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Meta-analyses

Egg consumption is associated with increased risk of ovarian cancer: Evidence from a meta-analysis of observational studies

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SUMMARY

Background: The findings of epidemiologic studies on the association between egg consumption and ovarian cancer risk remain conflicting. The aim of this meta-analysis was to investigate whether an association exists between egg intake and ovarian cancer risk in epidemiologic studies.
Methods: A literature search was carried out using PUBMED, EMBASE, and Cochrane Library Central database for all medical literature published in English-language journals up to August 2013. Before meta-analysis, between-study heterogeneity and publication bias were assessed using adequate statistical tests. Fixed-effect and random-effect models were used to estimate summary relative risks (RR) and the corresponding 95% confidence intervals (CIs). Subgroup analyses and sensitivity analysis were also performed.
Results: A total of 12 eligible studies (six case-control studies and six cohort studies) were included, involving 629,453 subjects and 3728 ovarian cancer cases. We found that high egg intake (comparing the highest with the lowest category) was associated with a significant increased risk of ovarian cancer (RR = 1.21, 95% CI [1.06, 1.38]). When we examined whether the associations differed by study type, statistically significant effect of egg intake on ovarian cancer was observed among case-control studies (RR = 1.22, 95% CI [1.03, 1.43]), but not among cohort studies (RR = 1.20, 95% CI [0.97, 1.48]).
Conclusions: Our findings suggest that egg consumption may increase ovarian cancer risk. Additional studies, especially large prospective cohort studies, are warranted to confirm the findings.

1. Introduction

Ovarian cancer is the sixth leading cause of cancer and the seventh most common cause of cancer death among women worldwide, however, the rates vary substantially by country [1]. The majority of cases are diagnosed with ovarian cancer at later stages [2]. Due to the current lack of availability of good screening methods for ovarian cancer and low survival rates among women diagnosed with disease at an advanced stage [3], identification of potentially modifiable factors contributing to its cause may help reduce the burden of this disease. Although the associations between oral contraceptive use, parity, and family history and ovarian cancer risk are well defined [4,5], the role of other factors, such as diet, remains controversial.

The association between egg consumption and ovarian cancer risk has received much attention since 1980s. Several observational studies had examined the impact of egg consumption on the development of ovarian cancer [6–17], however, their findings were controversial. The possible mechanism that may explain a possible detrimental effect of egg intake upon ovarian cancer risk involves the high cholesterol content of eggs, which could increase the formation of secondary bile acids in both humans and animals [18,19]. Previous meta-analyses have investigated the association between egg intake and the risk of several cancers [20–24]. However, to date, no quantitative assessment has been reported concerning the association between egg consumption and the risk of ovarian cancer. Hence, we performed a meta-analysis of observational studies to evaluate the effect of egg consumption on the risk of developing ovarian cancer.

2. Materials and methods

2.1. Data sources and searches

The present meta-analysis was conducted following the Preferred Reporting Items for Systematic reviews and Meta-

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Analyses guidelines (PRISMA) [25], and the meta-analysis of observational studies in epidemiology (MOOSE) guidelines [26]. A literature search was carried out using Pubmed, Embase, and Cochrane Library Central database for all medical literature published in English-language journals up to August 2013. Search terms included: "egg" or "diet" or "dietary" and "ovarian" or "ovary" and "cancer" or "neoplasm" or "malignancy". The reference lists of each comparative study included in this meta-analysis and previous reviews were manually examined to identify additional relevant studies.

2.2. Study selection criteria

Two reviewers independently selected eligible case-control and cohort studies that investigated egg intake and ovarian cancer risk. Disagreement between the two reviewers was settled by discussing with the third reviewer. Inclusion criteria were: (i) used a case-control or cohort study design; (ii) evaluated the association between egg intake and ovarian cancer risk; (iii) presented odds ratio (OR), relative risk (RR), or hazard ratio (HR) estimates with its 95% confidence interval (CI). When there were multiple publications from the same population, only data from the most recent report were included in the meta-analysis and the remaining were excluded.

