REVIEW

Egg Consumption and Risk of Upper Aero-Digestive Tract Cancers: A Systematic Review and Meta-Analysis of Observational Studies

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ABSTRACT

Limited data are available that summarize the relation between egg intake and the risk of upper aero-digestive tract (UADT) cancers. This systematic review and meta-analysis was conducted to investigate the association between egg intake and the risk of UADT cancers. Medline/PubMed, ISI web of knowledge, EMBASE, Scopus, and Google Scholar were searched using relevant keywords. Observational studies conducted on humans investigating the association between egg consumption and the risk of UADT cancers were included. Overall, 38 studies with a total of 164,241 subjects (27, 025 cases) were included. Based on 40 effect sizes from 32 case-control studies, we found a 42% increased risk of UADT cancers among those with the highest egg consumption (ranging from ≥1 meal/d to ≥1 time/mo among studies) compared to those with the lowest intake (ranging from 0–20 g/d to never consumed among studies) (overall OR: 1.42; 95% CI: 1.19, 1.68; $P < 0.001$). However, this association was only evident in hospital-based case-control (HCC) studies (OR = 1.50; 95% CI: 1.34, 1.68; $P < 0.001$ for 'oropharyngeal and laryngeal cancer' and OR: 1.27; 95% CI: 1.08, 1.50; $P = 0.004$ for esophageal cancer) and not in population-based case-control (PCC) studies (OR = 1.25; 95% CI: 0.59, 2.67; $P = 0.56$ for 'oropharyngeal and laryngeal cancer' and OR: 1.29; 95% CI: 0.92, 1.81; $P = 0.13$ for esophageal cancer). In addition, the association was not significant in prospective cohort studies (overall OR: 0.86; 95% CI: 0.71, 1.04; $P = 0.11$). Considering individual cancers, a positive association was observed between the highest egg consumption, compared with the lowest, and risk of oropharyngeal (OR: 1.88; 95% CI: 1.61, 2.20; $P < 0.001$), laryngeal (OR: 1.83; 95% CI: 1.45, 2.32; $P < 0.001$), oral & pharyngeal & laryngeal (OR: 1.37; 95% CI: 1.12, 1.67; $P < 0.001$), and esophageal cancers (OR: 1.28; 95% CI: 1.10,1.48; $P = 0.001$). We also found an inverse association between egg intake and the risk of oral cancer (OR: 0.78; 95% CI: 0.62, 0.99; $P = 0.04$). In conclusion, high egg consumption (ranging from ≥1 meal/d to ≥1 time/mo among studies) was associated with increased risk of UADT cancers only in HCC studies but not in PCC or prospective cohort studies. PROSPERO registration number: CRD42018102619. *Adv Nutr* 2019;10:660–672.

Keywords: Egg, upper aero-digestive tract cancer, oral cancer, pharyngeal cancer, laryngeal cancer, esophageal cancer

Introduction

Upper aero-digestive tract (UADT) cancers, including cancer of the oral cavity, pharynx, larynx, and esophagus, are the seventh most frequent cancer type and the seventh most common cause of death from cancer worldwide (1). The number of new cases of esophageal cancer in 2018 was estimated to be 572,034, and the corresponding figures for cancers of the 'lip and oral cavity' and 'oropharynx' were estimated to be 354,864 and 92,887, respectively. The mortality rate of oral cancer is higher than that of other cancers including kidney cancer, Hodgkin's lymphoma, and skin cancer (2, 3).

Genetic and environmental factors, including tobacco smoking, alcohol consumption and betel quid chewing, human papillomavirus (HPV), poor immune system, and inadequate diet, are well-known risk factors for UADT cancers (4–6). Some studies have reported lower serum concentrations of vitamins A, B-12, C, E, and folate, beta-carotene, and zeaxanthin/lutein in subjects with oral cancer compared with controls (7, 8). Previous studies have

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Abbreviations used: HCC, hospital-based case-control; HPV, human papillomavirus; PCC, population-based case-control; UADT, upper aero-digestive tract.

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investigated the association between egg consumption and the risk of several cancers, including UADT cancers. Some studies showed a positive association between the consumption of >3 eggs per wk and risk of UADT cancers (9, 10); however, others did not find a significant association or found an inverse relation between egg consumption and the risk of UADT cancers (11, 12).

Eggs are a good source of vitamins D, E, and B-12, lutein, and zeaxanthin, which have been previously linked with a reduced risk of UADT cancers (7, 8, 13–16). Eggs are also an excellent source of animal protein, which has been associated with increased risk of UADT cancers (15, 17). Findings on the association between egg consumption and UADT cancers are conflicting. The World Cancer Research Fund (WCRF) report in 2018, which summarized earlier prospective studies published until 2015 on diet and cancer prevention, revealed that there is 'limited-no conclusion' evidence with regards to egg intake and cancers of the oral cavity, larynx, pharynx, and esophagus (18, 19). However, case-control studies and those published after 2015 were not included in that report. This study aimed to systematically review the current evidence regarding egg consumption and the risk of UADT cancers and to summarize earlier findings through a meta-analysis.

Methods

Search strategy

We selected articles published up until May 2018 searching through the following databases: Medline/PubMed, ISI web of knowledge, EMBASE, Scopus, and Google Scholar. We further searched in social networks including ResearchGate and Mendeley to find additional relevant articles. The following keywords and their combinations were used in our literature search: ('egg intake' OR 'ovum' OR 'egg consumption' OR 'diet cholesterol' OR 'meat' OR 'animal products' OR 'diet' OR 'food intake' OR 'nutrition' OR 'dietary indicators of' OR 'risk factors' OR 'food group' OR 'dietary factors') AND ('oropharynx' OR 'oral squamous cell' OR 'mouth' OR 'bucca' OR 'oral cavity' OR 'oral mucosa' OR 'mouth mucosa' OR 'intra-oral' OR 'head and neck' OR 'upper aero-digestive tract' OR 'oral pharyngeal' OR 'oral-pharyngeal' OR 'laryngeal' OR 'oral epithelial' OR 'intra-epithelial' OR 'oro-pharyngeal' OR 'esophageal' OR 'upper aero-digestive tract') AND ('carcinoma' OR 'cancer' OR 'tumour' OR 'tumor' OR 'carcinogen' OR 'neoplasm" OR 'metastasis∗' OR 'malignancies' OR 'leukoplakia' OR 'hyperplasia' OR 'biopsy'). All keywords were selected from the Medical Subject Headings (MeSH) database. No filter or limitation was used while searching the mentioned databases. We completed the search by reviewing the reference list of all relevant publications. All these steps were performed by two independent investigators (AA, RFM). Any disagreements were resolved by discussion or if necessary by the third investigator (AE). Duplicate citations were then removed. The full text of related articles was obtained, in some cases through contacting the corresponding author. The study protocol was registered at the International Prospective Register of Systematic Reviews (PROSPERO): CRD42018102619.

