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Association between dietary antioxidant vitamins intake/blood level and risk of gastric cancer

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We aimed to systematically evaluate the association between dietary intake/blood levels of antioxidant vitamins (vitamin C, vitamin E, β-carotene, and α-carotene) and gastric cancer risk. Systematic literature searches were conducted until April 2013 in Pubmed and Embase to identify relevant studies. Either a fixed- or a random-effects model was adopted to estimate overall odds ratios (ORs). Dose–response, meta-regression, subgroup, and publication bias analyses were applied. Forty articles were finally included in the present study. Higher dietary intake of vitamin C, vitamin E, β-carotene, and α-carotene was inversely associated with gastric cancer risk (for vitamin C, pooled OR = 0.58, 95% CI 0.51–0.65; for vitamin E, pooled OR = 0.65, 95% CI 0.57–0.74; for β-carotene, pooled OR = 0.59, 95% CI 0.49–0.70; for α-carotene, pooled OR = 0.69, 95% CI 0.52–0.93). Subgroup analyses suggested the effects of these antioxidant vitamins were different in gastric cancer subtypes. As indicated by dose–response analysis, a 100 mg/day increment of vitamin C intake conferred an OR of 0.78 (95% CI 0.67–0.90); a 15 mg/day increment of vitamin E intake conferred an OR of 0.79 (95% CI 0.66–0.94); and a 5 mg/day increment in β-carotene intake conferred an OR of 0.80 (95% CI 0.60–1.04). No significant association was observed between blood vitamin C, α-tocopherol, γ- tocopherol, β-carotene and α-carotene levels and gastric cancer risk. In conclusion, dietary intake of vitamin C, vitamin E, β-carotene and α-carotene was inversely associated with gastric cancer risk while no such association was observed for blood levels of these antioxidant vitamins, thus the results should be interpreted cautiously.

Epidemiology

Gastric cancer remains the fourth most common cancer in men and fifth most common cancer in women worldwide.[1] Gastric cancer accounts for about 10% of annual cancer-related deaths overall, and it was estimated that 737,000 patients died from gastric cancer in 2011.[2] Although the exact mechanism for gastric cancer progress is not clear, oxidative stress can affect many cellular functions and has been implicated in the pathogenesis of many diseases, including gastric cancer.[3] Oxidative injury may contribute to the occurrence of gastric cancer by inducing gene mutation[4] and leading to apoptosis.[5] On the other hand, the human diet contains many antioxidants, including antioxidant vitamins, which may protect against oxidative stress.[6] And the gastrointestinal tract is thought to be the major site of antioxidant action.[7]

Previously it has been shown that a high intake of fruit and vegetables, which are rich in antioxidant vitamins, might be associated with a lower risk of gastric cancer.[8] Observational studies have examined the association between intake/blood levels of antioxidant vitamins and gastric cancer risk, while the results were inconsistent.[9–13] The World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) Report in 2007 assessed the role of food, nutrition, and physical activity in the prevention of gastric cancer and other types of cancer.[14] However, no clear conclusion could be drawn from this report for the role of antioxidant vitamins, including vitamin C, vitamin E, β-carotene,

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Additional Supporting Information may be found in the online version of this article.
*P.W.L. and H.H.Z. contributed equally to this work
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What's new?

Although implicated as possible agents of cancer prevention, whether the intake of antioxidant vitamins is associated with a reduced risk of cancer remains unclear. To explore possible relationships, the authors of the present report systematically analyzed 40 studies that assessed associations between dietary intake or blood levels of antioxidant vitamins and gastric cancer risk. The analysis offers evidence for an inverse association between gastric cancer risk and dietary intake of vitamin C, vitamin E, β-carotene, and α-carotene. No association was found to exist, however, between gastric cancer risk and blood levels of the vitamins.

and α-carotene, on gastric cancer risk, and therefore this issue remains unsettled. Therefore, the aim of present study was to assess the current evidence on the association between antioxidant vitamins intake/blood levels and gastric cancer risk.

Methods

Literature search and study selection

Systematic literature searches were conducted before April 2013 in the Pubmed and Embase databases without restrictions. The following terms were used: ("vitamin" or "antioxidant" or "vitamin C" or "vitamin E" or "carotene" or "tocopherol" or "ascorbic acid") and ("gastric cancer" or "stomach cancer" or "gastric adenocarcinoma" or "stomach adenocarcinoma"). References of relevant articles and reviews were also scanned to include potentially missing studies. The retrieved studies were carefully examined to exclude potential duplicates or overlapping data. Titles and abstracts of articles selected from the initial search were first scanned, and then full papers of potential eligible studies were reviewed. This meta-analysis was designed, conducted and reported according to the PRISMA and MOOSE statements.[15,16]

Articles were included if they met all the following criteria: (*i*) study should be designed as case–control or cohort study; (*ii*) study should evaluate the association between dietary intake or blood levels of antioxidant vitamin (or antioxidant vitamins) and gastric cancer risk; (*iii*) odds ratio (OR) or relative risk (RR) estimates with 95% confidence intervals (95% CI) were reported or could be calculated.

Data extraction

Two reviewers (P.W.L. and H.H.Z.) independently extracted study characteristics using standardized forms, and discrepancies were resolved by a third investigator. The following information was extracted from each study: first author, year of publication, study design (case–control or cohort), sample size of the study, sex and age of participants, country of origin, variables adjusted for in the analysis, and OR (or RR) estimates with 95% CIs for the highest versus lowest categories of antioxidant vitamin intake or blood level. Estimates of nutrients intakes in this study referred to dietary intake only, as most of the included studies did not report supplements intake. ORs (RRs) that reflected the greatest degree of control for potential confounders were adopted in this meta-analysis. Newcastle-Ottawa Scale was applied to assess the study quality.[17]

Statistical analysis

Study-specific OR (RR) estimates were pooled using a fixed-effects model if no significant heterogeneity existed, otherwise a random-effects model was applied. The extent of heterogeneity across studies was checked using the χ^2 test and I^2 test; $p \leq 0.10$ and/or $I^2 > 50\%$ indicates significant heterogeneity. Meta-regression and subgroup analyses were performed to explore the possible source of heterogeneity: experimental design, geographic region, sample size and study quality. Subgroup analyses were also applied to evaluate potential effect modification of variables including design, geographic region, sex, gastric cancer subtype, sample size and study quality on outcomes. Meta-regression and subgroup analyses were applied only if the number of studies included in the meta-analysis was larger than 10.

To assess the dose–response relationship between antioxidant vitamins intake/blood level and gastric cancer risk, the method of restricted cubic splines with three knots at percentiles 25%, 50%, and 75% of the distribution was adopted.[18] Studies were included for dose–response analyses only if they reported the number of cases and controls, and the OR with 95% CI for at least three quantitative exposure categories. The mean antioxidant vitamin intake (or blood level) for each category was assigned to each corresponding OR. Begg's funnel plots and Egger's linear regression test were used to assess publication bias. All analyses were conducted using the Stata software (version 11.0; StatCorp, College Station, TX). $p < 0.05$ was considered statistically significant.

