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Meta-analyses

Association between vitamin A, retinol intake and blood retinol level and gastric cancer risk: A meta-analysis

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SUMMARY

Background & aims: The association between dietary vitamin A, retinol intake and blood retinol level and gastric cancer risk has been investigated by many studies. However, the results of these studies were controversial. The aim of our study was to systematically assess this issue.
Methods: PUBMED and EMBASE were searched, supplemented with manual-screening for relevant publications. Meta-analyses were performed to evaluate the association between vitamin A, retinol dietary intake or blood retinol level and gastric cancer risk.
Results: Thirty-one studies were included in this meta-analysis. Comparing the highest with the lowest categories, vitamin A intake significantly reduced gastric cancer risk (pooled RR = 0.66, 95% CI: 0.52−0.84), whereas a marginally inverse association was found between retinol intake (pooled RR = 0.94, 95% CI: 0.87−1.03) or blood retinol level (pooled RR = 0.87, 95% CI: 0.73−1.05) and gastric cancer risk. Interestingly, the results of subgroup analysis indicated that high vitamin A intake and blood retinol level were associated with reduced gastric cancer risk in Western countries, while a marginally inverse association was found between retinol and gastric cancer risk in Western countries.
Conclusions: Vitamin A intake was inversely associated with gastric cancer risk, while no significant association was found with retinol intake or blood retinol level.

1. Introduction

There were 989,600 new gastric cancer cases and 738,000 deaths occurred in 2008 all over the world, which ranked 4th in incidence and 2nd in death [1]. Previous studies have suggested that dietary intake of food rich in vitamin A might be involved in gastric cancer pathogenesis [2–19]. Vitamin A is a generic term referring to a group of unsaturated hydrocarbons including retinol and its derivatives, such as retinal, retinoic acid and provitamin A carotenoids including β-carotene, α-carotene and so on [20]. The most common retinoid is retinol which is mainly absorbed through animal food [20]. Retinol can be irreversibly oxidized to retinoic acid , which participates in the regulation of certain cellular functions such as cell growth, proliferation, and differentiation. For example, it can significantly inhibit growth of human gastric cancer cell lines MGC80-3, BGC-823 and SGC-7901 [21,22]. Meanwhile provitamin A carotenoids such as β-carotene, α-carotene, might also be involved in gastric cancer prevention because of their antioxidant property and other functions [23]. Previous case-control and cohort studies provided controversial results for the correlation between dietary intake of vitamin A, retinol or blood

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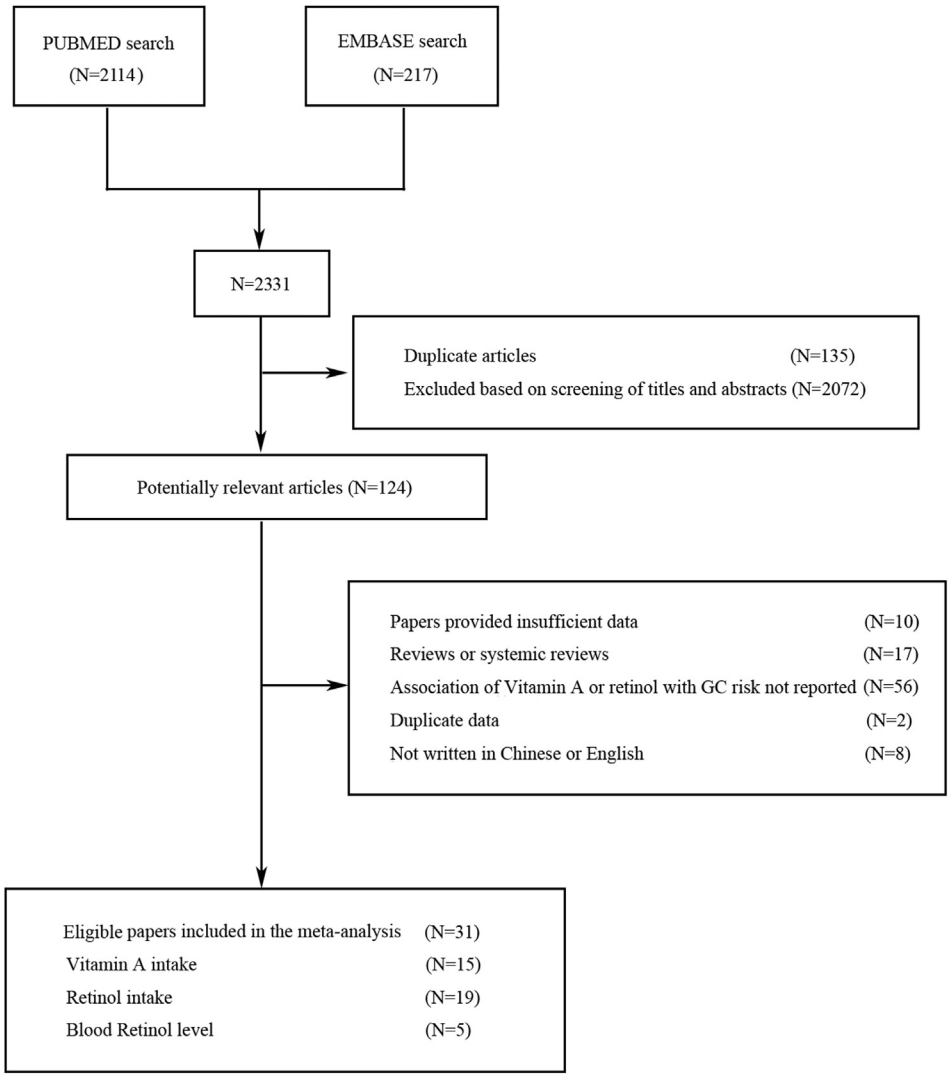