Eligibility criteria

Studies that fulfilled the following criteria were included in the meta-analysis: *1*) conducted on humans; *2*) were of observational design investigating the relation between egg consumption and the risk of oral cavity, oropharyngeal, pharyngeal, laryngeal, esophageal, and UADT cancers; *3*) reported RRs or rate ratios and corresponding 95% CIs or provided figures enabling us to calculate these estimates. All potentially relevant studies were screened by two independent investigators (AA, RFM) on the basis of the study title and abstract. In the case of disagreements, the principal investigator (AE) was consulted.

Excluded studies

We excluded duplicate citations and studies that did not meet the above-mentioned inclusion criteria. In total 1673 articles were found in our initial search. Through screening for the title and abstract, 1629 articles were excluded. In addition, 6 studies were excluded because of the following reasons: the study by Bosetti et al. (20) was not included in the current analysis due to the overlap of subjects with another publication of the same group (21). Another study that had reported OR and 95% CIs for consumption of egg and dairy products together was excluded (22). Two other studies (23, 24) were excluded because of the overlap in participants with another study (10). The studies of Ren et al. (25) and Xibib et al. (26) were not included in the meta-analysis due to inadequate data. Despite our efforts to contact the authors of these publications, no results were obtained; however, we included them in our systematic review. After these exclusions, 40 studies remained for our systematic review (9–12, 15, 21, 25–58) and 38 studies for the meta-analysis (9–12, 15, 21, 27–58) (**Figure 1**).

Data extraction

Required data were extracted using a standardized data collection form. The primary exposure was consumption of egg. The main outcome of interest in the current study was all cancers of the aero-digestive tract including oral, pharyngeal, oropharyngeal, laryngeal, and esophageal cancer. The following information was extracted by two independent reviewers (AA, RFM): the first author's last name, date of publication, study design, participants' age range, gender, number of cases and controls, comparisons, method of assessment of egg intake, ascertainment of outcomes, ORs or RRs for the risk of oropharyngeal, laryngeal, esophageal, or UADT cancers, 95% CIs, and covariates controlled for. In the case of any disagreements between the two reviewers, the principal investigator (AE) was consulted.

Quality assessment of studies

The quality of studies included in this meta-analysis was assessed using the Newcastle-Ottawa Scale (59). Based on this method, a maximum of nine scores can be awarded to

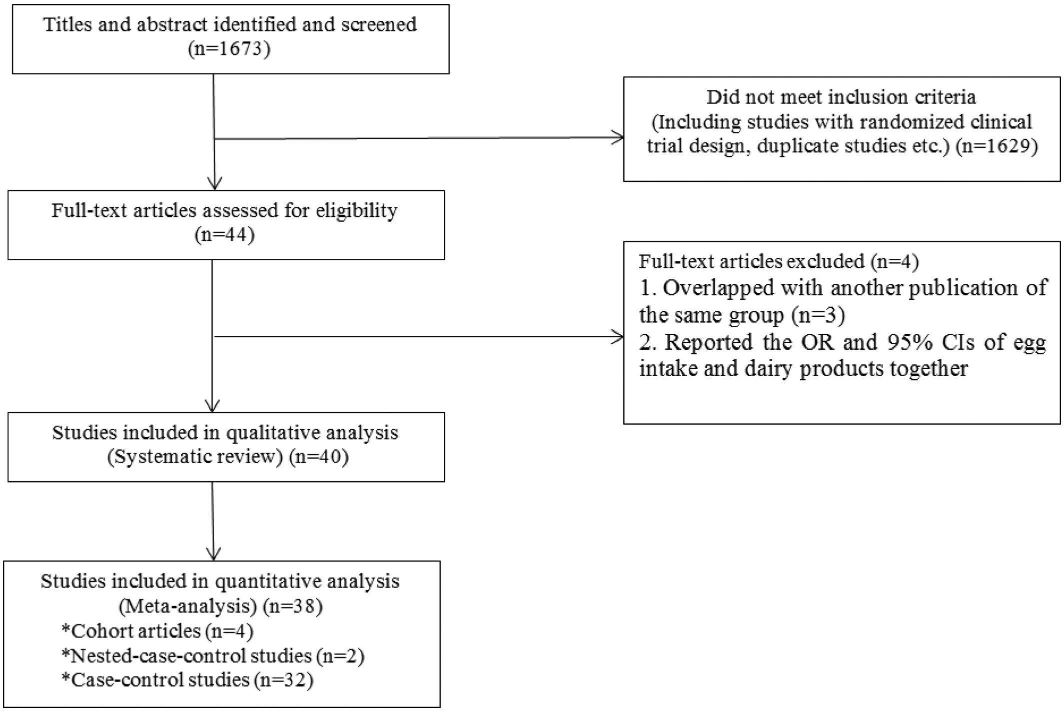

FIGURE 1 Flow diagram of study selection.

each study for selection of study groups (cancer patients and control group), comparability of groups, and substantiation of exposure (egg consumption). The quality score ranged from 4.0 to 8.0, with a median of 7.0. In the present analysis, we considered the quality scores of ≥7.0 as high-quality studies and those with a score of <7.0 were considered as low-quality studies.

Statistical analysis

RRs, HRs, or ORs for comparison of the highest versus the lowest categories of egg consumption were used as the measure of association between egg consumption and the risk of oropharyngeal, laryngeal, esophageal, or UADT cancers. Since the prevalence of these cancers was relatively low, ORs and HRs were directly considered as RRs. One study (35) did not report 95% CI; therefore, we calculated it using the number of patients with cancers in the highest (ranging from ≥1 meal/d to ≥1 time/mo among studies) and lowest categories of egg consumption (ranging from 0–20 g/d to never consumed among studies). For another study (48) that reported risk estimates for the lowest versus highest categories of egg consumption, the risk estimates were recalculated for the highest versus the lowest categories of egg intake. We applied a random-effects model to compute overall RRs. In addition, Q-statistic and I^2 were considered as indicators of heterogeneity. In the case of significant between-study heterogeneity, we used subgroup analysis to determine possible sources of heterogeneity. To assess publication bias, we constructed funnel plots for each outcome, in which log RRs were plotted against their SEs. We also conducted sensitivity analysis to examine the influence of any specific study on the overall estimate. Statistical analyses were conducted using STATA version 14 (STATA Corp.) and P values <0.05 were considered as statistically significant.