Results

Study selection and characteristics

Searching PUBMED and EMBASE resulted in the identification of 1,941 articles. After removing 484 duplicate papers, 1,457 articles were assessed. Review of titles and abstracts resulted in the exclusion of 1,324 articles. For the remaining articles, 93 were excluded for the following reasons: did not report association between antioxidant vitamin intake/blood level and gastric cancer risk ($n = 21$); not original articles

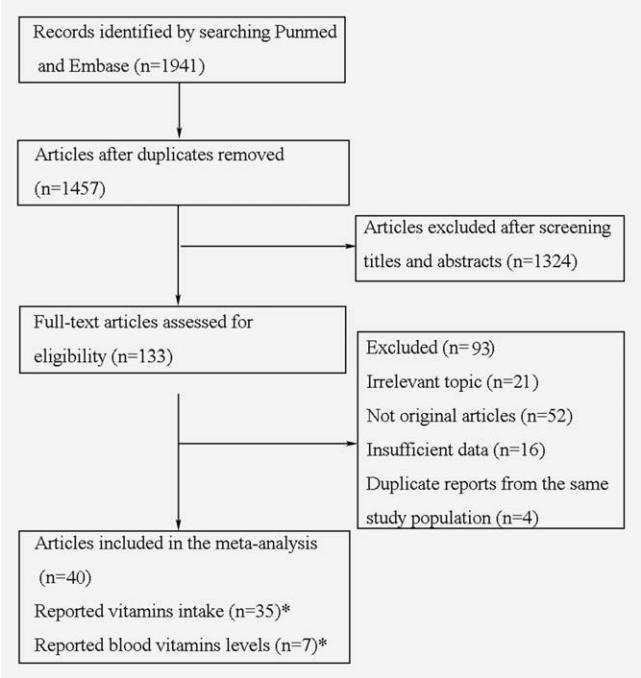

Figure 1. Flow diagram of study selection process (*two articles reported both antioxidant intake and blood level).

($n = 52$); insufficient data ($n = 16$); duplicate reports from the same study population ($n = 4$). Finally, forty articles were included in this meta-analysis.[9–13,19–53] The selection process was shown in Figure 1 and the characteristics of the included studies were presented in Supporting Information Tables S1 and S2. Among the included articles, 35 articles examined antioxidant intake,[9–13,19–48] while 7 examined blood antioxidant level (2 articles reported both antioxidant intake and blood level).[10,11,49–53]

Association between vitamin C and gastric cancer risk

Meta-analysis of dietary vitamin C intake. A total of 32 studies with 733,894 subjects (9,455 patients) assessed the association between dietary vitamin C intake and gastric cancer risk. The pooled OR of gastric cancer risk for the highest versus lowest categories of vitamin C intake was 0.58 (95% CI 0.51–0.65), indicating a significant inverse association (Fig. 2*a*, Table 1). Significant heterogeneity among studies was found ($I^2 = 46.7\%$, $p = 0.002$) (Fig. 2*a*, Table 1).

Subgroup analyses were then applied, and by stratifying gastric cancer subtype, significant association was found between vitamin C intake and gastric noncardia cancer (pooled OR = 0.56, 95% CI 0.48–0.67) and the intestinal type of gastric cancer (pooled OR = 0.69, 95% CI 0.51–0.93), while vitamin C intake was not significantly associated with gastric cardia cancer (pooled OR = 0.69, 95% CI 0.44–1.09) and the diffuse type of gastric cancer (pooled OR = 0.71, 95% CI 0.29–1.73) (Table 2). The subgroup analyses results for study design, geographic region, sex, sample size and study quality, were shown in Table 2. Meta-regression and subgroup analyses suggested that heterogeneity was influenced by several factors, including study design, geographic region, sample size and study quality (Table 2).

Meta-analysis of blood vitamin C level. Two studies with 406 patients and 986 controls assessed the association between blood vitamin C level and gastric cancer risk. No significant association was found between blood vitamin C level and gastric cancer risk (pooled OR = 0.72, 95% CI 0.44–1.19) (Fig. 3*a*, Table 1). No significant heterogeneity was observed ($I^2 = 41.6\%$, $p = 0.191$) (Fig. 3*a*, Table 1).

Association between vitamin E and gastric cancer risk

Meta-analysis of dietary vitamin E intake. Twenty-four studies with 694,806 subjects (7,095 patients) evaluated the association between dietary vitamin E intake and gastric cancer risk. Comparing the highest versus lowest categories of vitamin E intake, the pooled OR was 0.65 (95% CI 0.57–0.74) for gastric cancer, suggesting an inverse association. There was significant heterogeneity across studies ($I^2 = 48.3\%$, $p = 0.005$) (Fig. 2*b*, Table 1).

Subgroup analyses showed that effect of vitamin E intake was different in gastric cancer subtype. Significant association was found for vitamin E intake with gastric noncardia cancer (pooled OR = 0.65, 95% CI 0.56–0.75) and the intestinal type of gastric cancer (pooled OR = 0.65, 95% CI 0.49–0.87), while it was not significantly associated with gastric cardia cancer (pooled OR = 0.90, 95% CI 0.67–1.22) and the diffuse type of gastric cancer (pooled OR = 0.74, 95% CI 0.51–1.08) (Table 2). The subgroup analyses results for study design, geographic region, sex, sample size, and study quality, were shown in Table 2. Meta-regression and subgroup analyses suggested that heterogeneity could be partially explained by several factors including study design, geographic region, and sample size (Table 2).

Meta-analysis of blood vitamin E level. Five studies with 1,648 patients and 29,669 controls assessed the association between blood α-tocopherol level and gastric cancer risk. No significant association was found between blood α-tocopherol level and gastric cancer risk (pooled OR = 1.01, 95% CI 0.72–1.42) (Fig. 3*b*, Table 1). There was no significant heterogeneity across studies ($I^2 = 43.4\%$, $p = 0.132$) (Fig. 3*b*, Table 1).

Four studies with 1,428 patients and 2,779 patients assessed the association between blood γ- tocopherol level and gastric cancer risk. No significant association was found between blood γ-tocopherol level and gastric cancer risk (pooled OR = 0.97, 95% CI 0.78–1.21), and there was no significant heterogeneity across studies ($I^2 = 0\%$, $p = 0.847$) (Fig. 3*c*, Table 1).