Fig. 1. Flow diagram of study selection process.

retinol level and the risk of gastric cancer [2–19,24–35]. For example, while some studies reported that high intake of vitamin A or retinol could reduce gastric cancer risk [6,17,28,32,35,36], others showed no such association [2,3,7–19,24,25,29–34]. Therefore, the aim of the present study was to systemically evaluate the association between vitamin A, retinol intake and blood retinol level and the risk of gastric cancer.

2. Methods

2.1. Data sources, search strategy, and selection criteria

We performed the literature search in PUBMED and EMBASE (up to January 2013) without restriction. The keywords "vitamin A", "retinol", "retinoid", "retinal" or "retinoic acid" were used as search terms together with "gastric cancer", "the cancer of stomach", "gastric carcinoma", "stomach cancer" and "stomach carcinoma". References of relevant articles were also scanned for potential missing studies. This meta-analysis was designed, conducted and reported according to the PRISMA statement [37].

The articles were included if they met all the following criteria: (1) the outcome of interest was gastric cancer; (2) the study of interest was dietary vitamin A, retinol or blood retinol level; (3) the relative risk (RR), or odds ratio (OR) estimates and their 95% confidence intervals (95% CI) were given or sufficient data were available for evaluation; (4) the articles were written in English or Chinese. For duplicate studies, the most recent or most detailed one was included.

2.2. Data extraction and quality assessment

Two investigators (Drs. Wu YH and Ye Y) independently extracted data from each study and reached a consensus. The following information was extracted from each study: author, year of publication, study design (case-control or cohort), country of origin, number of participants, characteristics of participants (e.g., gender and age), variables adjusted for in the analysis, RR (or OR) estimates with 95% CIs for the highest versus lowest categories of vitamin A intake, retinol intake or blood retinol level. ORs (RRs) that reflected the greatest degree of control for potential confounders were adopted in this meta-analysis.

We assessed the quality of each study according to NEWCASTLE–OTTAWA quality assessment [38].

