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ORIGINAL CONTRIBUTION

Egg consumption and risk of GI neoplasms: dose–response meta-analysis and systematic review

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Abstract
Purpose Previous epidemiological studies on egg consumption and the risk of gastrointestinal (GI) neoplasms suggest a positive association; however, data are limited and the evidence remains controversial. This study aims to investigate and quantify the potential dose–response relationship with an evaluation of cancer site-specific differences.
Methods Relevant studies were identified after the literature search via electronic databases until January 2014. Subgroup analysis for serving portions was performed using two standardized classification methods: (1) less than 3, or 3 or more eggs per week; (2) less than 3, 3–5, or more than 5 eggs per week. Method two excludes studies that only reported consumption frequency. Pooled adjusted odds ratios (ORs) comparing highest and lowest categories of dietary pattern scores were calculated using a random-effects model.
Results Thirty-seven case–control and seven cohort studies were included for meta-analysis, which contained a total of 424,867 participants and 18,852 GI neoplasm cases. The combined odds ratio (OR) was calculated to 1.15 (95 % CI 1.09–1.22; p value heterogeneity <0.001), showing only a slight increase in risk. The correlation was stronger for colon cancers 1.29 (95 % CI 1.14–1.46; p value heterogeneity <0.22). Dose–response analysis revealed similar results with stratification methods, and the ORs for an intake of <3 and ≥3 eggs per week were 1.14 (95 % CI 1.07–1.22; p value heterogeneity = 0.38) and 1.25 (95 % CI 1.14–1.38; p value heterogeneity = 0.25), respectively. With method 2, the ORs for an intake of <3, 3–5, and >5 eggs per week were 1.13 (95 % CI 1.06–1.21; p value heterogeneity = 0.25), 1.14 (95 % CI 1.01–1.29; p value heterogeneity = 0.06), and 1.19 (95 % CI 1.01–1.39; p value heterogeneity <0.001), respectively.
Conclusion This study provides evidence that egg consumption is associated with a positive dose–response association with the development of GI neoplasms.

Keywords Egg · Gastrointestinal neoplasms · Colon cancer · Meta-analysis

Introduction

The association between risk of GI neoplasms and consumption of foods of animal origin has been investigated in many studies. Eggs provide roughly 1.2 % of available food energy worldwide, with consumption being highest in the Far East, North America, and Europe, contributing a significant portion of dietary cholesterol, protein, minerals, folate, and B group vitamins [1]. Given that eggs are an important component of diet in the developed world, an evaluation of their specific role in GI neoplasm development is warranted.

Epidemiological studies have yielded conflicting and controversial results, although a positive, insignificant relation was found in most studies. One systematic review reported a consistent positive association between egg intake and colorectal cancer (CRC) risk in nine out of eleven studies included, with odds ratios (OR) or relative risks (RR) ranging from 1.1 to 8.2 for high- versus low-intake [2]. Some studies also suggested an increased risk of

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oesophageal and gastric cancers [3–7]. Despite this, little is known about the potential relation between egg consumption and the risk of GI cancers. Currently, no systematic review exists to thoroughly assess and unify the epidemiological evidence.

The mechanisms that underlie the associations between eggs and GI cancer risk remain hypothetical. Previous studies have suggested that eggs could promote colorectal carcinogenesis due to their high cholesterol content [2]. Eggs are among the top contributors of cholesterol to the average Australian and US diet [8]. High intakes of cholesterol have been shown to increase the formation of secondary bile acids in humans and animals and promote the induction of colorectal tumours in animal models [9, 10]. Egg yolk was also shown to increase the frequency of gallbladder contraction and subsequent exposure of bile acids to the intestine [11]. There is strong evidence to suggest that bile acids are carcinogens in GI cancer [12]. Another cohort study reported a positive correlation between egg consumption and colorectal adenomas, precursors of CRC [13]. In addition, eggs are one of the few food sources that contain high concentrations of choline [14]. Animal studies showed that a choline-enriched diet was associated with a higher incidence of hepatocellular carcinoma [15]. Choline kinase, an enzyme that breaks down choline, is also elevated in colon cancer [16].

Although current understanding of the biological mechanisms involved is very limited, a multifactorial process is plausible and warrants further investigation, especially given the relatively strong evidence in risk reported with greater egg consumption in some epidemiological studies. Information on the amount consumed and the frequency of consumption would help to identify dose relationships and substantiate any association. Various epidemiological studies have used different parameters in reporting the serving sizes, and hence, descriptions of "high" and "low" intakes are highly varied, which undermines the collective evidence of the presence of an association.

This systematic review aims to summarize epidemiological findings as well as provide a unified body of evidence of the serving portions of egg consumed and its effect on GI neoplasm development so as to form guidelines for egg consumption and guide future investigations.

