

Diet and Esophageal Cancer Risk: An Umbrella Review of Systematic Reviews and Meta-Analyses of Observational Studies

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ABSTRACT

Diet may play an important role in the occurrence of esophageal cancer (EC). The aim of this umbrella review was to grade the evidence for the association between dietary factors and EC risk. A protocol for this review was registered with the PROSPERO database (CRD42021283232). Publications were identified by searching PubMed, EMBASE, Web of Science, Cochrane Database of Systematic Reviews, and CINAHL databases. Only systematic reviews and meta-analyses of observational studies (cohort studies, case-cohort studies, nested case-control studies) were eligible. AMSTAR-2 (A Measurement Tool to Assess Systematic Reviews) was used to assess the methodological quality of included systematic reviews. For each association, random-effects pooled effect size, 95% CI, number of cases, 95% prediction interval, heterogeneity, small-study effect, and excess significance bias were calculated to grade the evidence. From 882 publications, 107 full-text articles were evaluated for eligibility, and 20 systematic reviews and meta-analyses describing 32 associations between dietary factors and EC risk were included in the present umbrella review. By assessing the strength and validity of the evidence, 1 association (positively associated with alcohol intake) was supported by highly suggestive evidence and 1 (inversely associated with calcium intake) showed a suggestive level of evidence. Evidence for 7 associations was weak (positively associated with red meat and processed-meat intake; inversely associated with whole grains, fruits, green leafy vegetables, green tea, and zinc intake). The remaining 23 associations were nonsignificant. In conclusion, the findings of this umbrella review emphasize that habitually consuming calcium, whole grains, fruits, green leafy vegetables, green tea, and zinc and reducing alcohol, red meat, and processed-meat intake are associated with a lower risk of EC. Since this umbrella review included only observational study data and some of the associations were graded as weak, caution should be exercised in interpreting these relations. *Adv Nutr* 2022;13:2207–2216.

Statement of Significance: The previous umbrella review's data for associations between dietary factors and esophageal cancer risk were up to 28 February 2014, and since 2014, several relevant meta-analyses have been published, so we believe it is necessary to combine these additional results to assess the robustness of the evidence. Among 4 associations (calcium, whole grains, green tea, and zinc intake), which were not evaluated in the previous review, 1 association (inversely associated with calcium intake) was supported by suggestive evidence and 3 associations (inversely associated with whole grains, green tea, and zinc intake) showed a weak level of evidence in the present umbrella review.

Keywords: diet, esophageal cancer, evidence, meta-analyses, umbrella review

Introduction

Esophageal cancer (EC) is the seventh most commonly diagnosed cancer and the sixth leading cause of cancer deaths worldwide in 2020, with approximately 604,000 new cases and 544,000 deaths (1). Since the early clinical symptoms are relatively insidious, EC is often diagnosed during its advanced stages (2). Despite improvements in the management and treatment of patients with EC, the

overall outcomes for 5-y survival rate (~10%) and 5-y post-esophagectomy survival rate (~15–40%) remain poor (2, 3). Identifying, exploring, and intervening on potential risk factors may have an important impact on the incidence rates of EC. Recent evidence suggests that modifiable lifestyle factors, including excessive obesity, poor diet, and physical inactivity, play an important role in the occurrence and progression of this disease (2–4).

Numerous observational studies have been conducted to investigate the association between dietary factors and EC incidence. Most of these studies were usually summarized through the results of systematic reviews and meta-analyses. However, pooled estimates from meta-analyses of observational studies might not represent causal associations due to the prevalence of bias in those studies (e.g., recall bias, selection bias), subsequently reducing the strength of aggregated scientific evidence (5, 6). Therefore, the robustness of the evidence needs to be assessed before using the evidence to inform public health policy. In 2021, Papadimitriou et al. (7) conducted an umbrella review to evaluate the strength and validity of the evidence for the association between food/nutrient intake and the risk of developing or dying from 11 primary cancers, including EC. Data for that review were extracted from the World Cancer Research Fund (WCRF) Third Expert Report, and the search for EC was up to 28 February 2014 (8). Since 2014, several relevant meta-analyses have been published, and we believe it is necessary to combine these additional results to assess the robustness of the evidence. Therefore, we conducted this umbrella review of systematic reviews and meta-analyses to evaluate the evidence for the association between dietary factors and EC risk.