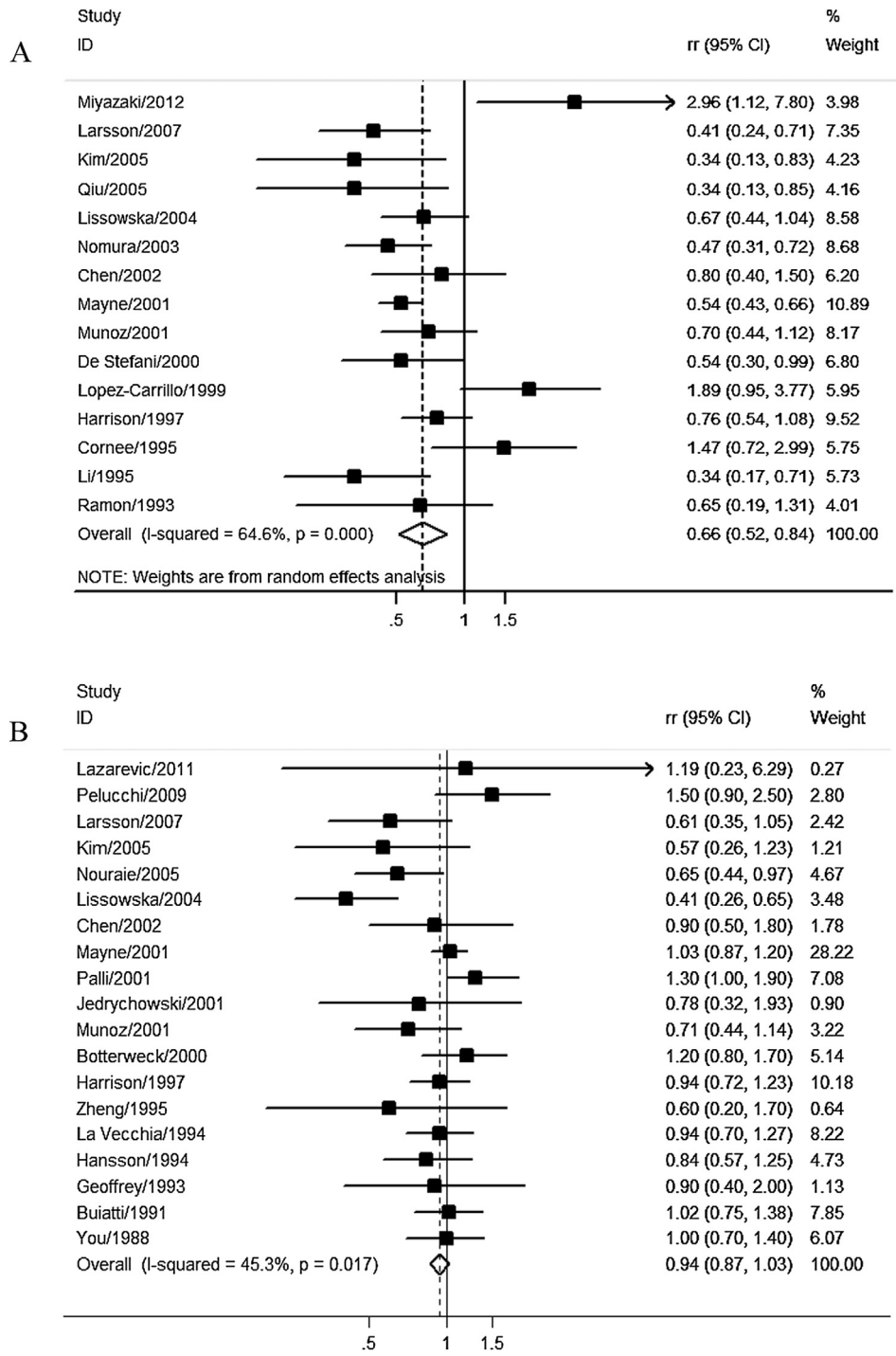

Fig. 2. Forest plot of the association between vitamin A intake (A), retinol intake (B) and gastric cancer risk.

2.3. Data synthesis and statistical analysis

Meta-analysis methods were used to assess the association between vitamin A, retinol intake or blood retinol level and gastric cancer risk. Either a fixed-effect model or a random-effect model was adopted to pool the study-specific RR (OR) according to the heterogeneity (if the heterogeneity was significant, the random-effect model was applied, otherwise the fixed-effect model was used). Heterogeneity across studies was tested with the chi-square test and I^2 test (I^2 test quantifies the proportion of total variation across studies due to heterogeneity rather than chance). $P \leq 0.10$ in combination with $I^2 > 50\%$ indicated significant heterogeneity.

We analyzed the dose–response relationship using fractional polynomial regression of the inverse variance-weighted data. Best-fit curves were selected using decreased deviance compared with the reference model [39]. Comparisons of curves to determine best fit were done using a chi-square distribution.

To assess publication bias, funnel plots (ie, plots of study results against precision) were constructed and Begg's and Egger's tests were used. $P \leq 0.10$ was considered to be statistically significant. All

analyses were conducted using the Stata software (version 12.0; StatCorp, College Station, TX, USA).

3. Results

3.1. Literature search

After searching PUBMED and EMBASE, 2331 articles were identified. After exclusion of 135 duplicated articles, 2196 articles were assessed. Review of the titles and abstracts resulted in the exclusion of 2072 articles. For the remaining 124 full-text articles, reasons for exclusion were articles not on the right topic or targeted population (56 papers), insufficient data (10 papers), multiple publications (2 papers), language in neither English nor Chinese (8 papers), reviews or systemic reviews (17 papers). Finally, 31 studies with approximate 300,000 participants were included in this study, as detailed in Fig. 1. Among the included studies 15 articles assessed vitamin A intake, 19 articles investigated retinol intake and 5 articles was on blood retinol level.