Results

Study characteristics

The main characteristics of included studies in our systematic review are summarized in **Table 1**. Out of 1,673 articles found in our initial research, 40 studies were included in the systematic review. Four cohort studies (32, 33, 40, 56), 2 nested case-control (12, 38), 10 population-based case-control (PCC) (9, 26, 28, 29, 36, 47, 50, 54, 55, 58), 22 hospital-based case-control (HCC) studies (10, 11, 15, 21, 25, 27, 30, 34, 35, 37, 39, 41–46, 49, 51–53, 57), 1 pooled analysis (31), and 1 study with both PCC and HCC design (48) met our criteria. These studies were published between 1987 and 2017. The sample size of these studies ranged from 54 to 37,257 participants. In total, 165,197 subjects (27,348 cases and 13,7849 controls) were included. Nineteen studies (9, 11, 12, 25, 26, 30, 33, 36, 38, 39, 41, 47, 48, 50, 51, 54, 55, 57, 58) were conducted in Asian countries, 12 investigations (15, 21, 27, 34, 35, 40, 42–46, 49) were from Europe, 4 (10, 37, 52, 53) were from South America, and 4 (28, 29, 32, 56) were from North America. In a pooled analysis study (31) based on 22 studies, 20 studies were from non-Asian countries, 1 was from an Asian country, and 1 study was international. None of these studies had overlap, in terms of population studied, with the other included studies in our meta-analysis. Out of

TABLE 1 Characteristics of included studies in the systematic review[1]

First Author, Year (Ref)	Study design	Country	Age range	Gender	Number of cases/controls	Assessment of exposure	Outcome variable	Comparison	OR or RR or HR (95% CI)	Study quality	Matching or Adjustments[2]
Butler et al. (28)	HCC	China and Taiwan	18–85	M/F	921/806	Questionnaire 12-item	Cancers of the oral cavity, oropharynx, hypopharynx, and larynx	≥1 meal every d vs. never consumed	OR: 0.54 (0.26, 1.11)	8	1, 2, 5, 6,7, 22, 23 24, 25
Bravi et al. (15)	HCC	Italy and Switzerland	19–79	M/F	768/2,078	FFQ 78-item	Cancers of the oral cavity and pharynx	Q5 vs. Q1	OR: 1.71 (1.14, 2.58)	7	1,2,3,4,5,6,7,8
Chuang et al. (29)	-[3]	Multi-national study	All ages	M/F	14,520/22,737	Food questionnaire	Cancers of the oral cavity, pharynx, and larynx	Q4 vs. Q1 (≥ 7 vs. <1 times/wk)	OR: 1.48 (1.20, 1.82)	—	—
Toporcov et al. (51)	HCC	Brazil	NR	M/F	296/296	FFQ 41-item	Cancers of the mouth and oropharyngeal tract	≥5 vs. <1 times/wk	OR: 22.23 (8.51, 60.17)	5	1,2,7, 9,10
Gao et al. (34)	PCC	China	51–65	M/F	600/1,514	Questionnaire	Esophageal cancer	Daily vs. monthly/seldom/never	OR: 1.12 (0.84, 1.49)	6	1,2,13
Aune et al. (10)	HCC	Uruguay	23–89	M/F	283/2,032	FFQ 60-item	Cancers of the oral cavity and pharynx	>3.5 vs. 0 eggs/wk	OR: 2.02 (1.19, 3.44)	6	1,2,3,4,5,6,7,8, 9,10,11,12
					281/2,032		Laryngeal cancer		OR: 1.17 (0.69, 1.97)		
					234/2,032		Esophageal cancer		OR: 1.69 (0.98, 2.93)		
Fan et al. (31)	Cohort 20-Y	China	45–64	M	101/18,244	Questionnaire	Esophageal cancer	T3 vs. T1	HRs: 0.83 (0.51, 1.35)	8	1,2,3,4,5,6,7
Wu et al. (52)	PCC	China Dafeng	Mean: 64.6 ± 8.9	M/F	291/291	FFQ 90-item	Esophageal cancer	Q4 vs. Q1	OR: 1.99 (0.72, 5.49)	7	1,2,5,6,7,17, 19,20,22,23
		China Ganyu	Mean: 65.4 ± 10.3		240/240				OR: 0.95 (0.41, 2.22)		
Kapil et al. (37)	HCC	India	41–80	M/F	305/305	Semi-structured questionnaire	Laryngeal cancer	Consumption vs. no-consumption	OR: 2.69 (1.89, 3.85)	6	1,2,13
Yang et al. (53)	PCC	China	35–85	M/F	185/185	Questionnaire	Esophageal cancer	>1 vs. ≤1 times/wk	OR: 0.59 (0.25, 1.39)	7	6,7,10,12,14,17,19,20
Toporcov et al. (50)	HCC	Brazil	34–81	M/F	31/23	FFQ 41-item	Oral cavity cancer	≥3 vs. <3 times per/wk	OR: 1.727 (0.781, 4.018)	6	1,2,6
Sanchez et al. (47)	HCC	Spain	20–91	M/F	375/375	FFQ 25-item	Cancers of the oral cavity and oropharynx	T3 vs.T1 (≥4 vs. ≤1 servings/wk)	OR: 0.97 (0.61, 1.52)	7	1,2,3,6,7,16
Lissowska et al. (44)	HCC	Poland	23–80	M/F	122/124	Questionnaire 25-item	Oral cavity cancer	T3 vs.T1 (≥6 vs. <3/wk)	OR: 0.51 (0.23, 1.15)	7	1,2,6,13
Rajkumar et al. (11)	HCC	India	22–85	M/F	591/582	Questionnaire 21-item	Oral cavity cancer	≥3 vs. <1 servings/wk	OR:0.41 (0.25, 0.66)	8	1,2,3,6,7,13
Xibib et al. (24)	PCC	China	30–75	M/F	211/633	Questionnaire	Esophageal cancer	High vs. low intake	OR:0.93$P = 0.98$	5	1,2,3,9,13
Bosetti et al. (18)	HCC	Italy	30–79	M/F	527/1,297	FFQ 78-item	Laryngeal cancer	Q5 vs. Q1 (12.5 vs. 0.4 servings/wk)	OR: 1.74 (1.07, 2.82)	6	1,2,3,6,7,8,13
Garrote et al. (35)	HCC	Cuba	28–91	M/F	200/200	Questionnaire 25-item	Cancers of the oral cavity and oropharynx	T3 vs.T1 (≥6 vs. <3servings/wk)	OR: 1.64 (0.91, 2.98)	6	1,2,3,6,7,13
Phukan et al. (39)	HCC	India	Mean: 55 ± 8.1	M/F	502/1,004	Questionnaire	Esophageal cancer	Daily vs. never	OR: 1.2 (0.08, 6.30)	4	1,2
Takezaki et al. (48)	PCC	China	40–79	M/F	199/333	Questionnaire 152-item	Esophageal cancer	Q4 vs. Q1 (every day vs. <1 times/wk)	OR: 1.55 (0.86, 2.79)	8	1,2,6,7,21
Bosetti et al. (19)	HCC	Italy	39–77	M/F	304/743	Questionnaire 78-item	Esophageal cancer	Q5 vs. Q1 (>2.9 vs. ≤0.4 servings/wk)	OR: 1.86 (1.00, 3.43)	7	1,2,3,4,6,7,8,13
Levi et al. (43)	HCC	Italy	34–74	M/F	101/327	FFQ 79-item	Esophageal cancer	T3 vs. T1 (>2.5 vs. ≤1 serving/wk)	OR: 5.75 (2.5, 13.1)	7	1,2,3,6,7,8
Franceschi et al. (33)	HCC	Italy	22–77	M/F	598/1,491	FFQ 78-item	Cancers of the oral cavity and pharynx	Q5 vs. Q1 (>4 vs. ≤1 serving/wk)	OR: 2.5 (1.7, 3.7)	7	1,2,3,6,7,8,13

