REVIEW

Tea Consumption and Risk of Cancer: An Umbrella Review and Meta-Analysis of Observational Studies

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ABSTRACT

Tea is one of the most widely consumed beverages, but its association with cancer risk remains controversial and unclear. We performed an umbrella review to clarify and determine the associations between tea consumption and various types of cancer by summarizing and recalculating the existing meta-analyses. Meta-analyses of observational studies reporting associations between tea consumption and cancer risk were searched on PubMed and Embase. Associations found to be statistically significant were further classified into levels of evidence (convincing, suggestive, or weak), based on *P* value, between-study heterogeneity, prediction intervals, and small study effects. Sixty-four observational studies (case-control or cohort) corresponding to 154 effect sizes on the incidence of 25 types of cancer were included. Forty-three (27.9%) results in 15 different types of cancer were statistically significant. When combining all studies on the same type of cancer, 19 results in 11 different types of cancer showed significant associations with lower risk of gastrointestinal tract organ cancer (oral, gastric, colorectal, biliary tract, and liver cancer), breast cancer, and gynecological cancer (endometrial and ovarian cancer) as well as leukemia, lung cancer, and thyroid cancer. Only the reduced risk of oral cancer in tea-consuming populations (OR = 0.62; 95% CI: 0.55, 0.72; *P* value $< 10^{-6}$) was supported by convincing evidence. Suggestive evidence was found for 6 results on biliary tract, breast, endometrial, liver, and oral cancer. To summarize, tea consumption was shown to have protective effects on some types of cancer, particularly oral cancer. More well-designed prospective studies are needed with consideration of other factors that can cause biases. *Adv Nutr* 2020;11:1437–1452.

Keywords: tea, cancer, oral cancer, meta-analysis, umbrella review

Introduction

Tea produced from the leaves of the plant *Camellia sinensis* has been cultivated and consumed for centuries, and is still one of the most widely consumed beverages worldwide (1). Tea components vary with factors such as tea variety, climate, season, agricultural practices, the age of the leaf, and manufacturing processes (2). Green tea manufacturing involves steaming or pan-frying fresh tea leaves, thereby

rapidly inactivating enzymes and preventing the oxidation of polyphenols, mainly catechins (3). Black tea is made by rolling the tea leaves to promote oxidation, followed by fermenting the leaves, which forms compounds such as theaflavins and thearubigins (4).

Historically tea has been claimed to have various beneficial health benefits and used for medical purposes (5). The compounds of tea have been suggested to have cancer-preventive effects in several studies (6–8). However, there has been no clear consensus in epidemiological literature about whether tea consumption is beneficial to health or not, especially concerning cancer (8). Because a large population consumes tea regularly throughout adult life, potential minor health benefits or risks associated with its consumption can have profound health implications at the population level. There are multiple quantitative studies on the association between tea and different types of cancer; however, there is still a need for a comprehensive appraisal of uncertainty and/or biases in the claimed associations. Recently, a new quantitative approach called "umbrella reviews" has been developed to understand the epidemiological credibility of complex health areas such as cardiovascular diseases, cancer, and multiple health outcomes (9–11).

Using existing meta-analyses of observational studies, we conducted an umbrella review of the meta-analyses and critically appraised the strengths and breadth of claimed associations between tea consumption and risk of cancer. In this study, we summarized the results from previously published meta-analyses and also performed the most updated meta-analysis by combining individual studies or the same subject (same type of cancer). To the best of our knowledge, this study is the first umbrella review to consider the whole breadth of evidence concerning tea consumption and cancer incidence.

Methods

Data sources and searches

Three investigators (TLK, GHJ, and JIS) independently searched PubMed and Embase databases for meta-analyses on the effect of tea consumption on different types of cancers. Articles were limited to those written in English published up to April 30, 2019. Keywords used in the search were "(Tea) AND (cancer OR carcinoma OR tumor) AND (meta-analysis OR systematic review)." The articles found using the two databases were screened and selected for eligibility based on examination of titles, abstracts, and full texts. Meta-analyses included prospective cohort studies, case-control studies (hospital-based and population-based), or both study designs (hereinafter referred to combined observational studies). Studies of unrelated topics, letters, and case reports were excluded while screening by title.

Eligibility criteria and extraction of data

Only systematic reviews and meta-analyses investigating the association between tea consumption and cancer were eligible for inclusion. Studies that did not specifically include tea as an independent exposure, such as combined caffeine exposure or maté tea, were not included. Tea consumption was divided into consumption of 2 specific types of tea (green tea and black tea) or consumption of any tea (regardless of type). The comparison groups of tea exposure were subclassified as high compared with low, any compared with none, and increments of 1–3 cups/d. The definition of criteria of high compared with low consumption of tea and size of a cup followed that of the original meta-analysis included in our review. Only meta-analyses that reported outcomes with metrics that were relevant to the risk of cancer, such as RR, OR, or HR, were included.

From the eligible meta-analyses, the following data were extracted: title, first author, year of publication, number of studies included, type of study (case-control, cohort, or observational studies including both case-control and cohort), type of tea, comparison groups of tea consumption, type of cancer, number of cancer cases/total number of participants, type of outcome metrics (RR or OR), meta-analysis model, effect size and its 95% CI, and largest effect size among included studies from each meta-analysis.

Statistical analysis

The primary studies obtained from the original articles were recalculated to receive additional information to evaluate the evidence level of meta-analyses. Comprehensive Meta-Analysis (v. 3.3.070; Biostat) and Microsoft Excel (v. 16.0) were used for the recalculation. The summary effect size, 95% CI, and P values were calculated under both random- and fixed-effects models using the identical type of metrics used as in the original meta-analyses. The summary effect size (represented as RR, HR, or OR) and 95% CI were recalculated using meta-analysis with both random-effects and fixed-effects models.

The between-study heterogeneity was recalculated using the I^2 statistic and the P value from the χ^2-based Cochran Q test. The I^2 statistic describes the percentage of variation among studies that is due to heterogeneity rather than due to chance. I^2 <50% is considered as low-to-moderate heterogeneity between studies, whereas I^2 > 50% is considered as large and I^2 > 75% as very large heterogeneity, respectively (12). If the heterogeneity between studies was large or very

The authors reported no funding received for this study. BS is supported by a Clinical Lectureship (ICA-CL-2017-03-001) jointly funded by Health Education England (HEE) and the National Institute for Health Research (NIHR). BS is part funded by the NIHR Biomedical Research Centre at South London and Maudsley NHS Foundation Trust. BS is also supported by the Maudsley Charity, King's College London, and the NIHR South London Collaboration for Leadership in Applied Health Research and Care (CLAHRC) funding.
Author disclosures: The authors report no conflicts of interest.
This article presents independent research. The views expressed in this publication are those of the authors and not necessarily those of the acknowledged institutions.
Supplemental Tables 1–4 and Supplemental References are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/advances.
TLK and GHJ contributed equally to this work.
Address correspondence to JIS (e-mail: shinji@yuhs.ac).
Abbreviations used: AICR, American Institute for Cancer Research; EGCG, epigallocatechin gallate; ES, excess of significance; IARC, International Agency for Research on Cancer; PI, prediction interval; WCRF, World Cancer Research Fund Network.

large, the meta-analysis was re-examined to determine if the heterogeneity was due to differences in the size of the association or due to differences in the direction of the effect. Using the recalculated data, the 95% prediction interval (PI) was also estimated. A 95% PI represents the distribution of true effects in which 95% of new and unique studies on the same subject will fall (13). Therefore, 95% PI further signifies between-study heterogeneity, whereas a 95% CI of each meta-analysis represents the accuracy of the summary effect size (14).

The *P* value of the Egger regression test was also calculated to evaluate small study effects. The Egger test assumes that when meta-analyses are based on a limited number of small trials the results are more prone to bias than larger studies (15). The threshold for the implications of small study effects was $P < 0.10$ from the Egger test. The random-effects summary effect size of the largest component study of each meta-analysis was compared with the random-effect summary effect size of each recalculated meta-analysis to evaluate whether the 2 effect sizes were concordant or discordant. Moreover, within each meta-analysis, we recorded the number of component studies that were statistically significantly associated with decreased risk, not statistically significant, or statistically significantly associated with increased risk—D (decreased risk), N (no association), I (increased risk), respectively.

Determination of the level of evidence in meta-analyses

Associations between tea consumption and the risk of different types of cancer were classified into 5 levels of evidence strength in accordance with grading schemes applied in previously published umbrella reviews (16–18). Evidence of strong statistical significance using random-effects meta-analyses at *P* value $<10^{-6}$ (19), magnitude of between-study heterogeneity ($I^2 < 50\%$), absence of small study effects (Egger *P* value >0.10), and 95% PI excluded the null.

The criteria for determining the level of evidence were as follows:

- Nonsignificant association: random-effects *P* value did not meet the significance threshold (random-effects *P* value >0.05).
- Weak evidence: result was significant (random-effects *P* value <0.05), but there was evidence of between-study heterogeneity ($I^2 > 50$ and 95% PI included the null) or small study effect.
- Suggestive evidence: result was significant (random-effects *P* value <0.05), and there was no evidence of both between-study heterogeneity ($I^2 < 50$) and small study effect, number of cases >1000, but 95% PI failed to reject the null hypothesis.
- Convincing evidence: result was highly significant for random-effects *P* value $<10^{-6}$, low to moderate heterogeneity ($I^2 < 50$), 95% PI rejected the null hypothesis, no evidence of small study effect, number of cases >1000, and the largest study was concordant in terms of statistical significance with the random-effects result.

