

Associations between dietary folate intake and risks of esophageal, gastric and pancreatic cancers: an overall and dose-response meta-analysis

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ABSTRACT

There are still some controversies on the association between dietary folate intake and the risk of upper gastrointestinal cancers including esophageal, gastric and pancreatic cancers. Hence, a comprehensive meta-analysis on all available literatures was performed to clarify the relationship between dietary folate intake and risks of upper gastrointestinal cancers. An electric search was performed up to December 12th, 2016 within the PubMed, MEDLINE AND EMBASE databases. Ultimately, a total of 46 studies which evaluated the association between folate intake and risks of upper gastrointestinal cancers were included. According to the data from included studies, the pooled results showed significant association between folate intake and esophageal (OR = 0.545, 95%CI = 0.432-0.658), gastric (OR=0.762, 95%CI=0.648-0.876) and pancreatic (OR=0.731, 95%CI=0.555-0.907) cancers. Linearity dose-response analysis indicated that with 100µg/day increment in dietary folate intake, the risk of esophageal, gastric and pancreatic cancers would decrease by 9%, 1.5% and 6%, respectively. These findings indicated that higher level of dietary folate intake could help for preventing upper gastrointestinal cancers including esophageal, gastric and pancreatic cancers.

INTRODUCTION

Folate, also named vitamin B9, is a naturally occurring nutrient and is found in many foods including fruits, vegetables legumes, cereals, and liver. Human can't produce folate *de novo* and need to uptake folate from dietary intake. Evidences implicated deficient folate is related to increased risks of many cancers [1].

Folate plays an important role in the process of DNA synthesis, repair, and methylation, and was hypothesized to decrease risks of gastrointestinal cancers. The main carcinogenesis mechanisms of folate are inducing DNA

strand breaks by causing uracil mis-incorporation into DNA and changing levels of DNA methylation [2]. These aberrant changes may result in potential alterations of critical proto-oncogene and tumor suppressor gene expressions [3]. Animal experiments referring mice and dogs suggested that high levels of folate intake affected DNA methylation and eventually decreased the risks of gastric cancer [4, 5]. In addition, the polymorphisms of genes in folate metabolizing pathway may modulate the susceptibility of several cancers.

Previous studies have summarized published data and indicated that increased folate intake was associated

with the increased risks of prostate [6] and breast [7] cancers, but decreased the risks of colorectal [8] and cervical [9] cancers. Two previous meta-analysis have estimated the associations of folate intakes and risks of esophageal, gastric and pancreatic carcinomas and indicated that increased folate intakes were associated with decreased risks of esophageal and pancreatic cancers [10, 11]. However, the results of these studies about the relationship between folate intake and gastric cancer risk remained inconsistent. Larsson et al. indicated that increased folate intake were associated with decreased risks of cardia and non-cardia gastric cancers [11]. Basing on more studies, another systematic review showed no relationship between dietary folate intake and risks of gastric cancers [10]. Therefore, to clarify the associations between folate intake and upper gastrointestinal cancers and evaluate the dose-response relationship between them, we performed an overall meta-analysis based on current observational studies.

RESULTS

Summary of studies' characteristics

Total 1284 studies were collected from our initial search including studies about esophageal cancer (n=398), gastric cancer (n=335) and pancreatic cancer (n=551). After duplicates automatically removing with EndNote, total 1154 potential articles were remained. Then, after screening titles and abstracts, 983 irrelevant studies were excluded; the remained 171 records, which investigated the associations between upper gastrointestinal cancers and folate intake, were eligibly evaluated with full text reading. Based on our inclusive criteria mentioned in Materials and Methods, 46 articles were eventually included in our meta-analysis. Among all the selected studies, 19 were conducted in patients of esophageal cancer [12-30], 21 were in patients of gastric cancer [12, 14, 15, 22, 26, 28, 31-45] and 12 were in patients of pancreatic cancer [46-57]. Figure 1 shows the eligible selecting process. Main characteristics of all include articles were showed in Table 1.

Esophageal cancer

Probands of 4 studies were in American participants [15, 26, 28, 29], 5 in Chinese [12, 14, 17, 19, 30] and 5 in Europeans [13, 16, 18, 23, 27]. In terms of the study design, 2 were cohort studies [12, 15, 18] and 17 were case-control studies [13, 14, 16-25, 58]. Seven studies clearly reported patients with Esophageal squamous cell cancer (ESCC) [12, 13, 15, 17, 19-21, 23, 24, 27, 28, 30] and six studies were about esophageal adenocarcinoma (EAC) [13, 15, 16, 21, 26-28]. Eleven studies investigated dietary folate intake from food [18-28] and 3 studies further examined dietary folate intake from food and

supplement [15, 16, 29]. Five studies reported detecting folate concentration in serum samples from patients [12-14, 17, 30]. Six case-control studies [18, 19, 21, 22, 25, 27] and 1 cohort study [15] which evaluated the association between dietary folate intake without supplement and risk of esophageal cancer were included in dose-response analysis. Two studies didn't set the lowest dose concentration group as reference group [15, 27]. The reference group transformation has been described above.

To assess the relationship between the risk of esophageal cancer and dietary folate intake, total 19 studies including 2036 patients and 7086 controls were collected. The forest plot is shown in Figure 2A. Significant heterogeneity ($p < 0.001$, $I^2 = 73.7\%$) between these studies suggested that a random effect model was selected. The pooled results showed that dietary folate intake comparing highest levels vs. lowest levels was associated with the decreased risk of esophageal cancer (odds ratio (OR) = 0.545, 95% confidence interval (CI) = 0.432-0.658, Table 2).

Table 2 showed the results of specific subgroup analysis based on study designs, countries, histological type and folate intake measurement. All these results were similar in subgroup analysis suggested that folate intake were comprehensive associated with reduced risk of esophageal cancer.