(*Continued*)

TABLE 1 (*Continued*)

First Author, Year (Ref)	Study design	Country	Age range	Gender	Number of cases/controls	Assessment of exposure	Outcome variable	Comparison	OR or RR or HR (95% CI)	Study quality	Matching or Adjustments[2]
Gao et al. (9)	PCC	China	30–79	M/F	81/234	Questionnaire	Esophageal cancer	≥3 vs. <1 times/week	OR: 3.35 (1.54, 7.30)	5	1,2,13
Pan et al. (12)	Nested case-control	China	Mean: 61.5 ± 7.7	M	125/250	Questionnaire	Esophageal cancer	High vs. low intake	OR: 0.55 (0.36, 0.86)	5	1
Levi et al. (42)	HCC	Italy (Vaud, Switzerland)	26–72	M/F	156/284	FFQ 79-item	Cancers of the oral and pharynx	T3 vs. T1 (>3 vs. ≤1 serving/wk)	OR: 2.32 (1.28, 4.22)	7	1,2,3,6,7,8,13
Kjaerheim et al. (38)	Cohort 24-Y	Norway	Mean:59	M	71/10,960	FFQ 32-item	Cancers of the oral cavity, pharynx, larynx, and esophageal	≥6 vs. <1 times/mo	RR: 1.1 (0.3, 3.4)	8	1,6,7
Brown et al. (27)	PCC	USA	30–79	White men	114/681	FFQ 60-item	Esophageal cancer	Q4 vs. Q1	OR: 1.4 (0.6, 2.9)	8	1,2,6.7,8,13,15
				Black men	219/557				OR: 2.7 (1.3, 5.5)		
Launoy et al. (41)	HCC	France	NR	M	208/399	Questionnaire	Esophageal cancer	>45 vs. 0–20 g/d	OR: 1.17 (0.68, 2.08)	7	1,6,7,8,13,16,18
Takezaki et al. (49)	HCC	Japan	20–79	M/F	266/36,527	Questionnaire	Oral cavity cancer	T3 vs. T1	OR: 1.4 (0.8, 2.2)	7	1,2,6,7
Chyou et al. (30)	Cohort 24-Y	USA (Japanese American)	45–68	M	92/7,902	FFQ 23-item	Cancers of the upper aerodigestive tract	≥5 vs. <1 time/wk	RR: 1.33 (0.72, 2.45)	7	1,6,7
Guo et al. (36)	Nested case-control	China	40–69	M/F	640/3,200	Questionnaire	Esophageal cancer	>5 vs. 0 times/mo	OR: 0.8 (0.6, 1.1)	5	6,17
Zheng et al. (55)	HCC	China	18–80	M/F	404/404	FFQ 63-item	Oral cavity cancer	Fresh egg:≥4/wk vs. ≤2/mo	OR: 0.68 (0.35, 1.32)	6	1,2,3,5,6,7
								Salted egg: ≥3 vs. <1/mo	OR: 0.69 (0.24, 1.79)		
Yu et al. (54)	Cohort 15-Y	China	20–67	M/F	1,162/12,693	Questionnaire	Esophageal cancer	≥1/mo vs. never	RR: 0.94 (0.83, 1.07)	6	1,2
Zheng et al. (56)	PCC	China	20–75	M	115/269	FFQ 42-item	Cancers of the oral cavity and pharynx	Daily vs. seldom	OR: 1.25 (0.49, 3.23)	8	1,2,6,7
				F	89/145				OR: 1.25 (0.35, 4.48)		
La Vecchia et al. (40)	HCC	Italy	37–74	M/F	105/1,169	Questionnaire 17-item	Cancers of the oral cavity and pharynx	>1 vs. <1 portion/wk	OR: 1.5 (0.9, 2.4)	7	1,2
Franceschi et al. (32)	HCC	Italy	Median:Case: 59control: 58	M/F	302/699	Questionnaire 40-item	Cancer of the oral cavity and pharynx	T3 vs. T1	OR: 2.0*P* < 0.01	7	1,2,6,7,14
Ren et al. (23)	HCC	China	—	M/F	Cases: 112	—	Esophageal cancer	—	OR: 0.30	—	—
Brown et al. (26)	PCC	USA	30–79	M	207/422	Questionnaire 65-item	Esophageal cancer	T3 vs. T1	OR: 0.7 (0.4, 1.2)	7	1,6,7,13,15,16
Yu et al. (45)	PCC	USA	20–64	M/F	275/275	Questionnaire	Esophageal cancer	>5/wk vs. <1/wk	OR: 0.8 (0.5, 1.3)	6	1,2,15
Notani and Jayant (46)	HCC	India	All ages	M	278/215	Questionnaire	Oral cavity cancer	<1/wk vs. 1/wk	OR: 1.20 (0.7, 1.9)	6	1,7
					225/215		Pharyngeal cancer		OR: 0.68 (0.4, 1.1)		
					80/215		Esophageal cancer		OR: 1.01 (0.6, 1.7)		
					236/215		Laryngeal cancer		OR: 0.97 (0.5, 2.0)		
	PCC				278/177		Oral cavity cancer		OR: 0.83 (0.5, 1.5)	7	
					225/177		Pharyngeal cancer		OR: 0.43 (0.2, 0.8)		
					80/177		Esophageal cancer		OR: 0.79 (0.4, 1.4)		
					236/177		Laryngeal cancer		OR: 0.64 (0.3, 1.4)		

[1] HCC, hospital case-control; PCC, population case-control; NR, not reported; Ref, reference.
[2] Age (1), sex (2), education (3), year of interview (4), BMI (5), smoking (6), alcohol consumption (7), energy intake (8), income (9), food intake (vegetables, fruits, grain, dairy, meat), (10), mate (11), tea (12), area of residence (13), occupation (14), race (15), hospital (16), cancer history (17), interviewer (18), eating hot foods (19), eating speed (20), ethnicity (21), level of education (22), past economic status (23), betel quid use (24), center of data collection (25).
[3] Pooled analysis: both HCC and PCC studies.

40 publications we included, 22 studies (11, 15, 21, 28–30, 32–35, 40, 42–46, 49–51, 54, 55, 58) were scored as high-quality studies, and 16 articles (9, 10, 12, 26, 27, 36–39, 41, 47, 48, 52, 53, 56, 57) were defined as low-quality studies. Due to lack of information for individual studies in the pooled analysis article (31), the Newcastle-Ottawa Scale was not completed for this case. For the study of Ren et al. (25), we could not find the full article and therefore, we failed to examine the study quality.

