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Intakes of folate, methionine, vitamin B6, and vitamin B12 with risk of esophageal and gastric cancer in a large cohort study

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Background: Nutrients in the one-carbon metabolism pathway may be involved in carcinogenesis. Few cohort studies have investigated the intakes of folate and related nutrients in relation to gastric and esophageal cancer.

Methods: We prospectively examined the association between self-reported intakes of folate, methionine, vitamin B6, and vitamin B12 and gastric and esophageal cancer in 492 293 men and women.

Results: We observed an elevated risk of esophageal squamous cell carcinoma with low intake of folate (relative risk (95% confidence interval): Q1 *vs* Q3, 1.91 (1.17, 3.10)), but no association with high intake. Folate intake was not associated with esophageal adenocarcinoma, gastric cardia adenocarcinoma, or non-cardia gastric adenocarcinoma. The intakes of methionine, vitamin B6, and vitamin B12 were not associated with esophageal and gastric cancer.

Conclusion: Low intake of folate was associated with increased risk of esophageal squamous cell carcinoma.

Folate is critically involved in DNA synthesis, repair, and methylation. Folate deficiency may lead to genetic mutation, chromosomal damage, and altered epigenetic modification (Ulrich, 2007). Previous studies have linked folate deficiency with elevated risk of colorectal cancer (Robinson *et al*, 2013) and breast cancer (Kamangar *et al*, 2009; Stevens *et al*, 2010; Shrubsole *et al*, 2011). The link between folate intake and esophageal and gastric cancer remain unclear (Larsson *et al*, 2006). All but two studies on folate and esophageal or gastric cancer are case-control in design, making them potentially susceptible to recall bias. Moreover, many previous studies did not distinguish between subtypes of esophageal cancer and gastric cancer. In addition to folate, other nutrients such as methionine, vitamin B6, and vitamin B12 are key elements of the one-carbon metabolism pathway and may also influence cancer risk. (Bailey, 2003). Few studies, however, have assessed these associations. Finally, alcohol consumption and smoking may impair folate status (Bailey, 2003, Li *et al*, 2013), yet it also remains unclear how alcohol and smoking may modulate potential associations between folate and these cancers.

Given the limitations of previous investigations, we studied the intake of folate, methionine, vitamin B6, and vitamin B12 in relation to the risk of esophageal squamous cell carcinoma (ESCC), esophageal adenocarcinoma (EAC), gastric cardia adenocarcinoma (GCA), and non-cardia gastric adenocarcinoma (NCGA) in a large cohort of nearly 500 000 US men and women.

MATERIALS AND METHODS

Details of the NIH-AARP Diet and Health Study were reported previously (Schatzkin *et al*, 2001). In brief, AARP members who were 50–71-years old in eight states were recruited in 1995–1996. Of the 566 398 participants who satisfactorily completed the baseline questionnaire, we excluded proxy respondents ($n = 15\,760$) and those who had cancer other than nonmelanoma skin cancer ($n = 51\,234$) or self-reported end-stage renal disease at baseline ($n = 986$). Additionally, we excluded individuals reporting

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extreme intakes (>2 times the interquartile ranges) of total energy ($n=4416$) and dietary folate, methionine, vitamin B6, or vitamin B12 ($n=1710$). The analytical cohort consisted of 492 292 men and women. The study was approved by the National Cancer Institute Special Studies Institutional Review Board, and informed consent was implied by completing the questionnaire.

Incident cancer cases were identified through linkage to cancer registries in eight original states and three additional states that our participants tended to move. Cases were defined using the International Classification of Diseases for Oncology, Third Edition (ICD-O-3) (Esophageal cancer: C15.0–15.9; Gastric cancer: C16.0 (GCA) and C16.1–16.7 (NCGA)). The esophageal cancer cases were further classified into ESCC (code: 8050–8076) and EAC (code: 8140, 8142, 8144, 8261, 8310, 8480, 8481, 8570, 8260, 8263, and 8490). We followed cohort members periodically for change of address using the National Change of Address database maintained by the US Postal Service, other address change update services, and direct reports from participants. During the follow-up, 5% of participants were no longer living within the 11 states and were therefore outside of our cancer catchment areas.