Association between carotene and gastric cancer risk

Meta-analyses of dietary β-carotene and α-carotene intake. Twenty studies with 245,858 subjects (6,258 patients) evaluated the association between dietary β-carotene intake and gastric cancer risk, while the association between α-carotene

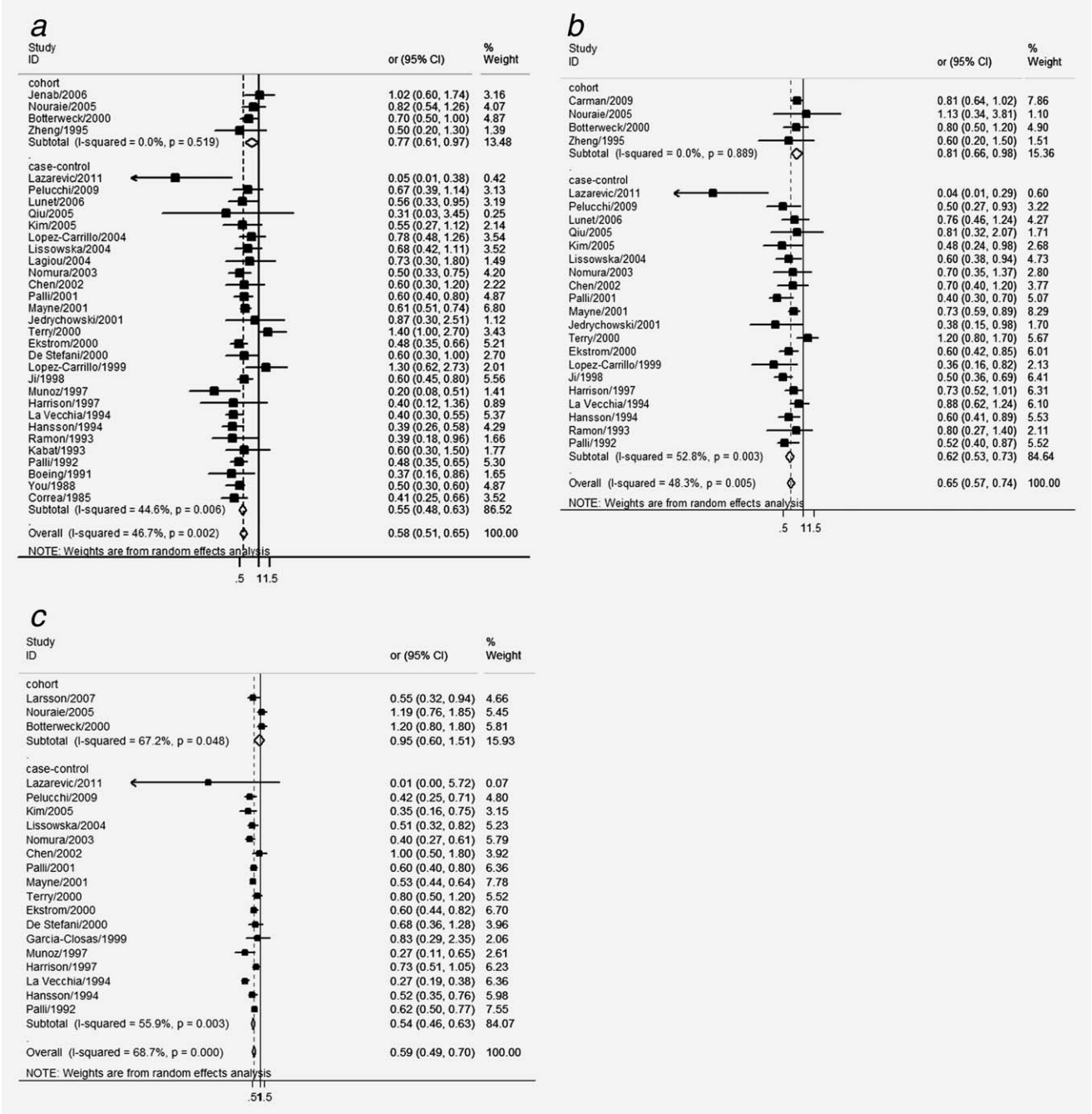

Figure 2. The association between antioxidant vitamins intake and gastric cancer risk. (*a*) Pooled odds ratios of gastric cancer for the highest versus the lowest categories of vitamin C intake. (*b*) Pooled odds ratios of gastric cancer for the highest versus the lowest categories of vitamin E intake. (*c*) Pooled odds ratios of gastric cancer for the highest versus the lowest categories of β-carotene intake

intake and gastric cancer risk was assessed in eight studies with 206,345 subjects (1,614 patients). Comparing the highest category with the lowest category, both β-carotene and α-carotene intake were shown to be inversely associated with gastric cancer risk (for β-carotene, pooled OR = 0.59, 95% CI 0.49–0.70; for α-carotene, pooled OR = 0.69, 95% CI 0.52–0.93) (Fig. 2*c*, Supporting Information Fig. S1A, Table 1). There was significant heterogeneity among the studies of β-carotene intake ($I^2 = 68.7\%$, $p < 0.001$), as well as the studies of α-carotene intake ($I^2 = 58.4\%$, $p = 0.019$) (Fig. 2*c*, Supporting Information Fig. S1A, Table 1).

Table 2 showed the results of subgroup analyses. We found β-carotene intake was significantly associated with gastric cancer risk among case-control studies (pooled OR = 0.54, 95% CI 0.46–0.63) but not among cohort studies (pooled OR = 0.95, 95% CI 0.60–1.51) (Table 2). Stratifying

Table 1. Pooled analyses of association between vitamin C, vitamin E, β-carotene intake/blood level and gastric cancer risk

Vitamin intake	No. studies	No. patients	Pooled OR (95% CI)	Heterogeneity	
				I^2 (%)	*p*
Vitamin C	32	9,455	0.58 (0.51–0.65)	46.7	0.002
Vitamin E	24	7,095	0.65 (0.57–0.74)	48.3	0.005
β-carotene	20	6,258	0.59 (0.49–0.70)	68.7	<0.001
α-carotene	8	1,614	0.69 (0.52–0.93)	58.4	0.019
Blood vitamin level					
Vitamin C	2	406	0.72 (0.44–1.19)	41.6	0.191
α-Tocopherol	5	1,648	1.01 (0.72–1.42)	43.4	0.132
γ-Tocopherol	4	1,428	0.97 (0.78–1.21)	0	0.847
β-Carotene	5	1,648	0.83 (0.57–1.19)	62.2	0.032
α-Carotene	3	946	0.79(0.47–1.31)	53.0	0.119