2.3. Data extraction

The following data was collected by two reviewers independently using a purpose-designed form: name of first author, publishing time, country of the population studied, study design, study period, number of cancer cases and subjects, dietary assessment method, control source, the study-specific adjusted ORs, RRs, or HRs with their 95% CIs for the highest category of egg consumption versus the lowest, confounding factors for matching or adjustments.

2.4. Statistical analysis

The study-specific adjusted RRs were used as the common measure of association across studies. Because the absolute risk of ovarian cancer is low in humans, the ORs in case-control studies should approximate the RRs or HRs; therefore, we reported all results as RRs for simplicity. Heterogeneity was assessed using the Cochran Q and I^2 statistics. For the Q statistic, a P value<0.10 was considered statistically significant for heterogeneity; for the I^2 statistic, heterogeneity was interpreted as absent (I^2: 0%–25%), low (I^2: 25.1%–50%), moderate (I^2: 50.1%–75%), or high (I^2: 75.1%–100%) [27]. Subgroup analyses were carried out according to (i) study design (cohort studies versus case-control studies), (ii) geographic location (Europe versus North America versus Asia), (iii) control source (population-based versus hospital-based), (iv) number of adjustment factors ($n \geq 9$ versus $n \leq 8$), adjustment for smoking status (yes, no), adjustment for alcohol intake (yes, no), adjustment for BMI (yes, no), adjustment for oral contraceptive use (yes, no), adjustment for family history of ovarian cancer (yes, no), adjustment for parity (yes, no), adjustment for total energy intake (yes, no). Pooled RR estimates and corresponding 95% CIs were calculated using the inverse variance method. When substantial heterogeneity was detected ($I^2 \geq 50\%$), the summary estimate based on the random-effect model (DerSimonian-Laird method) [28] was reported, which assumes that the studies included in the meta-analysis had varying effect sizes. Otherwise, the summary estimate based on the fixed-effect model (the inverse variance method) [29] was reported, which assumes that the studies included in the meta-analysis had the same effect size. We carried out sensitivity analysis by excluding one study at a time to explore whether the results were strongly influenced by a specific study. Cumulative meta-analysis was also performed to identify the change in trend of reporting risk over time. In cumulative meta-analysis, studies were chronologically ordered by publication year, then the pooled RRs were obtained at the end of each year. Publication bias was assessed using Begg and Mazumdar adjusted rank correlation test and the Egger regression asymmetry test [30,31]. All analyses were performed using Stata version 11.0 (StataCorp, College Station, TX).

3. Results

3.1. Search results and characteristics of studies included in the meta-analysis

The process of study selection was shown in Fig. 1. The primary literature search identified 5654 citations. On the basis of the titles and abstracts, we identified 33 full-text articles. After further evaluation, 18 studies were excluded for lack of available data, and three studies were excluded for they were from the same population. At last, a total of 12 eligible studies published between 1984 and 2007 were identified, including six case-control studies [6,7,10,11,14,17] and six cohort studies [8,9,12,13,15,16] (Baseline data and other details of included studies are shown in Table 1). A total of 629,453 subjects, including 3728 ovarian cancer cases were involved. Of the 12 included studies, three studies were conducted in Europe [7,11,15], three studies in Asia [10,12,13], five studies in North America [6,8,14,16,17], and one study in Australia [9]. Most

