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Narrative Review

Diet and ovarian cancer risk: An umbrella review of systematic reviews and meta-analyses of cohort studies

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SUMMARY

Background & aims: Diet may play an important role in the etiology of ovarian cancer (OC). We aimed to evaluate the strength and credibility of evidence pertaining to dietary risk factors for OC.
Methods: We comprehensively searched PubMed, Web of Science, Cochrane, CINAHL, JBI Database of Systematic Reviews and Implementation Reports, PROSPERO and EMBASE databases to identify related systematic reviews and meta-analyses of prospective cohort studies. This study had been registered at PROSPERO. The registration number is CRD42020187651. For each association, we estimated the summary effect size using fixed and random effects models, the 95% confidence interval and the 95% prediction interval. We assessed heterogeneity, evidence of small-study effects, and excess significance bias.
Results: A total of 22 systematic reviews and meta-analyses were included in the present study. These previous reports evaluated 184 individual studies, which proposed a total of 36 associations between dietary factors and OC risk. Out of the 36 associations, there were no strong, highly suggestive and suggestive evidence, only four (black tea, skim/low-fat milk, lactose, and calcium) were determined to be supported by weak evidence. OC risk was inversely associated with intake of black tea or calcium, and positively associated with intake of skim/low-fat milk or lactose.
Conclusions: Our studies revealed that four associations between OC risk and dietary factors (black tea, skim/low-fat milk, lactose, and calcium) were supported by weak evidence. The remaining 32 associations were not confirmed. Additional studies are needed to carefully evaluate the relationship between dietary factors and OC risk.

1. Introduction

Ovarian cancer (OC) is one of the most severe gynecologic malignancies and the fifth leading cause of death by cancer in women worldwide [1,2]. Globally, 239,000 new cases and 152,000 deaths are reported annually [3]. Recent evidence has demonstrated that many factors contribute to the development of OC, including reproductive factors, the use of exogenous hormones, and BRAC1/2 mutations [4–7]. However, these unmodifiable risk factors do not provide an appropriate avenue to make recommendations for OC prevention in the general population [8].

Diet is a key modifiable risk factor that can be used to make recommendations for the prevention of non-communicable diseases, including cancers [9]. Typical dietary patterns include a combination of multiple diets, composed of numerous nutrients that have synergistic interactions. Hence, to understand the association between diets and OC risk, we must consider food groups, nutrients, and dietary patterns. Furthermore, dietary intake has been demonstrated to play an important role in the etiology of OC

Abbreviations: OC, ovarian cancer; RR, relative risk; CI, confidence interval; PI, prediction interval; SE, standard error; GALT, galactose-1-phosphouridase transferase; NOS, Newcastle–Ottawa Quality Assessment scale.

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[10–12]. Numerous epidemiological studies have been published that investigated the association between dietary factors and OC risk [13–16]. However, to date, there have been no conclusive studies that evaluated both the direction (i.e., increased or reduced risk) and strength of the associations between dietary factors and OC risk [17]. In addition, previous efforts to systematically evaluate data from these studies have focused on exposure to individual dietary factors. To our knowledge, there has been no attempt to summarize the data from existing systematic reviews or from meta-analyses of dietary risk factors in OC. Therefore, to gain a better understanding of the strength of the data and the extent of potential biases in the claimed associations between individual dietary factors and OC risk, we performed an umbrella review of the most recent data in published systematic reviews and meta-analyses. We evaluated any evidence of bias in the findings and identified the most robust associations with the fewest potential biases.

2. Methods

2.1. Search strategy

We strictly conducted the umbrella review following the guidelines [18]. We systematically searched PubMed, Web of Science, Cochrane Database of Systematic Reviews, CINAHL, JBI Database of Systematic Reviews and Implementation Reports, PROSPERO and EMBASE databases for meta-analyses or systematic reviews of observational studies that investigated the association between dietary factors and risk of OC. We included studies published from database inception through May 12, 2020. The search algorithm used the keywords: "(diet OR dietary OR food OR nutrition OR nutritional factors) AND (ovarian cancer OR ovarian carcinoma OR ovarian neoplasms OR ovarian tumor OR ovarian neoplasm OR ovarian mass OR ovarian masses) AND (meta-analysis OR systematic review OR systematic overview)". Subsequently, we performed a manual search of reference lists from the retrieved articles. The protocol of the study was registered on PROSPERO. The registration number is CRD42020187651.

2.2. Selection criteria

Articles were initially screened by reviewing titles and abstracts. The full-texts of potentially eligible articles were then examined by three independent authors (HS, Z-YW and T-TG). Any discrepancies were resolved by a third author (T-TG) who is dedicated to OC and has expertise of clinical epidemiology and evidence-based medicine. The criteria for eligibility were: (1) systematic reviews and meta-analyses of prospective cohort studies on the associations between diet and OC incidence in humans; (2) studies investigating the incidence of OC in different dietary categories or dietary patterns; and (3) studies focusing on the subtypes of OC. If a systematic review or meta-analysis performed a subgroup analysis stratified by the study design (case–control and cohort studies), then the results for cohort studies were included. Meta-analyses of randomized controlled trials were not available for the present study.

We excluded individual studies from eligible systematic reviews or meta-analyses according to the following criteria: (1) studies in which dietary factor was not the exposure of interest and OC incidence was not the outcome of interest (such as OC mortality); and (2) systematic reviews or meta-analyses that did not present study-specific data [risk estimates, 95% confidence intervals (CIs), and numbers of cases/population]; (3) animal studies; (4) non-English articles. We included separate studies of dietary ingredients and dietary patterns. If an article presented separate meta-analyses of more than one eligible dietary factor, each was assessed individually. If the association between dietary factors and OC incidence was evaluated from highest to lowest and a dose–response analysis was used, we included the dose–response analysis [19]. Whenever a meta-analysis included a lower number of component studies compared to other meta-analyses related to the same research question, we chose to include the review with the larger number of studies, since the number of studies was part of our criteria [19].

2.3. Data extraction

Data extraction was performed independently by two authors (HS and Z-YW). In the case of a discrepancy, the final decision was made by a third author (Q-JW). For each eligible article, we recorded the first author, publication year, dietary factor, number of included studies, case number, study population, most adjusted risk estimates (relative risk, odds ratio, hazard ratio, or incident risk ratio), and corresponding 95% CIs. For each primary study from an included systematic review or meta-analysis, the first author, number of cases and subjects, maximally adjusted relative risk, and corresponding 95% CI was extracted for further analysis.