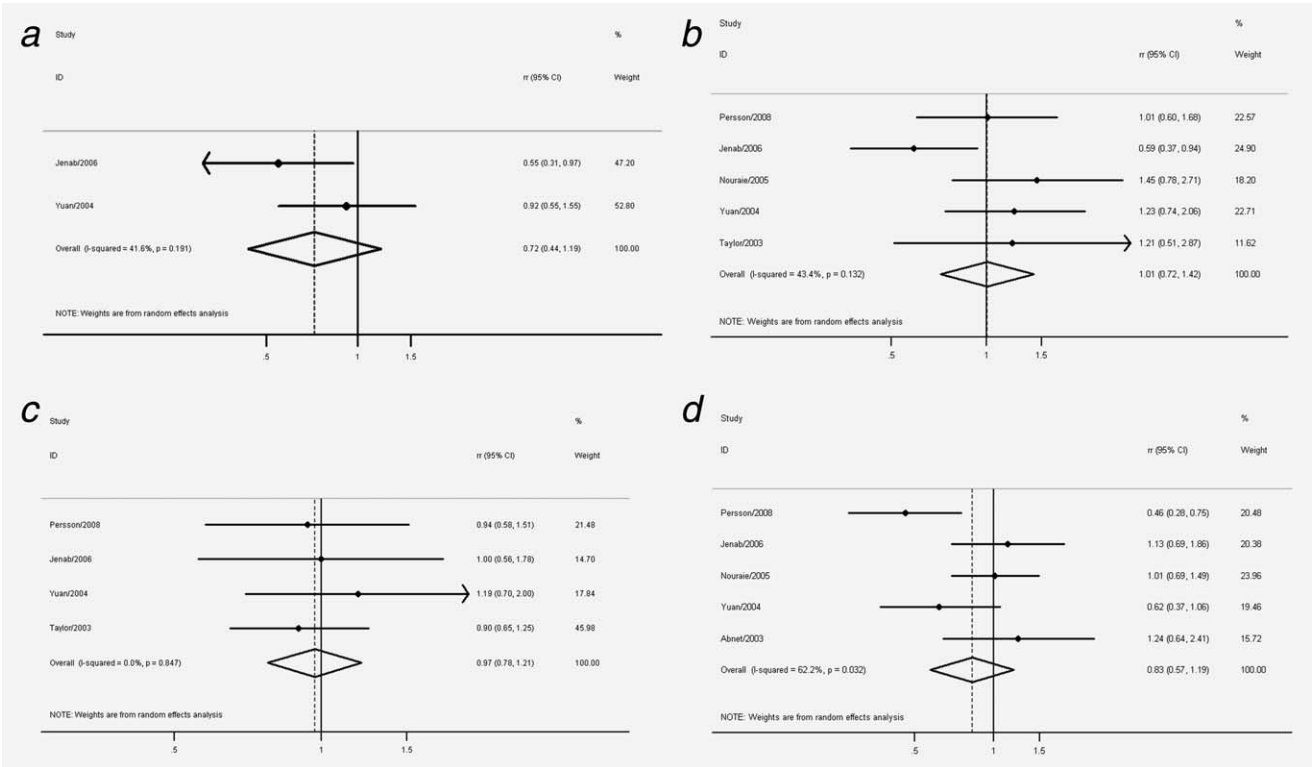

Figure 3. Pooled odds ratios of gastric cancer for the highest versus the lowest categories of (*a*) blood vitamin C level, (*b*) blood α-tocopherol level, (*c*) blood γ- tocopherol level, (*d*) blood β-carotene level.

by gender, significant association was found with females (pooled OR = 0.44, 95% CI 0.26–0.73) but not with males (pooled OR = 0.57, 95% CI 0.32–1.02) (Table 2). Stratifying by gastric cancer subtype, significant association was found only with gastric cardia cancer (pooled OR = 0.57, 95% CI 0.46–0.71), but not with noncardia cancer, the intestinal type and diffuse type of gastric cancer (Table 2). Heterogeneity across studies could be partially explained by several factors including study design, geographic region, and sample size (Table 2).

Meta-analyses of blood β-carotene and α-carotene level. Five studies with 1,648 patients and 29,669 controls evaluated the association between blood β-carotene level and gastric cancer risk while blood α-carotene level was assessed in three studies with 946 patients and 1,726 controls. No significant association was found for blood β-carotene level (pooled OR = 0.83, 95% CI 0.57–1.19) and for blood α-carotene level (pooled OR = 0.79, 95% CI 0.47–1.31) with gastric cancer risk (Fig. 3*d* and Supporting Information Fig. S1B, Table 1). There was significant heterogeneity among studies of plasma

Table 2. Subgroup analyses of association between vitamin C, vitamin E, β-carotene intake and gastric cancer risk

	Vitamin C intake Heterogeneity			Vitamin E intake Heterogeneity			β-Carotene intake Heterogeneity		
Factor	Pooled OR (95% CI)	I^2	*p*	Pooled OR (95% CI)	I^2	*p*	Pooled OR (95% CI)	I^2 (%)	*p*
Design									
Cohort	0.77 (0.61–0.97)	0	0.519	0.81 (0.66–0.98)	0	0.889	0.95 (0.60–1.51)	67.2	0.048
All case–control	0.55 (0.48–0.63)	44.6	0.006	0.62 (0.53–0.73)	52.8	0.003	0.54 (0.46–0.63)	55.9	0.003
Population-based	0.58 (0.50–0.67)	46.8	0.024	0.64 (0.54–0.74)	45.0	0.035	0.57 (0.52–0.64)	19.4	0.270
Hospital-based	0.50 (0.39–0.63)	39.9	0.068	0.52 (0.34–0.81)	69.7	0.005	0.45 (0.30–0.67)	66.9	0.004
Geographic region									
Europe	0.57 (0.47–0.70)	64.4	<0.001	0.63 (0.51–0.79)	62.4	0.001	0.59 (0.47–0.75)	74.1	<0.001
America	0.56 (0.49–0.66)	0	0.797	0.75 (0.66–0.85)	0	0.977	0.59 (0.44–0.80)	63.3	0.043
Asian and others	0.61 (0.51–0.73)	10.0	0.352	0.50 (0.38–0.65)	0	0.646	0.52 (0.32–0.85)	41.0	0.193
Sex									
Male	0.61 (0.48–0.77)	0	0.536	0.54 (0.41–0.71)	0	0.716	0.57 (0.32–1.02)	77.5	0.004
Female	0.62 (0.46–0.83)	12.0	0.337	0.65 (0.47–0.90)	0	0.460	0.44 (0.26–0.73)	0	0.627
Gastric cancer subtype									
Anatomical subsite									
Cardia cancer	0.69 (0.44–1.09)	69.7	0.010	0.90 (0.67–1.22)	55.7	0.046	0.57 (0.46–0.71)	40.8	0.167
Noncardia cancer	0.56 (0.48–0.67)	0	0.462	0.65 (0.56–0.75)	37.2	0.173	0.73 (0.48–1.12)	76.7	0.014
Histological subtype									
Intestinal type	0.69(0.51–0.93)	0	0.702	0.65 (0.49–0.87)	0	0.869	0.59 (0.30–1.15)	68.4	0.075
Diffuse type	0.71(0.29–1.73)	75.5	0.017	0.74 (0.51–1.08)	0	0.431	0.72 (0.49–1.06)	0	0.484
Sample size[1]									
Large	0.60(0.52–0.70)	60.4	0.001	0.66 (0.56–0.78)	56.9	0.004	0.61 (0.49–0.76)	78.4	<0.001
Small	0.55(0.46–0.65)	19.7	0.233	0.65 (0.54–0.78)	35.9	0.121	0.55 (0.41–0.73)	44.1	0.074
Study quality[2]									
High	0.62(0.54–0.72)	48.9	0.011	0.67 (0.58–0.76)	39.0	0.046	0.66 (0.56–0.77)	61.9	0.002
Low	0.51(0.41–0.62)	35.2	0.094	0.51 (0.31–0.83)	69.7	0.006	0.39 (0.27–0.57)	44.6	0.094