Overall, almost all studies reported ORs except for 4 studies that reported HRs (33) and RRs (32, 40, 56). Ten studies (10, 15, 34, 35, 34, 42, 44, 49, 53, 58) examined oropharyngeal cancer, 6 studies (11, 46, 48, 51, 52, 57) investigated oral cavity cancer, 4 investigations (10, 27, 39, 48) provided risk estimates for laryngeal cancer, 1 article (48) reported the risk of pharyngeal cancer, 2 studies (30, 31) investigated oral cavity, pharyngeal, and laryngeal cancers, 2 articles (32, 40) evaluated the risk of UADT cancers, and 20 studies (9, 10, 12, 21, 25, 26, 28, 29, 33, 36, 38, 41, 43, 45, 47, 48, 50, 54–56) presented data for esophageal cancer.

Among included studies, 31 articles reported their findings for males and females combined (9–11, 15, 21, 25–27, 30, 31, 34–39, 41, 42, 44–47, 49–57), 9 studies for males only (12, 28, 29, 32, 33, 40, 43, 48, 58), and 1 article for females only (58). Egg consumption was assessed using an FFQ in 15 investigations (10, 15, 27, 29, 32, 35, 40, 44, 45, 49, 52–54, 57, 58) and through the use of other questionnaires in 23 studies. The mean follow-up duration for cohort and nested case-control studies ranged from 5 to 24 y (32, 38, 40). For almost all case-control studies, cases were matched with controls in terms of age and sex. One study (31) did not control for any confounder. Nine studies adjusted for total energy intake (10, 15, 21, 27, 29, 35, 43–45), others did not. Smoking/alcohol ($n = 29$) (10, 11, 15, 21, 27–30, 32–35, 37, 38, 40, 43–46, 48–55, 57, 58), area of residence ($n = 14$) (9, 11, 21, 26–29, 35–37, 39, 43, 44, 46), and BMI ($n = 6$) (10, 15, 30, 33, 54, 57) were also controlled for in some studies. The minimum ORs for oral cavity, oropharyngeal, laryngeal, and esophageal cancers were 0.41 (11), 0.97 (49), 0.97 (48), and 0.3 (25), respectively, and the maximum corresponding ORs were 1.72 (52), 22.23 (53), 2.96 (39), and 5.75 (45), respectively.

Findings from the meta-analysis on case-control studies

In total, out of 40 studies included in the systematic review, 38 studies (32 case-control studies, 2 nested case-control studies, and 4 cohort studies) met our criteria for meta-analysis. Total sample size enrolled in these studies was 164,241 (27,025 cases and 13,7216 controls). Case-control studies ($n = 32$) that examined the relation between egg consumption and a certain UADT cancer (oral cavity, pharyngeal, laryngeal, and esophageal) included a total of 108,361 subjects. The total number of cases with oral, pharyngeal, oropharyngeal, laryngeal, 'oral & pharyngeal & laryngeal', and esophageal cancer was 1,692, 225, 3,287, 1,349, 15,441, and 3,840, respectively. Based on 40 effect sizes from 32 case-control studies (9–11, 15, 21, 27–31, 34–37, 39, 41–55, 57, 58), we found a significant association between the highest egg consumption (ranging from ≥1 meal/d to ≥3 times/mo among studies) compared with the lowest (ranging from 0–20 g/d to never consumed among studies) and increased risk of UADT cancers (overall OR:1.42; 95% CI: 1.19,1.68; $P < 0.001$) (**Figure 2**). However, between-study heterogeneity was significant ($I^2 = 74.8\%$; P-heterogeneity <0.001). When we removed the study of Chuang et al. (31), which was a pooled analysis study, the results did not change (OR: 1.42; 95%: 1.17, 1.70; $P < 0.001$). In addition, excluding the study of Toporcov et al. (52), which had a small number of controls and wider ORs than other publications, did not affect the findings (OR: 1.41; 95% CI: 1.18, 1.68; $P < 0.001$).

To find the source of heterogeneity, we conducted subgroup analysis for two mainly reported outcomes: 'oropharyngeal and laryngeal' and 'esophageal' cancers. Combining 24 effect sizes from 20 studies (10, 11, 15, 27, 30, 31, 34, 35, 37, 39, 42, 44, 46, 48, 49, 51–53, 57, 58) on 'oropharyngeal and laryngeal' cancer, we found that individuals with the highest egg consumption had a 49% increased risk of these cancers (OR: 1.49; 95% CI: 1.35, 1.64; $P < 0.001$). When we excluded the study of Toporcov et al. (53), the same findings were obtained (OR: 1.49; 95% CI: 1.35, 1.64; $P < 0.001$). Based on 16 effect sizes from 14 case-control studies on esophageal cancer (9, 10, 21, 28, 29, 36, 41, 43, 45, 47, 48, 50, 54, 55), we reached an overall effect size of 1.28, meaning a 28% increased risk of esophageal cancer for individuals with the highest egg consumption compared with those of the lowest egg intake (OR: 1.28; 95% CI: 1.10, 1.48; $P = 0.001$).

Due to a high between-study heterogeneity in these two sets of studies (for studies on 'oropharyngeal and laryngeal cancer': $I^2 = 79.9\%$; P-heterogeneity <0.001 and for studies on 'esophageal cancer': $I^2 = 62.5\%$; P-heterogeneity <0.001), we performed subgroup analysis by outcome, study design, energy adjustment, gender, country, smoking adjustment, alcohol adjustment, and study quality (**Table 2**).

In the subgroup analysis based on studies on 'oropharyngeal and laryngeal cancer', we found a positive association between the highest egg consumption compared with the lowest and risk of oropharyngeal (OR: 1.88; 95% CI: 1.61, 2.20; $P < 0.001$), laryngeal (OR: 1.83; 95% CI: 1.45, 2.32; $P < 0.001$), and 'oral & pharyngeal & laryngeal' cancers (OR: 1.37; 95% CI: 1.12, 1.67; $P = 0.002$) and an inverse association between egg intake and the risk of oral cancer (OR: 0.78; 95% CI: 0.62, 0.99; $P = 0.04$). In addition, a significant positive association was seen between egg intake and risk of 'oropharyngeal and laryngeal cancer' in HCC studies (OR = 1.50; 95% CI: 1.34, 1.68; $P < 0.001$), as well as in studies either adjusted (OR: 1.89; 95% CI: 1.56, 2.29 $P < 0.001$) or not for total energy intake (OR: 1.38; 95% CI: 1.23, 1.54; $P < 0.001$). This association was also seen in studies that involved both genders (OR: 1.55; 95% CI: 1.40, 1.72; $P < 0.001$), performed in non-Asian countries (OR: 1.76; 95% CI: 1.53, 2.02; $P < 0.001$) and those that adjusted (OR: 1.39; 95% CI: 1.22, 1.58; $P < 0.001$) or not for smoking (OR: 1.63; 95% CI: 1.41, 1.89; $P < 0.001$). Sensitivity analysis revealed that none of the single studies had a significant effect