2.4. Assessment of summary effects and heterogeneity

For each meta-analysis, we estimated the summary effect size and its 95% CI using both fixed-effects and random-effects models [20,21]. After taking into account the uncertainty of the estimated summary effect in the random effects model and the heterogeneity between the studies, the 95% prediction interval (PI) was calculated to predict the expected effect size range in the new original studies [22]. For the largest data set of each meta-analysis, we calculated the standard error (SE) of the effect size and determined whether the SE was less than 0.10. We used the I^2 statistic to assess heterogeneity among studies [23]. Where I^2 was beyond 50% or 75%, the heterogeneity was considered to be substantial or considerable, respectively. We also calculated the 95% CI of I^2 to assess the uncertainty around heterogeneity estimates [24].

2.5. Assessment of small-study effects

Egger's regression asymmetry test was performed to identify small-study effects [25]. Although small-study effects can indicate publication bias and other reporting biases, they can also reflect genuine chance, heterogeneity, or other reasons for differences between small and large studies. We calculated the SE of the effect size for the largest study of each meta-analysis to determine whether larger estimates of effect size were predicted by small studies compared to large studies. If the p value for Egger's test was smaller than 0.10 and the largest study had a smaller effect size than the summary effect size, both criteria for the existence of small-study effects were fulfilled [25].

2.6. Evidence of excess significance bias

We used the excess significance test to investigate whether the observed number of studies (O) with nominally significant results ("positive" studies, $p < 0.05$) was larger than the expected number of significant results (E) [26]. In each meta-analysis, E is calculated from the sum of the statistical power estimates for each component study. We used the effect size of the largest study in a meta-analysis to estimate the power of each component study [27]. We calculated the power of each study by using a non-central t distribution [28]. The excess significance test was considered positive for p values < 0.10, given that $O > E$.

2.7. Reviewing the existing evidence

Statistically significant ($p < 0.05$) associations between dietary factors and OC risk were rated into four levels (strong, highly suggestive, suggestive, and weak) using specific criteria. For strong evidence: $p < 10^{-6}$, number of cases >1000, $I^2 < 50\%$, $p < 0.05$ of the largest study in the meta-analysis, 95% PI excludes the null value, absence of small-study effects ($p > 0.1$ for Egger's test), and no excess significance bias ($p > 0.1$). For highly suggestive evidence: $p < 10^{-6}$, number of cases >1000, and $p < 0.05$ of the largest study in the meta-analysis. For suggestive evidence: $p < 10^{-3}$, and number of cases >1000. For weak evidence, the sole criterion was $p < 0.05$ [29]. When p value > 0.05, there was no association.

3. Results

3.1. Literature review

We obtained 999 records from seven electronic databases after the systematic search. After deleting duplicates, 585 records were excluded through browsing titles and abstracts, and 58 were excluded after assessment of the full-text (Fig. 1 and Supplementary Table S1). Ultimately, 22 studies met the inclusion criteria for our study and were included in the final analysis [12,30–50].

3.2. Characteristics of included articles

The characteristics of these 22 studies are shown in Table 1. Among 22 studies, thirteen did not conduct methodological quality assessment for individual studies [12,32–34,37,38,40–42,45–48], only 8 used the Newcastle–Ottawa Quality Assessment scale (NOS) [30,31,35,36,39,43,44,50] and 1 used the Jadad scale for assessment [49]. The included studies covered 36 different associations between dietary factors and OC risk. All articles were published between 2006 and 2020. The number of original prospective cohort studies included in these systematic reviews or meta-analyses ranged from three to 14. The number of participants ranged from 170,327 to 199,6841, and the number of cases ranged from 728 to 5857. All eligible systematic reviews or meta-analyses used summary-level data from published literature and none provided access to individual participant data. Ten of 22 studies focused on 15 food items, including eggs, fish, red meat, processed meat, poultry, cruciferous vegetables, coffee, caffeine, caffeinated coffee, decaffeinated coffee, tea, black tea, alcohol, skim/low-fat milk, and cheese [12,33,41,43,44,46–50]. Twelve of the studies focused on 19 nutrients, including lactose, vitamin A, vitamin C, vitamin E, total fat, animal fat, plant fat, saturated fat, monounsaturated fat, polyunsaturated fat, dairy fat, fiber, nitrate and nitrite, acrylamide, phytoestrogen, lycopene, calcium, and folate [30–32,34,36–40,42,45,48]. One of them focused on two types of dietary patterns, including a healthy pattern and Western-style pattern [35]. Dose–response analyses were carried out for three associations (acrylamide, red meat, and processed meat) [40,47].

3.3. Summary effect size

The meta-analyses of the 36 associations were re-performed using a random-effects model (Table 2). Out of the 36 meta-analyses, the summary fixed-effects and random-effects estimates were significant at $p \leq 0.05$ in four meta-analyses. These included associations with black tea, skim/low-fat milk, lactose, and calcium.

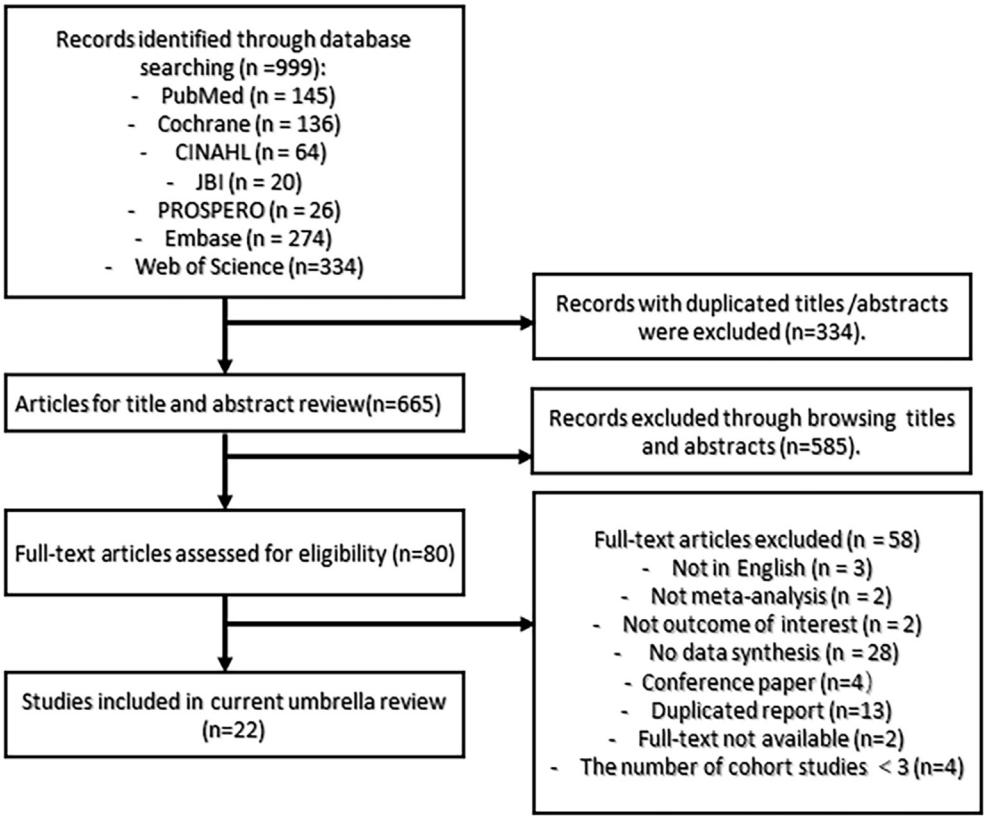

Fig. 1. Flow diagram of the study selection process.