As shown in Figure 3A, the linearity test of dose-response analysis suggested that with increased 100 $\mu\text{g}/\text{day}$ folate intake from diet, the risk of esophageal cancer decreased 9% degree (OR=0.91, 95%CI=0.88-0.94). The non-linearity test ($p < 0.001$) indicated that the lowest risk of esophageal cancer was at the dose of 405 $\mu\text{g}/\text{day}$ (OR=0.69, 95%CI=0.57-0.83). After the dose of folate intake $> 405 \mu\text{g}/\text{day}$, the risk of esophageal cancer would increase after the fall.

Gastric cancer

Totally 5 studies were about American participants [15, 26, 28, 37, 42, 43], 5 were about European participants [35, 39, 42, 44, 58] and 7 were about Chinese participants [12, 14, 22, 31, 32, 34, 45]. In terms of the study design, 5 were cohort studies [12, 15, 34, 38, 39] and 16 were case-control studies [14, 22, 26, 28, 31, 32, 35-37, 40-45, 58]. Three studies clearly reported patients with gastric cardiac adenocarcinoma (GAC) [15, 28, 44] and 4 studies were about Non-GAC [15, 28, 32, 44]. Eighteen studies investigated dietary folate intake from food [22, 26, 28, 31, 32, 34-38, 40-43, 58] and 2 studies further examined dietary folate intake from food and supplement [15, 39]. Four studies reported detecting folate concentration in serum samples from patients [12, 14, 44, 45]. Two studies have respectively investigated the association between folate intake and risk of gastric cancer by sex [34, 37]. One study only included women participant [39]. Five case-control studies [22, 31, 32, 41, 42] and four cohort

studies [15, 34, 38, 39] which evaluated the associations between dietary folate intake and risks of gastric cancer were included in dose-response analysis. One study didn't set the lowest dose concentration group as reference group [15]. The reference group transformation has been described above.

As shown in Figure 2B, 5 cohort studies and 16 case-control studies were collected to analyze the association between dietary folate intake and risk of gastric cancer. The comprehensive pooled relative risk (RR) indicated a significant association between increased folate intake and decreased risk of gastric cancer (OR=0.762, 95%CI=0.648-0.876, Table 2). There was a significant heterogeneity ($p<0.001$, $I^2=67.6\%$) which suggested a further subgroup analysis.

Table 2 showed the results of specific subgroup analysis based on study designs, countries, histological type, folate intake measurement and sex. When stratified by cohort studies, 5 studies were included and indicated no statistically significant association existing between dietary folate intake and risk of gastric cancer (OR=0.967, 95%CI=0.801-1.134). The pooled OR of case-control studies suggested a high dietary folate intake was associated with a statistically significant decreased risk of gastric cancer (OR=0.696, 95%CI=0.563-0.829).

Subgroup analysis by country demonstrated that there was a significant association between increased folate intake with decreased risk of gastric cancer in Americans (OR=0.627, 95%CI=0.539-0.715) and no associations in Chinese (OR=0.864, 95%CI=0.579-1.149), Europeans (OR=0.889, 95%CI=0.562-1.215) and other countries (OR=0.859, 95%CI=0.552-1.166). Subgroup analysis by histological type indicated that increased dietary folate intake were significantly associated both with Gastric cardiac adenocarcinoma (GCA) (OR=0.729, 95%CI=0.531-0.927) and non-GCA (OR=0.681, 95%CI=0.549-0.813). Subgroup analysis by measurement suggested that high dietary folate intake from diet was associated with a statistically significant decreased risk of gastric cancer (OR=0.714, 95%CI=0.591-0.836). However, there was no association between high dietary folate intake from diet and supplement and risk of gastric cancer (OR=0.884, 95%CI=0.654-1.115). Detecting folate levels in serum suggested that there was no association between folate intake and risk of gastric cancer (OR=1.217, 95%CI=0.475-1.960). Increased folate intake was associated with decreased risk of gastric cancer in men (OR=0.599, 95%CI=0.088-1.109, but not in women (OR=0.857, 95%CI=0.405-1.309).