[1]Large sample size means the sample size ≥750 while small sample size means the sample size <750.
[2]High study quality means quality score≥6 while low study quality means quality score <6.

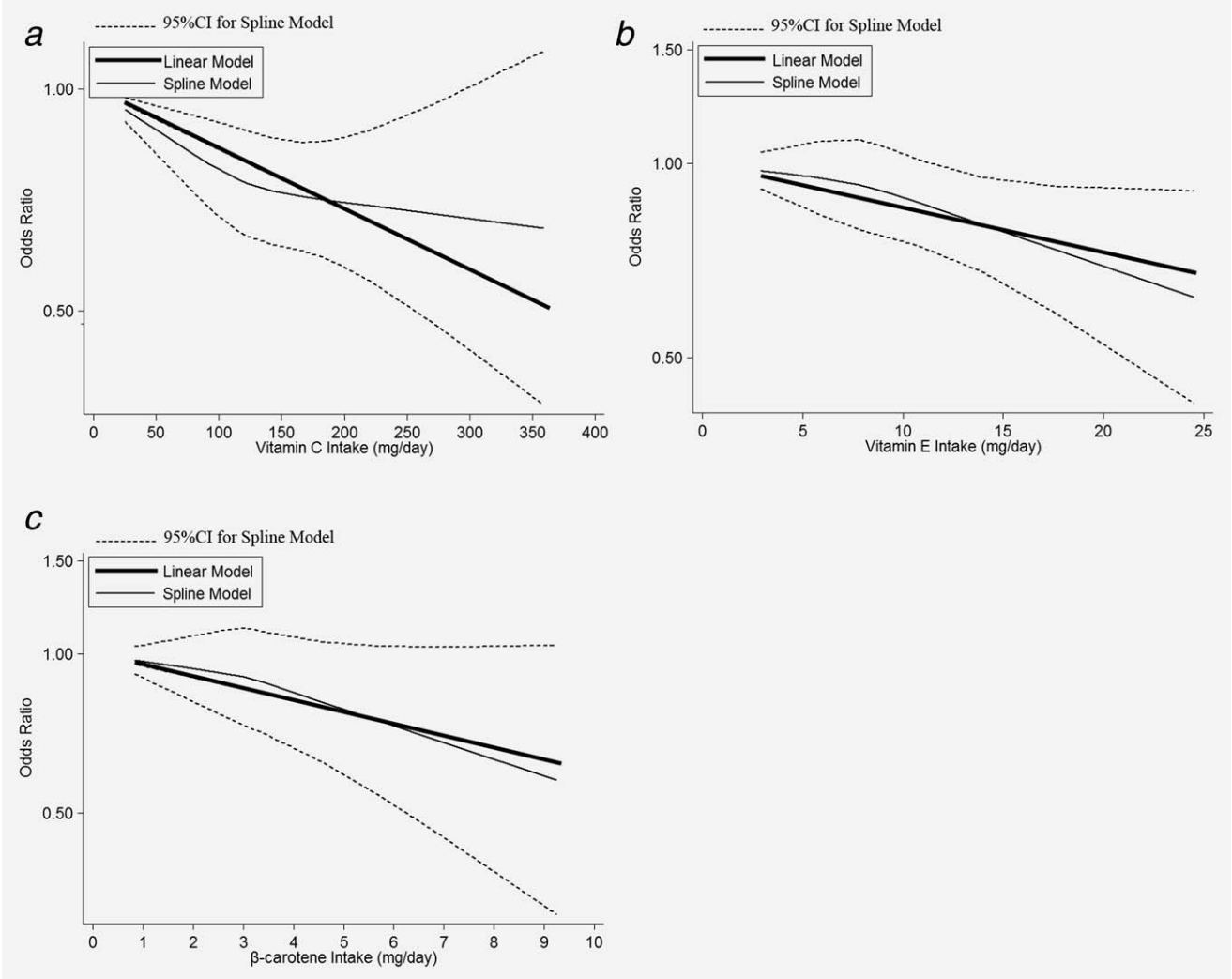

Figure 4. Dose–response relationships between vitamin C, vitamin E, β-carotene intake and gastric cancer risk. (*a*) Dose–response analysis of vitamin C intake, (*b*) dose–response analysis of vitamin E intake, (*c*) dose–response analysis of β-carotene intake.

β-carotene level ($I^2 = 62.2\%$, $p = 0.032$) and among studies of plasma α-carotene level ($I^2 = 53.0\%$, $p = 0.119$).

Dose–response meta-analyses. Dose–response relationship was assessed between vitamin C, vitamin E, β-carotene intake and gastric cancer risk, while α-carotene intake and blood antioxidant vitamins levels were not analyzed due to insufficient data. Two models namely the spline model and the linear model, were applied to assess the dose–response relationship, and the results from both models were similar for these three vitamins (as shown in Fig. 4). For vitamin C intake, the summary OR for an increment of 100 mg/day was 0.78 (95% CI 0.67–0.90); for vitamin E intake, the summary OR for an increment of 15 mg/day was 0.79 (95% CI 0.66–0.94); and a 5 mg/day increment in β-carotene intake conferred an OR of 0.80 (95% CI 0.60–1.04) (Fig. 4).

Publication bias

Begg's funnel plots and Egger's linear regression test indicated no evidence of publication bias in the present study.

Discussion

Diet has been reported to be involved in the etiology of gastric cancer, and antioxidants are thought to be the strongest protective dietary components.[1] Epidemiological studies have indicated an inverse association between antioxidant vitamins intake and gastric cancer risk.[10,13,20] However, previous clinical trials showed contradictive results. In a cohort study with 521,457 subjects, dietary antioxidant capacity was suggested to be associated with a reduction in gastric cancer risk.[54] In the current study, we summarized the results of published observational studies, including 35 studies evaluating antioxidant vitamins intake and seven reports evaluating blood antioxidant vitamins level. The results indicated that vitamin C, vitamin E, β-carotene and α-carotene intakes were inversely associated with gastric cancer risk. Subgroup analyses suggested that the effect of these antioxidant vitamins was different in gastric cancer subtype. However, blood levels of these antioxidant vitamins were not significantly associated with gastric cancer risk.