Table 1
Main characteristics of included systematic reviews or meta-analyses that evaluate dietary factors and ovarian cancer risk.

First author (Ref), Year	Dietary factor	No. of studies	No. of cases	No. of population	Original article retrieval time	Comparison	Summary relative risk estimate (95% CI)	Quality Assessment
Wang [30], 2020	Vitamin A	5	1435	430,133	September 1 2019	Highest vs. lowest	0.90 (0.74–1.09)	NOS
Salari [33], 2019	Coffee	13	3927	860,106	October 31 2018	Highest vs. lowest	1.08 (0.89–1.33)	NOS
	Caffeine	5	1443	253,784		Highest vs. lowest	0.91 (0.69–1.19)	
	Caffeinated coffee	5	2384	534,070		Highest vs. lowest	0.98 (0.65–1.49)	
	Decaffeinated coffee	5	2256	534,070		Highest vs. lowest	0.87 (0.67–1.14)	
Long [31], 2019	Vitamin C	5	1435	430,133	May 31 2019	Highest vs. lowest	1.15 (0.93–1.42)	NA
Leng [32], 2019	Vitamin E	4	1155	332,858	June 1 2019	Highest vs. lowest	1.08 (0.83–1.40)	NA
Xu [34], 2018	Dietary fiber	5	1941	548,115	September 30 2017	Highest vs. lowest	0.97 (0.85–1.12)	NA
Wang [35], 2018	Healthy pattern	6	1787	404,714	December 31 2016	Highest vs. lowest	0.95 (0.85–1.06)	NOS
	Western-style pattern	4	752	294,869		Highest vs. lowest	1.09 (0.93–1.28)	
Song [36], 2017	Calcium	5	1726	351,192	April 30 2017	Highest vs. lowest	0.86 (0.74, 0.99)	NOS
Zhan [49], 2017	Tea	7	2277	686,654	April 30 2016	Highest vs. lowest	0.80 (0.62–0.97)	Jadad scale
Xie [37], 2016	Nitrate	3	1126	201,848	April 30 2016	Highest vs. lowest	0.90 (0.54–1.52)	NA
	Nitrite	3	1104	192,451		Highest vs. lowest	0.99 (0.75–1.32)	
Qiu [38], 2016	Total fat	6	2850	745,748	December 31 2015	Highest vs. lowest	1.10 (0.97–1.24)	NA
	Saturated fat	6	2850	745,748		Highest vs. lowest	1.06 (0.89–1.26)	
	Animal fat	5	2570	648,473		Highest vs. lowest	1.09 (0.93–1.28)	
	Plant fat	5	2570	648,473		Highest vs. lowest	0.93 (0.74–1.17)	
	Monounsaturated fat	5	2570	648,473		Highest vs. lowest	1.04 (0.88–1.22)	
	Polyunsaturated fat	5	2570	648,473		Highest vs. lowest	1.06 (0.86–1.31)	
	Dairy fat	5	1728	253,780		Highest vs. lowest	1.10 (0.94–1.28)	
Yan [50], 2015	Alcohol	14	5857	1,996,841	May 31 2014	Highest vs. lowest	1.03 (0.96–1.10)	NOS
Zeng [41], 2015	Egg	6	984	620,121	August 31 2013	Highest vs. lowest	1.20 (0.97–1.48)	NA
Pelucchi [40], 2015	Acrylamide	3	979	212,302	July 31 2014	Per 10 ug/day	1.20 (0.81–1.79)	NA
Qu [39], 2014	Phytoestrogen	4	867	274,896	April 30 2014	Highest vs. lowest	0.77 (0.53–1.10)	NOS
Li [42], 2014	Lycopene	3	2534	668,806	December 31 2013	Highest vs. lowest	0.87 (0.62–1.23)	NA
Jiang [43], 2014	Fish	5	1288	861,267	August 31 2013	Highest vs. lowest	1.04 (0.89–1.22)	NOS
Han [44], 2014	Cruciferous vegetables	5	1379	365,585	December 05 2013	Highest vs. lowest	1.00 (0.85–1.11)	NOS
Li [45], 2013	Folate	4	1158	217,309	December 31 2012	Highest vs. lowest	0.84 (0.61–1.14)	NA
Butler [46], 2011	Black tea	5	1299	203,998	December 31 2010	Highest vs. lowest	0.73 (0.57–0.93)	NA
Wallin [47], 2011	Red meat	7	2272	691,295	January 21 2011	Per 100 g/ week	1.02 (0.99–1.04)	NA
	Processed meat	4	1761	568,673		Per 100 g/ week	1.06 (0.98–1.14)	
Kolahdooz [12], 2010	Poultry	3	953	419,270	November 30 2009	Highest vs. lowest	1.03 (0.84–1.27)	NA
Larsson [48], 2006	Cheese	3	728	170,327	January 31 2005	Highest vs. lowest	1.04 (0.60–1.81)	NA
	Skim/low-fat milk	3	728	170,327		Highest vs. lowest	1.35 (1.09–1.68)	
	Lactose	3	728	170,327		Highest vs. lowest	1.47 (1.17–1.84)	

CI: confidence intervals.
NOS: Newcastle–Ottawa Quality Assessment Scale.
NA: Not available.

When we used $p \leq 0.001$ as a threshold for significance, only one meta-analysis (lactose) produced significant summary results using the random- and fixed-effects methods. Two associations (skim/low-fat milk and lactose) for the highest versus lowest categories showed $p \leq 0.05$ by the random-effects model, suggesting increased OC risk. Additionally, two associations (black tea and calcium) for the highest versus lowest categories showed $p \leq 0.05$ by the random-effects model, suggesting decreased OC risk. The magnitude of the observed summary random effect estimates ranged from 0.73 to 1.47 (Fig. 2). However, after excluding null values of 95% PI, no association was found between diet factors and OC risk (Table 2). The studies with the smallest SE for each association suggested that seven of 36 were significant at $p \leq 0.05$. Most studies (75%, 27/36) showed low heterogeneity ($I^2 \leq 50\%$). Seven (19.4%) meta-analyses had substantial heterogeneity estimates ($I^2 > 50\%$ and $I^2 \leq 75\%$), and two (5.6%) meta-analyses had considerable heterogeneity estimates ($I^2 > 75\%$; Table 2).