In case of inadequate number of individual studies or unavailable information for calculating 95% PI, I^2, and Egger *P* value, we determined that the evidence was insufficient to state conclusions (see **Supplemental Table 1**).

In addition, we performed random-effects meta-analysis under a credibility ceiling for associations that satisfy the criteria of convincing level of evidence to determine the robustness of the associations. Credibility ceilings account for inherent methodological bias that can result in spurious significant results of the meta-analyses due to reporting of exaggerated associations in small studies (20, 21). We checked whether statistical significance was retained under a credibility ceiling of 10%, which is considered to be relatively lenient, to adjust each study included in the meta-analysis so as not to exceed a maximum certainty of 90%.

Meta-analysis combining all individual studies of the meta-analyses

To account for the inconsistencies of the results between multiple meta-analyses studying the same subject (same type of cancer) but consisting of different individual studies, we combined all the individual studies of the meta-analyses of the same subjects and performed "the most updated" meta-analysis. While combining the meta-analyses, we identified and excluded the individual studies duplicated in >1 meta-analysis. If ≥2 individual studies based on identical population groups were identified, only the most recently published studies were included. We then meta-analyzed this new set of individual studies (the most updated meta-analysis) and evaluated the level of evidence of the associations. Finally, we performed subset analyses of case-control and cohort studies, with respect to the statistically significant results of meta-analyses. We also compared the results with those of meta-analyses of overall studies and cohort studies with the highest number of individual studies, respectively. The flowchart of the analysis is presented in **Figure 1**.

Results

Characteristics of studies included in the final analyses

Initially 556 unique articles were screened, and 64 original articles corresponding to 154 effect sizes (25 case-control studies, 24 cohort studies, 105 combined observational study effect sizes) met the eligibility criteria, as shown in the flowchart in **Figure 2**. Of the 154 effect sizes including 25 different types of cancer, 25 (16.2%) effect sizes were estimated from case-control studies (hospital-based or population-based), 24 (15.6%) from prospective cohort studies, and 105 (68.2%) from both case-control and cohort studies (combined observational studies) (see **Table 1** and **Supplemental references**).

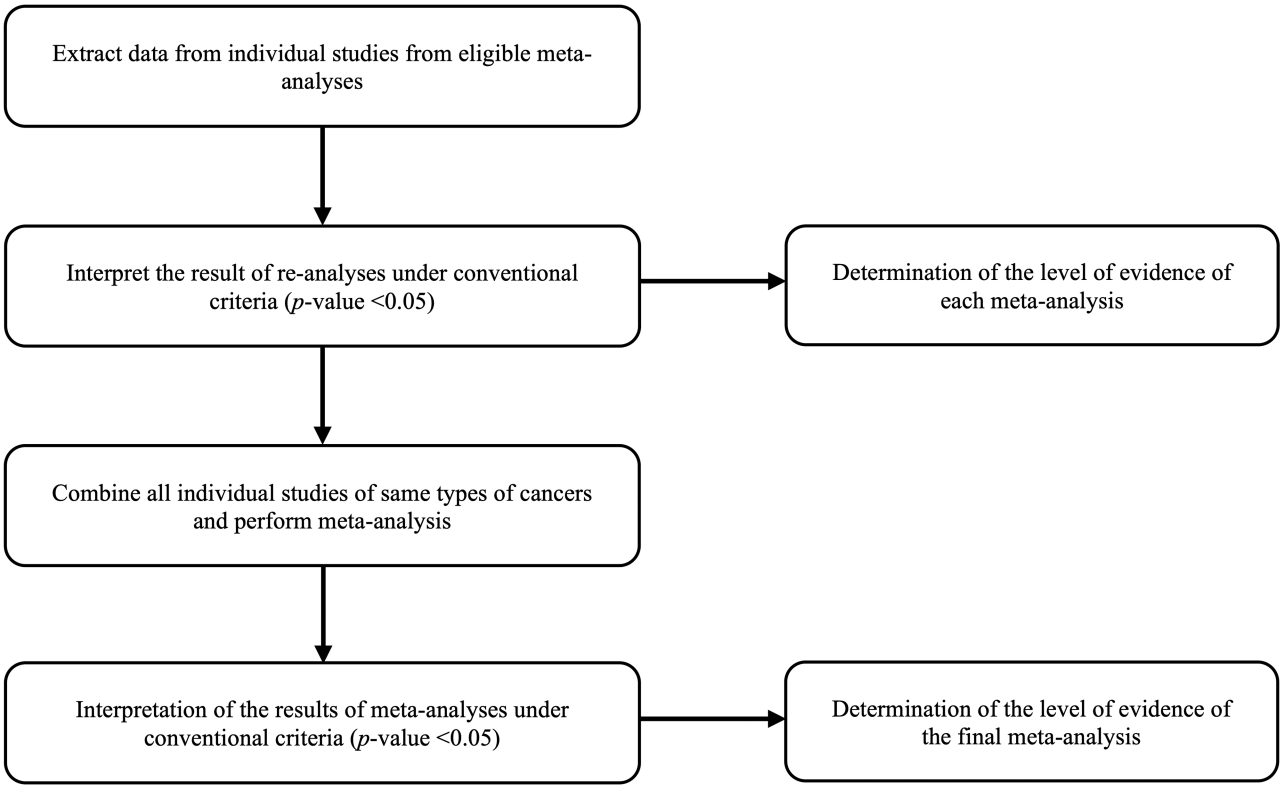

FIGURE 1 Flow diagram of our umbrella review.

Summary of individual meta-analyses under conventional interpretation of meta-analysis criteria (random-effects *P* value <0.05)

We evaluated 154 meta-analyses including tests for bias and heterogeneity (see Table 1 and **Supplemental Tables 2** and **3**). Under conventional thresholds of statistical significance (random-effects *P* value <0.05), 43 (27.9%) meta-analyses on 15 types of cancer were significant and adequately assessed, and 42 (27.2%) showed decreased associations between tea consumption and risks of cancer incidence. The only original meta-analysis that showed significant increased risk of cancer was for breast cancer (high compared with low black tea consumption). Within 43 significant associations, 7 (16.3%) meta-analyses were significant at $P < 0.001$ using random-effects model.

Results of meta-analyses combining all individual studies under conventional interpretation of meta-analysis criteria (random-effects *P* value <0.05)

The original studies from each of the meta-analyses were combined for a comprehensive umbrella review comprising all the studies that were on the comparison regarding tea consumption and type of cancer. This resulted in 66 results on 25 types of cancer comparing different patterns of tea consumption (see **Table 2** and **Supplemental Tables 3** and **4**).

Within 66 results, 19 (28.8%) showed significant results (random-effects *P* value <0.05) between tea consumption and decreased risk of 11 different types of cancer. The 19 statistically significant results were as follows: biliary tract cancer (any tea, any compared with none), breast cancer (green tea, any compared with none; green tea, high compared with low; any tea, any compared with none), colorectal cancer (green tea, high compared with low; any tea, high compared with low), endometrial cancer (green tea, high compared with low), gastric cancer (any tea, any compared with none), leukemia (any tea, high compared with low; any tea, any compared with none), liver cancer (green tea, any compared with none; green tea, high compared with low), lung cancer (any tea, any compared with none), oral cancer (green tea, high compared with low; any tea, high compared with low; any tea, any compared with none), ovarian cancer (any tea, any compared with none), and thyroid cancer (any tea, high compared with low) (see Table 2).

Level of evidence

After recalculating the data by considering heterogeneity between estimates and biases in the literature, 2 results (1.3%) were supported by convincing evidence. Sixteen results (10.4%) were supported by suggestive evidence, 25 results (16.2%) showed weak evidence, 107 results (69.5%) were nonsignificant, and 4 results (2.6%) were not adequately assessed due to insufficient information (see Supplemental Table 2).

