Supplementary Table 1. PRISMA checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3, Table 1
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	CRD42020157937
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4, Table 1
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplementary Table 2
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4,5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Tables 1-4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5-6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5-6

Section/topic	#	Checklist item	Reported on page #

Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	5-6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6, Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	6,7, Tables 2-4
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	7,8, Supplementary Tables 3-4
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	8-11, Figure 2-3
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	12-13
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	12
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	12-13
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	13-16
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	16
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	13-15
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	17

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

Supplementary Table 2: Search Strategies

database	Search strategy
MEDLINE (Pubmed)	(((((((caffeine[Title/Abstract]) OR theophylline[Title/Abstract]) OR theobromine[Title/Abstract]) OR methylxanthine*[Title/Abstract]) OR paraxanthine[Title/Abstract])) AND (((colon[Title/Abstract]) OR colorect*[Title/Abstract]) OR rect*[Title/Abstract])) AND ((((((((((((((((((cancer*[Title/Abstract]) OR tumor*[Title/Abstract]) OR tumour*[Title/Abstract]) OR neoplas*[Title/Abstract]) OR malignan*[Title/Abstract]) OR carcinogen*[Title/Abstract]) OR carcinoma[Title/Abstract]) OR adenocarcinoma[Title/Abstract]) OR adenoma[Title/Abstract]) OR anticancer[Title/Abstract]) OR antineoplastic[Title/Abstract]) OR metastasis[Title/Abstract]) OR antitumour[Title/Abstract]) OR antitumor[Title/Abstract]) OR "anti tumor"[Title/Abstract]) OR "anti tumour"[Title/Abstract]) OR anti-tumour[Title/Abstract]) OR anti-tumor[Title/Abstract])

Supplementary Table 3: The risk of bias assessment and tier classifications of animal studies (OHAT tool)

CATEGORY	QUESTIONS	Tanaka, 1999[26]	Hagiwara, 1999[25]	Tsuda, 1999[24]	Ju, 2005[23]	Ma, 2014[22]	Carter, 2007[27]	Wang, 2008[29]	Soares, 2018[28]
Selection Bias	1. Was administered dose or exposure level adequately randomized?	++	++	-	+	++	-	++	++
	2. Was allocation to study groups adequately concealed?	+	+	-	+	+	-	+	+
Performance Bias	3. Were experimental conditions identical across study groups?	++	++	-	++	+	++	++	++
	4. Were the research personnel and human subjects blinded to the study group during the study?	-	-	-	-	++	++	+	-
Attrition/Exclusion Bias	5. Were outcome data complete without attrition or exclusion from analysis?	++	++	+	++	++	++	++	++
Detection Bias	6. Can we be confident in the exposure characterization?	-	-	-	-	-	-	-	++
	7. Can we be confident in the outcome assessment?	-	-	- -	- -	+	+	+	-
Selective Reporting Bias	8. Were all measured outcomes reported?	++	++	++	++	++	++	++	++
Other Sources of Bias	9. Were there no other potential threats to internal validity (e.g., statistical methods were appropriate and researchers adhered to the study protocol)?	++	++	++	++	++	++	++	++
Overall Tier		1	1	2	2	1	1	1	1

Risk of bias response options for individual items:

++ Definitely low risk of bias

\+ Probably low risk of bias

- - Definitely high risk of bias

\- Probably high risk of bias

Supplementary Table 4: The risk of bias assessment and tier classifications of epidemiological studies (OHAT tool)

CATEGORY	QUESTIONS	L. Slattery, 1990[32]	Lee, 1993[31]	L. Slattery, 1999[33]	F. Tayyem, 2015[30]	B. Michels, 2005[35]	J. Guercio, 2015[9]	Nakamura, 2016[34]	Guertin KA, 2015[36]
Selection Bias	1. Did selection of study participants result in appropriate comparison groups?	-	-	+	-	++	++	++	+
Confounding Bias	2. Did the study design or analysis account for important confounding and modifying variables?	-	- -	+	- -	+	+	+	++
Attrition/Exclusion Bias	3. Were outcome data complete without attrition or exclusion from analysis?	++	++	++	++	++	++	++	++
Detection Bias	4. Can we be confident in the exposure characterization?	-	-	-	- -	++	++	+	++
	5. Can we be confident in the outcome assessment?	+	+	+	+	++	+	+	+
Selective Reporting Bias	6. Were all measured outcomes reported?	++	++	++	+	++	++	++	++
Other Sources of Bias	7. Were there no other potential threats to internal validity (e.g., statistical methods were appropriate and researchers adhered to the study protocol)?	++	++	++	++	++	++	++	++
Overall Tier		2	2	1	2	1	1	1	1

Risk of bias response options for individual items:

- ++ Definitely low risk of bias
- + Probably low risk of bias
- - Definitely high risk of bias
- - - Probably high risk of bias

Supplementary Figure 1: Publication bias assessed by the trim and fill method. Navy circles represent the included studies found by our search, while dark orange circles represent the missing unpublished studies detected in the trim-and-fill analysis