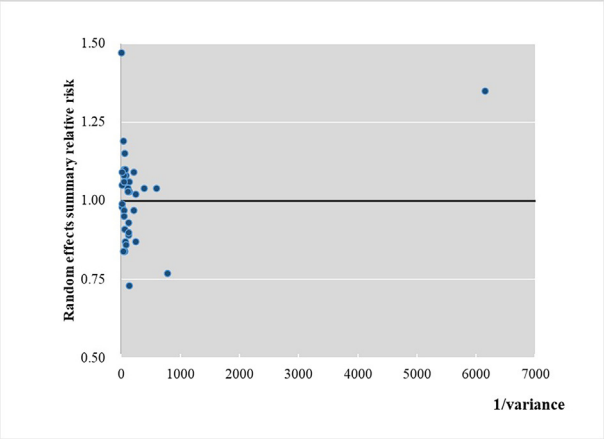

Fig. 2. Association of meta-analysis summary effect sizes with inverse of the variance.

3.4. Small-study effects

With the exception of cheese ($p < 0.10$ with more conservative effects in the larger studies), there was no evidence for the presence of small-study effects according to Egger's test (Table 3). However, only two associations (coffee and alcohol) included 10 or more studies and, therefore, provided enough statistical power for the Egger's test to adequately identify the presence of small-study effects.

3.5. Excess significance

Only lactose association had evidence of excess significance bias using the largest study estimate as the plausible effect size.

Table 2
Description of 36 meta-analyses of diet factors and ovarian cancer risk included in umbrella review.

First author (Ref), Year	Dietary factor	Summary relative risk estimate (95% CI)			Random *p* value[b]	Fixed *p* value[c]	95% PI
		Random effects	Fixed effects	Largest study[a]			
Wang [30], 2020	Vitamin A	0.89 (0.74–1.09)	0.89 (0.74–1.09)	0.86 (0.60–1.23)	0.264	0.264	0.65–1.23
Salari [33], 2019	Coffee	1.08 (0.89–1.33)	1.09 (0.94–1.27)	1.05 (0.75–1.46)	0.439	0.273	0.64–1.83
	Caffeine	0.91 (0.69–1.19)	0.88 (0.74–1.05)	0.80 (0.60–1.07)	0.487	0.143	0.38–2.16
	Caffeinated coffee	0.98 (0.65–1.49)	0.98 (0.82–1.18)	1.05 (0.78–1.39)	0.929	0.871	0.24–4.09
	Decaffeinated coffee	0.87 (0.67–1.14)	0.87 (0.67–1.14)	0.90 (0.61–1.31)	0.311	0.311	0.57–1.34
Long [31], 2019	Vitamin C	1.15 (0.92–1.42)	1.14 (0.94–1.37)	1.07 (0.77–1.48)	0.213	0.180	0.70–1.88
Leng [32], 2019	Vitamin E	1.08 (0.83–1.40)	1.09 (0.89–1.34)	1.52 (1.04–2.21)	0.560	0.405	0.44–2.63
Xu [34], 2018	Dietary fiber	0.97 (0.85–1.12)	0.97 (0.85–1.12)	0.99 (0.83–1.18)	0.709	0.709	0.78–1.22
Wang [35], 2018	Healthy pattern	0.95 (0.85–1.06)	0.95 (0.86–1.04)	0.94 (0.83–1.06)	0.347	0.281	0.78–1.16
	Western-style pattern	1.09 (0.93–1.28)	1.10 (0.95–1.27)	1.22 (0.97–1.55)	0.299	0.203	0.68–1.74
Song [36], 2017	Calcium	0.86 (0.74–0.99)	0.86 (0.74–0.99)	0.86 (0.68–1.10)	0.041	0.041	0.67–1.09
Zhan [49], 2017	Tea	0.84 (0.68–1.03)	0.86 (0.73–1.01)	0.96 (0.70–1.30)	0.093	0.065	0.51–1.38
Xie [37], 2016	Nitrate	0.90 (0.54–1.52)	1.05 (0.85–1.29)	1.31 (1.01–1.68)	0.696	0.665	0.00–411.99
	Nitrite	0.99 (0.75–1.32)	1.02 (0.85–1.21)	1.18 (0.93–1.50)	0.954	0.868	0.05–18.12
Qiu [38], 2016	Total fat	1.10 (0.97–1.24)	1.10 (0.98–1.24)	1.16 (0.96–1.40)	0.125	0.100	0.91–1.34
	Animal fat	1.09 (0.93–1.28)	1.08 (0.95–1.22)	0.96 (0.80–1.15)	0.272	0.227	0.74–1.62
	Plant fat	0.93 (0.74–1.17)	0.99 (0.87–1.13)	1.22 (0.98–1.52)	0.543	0.868	0.45–1.94
	Saturated fat	1.06 (0.89–1.26)	1.08 (0.95–1.23)	1.17 (0.97–1.40)	0.521	0.231	0.69–1.62
	Monounsaturated fat	1.04 (0.88–1.22)	1.04 (0.89–1.22)	1.16 (0.93–1.44)	0.649	0.582	0.77–1.40
	Polyunsaturated fat	1.06 (0.86–1.31)	1.12 (0.98–1.28)	1.22 (1.02–1.48)	0.570	0.096	0.57–1.98
	Dairy fat	1.10 (0.94–1.28)	1.09 (0.95–1.25)	1.01 (0.80–1.27)	0.242	0.235	0.79–1.51
Yan [50], 2015	Alcohol	1.03 (0.96–1.10)	0.97 (0.94–1.00)	0.95 (0.92–0.99)	0.473	0.087	0.86–1.22
Zeng [41], 2015	Egg	1.19 (0.93–1.53)	1.20 (0.97–1.48)	1.19 (0.85–1.67)	0.177	0.087	0.69–2.06
Pelucchi [40], 2015	Acrylamide	1.05 (0.95–1.15)	1.03 (0.97–1.10)	0.97 (0.89–1.05)	0.327	0.286	0.38–2.87
Qu [39], 2014	Phytoestrogen	0.77 (0.53–1.10)	0.84 (0.70–1.00)	1.13 (0.87–1.47)	0.151	0.056	0.17–3.40
Li [42], 2014	Lycopene	0.87 (0.62–1.23)	0.96 (0.84–1.09)	0.97 (0.84–1.12)	0.436	0.498	0.02–36.75
Jiang [43], 2014	Fish	1.04 (0.89–1.22)	1.04 (0.89–1.22)	1.04 (0.83–1.32)	0.600	0.600	0.81–1.34
Han [44], 2014	Cruciferous vegetables	0.97 (0.86–1.11)	0.97 (0.86–1.11)	0.96 (0.80–1.15)	0.697	0.697	0.79–1.20
Li [45], 2013	Folate	0.84 (0.61–1.14)	0.82 (0.65–1.04)	0.76 (0.52–1.12)	0.265	0.100	0.28–2.54
Butler [46], 2011	Black tea	0.73 (0.56–0.93)	0.72 (0.57–0.91)	0.63 (0.40–0.99)	0.012	0.005	0.42–1.24
Wallin [47], 2011	Red meat	1.02 (0.99–1.04)	1.02 (0.99–1.04)	1.02 (0.98–1.06)	0.221	0.221	0.98–1.05
	Processed meat	1.06 (0.98–1.14)	1.06 (0.98–1.14)	1.06 (0.95–1.17)	0.163	0.163	0.89–1.25
Kolahdooz [12], 2010	Poultry	1.03 (0.84–1.27)	1.03 (0.84–1.27)	0.98 (0.73–1.32)	0.766	0.766	0.27–4.02
Larsson [48], 2006	Skim/low-fat milk	1.35 (1.09–1.68)	1.35 (1.09–1.68)	1.32 (0.97–1.82)	0.006	0.006	0.34–5.43
	Cheese	1.04 (0.60–1.81)	0.95 (0.71–1.26)	0.65 (0.43–0.97)	0.884	0.700	0.00–563.84
	Lactose	1.47 (1.17–1.84)	1.47 (1.17–1.84)	1.48 (1.05–2.09)	0.001	0.001	0.34–6.29