Methods

Study protocol

The literature searches of epidemiological studies in this systematic review were performed using the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines where possible [17]. The following electronic databases were searched: MEDLINE, PubMed, ISI Web of Science, Current Contents Connect, and Embase. The search included all observational studies published up to January 2014. Key terms including "Diet" and "GI neoplasm" were searched as text words and as exploded medical subject headings where possible. Titles and abstracts were then screened for relevant data on egg intake and GI neoplasm risk. References in the relevant review articles from the bibliographic database search were also checked for appropriate studies. No language restrictions were used in either the search or study selection. A search for the unpublished literature was not performed.

Study selection

The following inclusion criteria were applied in the screening of articles: (1) original data on egg consumption and GI neoplasms risk, that of the oesophagus, stomach, and/or colorectum, were provided; (2) the risk point estimate was reported as OR or RR, or the data were presented such that an OR could be calculated; and (3) the 95 % confidence interval (CI) was reported, or the data were presented such that the CI could be calculated.

Data extraction

Data were performed via a standardized data extraction form, collecting information on the publication year, study design, number of cases and controls, total sample size, temporal direction, population type, country, ethnicity of sample group, case–control matching, neoplasm type, number of adjusted variables, the risk estimates or data used to calculate the risk estimates, CIs. Quality of the studies was not assessed, and authors were not contacted for missing data. Adjusted odds ratios were extracted in preference to non-adjusted odds ratios; however, where odds ratios were not provided, unadjusted ORs and CIs were calculated. Where more than one adjusted ratio was reported, the ratio with the highest number of adjusted variables was chosen. Where multiple risk estimates were available in the same study, for example due to the use of different comparator groups, they were included as separate risk estimates.

Statistical analysis

Pooled odds ratios and 95 % confidence intervals were calculated for the effect of egg consumption on the risk of GI neoplasms using a random-effects model, model of DerSimmonian and Laird [18]. Heterogeneity with Cochran's Q statistic was tested, with $p < 0.10$ indicating heterogeneity, and the degree of heterogeneity was quantified

Table 1 Characteristics of included studies reporting odd ratios and 95 % CIs for the association between egg intake and GI neoplasm risk

References	Location	Ethnic group	Group	Type of neoplasm	Total cases/controls or cohort size	Serving sizes	OR
Case–control studies							
Risch 1985 [52]	Canada	Caucasian	Hospital	Gastric cancer	246/246	100 g/day	2.86 (1.09–7.51)
Macquart-Moulin 1987 [43]	Marseilles	Caucasian	Hospital	Colorectal polyps	252/238	>30 g/day	1.09 (0.64–1.88)
Yu 1988 [64]	USA	Multiethnic	Population	Gastric cancer	128/128	>5 eggs/week	1.20 (0.60–2.30)
Benito 1990 [2]	Spain	Caucasian	Hospital	CRC	286/295	>2.5 times/week	2.78 (1.36–5.67)
Gonzalez 1991 [22]	Spain	Caucasian	Population	Gastric cancer	354/354	>44 g/day	1.60 (0.90–2.70)
Hu 1991 [29]	China	Asian	Hospital	Rectal cancer	116/116 (Male)	High	3.07 (1.22–7.72)
Hoshiyama 1992 [26]	Japan	Asian	Hospital	Gastric cancer	294/202	>5 times/week	0.90 (0.50–1.70)
Iscovich 1992 [32]	Argentina	Caucasian	Population	Colon cancer	110/220	>87 times/year	4.66 (1.51–14.38)
Steinmetz 1993 [59]	Australia	Caucasian	Hospital	Colon cancer	90/180 (Male)	>7 eggs/week	1.29 (0.69–2.41)
					75/147 (Female)		2.69 (1.16–6.22)
Centonze 1994 [11]	Italy	Caucasian	Population	CRC	119/115	>12 g/day	0.46 (0.18–1.21)
Cornée 1995 [13]	France	Caucasian	Hospital	Gastric cancer	92/128	>29 g/day	0.84 (0.42–1.68)
Inoue 1995 [31]	Japan	Asian	Hospital	Proximal colon cancer	256/5,500 (Male)	>3 times/week	2.00 (1.00–4.00)
				Distal colon cancer			1.20 (0.70–1.90)
				Rectal cancer			1.00 (0.70–1.40)
				Proximal colon cancer	173/16,421 (Female)		1.00 (0.50–1.90)
				Distal colon cancer			1.00 (0.60–1.70)
				Rectal cancer			0.80 (0.50–1.40)
Kampman 1995 [35]	Netherlands	Caucasian	Hospital	Colon cancer	232/259	>19 g/day	1.17 (0.68–2.01)
Shannon 1996 [55]	USA	Caucasian	Population	Colon cancer	196/180 (Male)	>3 eggs/week	1.10 (0.65–1.85)
					149/144 (Female)		1.05 (0.59–1.86)
Franceschi 1997 [20]	Italy	Caucasian	Population	CRC	1,953/4,154	>2 eggs/week	0.92 (0.75–1.14)
Marchand 1997 [38]	USA	Multiethnic	Hospital	CRC	698/698 (Male)	>29 g/day	2.70 (1.70–4.00)
					494/494 (Female)	>19 g/day	2.30 (1.40–3.70)
Brown 1998 [9]	USA	African American, Caucasian	Population	Oesophageal cancer	114/681 (Caucasian Male)	High	2.50 (1.40–4.60)
					219/557 (Africa American Male)		1.40 (0.60–2.90)
Ji 1998 [34]	China	Asian	Population	Gastric cancer	770/819 (Male)	>17.5 eggs/month	0.60 (0.40–0.80)
					354/632 (Female)		0.50 (0.40–0.80)
Launoy 1998 [37]	France	Caucasian	Hospital	Oesophageal cancer	208/399 (Male)	>45 g/day	1.17 (0.68–2.08)
Boutron-Ruault 1999 [8]	France	Caucasian	Hospital	CRC	171/309	40.5 g/day	1.10 (0.60–2.10)
Gao 1999 [21]	China	Asian	Population	Oesophageal cancer	234/234	>3 times/week	3.35 (1.54–7.30)
				Gastric cancer			3.79 (2.20–7.10)
Levi 1999 [40]	Switzerland	Caucasian	Hospital	CRC	223/491	>2.5 eggs/week	1.30 (0.84–2.02)
Bosetti 2000 [7]	Italy	Caucasian	Hospital	Oesophageal cancer	304/743	>2.9 eggs/week	1.86 (1.00–3.43)
Mathew 2000 [44]	India	Asian	Hospital	Gastric cancer	305/194	Daily	1.70 (0.70–4.30)