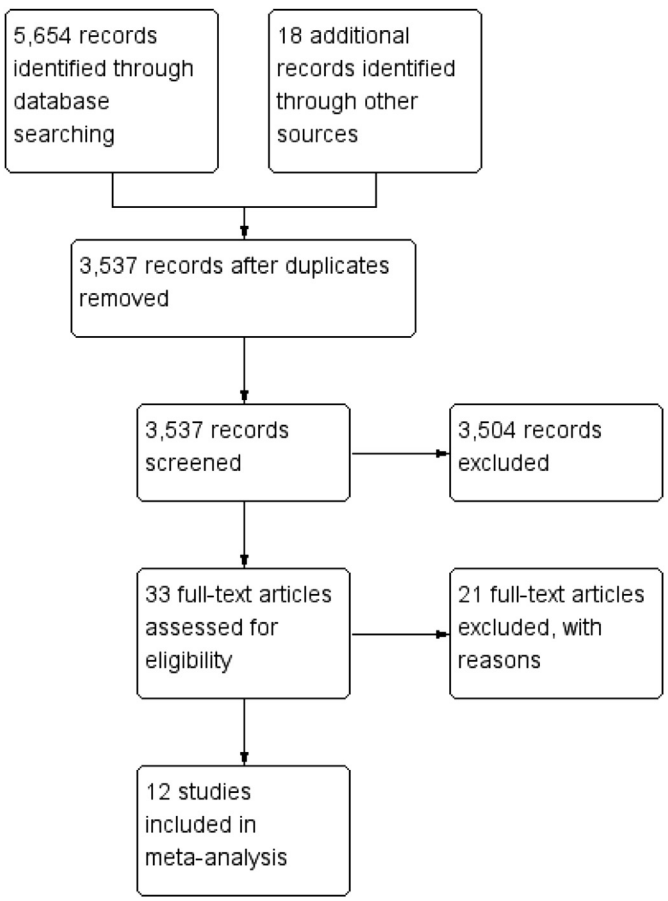

Fig. 1. Flow diagram of screened, excluded, and analysed publications.

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Table 1
Study characteristics of published cohort and case-control studies on egg intake and ovarian cancer.

Author	Publication year	Country	Study design	Female subjects	Ovarian cancer cases	Control source	Study period	Methods used for dietary assessment	Confounders for adjustment
Schulz M	2007	10 European countries	Cohort study	366,521	131	Population-based	1992–2000	FFQ	BMI, parity, menopausal status, ever use of oral contraceptives, total energy intake, education, smoking, unilateral ovariectomy, and hormone replacement therapy use at baseline
Sakauchi F	2007	Japan	Cohort study	64,327	54	Population-based	1988–2003	FFQ	Age, menopausal status, number of pregnancies, history of sex hormone use, BMI, physical activity, and education
Kiani F	2006	USA	Cohort study	13,281	71	Population-based	1976–1992	FFQ	Parity and BMI
Larsson SC	2005	Sweden	Cohort study	66,651	288	Population-based	1987–1990	FFQ	Age, BMI, educational level, parity, use of oral contraceptives and postmenopausal hormones, total energy intake, and quartiles of consumption of fruits, vegetables, and dairy products.
Pan SY	2004	Canada	Case-control study	2577	442	Population-based	1994–1997	FFQ	Age, 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.
Yen ML	2003	Taiwan	Case-control study	455	86	Hospital-based	1993–1998	FFQ	Age, income during marriage, and education
Zhang M	2002	China	Case-control study	906	254	Hospital-based	1999–2000	FFQ	Age, education, living area, BMI, smoking, alcohol drinking, tea drinking, family income marital and menopause status, parity, tubal ligation, oral contraceptive use, physical activity, family history of ovarian cancer, total energy intake, meat, vegetable, fruit, egg, milk intake
Pirozzo S	2002	Australia	Case-control study	1522	716	Population-based	NR	FFQ	Age, geographic location, education, parity, duration of oral contraceptive use, BMI, smoking history, ever use of perineal talc, tubal sterilization, hysterectomy, and history of breast or ovarian cancer in a first-degree relative
Bertone ER	2002	USA	Cohort study	80,258	301	Population-based	1980–1996	FFQ	Age, parity, age at menarche, menopausal status/postmenopausal hormone use, tubal ligation, and smoking status.
Bosetti C	2001	Italy	Case-control study	3442	1031	Population-based	1992–1999	FFQ	Age, study center, education, year of interview, parity, oral contraceptive use, meat, vegetable intake and energy intake
Kushi LH	1999	USA	Cohort study	29,083	139	Population-based	1986–1995	FFQ	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-hipratio, level of physical activity, cigarette smoking, and educational level
Cramer DW	1984	USA	Case-control study	430	215	Population-based	1978–1981	FFQ	Age, race, residence

BMI = body mass index; NR = not reported; FFQ = food frequency questionnaire.

studies used food frequency questionnaires (FFQ) for the assessment of egg consumption. About half of the included studies adjusted for some potential confounders, including alcohol drinking, oral contraceptive use, total energy intake, BMI, and parity. Ten studies were population-based [6–11,14–17], and only two studies were hospital-based [12,13].