Methods

The protocol of this umbrella review has been registered at PROSPERO. The registration number is CRD42021283232. This umbrella review adhered to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) reporting guideline (9).

Search strategy

A comprehensive literature search was performed to assess the association between dietary factors and EC risk. PubMed, EMBASE, Web of Science, Cochrane Database of Systematic Reviews, and CINAHL databases were searched from database inception to 4 October 2021. The following search terms were used: (diet* OR food* OR nutrition* OR eating) AND (esophageal OR esophagus) AND (Tumor* OR Neoplas* OR Cancer* OR Carcinoma* OR Malignanc*) AND (meta-analysis OR systematic review OR systematic overview). Additionally, we manually searched reference lists from original literature reports for potential complements.

Eligibility criteria

Two authors (XQ and GJ) independently screened titles and abstracts. Disagreements were resolved by consensus with another independent author (XZ). The full texts of all

potentially eligible articles were then retrieved and screened by the same 2 authors, and any discrepancies were resolved by a third author (XZ).

The criteria for eligibility were as follows: 1) systematic reviews and meta-analyses of observational studies (cohort studies, case-cohort studies, nested case-control studies) among adults, 2) studies investigating the incidence of EC in different dietary categories or dietary patterns, 3) multivariate-adjusted pooled risk estimates and corresponding 95% CIs were available, and 4) published in English. Meta-analyses of randomized controlled trials were not eligible for the present umbrella review. If an article conducted separate meta-analyses of multiple eligible dietary factors, each factor was evaluated separately. If the association between dietary factors and EC incidence was assessed by both highest versus lowest intake and dose-response analysis, we included the dose-response analysis (10). Whenever more than 1 meta-analysis focused on the same association, by searching the reference lists of each meta-analysis to assess study overlap we selected the most recent one with more available information and the largest number of cases, since the number of cases was part of our criteria.

Studies were excluded based on the following criteria: 1) cross-sectional or case-control studies, 2) the interest of studies focused between dietary factors and EC was not the incidence but the other outcome (e.g., mortality), 3) studies that did not provide sufficient data for quantitative synthesis, 4) animal and/or in vitro studies, 5) conference abstracts, and 6) published in other languages.

Data extraction

Data were extracted by 2 researchers (XQ and GJ), and any discrepancies were resolved by discussion and consultation with the third author (ZY). We recorded the following data from each eligible article: 1) name of first author, 2) year of publication, 3) dietary factors, 4) number of studies included, 5) number of cases and total participants, 6) meta-analyses metric (OR; RR), and 7) effect size and corresponding 95% CI. In addition, we extracted the data of the original study from the eligible meta-analyses for further analysis: 1) name of first author, 2) year of publication, 3) number of cases and total participants, 4) effect size and its 95% CI, and 5) comparison data from (highest vs. lowest intake; dose-response analysis).

Assessment of methodological quality

The AMSTAR-2 (A Measurement Tool to Assess Systematic Reviews) (11) is a tool to assess the quality of systematic review methods that contains 16 distinct domains. Seven of these domains are considered critical. This tool was used to evaluate the methodological quality of the included systematic reviews independently by 2 authors (XQ and GJ). Any disagreements were resolved by consulting a third author (ZY). The methodological quality of the reviews was rated as high, moderate, low, or critically low.

The authors reported no funding received for this study.

Author disclosures: The authors report no conflicts of interest.

Supplemental Tables 1 and 2 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/>.

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Abbreviations used: AMSTAR-2, A Measurement Tool to Assess Systematic Reviews; EC, esophageal cancer; PI, prediction interval; WCRF, World Cancer Research Fund.

Statistical analysis

The original studies data obtained from the eligible meta-analyses were recalculated to obtain additional information to evaluate the level of evidence for the associations (12). We used the DerSimonian and Laird random-effects model to estimate the pooled effect size and its 95% CI (13). We also calculated the effect size for the largest data study of each association. Statistical heterogeneity was checked with the I^2 statistic. An I^2 value below 25% or 50% indicated low or moderate heterogeneity of the data, while an I^2 value above 50% or 75% indicated significant or considerable heterogeneity, respectively (14). In addition, we estimated the 95% prediction interval (PI), which further accounts for between-study heterogeneity and evaluates the uncertainty of the effect size that would be anticipated in a new study addressing the same association (15, 16). We also assessed the small-study effects, commonly known as publication bias, to determine whether such studies tended to provide greater estimates of risk than larger studies (17). An Egger P value < 0.10 was considered statistical evidence for small-study effects (18). Furthermore, we applied the excess significance test to evaluate whether the observed number (O) of statistically significant studies in the meta-analysis was different from the expected number (E) (19). Excess significance bias was set at $P < 0.10$. The analysis was carried out using R software (version 4.1.2; R Core Team, 2021), meta package (version 5.2.0; Guido Schwarzer, 2022), and metafor package (version 3.0.2; Viechtbauer, 2021).