PI, prediction interval.
[a] Relative risk and 95% confidence interval of largest study (smallest SE) in each meta-analysis.
[b] *p* value of summary random effects estimate.
[c] *p* value of summary fixed effects estimate.

3.6. Grading the evidence

Out of 36 associations between dietary components and OC risk, four associations (black tea, skim/low-fat milk, lactose, and calcium) was supported by weak evidence. Comparing the highest and lowest consumers, the results showed that consuming black tea and calcium reduced the risk of OC by 17% and 14%, respectively, however, consumption of skim/low-fat milk and lactose increased the risk of OC by 35% and 47%. The remaining 32 associations were not confirmed. The detailed results of the analyses on which the evidence ratings were based are shown in Tables 2 and 3.

4. Discussion

To promote communication between clinicians and patients on the impact of diet on OC risk, we provide a comprehensive overview of reported associations between dietary factors and OC risk by incorporating evidence from systematic reviews with meta-analyses of prospective cohort studies. Overall, we evaluated associations between 36 different dietary factors and OC risk, including 65,971 cancer cases. Four associations (black tea, skim/low-fat milk, lactose, and calcium) were supported by weak evidence. With the detailed evaluation of bias in the literature, our studies revealed that OC risk was inversely associated with black tea and calcium, and positively associated with skim/low-fat milk and lactose.

Our umbrella review of the existing evidence supports an inverse association between OC risk and intake of black tea and calcium, based on two meta-analyses of 10 (total) prospective cohort studies [36,46]. Previous studies have examined the relationship between OC risk and black tea and dietary calcium intake [51,52]. However, while these studies described the association, they failed to fully evaluate potential heterogeneity and bias. Our study demonstrates that some issues remained that needed to be considered before reaching a definitive conclusion in these studies. Although our study included null values of 95% PI, there was no evidence of small-study effects or excess significance bias for black tea and calcium. For these associations, the number of cases exceeded 1000. Compared with previous umbrella reviews that studied associations between risk factors and health outcomes [53,54], this association study failed only one of our criteria, indicating that the presence of bias in this literature may be relatively modest. A previous study showed that black tea is rich in polyphenols, which have been shown to significantly reduce the risk of OC [55]. Tea polyphenols are one of the most beneficial compounds extracted from tea and have been shown to down-regulate tumor gene expression, induce tumor cell apoptosis, remove excess free radicals, and play a role in preventing and inhibiting tumor growth [56,57]. The exact biological mechanisms that allow for the inverse relationship between calcium intake and OC risk are not fully understood. One possible explanation is that high levels of calcium down-regulate circulating parathyroid hormone, which may be negatively correlated with OC risk [58].

Table 3
Evaluation of bias and heterogeneity in 36 meta-analyses of dietary factors and ovarian cancer risk.

First author (Ref), Year	Dietary factor	Egger's *p* value[a]	I^2 (95% CI)[b]	*p* value[b]	Observed[c]	Expected[c]	*p* value[d]
Wang [30], 2020	Vitamin A	0.137	0.0 (0–79)	0.7980	0	0.47	–
Salari [33], 2019	Coffee	0.926	36.6 (0–67)	0.0905	1	2.45	–
	Caffeine	0.371	56.0 (0–84)	0.0586	1	1.47	–
	Caffeinated coffee	0.906	75.9 (41–90)	0.0023	2	2.10	–
	Decaffeinated coffee	0.175	0.0 (0–79)	0.9411	0	0.35	–
Long [31], 2019	Vitamin C	0.389	20.2 (0–66)	0.2863	1	0.88	0.88
Leng [32], 2019	Vitamin E	0.304	35.9 (0–78)	0.1968	1	1.79	–
Xu [34], 2018	Dietary fiber	0.758	0.0 (0–79)	0.5010	0	0.66	–
Wang [35], 2018	Healthy pattern	0.734	10.0 (0–77)	0.3514	0	0.97	–
	Western-style pattern	0.070	17.9 (0–87)	0.3006	0	0.87	–
Song [36], 2017	Calcium	0.623	0.0 (0–79)	0.6145	0	0.57	–
Zhan [49], 2017	Tea	0.280	35.4 (0–73)	0.1579	2	1.66	0.76
Xie [37], 2016	Nitrate	0.434	78.8 (32–93)	0.0089	2	1.28	0.40
	Nitrite	0.810	51.2 (0–86)	0.1287	0	0.85	–
Qiu [38], 2016	Total fat	0.040	4.2 (0–76)	0.3896	1	1.01	–
	Animal fat	0.783	28.4 (0–72)	0.2319	1	1.25	–
	Plant fat	0.173	61.7 (0–86)	0.0336	1	2.02	–
	Saturated fat	0.595	31.9 (0–72)	0.1966	0	1.28	–
	Monounsaturated fat	0.060	4.5 (0–80)	0.3809	0	0.94	–
	Polyunsaturated fat	0.145	49.8 (0–82)	0.0931	1	1.28	–
	Dairy fat	0.167	13.7 (0–82)	0.3263	1	0.93	0.94
Yan [50], 2015	Alcohol	0.110	34.0 (0–65)	0.1027	2	2.99	–
Zeng [41], 2015	Egg	0.589	23.7 (0–68)	0.2563	1	1.09	–
Pelucchi [40], 2015	Acrylamide	0.146	56.8 (0–88)	0.0988	0	1.16	–
Qu [39], 2014	Phytoestrogen	0.430	68.4 (8–89)	0.0234	2	2.00	1.00
Li [42], 2014	Lycopene	0.442	64.3 (0–90)	0.0605	1	0.77	0.76
Jiang [43], 2014	Fish	0.589	0.0 (0–79)	0.8748	0	0.40	–
Han [44], 2014	Cruciferous vegetables	0.397	0.0 (0–79)	0.8990	0	0.38	–
Li [45], 2013	Folate	0.472	40.8 (0–80)	0.1675	0	0.81	–
Butler [46], 2011	Black tea	0.440	15.2 (0–82)	0.3173	2	0.97	0.24
Wallin [47], 2011	Red meat	0.786	0.0 (0–71)	0.9961	0	0.44	–
	Processed meat	0.553	0.0 (0–85)	0.4807	0	0.50	–
Kolahdooz [12], 2010	Poultry	0.186	0.0 (0–90)	0.8065	0	0.23	–
Larsson [48], 2006	Skim/low-fat milk	0.213	0.0 (0–90)	0.6376	0	0.26	–
	Cheese	0.015	70.6 (0–91)	0.0332	1	1.49	–
	Lactose	0.417	0.0 (0–90)	0.9185	1	0.17	0.04