3.2. Main analysis

Because substantial heterogeneity was not detected ($I^2 = 42.8\%$, $P = 0.06$), a fixed-effects model was chosen over a random-effects model and we found that high egg intake (comparing the highest with the lowest category) was associated with a significant increased risk of ovarian cancer (RR = 1.21, 95% CI [1.06, 1.38]). Both multivariable adjusted RR estimates with 95% CIs of each study and combined RR are shown in Fig. 2.

3.3. Subgroup analyses and sensitivity analysis

The results of subgroup analyses according to study design, geographic location, control source, and adjustment factors are presented in Table 2. A statistically significant effect of egg intake on ovarian cancer risk was observed among case-control studies (RR = 1.22, 95% CI [1.03, 1.43]), but not among cohort studies (RR = 1.20, 95% CI [0.97, 1.48]). When we examined whether the associations differed by control source, egg intake was significantly associated with increased risk of ovarian cancer among population-based studies (RR = 1.26, 95% CI [1.10, 1.44]), but not among hospital-based studies (RR = 0.88, 95% CI [0.60, 1.29]). When the studies were stratified by study location, egg intake was significantly associated with increased ovarian cancer risk among studies conducted in America (RR = 1.39, 95% CI [1.12, 1.71]) and Australia (RR = 1.82, 95% CI [1.30, 2.55]), however, egg intake had no significantly association with ovarian risk among studies conducted in Europe (RR = 1.03, 95% CI [0.83, 1.28]) and Asia (RR = 0.83, 95% CI [0.59, 1.17]). When we examined whether the associations differed by adjustment for smoking status, alcohol intake, BMI, oral contraceptive use, family history of ovarian cancer, parity, total energy intake, and the number of adjustment factors, all these factors affected the associations significantly (the details are shown in Table 2). To test the robustness of association, sensitivity analyses were carried out by excluding studies one-by-one. Sensitivity analysis indicated there was no significant variation in combined RR by excluding any of the studies, confirming the stability of the overall result.

3.4. Cumulative meta-analysis

A cumulative meta-analysis of the total 12 studies was carried out to evaluate the cumulative effect estimate over time. In 1984, Cramer DW et al. reported an effect estimate of 1.39 (95% CI [0.63, 3.08]). Between 1984 and 2002, five studies were published, with a cumulative RR being 1.29 (95% CI [1.07, 1.55]). Between 2005 and 2007, six more publications were added cumulatively, resulting in an overall effect estimate of 1.21 (95% CI [1.06, 1.38]) (Fig. 3).