Grading the quality of evidence

Statistically significant ($P < 0.05$) associations between dietary factors and EC incidence were classified into 4 levels of evidence strength according to the grading scheme applied in previously published umbrella reviews (20–22). When $P \geq 0.05$, there was no significant association.

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

- Convincing (class I): 1) statistical significance with $P < 10^{-6}$, 2) number of cases > 1000 , 3) largest component study with a statistically significant effect ($P < 0.05$), 4) 95% PI excluded the null, 5) no large heterogeneity ($I^2 < 50\%$), 6) no small-study effects ($P > 0.10$), and 7) no excess significance bias ($P > 0.10$).
- Highly suggestive (class II): 1) statistical significance with $P < 10^{-6}$, 2) number of cases > 1000 , and 3) largest component study with a statistically significant effect ($P < 0.05$).
- Suggestive (class III): 1) statistical significance with $P < 10^{-3}$ and 2) number of cases > 1000 .
- Weak (class IV): statistical significance with $P < 0.05$.
- Nonsignificant association: $P \geq 0.05$.

Results

Literature identification and selection

As shown in **Figure 1**, the systematic search retrieved 882 publications from 5 electronic databases. After removing

duplicates, 496 records were excluded through scanning titles and abstracts. A total of 107 full-text articles were identified for further evaluation, of which 87 were excluded according to the eligibility criteria. Finally, 20 systematic reviews and meta-analyses were included in the present umbrella review (23–42). Full details of the 87 articles we excluded are provided in **Supplemental Table 1**.

Description of included meta-analyses

These 20 meta-analyses describing 32 associations were published between 2013 and 2021. As shown in **Table 1**, 10 meta-analyses used the Newcastle-Ottawa Quality Assessment Scale (NOS) to assess the methodological quality of individual studies (24, 30, 31, 33–35, 38, 40–42); the remaining 10 meta-analyses did not conduct assessment (23, 25–29, 32, 36, 37, 39). The number of observational studies for each association ranged from 2 to 11. Of the 32 associations, 30 associations were evaluated using cohort studies alone and the remaining 2 associations were assessed using both cohort and nested case-control studies. The number of participants ranged from 7945 to 4,471,875, the number of cases ranged from 14 to 3526, and the number of cases was greater than 1000 for 15 associations.

The included meta-analyses provided summary estimates on the associations between dietary behaviors (1 association, the alcohol cessation) (23), food groups or food items (12 associations, including fish, poultry, red meat, processed meat, total meat, white meat, fruits, vegetables, and whole-grain intake) (24–32), beverages (4 associations, including milk, coffee, green tea, and alcohol intake) (32–34), macronutrients (4 associations, including total fat, saturated fat, polyunsaturated fat, and monounsaturated fat intake) (35), and micronutrients (11 associations, including nitrate, nitrite, folate, vitamin B-6, vitamin B-12, calcium, sodium, iron, copper, zinc, and selenium intake) (36–42) and the risk of EC.

As shown in **Table 1**, the assessment of methodological quality using AMSTAR-2 revealed 1 meta-analysis (40) of high quality and 7 (24, 30, 31, 33, 38, 41, 42) of moderate quality. A total of 8 (25–28, 32, 34–36) meta-analyses were of low quality, with the remaining 4 (23, 29, 37, 39) rated as critically low quality. The detailed assessments of methodological quality are shown in **Supplemental Table 2**.