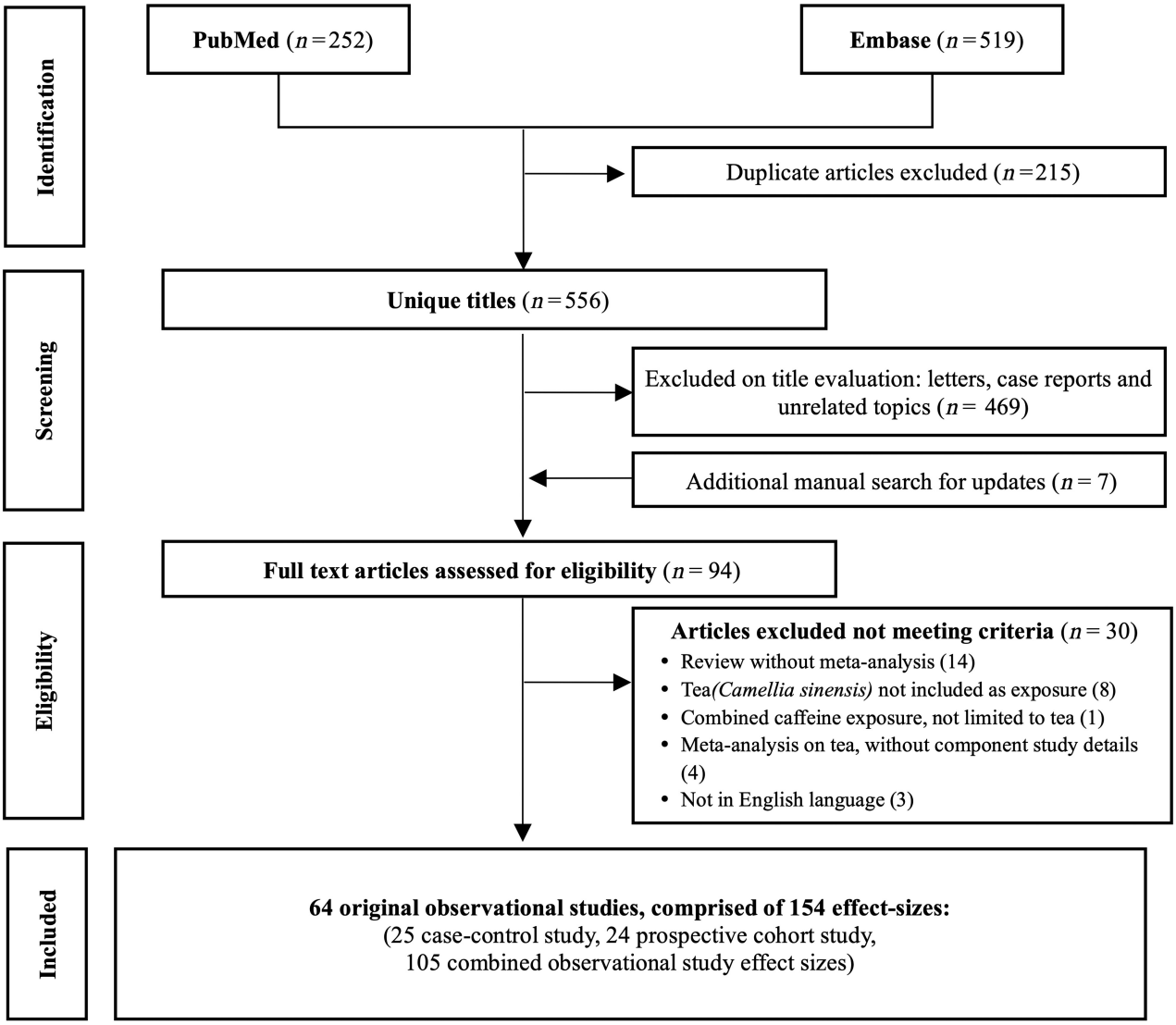

FIGURE 2 Flowchart of literature search.

From the 19 statistically significant results of updated meta-analyses combining all the individual studies, reduction in the incidence of oral cancer was found to have convincing evidence for any compared with none (OR = 0.62; 95% CI: 0.55, 0.72; $P < 10^{-6}$) consumption of any type of tea. Under the consideration of credibility ceilings, the result with convincing level of evidence preserved statistical significance with a ceiling of 10%. Six results were found to have suggestive levels of evidence. Consumption of any type of tea showed a lowered risk of biliary tract cancers (RR = 0.77; 95% CI: 0.64, 0.92; $P = 0.004$) compared with no tea consumption. Also, the reduced risk of oral cancer with a high dose of tea consumption (RR = 0.86; 95% CI: 0.79, 0.93; $P = 0.00024$) showed a suggestive level of evidence. High consumption compared with low green tea consumption significantly lowered the risk of breast cancer (RR = 0.75; 95% CI: 0.61, 0.92; $P = 0.006$), liver cancer (RR = 0.87; 95% CI: 0.78, 0.98; $P = 0.026$), and oral cancer (RR = 0.82; 95% CI: 0.69, 0.96; $P = 0.015$). High consumption of green tea reduced the risk of endometrial cancer (RR = 0.78; 95% CI: 0.61, 1.00; $P = 0.046$) compared with low consumption of green tea. Twelve results associated with breast cancer, colorectal cancer, gastric cancer, leukemia, liver cancer, lung cancer, ovarian cancer, and thyroid cancer were classified to have weak evidence.

Summary of meta-analyses separated by study design

In the case of oral cancer, high consumption of any kind of tea showed suggestive evidence in observational studies due to the threshold *P* value being unsatisfied; also, the outcomes in both case-control and cohort studies showed suggestive evidence because their 95% PI included null. Further, the meta-analysis with the largest number of individual studies showed suggestive evidence. Among the 5 results with

TABLE 1 Summary of individual effect sizes from original meta-analyses of the associations on tea consumption and risk of cancer included in the study

Category	Number of effect sizes	Comparison details, %	*n*
Total	154	100.0	
By exposure (tea type)			
Any tea	78	50.7	38 Any vs. none 32 High vs. low 8 Increment of 1–3 cups/d
Black tea	19	12.3	5 Any vs. none 11 High vs. low 3 Increment of 1–2 cups/d
Green tea	57	37.0	12 Any vs. none 41 High vs. low 4 Increment of 1–2 cups/d
By study type			
Case-control	25	16.2	
Cohort	24	15.6	
Observational (combined)	105	68.2	
By cancer type			
Biliary tract cancer	1	0.6	
Bladder cancer	7	4.5	
Brain cancer	3	1.9	
Breast cancer	31	20.1	
Colorectal cancer	8	5.2	
Colon cancer	1	0.6	
Rectal cancer	1	0.6	
Endometrial cancer	11	7.1	
Esophageal cancer	6	3.9	
Gastric cancer	17	11.0	
Gallbladder cancer	2	1.3	
Glioma	2	1.3	
Renal cell carcinoma	1	0.6	
Liver cancer	4	2.6	
Lung cancer	5	3.2	
Leukemia (childhood)	8	5.2	
Leukemia (adult)	2	1.3	
Ovarian cancer	12	7.8	
Laryngeal cancer	5	3.2	
Oral cancer	7	4.5	
Oropharyngeal cancer	3	1.9	
Pharyngeal cancer	3	1.9	
Pancreatic cancer	5	3.2	
Prostate cancer	7	4.5	
Thyroid cancer	1	0.6	
Skin cancer (nonmelanoma)	1	0.6	
By level of evidence			
Convincing	2	1.3	
Suggestive	16	10.4	
Weak	25	16.2	
Nonsignificant	107	69.5	
Not adequately assessed	4	2.6	

suggestive evidence, results on biliary tract cancer showed suggestive evidence in cohort studies but failed to show significance in case-control studies. In case of endometrial cancer, both cohort and case-control studies were not statistically significant. Besides the case of colorectal cancer with high compared with low tea consumption, all results that showed weak evidence presented nonsignificant results in cohort studies but showed significance in case-control studies (1 suggestive, 10 weak). In case of colorectal cancer with high compared with low tea consumption, the result of meta-analyses with both cohort and case-control studies failed to show its significance (see **Table 3** and **Figure 3**).

Discussion

In this study, we summarized and analyzed original meta-analyses to critically appraise the strength and breadth of claimed associations between tea consumption and risk of

TABLE 2 The results and the level of evidence of the effect of tea and risk of cancer[1]

