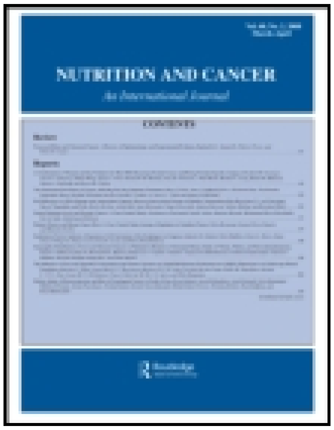

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Egg Consumption and Risk of Bladder Cancer: A Meta-Analysis

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The findings of epidemiologic studies on the association between egg consumption and bladder cancer risk remain conflicting. We conducted a meta-analysis to clarify the potential association between egg consumption and bladder cancer risk. Four cohort studies and 9 case–control studies in the PubMed database through February 2012 were identified on egg consumption and risk of bladder cancer involving 2715 cases and 184,727 participants. Random-effects models were used to calculate the summary relative risk estimates (SRRE) based on the highest compared with the lowest category of egg consumption. In addition, we performed stratified analyses and sensitivity and dose-response analyses to examine the association. Overall, no significant association was observed between egg consumption and bladder cancer (SRRE = 1.11 95% CI: 0.90–1.35). However, increased risk of bladder cancer was detected in North/South America (SRRE = 1.40 95% CI: 1.05–1.86) and, moreover, fried egg intake positively associated with bladder cancer as well (SRRE = 2.04, 95% CI: 1.41–2.95). In conclusion, our findings suggest no significant association between egg consumption and bladder cancer risk, except for a possible positive relationship with the intake of fried eggs based on the limited number of studies. Additional studies, especially large prospective cohort studies, are warranted to confirm these findings.

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INTRODUCTION

Bladder cancer is the second most common genitourinary malignancy in the world. The American Cancer Society estimated there were 70,530 new cases and 14,680 deaths from bladder cancer in 2010 in the United States (1). The rising incidence of bladder cancer is alarming and there are limited effective preventive measures against it. Moreover, bladder cancer has relatively higher recurrence rates. To date, it remains a major threat to public health. Smoking, occupational exposure to aromatic amines, and chronic bladder Schistosoma infection are well-established risk factors of bladder cancer (2).

Urinary bladder cancer incidence and mortality rates vary widely among geographic regions, suggesting that environmental factors, genetic background, dietary patterns, and lifestyle play roles in developing bladder cancer (3,4). Recently, more and more epidemiologic studies reported different dietary factors to be correlated with risk of bladder cancer. Some studies proposed that high intake of several specific types of fruits, vegetables, and nutrients may potentially lower the risk of bladder cancer (5,6).

The association between egg consumption and bladder cancer risk has received much attention since 1980. A few cohort (7–10) and case-control (11–19) studies had examined the impact of egg consumption on the development of this cancer form and their findings were controversial. The possible mechanism that may explain a possible detrimental effect of egg intake upon bladder cancer risk involves the high cholesterol content of eggs, which could increase the formation of secondary bile acids in both humans and animals (11,20). However, to date, no quantitative assessment has been reported concerning the association between egg consumption and risk of bladder cancer.

In response, we conducted the first meta-analysis to clarify the potential association between egg consumption and risk of bladder cancer on the basis of eligible cohort and case-control studies. We summarized the epidemiologic evidence according to characteristics of the studies. In addition, we identified several sources of heterogeneity by subgroup analyses. We also examined the dose-response pattern between egg consumption and bladder cancer risk.

METHODS

Literature Search Strategy

We performed this meta-analysis in accordance with Meta-analysis of Observational Studies in Epidemiology guidelines (21). We conducted a PubMed database search through February 2012 for the eligible studies that reported the association between egg consumption and risk of bladder cancer. The primary search included the following terms: *diet*, *egg*, *dietary cholesterol*, *bladder* and *carcinoma* OR *cancer* OR *tumor* OR *neoplasms*. The search focused on human studies, without restriction on language. Furthermore, we searched the references of all retrieved publications again to trace additional relevant studies.