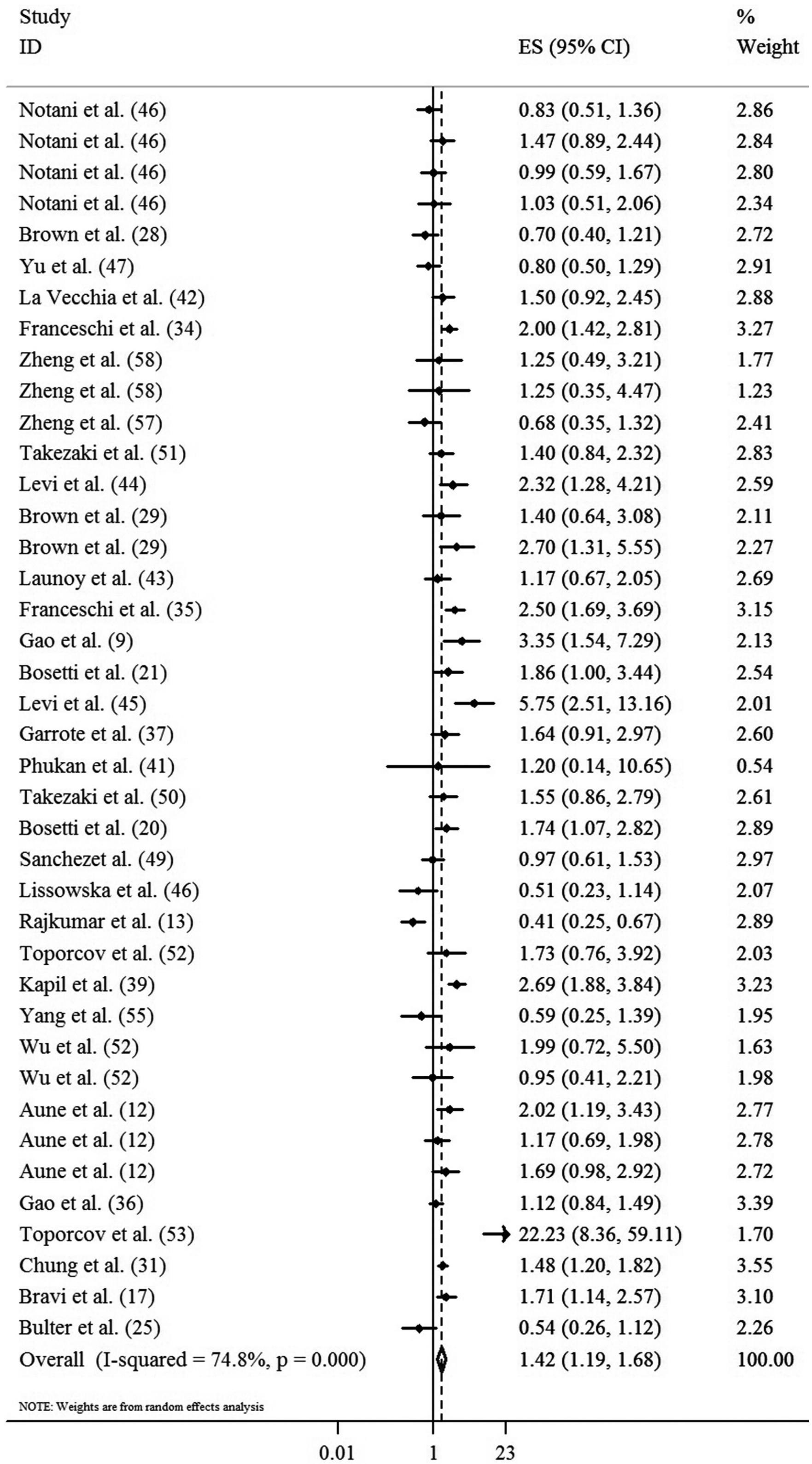

FIGURE 2 Forest plot derived from random-effects meta-analysis of case-control studies investigating the association between egg consumption and UADT cancers. UADT, upper-aero-digestive tract; ES, effect size.

TABLE 2 Results of subgroup analysis for egg consumption and risk of upper aero-digestive tract in case-control studies

	No. of effect sizes	OR (95% CI)	*P*-within[1]	I^2 (%)	*P*-between[2]
Subgroup analyses for oropharyngeal and laryngeal cancers					
Outcome					< 0.001
Oral cancer	6	0.78 (0.62, 0.99)	0.005	70.2	
Oropharyngeal cancer	11	1.88 (1.61, 2.20)	<0.001	73.4	
Laryngeal cancer	4	1.83 (1.45, 2.32)	0.019	69.9	
Oral & pharyngeal & laryngeal cancer	2	1.37 (1.12, 1.67)	0.009	85.4	
Study design					0.893
Population-based case-control	2	1.25 (0.59, 2.67)	1.00	0.00	
Hospital-based case-control	21	1.50 (1.34, 1.68)	<0.001	82.15	
Adjustment for energy intake					0.006
Yes	6	1.89 (1.56,2.29)	0.301	17.4	
No	18	1.38 (1.23, 1.54)	<0.001	82.7	
Gender					0.102
Both	19	1.55 (1.40, 1.72)	<0.001	82.8	
Male	4	1.10 (0.82, 1.48)	0.456	0.0	
Asian vs. non-Asian					0.001
Asian	10	1.15 (0.96, 1.37)	<0.001	81.7	
Non-Asian	13	1.76 (1.53, 2.02)	<0.001	75.5	
Adjustment for smoking					0.225
Yes	17	1.39 (1.22, 1.58)	<0.001	75.2	
No	7	1.63 (1.41, 1.89)	<0.001	86.6	
Adjustment for alcohol consumption					0.115
Yes	19	1.43 (1.26, 1.61)	<0.001	80.8	
No	5	1.62 (1.37, 1.90)	0.002	75.9	
Study quality[3]					0.73
High quality	11	1.44 (1.24, 1.67)	<0.001	79.9	
Low quality	12	1.57 (1.33, 1.84)	<0.001	82.1	
Subgroup analyses for esophageal cancer					
Outcome					
Study design					0.93
Population-based case-control	10	1.16 (0.97, 1.39)	0.006	60.7	
Hospital-based case-control	6	1.56 (1.20, 2.02)	0.016	64.1	
Adjustment for energy intake					0.001
Yes	6	1.87 (1.44, 2.44)	0.044	56.2	
No	10	1.08 (0.90, 1.28)	0.048	47.2	
Gender					0.31
Both	11	1.34 (1.12, 1.60)	0.001	66.6	
Male	5	1.13 (0.837, 1.49)	0.059	55.9	
Asian vs. non-Asian					0.41
Asian	8	1.20 (0.98, 1.47)	0.099	41.9	
Non-Asian	8	1.36 (1.10, 1.69)	<0.001	74.4	
Adjustment for smoking					0.085
Yes	11	1.44 (1.18, 1.77)	0.002	63.4	
No	5	1.11 (0.90, 1.38)	0.045	58.9	
Adjustment for alcohol consumption					
Yes	12	1.37 (1.14, 1.66)	0.002	62.2	
No	4	1.14 (0.90, 1.44)	0.023	68.4	
Study quality[3]					0.236
High quality	10	1.41 (1.13, 1.75)	0.001	66.6	
Low quality	6	1.18 (0.97, 1.44)	0.040	57.2	