The frequency and amount of dietary intakes were assessed at baseline using a self-administered 124-item food-frequency questionnaire (FFQ). The food items, portion sizes, and nutrient database were constructed using the US Department of Agriculture's 1994–1996 Continuing Survey of Food Intakes (Subar *et al*, 2000). Dietary intakes were adjusted for total energy intake using the residual method (Willett and Stampfer, 1986). Previous validation study found that the energy-adjusted correlation coefficients between intakes measured from the FFQ and 24-h dietary recalls were moderate to high: the correlation coefficients for folate, vitamin B6, and vitamin B12 were 0.64, 0.69, and 0.47 in men and 0.69, 0.70, and 0.47 in women, respectively (Thompson *et al*, 2008). The baseline questionnaire also collected information on how frequent participants took multivitamins, which contained 400 mcg folate. Total intakes of folate, vitamin B6, and vitamin B12 were calculated by combining supplemental and dietary intakes.

We estimated relative risks (RRs) and two-sided 95% confidence intervals (CIs) with the Cox proportional hazards model (SAS 9.3; SAS Institute, Cary, NC, USA). We evaluated and confirmed the proportional hazards assumption for the main exposures by including interaction terms with time and using the Wald χ^2 procedure to test if coefficients equaled zero. Person-years of follow-up time were calculated from the baseline until cancer diagnosis, relocation from the registry areas, death, or the end of follow-up (31 December 2006), whichever came sooner. Multivariate models were adjusted for risk factors that are potential confounders, including age, sex, race, education, marital status, health status, BMI, smoking status, smoking dose, time since quitting, physical activity, alcohol, multivitamin use, family history of cancer, and total caloric intake. To test for linear trend across quintiles and categories of intake, we used the median value of each quintile or category as a continuous variable in the regression models.

RESULTS

During 4 471 303 person-years of follow-up, we identified 185 ESCC, 574 EAC, 424 GCA, and 515 NCGA cases. Participant characteristics by quintiles of dietary folate and methionine intake are presented in Supplementary Table S1. Participants with high intakes of dietary folate were more likely to be college educated, report excellent health, exercise ⩾5 times per week, and use multivitamin supplements but less likely to be current smokers; they consumed more fruits and vegetables and whole grains but less alcohol. Participants with high intakes of dietary methionine had higher BMI and education but lower alcohol intake.

The median intake of dietary folate in the third quintile was 405 mcg per day, which is approximately the daily recommended amount in the US. Using the third quintile as the reference, lower intakes of folate were associated with increased risk of ESCC (RR first Q *vs* third Q: 1.91, 95% CI, 1.17–3.10), but higher intakes of folate were not related to risk of ESCC (Table 1). Higher intakes of folate, methionine, vitamin B6, or vitamin B12 were not associated with either ESCC risk or EAC risk. Furthermore, dietary intakes of folate, methionine, vitamin B6, or vitamin B12 were not associated with the risk of developing either GCA or NCGA (Table 2). Excluding cancer cases diagnosed within 3 years following baseline had little impact on the findings (data not shown). In subgroup analysis by alcohol and smoking (Supplementary Table S2), the elevated risk of ESCC with low intake of folate appeared to be stronger among people who consumed alcohol ⩾15 g per day or who were current or former smokers. However, these differences did not show a significant interaction between folate intake and alcohol consumption ($P=0.19$) or smoking ($P=0.45$).

We evaluated the risks of ESCC and EAC in relation to total folate intake, combining both dietary and supplemental folate (Figure 1). There was a significant inverse association between total folate intake and ESCC risk (P for trend $=0.003$), but only the lowest category was associated with a significant increase in risk. In contrast, there was no association between total folate intake and EAC risk ($P=0.15$). We also evaluated total vitamin B6 and vitamin B12 in relation to ESCC risk. Vitamin B6 was inversely associated with ESCC risk (P for trend: 0.01), but none of the individual RR estimates was significant. Vitamin B12 was not associated with ESCC risk (data not shown).

DISCUSSION

In this large prospective cohort study, we found that low intake of folate was associated with elevated risk of ESCC, but folate intake higher than the recommended amount may not offer additional protection over ESCC. Intakes of methionine, vitamin B6, or vitamin B12 were not associated with esophageal or gastric cancer risk.