Table 1 continued

References	Location	Ethnic group	Group	Type of neoplasm	Total cases/controls or cohort size	Serving sizes	OR
Slattery 2000 [56]	USA	Multiethnic	Population	Colon cancer	1,624/1,963	>3 eggs/week	1.30 (1.00–1.80)
Munoz 2001 [47]	Venezuela	Caucasian	Hospital	Gastric cancer	302/485	High	0.83 (0.52–1.34)
Nishimoto 2002 [50]	Brazil	Hispanic	Population	Gastric cancer	236/236	Daily	3.20 (1.70–6.00)
Senesse 2002 [54]	France	Caucasian	Population	Small colorectal adenoma	362/427	>45 g/day	1.40 (0.80–2.60)
				Large colorectal adenoma			1.00 (0.60–1.70)
Dray 2003 [17]	France	Caucasian	Population	CRC	148** (no # controls given)	High	1.10 (0.52–2.33)
Stefani 2004 [15]	Uruguay	Caucasian	Hospital	Gastric cancer	248/1,734	High	0.48 (0.33–0.69)
Hu 2007 [28]	Canada	Caucasian	Population	Proximal colon cancer	375/1,588 (Male)	>4 eggs/week	1.40 (0.70–2.50)
					345/1,441 (Female)		1.30 (0.60–2.90)
Hu 2007 [27]	Canada	Caucasian	Population	Rectal Cancer	814/1,588 (Male)	>4 eggs/week	1.30 (1.00–1.70)
					540/1,441 (Female)		0.90 (0.50–1.60)
Lucenteforte 2008 [42]	Italy	Caucasian	Population	Gastric cancer	230/547	>6 eggs/week	1.15 (0.77–1.70)
Aune 2009 [1]	Uruguay	Caucasian	Hospital	Oesophageal cancer	870/2,032	>3.5 eggs/week	1.69 (0.98–2.93)
				Gastric cancer			1.19 (0.69–2.04)
				Colon cancer			3.21 (1.68–6.11)
				Rectal cancer			0.90 (0.48–1.72)
Ramadas 2009 [51]	Malaysia	Asian	Population	Colorectal adenoma	59/59	>3 times/week	0.55 (0.23–1.34)
Williams 2009 [62]	USA	Caucasian, African American	Hospital	Rectal cancer	720/800 (Caucasian)	4.2 eggs/week	1.07 (0.76–1.50)
					225/159 (African American)	6.6 eggs/week	1.53 (0.73–3.20)
Icli 2011 [30]	Turkey	Caucasian	Population	Gastric cancer	253/253	>3 times/week	1.20 (0.70–2.10)
Cohort studies							
Guo 1994 [23]	China	Asian	Population	Oesophageal cancer	659/29,584	>5 times/month	0.80 (0.60–1.10)
				Gastric cancer			0.90 (0.70–1.20)
Ngoan 2002 [49]	Japan	Asian	Population	Gastric cancer	50/13,250	>1 egg/day	0.80 (0.40–1.60)
Ito 2003 [33]	Japan	Asian	Population	Gastric cancer	341/24,886 (Female)	>3 times/week	1.16 (0.96–1.40)
Kojima 2004 [36]	Japan	Asian	Hospital	Colon cancer	180/45,181 (Male)	Daily	1.54 (0.99–2.42)
				Rectal cancer			0.82 (0.54–1.26)
				Colon cancer	130/62,643 (Female)		1.17 (0.79–1.75)
				Rectal cancer			0.75 (0.39–1.46)
Tokui 2005 [61]	Japan	Asian	Population	Gastric cancer	497/45,181 (Male)	>1 egg/day	1.13 (0.79–1.62)
					252/62,643 (Female)		2.32 (1.22–4.42)
Fan 2008 [19]	China	Asian	Population	Oesophageal cancer	68/18,244 (Male)	High	0.83 (0.51–1.35)
Lee 2009 [39]	China	Asian	Population	CRC	109/73,224 (Female)	>44 g/day	1.40 (1.10–2.0)