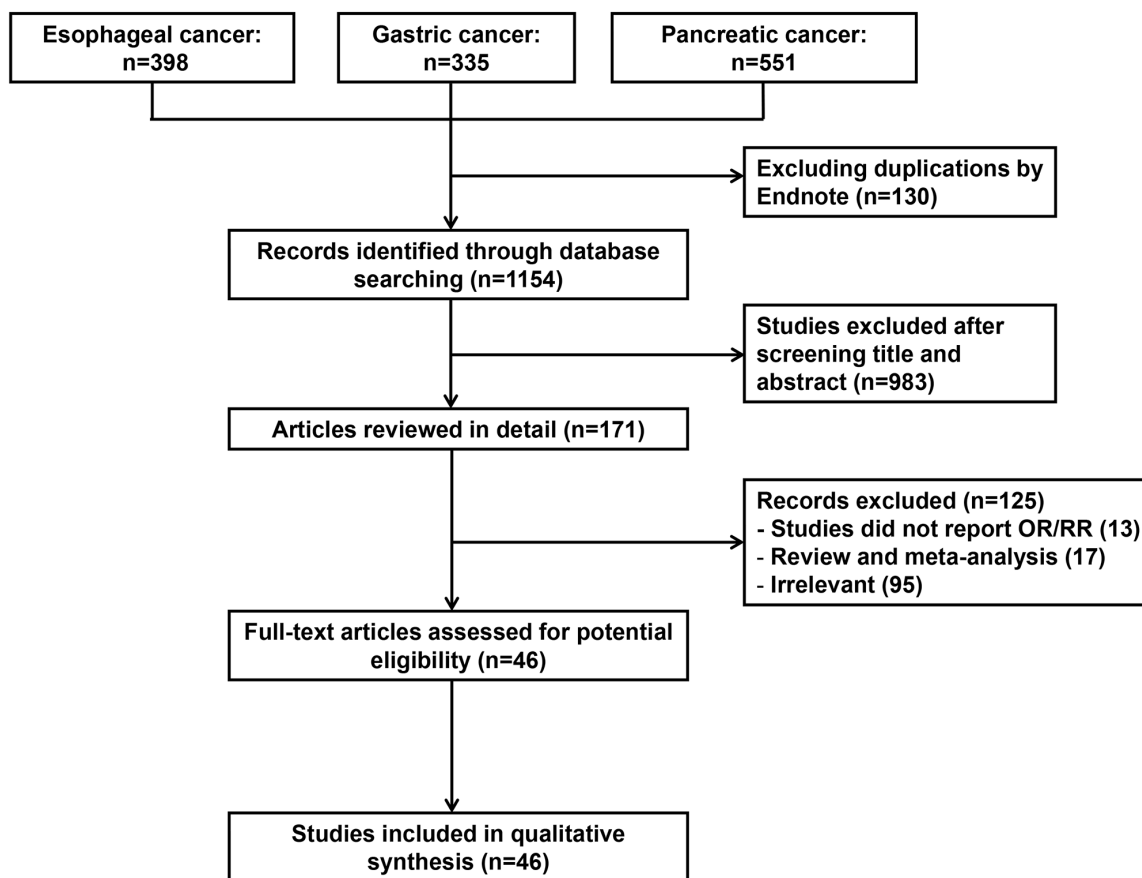


Figure 1: Flow chart of the literature search used in this meta-analysis.

Table 1: Characteristics of studies included in the meta-analysis

Studies	Country	Study Design	Year	Age	Sex	Sample Size (cases/controls)	Disease type	Exposure range (µg/day)	Measurement	Dose-response
2014 Xiao	USA	Cohort	1995-2004	50-71	M/W	GC: 939/492292 EC: 759/492292	GC/EC	566 vs 288	FFQ (Supplement and diet)	No
2014 Chen	China	Case-control	2008-2011	-	M/W	767/765	GCA/Non-GCA	>310 vs <230	FFQ (Diet)	Yes
2013 Gao	China	Case-control	2008-2012	28-76	M/W	264/535	Non-GCA	>310 vs <230	FFQ (Diet)	Yes
2011 Aune	Uruguay	Case-control	1996-2004	23-89	M/W	GC: 275/2032 EC: 234/2032	GC	275.31 vs 123.83	FFQ (Diet)	Yes
2010 Epplein	China	Cohort	1996-2006	40-70	M/W	338/136442	GCA/Non-GCA	>346.5 vs <218.7	FFQ (Diet)	Yes
2009 Pelucchi	Italy	Case-control	1997-2007	22-80	M/W	230/547	GC	The highest vs the lowest quintile	FFQ (Diet)	No
2005 Kim	Korea	Case-control	1997-1998	-	M/W	136/136	GCA/Non-GCA	>354 vs <234	FFQ (Diet)	No
2003 Nomura	USA	Case-control	1993-1999	-	M/W	300/446	GC	>315 vs <236	FFQ (Diet)	No
2002 Chen	USA	Case-control	1988-1994	-	M/W	GC: 154/449 EC: 124/449	GC/EC	The highest vs the lowest quintile	FFQ (Diet)	No
2000 Botterweck	Netherlands	Cohort	1986-1992	55-69	M/W	310/120852	GC	>384.16 vs <201.96	FFQ (Diet)	Yes
2006 Larsson	Sweden	Cohort	1987-2004	40-76	W	156/61433	GC	>260 vs <203	FFQ (Supplement and diet)	No
2001 Mayne	USA	Case-control	1993-1995	30-79	M/W	GC: 607/687 EC: 488/687	GC/EC	The highest vs the lowest quintile	FFQ (Diet)	No
2001 Munoz	Venezuela	Case-control	1991-1997	>35	M/W	302/485	GC	The highest vs the lowest quintile	FFQ (Diet)	No
1999 Lizbeth	Mexico	Case-control	1989-1990	24-88	M/W	220/752	GC	>466.26 vs <257.4	FFQ (Diet)	Yes
1994 Vecchia	Italy	Case-control	1985-1992	19-74	M/W	723/2024	GC	>262 vs <163	FFQ (Diet)	Yes
1997 Harrison	USA	Case-control	1992-1994	-	M/W	31/132	GC	The highest vs the lowest quintile	FFQ (Diet)	No
2004 Lissowska	Poland	Case-control	1994-1996	-	M/W	274/463	GC	The highest vs the lowest quintile	FFQ (Diet)	No
2016 Ren	China	Cohort	1985-1991	40-69	M/W	GC: 255/29584 ESCC: 498/29584	GC/ESCC	The highest vs the lowest quintile	serum	No
2015 Chang	China	Case-control	2000	>20	M/W	GC: 206/415 EC: 218/415	GC/EC	The highest vs the lowest quintile	serum	No

(Continued)