Outcome	Study type	Comparison	Type of tea	*P* value (random-effects)[2]	95% PI including null	Heterogeneity (I^2)[2]	Effect-size distribution (D/N/I)[3]	Small study effect[4]	Concordance	Metrics	Summary effect (random-effects)[5]
Associations supported by convincing evidence											
Oral cancer	CC	Any vs. none	Any tea	$<10^{-6}$	No	Not large	6/0/0	No	Yes	OR	0.62 (0.55, 0.72)
Associations supported by suggestive evidence											
Biliary tract cancer	Obs	Any vs. none	Any tea	<0.05 but $>10^{-6}$	Yes	Not large	4/4/0	No	Yes	RR	0.77 (0.64, 0.92)
Breast cancer	CC	High vs. low	Green tea	<0.05 but $>10^{-6}$	Yes	Large[6]	6/5/0	No	Yes	RR	0.75 (0.61, 0.92)
Endometrial cancer	Obs	High vs. low	Green tea	<0.05 but $>10^{-6}$	Yes	Not large	2/4/0	No	Yes	RR	0.78 (0.61, 1.00)[7]
Liver cancer	Obs	High vs. low	Green tea	<0.05 but $>10^{-6}$	Yes	Not large	2/9/0	No	No	RR	0.87 (0.78, 0.98)
Oral cancer	Obs	High vs. low	Green tea	<0.05 but $>10^{-6}$	Yes	Not large	1/4/0	No	No	RR	0.82 (0.69, 0.96)
Oral cancer	Obs	High vs. low	Any tea	<0.05 but $>10^{-6}$	No	Not large	5/26/0	No	Yes	RR	0.86 (0.80, 0.91)
Associations supported by weak evidence											
Breast cancer	Obs	High vs. low	Green tea	<0.05 but $>10^{-6}$	Yes	Large	6/10/0	No	No	RR	0.82 (0.71, 0.96)
Breast cancer	Obs	Any vs. none	Green tea	<0.05 but $>10^{-6}$	Yes	Large	3/11/0	No	Yes	OR	0.87 (0.76, 0.99)
Breast cancer	Obs	Any vs. none	Any tea	<0.05 but $>10^{-6}$	Yes	Very large	6/20/0	No	No	RR	0.81 (0.71, 0.94)
Colorectal cancer	Obs	High vs. low	Any tea	<0.05 but $>10^{-6}$	Yes	Not large	6/45/2	Yes	No	RR	0.93 (0.87, 0.99)
Colorectal cancer	Obs	High vs. low	Green tea	<0.05 but $>10^{-6}$	Yes	Large	4/11/0	No	No	RR	0.87 (0.75, 1.00)[7]
Gastric cancer	Obs	Any vs. none	Any tea	<0.001	Yes	Very large	23/30/3	Yes	No	RR	0.78 (0.70, 0.86)
Leukemia	Obs	High vs. low	Any tea	<0.001	No	Not large	4/4/0	Yes	No	RR	0.55 (0.43, 0.72)
Leukemia	Obs	Any vs. none	Any tea	<0.05 but $>10^{-6}$	No	Not large	1/7/0	Yes	No	RR	0.76 (0.65, 0.89)
Liver cancer	Obs	Any vs. none	Green tea	<0.05 but $>10^{-6}$	Yes	Large	3/7/0	No	No	RR	0.65 (0.48, 0.88)
Lung cancer	Obs	Any vs. none	Any tea	<0.001	Yes	Very large	18/24/1	No	Yes	RR	0.76 (0.67, 0.86)
Ovarian cancer	Obs	Any vs. none	Any tea	<0.05 but $>10^{-6}$	Yes	Very large	8/22/1	No	No	RR	0.82 (0.71, 0.94)
Thyroid cancer	Obs	High vs. low	Any tea	<0.05 but $>10^{-6}$	Yes	Not large	1/13/0	Yes	No	RR	0.77 (0.61, 0.97)
Nonsignificant associations											
Acute leukemia (childhood)	Obs	High vs. low	Any tea	>0.05	Yes	Not large	0/8/1	No	Yes	RR	0.93 (0.74, 1.18)
Acute leukemia (childhood)	Obs	Any vs. none	Any tea	>0.05	Yes	Not large	0/14/0	No	No	RR	0.93 (0.82, 1.05)
Bladder cancer	CC	High vs. low	Any tea	>0.05	Yes	Large	1/22/2	No	Yes	RR	0.97 (0.87, 1.09)
Bladder cancer	Obs	High vs. low	Any tea	>0.05	Yes	Large	2/29/2	No	Yes	RR	0.95 (0.86, 1.06)
Bladder cancer	Co	High vs. low	Any tea	>0.05	Yes	Large	1/7/0	No	Yes	RR	0.86 (0.65, 1.13)
Bladder cancer	Obs	High vs. low	Green tea	>0.05	Yes	Not large	0/5/0	No	Yes	RR	1.03 (0.82, 1.31)
Brain cancer	Obs	Any vs. none	Any tea	>0.05	Yes	Not large	2/6/0	No	No	RR	0.90 (0.74, 1.09)
Breast cancer	Co	High vs. low	Black tea	>0.05	Yes	Not large	0/15/0	No	No	RR	1.04 (0.97, 1.12)
Breast cancer	CC	High vs. low	Black tea	>0.05	Yes	Large	1/12/0	No	No	RR	0.91 (0.80, 1.03)
Breast cancer	Obs	High vs. low	Black tea	>0.05	Yes	Large	1/27/0	No	Yes	RR	0.98 (0.91, 1.06)
Breast cancer	Co	High vs. low	Green tea	>0.05	Yes	Not large	0/5/0	No	Yes	RR	0.99 (0.83, 1.77)
Breast cancer	Co	Any vs. none	Green tea	>0.05	Yes	Not large	0/9/0	No	Yes	OR	0.94 (0.83, 1.05)

(*Continued*)

TABLE 2 (*Continued*)

Outcome	Study type	Comparison	Type of tea	*P* value (random-effects)[2]	95% PI including null	Heterogeneity (I^2)[2]	Effect-size distribution (D/N/I)[3]	Small study effect[4]	Concordance	Metrics	Summary effect (random-effects)[5]
Breast cancer	CC	Any vs. none	Green tea	>0.05	Yes	Very large	3/2/0	No	No	OR	0.83 (0.62, 1.10)
Breast cancer	Co	High vs. low	Any tea	>0.05	Yes	Not large	0/12/2	No	Yes	RR	1.03 (0.96, 1.10)
Breast cancer	CC	High vs. low	Any tea	>0.05	Yes	Large	1/8/0	No	Yes	OR	0.90 (0.75, 1.10)
Breast cancer	Obs	High vs. low	Any tea	>0.05	Yes	Large	1/20/2	No	Yes	RR	0.98 (0.90, 1.06)
Colon cancer	Obs	High vs. low	Green tea	>0.05	Yes	Not large	1/9/1	Yes	Yes	RR	0.98 (0.85, 1.12)
Colorectal cancer	Obs	High vs. low	Black tea	>0.05	Yes	Large	2/14/4	No	Yes	RR	0.99 (0.87, 1.13)
Endometrial cancer	Obs	High vs. low	Any tea	>0.05	Yes	Large	3/12/1	Yes	Yes	RR	0.90 (0.75, 1.09)
Endometrial cancer	Obs	Increment of 1cup/d	Any tea	>0.05	Yes	Large	0/4/1	No	Yes	RR	1.04 (0.98, 1.10)
Endometrial cancer	Obs	High vs. low	Green tea	>0.05	Yes	Large	1/8/1	No	No	RR	0.99 (0.79, 1.23)
Esophageal cancer	Obs	High vs. low	Green tea	>0.05	Yes	Large	9/11/2	No	Yes	RR	0.81 (0.62, 1.06)
Gallbladder cancer	Obs	High vs. low	Any tea	>0.05	Yes	Very large	2/2/0	No	No	RR	0.57 (0.25, 1.30)
Gallbladder cancer	Obs	Any vs. none	Any tea	>0.05	Yes	Very large	3/3/0	No	No	RR	0.67 (0.40, 1.12)
Gastric cancer	Obs	High vs. low	Green tea	>0.05	Yes	Large	3/25/2	Yes	Yes	RR	0.93 (0.84, 1.04)
Gastric cancer	Obs	High vs. low	Black tea	>0.05	Yes	Not large	0/4/1	No	Yes	RR	1.18 (0.79, 1.77)
Gastric cancer	Obs	Increment of 3cups/d	Any tea	>0.05	Yes	Not large	0/5/0	No	Yes	RR	0.98 (0.89, 1.08)
Glioma	Obs	Any vs. none	Any tea	>0.05	Yes	Very large	0/4/0	No	No	RR	0.67 (0.40, 1.12)
Glioma	Obs	High vs. low	Any tea	>0.05	Yes	Very large	1/3/0	No	No	RR	0.57 (0.25, 1.30)
Laryngeal cancer	Obs	High vs. low	Any tea	>0.05	Yes	Large	2/5/1	No	Yes	RR	0.91 (0.67, 1.23)
Liver cancer	Obs	Any vs. none	Any tea	>0.05	Yes	Very large	3/9/0	No	No	RR	0.77 (0.57, 1.03)
Lung cancer	Obs	High vs. low	Green tea	>0.05	Yes	Very large	4/7/1	No	Yes	RR	0.78 (0.61, 1.01)
Lung cancer	Obs	High vs. low	Black tea	>0.05	Yes	Large	4/10/0	No	Yes	RR	0.86 (0.70, 1.05)
Oropharyngeal cancer	Obs	Any vs. none	Any tea	>0.05	Yes	Large	2/4/0	No	Yes	RR	0.68 (0.45, 1.03)
Ovarian cancer	Obs	Any vs. none	Green tea	>0.05	Yes	Very large	3/5/1	No	Yes	RR	0.76 (0.57, 1.02)
Ovarian cancer	Obs	Any vs. none	Black tea	>0.05	Yes	Large	4/12/0	Yes	Yes	RR	0.90 (0.78, 1.04)
Pancreatic cancer	Obs	High vs. low	Any tea	>0.05	Yes	Not large	1/20/1	No	Yes	RR	0.97 (0.85, 1.10)
Pancreatic cancer	Obs	Any vs. none	Any tea	>0.05	Yes	Large	2/25/2	No	Yes	RR	0.99 (0.89, 1.10)
Pancreatic cancer	Obs	High vs. low	Green tea	>0.05	Yes	Large	1/6/1	No	Yes	RR	0.99 (0.78, 1.25)
Pharyngeal cancer	Obs	Any vs. none	Any tea	>0.05	Yes	Not large	0/4/0	No	Yes	RR	0.88 (0.74, 1.04)
Prostate cancer	Obs	High vs. low	Green tea	>0.05	Yes	Very large	3/6/0	Yes	Yes	RR	0.73 (0.51, 1.06)
Prostate cancer	Obs	High vs. low	Any tea	>0.05	Yes	Large	6/15/2	Yes	Yes	RR	0.86 (0.71, 1.04)
Prostate cancer	Obs	Any vs. none	Any tea	>0.05	Yes	Large	7/20/2	Yes	Yes	RR	0.87 (0.75, 1.01)
Prostate cancer	Obs	High vs. low	Black tea	>0.05	Yes	Not large	1/9/1	No	Yes	RR	0.99 (0.82, 1.20)
Rectal cancer	Obs	High vs. low	Green tea	>0.05	Yes	Large	3/6/0	No	Yes	RR	0.97 (0.77, 1.22)
Renal cell carcinoma	Obs	Any vs. none	Any tea	>0.05	Yes	Very large	1/11/0	No	Yes	RR	1.03 (0.88, 1.21)
Skin cancer (non-melanoma)	Obs	Any vs. none	Any tea	>0.05	Yes	Not large	4/4/0	No	Yes	OR	0.88 (0.76, 1.02)

