Meta-Analysis

Journal of INTERNATIONAL MEDICAL RESEARCH

Journal of International Medical Research
2018, Vol. 46(10) 3995–4005

DOI: 10.1177/0300060518792801
journals.sagepub.com/home/imr
SAGE

Association between dietary fiber intake and risk of ovarian cancer: a meta-analysis of observational studies

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Abstract

Objective: To evaluate the associations between dietary fiber intake and ovarian cancer risk.
Methods: A literature survey was conducted by searching the PubMed, Web of Science, and Wanfang Med Online databases up to March 1st, 2018. The effect of dietary fiber intake on ovarian cancer risk was evaluated by calculating relative risks with 95% confidence intervals (95% CI) using Stata 12.0 software.
Results: A total of 17 articles with 149,177 participants including 7609 ovarian cancer patients were included in this analysis. The summarized relative risk for ovarian cancer in participants with the highest compared with the lowest fiber intake was 0.760 (95%CI=0.702–0.823), with no significant between-study heterogeneity (I^2=12.4%). Subgroup analysis according to study design demonstrated positive associations in both cohort studies and case-control studies. Moreover, the results were consistent among populations from America, Europe, and Asia. No publication bias was found by Egger's test or funnel plots.
Conclusion: This meta-analysis concluded that a high intake of dietary fiber could significantly reduce the risk of ovarian cancer compared with a low fiber intake.

Keywords

Diet, fiber intake, ovarian cancer, meta-analysis, cancer risk, observational studies

Date received: 11 June 2018; accepted: 13 July 2018

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Introduction

Ovarian cancer is the leading cause of death from gynecological cancers worldwide. It often remains undiagnosed until a late stage, by which time it may have spread throughout the abdominal cavity.[1,2] There were an estimated 22,240 new cases of ovarian cancer and 14,030 new deaths in 2013.[3] Despite continuous advances in ovarian cancer research and in its diagnosis and clinical treatment during the past 30 years, a cost-effective screening strategy that could significantly increase the survival rate of patients with early-stage ovarian cancer remains elusive.[4] Furthermore, although the disease has a major impact on public health, its etiology is still poorly understood.

A previous review that explored the association between dietary intake and ovarian cancer risk[5] found no relationship between ovarian cancer and dietary fiber intake. However, the authors only included one study on the effects of dietary fiber intake on ovarian cancer risk, though numerous observational studies assessing this association have now been published. Nevertheless, the effect of dietary fiber intake on ovarian cancer risk remains controversial. To address this question, we performed a comprehensive meta-analysis to reflect the current evidence on the subject.

Materials and methods

Publication search

We identified potentially eligible articles by performing a comprehensive literature search of Web of Science, PubMed, and Wanfang Med Online, up to March 1st, 2018, using the following keywords: 'fiber' OR 'nutrient' OR 'carbohydrates' AND 'ovarian cancer' OR 'ovarian tumor'. We also examined the relevant references to acquire the most comprehensive studies. Two investigators searched the databases independently, and any disagreements between the two investigators were resolved by discussion.

Inclusion criteria

The inclusion criteria for studies in this meta-analysis were: (1) observational studies; (2) studies investigating the association between dietary fiber intake and risk of ovarian cancer; (3) reported odds ratio (OR) or relative risk (RR) with corresponding 95% confidence intervals (CI); (4) studies on humans; and (5) studies published in English or Chinese.

Data extraction

Two investigators screened the potentially relevant studies and extracted the following data: first author's name; publication year; geographic areas; source of controls, cases, and participants; fiber type; mean age or age range; RR with 95%CI for the association between dietary fiber intake and risk of ovarian cancer; adjustment for covariates. Different data from the two investigators were discussed to reach an agreement.

Statistical analysis

The RR (95%CI) of ovarian cancer between the highest level of dietary fiber intake compared with the lowest level in each study was generated.[6] Heterogeneity was evaluated with the I^2 statistic,[7] and defined as low ($I^2<25\%$), moderate ($I^2=25\%–50\%$), or high ($I^2>50\%$).[8] The analysis was carried out using a random effects model. Sensitivity analysis was used to evaluate the potential effects of individual studies on the overall results, by removing one study at a time. Potential publication bias was examined by Egger's test[9] and Begg's funnel plots.[10] All statistical analyses were carried out using Stata version 12 (StataCorp LP, College Station,

TX, USA), and a P-value <0.05 was considered significant.