Inclusion and Exclusion Criteria

Studies would be included in this meta-analysis if they met the following criteria: 1) The study design is an original case-control or cohort study in human beings. 2) The study has examined the association between egg consumption and bladder cancer risk. 3) The study has reported a point estimate [i.e., relative risks (RR) or odds ratio (OR)] and its variability [i.e., 95% confidence intervals (CI)] for the highest vs. lowest level of egg consumption or information sufficient to calculate them. Considering that bladder cancer is a rare disease, the RR was assumed approximately the same as OR. To avoid confusion, "eggs" in this present analysis included eggs, fried and boiled eggs, and total eggs used in the original studies. A combined RR of fried or boiled eggs would be calculated if they were noted as an independent item in more than 2 studies. In cases of multiple publications of the same or overlapping cohort, only the studies with the largest sample size were included. The exclusion criteria were 1) duplicates; 2) irrelevant data reported; 3) cross-sectional and ecologic analyses.

Data Extraction

We extracted the information in a standardized data collection form. The following information was recorded: first author, year of publication, country, study design, number of cases, sample size, study duration, consumption level of eggs, number of exposed cases, RR or OR, 95% CIs, method of dietary assessment, number of food items in dietary assessment method, and adjusted confounding factors. If one study contained multiple data sets, we used the results from the main multivariable model that included most adjusted confounders. Two authors independently conducted literature search and extracted data. The discrepancy in data extraction was resolved by repeating the study review and discussion.

Statistical Analysis

We used summary relative risk estimate (SRRE) for the highest compared with the lowest category of egg consumption. It should be noted that the lowest category included people who did not consume any egg. Statistical heterogeneity across studies was examined by Q statistic (significant at $P < 0.10$). The I^2 statistic was also calculated to quantitatively measure the inconsistency across studies and we used the random-effects method to estimate the association (22). Forest plots were applied to assess the relationship between egg consumption and bladder cancer risk.

To explore the sources of heterogeneity across studies, subgroup analyses were conducted according to study design, gender, geographic region, cooking method of eggs, method of dietary assessment, and publication year. Because adjustments for confounding factors were not consistent between the studies, we also conducted the subgroup analysis according to whether the effect sizes had been adjusted for at least 3 of the following essential confounders: age, gender, BMI, smoking, and total energy intake. In addition, we further performed a sensitivity analysis to explore sources of heterogeneity. Each study was omitted at a time to assess robustness of the results. Meta-regression was also applied to measure the subgroup interaction. The P value for interaction between 2 groups is the comparison of 1 subgroup vs. the other. In the regression analysis of 3 groups, the Asian group is used as the reference for the other groups. We used $P < 0.10$ as the indicator of significant interaction.

Furthermore, we conducted a dose-response analysis based on the category data of average dose of egg consumption, number of cases, total subjects or person years, and logarithm of SRRE and its corresponding standard error. The eligible studies should provide sufficient information across at least 3 categories of exposure. Among the studies, we assigned median of egg consumption for each category to each SRRE. For the open-ended upper category of consumption, the amplitude was assumed the same as the previous one.

We used Begg's rank correlation and Egger's linear regression test to assess the possible bias captured by the funnel plot (23). Because both tests have low power to detect potential bias, we set $P = 0.1$ as our statistical penalty in these 2 tests. All statistical analyses were performed with STATA Statistical Software, version 11.0. We consider a P value of less than 0.05 as an indicator of significance except where specifically noted.