using the I^2 statistic, which represents the percentage of the total variability across studies due to heterogeneity. I^2 values of 25, 50, and 75 % corresponded to low, moderate, and high degrees of heterogeneity, respectively [19]. Publication bias was quantified using the Egger's regression model. All analyses were performed with comprehensive meta-analysis [20].

As different methods were used to report egg intake, subgroup analysis on serving sizes involved categorizing studies using a standardized measurement of consumption per week, based on an average weight of 55 g per egg. Two different classification methods were developed: (1) less than 3, or 3 or more eggs per week; (2) less than 3, 3–5, or more than 5 eggs per week. The second method did not include studies that only reported consumption frequency.

Analyses were performed to determine whether data collection design influenced the pooled estimate. Several parameters were evaluated: (1) interviews versus self-administered questionnaires; (2) the use of validated food frequency questionnaires versus non-validated ones; and (3) the inclusion of a pilot study versus without. An additional sensitivity analysis was done by excluding studies that measure dietary habits more than 1 year before diagnosis.

Results

The literature searches identified 538 articles for evaluation. Title and abstract screening excluded 475 articles due to duplicates, non-human or non-original research. Full-text screening excluded 19 articles—13 studies did not include eggs in the dietary assessment, confidence intervals could not be calculated in three studies, two studies did not present original data, and the risk estimate was not provided in one study. Thirty-seven case–control and seven cohort studies were eligible for inclusion, which contained a total of 424,867 participants and 18,852 GI neoplasm cases. Characteristics of included studies are outlined in Table 1. Exclusion reasons for the remainder included the following: original epidemiological data on the association between egg intake and GI neoplasm risk were not provided; risk estimates could not be obtained; CIs were not provided and could not be calculated (Fig. 1).

The combined OR was consistent with a positive association between egg consumption and GI neoplasm, calculated to be 1.15 (95 % CI 1.09–1.22; p value heterogeneity <0.001), showing only a slight increase in risk. Analysis of variables including country, gender, ethnicity, study population, study design, and neoplasm type was conducted (Table 2). Egger's regression analysis for assessment of publication bias of the studies included in this meta-analysis found significant bias ($p < 0.001$) (Fig. 2).

In our dose–response analysis, 38 studies reported either the serving sizes of eggs consumed or the frequency of consumption, 29 of which specified the amount of intake in quantifiable units. Stratification using the classification method 1 identified 22 articles that reported a serving size of <3 eggs per week and 30 articles that reported 3 or more eggs per week. Among these, 30 were case–control studies and five were cohort studies, representing a total of 923 oesophageal cases, 4,009 gastric cancer cases, 2,878 colon cancer cases, 2,215 rectal cancer cases, 2,225 CRC cases, and 498 colorectal adenoma cases. Stratification using the classification method 2 identified 17 studies which reported a serving size of <3 eggs per week, 13 studies reported 3–5 eggs per week, and 18 studies reported more than 5 eggs per week. Twenty-five were case–control studies and two were cohort studies. Among these, there were 1,051 oesophageal cancer cases, 2,378 gastric cancer cases, 2,385 colon cancer cases, 1,954 rectal cancer cases, 1,995 CRC cases, and 464 colorectal adenomas.

Both methods revealed a statistically significant dose–response relationship with egg intake and GI neoplasm risk (Table 3). With method 1, the ORs for an intake of <3 and 3 or more eggs per week were 1.14 (95 % CI 1.07–1.22; p value heterogeneity = 0.38) and 1.25 (95 % CI 1.14–1.38; p value heterogeneity = 0.25), respectively. With method 2, the ORs for an intake of <3, 3–5, and >5 eggs per week were 1.13 (95 % CI 1.06–1.21; p value heterogeneity = 0.25), 1.14 (95 % CI 1.01–1.29; p value heterogeneity = 0.06), and 1.19 (95 % CI 1.01–1.39; p value heterogeneity <0.001), respectively.