Our study is the first cohort analysis of the relationship between folate intake and esophageal cancer risk. Our finding of positive association between low folate intake and higher risk of ESCC is largely consistent with previous case-control studies (La Vecchia *et al*, 1994; Zhang *et al*, 1997; Brown *et al*, 1988; Lopez-Carrillo *et al*, 1999; Botterweck *et al*, 2000; Jessri *et al*, 2011; Zhao *et al*, 2011; Ibiebele *et al*, 2011). In contrast, although three of the five earlier case-control studies (Brown *et al*, 1988, 1995; Munoz *et al*, 2001; Kim *et al*, 2005; Ibiebele *et al*, 2011) found a significant inverse association between folate intake and EAC risk, our study did not find a significant relationship between EAC and dietary folate.

Our finding of a null association between dietary folate and gastric cancers is most comparable to that of the two cohort studies. The Netherlands Cohort Study found a relative risk of 0.9 (95% CI, 0.6–1.3) among those in the highest quintile of dietary folate intake, compared with those in the lowest (Cook *et al*, 2010). Similarly, a more recent study examined stomach cancer risk in relation to dietary folate intake in the Swedish Mammography Cohort and reported no association between the two (RR (95% CI), 1.04 (0.61, 1.86)) (Bailey, 1990). However, neither of these two studies distinguished GCA from NCGA.

It has been postulated that there might be a nonlinear relation between folate intake and cancer risk, with the optimal cancer-preventive effect achieved at moderate folate status while both low and excessively high intake associated with enhanced carcinogenesis and tumor growth (Ulrich, 2007). We found an inverse

Table 1. Age-adjusted and multivariate RRs and 95% CIs of risk of esophageal squamous cell carcinoma and esophageal adenocarcinoma for quintiles of dietary folate, methionine, and vitamin B6 intake in the NIH-AARP study

	Quintile					
	Q1	Q2	Q3	Q4	Q5	*P* for trend
Esophageal squamous cell carcinoma						
Folate						
Median intake, mcg per day	288	353	405	463	566	
No. of cases	70	43	23	28	21	
Age-adjusted RR	3.25 (2.03, 5.21)	1.91 (1.15, 3.18)	Ref.	1.21 (0.69, 2.09)	0.90 (0.50, 1.62)	<0.001
Multivariate RR[a]	1.91 (1.17, 3.10)	1.59 (0.95, 2.64)	Ref.	1.33 (0.77, 2.32)	1.07 (0.59, 1.94)	0.02
Methionine						
Median intake, g per day	1.1	1.3	1.5	1.7	2.0	
No. of cases	62	41	27	32	23	
Age-adjusted RR	2.28 (1.45, 3.59)	1.50 (0.93, 2.44)	Ref.	1.20 (0.72, 2.00)	0.89 (0.51, 1.55)	<0.001
Multivariate RR[a]	1.45 (0.91, 2.31)	1.34 (0.82, 2.18)	Ref.	1.30 (0.78, 2.16)	1.02 (0.58, 1.78)	0.16
Vitamin B6						
Median intake, mg per day	1.4	1.7	2	2.2	2.7	
No. of cases	65	39	34	22	25	
Age-adjusted RR	2.01 (1.33, 3.04)	1.17 (0.74, 1.86)	Ref.	0.63 (0.37, 1.08)	0.70 (0.42, 1.17)	<0.001
Multivariate RR[a]	1.38 (0.91, 2.12)	1.08 (0.68, 1.71)	Ref.	0.70 (0.41, 1.19)	0.86 (0.51, 1.45)	0.01
Vitamin B12						
Median intake, mcg per day	2.5	3.6	4.4	5.4	7.3	
No. of cases	53	39	34	31	28	
Age-adjusted RR	1.56 (1.01, 2.49)	1.15 (0.72, 1.82)	Ref.	0.91 (0.56, 1.48)	0.82 (0.50, 1.35)	0.004
Multivariate RR[a]	1.21 (0.78, 1.87)	1.06 (0.67, 1.68)	Ref.	0.96 (0.59, 1.56)	0.85 (0.52, 1.41)	0.13
Esophageal adenocarcinoma						
Folate						
No. of cases	163	111	115	87	98	
Age-adjusted RR	1.51 (1.19, 1.92)	0.99 (0.76, 1.28)	Ref.	0.75 (0.57, 0.99)	0.84 (0.64, 1.10)	<0.001
Multivariate RR[a]	1.23 (0.96, 1.57)	0.90 (0.70, 1.17)	Ref.	0.81 (0.61, 1.06)	1.00 (0.76, 1.31)	0.09
Methionine						
No. of cases	113	108	128	113	112	
Age-adjusted RR	0.88 (0.68, 1.13)	0.84 (0.65, 1.08)	Ref.	0.89 (0.69, 1.15)	0.91 (0.71, 1.17)	0.68
Multivariate RR[a]	0.94 (0.73, 1.22)	0.87 (0.67, 1.12)	Ref.	0.87 (0.67, 1.12)	0.85 (0.66, 1.10)	0.50
Vitamin B6						
No. of cases	153	123	106	112	98	
Age-adjusted RR	1.33 (1.03, 1.72)	1.18 (0.91, 1.53)	Ref.	1.04 (0.79, 1.35)	0.88 (0.67, 1.16)	<0.001
Multivariate RR[a]	1.20 (0.93, 1.55)	1.12 (0.86, 1.45)	Ref.	1.10 (0.84, 1.44)	1.00 (0.76, 1.32)	0.21
Vitamin B12						
No. of cases	98	113	114	126	123	
Age-adjusted RR	0.86 (0.66, 1.12)	0.99 (0.76, 1.28)	Ref.	1.11 (0.86, 1.43)	1.08 (0.84, 1.39)	0.08
Multivariate RR[a]	1.02 (0.78, 1.34)	1.04 (0.80, 1.34)	Ref.	1.08 (0.84, 1.39)	1.04 (0.80, 1.34)	0.83