[1] CC, case-control studies; Co, cohort studies; Obs, observational studies; PI, prediction interval.
[2] Heterogeneity is defined as "Very large" when $I^2 > 75\%$, "Large" when $50\% < I^2 < 75\%$, and "Not large" when $I^2 < 50\%$.
[3] Number of individual studies of effect size with statistical significance in direction of decreased cancer risk(D)/no association(N)/increased cancer risk(I).
[4] The presence of small study effects is determined if the Egger *P* value is <0.10.
[5] Summary effect with 95% CI value obtained from umbrella review combining meta-analyses of the same comparison.
[6] Although heterogeneity is large, the distribution of the effect sizes was considered over the I^2 metrics.
[7] The value is rounded up (to 2 decimal places), and hence is statistically significant.

TABLE 3 Summary of results of the associations on tea consumption and risk of cancer outlined by study design, largest meta-analysis of observational studies, and largest meta-analysis of cohort studies[1]

Cancer type	Study design	Metrics	Summary effect (random-effects)[6]	*P* value (random-effects)	95% PI including null	Heterogeneity (I^2)[2]	Small study effect[3]	Concordance	Level of evidence[4]
Oral cancer (any tea; any vs. none)	CC	OR	0.62 (0.55, 0.72)	<0.001	No	Not large	No	Yes	Convincing
Oral cancer (any tea; high vs. low)	Obs	RR	0.86 (0.79, 0.93)	<0.001	No	Not large	No	Yes	Suggestive
	Co	RR	0.80 (0.67, 0.94)	0.007	Yes	Not large	No	Yes	Suggestive
	CC	RR	0.87 (0.79, 0.96)	0.004	Yes	Not large	No	No	Suggestive
	Largest MA (Obs)	RR	0.84 (0.75, 0.94)	0.002	Yes	Not large	No	No	Suggestive
	Largest MA (Co)				NR				
Biliary tract cancer (any tea; any vs. none)	Obs	RR	0.77 (0.64, 0.92)	0.004	Yes	Not large	No	Yes	Suggestive
	Co	RR	0.82 (0.70, 0.95)	0.008	Yes	Not large	No	Yes	Suggestive
	CC	RR	0.66 (0.42, 1.03)	0.068	Yes	Not large	No	No	Nonsignificant
	Largest MA (Obs)	RR	0.77 (0.64, 0.92)	0.004	Yes	Not large	No	Yes	Suggestive
	Largest MA (Co)				NR				
Endometrial cancer (green tea; high vs. low)	Obs	RR	0.78 (0.61, 1.00)[5]	0.046	Yes	Not large	No	No	Suggestive
	Co	RR	0.75 (0.44, 1.30)	0.298	N/A	N/A	N/A	N/A	Nonsignificant
	CC	RR	0.78 (0.57, 1.06)	0.108	Yes	Not large	No	Yes	Nonsignificant
	Largest MA (Obs)	RR	0.78 (0.61, 1.00)[5]	0.046	Yes	Not large	No	No	Suggestive
	Largest MA (Co)				NR				
Liver cancer (green tea; high vs. low)	Obs	RR	0.87 (0.78, 0.98)	0.026	Yes	Not large	No	No	Suggestive
	Co	RR	0.87 (0.78, 0.98)	0.026	Yes	Not large	No	No	Suggestive
	CC				NR				
	Largest MA (Obs)	RR	0.87 (0.78, 0.98)	0.026	Yes	Not large	No	No	Suggestive
	Largest MA (Co)	RR	0.87 (0.78, 0.98)	0.026	Yes	Not large	No	No	Suggestive
Oral cancer (green tea; high vs. low)	Obs	RR	0.82 (0.69, 0.96)	0.015	Yes	Not large	No	No	Suggestive
	Co	RR	0.44 (0.19, 1.04)	0.058	N/A	N/A	N/A	N/A	N/A
	CC	RR	0.84 (0.72, 0.98)	0.030	Yes	Not large	No	No	Suggestive
	Largest MA (Obs)	RR	0.82 (0.69, 0.96)	0.015	Yes	Not large	No	No	Suggestive
	Largest MA (Co)				NR				
Breast cancer (green tea; high vs. low)	Obs	RR	0.82 (0.71, 0.96)	0.015	Yes	Large	No	No	Weak
	Co	RR	0.99 (0.83, 1.18)	0.895	Yes	Not large	No	Yes	Nonsignificant
	CC	RR	0.75 (0.61, 0.92)	0.006	Yes	Large	No	Yes	Weak
	Largest MA (Obs)	RR	0.81 (0.67, 0.98)	<0.001	Yes	Large	No	Yes	Weak
	Largest MA (Co)	RR	0.98 (0.83, 1.16)	0.821	Yes	Not large	No	Yes	Nonsignificant
Breast cancer (green tea; any vs. none)	Obs	OR	0.87 (0.76, 0.99)	0.040	Yes	Very large	No	Yes	Weak
	Co	OR	0.94 (0.83, 1.05)	0.278	Yes	Not large	No	Yes	Nonsignificant
	CC	OR	0.83 (0.62, 1.10)	0.196	Yes	Very large	No	No	Nonsignificant
	Largest MA (Obs)	OR	0.87 (0.76, 0.99)	0.040	Yes	Very large	No	Yes	Weak
	Largest MA (Co)	OR	0.94 (0.83, 1.05)	0.278	Yes	Not large	No	Yes	Nonsignificant
Breast cancer (any tea; any vs. none)	Obs	RR	0.81 (0.71, 0.94)	<0.001	Yes	Very large	No	No	Weak
	Co	RR	1.06 (0.91, 1.23)	0.451	Yes	Not large	No	Yes	Nonsignificant
	CC	RR	0.74 (0.63, 0.88)	<0.001	Yes	Very large	No	No	Weak
	Largest MA (Obs)	RR	0.79 (0.65, 0.95)	0.012	Yes	Very large	No	No	Weak
	Largest MA (Co)				NR				

(*Continued*)

TABLE 3 (*Continued*)