[1] *P* values were obtained through fixed-effects analysis.
[2] *P* values were obtained through random-effects analysis.
[3] Study quality: high: score ≥ 7, Low: score <7.

on the overall effect size. No evidence of publication bias was observed ($P_{\text{Egger's test}} = 0.55$).

When we performed subgroup analysis based on studies on 'esophageal cancer', a significant positive association between the highest egg consumption compared with the lowest intake and risk of esophageal cancer was seen in HCC studies (OR: 1.56; 95% CI: 1.20, 2.02; $P = 0.001$), as well as in studies adjusted for energy intake (OR: 1.87; 95% CI:

1.44–2.44; $P < 0.001$), smoking (OR: 1.44; 95% CI: 1.18, 1.77; $P < 0.001$), and alcohol (OR: 1.37; 95% CI: 1.14, 1.66; $P < 0.001$) and those that involved both genders (OR: 1.34; 95% CI: 1.12, 1.60; $P = 0.001$). The same findings were obtained for studies from non-Asian countries (OR: 1.36; 95% CI: 1.10, 1.69; $P = 0.005$) and those of high quality (OR: 1.41; 95% CI: 1.13, 1.75; $P = 0.002$). No single study influenced the overall effect size in our sensitivity analysis. No evidence of publication bias was observed ($P_{\text{Egger's test}} = 0.64$).

To conduct dose-response meta-analysis on egg consumption and UADT cancers, only 4 studies reported the required information; in these 4 studies, the outcome was esophageal cancer (9, 36, 41, 47). Consumption of one additional egg per wk was not associated with an increased risk of esophageal cancer (OR: 1.06; 95% CI: 0.95, 1.18; $P = 0.27$; $I^2 = 74.8\%$; P-heterogeneity $= 0.008$). No evidence of a significant nonlinear association was observed between egg intake and the risk of esophageal cancer ($P = 0.35$) (**Figure 3**). For other UADT cancers, sufficient information was not available to perform dose-response analysis.

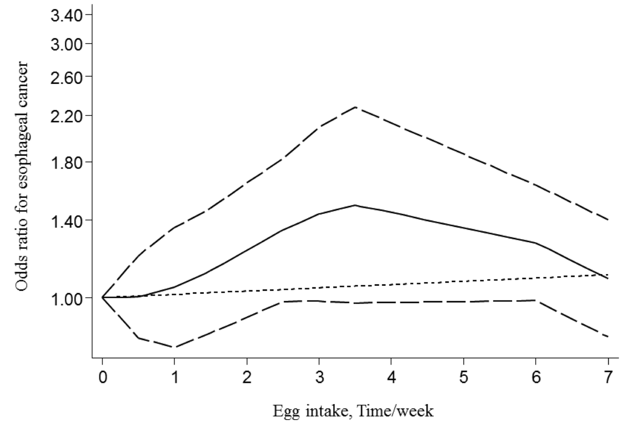

FIGURE 3 Nonlinear dose-response meta-analysis of case-control studies investigating the association between egg consumption and risk of esophageal cancer ($P = 0.35$).

Findings from the meta-analysis on cohort studies

Combining results from 4 cohorts (32, 34, 40, 56) and 2 nested case-control studies (12, 38), with 6 effect sizes, we found no significant association between the highest egg consumption (ranging from ≥5 times/wk to ≥1 time/mo among studies) compared with the lowest (ranging from <1 time/wk to never consumed among studies) and risk of UADT cancers (OR: 0.86; 95% CI: 0.71, 1.04; $P = 0.11$) (**Figure 4**). When we excluded nested case-control studies (12, 38) from the analysis, similar findings were obtained (OR: 0.95; 95% CI: 0.84, 1.07; $P = 0.37$; $I^2 = 0.0\%$, P-heterogeneity $= 0.67$). No significant between-study heterogeneity ($I^2 = 35.2\%$; $P = 0.173$) and publication bias ($P_{\text{Egger's test}} = 0.67$) was seen. Required data were not available to perform dose-response analysis.

Discussion

Based on findings of the present meta-analysis, we found a positive association between egg consumption and the risk of UADT cancers in case-control studies; however, this was not confirmed by prospective data. In the subgroup analysis, we found a positive significant association between egg intake and the risk of 'oropharyngeal', 'laryngeal', 'oral & pharyngeal & laryngeal', and 'esophageal' cancers but this association was inverse for oral cancer. This study is among the first publications to examine the relation between egg consumption and the risk of UADT cancers.

UADT cancers are associated with significant morbidity and mortality (60, 61) and diet is a potentially modifiable risk factor for UADT cancers (7). We found a positive association between egg consumption and the risk of UADT cancers in case-control studies, but not in prospective cohort studies. In addition, when we considered HCC versus PCC studies separately, we found this association only in hospital-based studies. Contradictory to our findings on case-control studies, several previous studies have reported a significant positive association between egg intake and oropharyngeal cancer (10, 15, 34, 35, 44, 53), laryngeal cancer (27, 39), and oral & pharyngeal & laryngeal cancer (31). However, some others did not find any significant association (10, 30, 37, 42, 48, 49, 58). Only 1 study (11) has reported a protective relation between egg consumption and the risk of oral cancer; others found no significant association (46, 48, 51, 52, 57). Earlier studies conducted on esophageal cancer concluded there was no significant association between egg intake and the risk of esophageal cancer (10, 28, 29, 36, 41, 43, 47, 48, 50, 54, 55). The 2018 report of the World Cancer Research Fund (WCRF), which has summarized the scientific evidence on cancer prevention, concluded that there is 'limited' evidence with regards to egg intake and risk of mouth, pharynx, larynx, and esophageal cancers and therefore they claimed that there could be 'no conclusion' regarding the association (18, 19). They defined 'limited-no conclusion' evidence as 'data were of too low quality, too inconsistent', or 'few number of studies'. However, the methodology used in that report was different from ours. They restricted their literature search to only Medline, up to April 2015, whereas in addition to Medline/PubMed, we searched several other databases including ISI Web of Knowledge, EMBASE, Scopus, and Google Scholar until May 2018. The report of the WCRF only included cohort and nested case-control studies and 1 pooled analysis, whereas we considered all observational studies examining the association between egg consumption and the risk of UADT cancers, including 4 cohort, 2 nested case-control, 1 pooled analysis, and 32 case-control studies. Furthermore, despite sufficient information on individual cancers of the mouth, pharynx, larynx, and pharyngeal cancers, they did not consider separately analyzing egg consumption in relation to these cancers.