Results

Research characteristics

A total of 2784 publications were identified that assessed the relationship between dietary fiber intake and ovarian cancer. We first reviewed the titles and abstracts for each retrieved document, and read the full articles if it was not possible to judge the eligibility of the article from the title or abstract. A total of 17 studies[11–27] met our inclusion criteria and were analyzed in this study. The publication years of the included studies ranged from 1983 to 2017. The detailed screening process is shown as a flow chart in Figure 1. Finally, 149,177 participants including 7609 ovarian cancer patients were included in the current study. Four studies were cohort studies and the remaining 13 were case-control studies. Ten studies were from the United States, four from Europe, and three from Asia. The main characteristics of the 17 articles are listed in Table 1.

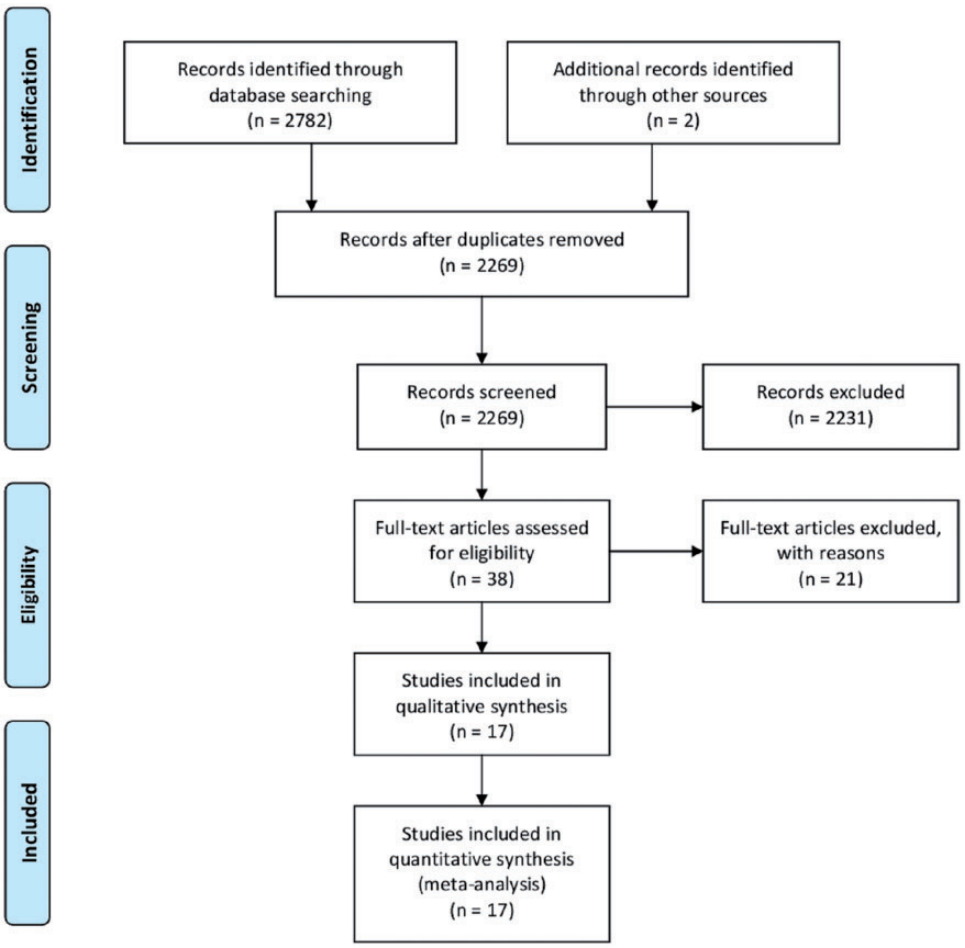

Figure 1. Study selection process for this meta-analysis.

Table 1. Characteristics of the included studies examining the association between dietary fiber intake and ovarian cancer risk.