RESULTS

PubMed search retrieved 442 records; 233 articles were excluded after screening by abstracts and titles. Furthermore, we identified and assessed 44 articles by full-text review which had examined the relationship between egg consumption and bladder cancer risk. Twenty-nine articles were excluded because their effect sizes and the corresponding 95% confidence intervals could not be estimated due to insufficient information. Furthermore, 2 studies were excluded because they (24,25) reported overlapping population with another 2 studies (11,14). Therefore, we only took studies with larger sample size into account (11,14). Finally, 13 eligible studies (including 14 data sets) were identified for analysis. These studies were published between 1980 and February 2012.

In summary, 13 studies on egg consumption (involving 2715 cases) with a sample size of 184,727 individuals were included in our analysis. Table 1 presents the characteristics of the included studies. There were 4 prospective cohort studies (7–10) with 173,804 participants, and 9 hospital-based (11–16,18) or population-based (17,19) case-control studies (11–19) with 10,923 participants. Among these, 4 studies were conducted in Asia (7,8,13,14), 5 in North/South America (9,11,15,16,19), and 4 in Europe (10,12,17,18). Most of the studies in our analysis used a food frequency questionnaire based on self-report or interviewer-administered questionnaires to ascertain dietary information pertaining to egg consumption, although the number of items list in the questionnaire varied across the studies.

The overall results of our meta-analysis are presented in Table 2. Fig. 1 shows the results from combing effect sizes for bladder cancer using the random-effects model. Overall, we found no significant association between egg consumption and risk of bladder cancer (SRRE = 1.11, 95% CI: 0.90–1.35). Substantial heterogeneity was observed across studies ($P = 0.001$, $I^2 = 63.3\%$) (Table 2, Fig. 1). Furthermore, meta-analysis restricted to the prospective cohort data showed no significant association (SRRE = 0.86, 95% CI: 0.66–1.12) without any variability (P value for heterogeneity = 0.894, $I^2 = 0$). The summary association for the 9 case-control studies was stronger in magnitude than the cohort studies (SRRE = 1.21, 95% CI: 0.94–1.56) though the results were more variable (P value for heterogeneity = 0.001, $I^2 = 70.5\%$).

Only 3 studies reported the association specifically for men and the pooled results were not significant (SRRE = 0.91, 95% CI: 0.61–1.34, P value for heterogeneity = 0.097, $I^2 = 52.7\%$). In the subgroups according to whether at least 3 crucial confounders of bladder cancer (age, gender, BMI, smoking, and total energy intake) had been adjusted, no significant associations were observed (adjustment: SRRE = 1.11, 95% CI: 0.73–1.69, P value for heterogeneity = 0.001, $I^2 = 75.8\%$; without at least 3 confounders adjusted: SRRE = 1.09, 95% CI: 0.87–1.36, P value for heterogeneity = 0.059, $I^2 = 50.5\%$). Summary associations were similar in the subgroups stratified by publication year (published prior to 2000, SRRE = 1.16, 95% CI: 0.96–1.37; published since 2000, SRRE = 1.05, 95% CI: 0.66–1.66); however, little variability was found among studies published prior to 2000 (P value for heterogeneity = 0.192, $I^2 = 32.5\%$) as compared with studies published since 2000 (P value for heterogeneity = 0.001, $I^2 = 76.3\%$). Similarly, the association between egg consumption and bladder cancer was not significant in the subgroups according to the interview assessments or mailed questionnaires (Table 2).

Interestingly, we found a significant positive association between egg consumption and bladder cancer in North/South America (U.S., Canada, and Uruguay). The bladder cancer risk increased remarkably by 40% on the basis of comparisons between the highest and lowest quartiles of egg consumption (SRRE = 1.40, 95% CI: 1.05–1.86; P value for heterogeneity = 0.008, $I^2 = 71.0\%$) (Table 2, Fig. 2A). In contrast, no statistically significant association was detected in Asia (SRRE = 0.83, 95% CI: 0.52–1.32; P value for heterogeneity = 0.085, $I^2 = 54.6\%$) or Europe (SRRE = 1.01, 95% CI: 0.79–1.30; P value for heterogeneity = 0.198, $I^2 = 35.8\%$).