[a] From Egger's regression asymmetry test.
[b] I^2 metric of inconsistency (95% CI) and *p* value of Q test.
[c] Observed and expected number of significant studies using effect of largest study (smallest SE) of each meta-analysis as plausible effect size.
[d] *p* value of excess significance test. All statistical tests two sided.

Our study also indicated that high consumption of skim/low-fat milk and lactose was associated with increased OC risk based on data of two meta-analyses of six (total) prospective cohort studies [48]. A previous meta-analysis based on four cohort and nine case–control studies [59] found no association between low-fat/skim milk intake and OC risk. However, this study did not conduct subgroup analysis according to research type, and we were unable to obtain the results of the prospective study for further analysis. Although there was no evidence of small-study effects or excess significance bias for skim/low-fat milk, our study included null values of 95% PI and the number of cases was less than 1000. Therefore, more caution should be exercised in interpreting the relationship between low-fat milk and OC risk. The mechanisms underlying the positive association between skim/low-fat milk and OC risk remains unclear, and more studies are needed to analyze the underlying biological mechanisms. For lactose, a pooled study of 12 cohort studies, including 553,217 women and 2132 epithelial OC cases assessed the relationship between lactose intake and OC risk [14] and was consistent with our findings. A significantly higher risk of OC was observed with lactose consumption (RR = 1.19, 95% CI, 1.01–1.40) comparing $\geq$ 30 g/day to $\leq$ 10 g/day. Animal models have shown that high dietary galactose causes ovarian toxicity [60]. Hypogonadism or ovarian failure occurs frequently in women with galactosemia due to an autosomal recessive defect of the galactose-1-phosphouridase transferase (GALT) gene [61,62]. Damage to the GALT gene causes the accumulation of galactose and other metabolites in the body, including the ovary [48]. However, the meta-analyses of this outcome had some limitations, including excess significance bias and PIs containing the null value. These biases may degrade the evidence and do not demonstrate cautious or prudent conclusions.

Dietary pattern analysis has emerged in the field of nutritional epidemiology as an alternative way to assess the association between overall diet and disease risk, because it takes into account the complexity of overall diet and can potentially encourage nutritional recommendations [63]. To date, limited systematic reviews and meta-analyses have addressed the role of dietary patterns in the risk of OC. A total of three meta-analyses of the relationship between dietary patterns and OC risk were retrieved in the present umbrella review [35,64,65]. However, two of them included primary studies with fewer than three cohorts [64,65]. Finally, we included only one article that investigated two dietary patterns (a healthy pattern and Western-style pattern), but we failed to detect any association [35]. The lack of association between these two dietary patterns and OC risk is consistent with our findings that many individual components of the dietary patterns, such as alcohol, vegetables, and meat, are not strongly associated with OC risk [12,44,50].

To our knowledge, our study is the first to provide an umbrella review of published systematic reviews and meta-analyses of dietary factors for OC risk. It is also the first to summarize existing data on dietary factors associated with OC risk in prospective cohort studies. According to the assessment results of a series of statistical analyses, we strictly rated the robustness and validity of a total of 36 associations. Firstly, compared to an individual systematic review or meta-analysis, the present study has obvious advantages. As the number of system reviews increases, the logical and appropriate next step is to review existing system reviews in order to compare and contrast the results of individual reviews, thus providing health care decision makers with the evidence they need. The purpose of an umbrella review is to provide an overview of the findings of a particular problem or phenomenon. This is more useful for guidelines and clinical practice when all treatment options need to be considered. Second, we only included systematic reviews or meta-analyses with prospective cohort studies. Information reflecting exposure is collected after a cancer diagnosis, and therefore, recall biases are inevitable and cannot be ignored in case–control studies.

This study also has several limitations that must be considered when interpreting the results. Firstly, there are few prospective cohort studies on diet and OC risk and, with the exception of coffee and alcohol, most of the associations do not include enough studies (i.e., at least 10) to support excess significance tests and Egger's tests for identifying the origin of biases [25]. Secondly, since umbrella reviews are observational studies, their reliability depends directly on the included meta-analyses and indirectly on the original studies. It was not possible for us to control for bias in the original studies. Thirdly, we only assessed dietary factors considered by meta-analyses of observational studies. Therefore, this study may exclude associations with adequate evidence if they have yet to be assessed through meta-analyses of randomized controlled trials or if they have not yet been assessed through meta-analysis at all. For example, Rinninella et al. [66] reviewed randomized controlled trials to assess the impact of nutritional interventions on clinical outcomes in patients with OC. They found that coffee consumption as well as supplementation with fruit and vegetable juice concentrate have been shown to be valid and well-tolerated nutritional strategies to improve clinical outcomes in OC. Lastly, although more than half of meta-analyses did not evaluate the methodological quality of individual articles, we did not appraise the quality of the individual component primary studies as this was beyond the scope of our review.

5. Conclusions

In conclusion, four associations between OC risk and dietary factors (black tea, skim/low-fat milk, lactose, and calcium) were supported by weak evidence. Intake of calcium or black tea was found to reduce the risk of OC, whereas intake of skim/low-fat milk or lactose was found to increase the risk of OC. However, data related to lactose consumption and OC risk presents evidence of excess significance bias. Further studies are needed to better elucidate the association between other dietary factors and OC risk.

Statement of authorship

The authors' contributions are as follows: Wu QJ and Zhao YH contributed to the study design; Sun H and Gong TT conducted the literature search; Sun H and Wen ZY extracted the data and conducted the analyses; Sun H, Gong TT, Xia Y and Zhao LG wrote the first draft of the manuscript and edited the manuscript. All authors read and approved the final manuscript. Sun H and Gong TT contributed equally to this work.