Cancer type	Study design	Metrics	Summary effect (random-effects)[6]	*P* value (random-effects)	95% PI including null	Heterogeneity (I^2)[2]	Small study effect[3]	Concordance	Level of evidence[4]
Colorectal cancer (any tea; high vs. low)	Obs	RR	0.93 (0.87, 0.99)	0.031	Yes	Not large	Yes	No	Weak
	Co	RR	0.94 (0.88, 1.01)	0.108	Yes	Not large	No	Yes	Nonsignificant
	CC	RR	0.91 (0.80, 1.03)	0.117	Yes	Large	Yes	Yes	Nonsignificant
	Largest MA (Obs)	RR	0.93 (0.87, 0.99)	0.031	Yes	Not large	Yes	No	Weak
	Largest MA (Co)	RR	0.94 (0.88, 1.01)	0.108	Yes	Not large	No	Yes	Nonsignificant
Colorectal cancer (green tea; high vs. low)	Obs	RR	0.87 (0.75, 1.00)[5]	0.050	Yes	Large	No	No	Weak
	Co	RR	0.93 (0.79, 1.10)	0.408	Yes	Large	No	Yes	Nonsignificant
	CC	RR	0.73 (0.60, 0.90)	0.003	Yes	Not large	No	Yes	Weak
	Largest MA (Obs)	RR	0.95 (0.81, 1.11)	0.493	Yes	Very large	Yes	Yes	Nonsignificant
	Largest MA (Co)					NR			
Gastric cancer (any tea; any vs. none)	Obs	RR	0.78 (0.70, 0.86)	<0.001	Yes	Very large	Yes	No	Weak
	Co	RR	1.01 (0.91, 1.13)	0.791	Yes	Not large	No	Yes	Nonsignificant
	CC	RR	0.70 (0.62, 0.80)	<0.001	Yes	Very large	Yes	Yes	Weak
	Largest MA (Obs)	RR	0.76 (0.72, 0.80)	0.010	Yes	Very large	Yes	Yes	Weak
	Largest MA (Co)					NR			
Leukemia (any tea; high vs. low)	Obs	RR	0.55 (0.43, 0.72)	<0.001	No	Not large	No	No	Weak
	Co					NR			
	CC	RR	0.52 (0.38, 0.72)	<0.001	No	Not large	No	No	Weak
	Largest MA (Obs)	RR	0.55 (0.43, 0.72)	<0.001	No	Not large	No	No	Weak
	Largest MA (Co)					NR			
Leukemia (any tea; any vs. none)	Obs	RR	0.76 (0.65, 0.89)	<0.001	No	Not large	No	No	Weak
	Co					NR			
	CC	RR	0.69 (0.54, 0.87)	0.002	No	Not large	No	No	Weak
	Largest MA (Obs)	RR	0.76 (0.65, 0.89)	<0.001	No	Not large	No	No	Weak
	Largest MA (Co)					NR			
Liver cancer (green tea; any vs. none)	Obs	RR	0.65 (0.48, 0.88)	0.004	Yes	Large	No	No	Weak
	Co	RR	0.83 (0.61, 1.11)	0.205	Yes	Large	No	Yes	Nonsignificant
	CC	RR	0.46 (0.29, 0.74)	0.001	Yes	Large	No	Yes	Weak
	Largest MA (Obs)	RR	0.65 (0.48, 0.88)	0.004	Yes	Large	No	No	Weak
	Largest MA (Co)					NR			
Lung cancer (any tea; any vs. none)	Obs	RR	0.76 (0.67, 0.86)	<0.001	Yes	Very large	No	Yes	Weak
	Co	RR	0.91 (0.76, 1.08)	0.273	Yes	Very large	No	No	Nonsignificant
	CC	RR	0.69 (0.59, 0.79)	<0.001	Yes	Very large	No	No	Weak
	Largest MA (Obs)	RR	0.77 (0.68, 0.88)	<0.001	Yes	Very large	No	No	Weak
	Largest MA (Co)					NR			
Ovarian cancer (any tea; any vs. none)	Obs	RR	0.82 (0.71, 0.94)	0.006	Yes	Very large	No	No	Weak
	Co	RR	0.92 (0.79, 1.06)	0.260	Yes	Not large	Yes	Yes	Nonsignificant
	CC	RR	0.76 (0.61, 0.95)	0.014	Yes	Very large	No	No	Weak
	Largest MA (Obs)	RR	0.89 (0.80, 1.00)[5]	0.045	Yes	Not large	Yes	Yes	Weak
	Largest MA (Co)	RR	0.71 (0.55, 0.93)	0.013	Yes	Not large	No	Yes	Suggestive
Thyroid cancer (any tea; high vs. low)	Obs	RR	0.76 (0.61, 0.96)	0.024	Yes	Not large	Yes	No	Weak
	Co	RR	0.88 (0.56, 1.37)	0.568	N/A	N/A	N/A	Yes	N/A
	CC	RR	0.74 (0.56, 0.97)	0.029	Yes	Large	Yes	No	Weak
	Largest MA (Obs)	RR	0.76 (0.61, 0.96)	0.024	Yes	Not large	Yes	No	Weak
	Largest MA (Co)					NR			

[1]CC, case-control studies; Co, cohort studies; MA, meta-analysis; N/A, not applicable; NR, not reported; Obs, observational studies; PI, prediction interval.
[2]Heterogeneity is defined as "Very large" when $I^2 > 75\%$, "Large" when $50\% < I^2 < 75\%$, and "Not large" when $I^2 < 50\%$.
[3]The presence of small study effects is determined if the Egger *P* value is <0.10.
[4]The definition of each category of the level of evidence is presented in Supplemental Table 1.
[5]The value is rounded up (to 2 decimal places), and hence is statistically significant.
[6]Summary effect with 95% CI value obtained from umbrella review combining meta-analyses of the same comparison.

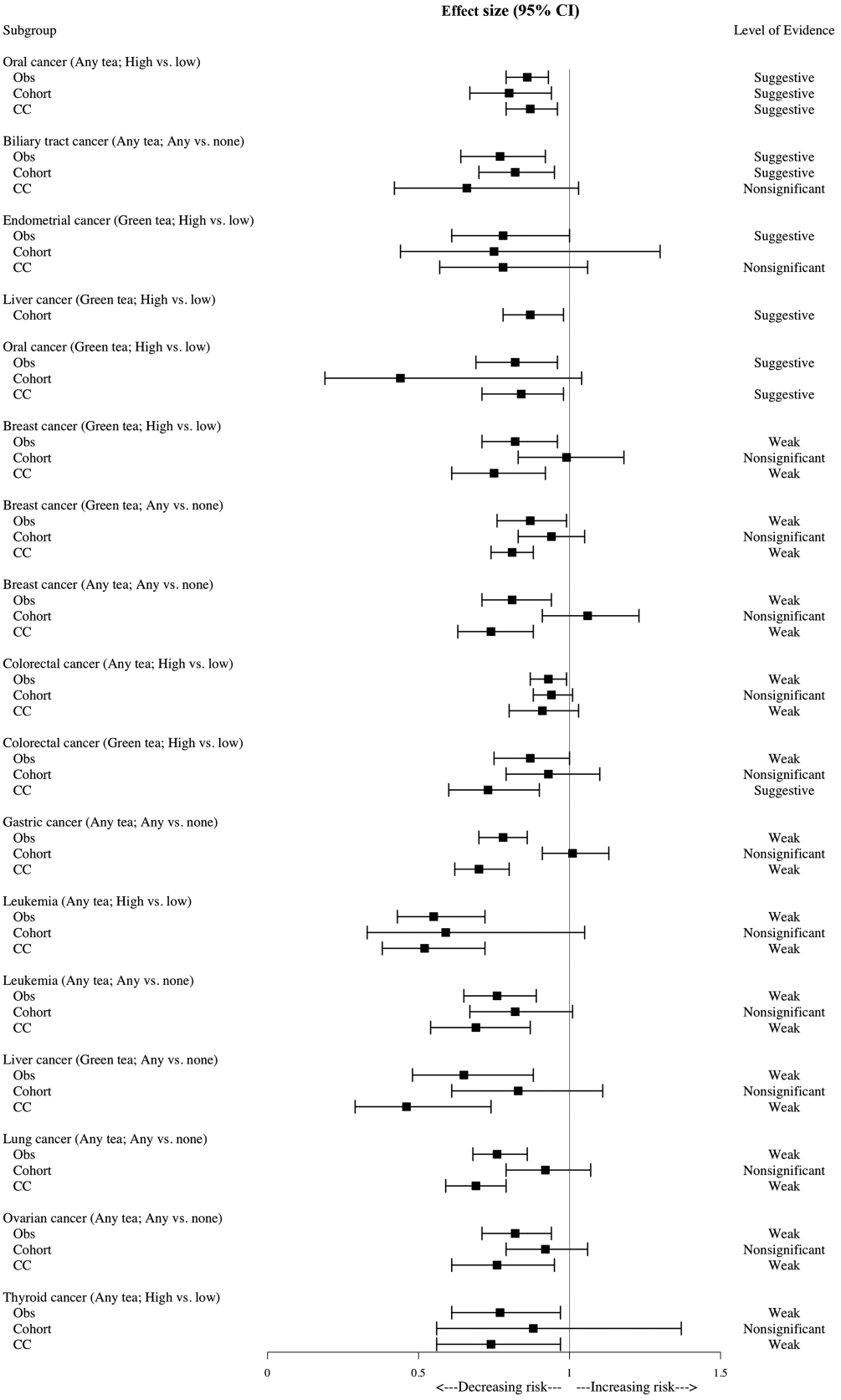

FIGURE 3 Statistically significant associations between cancer and tea exposure from umbrella review outlined by study design. The definition of each category of the level of evidence is presented in Supplemental Table 1. CC, case-control studies; Obs, observational studies.

cancer incidence. We found that consumption of any type of tea was associated with a lower risk of 11 types of cancer (oral, biliary tract, breast, colorectal, endometrial, gastric, leukemia, liver, lung, ovarian, and thyroid cancer). However, only the association between tea consumption and lower risk of oral cancer was supported by convincing evidence. Suggestive evidence was found for lowering risk of biliary tract, breast, endometrial, liver, and oral cancer.

The negative associations between tea and the risk of specific cancers can be explained by several biological mechanisms. In vitro and in vivo studies have suggested that tea polyphenols have preventive effects against several types of cancer, including oral (22), biliary tract (23), breast (24), endometrial (25), liver (26), colorectal (27), gastric (28), leukemia (29), lung (30), ovarian (31), and thyroid cancer (32). As key antioxidants in tea, polyphenols or tea catechins are thought to contribute to reducing the risk of some cancers, acting as scavengers of reactive oxygen species and potentially affecting transcription factors and enzyme activities (33). Some important polyphenols are (−)-epigallocatechin gallate (EGCG), (−)-epigallocatechin, (−)-epicatechin gallate, and (−)-epicatechin (34). EGCG is the most abundant tea catechin and is thought to play the most important role in inhibiting cancer initiation and progression (35). Tea polyphenols are thought to suppress the growth of cancer cells by various proposed mechanisms, such as inducing the apoptosis of cancer cells (36), suppression of receptor-dependent signaling pathways and angiogenesis (37), silencing genes related to epigenetic mechanisms such as methylation of DNA (38), and inhibiting the activities of enzymes (39). However, additional mechanistic studies and more in-depth analyses focusing on molecular changes are needed.