Study, year [reference]	Design	Age (yr)	Participants, cases	Country	Fiber type	OR/RR (95%CI) highest vs. lowest	Adjustment
Byers et al., 1983 [11]	HCC	30–79	1034, 274	United States	Total fiber	OR=0.77 (0.56–1.98)	Adjusted for age
Edefonti et al., 2008 [12]	HCC	18–79	4444, 1031	Italy	Total fiber	OR=0.77 (0.61–0.98)	Adjusted for age, education, parity, menopausal status, geographic area, BMI, history of female cancers, history of digestive cancers, energy intake
Hedelin et al., 2011 [23]	Cohort	30–49	47,140, 163	Sweden	Total fiber Cereal fiber Vegetable fiber	RR=0.82 (0.50–1.35) RR=1.17 (0.74–1.87) RR=1.02 (0.63–1.64)	Adjusted for age, oral contraceptives, age at menarche, parity, hormone replacement therapy, total energy intake, intake of alcohol, saturated fat, meat, and fish
Kushi et al., 1999 [24]	Cohort	55–69	29,083, 139	United States	Total fiber	RR=1.01 (0.61–1.68)	Adjusted for age, total energy intake, number of live births, age at menopause, family history of ovarian cancer in a first-degree relative, hysterectomy/unilateral oophorectomy status, waist-to-hip ratio, level of physical activity, cigarette smoking (number of pack-years), and educational level
McCann et al., 2001 [13]	HCC	20–87	1921, 496	United States	Total fiber	OR=0.57 (0.38–0.87)	Adjusted for age, education, region of residence, regularity of menstruation, family history of ovarian cancer, parity, age at menarche, oral contraceptive use, and total energy intake
McCann et al., 2003 [14]	PCC	40–85	820, 124	United States	Total fiber	OR=0.43 (0.20–0.94)	Adjusted for age, education, total months menstruating, difficulty becoming pregnant, oral contraceptive use (ever/never), menopausal status, and total energy
Nagle et al., 2011 [15]	PCC	18–79	2780, 1366	Australia	Total fiber	OR=0.78 (0.62–0.98)	Adjusted for age, oral contraceptive use, level of post-school education parity, BMI, menopausal status, and energy intake
Pan et al., 2004 [16]	PCC	20–76	2577, 442	Canada	Total fiber	OR=0.91 (0.66–1.25)	Adjusted for 10-year age group, province of residence, education, alcohol consumption, cigarette pack-years, BMI, total caloric intake, recreational physical activity, number of live births, menstruation years, and menopause status

(continued)

Table 1. Continued

Study, year [reference]	Design	Age (yr)	Participants, cases	Country	Fiber type	OR/RR (95%CI) highest vs. lowest	Adjustment
Pelucchi et al., 2001 [17]	HCC	18–79	3442, 1031	Italy	Total fiber Insoluble fiber Vegetable fiber Fruit fiber Cereal fiber	OR=0.68 (0.53–0.88) OR=0.70 (0.54–0.89) OR=0.59 (0.46–0.77) OR=0.96 (0.75–1.22) OR=1.32 (1.03–1.71)	Adjusted for age, center, education, occupational physical activity, parity, oral contraceptive use, family history of ovarian and/or breast cancer in first-degree relatives, menopausal status, and total energy intake
Playdon et al., 2017 [25]	Cohort	18–79	1709, 811	Australia	Total fiber	RR=0.69 (0.53–0.9)	Adjusted for age at diagnosis, International Federation of Gynaecology and Obstetrics (FIGO) stage, amount of residual disease, grade, tumor subtype, smoking status, BMI, physical activity index, and daily caloric intake
Qin et al., 2016 [18]	PCC	20–79	1015, 406	United States	Total fiber	OR=0.79 (0.53–1.17)	Adjusted for age, education, region, total energy intake, parity, oral contraceptive use, menopause status, tubal ligation, and family history of breast/ovarian cancer (first-degree relative); for added sugars, model additional adjusted for vegetable intake; for fiber, model additional adjusted for alcohol consumption
Risch et al., 1994 [19]	PCC	35–79	1014, 450	Canada	Total fiber Vegetable fiber Fruit fiber Cereal fiber	OR=0.82 (0.71–0.94) OR=0.63 (0.49–0.8) OR=1.03 (0.75–1.43) OR=0.88 (0.70–1.10)	Adjusted for age at diagnosis/interview and the continuous variables age, total daily calorie intake, number of full-term pregnancies, and total duration of oral contraceptive use; each line in this table represents two individual models
Salazar-Martinez et al., 2002 [20]	HCC	20–79	713, 84	Mexico	Total fiber Insoluble fiber Vegetable fiber Fruit fiber Cereal fiber	OR=1.15 (0.65–2.05) OR=0.72 (0.47–1.10) OR=0.94 (0.63–1.40) OR=0.76 (0.51–1.12) OR=1.09 (0.71–1.70)	Adjusted for age, total energy intake, number of live births, recent changes in weight, physical activity, and diabetes
Silvera et al., 2007 [26]	Cohort	40–59	49,613, 264	Canada	Total fiber	RR=0.77 (0.52–1.14)	Adjusted for age, BMI (kg/m^2), alcohol, use of hormone replacement therapy, use of oral contraceptives, parity, age at menarche, menopausal status at baseline, total energy intake, participation in vigorous physical activity, study center, and treatment allocation