In addition, after stratification according to cooking method of eggs, there was a strong positive association between fried egg consumption and bladder cancer risk, though it is based on only 2 case-control studies. The risk of bladder cancer was markedly elevated approximately twofold in a comparison between the highest and lowest intake of fried egg (SRRE = 2.04, 95% CI: 1.41–2.95) without any evidence of heterogeneity (P value for heterogeneity = 0.567, $I^2 = 0\%$) (Table 2, Fig. 2B). It is noted that no statistically significant association was detected between boiled egg intake and bladder cancer (95% CI: 0.82–1.91; P value for heterogeneity = 0.213, $I^2 = 35.5\%$). Moreover, there was no indication of heterogeneity in the subgroup of boiled egg intake.

TABLE 1
Characteristics of studies that analyzed egg consumption and bladder cancer

First author and year	Study location	Cases[a]/subjects	Following-up/period	Dietary assessment	Foodlist[b]	Items	Analytical comparison (high vs. low intake)	RR (95% CI)/trend *P*	Adjustments
Cohort									
Sakauchi 2005 (7)	Japan	123/110,792	7/1990–1997	Mailed questionnaire	32	Egg	3–4 wk+ vs. ≤1–2 times/mo	0.74 (0.38–1.44) 0.350	Age, sex, smoking
Nagano2000 (8)	Japan	114/38,540	14.0/1979–1993	Mailed questionnaire	22	Egg	5+ times /wk vs. 1–2 times /wk	0.83 (0.50–1.36) 0.510	Age, gender, smoking BMI, calendar time, radiation, education
Chyou1993 (9)	USA	96/7995	22.0/1968–1991	Interview	17	Egg	≥5 times /wk vs. ≤1time/wk	0.82 (0.48–1.38) 0.560	Age, smoking
Steineck 1988 (10)	Sweden	80/16,477	14/1968–1982	Mailed questionnaire	80	Egg	Yes vs. no	1.00 (0.60–1.60) NR	Age, sex
Case control									
Aune 2009 (11)	Uruguay	254/5571	1996–2004	Interview	64	Egg	>3.5 eggs/wk vs. 0	2.23 (1.30–3.83) 0.001	Age, sex, smoking, total energy, BMI, residence, education, income, interviewer, alcohol, intake of fruits and dairy foods, vegetables, grains, total meat, other fatty foods, mate drinking status
Baena 2006 (12)	Spain	74/163	–2005	Interview	NR	Egg	≥ 4 eggs/wk vs. 0	0.57 (0.28–1.14) NR	
Radosavljevic 2005 (13)	Japan	130/260	1997–1999	Interview	101	Egg	Tertile of intake T 3 vs. T1	1.81 (0.83–3.96) NR	Smoking
Wakai 2004 (14)	Japan	124/744	1994–2000	Interview	97	Egg	≥5 times /wk vs. 1–3 times/mo	0.50 (0.27–0.90) 0.03	Age, sex, smoking, year of first visit

(Continued on next page)

TABLE 1
Characteristics of studies that analyzed egg consumption and bladder cancer *(Continued)*