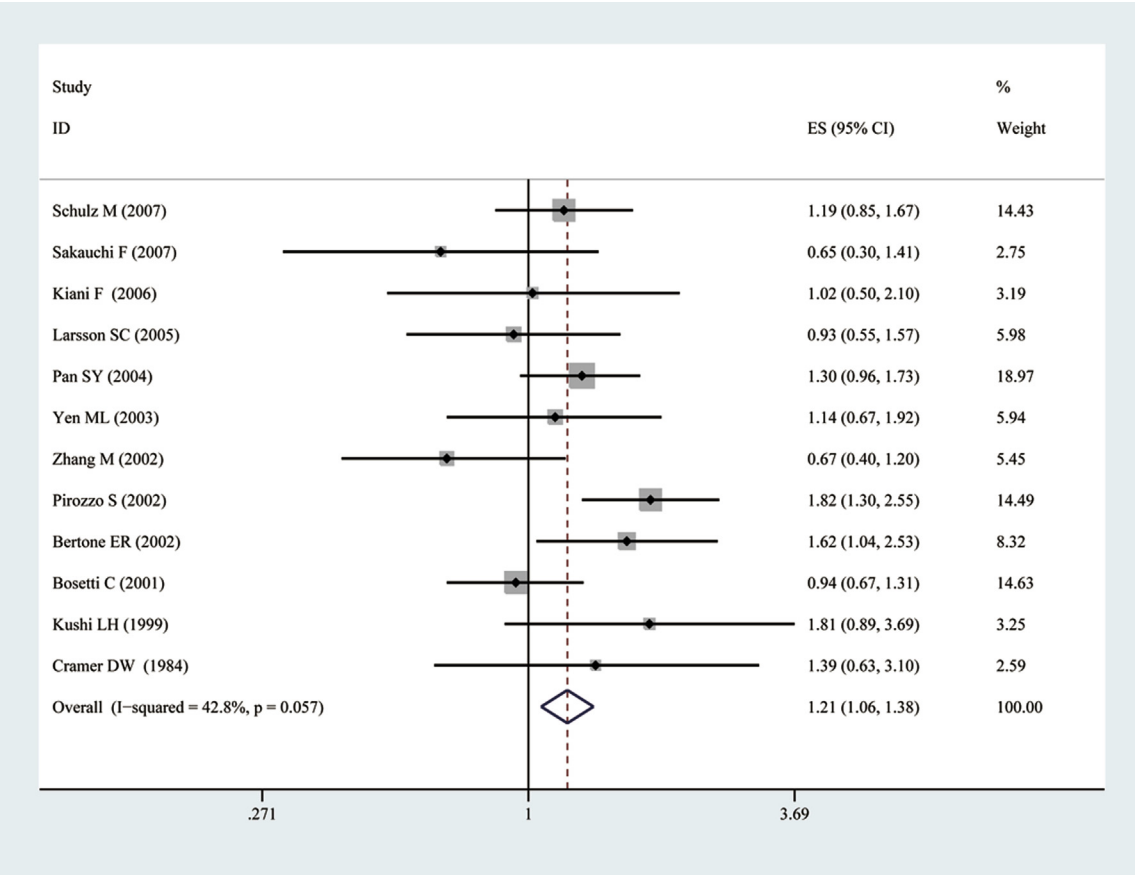

Fig. 2. Forest plot: overall meta-analysis of egg consumption and ovarian cancer risk. Squares indicated study-specific risk estimates (size of square reflects the study-statistical weight, i.e. inverse of variance); horizontal lines indicate 95% confidence intervals; diamond indicates summary relative risk estimate with its corresponding 95% confidence interval.

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Table 2
Summary risk estimates of the association between egg consumption and ovarian cancer risk.

Subgroup	No. of studies	Summary RR (95% CI)	Q-test for heterogeneity	
			I^2 score	*P* value
All studies	12	1.21 [1.06, 1.38]	42.80%	0.057
Study design				
Cohort	6	1.20 [0.97, 1.48]	23.70%	0.256
Case-control	6	1.22 [1.03, 1.43]	60.50%	0.027
Geographic location				
Europe	3	1.03 [0.83, 1.28]	0%	0.568
America	5	1.39 [1.12, 1.71]	0%	0.755
Asia	3	0.83 [0.59, 1.17]	15.40%	0.307
Australia	1	1.82 [1.30, 2.55]	N/A	N/A
Control source				
Population-based	10	1.26 [1.10, 1.44]	37.40%	0.109
Hospital-based	2	0.88 [0.60, 1.29]	46.70%	0.171
Adjusted for confounders				
Number of adjustment factors				
$n \geq 9$ confounders	7	1.21 [1.04, 1.40]	59.20%	0.023
$n \leq 8$ confounders	5	1.22 [0.93, 1.60]	11.40%	0.341
Major confounders adjusted				
BMI				
Yes	7	1.21 [1.03,1.42]	57.10%	0.030
No	5	1.21 [0.97, 1.51]	23.50%	0.264
Smoking status				
Yes	6	1.36 [1.16, 1.59]	55.20%	0.048
No	6	0.98 [0.79, 1.21]	0%	0.814
Alcohol intake				
Yes	2	1.12 [0.86, 1.45]	77.00%	0.037
No	10	1.24 [1.07, 1.44]	37.60%	0.108
Oral contraceptive use				
Yes	6	1.12 [0.95, 1.32]	66.40%	0.011
No	6	1.35 [1.11, 1.64]	0%	0.799
Total energy intake				
Yes	6	1.10 [0.93, 1.29]	35.00%	0.174
No	6	1.43 [1.16, 1.76]	36.10%	0.166
Family history of ovarian cancer				
Yes	3	1.44 [1.10, 1.88]	79.40%	0.008
No	9	1.15 [0.99, 1.33]	0%	0.492
Parity				
Yes	9	1.23 [1.08, 1.41]	51.50%	0.036
No	3	1.04 [0.71, 1.52]	2.10%	0.360

BMI = body mass index; CI = confidence interval; N/A = not available; RR = relative risk.