(continued)

Table 1. Continued

Study, year [reference]	Design	Age (yr)	Participants, cases	Country	Fiber type	OR/RR (95%CI) highest vs. lowest	Adjustment
Slattery et al., 1989 [21]	PCC	20–79	577, 85	United States	Total fiber	OR=0.8 (0.5–1.5)	Adjusted for age, BMI (weight/height^2), and number of pregnancies. All dietary variables are in separate logistic models
Tzonou et al., 1993 [22]	HCC	18–75	389, 189	Greece	Total fiber	OR=0.76 (0.64–0.9)	Adjusted for age, years of schooling, parity, age at first birth, menopausal status as well as for energy intake
Zhang et al., 2004 [27]	HCC	18–75	906, 254	China	Insoluble fiber	OR=0.36 (0.21–0.62)	Adjusted for age, locality, education, family income, BMI, total energy intake, tobacco smoking, alcohol consumption, ovarian cancer in first-degree relatives, parity, menopausal status, and oral contraceptive use

OR: odds ratio; RR: relative risk; CI: confidence intervals; HCC: hospital-based case-control study; PCC: population-based case-control study; BMI: body mass index.

Meta-analysis results

Analysis of the primary pooled statistics revealed that the highest category of dietary fiber intake was associated with a significantly reduced risk of ovarian cancer compared with the lowest category (summarized RR=0.760, 95%CI=0.702–0.823, $P<0.001$), with no evidence of significant between-study heterogeneity ($I^2=12.4\%$, $P=0.309$) (Figure 2).

In the analysis stratified by study design, the association between dietary fiber intake and ovarian cancer risk was significant in both case-control studies (RR=0.753, 95%CI=0.682–0.832) and cohort studies (RR=0.763, 95%CI=0.633–0.920) (Figure 2). Among the case-control studies, six were population-based case-control (PCC) studies and the other seven were hospital-based case-control (HCC) studies. The results suggested positive associations in PCC and HCC studies. Subgroup analysis according to geographic location revealed decreased risks of ovarian cancer in individuals with the highest compared with the lowest levels of fiber intake among European (RR=0.748, 95% CI=0.664–0.841), American (RR=0.809, 95%CI=0.730–0.897), and Asian populations (RR=0.630, 95%CI=0.452–0.879). Subgroup analysis according to fiber type showed inverse associations between dietary insoluble fiber and vegetable fiber intake and ovarian cancer risk, but no associations between cereal and fruit fiber intake and ovarian cancer risk. The detailed results are shown in Table 2.

Sensitivity analysis and publication bias analysis

Sensitivity analysis (Figure 3) showed that no single study affected the overall result, when studies were removed one at a time. Begg's funnel plots (Figure 4) and Egger's