Abbreviations: CI = confidence interval; NIH-AARP = National Institutes of Health—American Association of Retired Persons; RR = relative risk.

[a]Adjusted for age at baseline (continuous); sex (male and female); race/ethnicity (non-Hispanic white, non-Hispanic, black, and others); education (less than high school, high school graduate, some college and college graduate/postgraduate); marital status (married, not married); health status (excellent, very good, good, fair, and poor); body mass index (<18.5, 18.5–<25, 25–<30, 30–<35, ⩾35 kg m^{-2}); smoking status (never, former, and current); smoking dose (0, 1–10, 11–20, 21–30, 31–40, 41–50, 51–60, and >60 cigarettes per day); time since quitting (never quit, ⩾10, 5–9, 1–4, <1 years); vigorous physical activity (never/rarely; ⩽3 times per month; 1–2, 3–4, and ⩾5 times per week); alcohol (0, <5, 5–<15, 15–<30, and ⩾30 g per day); multivitamin use (nonuse, less than daily use, and daily use); family history of any cancer (yes or no); and total caloric intake (continuous).

association only among people in the lower quintiles, and no additional reduction in risk in the higher quintiles. Unfortunately, we were not able to evaluate the effect of even higher intake of folate due to relatively few subjects with a total folate intake >800 mcg per day and therefore cannot rule out the possibility that very high intake of folate may lead to increased risk.

Table 2. Age-adjusted and multivariate RRs and 95% CIs of risk of gastric cardia adenocarcinoma and non-cardia gastric adenocarcinoma for quintiles of dietary folate, methionine, and vitamin B6 intake in the NIH-AARP study