3.5. Publication bias

In the present meta-analysis, no publication bias was observed among studies using Begg's *P* value ($P = 0.411$) and Egger's ($P = 0.389$) test, which suggested there was no evidence of publication bias (Fig. 4).

4. Discussions

Higher intake of egg was hypothesized to increase the risk of ovarian cancer. Now we performed the first meta-analysis evaluating the association between egg intake and the risk of ovarian cancer. Six cohort studies and six case-control studies involving 629,453 participants and 3728 ovarian cancer cases were included in our investigation. There was no statistically significant heterogeneity among the 12 included studies, so a fixed-effects model was chosen over a random-effects model. We found that egg consumption was associated with a significant increased risk of ovarian cancer (comparing the highest with the lowest category). Our sensitivity analyses yielded similar and robust results, indicating that no study considerably influenced the overall risk estimate between egg consumption and ovarian cancer risk. Moreover, the results of Begg's test and Egger's test did not support the existence of major publication bias. In our subgroup analyses, the results were substantially affected by study design. Our findings from the case-control studies suggested that egg intake was associated with a significantly increased risk of ovarian cancer, however, the results from the cohort studies showed a nonsignificant association. Compared with case-control studies, cohort studies are less susceptible to bias (e.g. recall bias, selection bias) due to their nature. And we should notice that there were only six cohort studies investigating the association between egg intake and ovarian cancer risk. So more prospective cohort studies are needed to confirm this association in the future. When the studies were stratified by study location, we found a significantly increased risk in ovarian cancer among studies conducted in America and Australia, however, egg intake had no significant association with ovarian risk among studies conducted in Europe and Asia. The exact reason for the difference is unclear. The differences in genetic susceptibility, culture, and lifestyles may explain part of the inconsistency of the results. During subgroup analyses, we found that the source of controls also affected the association between egg intake and ovarian cancer risk. A significant association was observed in population-based studies, but not the hospital-based studies. The reason may be that the hospital-based studies have some inherent selection biases as such controls may just represent a sample of ill-defined reference population and may not be very representative of the study population or the general population. When we examined whether the associations differed by adjustment for smoking status, alcohol intake, BMI, oral contraceptive use, family history of ovarian cancer, parity, total energy intake, we found that all these factors affected the associations significantly. So, future studies should adjust factors which may influence the risk of ovarian cancer as much as possible.

It is biologically plausible that egg intake has a detrimental effect upon cancer risk. The most plausible explanation involves the high cholesterol content of eggs. Higher intake of cholesterol has been shown to increase the formation of secondary bile acids in both humans and animals [32–35] and to enhance the induction of cancer in animal models, such as colorectal cancer and lung cancer [36,37]. Furthermore, eggs can also be a source of heterocyclic amines which are formed during high temperature frying [38]. Heterocyclic amines have been shown to play roles as bacterial mutagens and animal carcinogens. They could induce different forms of cancer in mouse models and form DNA adducts in human beings [39–41]. However, most of the epidemiological studies reporting the associations of egg intake with risk of ovarian cancer were primarily designed to study either the effect of meat or a variety of risk factors. Thus, they focused on total egg consumption rather than different preparation methods, such as boiled or fried. As a result, we could not perform subgroup analysis according to different preparation methods. Recently, Fei Li et al. did a meta-analysis of egg consumption and bladder cancer risk. They found that the risk of bladder cancer was markedly elevated approximately twofold in a comparison between the highest and lowest intake of fried egg (RR = 2.04, 95% CI: 1.41–2.95). However, it was noted that no statistically significant association was detected between boiled egg intake and bladder cancer risk (RR = 1.25, 95% CI: 0.82–1.91). The strength of the present meta-analysis lies in a large sample size (629,453 subjects and 3728 ovarian cancer cases) and no significant evidence of publication bias. Two investigators independently performed the article identification, data extraction, and verification and resolved all discrepancies. Furthermore, our findings were stable and robust in sensitivity analyses. However, several limitations to this meta-analysis should be noted. Firstly, as a meta-analysis of observational data, the possibility of recall and selection biases cannot be ruled out. Compared with case-control studies, cohort studies are less susceptible to bias due to their nature. However, the present meta-analysis included only six cohort