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Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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Appendix A. Supplementary data

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References

[1] Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA A Cancer J Clin 2018;68:394–424.
[2] Mattila JP, Mirandola L, Chiriva-Internati M. Development of a M cell-targeted microparticulate platform, BSK02, for oral immunization against the ovarian cancer antigen, sperm protein 17. J Biomed Mater Res B Appl Biomater 2019;107:29–36.
[3] Lheureux S, Braunstein M, Oza AM. Epithelial ovarian cancer: evolution of management in the era of precision medicine. CA A Cancer J Clin 2019;69:280–304.
[4] Diaz-Zabala HJ, Ortiz AP, Garland L, Jones K, Perez CM, Mora E, et al. A recurrent BRCA2 mutation explains the majority of hereditary breast and ovarian cancer syndrome cases in Puerto Rico. Cancers (Basel) 2018;10.
[5] Udomsinkul P, Triratanachart S, Oranratanaphan S. Risk factors for endometriotic-cyst associated ovarian cancer: a case controlled study. Taiwan J Obstet Gynecol 2020;59:269–74.
[6] Huang T, Townsend MK, Wentzensen N, Trabert B, White E, Arslan AA, et al. Reproductive and hormonal factors and risk of ovarian cancer by tumor dominance: results from the ovarian cancer cohort consortium (OC3). Canc Epidemiol Biomarkers Prev 2020;29:200–7.
[7] Koushik A, Grundy A, Abrahamowicz M, Arseneau J, Gilbert L, Gotlieb WH, et al. Hormonal and reproductive factors and the risk of ovarian cancer. Cancer Causes Control 2017;28:393–403.
[8] Rice MS, Poole EM, Willett WC, Tworoger SS. Adult dietary fat intake and ovarian cancer risk. Int J Canc 2020 May 15;146(10):2757–72. https://doi.org/10.1002/ijc.32635.
[9] Afshin A, Sur PJ, Fay KA, Cornaby L, Ferrara G, Salama JS, et al. Health effects of dietary risks in 195 countries, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 2019;393:1958–72.
[10] Crane TE, Khulpateea BR, Alberts DS, Basen-Engquist K, Thomson CA. Dietary intake and ovarian cancer risk: a systematic review. Canc Epidemiol Biomarkers Prev 2014;23:255–73.
[11] Li D, Hao X, Li J, Wu Z, Chen S, Lin J, et al. Dose-response relation between dietary inflammatory index and human cancer risk: evidence from 44 epidemiologic studies involving 1,082,092 participants. Am J Clin Nutr 2018;107:371–88.
[12] Kolahdooz F, van der Pols JC, Bain CJ, Marks GC, Hughes MC, Whiteman DC, et al. Meat, fish, and ovarian cancer risk: results from 2 Australian case-control studies, a systematic review, and meta-analysis. Am J Clin Nutr 2010;91:1752–63.
[13] Silvera SA, Jain M, Howe GR, Miller AB, Rohan TE. Intake of coffee and tea and risk of ovarian cancer: a prospective cohort study. Nutr Canc 2007;58:22–7.
[14] Genkinger JM, Hunter DJ, Spiegelman D, Anderson KE, Beeson WL, Buring JE, et al. A pooled analysis of 12 cohort studies of dietary fat, cholesterol and egg intake and ovarian cancer. Cancer Causes Control 2006;17:273–85.
[15] Gilsing AM, Weijenberg MP, Goldbohm RA, van den Brandt PA, Schouten LJ. Consumption of dietary fat and meat and risk of ovarian cancer in The Netherlands Cohort Study. Am J Clin Nutr 2011;93:118–26.
[16] Schulz M, Nothlings U, Allen N, Onland-Moret NC, Agnoli C, Engeset D, et al. No association of consumption of animal foods with risk of ovarian cancer. Canc Epidemiol Biomarkers Prev 2007;16:852–5.
[17] World Cancer Research Fund/American Institute for Cancer Research. Continuous update Project expert report 2018. Diet, nutrition, physical and ovarian cancer. access date: atdietandcancerreport.org. [Accessed 10 April 2020].
[18] Aromataris E, Fernandez R, Godfrey CM, Holly C, Khalil H, Tungpunkom P. Summarizing systematic reviews: methodological development, conduct and reporting of an umbrella review approach. Int J Evid Base Healthc 2015;13:132–40.
[19] Kwok CS, Gulati M, Michos ED, Potts J, Wu P, Watson L, et al. Dietary components and risk of cardiovascular disease and all-cause mortality: a review of evidence from meta-analyses. Eur J Prev Cardiol 2019;26:1415–29.
[20] Lau J, Ioannidis JP, Schmid CH. Quantitative synthesis in systematic reviews. Ann Intern Med 1997;127:820–6.
[21] Chinn S. A simple method for converting an odds ratio to effect size for use in meta-analysis. Stat Med 2000;19:3127–31.
[22] Riley RD, Higgins JP, Deeks JJ. Interpretation of random effects meta-analyses. BMJ 2011;342:d549.
[23] Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002;21:1539–58.
[24] Ioannidis JP, Patsopoulos NA, Evangelou E. Uncertainty in heterogeneity estimates in meta-analyses. BMJ 2007;335:914–6.
[25] Sterne JA, Sutton AJ, Ioannidis JP, Terrin N, Jones DR, Lau J, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. BMJ 2011;343:d4002.
[26] Ioannidis JP, Trikalinos TA. An exploratory test for an excess of significant findings. Clin Trials 2007;4:245–53.
[27] Ioannidis JPA. Clarifications on the application and interpretation of the test for excess significance and its extensions. J Math Psychol 2013;57:184–7.
[28] Lubin JH, Gail MH. On power and sample size for studying features of the relative odds of disease. Am J Epidemiol 1990;131:552–66.
[29] Kalliala I, Markozannes G, Gunter MJ, Paraskevaidis E, Gabra H, Mitra A, et al. Obesity and gynaecological and obstetric conditions: umbrella review of the literature. BMJ 2017;359:j4511.
[30] Wang Q, He C. Dietary vitamin A intake and the risk of ovarian cancer: a meta-analysis. Biosci Rep 2020:40.
[31] Long Y, Fei H, Xu S, Wen J, Ye L, Su Z. Association about dietary vitamin C intake on the risk of ovarian cancer: a meta-analysis. Biosci Rep 2020 Aug 28;40(8):BSR20192385. https://doi.org/10.1042/BSR20192385.
[32] Leng Y, Zhou H, Meng F, Tian T, Xu J, Yan F. Association of vitamin E on the risk of ovarian cancer: a meta-analysis. Biosci Rep 2019;39.
[33] Salari-Moghaddam A, Milajerdi A, Surkan PJ, Larijani B, Esmaillzadeh A. Caffeine, type of coffee, and risk of ovarian cancer: a dose-response meta-analysis of prospective studies. J Clin Endocrinol Metab 2019;104:5349–59.
[34] Xu H, Ding Y, Xin X, Wang W, Zhang D. Dietary fiber intake is associated with a reduced risk of ovarian cancer: a dose-response meta-analysis. Nutr Res 2018;57:1–11.
[35] Wang HF, Yao AL, Sun YY, Zhang AH. Empirically derived dietary patterns and ovarian cancer risk: a meta-analysis. Eur J Canc Prev 2018;27:493–501.
[36] Song X, Li Z, Ji X, Zhang D. Calcium intake and the risk of ovarian cancer: a meta-analysis. Nutrients 2017;9.
[37] Xie L, Mo M, Jia HX, Liang F, Yuan J, Zhu J. Association between dietary nitrate and nitrite intake and sitespecific cancer risk: evidence from observational studies. Oncotarget 2016;7:56915–32.
[38] Qiu W, Lu H, Qi Y, Wang X. Dietary fat intake and ovarian cancer risk: a meta-analysis of epidemiological studies. Oncotarget 2016;7:37390–406.
[39] Qu XL, Fang Y, Zhang M, Zhang YZ. Phytoestrogen intake and risk of ovarian cancer: a meta- analysis of 10 observational studies. Asian Pac J Cancer Prev 2014;15:9085–91.
[40] Pelucchi C, Bosetti C, Galeone C, La Vecchia C. Dietary acrylamide and cancer risk: an updated meta-analysis. Int J Canc 2015;136:2912–22.
[41] Zeng ST, Guo L, Liu SK, Wang DH, Xi J, Huang P, et al. Egg consumption is associated with increased risk of ovarian cancer: evidence from a meta-analysis of observational studies. Clin Nutr 2015;34:635–41.
[42] Li X, Xu J. Meta-analysis of the association between dietary lycopene intake and ovarian cancer risk in postmenopausal women. Sci Rep 2014;4:4885.
[43] Jiang PY, Jiang ZB, Shen KX, Yue Y. Fish intake and ovarian cancer risk: a meta-analysis of 15 case-control and cohort studies. PloS One 2014;9:e94601.
[44] Han B, Li X, Yu T. Cruciferous vegetables consumption and the risk of ovarian cancer: a meta-analysis of observational studies. Diagn Pathol 2014;9:7.
[45] Li C, Chen P, Hu P, Li M, Li X, Guo H, et al. Folate intake and MTHFR polymorphism C677T is not associated with ovarian cancer risk: evidence from the meta-analysis. Mol Biol Rep 2013;40:6547–60.
[46] Butler LM, Wu AH. Green and black tea in relation to gynecologic cancers. Mol Nutr Food Res 2011;55:931–40.
[47] Wallin A, Orsini N, Wolk A. Red and processed meat consumption and risk of ovarian cancer: a dose-response meta-analysis of prospective studies. Br J Canc 2011;104:1196–201.
[48] Larsson SC, Orsini N, Wolk A. Milk, milk products and lactose intake and ovarian cancer risk: a meta-analysis of epidemiological studies. Int J Canc 2006;118:431–41.
[49] Zhan X, Wang J, Pan S, Lu C. Tea consumption and the risk of ovarian cancer: a meta-analysis of epidemiological studies. Oncotarget 2017;8:37796–806.
[50] Yan-Hong H, Jing L, Hong L, Shan-Shan H, Yan L, Ju L. Association between alcohol consumption and the risk of ovarian cancer: a meta-analysis of prospective observational studies. BMC Publ Health 2015;15.
[51] Steevens J, Schouten LJ, Verhage BA, Goldbohm RA, van den Brandt PA. Tea and coffee drinking and ovarian cancer risk: results from The Netherlands Cohort Study and a meta-analysis. Br J Canc 2007;97:1291–4.
[52] Liao MQ, Gao XP, Yu XX, Zeng YF, Li SN, Naicker N, et al. Effects of dairy products, calcium, and vitamin D on ovarian cancer risk: a meta-analysis of 29 epidemiological studies. Br J Nutr 2020:1–28.
[53] Belbasis L, Savvidou MD, Kanu C, Evangelou E, Tzoulaki I. Birth weight in relation to health and disease in later life: an umbrella review of systematic reviews and meta-analyses. BMC Med 2016;14:147.
[54] Kyrgiou M, Kalliala I, Markozannes G, Gunter MJ, Paraskevaidis E, Gabra H, et al. Adiposity and cancer at major anatomical sites: umbrella review of the literature. BMJ 2017;356:j477.
[55] Gao Y, Rankin GO, Tu Y, Chen YC. Inhibitory effects of the four Main theaflavin derivatives found in black tea on ovarian cancer cells. Anticancer Res 2016;36:643–51.

