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

Q Xiao *,1, N D Freedman 1, J Ren 2, A R Hollenbeck 3, C C Abnet 1 and Y Park 1

1Nutritional Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, Maryland, USA; 2National Office for Cancer Prevention and Control, National Cancer Center, Beijing, China and 3AARP, Washington, District of Columbia, USA

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...
RESULTS

During 4 471 503 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...
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 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* | 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* | 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 | 2.7 | 3.1 | | |
| 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* | 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 |

| **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* | 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* | 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* | 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 | 112 | 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* | 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.

*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, 1–4, 5–9, 10–14, >14 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).

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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

| 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 adenocarcinoma**      |               |                |                |                |                |                |                |
| Folate                                 |               |                |                |                |                |                |                |
| No. of cases                           | 110           | 85             | 86             | 76             | <0.001         |                |                |
| Age-adjusted RR                        | 1.37 (1.03, 1.81) | 1.01 (0.75, 1.37) | Ref            | 0.87 (0.64, 1.18) |                |                |                |
| Multivariate RR*                       | 1.12 (0.84, 1.50) | 0.93 (0.69, 1.26) | Ref            | 0.98 (0.72, 1.34) |                |                |                |
| Methionine                             |               |                |                |                |                |                |                |
| No. of cases                           | 78            | 77             | 83             | 91             |                |                |                |
| Age-adjusted RR                        | 0.82 (0.61, 1.10) | 0.80 (0.59, 1.08) | Ref            | 1.00 (0.75, 1.33) |                |                | 0.15           |
| Multivariate RR*                       | 0.82 (0.61, 1.12) | 0.82 (0.61, 1.11) | Ref            | 0.93 (0.70, 1.25) |                |                | 0.42           |
| Vitamin B6                             |               |                |                |                |                |                |                |
| No. of cases                           | 102           | 98             | 76             | 80             | <0.001         |                |                |
| Age-adjusted RR                        | 1.41 (1.05, 1.90) | 1.32 (0.98, 1.78) | Ref            | 1.07 (0.79, 1.47) |                |                |                |
| Multivariate RR*                       | 1.28 (0.95, 1.74) | 1.26 (0.93, 1.70) | Ref            | 0.92 (0.66, 1.27) |                |                |                |
| Vitamin B12                             |               |                |                |                |                |                |                |
| No. of cases                           | 73            | 89             | 82             | 94             |                |                |                |
| Age-adjusted RR                        | 0.89 (0.65, 1.22) | 1.08 (0.80, 1.46) | Ref            | 1.14 (0.85, 1.54) |                |                | 0.17           |
| Multivariate RR*                       | 0.99 (0.72, 1.37) | 1.12 (0.83, 1.51) | Ref            | 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            | 1.12 (0.85, 1.48) |                |                | 0.49           |
| Multivariate RR*                       | 1.05 (0.79, 1.40) | 1.15 (0.87, 1.51) | Ref            | 1.12 (0.85, 1.48) |                |                | 0.89           |
| Methionine                             |               |                |                |                |                |                |                |
| No. of cases                           | 114           | 109            | 98             | 84             |                |                |                |
| Age-adjusted RR                        | 1.15 (0.88, 1.51) | 1.10 (0.83, 1.44) | Ref            | 0.91 (0.68, 1.21) |                |                | 0.16           |
| Multivariate RR*                       | 1.06 (0.80, 1.39) | 1.08 (0.82, 1.42) | Ref            | 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            | 1.11 (0.84, 1.46) |                |                | 0.09           |
| Multivariate RR*                       | 1.17 (0.88, 1.55) | 1.24 (0.94, 1.63) | Ref            | 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            | 1.30 (0.98, 1.72) |                |                | 0.79           |
| Multivariate RR*                       | 1.10 (0.83, 1.47) | 1.32 (1.00, 1.73) | Ref            | 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.

*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/graduate); 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).

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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.
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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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