Site-specific risks

Subgroup site-specific analysis produced similar results using both classification methods; egg consumption posed a slight increase in risk of developing cancers of the stomach, colon, and colorectum; higher amounts posed a greater risk, indicating a possible but small dose effect. For the first classification method, the associations of egg intake and both colon cancer and CRC risk were statistically significant. With an intake of <3 eggs per week, the combined ORs for colon cancer and CRC were 1.16 (95 % CI 1.02–1.32; p value heterogeneity = 0.6) and 1.19 (95 % CI 1.04–1.36; p value heterogeneity = 0.18), respectively. With an intake of 3 or more eggs per week, the combined ORs for colon cancer and CRC were 1.28 (95 % CI 1.09–1.51; p value heterogeneity = 0.14) and 1.71 (95 % CI 1.26–2.32; p value heterogeneity = 0.08), respectively. For the second method, the association was statistically significant for colon cancer only. The ORs for an intake of <3, 3–5, and >5 eggs per week were 1.16 (95 % CI 1.02–1.32; p value heterogeneity = 0.62), 1.15 (95 % CI 0.95–1.41; p value heterogeneity = 0.47) and 1.42 (95 % CI 1.08–1.87; p value heterogeneity = 0.34), respectively.

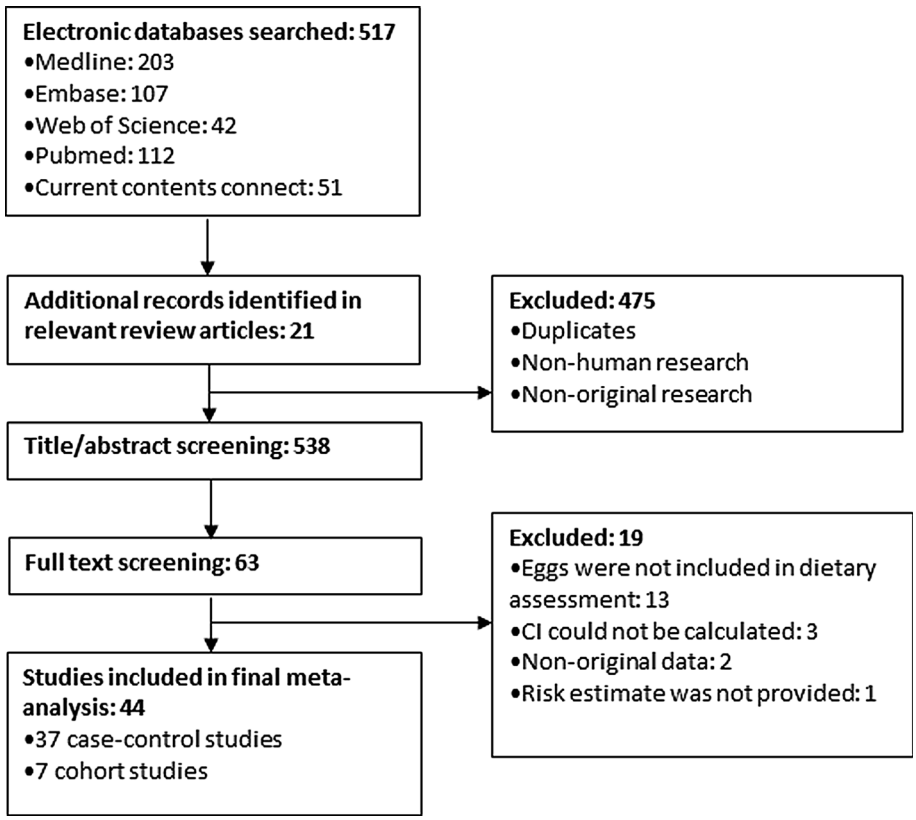

Fig. 1 Flowchart of the study selection process

Ethnicity

With the first classification method, a borderline increased risk of GI cancers was found in Caucasians, with an observed dose effect; the OR for <3 eggs consumed per week is 1.17 (95 % CI 1.1–1.25; p value heterogeneity = 0.49) and 1.26 for 3 or more eggs per week (95 % CI 1.16–1.38; p value heterogeneity = 0.3).

With the second method, Caucasians were also shown to have a slight increase in risk of GI cancers with egg consumption; however, there is no observable dose effect; the ORs for serving sizes of <3, 3–5, and >5 eggs per week are 1.14 (95 % CI 1.07–1.21; p value heterogeneity = 0.5), 1.18 (95 % CI 1.04–1.34; p value heterogeneity = 0.41), and 1.29 (95 % CI 1.07–1.55; p value heterogeneity = 0.47), respectively.

