictive interval estimation and assessment of small study and excess significant bias effects were not available. Instead, we summarized the findings as originally reported by the authors of meta-analysis studies. The review has excluded the findings from meta-analyses that evaluated the use of various interventions associated with an increased risk of GI cancer occurrence. As an example, we observed that proton pump inhibitor use is associated with a decreased risk of esophageal cancer in individuals with Barrett's esophagus. However, meta-analyses of cohort studies also suggest these agents may increase the risk of certain gastrointestinal cancers, such as gastric, pancreatic, and liver cancers [81]. Finally, we restricted this review to publications written only in the English language.

5 | Conclusion

Overall, the association between several CPAs and GI cancers has been extensively studied, but only a few associations with CPAs targeting well-established risk factors are graded as good-quality evidence. A number of CPA approaches, including the use of aspirin, metformin, and statins, have demonstrated promising effects in reducing the risk of several GI cancers. Despite less established evidence, these approaches merit further research.

Author Contributions

Jia En Chan and Sajesh K. Veettil wrote the manuscript; Sajesh K. Veettil, Nathorn Chaiyakunapruk, and Jia En Chan designed the study; Jia En Chan, Suresh Shanmugham, and Suresh Kumar performed the research; Jia En Chan., Sajesh K. Veettil, Yeong Yeh Lee, and Siew Mooi Ching analyzed the data. Registration details: PROSPERO (CRD42024575101) https://www.crd.york.ac.uk/PROSPERO/view/CRD42024575101. All authors interpreted the data, read the manuscript, and approved the final version. All authors have contributions that meet the criteria for authorship and all authors will sign a statement attesting to authorship, disclosing all potential conflicts of interest, and releasing the copyright should the manuscript be accepted for publication.

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Ethics Statement

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Dr. Sajesh K Veettil had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Data were extracted from published meta-analyses and randomized controlled trials, all of which are available and accessible.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.