First author and year	Study location	Cases[a]/subjects	Following-up/period	Dietary assessment	Foodlist[b]	Items	Analytical comparison (high vs. low intake)	RR (95% CI)/trend *P*	Adjustments
Balbi 2001 (15)	Uruguay	144/720	1998–1999	Interview	64	Egg	Tertile of intake T3 vs. T1	1.82 (1.15–2.86) 0.010	Age, sex, smoking, calories, BMI, mate drinking, education, residence, urban/rural status,
						Fried egg	T3 vs. T1	2.24 (1.37–3.66) 0.001	
						Boiled egg	T3 vs. T1	1.54 (0.96–2.46) 0.070	
Wilkens1996 (16)	USA	261/783	1979–1986	Interview	29	Egg	Mean values Male: 230.8 g/wk vs. 202.5 g/wk Female:230.8 g/wk vs. 202.5 g/wk	1.13 (0.99–1.29) NR	Age, smoking, high risk occupation ethnicity, and dark green vegetables in men and vitamin C in women
Steineck 1990 (17)	Sweden	326/720	1985–1987	Mailed questionnaire	56	Fried egg	wkly vs. more seldom	1.80 (1.00–3.10) NR	Year of birth, gender, smoking
						Boiled egg	wkly vs. more seldom	1.00 (0.60–1.60) NR	
La Vecchia 1989 (18)	Italy	163/344	1985–1987	Interview	10	Egg	high vs. low	0.82 (0.44–1.54) 0.510	
Risch1988 (19)	Canada	826/1618	1979–1982	Interview	19	Egg	Quartile of intake Q4 vs. Q1	1.57 (1.16–2.14) NR	Smoking, history of diabetes

BMI = body mass index; NR = not reported.
[a]Number of bladder cancer in study.
[b]Number of food items in dietary assessment method.

TABLE 2
Summary of meta-analysis results for egg consumption (high intake vs. low intake[a]) and bladder cancer

Analysis specifications	Studies	Total cases	Total population	SRRE (95% CI)	P heterogeneity	I^2	Interaction[b]
Egg	13 (7–19)	2715	184, 727	1.11 (0.90–1.35)	0.001	63.3%	
Cohort studies	4 (7–10).	413	173, 804	0.86 (0.66–1.12)	0.894	0.0%	0.114
Case-control studies	9 (11–19)	2302	10,923	1.21 (0.94–1.56)	0.001	70.5%	
The American continent	5 (9,11,15,16,19)	1581	16,687	1.40 (1.05–1.86)	0.008	71.0%	0.037** 0.618
Europe	4 (10,12,17,18)	643	17,704	1.01 (0.79–1.30)	0.198	35.8%	
Asia	4 (7,8,13,14)	491	150,336	0.83 (0.52–1.32)	0.085	54.6%	
Fried egg	2 (15,17)	440	1440	2.04 (1.41–2.95)	0.567	0.0%	0.057*
Boiled egg	2 (15,17)	440	1440	1.25 (0.82–1.91)	0.213	35.5%	
Studies that adjusted for at least 3 of the following factors: age, gender, energy, smoking and BMI	6 (7,8,11,14,15,17)	1085	157,087	1.11 (0.73–1.69)	0.001	75.8%	0.996
Studies that did not simultaneously adjust for 3 of the above factors	7 (9,10,12,13,16,18,19)	1583	27,640	1.09 (0.87–1.36)	0.059	50.5%	
Published since 2000	7 (7,8,11–15)	963	156,790	1.05 (0.66–1.66)	0	76.3%	0.833
Published prior to 2000	6 (9,10,16–19)	1752	27,937	1.16 (0.96–1.37)	0.192	32.5%	
Face-to-face interview	9 (9,11–16,18,19)	2072	18198	1.14 (0.87–1.50)	<0.001	72.4%	0.735
Mailed questionnaire	4 (7,8,10,17)	643	166,529	1.02 (0.80–1.30)	0.097	49.0%	
Man	3 (9,12,16)	437	8941	0.91 (0.61–1.34)	0.097	52.7%	0.582
Woman	1 (16)	261	783	1.10 (0.83–1.38)			

SRRE = summary relative risk estimates; BMI = body mass index.
[a]The intake contrast (i.e., exposure vs. referent group) for each study is reported in Table 1.
[b]This column is a *P* value for the comparison of that subgroup vs. the other or reference. Asian group is used as the reference in the regression analysis of 3 groups.

Further sensitivity test by exclusion of each study in turn did not materially affect the overall results in our meta-analysis, with a narrow range from 0.95 (95% CI: 0.74–1.17; *P* value for heterogeneity = 0.001) to 1.06 (95% CI: 0.86–1.26; *P* value for heterogeneity = 0.001).