Summary of associations

As shown in **Table 2**, the 32 associations included in the 20 meta-analyses were recalculated using random-effects models to assess the level of evidence. A total of 9 associations yielded nominal statistical significance at $P < 0.05$. Of these, only 2 reached statistical significance at $P < 10^{-6}$. Six of nine associations were associated with a lower risk of EC, including higher intakes of whole grains, fruits, green leafy vegetables, green tea, calcium, and zinc; the remaining 3 associations were associated with a higher risk of EC, including

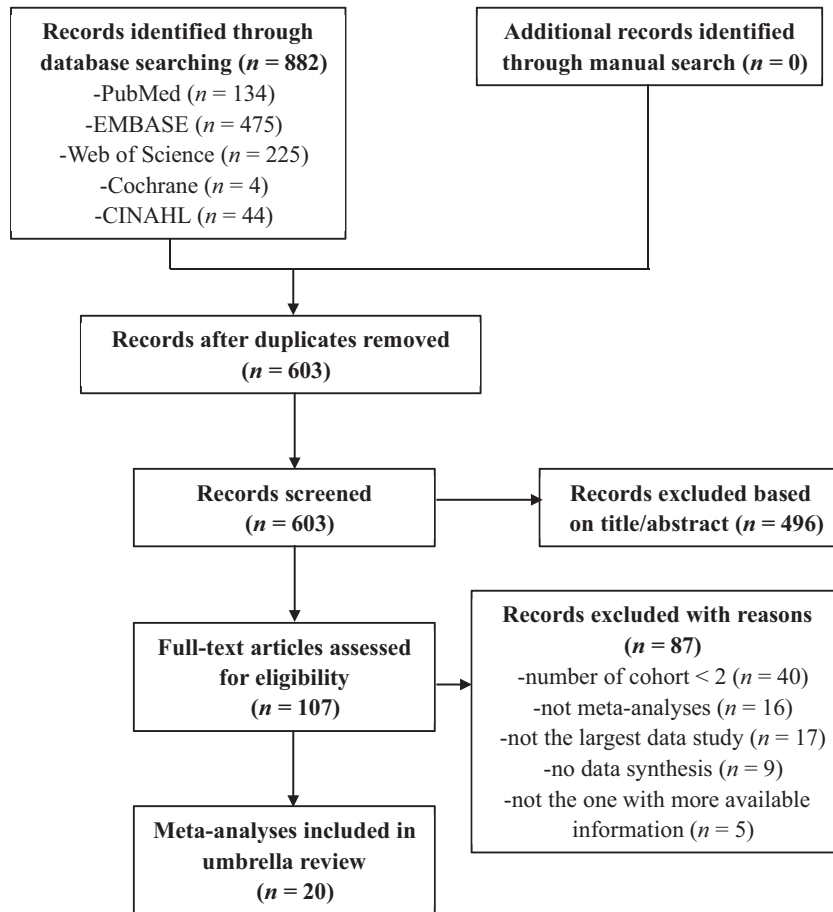


FIGURE 1 Flowchart of the literature selection process.

higher intake of red meat, processed meat, and alcohol.

After calculating the effect size of the largest data study for each association, 6 of the 9 associations (whole grains, fruits, green leafy vegetables, zinc, red meat, and alcohol intake) showed statistical significance. The minimum number of studies to test for 95% PI was 3. After estimating the 95% PI, all 9 associations were excluded because their 95% PI included the null or had fewer than 3 studies.

Some associations (9/32) showed large heterogeneity ($I^2 > 50\%$). According to Egger's test, there was no evidence of small-study effects. However, the minimum number of studies for assessing small-study effects was 10, and only 1 association (32) (alcohol intake) contained 11 original studies that provided statistical power for Egger's test. No excess significance bias was found for any association.

Grading the quality of evidence

Convincing evidence (class I).

After calculating the random-effects summary effect size, 95% CI, 95% PI, and assessing heterogeneity, evidence for small-study effect, and evidence for excess significance bias, no association was supported by convincing evidence.

Highly suggestive evidence (class II).

There is a positive association between higher intake of alcohol and EC risk by highly suggestive evidence. The estimated increased RR of EC was 21% for each 10 g (~0.35 ounces)/d increment of alcohol intake (32).

Suggestive evidence (class III).

Our results supported an inverse association between higher intake of calcium and EC risk by suggestive evidence (38).

Weak evidence (class IV).

Evidence for 7 associations was weak. Five associations, including higher intake of whole grains, fruits, green leafy vegetables, green tea, and zinc, were inversely associated with the EC risk (30–32, 34, 40). The remaining 2 associations, including higher intake of red meat and processed meat, were positively associated with the EC risk (24, 32).

Nonsignificant association.

A total of 23 associations were nonsignificant.

The detailed analysis results on which the evidence grading is based are shown in Table 2.