The different effect between antioxidant vitamins intake and blood levels might be explained by several reasons. Firstly, dietary intake measurements of these antioxidant vitamins might represent long term consumption, while blood levels indicate the concentration at only one time point and may not reflect tissue levels.[10] Besides, both dietary intake and blood level measurements may be confounded by unaccounted for factors and have measurement errors.[10] In addition, the blood levels of antioxidant vitamins may also be influenced by factors such as efficiency of uptake[11]. Blood levels of antioxidant vitamins may also reflect antioxidant vitamins intake from supplements, while most of the studies included in this meta-analysis only evaluated dietary intake of antioxidant vitamins. Besides the absence of a significant association between blood levels of antioxidant vitamins and gastric cancer risk reported here, a systematic review including randomized trials concluded that supplementation with β-carotene, vitamin C, vitamin E, vitamin A and selenium could not reduce gastric cancer risk.[55] One possible reason is that in the clinical trials the supplementation of antioxidant vitamins were at very high doses and the duration was usually long, thus the endogenous redox network might be "disturbed."[54] However, it should be noted that the inverse associations observed for vitamin C, vitamin E, β-carotene and α-carotene may just reflect the multitude of bioactive compounds in related food sources such as vegetables, fruits, cereals, nuts and seeds. Thus, the inverse association between dietary antioxidant vitamins intake and gastric cancer risk observed in this study should be interpreted with caution.

Vitamin C is one of the most effective dietary antioxidants, which can reduce free radical-mediated damage for gastric epithelium by terminating reactive oxygen species in the stomach.[56] Besides, vitamin C might prevent gastric carcinogenesis by its potential to modulate cell growth kinetics, the antimicrobial activity against *H. pylori*, and the inhibition of N-nitroso compound formation in the stomach.[57,58] In this study, higher vitamin C intake was associated with reduced gastric cancer risk and this effect was not influenced by study design, geographic area, gender, sample size and study quality. However, the effect of vitamin C could be modulated by gastric cancer anatomical subsite and the histological subtype. We found significant association between vitamin C intake with gastric noncardia cancer and the intestinal type of gastric cancer, but not with gastric cardia cancer and the diffuse type of gastric cancer. It has been suggested that gastric cardia cancer and gastric noncardia cancer might have different etiologic factors.[59] For example, *Helicobacter pylori* infection has shown to be a strong risk factor for gastric noncardia cancer, while the role of *H. pylori* in gastric cardia cancer development is not clear.[60] Studies have also indicated that the intestinal type of gastric cancer is linked more to environmental factors than the diffuse type,[61] which is consistent with our finding in this study. We did not find a significant association between blood vitamin C level and gastric cancer risk. However, since only two studies evaluated blood vitamin C level, more studies are warranted to clarify this question.

Vitamin E is a potent lipid-soluble antioxidant and might also be involved in gastric cancer prevention by reducing oxidative stress.[62] Besides, vitamin E could inhibit nitrosation and reduce the chemically induced gastric tumors.[62] We found that higher vitamin E intake was associated with reduced gastric cancer risk and the protective effect was different by gastric cancer anatomical subsite and the histological subtype. Higher vitamin E intake was shown to decrease the risk of gastric noncardia cancer and the intestinal type of gastric cancer, while no significant association was indicated with gastric cardia cancer and the diffuse type of gastric cancer. Again, we did not find significant association between blood α-tocopherol or γ- tocopherol level and gastric cancer risk. Results from previous studies analyzing blood tocopherol levels were conflicting.[10,50,52] The difference between studies was probably due to the differences in the study population and the blood tocopherol levels.

Carotenoids have been shown to inhibit the incidence and growth of chemically induced gastric tumors.[63] Several mechanisms might contribute to such effect, including the antioxidant function against oxidative DNA damage,[64] the induction of apoptosis in transformed cells[65] and the regulation of immune response.[66] In the present study, pooled results of all the included studies indicated that β-carotene and α-carotene intake was significantly associated with decreased gastric cancer risk. However, the significant association was not found in meta-analyses of cohort studies for both β-carotene and α-carotene blood level. As the number of cohort studies was small (three for β-carotene and two for α-carotene), more cohort studies are needed to confirm or refute this conclusion. For different gastric cancer subsites, higher β-carotene intake was inversely associated with gastric cardia cancer risk but not with gastric noncardia cancer risk. It should be noted that in the three studies analyzing gastric noncardia cancer, only one study including male smokers reported a positive association,[10] while the other two reported an inverse association.[30,33] Thus this result should be interpreted with caution. When stratifying by sex, β-carotene intake was inversely associated with gastric cancer risk in women but not in men. One possible explanation could be that men smoke more frequently than women, and β-carotene might increase DNA oxidative damage and modify cell proliferation and apoptosis in cells exposed to tobacco smoke condensate.[67,68] Results did not indicate a significant association between blood β-carotene and α-carotene levels and gastric cancer risk.

The current study has several advantages. First, the number of total participants was substantial, which increased the statistical power. Second, dose–response analyses were applied to assess the association between vitamin C, vitamin E, β-carotene and gastric cancer risk, which further strengthened the association. Besides, no publication bias was observed, indicating the pooled results might be unbiased.

The current analysis also has some limitations. First, although most studies were adjusted for other known risk factors for gastric cancer, there is still the possibility that control of confounders is inadequate. And the confounders in each study may not be the same, which might also cause bias in the risk estimates. Second, the range of the cutoff points between the lowest and highest categories for both antioxidant vitamins intake and the blood antioxidant vitamins levels was very different among studies, which may impact the current analyses. Third, when assessing the association between antioxidant vitamins intake and gastric cancer risk, most of the included studies were case-control studies. Case–control studies are relatively easy to conduct, but tend to rely on recall for exposure measurement, which is prone to bias. Cohort studies could measure exposure more precisely and are more adept at identifying causal relationships, and thus evidence from cohort studies is usually judged stronger than that from case–control studies. Thus, more cohort studies, especially cohort studies with multiple blood antioxidant vitamins measurements, are warranted. Finally, most of the included studies only reported dietary antioxidant vitamins intakes, thus the effects of supplements should be further assessed.

In summary, dietary intakes of vitamin C, vitamin E, β-carotene and α-carotene were inversely associated with gastric cancer risk, while no significant association was observed for blood levels of these antioxidant vitamins, thus the conclusions should be interpreted cautiously.