We found a total of 19 significant meta-analyses with combined individual studies comprising 11 types of cancer. Specific findings of our outcome must be interpreted with caution. In case of some cancers such as endometrial cancer, a suggestive level of evidence in combined observational studies (cohort and case-control) was found, whereas the results were nonsignificant in both cohort and case-control, respectively. The combination of different study designs possibly has an impact on the results due to the heterogeneity between studies. The potential heterogeneity in nutritional epidemiology comes from the difference in the definition of the consumption amounts and follow-up periods. To conclude, because the outcomes were nonsignificant in both study designs, the outcome with suggestive evidence of endometrial cancer could overestimate the true effect and could thus be reconsidered. In addition, a convincing level of evidence was derived from a single meta-analysis of oral cancer including 8 individual case-control studies only. In general, this is a small number for umbrella review, further underlining our concern related to the level of evidence.

In our findings, meta-analyses of cohort studies tended to show null results whereas those of case-control studies were statistically significant. Cohort studies are usually thought to have higher levels of evidence than case-control studies. In general, case-control studies are prone to biases, including the possibility of recall bias and the presence of selection bias. Thus, we can assume that there might be a spurious association in meta-analyses of case-control studies.

Furthermore, we compared the relative risks and level of evidence from our study with reports published by the WHO International Agency for Research on Cancer (IARC) and the World Cancer Research Fund Network/American Institute for Cancer Research (WCRF/AICR). The IARC report states that there is inadequate evidence for the carcinogenicity of tea consumption in humans, and hence states that tea is not classifiable as to its carcinogenicity (40, 41). Our study is in line with this statement, because no result showed that tea consumption was associated with an increased risk of cancer. Moreover, the WCRF/AICR reports have stated that the evidence is limited and no firm conclusions can be drawn for any type of cancer (see **Table 4**). This includes all cancer types that were found to have decreased associations in our study (42). Especially for oral cancer, where our analyses revealed convincing evidence, the WCRF states there is no evidence for this association. Also, the limited suggestive evidence reported by the WCRF for reduced risk of bladder cancer by tea consumption (RR = 0.94; 95% CI: 0.89, 0.98, for 1 cup/d increment) was not reproduced in our analyses, because only 1 meta-analysis included in our study was significant and our final meta-analysis remained nonsignificant in this context.

There are several reasons why our results differ from those of the WCRF. First, the criteria for grading evidence are different. According to the WCRF criteria, the evidence level is determined by the presence of between-study heterogeneity, the quality of studies, biological rationale, and the number of cohort studies included. However, except for the statistical heterogeneity, the rest were not included as criteria of our study. Second, the WCRF largely relied on prospective cohort studies, whereas our review included both cohort and case-control studies. Finally, the WCRF attempted a dose–response meta-analysis of cohort studies whenever possible and presented summary estimates in continuous scale (e.g., 1 cup/d). However, we used the effect estimates from each meta-analysis, which were largely based on categorical comparisons of high compared with low or any compared with none intakes instead of a continuous scale of tea intake.

Despite the above differences, our study has several strong points compared with the results from the WCRF. First, our study not only summarized the existing meta-analyses of the same subject but also performed the most updated meta-analyses with combined primary studies. This made it possible to understand the effects of tea consumption over a wider range and expanded statistical power due to the inclusion of overall studies. Second, the WCRF separately evaluated different sorts of tea (green and black tea), whereas we included any of type of tea in our analyses. Therefore, studies reporting the results of green or black tea but not tea overall contributed to "any" tea in our review but were excluded in the review performed by the WCRF. Again, this

TABLE 4 Summary and comparison of individual meta-analysis articles, our umbrella review, and the WCRF report on associations of tea and cancer[1]

		Meta-analyses from original articles			Umbrella review					WCRF
Cancer type	Tea type	No. of meta-analyses	D/N/I	Evidence C/S/W/N/X	Comparison	No. of studies	D/N/I	RR (95% CI)	Level of evidence[2]	Level of evidence
Biliary tract	Any	1	1/0/0	0/1/0/0/0	Any vs. none	8	4/4/0	0.77 (0.64, 0.92)	Suggestive	N/A
Brain cancer	Any	1	0/1/0	0/0/0/1/0	Any vs. none	8	2/6/0	0.89 (0.76, 1.05)	Nonsignificant	N/A
Breast	Any	3	1/2/0	0/0/1/2/0	Any vs. none	26	6/20/0	0.81 (0.71, 0.94)	Weak	Limited—no conclusion
					High vs. low	23	1/20/2	0.98 (0.90, 1.06)	Nonsignificant	
	Black	9	0/8/1	0/0/1/8/0	High vs. low	28	1/27/0	0.98 (0.91, 1.06)	Nonsignificant	
					High vs. low (cohort)	15	0/15/0	1.04 (0.97, 1.12)	Nonsignificant	
					High vs. low (CC)	13	1/12/0	0.91 (0.80, 1.03)	Nonsignificant	
	Green	15	7/8/0	0/3/3/8/1	High vs. low (CC)	11	6/5/0	0.75 (0.61, 0.92)	Suggestive	
					High vs. low	16	6/10/0	0.82 (0.71, 0.96)	Weak	
					High vs. low (cohort)	5	0/5/0	0.99 (0.83, 1.77)	Nonsignificant	
					Any vs. none (CC)	5	3/2/0	0.94 (0.83, 1.05)	Nonsignificant	
					Any vs. none	14	3/11/0	0.87 (0.76, 0.99)	Weak	
					Any vs. none (cohort)	9	0/9/0	0.83 (0.62, 1.10)	Nonsignificant	
Bladder	Any	5	0/5/0	0/0/0/5/0	High vs. low (CC)	25	1/22/2	0.97 (0.87, 1.09)	Nonsignificant	Limited—suggestive: decreases risk RR = 0.94 (95% CI: 0.89, 0.98)
					High vs. low (cohort)	8	1/7/0	0.86 (0.65, 1.13)	Nonsignificant	
					High vs. low	33	2/29/2	0.95 (0.86, 1.06)	Nonsignificant	
	Green	2	1/1/0	0/1/0/1/0	High vs. low	5	0/5/0	1.03 (0.82, 1.31)	Nonsignificant	
Colorectal	Any	4	1/3/0	0/0/1/3/0	High vs. low	53	6/45/2	0.93 (0.87, 0.99)	Weak	Limited—no conclusion
	Black	1	0/1/0	0/0/0/1/0	High vs. low	20	2/14/4	0.99 (0.87, 1.13)	Nonsignificant	
	Green	3	1/2/0	0/0/1/2/0	High vs. low	15	4/11/0	0.87 (0.75, 1.00)[3]	Weak	
Colon	Green	1	0/1/0	0/0/0/1/0	High vs. low	11	1/9/1	0.98 (0.85, 1.12)	Nonsignificant	Limited—no conclusion
Rectal	Green	1	0/1/0	0/0/0/1/0	High vs. low		3/6/0	0.97 (0.77, 1.22)	Nonsignificant	Limited—no conclusion
Endometrial	Any	5	3/2/0	0/3/0/2/0	High vs. low	16	3/12/1	0.90 (0.75, 1.09)	Nonsignificant	Limited—no conclusion
					Increment of 1 cup/d	5	0/4/1	1.04 (0.98, 1.10)	Nonsignificant	
	Black	3	0/3/0	0/0/0/3/0	High vs. low	6	2/4/0	0.78 (0.61, 1.00)[3]	Suggestive	
	Green	3	3/0/0	0/3/0/0/0	High vs. low	10	1/8/1	0.99 (0.79, 1.23)	Nonsignificant	
Esophageal	Green	6	1/5/0	0/0/1/5/0	High vs. low	22	9/11/2	0.81 (0.62, 1.06)	Nonsignificant	N/A
Gastric	Any	2	1/1/0	0/0/1/1/0	Any vs. none	56	23/30/3	0.78 (0.70, 0.86)	Weak	Limited—no conclusion
					Increment of 3 cup/d	5	0/5/0	0.98 (0.89, 1.08)	Nonsignificant	
	Black	1	0/1/0	0/0/0/1/0	High vs. low	5	0/4/1	1.18 (0.79, 1.77)	Nonsignificant	
	Green	14	4/10/0	0/1/3/10/0	High vs. low	30	3/25/2	0.93 (0.84, 1.04)	Nonsignificant	
Gallbladder	Any	2	0/2/0	0/0/0/2/0	High vs. low	4	2/2/0	0.57 (0.25, 1.30)	Nonsignificant	Limited—no conclusion
					Any vs. none	6	3/3/0	0.67 (0.40, 1.12)	Nonsignificant	
Glioma	Any	2	1/1/0	0/0/1/1/0	Any vs. none	4	0/4/0	0.67 (0.40, 1.12)	Nonsignificant	N/A
					High vs. low	4	1/3/0	0.57 (0.25, 1.30)	Nonsignificant	

(*Continued*)

TABLE 4 (*Continued*)