TABLE 1 Methodological quality of included meta-analyses that evaluate dietary factors and esophageal cancer risk¹

First author, year (reference)	Dietary factor	Studies, <i>n</i>	Cases, <i>n</i>	Participants, <i>n</i>	Quality assessment	AMSTAR-2
Miyazaki, 2017 (23)	Alcohol cessation	2	14	28,638	NA	Critically low
Choi, 2013 (24)	Red meat	8	2324	1,149,981	NOS	Moderate
Han, 2013 (25)	Fish	4	1279	730,702	NA	Low
Salehi, 2013 (26)	Total meat	3	2124	569,284	NA	Low
	White meat	2	845	494,979		
Jiang, 2016 (27)	Poultry	3	805	1,013,643	NA	Low
Vingeliene, 2016 (28)	Citrus fruits	8	1059	1,160,130	NA	Low
Yan, 2018 (29)	Pickled vegetables	2	3120	42,277	NA	Critically low
Zhang, 2020 (30)	Whole grains	2	281	148,584	NOS	Moderate
Sakai, 2021 (31)	Fruits	6	2818	177,648	NOS	Moderate
Vingeliene, 2017 (32)	Vegetables	8	3229	1,528,067	NA	Low
	Green leafy vegetables	6	730	1,015,145		
	Processed meat	6	1385	1,320,178		
	Coffee	6	1074	1,448,033		
	Alcohol	11	3526	2,937,707		
Li, 2016 (33)	Milk	2	541	238,516	NOS	Moderate
Yi, 2020 (34)	Green tea	4	473	708,139	NOS	Low
He, 2017 (35)	Total fat	2	845	494,978	NOS	Low
	Saturated fat	2	845	494,978		
	Polyunsaturated fat	2	845	494,978		
	Monounsaturated fat	2	845	494,978		
Hong, 2016 (36)	Selenium	2	111	7945	NA	Low
Xie, 2016 (37)	Nitrate	6	1106	687,254	NA	Critically low
	Nitrite	7	1161	710,617		
Li, 2017 (38)	Calcium	3	1412	343,431	NOS	Moderate
Liu, 2017 (39)	Folate	3	1257	521,876	NA	Critically low
Ma, 2018 (40)	Iron	6	1385	1,329,168	NOS	High
	Copper	2	944	49,922		
	Zinc	2	944	49,922		
Ma, 2018 (41)	Vitamin B-6	4 ²	267	4,471,830	NOS	Moderate
	Vitamin B-12	4 ²	314	4,471,875		
Banda, 2020 (42)	Sodium	3	895	501,798	NOS	Moderate

¹AMSTAR, A Measurement Tool to Assess Systematic Reviews; NA, not available; NOS, Newcastle-Ottawa Quality Assessment Scale.

²Four studies = 2 cohort studies + 2 nested case-control studies.

Discussion

Within single meta-analysis, statistical methods are frequently inadequate or misused, which can lead to misleading results, distortions, and bias. Therefore, in 2009, Ioannidis et al. (43) first proposed the concept of an umbrella review, which aims to provide a conclusive summary of the report, highlighting the level of evidence. Recently, the practice of establishing the level of evidence has become more important to provide summaries of information for health care decision makers (12).

We conducted this umbrella review to evaluate the robustness of the evidence from systematic reviews and meta-analyses of observational studies on the relation between dietary factors and EC risk for further applications to inform health policy or dietary guidelines. Overall, we included 20 published meta-analyses describing 32 associations. After grading the quality of evidence, we found 9 associations that were statistically significant and the strength of the evidence for associations between alcohol, fruits, green leafy vegetables, red meat, processed meat, and EC risk is consistent with previous umbrella analyses (7). In addition,

calcium, whole grains, green tea, and zinc, which were not evaluated in the previous review, were identified as being inversely associated with EC risk in the present umbrella review.

Based on 11 studies including 3526 cases and 2,937,707 participants, our umbrella review supports a positive association between higher intake of alcohol and EC risk by highly suggestive evidence, which is consistent with the WCRF/American Institute for Cancer Research Continuous Update Project report (44). The mechanisms by which alcohol consumption exerts its carcinogenic effects are diverse and not fully understood. The main mechanism of carcinogenesis is related to the alcohol metabolite acetaldehyde and the production of reactive oxygen species by enzymes induced by chronic alcohol consumption (45). Finally, alcohol may cause direct damage to the esophageal epithelium and facilitate the absorption of carcinogens (46). Although the 95% PI for this association includes the null value, there were no small-study effects or excess significance bias, and the number of cases exceeded 1000, suggesting that the evidence is likely robust.