Studies	Country	Study Design	Year	Age	Sex	Sample Size (cases/controls)	Disease type	Exposure range (µg/day)	Measurement	Dose-response
2007 Vollset	Europe	Case-control	1992-1998	42.7-71.4	M/W	245/631	GCA/Non-GCA	The highest vs the lowest quintile	serum	No
2014 Lee	China	Case-control	1998-2006	-	M/W	149/155	GC	The highest vs the lowest quintile	serum	No
2015 Fanidi	Europe	Case-control	1992-2000	41-71	M/W	ESCC: 126/255 EAC: 26/274	ESCC/EAC	The highest vs the lowest quintile	serum	No
2013 Sharp	Northern Ireland	Case-control	2002-2005	<85	M/W	223/256	EAC	≥421 vs ≤318	FFQ (Supplement and diet)	No
2013 Huang	China	Case-control	2010-2012	-	M/W	126/167	ESCC	The highest vs the lowest quintile	serum	No
2012 Tavani	Italy	Case-control	1991-2009	-	M/W	505/22828	EC	≥312.5 vs ≤257.3	FFQ (Diet)	Yes
2011 Zhao	China	Case-control	2008-2010	-	M/W	155/310	ESCC	>300 vs <230	FFQ (Diet)	Yes
2011 Jessri	Iran	Case-control	-	40-75	M/W	47/96	ESCC	The highest vs the lowest quintile	FFQ (Diet)	No
2011 I biebele	Australia	Case-control	2003-2006	18-79	M/W	267/393	ESCC/EAC	379 vs 196	FFQ (Diet)	Yes
2006 Galeone	Italy	Case-control	1992-1999	<80	Men	351/875	ESCC	The highest vs the lowest quintile	FFQ (Diet)	No
2006 De Stefani	Uruguay	Case-control	1996-2004	40-89	M/W	234/1032	ESCC	The highest vs the lowest quintile	FFQ (Diet)	No
2005 Yang	Japan	Case-control	2001-2004	18-80	M/W	165/495	EC	>400 vs <300	FFQ (Diet)	Yes
2002 Bollschweiler	Germany	Case-control	1997-2000	-	M/W	117/100	ESCC/EAC	>164 vs <100	EBIS (Diet)	Yes
2013 Bao	China	Case-control	2010-2011	-	M/W	106/106	ESCC	The highest vs the lowest quintile	serum	No
1988 Brown	USA	Case-control	1982-1984	<79	M	74/157	EC	The highest vs the lowest quintile	FFQ (Supplement and diet)	No
2011 Chuang	Europe	Cohort	1994	25-70	M/W	638/520000	PC	The highest vs the lowest quintile	serum	No
2011 Bravi	Italy	Case-control	1991-2008	34-80	M/W	326/652	PC	The highest vs the lowest quintile	FFQ (Diet)	No
2010 Oaks	USA	Cohort	1993-2001	55-74	M/W	266/51988	PC	The highest vs the lowest quintile	FFQ (Supplement and diet)	No
2009 Keszei	Netherlands	Cohort	1986-1999	55-69	M/W	363/120852	PC	>259.1 vs <176.3	FFQ (Diet)	Yes
2009 Gong	USA	Case-control	1995-1999	21-85	M/W	532/1701	PC	≥738 vs <280	FFQ (Supplement and diet)	No

(Continued)

Studies	Country	Study Design	Year	Age	Sex	Sample Size (cases/controls)	Disease type	Exposure range (µg/day)	Measurement	Dose-response
2007 Schernhammer	USA	Case-control	1989-1990	40-75	M/W	247/740	PC	The highest vs the lowest quintile	serum	No
2006 Larsson	Sweden	Cohort	1987-1990	45-83	W	135/81922	PC	≥350 vs <200	FFQ (Diet)	Yes
2004 Skinner	USA	Cohort	1976-1986	40-75	M/W	187/125480	PC	≥500 vs <300	FFQ (Supplement and diet)	Yes
2001 Stolzenberg	Finland	Cohort	1985-1988	50-69	M/W	157/27101	PC	≥373 vs <280	FFQ (Diet)	Yes
1999 Stolzenberg	Finland	Case-control	1985-1988	50-69	M/W	126/247	PC	The highest vs the lowest quintile	serum	No
2016 Huang	China	Cohort	1993-1998	45-74	M/W	271/63257	PC	207 vs 108	FFQ (Diet)	Yes
2009 Anerson	Canada	Case-control	2003-2007	<75	M/W	422/312	PC	Folate supplement vs non-folate supplement	FFQ (Supplement and diet)	No

Abbreviations: EBIS, ErnährungsBeratungs und Informations-System; EC, Esophageal Cancer; EAC, esophageal adenocarcinoma; ESCC, Esophageal squamous cell cancer; FFQ, food frequency questionnaire; GC, Gastric Cancer; GCA, Gastric cardiac adenocarcinoma; PC, Pancreatic Cancer.

As shown in Figure 3B, non-linearity ($p=0.20$) dose-response analysis indicated no relationship between folate intake from diet and risk of gastric cancer. However, a linearity relationship ($p=0.03$) was found and suggested that 1.5% decrease of gastric cancer for each 100 µg/day increase of dietary folate intake (OR=0.985, 95%CI=0.972-0.998).

Pancreatic cancer

Proband of 4 studies were in American participants [48, 50, 51, 53], 5 in Europeans [46, 47, 52, 54, 55] and 5 in other countries. In terms of the study design, 7 were cohort studies [46, 48, 49, 52-54, 56] and 5 were case-control studies [47, 50, 51, 55, 57]. Eight studies investigated dietary folate intake from food [47-50, 52, 56] and 5 studies further examined dietary folate intake from food and supplement [48, 50, 53, 54, 57]. Three studies reported detecting folate concentration in serum samples from patients [46, 51, 55]. Five studies have respectively investigated the association between folate intake and risk of pancreatic cancer by sex [46-48, 53, 56]. Total 7 studies were included in dose-response analysis [48-50, 52-54, 56].

As shown in Figure 2C, 7 cohort studies and 5 case-control studies were collected to analyze the association between dietary folate intake and risk of pancreatic cancer. The comprehensive pooled RR indicated a significant association between increased folate intake and decreased risk of pancreatic cancer (OR=0.731, 95%CI=0.555-0.907,

Table 2). There was a significant heterogeneity ($p<0.001$, $I^2=69.0\%$) which suggested a further subgroup analysis.

Table 2 showed the results of specific subgroup analysis based on study designs, countries, folate intake measurement and sex. The pooled result of cohort studies suggested a weak association existing between dietary folate intake comparing highest levels vs. lowest levels and decreased risk of pancreatic cancer (OR = 0.800, 95%CI = 0.512-1.089). The pooled OR of case-control studies suggested a high dietary folate intake was associated with a statistically significant decreased risk of pancreatic cancer (OR=0.589, 95%CI=0.456-0.722). Subgroup analysis by country demonstrated that there was a significant association between increased folate intake with decreased risk of pancreatic cancer in Europeans (OR=0.457, 95%CI=0.326-0.588) and no associations in Americans (OR=0.885, 95%CI=0.565-1.206) and other countries (OR=1.006, 95%CI=0.759-1.252). Evaluating the association between risks of pancreatic cancer and increased folate intake from diet with (OR=0.756, 95%CI=0.559-0.952) or without supplement (OR=0.669, 95%CI=0.450-0.888) suggested that a superfluous folate supplement is not needed. Detecting folate levels in serum suggested that there was a statistically significant association between folate intake and risk of pancreatic cancer (OR=0.763, 95%CI=0.338-1.189). Increased folate intake was associated with decreased risk of pancreatic cancer in women (OR=0.716, 95%CI=0.557-0.874), but not in men (OR=0.856, 95%CI=0.709-1.003).