High- versus low-intake analysis

When examining the effect of egg consumption without taking into account the serving sizes, there is a small but statistically significant positive association between egg consumption and CRC (OR, 1.32; 95 % CI 1.13–1.53; p value heterogeneity <0.001), colon cancer (OR, 1.29; 95 % CI 1.14–1.46; p value heterogeneity = 0.22), and proximal colon cancer (OR, 1.31; 95 % CI 1.05–1.62; p value heterogeneity = 0.86) (Table 2).

Geography

Western countries including USA (OR, 1.25; 95 % CI 1.05–1.49; p value heterogeneity <0.001), Australia (OR, 1.46; 95 % CI 1.11–1.94; p value heterogeneity = 0.71), and Canada (OR, 1.21; 95 % CI 1.06–1.38; p value heterogeneity = 0.36) exhibit increased risk in GI cancers with egg consumption (Table 2).

Data collection design

Thirty-three case–control studies collected data using trained interviewers (OR, 1.16; 95 % CI 1.08–1.24; p value heterogeneity <0.001) and 4 studies used self-administered questionnaires (OR, 1.21, 95 % CI 1.10–1.33; p value heterogeneity = 0.47). Five studies included a pilot study in their methods (OR, 1.18; 95 % CI 1.03–1.37; p value heterogeneity = 0.36), while 32 did not (OR, 1.16; 95 % CI 1.09–1.24; p value heterogeneity <0.001). Twenty studies used validated food frequency questionnaires (OR, 1.17; 95 % CI 1.09–1.27; p value heterogeneity <0.001), 17 used questionnaires without stating the validity or reproducibility (OR, 1.15; 95 % CI 1.04–1.28; p value heterogeneity <0.001). The sensitivity analysis showed that studies which asked about dietary habits within a year before diagnosis had a pooled OR of 1.26 (95 % CI 1.17–1.37; p value heterogeneity <0.001) and those that

Table 2 Odd ratios with 95 % CIs for variables examined for the association between egg intake and gastrointestinal neoplasm risk

Factor	OR (95 % CI)
Ethnicity	
Asian	1.07 (0.96–1.18)
Caucasian	1.16 (1.09–1.24)
African American	1.40 (0.85–2.31)
Study design	
Cohort	1.02 (0.91–1.14)
Case–control	1.19 (1.12–1.28)
Population type	
Population	1.12 (1.05–1.20)
Hospital	1.24 (1.11–1.39)
Population gender	
Male	1.08 (0.94–1.23)
Female	1.12 (0.98–1.28)
Neoplasm type	
Oesophageal cancer	1.25 (0.98–1.61)
Gastric cancer	1.07 (0.96–1.20)
Proximal colon cancer	1.31 (1.05–1.62)
Distal colon cancer	1.11 (0.79–1.56)
Colon cancer	1.29 (1.14–1.46)
Rectal cancer	1.02 (0.89–1.15)
CRC	1.32 (1.13–1.53)
Colorectal adenoma	1.23 (1.01–1.51)
Country	
USA	1.25 (1.05–1.49)
Australia	1.46 (1.11–1.94)
Canada	1.21 (1.06–1.38)
China	1.04 (0.87–1.24)
India	1.68 (1.01–2.82)
Japan	1.10 (0.99–1.22)
France	1.16 (0.99–1.36)
Netherlands	1.07 (0.79–1.47)
Switzerland	1.07 (0.72–1.58)
Turkey	1.11 (0.74–1.65)

measured dietary patterns a year or more before had an estimate of 1.21 (95 % CI 1.14–1.28; p value heterogeneity <0.001).

Discussion

Our results show that egg consumption is associated with a very modest increase in the risk of developing neoplasms of the oesophagus, stomach, colon, and colorectum. This correlation was stronger for Western populations. After stratification according to serving sizes, a significant and positive association persisted for colon cancer, with a small dose effect being observed.