		Meta-analyses from original articles			Umbrella review					WCRF
Cancer type	Tea type	No. of meta-analyses	D/N/I	Evidence C/S/W/N/X	Comparison	No. of studies	D/N/I	RR (95% CI)	Level of evidence[2]	Level of evidence
Renal cell carcinoma	Any	1	0/1/0	0/0/0/1/0	Any vs. none	12	1/11/0	1.03 (0.88, 1.21)	Nonsignificant	Limited—no conclusion
Liver	Any	2	0/2/0	0/0/0/2/0	Any vs. none	12	3/9/0	0.77 (0.57, 1.03)	Nonsignificant	N/A
	Green	2	2/0/0	0/1/1/0/0	High vs. low	11	2/9/0	0.87 (0.78, 0.98)	Suggestive	
					Any vs. none	10	3/7/0	0.65 (0.48, 0.88)	Weak	
Lung	Any	1	1/0/0	0/0/1/0/0	Any vs. none	44	18/24/2	0.76 (0.68, 0.86)	Weak	Limited—no conclusion
	Black	2	0/2/0	0/0/0/2/0	High vs. low	14	4/10/0	0.86 (0.70, 1.05)	Nonsignificant	
	Green	2	1/1/0	0/0/1/1/0	High vs. low	12	4/7/1	0.78 (0.61, 1.01)	Nonsignificant	
Leukemia (in childhood)	Any	8	0/8/0	0/0/0/8/0	High vs. low	9	0/8/1	0.93 (0.74, 1.18)	Nonsignificant	N/A
					Any vs. none	14	0/14/0	0.93 (0.82, 1.05)	Nonsignificant	
Leukemia	Any	2	2/0/0	0/0/2/0/0	High vs. low	8	4/4/0	0.55 (0.43, 0.72)	Weak	N/A
					Any vs. none	8	1/7/0	0.76 (0.65, 0.89)	Weak	
Ovarian	Any	9	5/4/0	0/1/4/4/0	Any vs. none	21	8/22/1	0.82 (0.71, 0.94)	Weak	Limited—no conclusion
	Black	1	0/1/0	0/0/0/1/0	Any vs. none	16	4/12/0	0.90 (0.78, 1.04)	Nonsignificant	
	Green	2	1/1/0	0/0/1/1/0	Any vs. none	9	3/5/1	0.76 (0.57, 1.02)	Nonsignificant	
Laryngeal	Any	5	0/5/0	0/0/0/4/1	High vs. low	8	2/5/1	0.91 (0.67, 1.23)	Nonsignificant	Limited—no conclusion
Oral	Any	1	1/0/0	1/0/0/0/0	Any vs. none	6	6/0/0	0.62 (0.55, 0.72)	Convincing	Limited—no conclusion
	Any	5	2/2/0	0/2/0/2/0	High vs. low	31	5/26/0	0.86 (0.80, 0.91)	Suggestive	
	Green	1	1/0/0	0/1/0/0/0	High vs. low	5	1/4/0	0.82 (0.69, 0.96)	Suggestive	
Oropharyngeal	Any	3	1/2/0	0/0/1/1/1	Any vs. none	6	2/4/0	0.68 (0.45, 1.03)	Nonsignificant	Limited—no conclusion
Pharyngeal	Any	3	0/3/0	0/0/0/2/1	Any vs. none	4	0/4/0	0.88 (0.74, 1.04)	Nonsignificant	Limited—no conclusion
Pancreatic	Any	4	0/4/0	0/0/0/4/0	High vs. low	22	1/20/1	0.97 (0.85, 1.10)	Nonsignificant	Limited—no conclusion
					Any vs. none	29	2/25/2	0.99 (0.89, 1.10)	Nonsignificant	
	Green	1	0/1/0	0/0/0/1/0	High vs. low	8	1/6/1	0.99 (0.78, 1.25)	Nonsignificant	
Prostate	Any	1	0/1/0	0/0/0/1/0	High vs. low	23	6/15/2	0.86 (0.71, 1.04)	Nonsignificant	Limited—no conclusion
					Any vs. none	29	7/20/2	0.87 (0.75, 1.01)	Nonsignificant	
	Black	2	0/2/0	0/0/0/2/0	High vs. low	11	1/9/1	0.99 (0.82, 1.20)	Nonsignificant	
	Green	4	0/4/0	0/0/0/4/0	High vs. low	9	3/6/0	0.73 (0.51, 1.06)	Nonsignificant	
Thyroid	Any	1	1/0/0	0/0/1/0/0	High vs. low	14	1/13/0	0.77 (0.61, 0.97)	Weak	N/A
Skin (nonmelanoma)	Any	1	0/1/0	0/0/0/1/0	Any vs. none	8	4/4/0	0.88 (0.76, 1.02)	Nonsignificant	N/A

[1]CC, case-control studies; C/S/W/N/D, convincing/suggestive/weak/nonsignificant/not adequately assessed; D/N/I, decrease in risk/no association/increase in risk; N/A, not applicable; WCRF, World Cancer Research Fund network.
[2]The definition of each category of the level of evidence is presented in Supplemental Table 1.
[3]The value is rounded up (to 2 decimal places), and hence is statistically significant.

might have increased statistical power for the evaluation of tea.

The main strength of our umbrella review is the comprehensive summary and assessment of the level of evidence of tea consumption and cancer risk by including 64 original meta-analyses and 25 cancer sites. The umbrella review conducted in this study used standardized methods including the use of random-effects analysis and various measures of heterogeneity and publication bias. When studies reached the conventional threshold of statistical significance (P value <0.05), we further evaluated the results using the criteria for the level of evidence. The strength of classifying the level of evidence further provides information on the extent to which the different results are supported by evidence even though the standard significance threshold was reached. Also, we re-evaluated the results with a convincing level of evidence by applying the method of credibility ceilings. The aim of an umbrella review is to find out the trustworthy associations from prevailed significant result. In addition, the confirmation process of any significant results, such as by using credibility ceilings, has recently been suggested by some researchers. Otherwise, testing for excess significance bias has been proposed to evaluate the noteworthiness of statistically significant results. However, we did not evaluate ES due to lack of the data for calculating; also some authors opine that testing for ES has limited power, so it has not been recommended (43).

Generally, RR with 95% CI is used for determining associations between exposures and outcomes, but such associations must be questioned if the studies show high heterogeneity or publication bias (16). To overcome this issue, we used multiple criteria to estimate the results from the meta-analyses. In addition to 95% CI, 95% PI has been suggested in multiple umbrella reviews to yield robust conclusions (44). Moreover, we classified the I^2 metrics to differentiate from conventional meta-analyses. If the heterogeneity using I^2 metrics was large, the results were re-examined by considering the distribution of the effect size of the studies included. If more than half of the total number of studies were in the same direction, the analysis was not considered to have high heterogeneity. The rationale behind this decision is that I^2 statistic can be biased in small meta-analyses and might not be useful in estimating heterogeneity with much precision in small studies (45). This was applied in the case of breast cancer (high compared with low green tea consumption) being classified as suggestive evidence despite showing very large heterogeneity ($I^2 > 75\%$) (see Supplemental Table 3).

However, several limitations to this study can be considered. First, we carried out recalculation and meta-analysis only with data that were available, therefore some individual studies could have been missed. Second, factors that could be relevant to the incidence of cancer, such as gender, ethnicity, age group, or smoking status, were not considered for the umbrella review. Some studies did not provide information needed to perform subgroup analysis. Third, the application of heterogeneity, publication bias, and 95% PI in the criteria for level of evidence might not be definitive. We included meta-analyses with both case-control studies and cohort studies. Because of the potential biases that can affect case-control studies, such as recall bias and selection bias, further prospective studies are needed before firm conclusions can be drawn. Furthermore, the summary effects of the meta-analyses about the same question might have variations due to multiple reasons (46). Also, evaluating any discrepancies or errors of individual meta-analyses was beyond the scope of our review. Another problem is that the summary effect size could be from a combination of studies with different measures, such as OR, RR, and HR. OR is statistically similar to RR when the outcome is uncommon (47). Moreover, the main comparisons for tea exposure used in this study (high compared with low, any compared with none) can vary over a wide range. The exact amount of tea polyphenol intake cannot be determined, because it can be affected by multiple factors such as individual tea preferences, the size of a cup, addition of sugar, different cultural practices, natural variability in polyphenol concentration in tea sorts, and other possible organic influencing factors.

Regardless of these limitations, the findings of this study show health implications that could be beneficial to individuals and populations. The association between tea consumption and the risk of oral cancer was supported by convincing evidence. It is possible that tea consumption can reduce the risk of some other cancers, but further prospective and mechanistic studies are needed before more robust conclusions can be made.

Acknowledgments

The authors' responsibilities were as follows—TLK, GHJ, KHL, A Kronbichler, G Grosso, HJvdV, G Gamerith, FG, DA, JYK, BS, A Koyanagi, MS, SHH, ED, EC, LFMdR, ELG, JIS: contributed to the concept and design of the study; TLK, GHJ, JIS: acquired, collected, and analyzed the data; JIS: had final responsibility for the decision to submit for publication; and all authors: had full access to all the study data, participated in drafting the manuscript, and read and approved the final manuscript.

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