References

1. Guggenheim DE, Shah MA. Gastric cancer epidemiology and risk factors. *J Surg Oncol* 2013;107: 230–6.
2. Jemal A, Bray F, Center MM, et al. Global cancer statistics. *CA Cancer J Clin* 2011;61:69–90.
3. Seifried HE. Oxidative stress and antioxidants: a link to disease and prevention? *J Nutr Biochem* 2007;18:168–71.
4. Sporn MB, Suh N. Chemoprevention of cancer. *Carcinogenesis* 2000;21:525–30.
5. Salganik RI. The benefits and hazards of antioxidants: controlling apoptosis and other protective mechanisms in cancer patients and the human population. *J Am Coll Nutr* 2001;20:464S–72S; discussion 73S-75S.
6. Halliwell B. Biochemistry of oxidative stress. *Biochem Soc Trans* 2007;35:1147–50.
7. Halliwell B, Zhao K, Whiteman M. The gastrointestinal tract: a major site of antioxidant action? *Free Radic Res* 2000;33: 819–30.
8. Lunet N, Lacerda-Vieira A, Barros H. Fruit and vegetables consumption and gastric cancer: a systematic review and meta-analysis of cohort studies. *Nutr Cancer* 2005;53:1–10.
9. Larsson SC, Bergkvist L, Naslund I, et al. Vitamin A, retinol, and carotenoids and the risk of gastric cancer: a prospective cohort study. *Am J Clin Nutr* 2007;85:497–503.
10. Nouraie M, Pietinen P, Kamangar F, et al. Fruits, vegetables, and antioxidants and risk of gastric cancer among male smokers. *Cancer Epidemiol Biomarkers Prev* 2005;14:2087–92.
11. Jenab M, Riboli E, Ferrari P, et al. Plasma and dietary vitamin C levels and risk of gastric cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC-EURGAST). *Carcinogenesis* 2006;27:2250–7.
12. Botterweck AA, van den Brandt PA, Goldbohm RA. Vitamins, carotenoids, dietary fiber, and the risk of gastric carcinoma: results from a prospective study after 6.3 years of follow-up. *Cancer* 2000;88:737–48.
13. Carman S, Kamangar F, Freedman ND, et al. Vitamin E intake and risk of esophageal and gastric cancers in the NIH-AARP Diet and Health Study. *Int J Cancer* 2009;125:165–70.
14. Wiseman M. The second World Cancer Research Fund/American Institute for Cancer Research expert report. Food, nutrition, physical activity, and the prevention of cancer: a global perspective. *Proc Nutr Soc* 2008;67:253–6.
15. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009; 6:e1000097.
16. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA* 2000;283:2008–12.
17. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol* 2010;25:603–5.
18. Larsson SC, Orsini N, Wolk A. Vitamin B6 and risk of colorectal cancer: a meta-analysis of prospective studies. *JAMA* 2010;303: 1077–83.
19. Lazarevic K, Nagorni A, Bogdanovic D, et al. Dietary micronutrients and gastric cancer: Hospital based study. *Central Eur J Med* 2011;6: 783–7.
20. Pelucchi C, Tramacere I, Bertuccio P, et al. Dietary intake of selected micronutrients and gastric cancer risk: an Italian case-control study. *Ann Oncol* 2009;20:160–5.
21. Lunet N, Valbuena C, Carneiro F, et al. Antioxidant vitamins and risk of gastric cancer: a case-control study in Portugal. *Nutr Cancer* 2006;55: 71–7.
22. Qiu JL, Chen K, Zheng JN, et al. Nutritional factors and gastric cancer in Zhoushan Islands, China. *World J Gastroenterol* 2005;11:4311–16.
23. Kim HJ, Kim MK, Chang WK, et al. Effect of nutrient intake and *Helicobacter pylori* infection on gastric cancer in Korea: a case-control study. *Nutr Cancer* 2005;52:138–46.
24. Lopez-Carrillo L, Torres-Lopez J, Galvan-Portillo M, et al. *Helicobacter pylori*-CagA seropositivity and nitrite and ascorbic acid food intake as predictors for gastric cancer. *Eur J Cancer* 2004;40: 1752–9.
25. Lissowska J, Gail MH, Pee D, et al. Diet and stomach cancer risk in Warsaw, Poland. *Nutr Cancer* 2004;48:149–59.
26. Lagiou P, Samoli E, Lagiou A, et al. Flavonoids, vitamin C and adenocarcinoma of the stomach. *Cancer Causes Control* 2004;15:67–72.
27. Nomura AM, Hankin JH, Kolonel LN, et al. Case-control study of diet and other risk factors for gastric cancer in Hawaii (United States). *Cancer Causes Control* 2003;14:547–58.
28. Chen H, Tucker KL, Graubard BI, et al. Nutrient intakes and adenocarcinoma of the esophagus and distal stomach. *Nutr Cancer* 2002;42:33–40.
29. Palli D, Russo A, Decarli A. Dietary patterns, nutrient intake and gastric cancer in a high-risk area of Italy. *Cancer Causes Control* 2001;12:163–72.
30. Mayne ST, Risch HA, Dubrow R, et al. Nutrient intake and risk of subtypes of esophageal and gastric cancer. *Cancer Epidemiol Biomarkers Prev* 2001;10:1055–62.
31. Jedrychowski W, Popiela T, Steindorf K, et al. Nutrient intake patterns in gastric and colorectal cancers. *Int J Occup Med Environ Health* 2001;14: 391–5.
32. Terry P, Lagergren J, Ye W, et al. Antioxidants and cancers of the esophagus and gastric cardia. *Int J Cancer* 2000;87:750–4.
33. Ekstrom AM, Serafini M, Nyren O, et al. Dietary antioxidant intake and the risk of cardia cancer and noncardia cancer of the intestinal and diffuse types: a population-based case-control study in Sweden. *Int J Cancer* 2000;87:133–40.
34. De Stefani E, Boffetta P, Brennan P, et al. Dietary carotenoids and risk of gastric cancer: a case-control study in Uruguay. *Eur J Cancer Prev* 2000;9:329–34.
35. Lopez-Carrillo L, Lopez-Cervantes M, Ward MH, et al. Nutrient intake and gastric cancer in Mexico. *Int J Cancer* 1999;83:601–5.
36. Garcia-Closas R, Gonzalez CA, Agudo A, et al. Intake of specific carotenoids and flavonoids and the risk of gastric cancer in Spain. *Cancer Causes Control* 1999;10:71–5.
37. Ji BT, Chow WH, Yang G, et al. Dietary habits and stomach cancer in Shanghai, China. *Int J Cancer* 1998;76:659–64.
38. Munoz SE, Ferraroni M, La Vecchia C, et al. Gastric cancer risk factors in subjects with family history. *Cancer Epidemiol Biomarkers Prev* 1997;6: 137–40.
39. Harrison LE, Zhang ZF, Karpeh MS, et al. The role of dietary factors in the intestinal and diffuse histologic subtypes of gastric adenocarcinoma: a case-control study in the U.S. *Cancer* 1997;80: 1021–8.
40. Zheng W, Sellers TA, Doyle TJ, et al. Retinol, antioxidant vitamins, and cancers of the upper digestive tract in a prospective cohort study of postmenopausal women. *Am J Epidemiol* 1995; 142:955–60.