Visual inspection of the funnel plot (not shown) did not suggest substantial asymmetry. There was no statistical evidence of publication bias based on the Begg's rank correlation (P = 0.127) and the Egger's linear test ($P = 0.549$).

Dose-response analysis of 6 studies (7,9,11,14,17,18) that provide sufficient information suggested no evidence of significantly elevated risk of bladder cancer for each incremental increase of consuming on the average 6 eggs per wk (SRRE = 1.08, 95% CI: 0.89–1.30). This was consistent with our overall results estimated from full data by meta-analysis. However, we observed a rising pattern of relative risk with increasing consumption of fried eggs in the study by Steineck et al. (17).

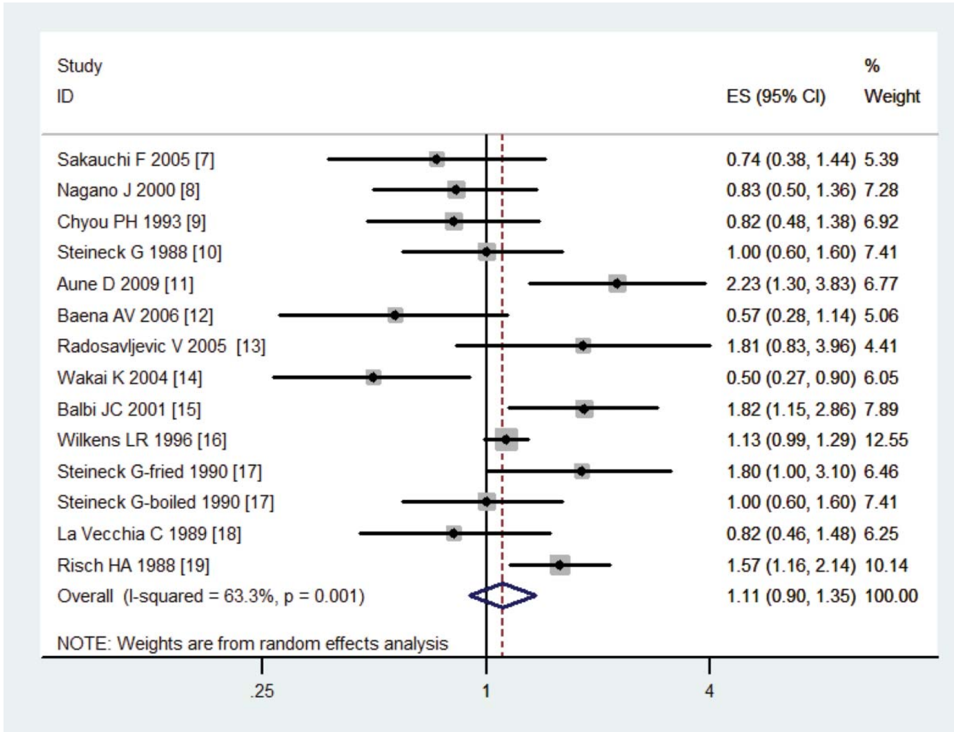

FIG. 1. Meta-analysis of studies that examined egg consumption and bladder cancer risk. The squares and horizontal lines correspond to summary relative risk estimates (SRRE) and 95% confidence interval (CI). The area of the squares reflects the weight of the study, which is the inverse variance of the effect estimate. The diamond data marker indicates SRRE and 95% CI. (Color figure available online).

DISCUSSION

Here, we performed the first meta-analysis for clarification of the association between egg consumption and risk of bladder cancer. Four cohort studies and 9 case-control studies involving 184,727 participants were included in our investigation. The results suggested no significant overall association between egg consumption and bladder cancer incidence. The findings were consistent independent of study design, gender, Asian or European continent, publication year, method of dietary assessment, and adjustment for several essential confounders or not (i.e., age, gender, BMI, smoking, and total energy intake). Interestingly, however, we found that egg consumption was associated with increased risk of bladder cancer in North/South America. Moreover, fried egg intake positively associated with bladder cancer. Noticeably, these positive associations are mainly driven by studies and findings in Uruguay.