	Quintile					
	Q1	Q2	Q3	Q4	Q5	*P*for trend
Gastric cardia andenocarcinoma						
Folate						
No. of cases	110	85	86	67	76	
Age-adjusted RR	1.37 (1.03, 1.81)	1.01 (0.75, 1.37)	Ref.	0.77 (0.56, 1.06)	0.87 (0.64, 1.18)	<0.001
Multivariate RR[a]	1.12 (0.84, 1.50)	0.93 (0.69, 1.26)	Ref.	0.82 (0.59, 1.12)	0.98 (0.72, 1.34)	0.30
Methionine						
No. of cases	78	77	95	83	91	
Age-adjusted RR	0.82 (0.61, 1.10)	0.80 (0.59, 1.08)	Ref.	0.89 (0.66, 1.19)	1.00 (0.75, 1.33)	0.15
Multivariate RR[a]	0.82 (0.61, 1.12)	0.82 (0.61, 1.11)	Ref.	0.87 (0.65, 1.16)	0.93 (0.70, 1.25)	0.42
Vitamin B6						
No. of cases	102	98	76	80	68	
Age-adjusted RR	1.41 (1.05, 1.90)	1.32 (0.98, 1.78)	Ref.	1.03 (0.75, 1.41)	0.85 (0.61, 1.18)	<0.001
Multivariate RR[a]	1.28 (0.95, 1.74)	1.26 (0.93, 1.70)	Ref.	1.07 (0.79, 1.47)	0.92 (0.66, 1.27)	0.02
Vitamin B12						
No. of cases	73	89	82	86	94	
Age-adjusted RR	0.89 (0.65, 1.22)	1.08 (0.80, 1.46)	Ref.	1.05 (0.78, 1.42)	1.14 (0.85, 1.54)	0.17
Multivariate RR[a]	0.99 (0.72, 1.37)	1.12 (0.83, 1.51)	Ref.	1.02 (0.76, 1.39)	1.09 (0.81, 1.47)	0.73
Non-cardia gastric adenocarcinoma						
Folate						
No. of cases	103	111	95	97	109	
Age-adjusted RR	1.18 (0.89, 1.56)	1.20 (0.92, 1.58)	Ref.	1.01 (0.76, 1.34)	1.12 (0.85, 1.48)	0.49
Multivariate RR[a]	1.05 (0.79, 1.40)	1.15 (0.87, 1.51)	Ref.	1.02 (0.77, 1.35)	1.12 (0.85, 1.48)	0.89
Methionine						
No. of cases	114	109	98	110	84	
Age-adjusted RR	1.15 (0.88, 1.51)	1.10 (0.83, 1.44)	Ref.	1.14 (0.87, 1.50)	0.91 (0.68, 1.21)	0.16
Multivariate RR[a]	1.06 (0.80, 1.39)	1.08 (0.82, 1.42)	Ref.	1.15 (0.87, 1.50)	0.89 (0.66, 1.19)	0.34
Vitamin B6						
No. of cases	111	114	92	89	109	
Age-adjusted RR	1.29 (0.98, 1.69)	1.27 (0.97, 1.68)	Ref.	0.94 (0.70, 1.26)	1.11 (0.84, 1.46)	0.09
Multivariate RR[a]	1.17 (0.88, 1.55)	1.24 (0.94, 1.63)	Ref.	0.96 (0.72, 1.29)	1.13 (0.86, 1.50)	0.43
Vitamin B12						
No. of cases	103	117	88	92	115	
Age-adjusted RR	1.17 (0.88, 1.56)	1.33 (1.01, 1.75)	Ref.	1.05 (0.78, 1.40)	1.30 (0.98, 1.72)	0.79
Multivariate RR[a]	1.10 (0.83, 1.47)	1.32 (1.00, 1.73)	Ref.	1.06 (0.79, 1.41)	1.27 (0.96, 1.68)	0.60

Abbreviations: CI = confidence interval; NIH-AARP = National Institutes of Health—American Association of Retired Persons; RR = relative risk.

[a]Adjusted for age at baseline (continuous); sex (male and female); race/ethnicity (non-Hispanic white, non-Hispanic, black, and others); education (less than high school, high school graduate, some college and college graduate/postgraduate); marital status (married, not married); health status (excellent, very good, good, fair, and poor); body mass index (<18.5, 18.5–<25, 25–<30, 30–<35, ⩾35 kg m^{-2}); smoking status (never, former, and current); smoking dose (0, 1–10, 11–20, 21–30, 31–40, 41–50, 51–60, and >60 cigarettes per day); time since quitting (never quit, ⩾10, 5–9, 1–4, <1 years); vigorous physical activity (never/rarely; ⩽3 times per month; 1–2, 3–4, and ⩾5 times per week); alcohol (0, <5, 5–<15, 15–<30, and ⩾30 g per day); multivitamin use (nonuse, less than daily use, and daily use); family history of any cancer (yes or no); and total caloric intake (continuous).

Our study had several limitations. First, we could not exclude the possibility that the observed association between folate and ESCC was due to residual confounding. People with low folate intake tended to have unhealthy behaviours, which may also affect esophageal and gastric cancer risk. Second, diet sources rich in folate contain other nutrients that may influence the development of esophageal and gastric cancer. A recent study in the NIH-AARP Health and Diet Study showed that dietary patterns with high intake of plant-based food sources, evaluated by high scores of Healthy Eating Index-2005 and alternate Mediterranean Diet, were inversely associated with ESCC risk (Li *et al*, 2013). Third, we lacked information on important factors such as gastroesophageal reflux disease and *Helicobacter pylori* infection status among participants, both of which are known strong risk factors for esophageal and gastric cancer. Finally, we lacked information on the use of individual folate supplements. Our study also has several