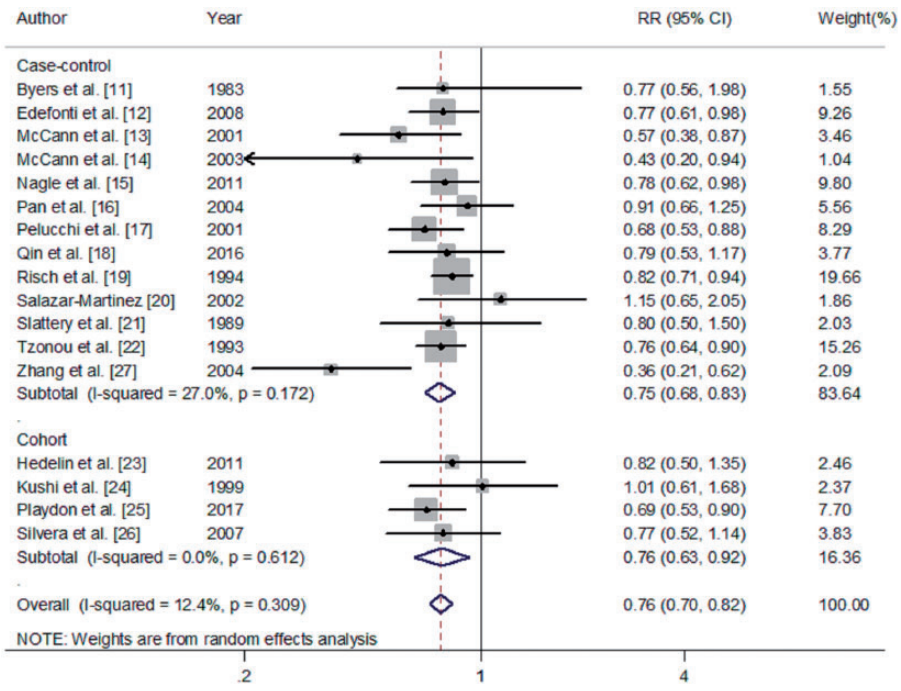

Figure 2. Forest plot for assessment of association between dietary fiber intake and risk of ovarian cancer.

Table 2. Summary RR and 95%CI for the association between dietary fiber intake and ovarian cancer risk.

Subgroup	Number of studies	Number of cases	RR	95% CI	*P* for trend	Heterogeneity test	
						I^2 (%)	*P*
Overall	17	7609	0.760	0.702–0.823	<0.001	12.4	0.309
Fiber type							
Cereal	4	1908	1.088	0.872–1.356	0.455	47.0	0.129
Fruit	3	1745	0.936	0.786–1.114	0.457	0.0	0.483
Insoluble	3	1549	0.599	0.416–0.862	0.006	61.0	0.077
Vegetable	4	1908	0.728	0.569–0.931	0.011	56.0	0.078
Study design							
Cohort	4	1377	0.763	0.633–0.920	0.005	0.0	0.612
Case-control	13	6232	0.753	0.682–0.832	<0.001	27.0	0.172
PCC	6	2873	0.808	0.728–0.897	<0.001	0.0	0.664
HCC	7	3359	0.701	0.591–0.832	<0.001	45.5	0.088
Geographic location							
Europe	4	2414	0.748	0.664–0.841	<0.001	0.0	0.858
America	10	2764	0.809	0.730–0.897	<0.001	0.0	0.520
Asia	3	2431	0.630	0.452–0.879	0.007	69.9	0.036

RR: relative risk; CI: confidence interval; PCC: population-based case-control study; HCC: hospital-based case-control study.

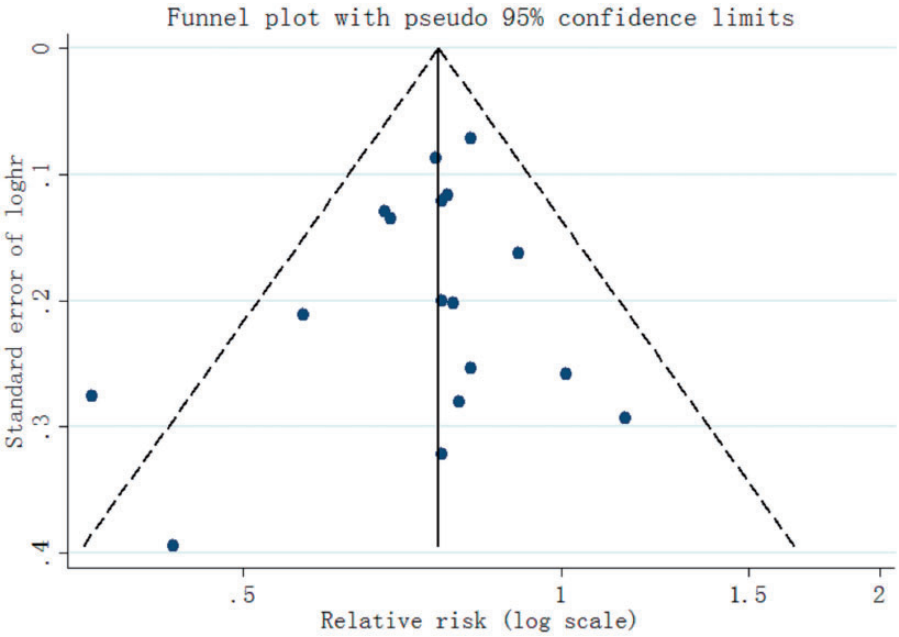

Figure 3. Funnel plot for assessment of publication bias.