TABLE 2 Quality of evidence of associations between dietary factors and esophageal cancer risk¹

First author (reference)	Dietary factor	Comparison	MA metric	Random effect size (95% CI)	P	I ² , %	Largest study, 95% CI	95% prediction interval	Egger's P value	Excess significance test		Evidence class ²
										O/E	P	
Miyazaki, 2017 (23)	Alcohol cessation	Quit drinking vs. current drinking	RR	0.57 (0.27, 1.17)	0.12	36.1	0.33–2.6	NE	NA	1/0.7	0.58	No
Choi, 2013 (24)	Red meat	Highest vs. lowest	RR	1.28 (1.07, 1.53)	0.008	35.5	1.11–1.69	0.93–1.75	NA	2/1.6	0.51	IV
Han, 2013 (25)	Fish	Highest vs. lowest	RR	0.84 (0.65, 1.09)	0.19	36.1	0.72–1.26	0.36–1.99	NA	1/0.8	0.59	No
Salehi, 2013 (26)	Total meat	Highest vs. lowest	RR	0.92 (0.58, 1.44)	0.7	63.5	0.62–0.86	0.006–148.5	NA	1/1	NP ⁵	No
Jiang, 2016 (27)	White meat	Highest vs. lowest	RR	0.8 (0.64, 1.0)	0.051	0	0.65–1.09	NE	NA	0/0.6	NP	No
Vingeliene, 2016 (28)	Poultry	Highest vs. lowest	RR	1.03 (0.62, 1.73)	0.91	66.2	0.72–1.26	0.001–385	NA	0/1	NP	No
Yan, 2018 (29)	Citrus fruits	Per 100-g/d increment	RR	0.9 (0.79, 1.02)	0.1	0	0.78–1.25	0.76–1.05	NA	1/0.7	0.53	No
Zhang, 2020 (30)	Pickled vegetables	Highest vs. lowest	OR	1.04 (0.93, 1.15)	0.53	0	0.92–1.15	NE	NA	0/0.1	NP	No
Sakai, 2021 (31)	Whole grains	Highest vs. lowest	RR	0.54 (0.38, 0.76)	0.0004	0	0.34–0.82	NE	NA	2/1.4	0.46	IV
Vingeliene, 2017 (32)	Fruits	Highest vs. lowest	RR	0.75 (0.6, 0.92)	0.01	80.9	0.7–0.91	0.39–1.45	NA	3/2.8	0.62	IV
	Vegetables	Per 100-g/d increment	RR	0.93 (0.86, 1.01)	0.07	33.7	0.93–1.1	0.77–1.13	NA	1/1.8	NP	No
	Green leafy vegetables	Per 50-g/d increment	RR	0.86 (0.78, 0.95)	0.004	0	0.74–0.97	0.74–0.99	NA	1/1.3	NP	IV
	Processed meat	Per 50-g/d increment	RR	1.35 (1.06, 1.74)	0.02	56.5	0.87–1.36	0.66–2.78	NA	2/2.3	0.75	IV
	Coffee	Per 1-cup/d increment	RR	0.99 (0.94, 1.03)	0.56	30.6	0.91–1.05	0.92–1.06	NA	0/0.3	NP	No
	Alcohol	Per 10-g/d increment	RR	1.21 (1.13, 1.31)	<10 ⁻⁶	95.4	1.35–1.6	0.93–1.57	0.004	8/7.8	0.61	II
Li, 2016 (33)	Milk	Highest vs. lowest	RR	0.8 (0.48, 1.33)	0.39	62.7	0.71–1.41	NE	NA	0/0.7	NP	No
Yi, 2020 (34)	Green tea	Highest vs. lowest	RR	0.75 (0.61, 0.93)	0.007	23.4	0.51–1.08	0.48–1.19	NA	1/1.1	0.73	IV
He, 2017 (35)	Total fat	Highest vs. lowest	RR	0.93 (0.64, 1.34)	0.69	0	0.6–1.42	NE	NA	0/0.1	NP	No
	Saturated fat	Highest vs. lowest	RR	1.17 (0.88, 1.56)	0.27	0	0.91–1.78	NE	NA	0/0.2	NP	No
	Polyunsaturated fat	Highest vs. lowest	RR	0.97 (0.77, 1.22)	0.79	0	0.7–1.19	NE	NA	0/0.1	NP	No
	Monounsaturated fat	Highest vs. lowest	RR	1.28 (0.96, 1.71)	0.1	0	0.84–1.66	NE	NA	0/0.4	NP	No