As shown in Figure 3C, the linearity test of dose-response analysis suggested that with increased 100 µg/

day folate intake from diet, the risk of pancreatic cancer decreased 6% degree (OR=0.94, 95%CI=0.92-0.97,). The non-linearity test ($p<0.001$) also indicated that the risk of pancreatic cancer decreased with folate intake increasing.

Sensitivity analysis and publication bias

One included study of this meta-analysis was omitted each time to evaluate the stability of pooled results. The results remained similar when any result was removed from the pooled results in this meta-analysis. Begg's test and Egger's test were used to evaluate the publication bias, the results were summarized in Table 2. There were significant publication biases in the results which evaluate the associations between folate intake and esophageal cancer (Egger's test: $p=0.027$; Begg's test: $p=0.023$); esophageal cancer in diet (Egger's test: $p=0.01$; Begg's test: $p=0.01$); pancreatic cancer in cohort subgroup analysis (Egger's test: $p=0.029$; Begg's test: $p=0.015$) and gastric cancer in supplement and diet subgroup analysis

(Egger's test: $p=0.015$; Begg's test: $p=0.043$). The trim-and-fill method was used to re-calculate the publication bias. All the new results remained similar to the original results. These results were considered as steady.

DISCUSSION

Folate is a water-soluble B vitamin and is found in many foods including fruits, vegetables legumes, cereals, and liver. Human can't produce folate *de novo* and need to uptake folate from dietary intake [1, 59]. Folate plays an important role in the process of DNA synthesis, repair, and methylation, and was hypothesized to decrease risks of gastrointestinal cancers. Two main mechanisms of folate deficiency leads to carcinogenesis: (1) by leading complete conversion of dUMP to dTMP, which makes mis-incorporation of uracil into DNA and induces breaks and mutations of chromosome; and/or (2) inducing alternations in expression of critical proto-oncogenes and tumor suppressor genes by causing aberrant methylated

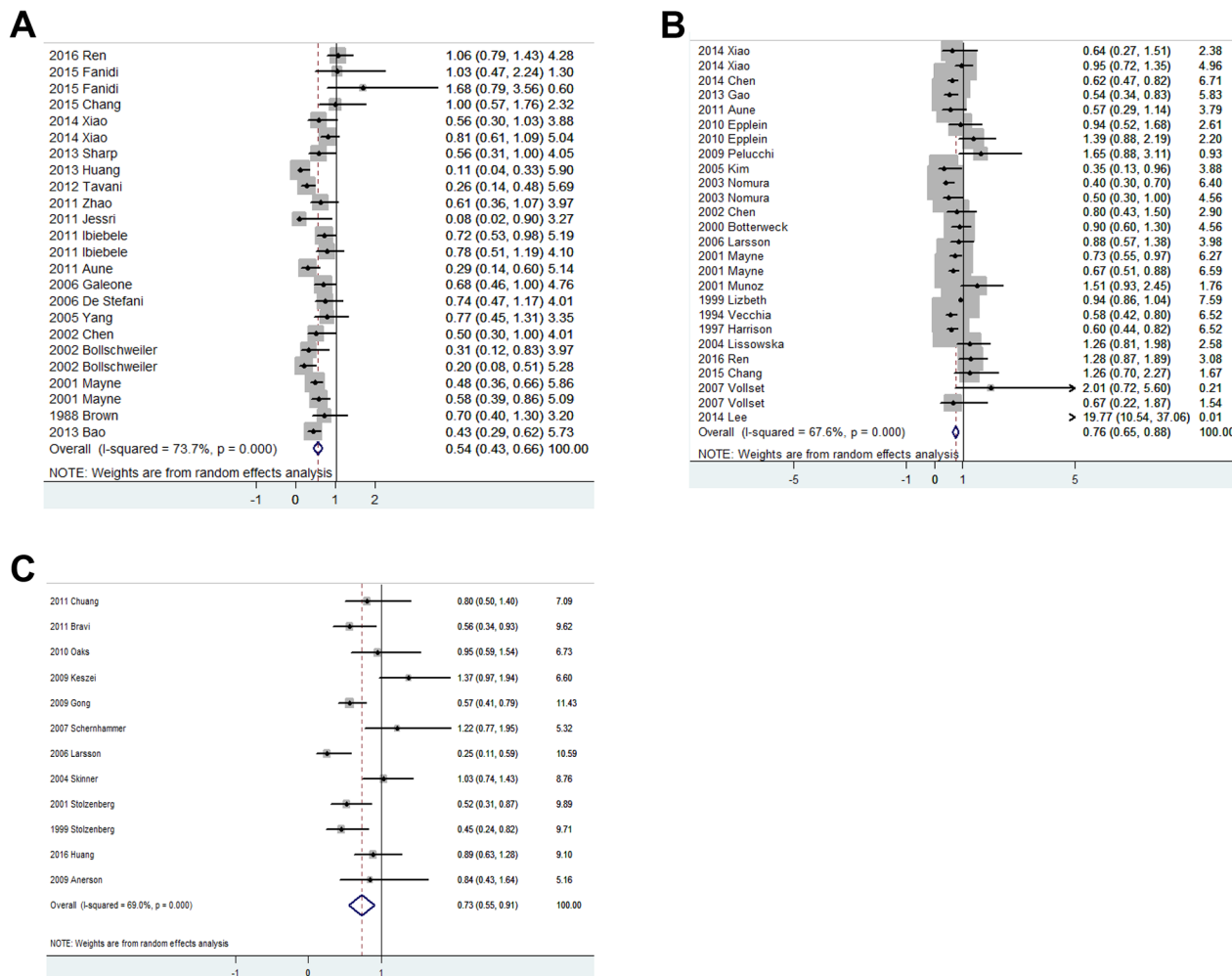


Figure 2: Forest plots of the association between dietary folate intake and risk of esophageal cancer (A), gastric cancer (B) and pancreatic cancer (C).