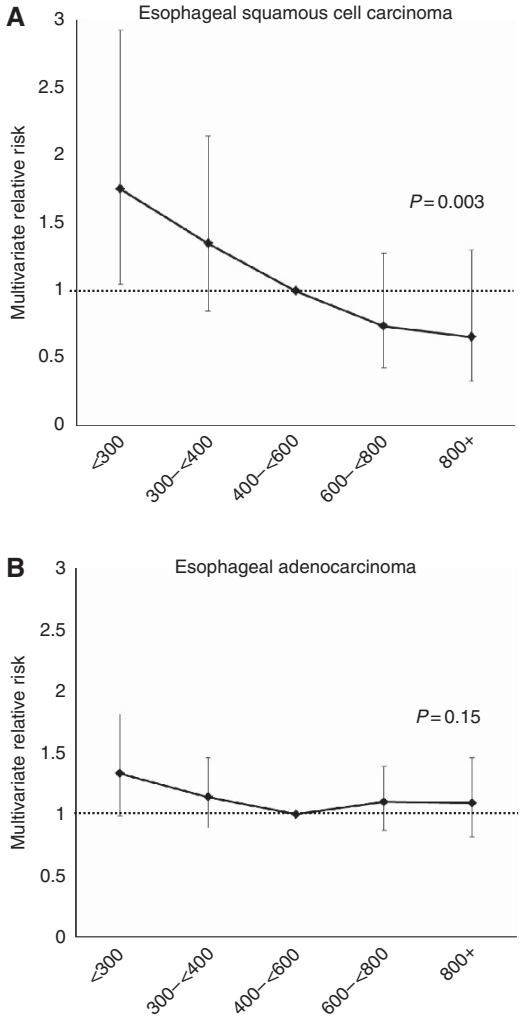

Figure 1. The multivariate association of total folate intake with esophageal squamous cell carcinoma and esophageal adenocarcinoma. Multivariate RRs and 95% CIs of risk of (**A**) esophageal squamous cell carcinoma and (**B**) esophageal adenocarcinoma for categories of total intake (dietary and supplemental intake combined) of folate in the NIH-AARP study. Squares represent the HRs corresponding to each intake category. Vertical lines represent the 95% CIs. Models were adjusted for age at baseline (continuous); sex (male and female); race/ethnicity (non-Hispanic white, non-Hispanic, black, and others); education (less than high school, high school graduate, some college and college graduate/postgraduate); marital status (married, not married), health status (excellent, very good, good, fair, and poor); BMI (<18.5, 18.5–<25, 25–<30, 30–<35, ⩾35 kg m^{-2}); smoking status (never, former, and current); smoking dose (0, 1–10, 11–20, 21–30, 31–40, 41–50, 51–60, and >60 cigarettes per day); time since quitting (never quit, ⩾10, 5–9, 1–4, <1 years); vigorous physical activity (never/rarely; ⩽3 times per month; 1–2, 3–4, and ⩾5 times per week); alcohol (0, <5, 5–<15, 15–<30, and ⩾30 g per day); multivitamin use (nonuse, less than daily use, and daily use); family history of any cancer (yes or no), and total caloric intake (continuous). The numbers of cases were 19, 39, 36, 42, and 39 ESCC and 62, 121, 136, 132, and 68 EAC for categories of <300, 300–<400, 400–<600, 500–<800, and 800+ mcg per day, respectively.

strengths. This is the largest prospective study of folate and other B vitamin intakes with esophageal and gastric cancer to date. Also, our large sample size allowed us to study ESCC, EAC, GCA, and NCGA separately and evaluate folate effect by alcohol and smoking.

In conclusion, in this large cohort of US men and women, we found that low folate intake is associated with elevated risk of ESCC, but higher folate intake did not provide further reduction in ESCC risk. Additional prospective studies are needed to clarify the effect of folate and other nutrients in the one-carbon metabolism pathway on the risk of developing esophageal and gastric cancer. Large studies that assess the interrelation between folate intake, genetic polymorphism in folate pathway, and other factors such as alcohol and smoking would be particularly valuable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Study concept and design: QX and YP. Acquisition of data: ARH. Analysis and interpretation of data: QX, NDF, JR, CCA, and YP. Drafting of the manuscript: QX. Critical revision of the manuscript for important intellectual content: QX, NDF, JR, CCA, and YP. Statistical analysis: QX. Administrative, technical, and material support: ARH. Study supervision: YP.

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