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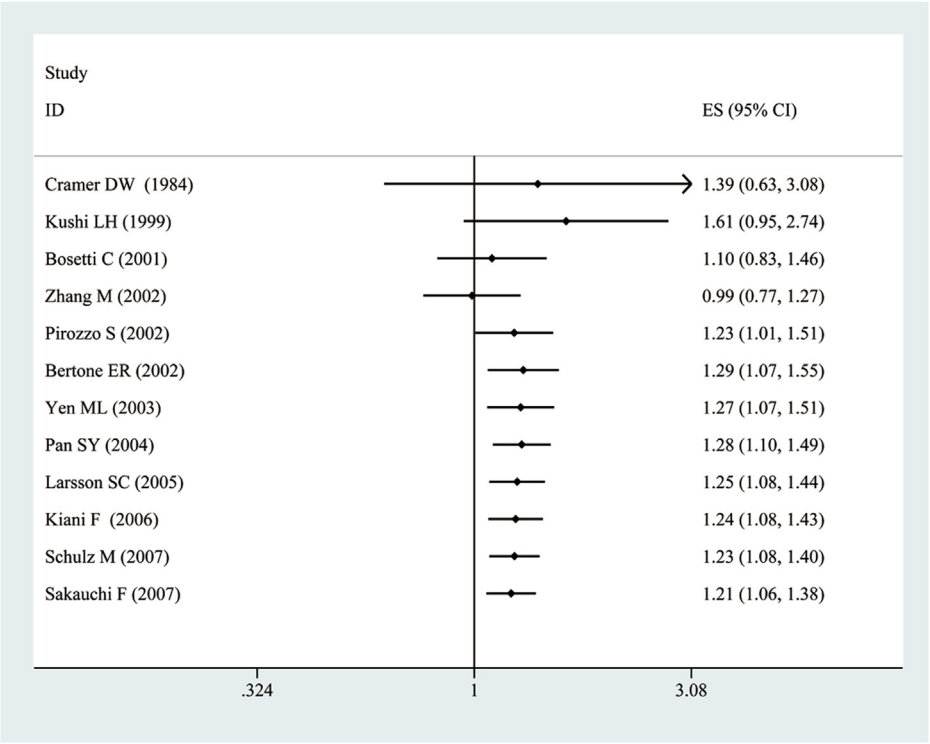

Fig. 3. Forest plot: cumulative meta-analysis of egg intake and ovarian cancer risk.

studies, so more prospective cohort studies are need to confirm the association in the future. Secondly, we did not search for unpublished studies, so only published studies were included in our meta-analysis. Therefore, publication bias may have occurred although no publication bias was indicated from both visualization of the funnel plot and Egger's test. Last but not least, due to different methods used to report egg intake among studies, we were unable to carry out a dose-response analysis between egg intake and ovarian cancer risk.

In summary, the results of this meta-analysis suggested that high intake of egg can increase the risk of ovarian cancer. Additional studies, especially large prospective cohort studies with more information are warranted, including stratified results by food preparation methods.

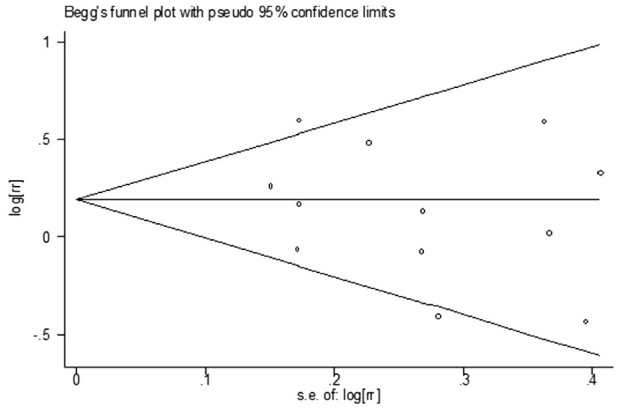

Fig. 4. Funnel plot for publication bias in the studies investigating risk for ovarian cancer associated with egg intake.

Conflict of interest

None.

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