Table 2: Results including overall and subgroup analysis of pooled OR, 95%CI, heterogeneity test and publication bias

Overall and subgroup analysis	Numbers of studies	Pooled OR	95%CI	Heterogeneity Test			Publication Bias (P)	
				Q	P	I ² , %	Egger's test	Begg's test
Esophageal cancer								
Total	20	0.545	0.432-0.658	87.57	<0.001	73.7	0.027	0.023
Study design								
Cohort	2	0.821	0.569-1.073	4.11	0.128	51.4	0.466	0.602
Case-control	17	0.496	0.386-0.606	59.90	<0.001	68.3	0.080	0.130
Histological type								
ESCC	7	0.551	0.370-0.731	51.39	<0.001	80.5	0.152	0.091
EAC	6	0.561	0.373-0.749	20.15	0.003	70.2	0.141	0.142
Country								
USA	4	0.573	0.474-0.673	5.70	0.336	12.3	0.573	0.708
China	5	0.596	0.255-0.938	36.06	<0.001	91.7	0.174	0.125
Europe	5	0.443	0.238-0.647	15.91	0.014	62.3	0.348	0.125
Others	6	0.770	0.450-1.310	15.35	0.009	67.4	0.188	0.043
Measurement								
Diet	11	0.547	0.426-0.667	33.92	0.001	61.7	0.01	0.01
Supplement and diet	3	0.692	0.530-0.853	1.99	0.574	0	0.412	0.327
Serum	5	0.708	0.329-1.088	40.56	<0.001	87.7	0.458	0.117
Gastric cancer								
Total	21	0.762	0.648-0.876	77.08	<0.001	67.6	0.808	0.270
Study design								
Cohort	5	0.967	0.801-1.134	4.46	0.615	0	0.548	0.652
Case-control	16	0.696	0.563-0.829	65.83	<0.001	72.7	0.960	0.248
Histological type								
GCA	3	0.729	0.531-0.927	1.14	0.566	0	0.590	0.117
Non-GCA	4	0.681	0.549-0.813	4.09	0.252	26.6	0.761	1
Other GC	17	0.796	0.646-0.947	70.20	<0.001	74.4	0.725	0.278
Country								
USA	5	0.627	0.539-0.715	11.11	0.134	37.0	0.510	0.621
Europe	5	0.889	0.562-1.215	9.70	0.084	48.5	0.226	0.573
China	7	0.864	0.579-1.149	22.58	0.002	69.0	0.236	0.322
Others	4	0.859	0.552-1.166	9.76	0.021	69.3	0.885	1
Measurement								
Diet	18	0.714	0.591-0.836	60.25	<0.001	71.8	0.216	0.622
Supplement and diet	2	0.884	0.654-1.115	0.76	0.683	0	0.015	0.043

(Continued)

Overall and subgroup analysis	Numbers of studies	Pooled OR	95%CI	Heterogeneity Test			Publication Bias (P)	
				<i>Q</i>	<i>P</i>	<i>I</i> ² , %	Egger's test	Begg's test
Serum	4	1.217	0.475-1.960	9.65	0.047	58.6	0.849	0.624
Sex								
Women	3	0.857	0.405-1.309	6.01	0.050	66.7	0.416	0.602
Men	2	0.599	0.088-1.109	2.98	0.085	66.4	0.656	0.251
Pancreatic cancer								
Total	12	0.731	0.555-0.907	35.44	<0.001	69.0	0.089	0.054
Study design								
Cohort	7	0.800	0.512-1.089	28.43	<0.001	78.9	0.029	0.015
Case-control	5	0.589	0.456-0.722	6.01	0.198	33.5	0.829	1
Country								
USA	4	0.885	0.565-1.206	9.08	0.028	67.0	0.604	0.497
Europe	5	0.457	0.326-0.588	5.75	0.218	30.5	0.069	0.050
Others	3	1.006	0.759-1.252	2.94	0.230	32.0	0.709	0.602
Measurement								
Diet	8	0.669	0.450-0.888	21.93	0.001	72.6	0.156	0.099
Supplement and diet	5	0.756	0.559-0.952	6.65	0.156	39.8	0.831	0.49
Serum	3	0.763	0.338-1.189	5.84	0.054	65.7	0.068	0.117
Sex								
Men	5	0.856	0.709-1.003	1.97	0.742	0	0.836	1
Women	5	0.716	0.557-0.874	2.89	0.577	0	0.563	0.624

Abbreviations: EC: Esophageal Cancer; EAC: esophageal adenocarcinoma; ESCC: Esophageal squamous cell cancer; GC: Gastric Cancer; GCA: Gastric cardiac adenocarcinoma; OR: odds ration; CI: confidence interval.

level of DNA [2, 3]. In addition, the polymorphisms of 5,10-methylenetetrahydrofolate reductase, a critical junction protein in folate metabolizing pathway by leading folate metabolites to DNA methylation pathway and away from the DNA synthesis pathway, can regulate the susceptibilities of several cancers [60-62].

Our meta-analysis found that increased folate intake was associated with reduced risks of upper gastrointestinal cancers including esophageal, gastric and pancreatic cancers. The dose-response further certified their relationship. Subgroup analysis indicated that the comprehensive inverse associations between dietary folate intake and esophageal cancer. Our data suggested different relationships between dietary folate intake and cancer risks in country, study design, disease type, measurement and sex subgroup analysis of gastric and pancreatic cancers.