(Continued)

TABLE 2 (Continued)

First author (reference)	Dietary factor	Comparison	MA metric	Random effect size (95% CI)	P	I ² , %	Largest study, 95% CI	95% prediction interval	Egger's P value	Excess significance test		Evidence class ²
										O/E	P	
Hong, 2016 (36)	Selenium	Highest vs. lowest	RR	0.99 (0.55, 1.78)	0.96	32.6	0.41–1.4	NE	NA	0/0.2	NP	No
Xie, 2016 (37)	Nitrate	Highest vs lowest	RR	1.06 (0.82, 1.39)	0.65	0	0.75–1.61	0.73–1.55	NA	0/0.3	NP	No
	Nitrite	Highest vs. lowest	RR	1.1 (0.92, 1.32)	0.31	11.5	0.84–1.68	0.87–1.39	NA	0/0.5	NP	No
Li, 2017 (38)	Calcium	Highest vs. lowest	OR	0.67 (0.54, 0.84)	0.0004	23.7	0.56–1.26	0.16–2.84	NA	2/1.6	0.53	III
Liu, 2017 (39)	Folate	Highest vs. lowest	OR	0.85 (0.64, 1.14)	0.27	48.6	0.61–1.08	0.05–15.28	NA	0/0.7	NP	No
Ma, 2018 (40)	Iron	Highest vs. lowest	OR	1.15 (0.89, 1.47)	0.28	56.7	0.99–2.17	0.56–2.34	NA	1/1.6	NP	No
	Copper	Per 1-mg/d increment	OR	1.02 (0.64, 1.62)	0.93	95.7	1.2–1.37	NE	NA	2/1.4	0.5	No
	Zinc	Per 5-mg/d increment	OR	0.78 (0.71, 0.86)	<0.0001	0	0.7–0.89	NE	NA	2/1.7	0.71	IV
Ma, 2018 (41)	Vitamin B-6	Highest vs. lowest	OR	1.02 (0.7, 1.48)	0.93	51.8	0.76–1.32	0.25–4.2	NA	1/0.7	0.58	No
	Vitamin B-12	Highest vs. lowest	OR	1.02 (0.82, 1.25)	0.89	0	0.8–1.35	0.64–1.61	NA	0/0.2	NP	No
Banda 2020 (42)	Sodium	Highest vs. lowest	OR	1.04 (0.99, 1.08)	0.06	0	0.98–1.07	0.81–1.33	NA	0/0.6	NP	No

¹MA, meta-analyses; NA, not applicable because number of studies (<10) too small to test for small study effects; NE, not estimated because number of studies (<3) too small to test for 95% prediction interval; NP, not pertinent because estimated number is larger than observed; O/E, observed/expected number of studies with significant results.

²Evidence class—class I (convincing): statistical significance at $P < 10^{-6}$, > 1000 cases; the largest component study with a significant effect ($P < 0.05$), the 95% prediction interval excluded the null, no large heterogeneity ($I^2 < 50\%$), no small-study effects ($P > 0.10$), and no excess significance bias ($P > 0.10$); class II (highly suggestive): significance at $P < 10^{-6}$, > 1000 cases, the largest component study with a significant effect ($P < 0.05$); class III (suggestive): statistical significance at $P < 10^{-3}$, > 1000 cases; class IV (weak): the remaining significant associations at $P < 0.05$; No, nonsignificant association $P \geq 0.05$.

We found an inverse association between high consumption of calcium and the incidence of EC by suggestive evidence. As a ubiquitous second messenger, calcium plays a crucial role in human health (47). Calcium intake was hypothesized to reduce cancer risk by downregulating 1,25-dihydroxyvitamin D synthesis, promoting activation of the transcription factor cAMP response element-binding protein, inducing cell cycle arrest, and promoting cell differentiation and tumor cell apoptosis (48, 49). In addition, previous studies showed that a high-calcium diet induced cell differentiation and inhibited cell proliferation and carcinogenesis by promoting p120-catenin expression and p120-dependent E-cadherin- β -catenin-p120-catenin complex formation in mouse epithelial tissues (50, 51). However, this meta-analysis did not include a dose-response effect analysis due to the incomplete data on dietary calcium intake, and the average highest dietary calcium intake in Asian populations (621 mg/d) is much lower than in Americans (1284 mg/d) and Europeans (1232 mg/d), so it is difficult to define the accurate intake in grams per day for health recommendations (38).