[56] Beltz LA, Bayer DK, Moss AL, Simet IM. Mechanisms of cancer prevention by green and black tea polyphenols. Anticanc Agents Med Chem 2006;6:389–406.
[57] Mandel SA, Weinreb O, Amit T, Youdim MB. Molecular mechanisms of the neuroprotective/neurorescue action of multi-target green tea polyphenols. Front Biosci (Schol Ed) 2012;4:581–98.
[58] Goodman MT, Wu AH, Tung KH, Mcduffie K, Cramer DW, Wilkens LR, et al. Association of galactose-1-phosphate uridyltransferase activity and N314D genotype with the risk of ovarian cancer. Am J Epidemiol 2002;156:693–701.
[59] Liu J, Tang W, Sang L, Dai X, Wei D, Luo Y, et al. Milk, yogurt, and lactose intake and ovarian cancer risk: a meta-analysis. Nutr Canc 2015;67:68–72.
[60] Swartz WJ, Mattison DR. Galactose inhibition of ovulation in mice. Fertil Steril 1988;49:522–6.
[61] Kaufman FR, Kogut MD, Donnell GN, Goebelsmann U, March C, Koch R. Hypergonadotropic hypogonadism in female patients with galactosemia. N Engl J Med 1981;304:994–8.
[62] Kaufman FR, Xu YK, Ng WG, Donnell GN. Correlation of ovarian function with galactose-1-phosphate uridyl transferase levels in galactosemia. J Pediatr 1988;112:754–6.
[63] Hu FB. Dietary pattern analysis: a new direction in nutritional epidemiology. Curr Opin Lipidol 2002;13:3–9.
[64] Alizadeh S, Djafarian K, Alizadeh M, Shab-Bidar S. The relation of healthy and Western dietary patterns to the risk of endometrial and ovarian cancers: a systematic review and meta-analysis. Int J Vitam Nutr Res 2019:1–11.
[65] Grosso G, Bella F, Godos J, Sciacca S, Del RD, Ray S, et al. Possible role of diet in cancer: systematic review and multiple meta-analyses of dietary patterns, lifestyle factors, and cancer risk. Nutr Rev 2017;75:405–19.
[66] Rinninella E, Fagotti A, Cintoni M, Raoul P, Scaletta G, Quagliozzi L, et al. Nutritional interventions to improve clinical outcomes in ovarian cancer: a systematic review of randomized controlled trials. Nutrients 2019;11.