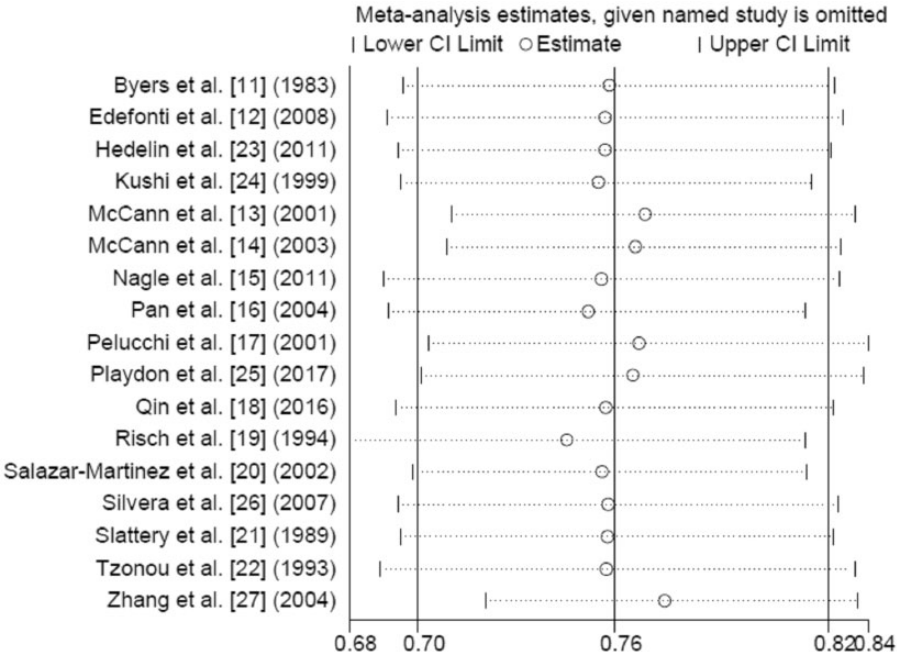

Figure 4. Sensitivity analysis of the association between dietary fiber intake and ovarian cancer risk.

test (P=0.351) indicated that there was no publication bias in the overall analysis.

Discussion

The results of this meta-analysis suggested that the highest category of dietary fiber intake could significantly reduce the risk of ovarian cancer compared with the lowest intake. This association was significant in case-control and in cohort studies, and in populations from the United States, Europe, and Asia.

Previous studies confirmed that increased in dietary fiber intake was associated with lower serum estrogen levels and decreased availability of steroid hormones.[28,29] Given that serum estrogen has been shown to stimulate ovarian epithelial cell proliferation and promote ovarian tumor progression,[30] it seems reasonable that dietary fiber intake may thus also be inversely associated with ovarian cancer risk. Moreover, high dietary fiber intake is characteristic of diets high in whole grains, which contain other compounds, including phenolic compounds and antioxidants, which may also lower the risk of cancer in general.[31] High dietary fiber intake may also be a sign of a generally 'healthier' dietary pattern and lifestyle, including other factors that are less related to ovarian cancer, such as increased vegetable consumption,[32,33] lower fat intake,[34] and increased physical activity.[35,36] A previous meta-analysis also indicated that high dietary fiber intake was inversely associated with colorectal cancer risk,[37,38] all-cause mortality,[39] pancreatic cancer,[40] gastric cancer,[41] breast cancer,[42,43] renal cell carcinoma,[44] and endometrial cancer.[45] All these findings were consistent with our current results.

The current meta-analysis had several important strengths. First, it included a large numbers of cases and participants, thus yielding a more comprehensive result. Second, there was no between-study heterogeneity in the analysis and no single study affected the overall result, which also implied that the results were robust. Third, no bias was detected by Begg's funnel plots or Egger's test.

However, the study also had some limitations. First, we only searched for and included openly published articles, and unpublished articles or gray literature which might have met our inclusion criteria could have been missed. Second, 13 of the included studies were case-control studies, in which it was difficult for patients to report their pre-illness diet, potentially leading to recall bias. Although the overall analysis included different kinds of studies, we carried out subgroup analysis and showed that both cohort studies and case-control studies demonstrated a significant relationship between dietary fiber intake and ovarian cancer risk. Third, ovarian cancer is a complex disease with a variety of causative factors, including environmental and genetic factors. Although we extracted the RR and 95%CI adjusted for most covariates, some possible influencing factors were not adjusted for in some studies.

In summary, this meta-analysis concluded that the highest category of dietary fiber intake could significantly reduce the risk of ovarian cancer compared with the lowest fiber intake, suggesting that the consumption of dietary fiber could prevent the development of ovarian cancer.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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