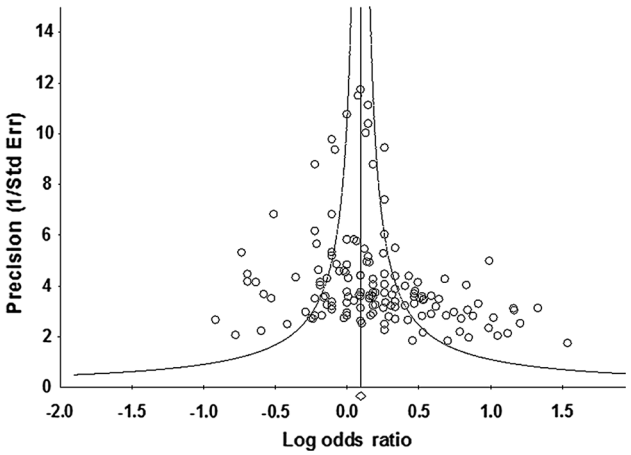

Fig. 2 Funnel plot suggesting publication bias

Different methods of quantifying the amount of eggs consumed have been used in dietary assessments. One study categorized a serving size of >19 g per day as high [21], while a similar serving size was classified as low in another study [3]. Steinmetz's study, the only systematic review on this topic to date, included 15 case–control and cohort studies in his analysis, in which he reported over 70 % of studies of CRC showed increased risk with high egg consumption [2]. However, some of these studies reported different values as high consumption levels. This inconsistency is found in a large number of studies and as such undermines existing evidence. This paper attempts to address this issue by standardizing the measurement of serving sizes across all relevant studies to provide a more unified body of evidence. Two different measurement standards were used in the meta-analysis and compared to reduce error from selection bias. The second method did not include studies that only listed frequency as a measure of egg intake as the absolute amount could not be quantified. Analysis showed that both methods produced similar findings.

When examining site-specific differences, currently there are no hypothesized mechanisms for eggs contributing to the development of oesophageal or gastric cancer, but it could be postulated that mechanisms proposed for colon cancer could be similar. A statistically significant dose-related association was found only for colon cancer when both methods serving size stratification were considered. Reasons underpinning such an association remain poorly understood. An experimental study was conducted to examine egg intake and markers of crypt cell proliferation in the colon and rectum of patients with either disease-free mucosa or adenomatous polyps [22]. High frequency of cell division within the crypt and displacement of proliferative zone towards the bowel lumen are

Table 3 Odd ratios with 95 % CIs for variables examined for the association between egg intake and GI neoplasm stratified by serving sizes using 2 classification methods, and method 2 did not include studies which only reported consumption frequency

Serving sizes (eggs/week)		Method 1		Method 2		
		<3	≥3	<3	3–5	>5
GI divisions	Oesophageal	1.19 (0.89–1.60)	1.32 (0.83–2.09)	1.28 (0.98–1.68)		
	Gastric	1.11 (0.92–1.32)	1.19 (1.02–1.40)	0.99 (0.80–1.24)	1.05 (0.89–1.24)	1.26 (0.88–1.79)
	Colon	1.16 (1.02–1.32)	1.28 (1.09–1.51)	1.16 (1.02–1.32)	1.15 (0.95–1.41)	1.42 (1.08–1.87)
	Rectal	1.06 (0.90–1.26)	0.91 (0.78–1.07)	1.06 (0.90–1.26)	1.09 (0.80–1.48)	0.90 (0.68–1.20)
	CRC	1.19 (1.04–1.36)	1.71 (1.26–2.32)	1.15 (1.04–1.26)		1.32 (0.97–1.80)
Gender	Male	1.11 (0.99–1.24)	1.02 (0.92–1.12)	1.11 (0.99–1.24)	0.89 (0.76–1.05)	0.94 (0.81–1.10)
	Female	1.14 (0.95–1.38)	1.06 (0.95–1.18)	1.14 (0.95–1.38)	1.12 (0.96–1.31)	1.12 (0.93–1.35)
Ethnicity	African American	0.78 (0.38–1.60)	1.33 (0.80–2.21)	0.78 (0.38–1.60)	1.18 (0.59–2.36)	1.53 (0.73–3.20)
	Asian	0.99 (0.89–1.10)	1.00 (0.93–1.09)	0.94 (0.79–1.11)	1.00 (0.89–1.13)	0.97 (0.85–1.10)
	Caucasian	1.17 (1.10–1.25)	1.26 (1.16–1.38)	1.14 (1.07–1.21)	1.18 (1.04–1.34)	1.29 (1.07–1.55)
	Multiethnic	1.11 (0.87–1.41)	1.60 (1.23–2.09)	1.11 (0.87–1.41)	1.00 (0.66–1.52)	1.20 (0.62–2.35)
Overall		1.14 (1.07–1.22)	1.25 (1.14–1.38)	1.13 (1.06–1.21)	1.14 (1.01–1.29)	1.19 (1.01–1.39)

biomarkers for increased risk of neoplasia. Results showed no indication of a causal association. A systematic review also showed that egg consumption did not have a substantial effect on the development of colorectal polyps [23]. It was suggested that egg consumption might be involved in the promotional, but not in the initiating phase of colorectal carcinogenesis.