41. La Vecchia C, Ferraroni M, D'Avanzo B, et al. Selected micronutrient intake and the risk of gastric cancer. *Cancer Epidemiol Biomarkers Prev* 1994;3:393–8.
42. Hansson LE, Nyren O, Bergstrom R, et al. Nutrients and gastric cancer risk. A population-based case-control study in Sweden. *Int J Cancer* 1994;57:638–44.
43. Ramon JM, Serra-Majem L, Cerdo C, et al. Nutrient intake and gastric cancer risk: a case-control study in Spain. *Int J Epidemiol* 1993;22:983–8.
44. Kabat GC, Ng SK, Wynder EL. Tobacco, alcohol intake, and diet in relation to adenocarcinoma of the esophagus and gastric cardia. *Cancer Causes Control* 1993;4:123–32.
45. Palli D, Bianchi S, Decarli A, et al. A case-control study of cancers of the gastric cardia in Italy. *Br J Cancer* 1992;65:263–6.
46. Boeing H, Frentzel-Beyme R, Berger M, et al. Case-control study on stomach cancer in Germany. *International Journal of Cancer* 1991;47: 858–64.
47. You WC, Blot WJ, Chang YS, et al. Diet and high risk of stomach cancer in Shandong, China. *Cancer Res* 1988;48:3518–23.
48. Correa P, Fontham E, Pickle LW, et al. Dietary determinants of gastric cancer in south Louisiana inhabitants. *J Natl Cancer Inst* 1985;75:645–54.
49. Persson C, Sasazuki S, Inoue M, et al. Plasma levels of carotenoids, retinol and tocopherol and the risk of gastric cancer in Japan: a nested case-control study. *Carcinogenesis* 2008;29:1042–8.
50. Jenab M, Riboli E, Ferrari P, et al. Plasma and dietary carotenoid, retinol and tocopherol levels and the risk of gastric adenocarcinomas in the European prospective investigation into cancer and nutrition. *Br J Cancer* 2006;95:406–15.
51. Yuan JM, Ross RK, Gao YT, Qu YH, Chu XD, Yu MC. Prediagnostic levels of serum micronutrients in relation to risk of gastric cancer in Shanghai, China. *Cancer Epidemiol Biomark Prev* 2004;13:1772–80.
52. Taylor PR, Qiao YL, Abnet CC, Dawsey SM, Yang CS, Gunter EW, Wang W, Blot WJ, Dong ZW, Mark SD. Prospective study of serum vitamin E levels and esophageal and gastric cancers. *J Natl Cancer Inst* 2003;95:1414–6.
53. Abnet CC, Qiao YL, Dawsey SM, Buckman DW, Yang CS, Blot WJ, Dong ZW, Taylor PR, Mark SD. Prospective study of serum retinol, beta-carotene, beta-cryptoxanthin, and lutein/zeaxanthin and esophageal and gastric cancers in China. *Cancer Causes Control* 2003;14:645–55.
54. Serafini M, Jakszyn P, Lujan-Barroso L, Agudo A, Bas Bueno-de-Mesquita H, van Duijnhoven FJ, Jenab M, Navarro C, Palli D, Boeing H, Wallstrom P, Regner S, et al. Dietary total antioxidant capacity and gastric cancer risk in the European prospective investigation into cancer and nutrition study. *Int J Cancer* 2012;131: E544–54.
55. Bjelakovic G, Nikolova D, Simonetti RG, Gluud C. Antioxidant supplements for prevention of gastrointestinal cancers: a systematic review and meta-analysis. *Lancet* 2004;364:1219–28.
56. Drake IM, Davies MJ, Mapstone NP, Dixon MF, Schorah CJ, White KL, Chalmers DM, Axon AT. Ascorbic acid may protect against human gastric cancer by scavenging mucosal oxygen radicals. *Carcinogenesis* 1996;17:559–62.
57. Zhang ZW, Abdullahi M, Farthing MJ. Effect of physiological concentrations of vitamin C on gastric cancer cells and Helicobacter pylori. *Gut* 2002;50:165–9.
58. Akyon Y. Effect of antioxidants on the immune response of Helicobacter pylori. *Clin Microbiol Infect* 2002;8:438–41.
59. Engel LS, Chow WH, Vaughan TL, Gammon MD, Risch HA, Stanford JL, Schoenberg JB, Mayne ST, Dubrow R, Rotterdam H, West AB, Blaser M, et al. Population attributable risks of esophageal and gastric cancers. *J Natl Cancer Inst* 2003;95:1404–13.
60. Gastric cancer and Helicobacter pylori: a combined analysis of 12 case control studies nested within prospective cohorts. *Gut* 2001;49:347–53.
61. Lauren PA, Nevalainen TJ. Epidemiology of intestinal and diffuse types of gastric carcinoma. A time-trend study in Finland with comparison between studies from high- and low-risk areas. *Cancer* 1993;71:2926–33.
62. Sun YQ, Girgensone I, Leanderson P, Petersson F, Borch K. Effects of antioxidant vitamin supplements on Helicobacter pylori-induced gastritis in Mongolian gerbils. *Helicobacter* 2005;10:33–42.
63. Goswami UC, Sharma N. Efficiency of a few retinoids and carotenoids in vivo in controlling benzo[a]pyrene-induced forestomach tumour in female Swiss mice. *Br J Nutr* 2005;94:540–3.
64. Steinmetz KA, Potter JD. Vegetables, fruit, and cancer. II. Mechanisms. *Cancer Causes Control* 1991;2:427–42.
65. Muller K, Carpenter KL, Challis IR, Skepper JN, Arends MJ. Carotenoids induce apoptosis in the T-lymphoblast cell line Jurkat E6.1. *Free Radic Res* 2002;36:791–802.
66. Chew BP, Park JS. Carotenoid action on the immune response. *J Nutr* 2004;134:257S–61S.
67. Palozza P, Serini S, Di Nicuolo F, Piccioni E, Calviello G. Prooxidant effects of beta-carotene in cultured cells. *Mol Aspects Med* 2003;24:353–62.
68. Palozza P, Serini S, Di Nicuolo F, Boninsegna A, Torsello A, Maggiano N, Ranelletti FO, Wolf FI, Calviello G, Cittadini A. beta-Carotene exacerbates DNA oxidative damage and modifies p53-related pathways of cell proliferation and apoptosis in cultured cells exposed to tobacco smoke condensate. *Carcinogenesis* 2004;25:1315–25.