Heterogeneity is often a major concern in meta-analysis. Several issues may have some contribution to the observed heterogeneity in many of the meta-analysis models. Firstly, analytic comparisons in the included studies were various and quite heterogeneous. The exposure data on consumption were in different units (frequency/wk, times/mo, and servings/wk). Furthermore, the individual RR estimate included in our meta-analysis was adjusted for different covariates in the different studies. Moreover, the methodological difference could, to some extent, explain proportion of the observed heterogeneity. Indeed, in our analysis, the model of cohort studies showed little variability, while significant heterogeneity was observed across the case-control studies. In addition, differences in follow-up period, dietary assessment method, publication year, geographical region, coupled with cooking method of eggs might lead to heterogeneity between the individual studies. Little heterogeneity was observed among cohort studies, studies published prior to 2000, studies conducted in Europe, and studies that assessed fried eggs or boiled eggs separately. Finally, we could not exclude the possibility that some other unknown or unmeasured factors may contribute to the variability.

Our sensitivity analyses yielded similar and robust results, indicating that no study considerably influenced the overall risk estimate between egg consumption and bladder cancer risk. The summary results from other subgroups were similar with evidences of heterogeneity. In addition, there was no evidence of publication bias in our meta-analysis based on Egger's test and Begg's rank correction.

Concerning significant association between fried egg intake and risk of bladder cancer, one plausible reason is the formation of heterocyclic amines during the frying of eggs at a high temperature (26–28). 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