The results of this meta-analysis showed that increased dietary folate intake significant decreased risk of esophageal cancer. These results are similar to previous study [10, 11, 63]. In the subgroup analysis based on

country, histological type, study design and dietary measurement, our results suggested an inverse association between dietary folate intake and risks of esophageal cancer in all subgroups. Interesting, we observed a higher OR which suggested a weaker link between folate intake and esophageal cancer in supplement and diet subgroup than in diet subgroup. These results suggested an extra folate supplement is not needed in diet for preventing esophageal cancer. The results of dose-response analysis also indicated that with the folate intake > 450 µg/day, the risk of esophageal cancer would increase weakly comparing with the lowest OR, which suggested that a redundant and supplementary folate is not necessary. Zhang et al. found that the risk ration of breast cancer decreased when the dose of folate was low. However, with the folate dose increasing, a positive association was found between folate intake and breast cancer risk [7].

Different from previous studies [10, 11], our results showed a significant association between increased dietary folate intake and reduced gastric cancer risk.

Although non-linearity model of dose-response analysis suggested no statistically significant association between folate intake and risk of gastric cancer, linearity model indicated a different result ($p=0.03$) which certificated our comprehensive pooled OR. Meta-analysis of genetic polymorphisms demonstrated that folate deficiency was associated with increased risk of gastric cancer [11, 64, 65]. Folate supplement can reverse methylation deficiency, stop global hypomethylation and prevent gastric carcinogenesis in hypergastrinemic transgenic mice [5]. Subgroup analysis indicated an inverse association between dietary folate intake and gastric cancer risk in case-control studies, but no association in cohort studies. A possible reason is that only 5 cohort studies were included in this analysis. Small number of studies and effects of multiple factors may affect recall bias and selection bias and restrict the precision of the last results. Similar to previous studies [11], our data showed a significant inverse association between folate intake and GCA or non-GCA, and a weak inverse link between folate intake and other gastric cancer. These results suggested that dietary folate intake plays different roles in different gastric cancers. In the subgroup analysis based on country, we observed an inverse association between folate intake and

gastric cancer only in USA, but not in other countries. In addition, in the subgroup analysis based on measurement, our results showed an inverse association between folate intake coming from diet and risk of gastric cancer. However, no association between folate intake coming from diet and supplement and risk of gastric cancer was found. These results also suggested that an extra folate supplement is not needed in diet for preventing gastric cancer. And the excessive intake of folate may be a risk for gastric cancer since the highest values of 95%CI > 1.00. Different from previous estimate, serum evaluating suggested an increased risk of gastric cancer with high serum concentration. One possible explanation is that since the number of included studies about serum detection of folate and gastric cancer risk is too small, which provide insufficient statistical power to evaluate the risk. Animal experiments suggested a dual role of folate in cancer carcinogenesis: prevention or promotion, depending on the stage of cell transformation at the time of intervention and the dose of folate supplement [66, 67]. Significant decreased risks of gastric cancers were observed both in men and women with folate intake increased.

Results of previous meta-analysis about folate intake and pancreatic cancer risk were inconsistent. Bao et al.

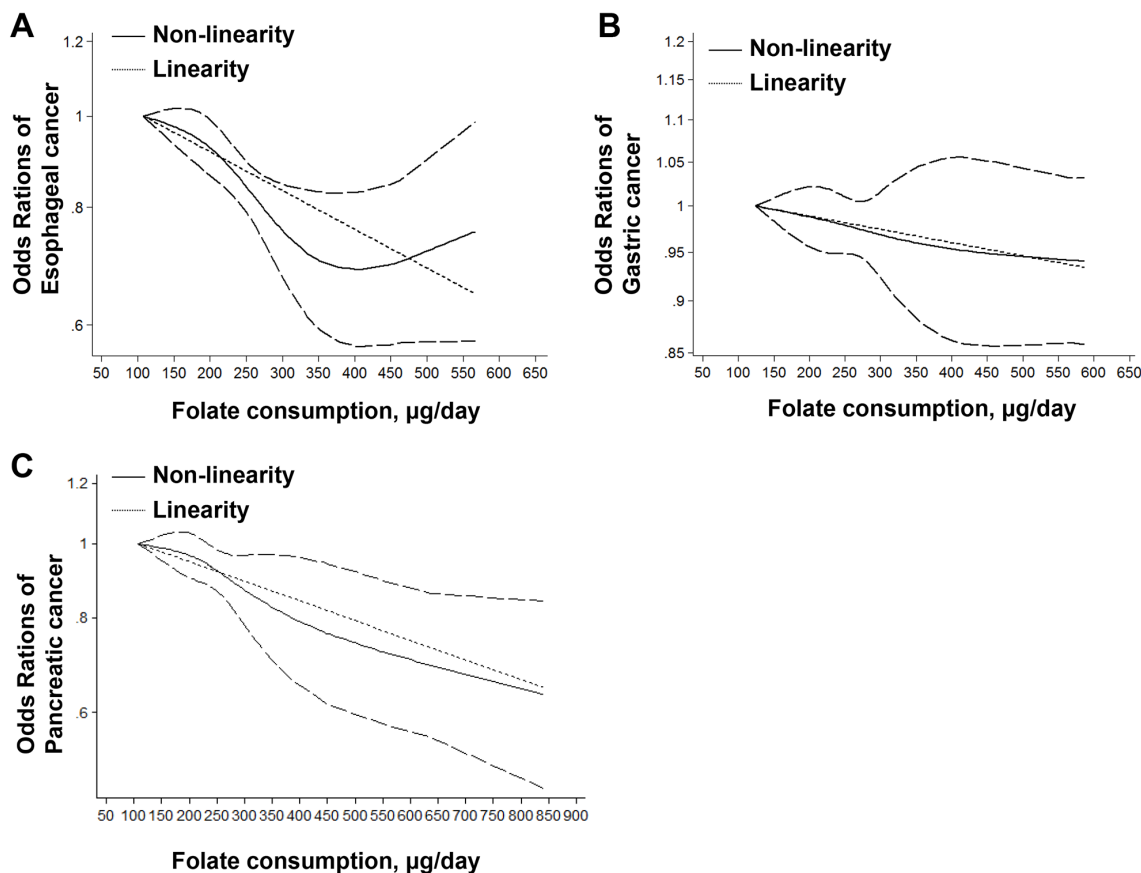


Figure 3: Linearity and non-linearity relationships between dietary folate intake and risk of esophageal cancer (A), gastric cancer (B) and pancreatic cancer (C).