Eggs are cooked by different methods in various countries based on food culture. Boiled or fried eggs are different

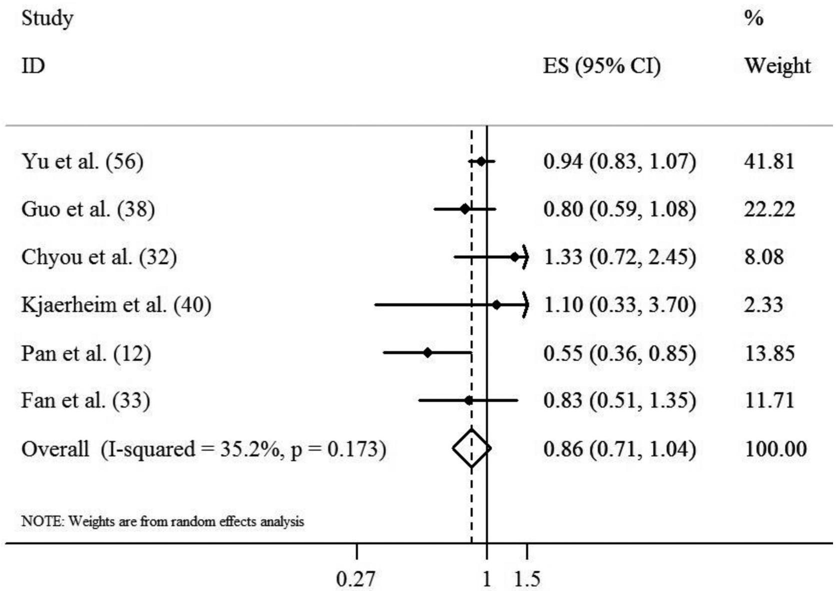

FIGURE 4 Forest plot derived from random-effects meta-analysis of cohort and nested case-control studies investigating the association between egg consumption and risk of UADT cancers. UADT, upper-aero-digestive tract; ES, effect size.

in their nutrient content, in particular, in terms of fatty acids (SFA, PUFA, MUFA, trans-FA) and heterocyclic amines which are formed during high temperature frying (62). Therefore, cooking methods might be an effect modifier when investigating the association between egg and risk of diseases. However, most studies we included did not provide data on the egg preparation method. Moreover, the comparison ranges for egg intake varies across studies; the highest egg intake ranged from ≥1 meal/d to ≥1 time/mo and the range for the lowest intake varied from 0–20 g/d to never consumed. Another important point that should be considered when interpreting our findings is lack of controlling for several confounding factors in the included studies. The WCRF report listed important contributors to UADT cancers including alcohol intake, mate, body fat, physical activity, and dietary intake of coffee, vegetables, fruit, and processed meat which were not controlled in most included studies in our meta-analysis. It should also be kept in mind that the significant associations we found were confined to only HCC studies. These associations were not found in PCC studies or in prospective cohort studies. We all know that findings from case-control studies, in particular HCC, might be misleading because of several methodological limitations that have been mentioned previously (63). Recall bias and selection bias should be considered in these surveys. Although similar covariates were controlled for in HCC and PCC studies, the difference in their findings might be explained by the additional major sources of bias in hospital-based studies compared with population-based studies. For instance, dietary habits of hospital-based controls might not represent those of the general population (64, 65). In addition, the limited number of PCC studies for some cancers might also help explain this difference. In contrast to case-control studies, cohort studies have several strengths (66); however, not all cohort studies we included were of high quality. When we performed the meta-analysis on 4 cohort and 2 nested case-control studies, no significant association was observed between high egg consumption and the risk of UADT cancers. Such differences between findings of case-control and cohort studies were also seen in other investigations on diet–cancer relations (63, 67). In the dose-response meta-analysis, we found no significant association between 1 additional egg intake per wk and increased risk of esophageal cancer. Considering the limitations of case-control studies and limited number of cohort studies in this field, it seems additional data are required to shed light on this issue.

Several potential mechanisms may explain the association of egg consumption with UADT cancers. The most plausible explanation for the positive association between egg intake and the risk of UADT is the role of animal fat and protein and the high cholesterol content of eggs. Several previous investigations found a direct association between animal fats, proteins, saturated fatty acids, and cholesterol intake and risk of oropharyngeal and laryngeal cancers (15, 34, 52, 68). Fatty acids may also influence carcinogenesis, including their effect on cell membrane integrity, increasing lipid peroxidase, alteration of hormone concentrations, and impairment of nutrient metabolism (69). Moreover, high egg consumption, which is a cheap source of animal protein, may be a general indicator of low income and poor diet (44). Frequent egg intake was associated with poor and unhealthy diets and higher intakes of total, red, and processed meats (10), all of which were defined as risk factors for esophageal squamous cell carcinoma (19). On the other hand, egg contains high amounts of some micronutrients including vitamin A and riboflavin. These nutrients are involved in repairing damaged mucosal lining and might have anti-carcinogenic effects (70–72), which can in turn explain the inverse association of egg intake and oral cancer.

This meta-analysis was among the first studies to summarize the relation between egg intake and the risk of UADT cancers. A large sample size (164,241 subjects and 27,025 cases) from different geographic regions with different dietary patterns are among the strengths of this study. Furthermore, our findings were stable and robust in sensitivity analysis. We used a prospectively defined protocol, explicit study inclusion criteria, and comprehensive literature search with the least limitations; however, some limitations should be noted. Total energy intake, alcohol consumption, and smoking were not considered as confounding factors in all included studies. In addition, none of the studies considered physical activity. Residual confounding by other inadequately measured covariates could also be of concern. Self-reported egg intake through questionnaires that might inevitably result in some misclassification of participants in terms of exposure must be noted. We have considered the amount of egg intake in different categories of egg consumption if they were reported in the original articles. However, we were not able to perform a meta-regression on the actual egg intake data due to lack of such information in the included studies. In addition, we did not consider cooking methods of egg due to lack of data. Moreover, we performed dose-response meta-analysis on a limited number of studies (only 4 studies regarding esophageal cancer) that provided adequate data.

Conclusion

In conclusion, we found no significant association between egg consumption and risk of UADT cancers in PCC and prospective cohort studies; however, a positive significant relation was observed in HCC studies for egg intake and UADT cancers, except for oral cancer, which was inversely associated with egg consumption.

Acknowledgments

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