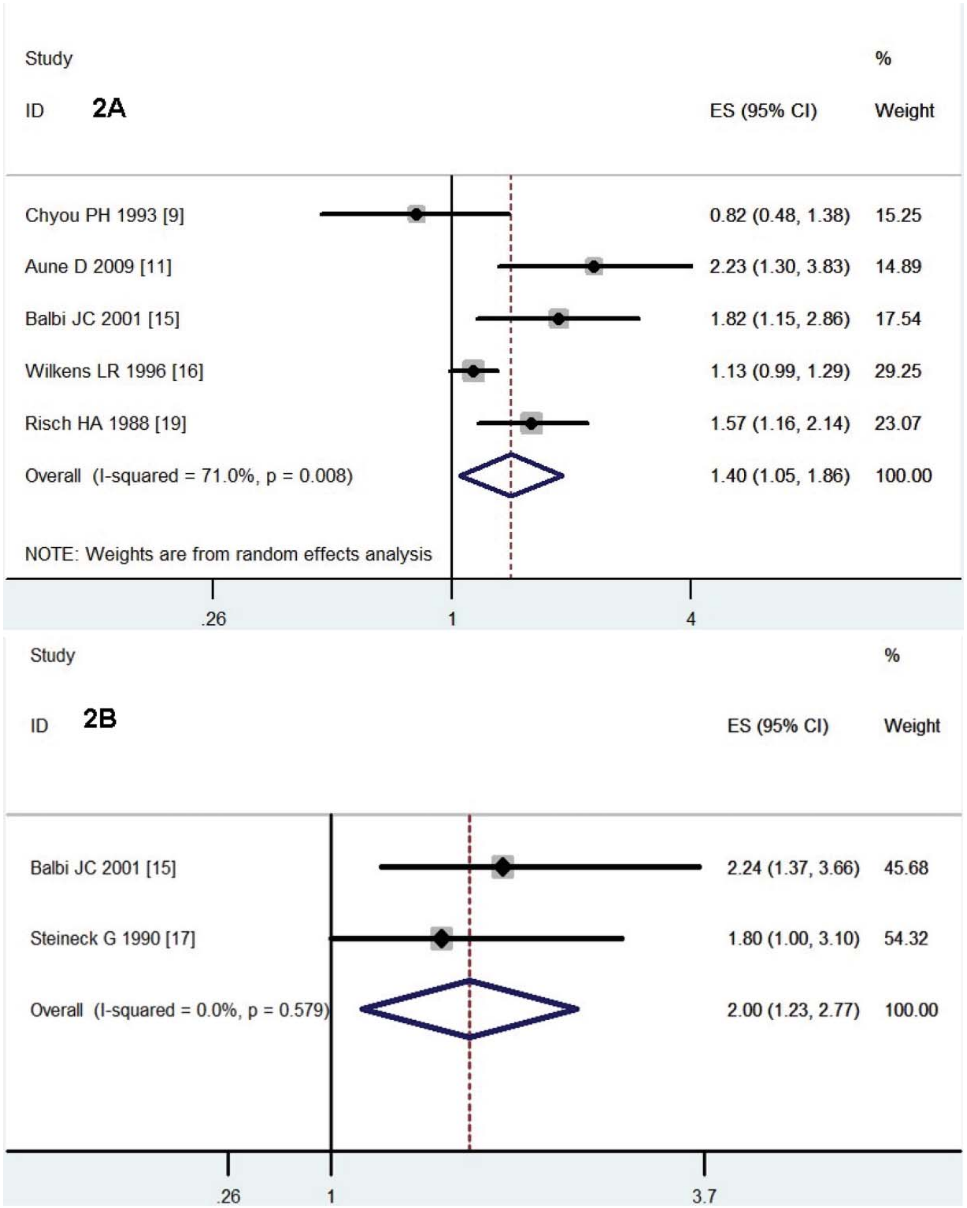

FIG. 2. Meta-analysis of studies in North/South America that examined egg consumption and bladder cancer risk (2A), and studies that examined fried egg consumption and bladder cancer risk (2B). The squares and horizontal lines correspond to summary relative risk estimates (SRRE) and 95% confidence interval (CI). The area of the squares reflects the weight of the study, which is the inverse variance of the effect estimate. The diamond data marker indicates SRRE and 95% CI. (Color figure available online).

DNA adducts in human beings (29). Another reason is that in the frying process it is much more difficult to limit sources of cholesterol than in boiling. A recent case-control study reported that dietary cholesterol intake was positively associated with risk of bladder cancer (30).

Several important strengths should be noted in our study. This is the first systematic epidemiologic assessment of the relationship between egg consumption and bladder cancer. Because the statistical power of the individual studies is insufficient, our meta-analysis of 13 studies involving enlarged sample size enhanced the statistical power to detect more stable association and provide more reliable estimation. Moreover, the results were further analyzed according to the study designs and yielded a similar conclusion. In addition, we found arising associations between egg consumption and bladder cancer according to several factors that had never been paid sufficient attention to the dietary recommendations.

The current study was subject to several limitations that should be considered carefully when interpreting the results. First, substantial heterogeneity was observed among the studies, although we were able to find the major sources of heterogeneity through subgroup analyses. Second, studies reported consumption by using different measurements (frequency/wk, times/month, and servings/wk) which might cause random misclassifications. Third, although most studies included in our analysis had performed adjustment for a wide range of confounders, we could not rule out the possibility that other unidentified or unmeasured factors could affect the association. Fourth, our results according to the cooking method were based on the limited data. However, no evidence of heterogeneity in the subgroups probably indicated the robustness of our findings.

In conclusion, our study on the basis of 184,727 participants summarizes the available evidence regarding the etiological role of egg consumption on the risk of bladder cancer by meta-analysis. Overall, the findings suggest no significant association between egg consumption and bladder cancer risk, except for a possible positive relationship with the intake of fried eggs based on the limited number of studies. Additional studies, especially large prospective cohort studies, are warranted to confirm these findings.

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