found folate intake was not associated with overall risk of pancreatic cancer using only prospective cohort studies [68]. However, other studies considered increased folate intake was associated with decreased pancreatic cancer risk [11, 69]. Our comprehensive meta-analysis found an inverse association between dietary folate intake and pancreatic cancer risk. Dose-response analysis indicated that a 100 µg/day increment in dietary folate intake was associated with a 6% risk decreasing for pancreatic cancer. Results of subgroup analysis based on country showed an inverse association between folate intake and pancreatic cancer risk in European. However, this association was not found in American and other countries. These results suggested that geographic variation or dietary habit may play an important role in the association. Subgroup analysis by sex indicated that women had higher pancreatic risk with low folate intake when compared with men. Similar to esophageal and gastric cancers, our data showed that an extra folate supplement is not needed in diet for preventing pancreatic cancer.

There are several limitations to current meta-analysis. First, the included studies about esophageal, gastric and pancreatic cancer have few cohort studies which may make influence on the actual result. Since, dose-response analysis didn't separate cohort and case-control studies. Second, subgroup analysis based on measurement only included diet, diet and supplement and serum. Total folate intake and other folate intake measurements were not evaluated for lack of related studies. Third, significant heterogeneity were detected between the studies included in quantitative synthesis. Through further subgroup analysis, we still can't find all the origin of heterogeneity. Forth, this meta-analysis used pooled results for lacking of individual data, which prevents us from finishing a more precise analysis. Last, some subgroup analysis which included small number of studies may not represent objective and exact results. Hence, our results should be treated as exploratory and with caution.

In conclusion, results of current meta-analysis indicated that higher level of dietary folate intake could help for preventing upper gastrointestinal cancers including esophageal, gastric and pancreatic cancers. Dose-response analysis indicated that with 100µg/day increment in dietary folate intake, the risk of esophageal, gastric and pancreatic cancers would decrease by 9%, 1.5% and 6%, respectively. In addition, our analysis indicated that more well-designed studies about associations between esophageal, gastric and pancreatic cancers and folate intake are necessary for further accurately evaluating subgroup analysis based on country, measurement, histological type and sex.

MATERIALS AND METHODS

Literature search

A systematically search was performed up to May 2th, 2017 by two reviewers (H. Z. and Y. Z.)

within Pubmed, MEDLINE AND EMBASE, using the terms “folate, folic acid or vitamin B9”, “esophageal, oesophagus, gastric, stomach, or pancreatic” and “cancer, neoplasm or carcinoma”. In addition, we reviewed the reference lists from original reports and manually selected for other available publications. No language restrictions were imposed in the searching process.

Study selection

The studies were included with the following inclusion criteria: (i) the experimental design was a case-control or cohort study; (ii) studies reported the associations of esophageal, gastric, or pancreatic cancer risk with dietary folate intake from diet, dietary folate intake from diet and supplement and serum levels of folate; (iii) RR, hazard ration (HR) or OR with 95% CI was reported to estimate the relative risk of the highest folate intake vs. lowest folate intake; (iv) patient with disease was identified by histological diagnosis; (v) for dose-response analysis, the number of cases and participants and eligible dose concentration must be provided. The selected studies were only limited in using dietary folate intake as only measurement standard. The most recent study was included for duplicate publications.

Data extraction

The following information was selected independently by two authors (H. Z. and Y. Z.) according to the criteria listed previously: the first author's name, publication year, country, study design, total sample size, sex, number of cases, number of controls, lowest folate level, highest folate level, difference between highest and lowest folate levels, measurement, range of exposure, histological type (ESCC, EAC, gastric cardiac adenocarcinoma (GAC); non-GAC), risk estimates and 95%CI for evaluating the highest folate levels vs. lowest folate levels. Adjusted rations were chosen in preference to the rations with the highest number of adjusted variables. For the studies which the reference groups were not the lowest dose concentration, the EXCEL macro document (RRest9) was used for the reference group transforming and data re-calculating according to the instructions [70]. All controversial questions were resolved by asking a third author.

Statistical analysis

The association of folate intake with esophageal, gastric and pancreatic cancers were examined by the pooled risk estimates (RR or OR) with 95%CI. The heterogeneity test was detected with I² statistic. Cut-off points of I² value for low, moderate and high degrees of heterogeneity were 25%, 50% and 75%, respectively. A fixed effect model was chosen when heterogeneity was negligible, otherwise, the random effects model was

chosen [71]. Sensitivity analysis was investigated to assess robustness of pooled results by omitting one study each time. The publication bias was determined by the Begg rank correlation test and Egger's linear regression test [72]. $P < 0.05$ was considered statistically significant, and all p -values were two-sided. The trim-and-fill method was used to re-calculate the publication bias when the P values of Begg test or Egger test > 0.05 . The new pooled results (RR or OR) were compared with the original results. The results were considered as steady if the new pooled results are similar to the original results. At last, we conducted a dose-response meta-analysis using the correlated natural logs of the RRs or ORs with their standard error (SE) across all folate intake categories [73]. To derive the dose-response curve, restricted cubic splines with four knots at the 5%, 35%, 65% and 95% percentiles of the distribution were used to assess for potential curvilinear relations. All data in this meta-analysis were performed using Stata 12.0 (StataCorp LP, College Station, TX, USA).

Abbreviations

CI, confidence interval; ESCC, esophageal squamous cell cancer; EAC, esophageal adenocarcinoma; EBIS, ErnährungsBeratungs und Informations-System; FFQ, food frequency questionnaire; GAC, gastric cardiac adenocarcinoma; HR, hazard ratio; OR, odds ratio; PC, Pancreatic Cancer; RR, relative risk.

Author contributions

H. Z. performed search, Y. Z. and W. L. prepared tables and figures, C. T. wrote the manuscript and performed power calculation. All authors reviewed the manuscript.

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CONFLICTS OF INTEREST

No conflict of interests is stated by authors.

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