The present umbrella review also indicated inverse associations between high consumption of whole grains, fruits, green leafy vegetables, green tea, and zinc and EC risk by weak evidence. Whole grains may influence EC risk through a variety of mechanisms. First, whole grains are an important source of dietary fiber. Inositol hexaphosphate, 1 component of food sources high in dietary fiber, has been demonstrated to inhibit the growth rate of Barrett's-associated esophageal adenocarcinoma cells by reducing cell proliferation and stimulating apoptosis in vitro (52). Second, whole grains are rich sources of antioxidants, including vitamins (such as vitamin E), trace minerals (such as selenium), phenolic acids, lignans, and phytoestrogens, which together reduce oxidative damage and stress, thereby reducing cancer risk (53). With regard to fruits and green leafy vegetables, they are rich in a variety of antioxidants, vitamins, minerals, and other bioactive substances (including vitamin C, lycopene, selenium, folate, and flavonoids) that reduce oxidative stress and inflammation, and maintain nucleotide synthesis and methylation, which play an important role in EC prevention (54–56). With respect to green tea, the main active ingredients are polyphenols, with the most common being epigallocatechin gallate and epicatechin (57). Studies have shown that epigallocatechin gallate has significant antitumor effects because it can inhibit the proliferation of cancer cells and promote their apoptosis by reducing the activity of enzymes and hindering signal transduction pathways (58). With regard to zinc, it plays an important role in immune function and transcription and controls cell proliferation, apoptosis, and various signaling pathways, but the exact biological mechanisms leading to the inverse relation between zinc intake and EC risk are not fully understood (59). Although there were no small-study effects or excess significance bias, our results included null values for the 95% PI; the heterogeneity for an association between

fruit intake and EC risk was large; and the numbers of cases for whole grains, green leafy vegetables, green tea, and zinc were all less than 1000. Therefore, more caution should be exercised in interpreting these relations.

We also found positive associations between red meat, processed-meat intake, and EC risk by weak evidence. Several potential mechanisms may underlie the effects of red and processed-meat consumption on EC risk. First, cooked red meat is one of the major sources of carcinogens, such as polycyclic aromatic hydrocarbons, heterocyclic amines, nitrates, and N-nitroso compounds, which are thought to play an important role in the development of EC (60). Second, the practice of cooking red meat at high temperature may lead to the production of heterocyclic amines and polycyclic aromatic hydrocarbons, both of which are thought to increase the risk of cancer in humans (61, 62). Third, processed meat is a source of nitrate and nitrite, thereby increasing the formation of N-nitroso compounds, which are considered animal carcinogens and possible human carcinogens (63, 64).

However, several limitations of this umbrella review should be considered. First, we included studies from published meta-analyses, so individual studies may have been missed if they have not yet been assessed through meta-analyses. Second, we did not perform subgroup analyses (e.g., by sex, age group, or pathological type of EC such as squamous cell carcinoma or adenocarcinoma) due to a lack of subgroup data to grade the quality of evidence for most exposures. Third, since this umbrella review only included observational study data, which often contain recall bias and selection bias, while we can describe and assess the associations, we cannot establish causality, nor can we accurately give an individual's daily dietary intake standard. Fourth, the umbrella review's reliability depends directly on the included meta-analyses and indirectly on the original studies, and it was not possible for us to control for biases in the original study, so further prospective studies are needed to draw firm conclusions.

In conclusion, the findings of this umbrella review emphasize that habitually consuming calcium, whole grains, fruits, green leafy vegetables, green tea, and zinc and reducing alcohol, red meat, and processed-meat intake are associated with a lower risk of EC. Since this umbrella review included only observational study data and some of the associations were graded as weak, caution should be exercised in interpreting these relations.

Acknowledgments

The authors' responsibilities were as follows—ZY and XQ: contributed to the umbrella review design; XQ, GJ, and XZ: conducted the literature search, extracted the data, and conducted the analyses; XQ: wrote the first draft of the manuscript; ZY is the guarantor of the paper; and all authors: contributed to writing and reviewing the manuscript and read and approved the final manuscript.

Data Availability

Data described in the manuscript, code book, and analytic code will be made available upon request.

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