One of the main mechanisms that has been proposed is based on the high cholesterol content found in eggs. Animal studies have reported that animals fed a high-cholesterol diet displayed a high rate of chemically induced tumours [24]. However, there has been a lack of consistent evidence to support the notion that regular or near-regular egg ingestion leads to substantial elevation in serum lipids and total cholesterol levels. One study found that participants eating less than one egg per week had serum cholesterol levels greater than participants eating more than four eggs per week [25]. Therefore, biological processes involving pathways other than direct effects on serum cholesterol levels may be considered. The metabolites of cholesterol such as cholesterol oxide are formed via bacterial oxidation in bowel and may act to promote colon carcinogenesis [26]. Furthermore, higher intake of cholesterol has been shown to increase the formation of secondary bile acids in both humans and animals [9]. Dietary fat-dependent increases in secondary bile acids were found to damage colonic lumen epithelial cells, consequently promoting the proliferation of the colorectal epithelium and tumour formation [27].

Other more speculative carcinogenic mechanisms for eggs might also be considered. Egg yolk in the duodenum leads to a potent stimulation of cholecystokinin secretion which induces gallbladder contraction [28]. Increased frequency of gallbladder contraction could presumably lead to increased frequency of colonic exposure to potentially carcinogenic bile acids [12]. Eggs may also contribute to the dietary intake of heterocyclic amines which are formed when proteins are cooked at high temperatures [29]. Heterocyclic amines have been associated with the development of oesophageal, gastric, and colon cancers [30]. However, results from two case–control studies indicate that this mechanism is unlikely; no difference in risk was observed for eggs cooked at a high temperature (fried or scrambled) compared with eggs cooked at a lower temperature (boiled or poached) [31, 32]. Further, egg is a rich source of dietary choline. One cohort study found an elevated risk of colorectal adenoma with increasing choline intake [13]. Once a tumour is initiated, growth into a detectable adenoma depends in part on choline availability because choline is needed in membrane production in all rapidly growing cells. The same study reported a statistically significant positive association with egg intake. Rats fed a choline-deficient diet for 3 or 6 months followed by a choline-supplemented diet had higher incidence of hepatocellular carcinoma than animals fed continuously a diet deficient in choline [15]. Choline kinase, an enzyme that converts choline to phosphocholine, an intermediate in the generation of membrane phospholipids, is elevated in human cancers, including colon cancer [16]. While there is limited evidence to provide a biological explanation of the possible dose-related association between eggs and GI cancer, the process is likely to be multifactorial, and it can be speculated that increasing consumption of increases exposure to potential cancer-causing agents.

Several limitations should be taken into account when interpreting the findings from the current study. Most methods involving diet recall often lack validation against some objective reference method which again may lead to

measurement and reporting bias. The studies included in our analysis largely differ in their dietary assessment of egg intake, with some studies reporting exposure in descriptive terms "high vs low" rather than in absolute quantities, and as such serve as a potential source of measurement error. While this issue was addressed by standardizing the measurement of exposure across the studies in our analysis, inherent observational bias would not be eliminated. However, an evaluation of different data collection designs of the case–control studies included showed little differences in the risk estimates, suggesting that such bias did not play a prominent role.

Differences between cases and controls in their ability to recall past dietary habits are of concern in case–control studies. An evaluation of this issue in population samples has shown that such differences in recall are minor when cases are interviewed soon after diagnosis. Most studies in this paper were conducted within 3 months of diagnosis and thus were able to keep recall bias between cases and controls to as low a level as possible. Measurement error may be greater in studies where patients were asked to recall their dietary intake several years before their diagnosis compared with studies that asked patients the same information from a more recent period (<1 year). Results from the sensitivity analysis showed little difference between the two. Moreover, bias in the recall of egg intake by cases should be limited given the limited knowledge and attention paid in the population to specific relations between eggs and GI cancer.

In addition, while most studies adjusted for age and gender in the calculation of risk estimates, not all parameters were considered. Intake of diets high in eggs may be associated with other behaviours including physical inactivity, overweight and obesity, high intake of red and processed meats. A meta-analysis would not adequately adjust for this. This may also serve as possible explanation for the positive correlation found between egg consumption and GI neoplasm among the Western population in which such factors are more prominent. The method preparation of eggs may be another confounding factor, but in the several studies that adjusted for this factor found that the association with eggs appears independent from the method of preparation since increased ORs were found for fried or scrambled eggs, as well as for boiled eggs.

Recommendations for further epidemiological research on the relation of diet and GI neoplasms should include measurements of egg exposure in absolute quantifiable terms with details on the methods of preparation of eggs consumed when possible. A number of previous studies included eggs in their dietary assessment, but have not reported the risk estimates due to either lack of interest in reporting null findings or lack of interest in eggs as an aetiological hypothesis; investigators are encouraged to report relevant results in an effort to arrive at a more definitive conclusion.

In summary, this systematic review provides evidence that egg consumption is associated with the risk of GI neoplasm development, more strongly correlated with Western populations. A statistically significant dose effect is observed in cancers of the colon in particular. The associations observed, however, appear weak, with only small differences between high versus low levels of consumption; thus, the hypothesis that egg consumption is involved in the development of GI neoplasms remains at best tenuous.

Conflict of interest None.

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