3.2. Data quality

Most studies provided risk estimates that were adjusted for age, gender, body mass index (BMI), smoking, alcohol consumption, education, family history of gastric cancer and energy intake.

The results of quality assessment were shown in Tables S4 and S5.

3.3. Association between vitamin A intake and gastric cancer risk

A total of 15 studies (13 case-control studies and 2 cohort studies) with approximate 90,000 participants assessed the association between vitamin A intake and gastric cancer risk, as detailed in Table S1. The pooled RR of gastric cancer for the highest versus lowest categories of vitamin A intake was 0.66 (95% CI: 0.52–0.84), as shown in Fig. 2A. Significant heterogeneity across studies was found ($I^2 = 64.6\%$, $p < 0.001$). The result of dose–response analysis indicated an inverse relationship between the dose of vitamin A intake and gastric cancer risk, as shown in Fig. 4A. Begg's funnel plot and Egger-weighted regression indicated that there was no significant publication bias ($P_{Egger} = 0.350$), as shown in Fig. S1A.

Subgroup analysis was conducted according to gender, region, study design and histological type, as shown in Table 1. The pooled RRs were 0.41 for male (95% CI: 0.25–0.66) and 0.52 for female (95% CI: 0.28–0.97), indicating that vitamin A intake had a protective effect against gastric cancer in both male and female. When stratifying the studies according to region, high intake of vitamin A was significantly associated with reduced gastric cancer risk in Western countries (pooled RR = 0.62, 95% CI: 0.53–0.72), but not in Asian countries (pooled RR = 0.57, 95% CI: 0.21–1.55). For study design, significant association was found in case-control studies (pooled RR = 0.65, 95% CI 0.52–0.81) but not in cohort studies (pooled RR = 1.06, 95% CI 0.15–7.31). When histological type was considered, no significant association was found between vitamin A intake and intestinal type (pooled RR = 1.36, 95% CI: 0.63–2.95) or diffuse type (pooled RR = 1.06, 95% CI: 0.71–1.59) of gastric cancer. The heterogeneity could be explained partially by region and study design.

Table 1
Subgroup analysis of the association between vitamin A intake and gastric cancer risk.

Factor	Number of study	RR	95% CI	*P* for trend	Heterogeneity	
					P	I^2
Gender						
Male	2	0.41	0.25–0.66	<0.001	0.902	0.00%
Female	2	0.52	0.28–0.97	0.041	0.133	55.70%
Region						
Asia	4	0.57	0.21–1.55	0.271	0.002	80.40%
Europe and USA	7	0.62	0.53–0.72	<0.001	0.139	47.90%
Others	4	0.66	0.51–0.85	0.002	0.008	74.90%
Design						
Case-control	13	0.65	0.52–0.81	<0.001	0.007	56.10%
Cohort	2	1.06	0.15–7.31	0.956	<0.001	91.80%
Histological type						
Intestinal type	3	1.36	0.63–2.95	0.428	0.073	61.70%
Diffuse type	3	1.06	0.71–1.59	0.772	0.135	50.00%

3.4. Association between retinol intake and gastric cancer risk

A total of 19 studies were included on retinol intake (15 case-control studies and 4 cohort studies), as detailed in Table S1. The pooled RRs of gastric cancer for the highest versus lowest categories of retinol intake was 0.94 (95% CI: 0.87–1.03), as shown in Fig. 2B. The heterogeneity across studies was significant ($I^2 = 45.3\%$, $p = 0.017$). The result of dose–response analysis indicated an approximately *U*-shaped relationship between the dose of retinol intake and gastric cancer risk, as shown in Fig. 4B. Begg's funnel plot and Egger-weighted regression indicated no significant publication bias for retinol intake ($P_{Egger} = 0.123$), as shown in Fig. S1B.

Subgroup analysis was conducted according to region, study design and histological type, as shown in Table 2. The pooled RRs of gastric cancer for the highest versus lowest categories of retinol intake were 0.91 (95% CI: 0.66–1.25) for Asian countries and 0.91 (95% CI: 0.79–1.06) for Western countries. The pooled RRs were 0.96 (95% CI: 0.88–1.05) for case-control studies and 0.78 (95% CI: 0.53–1.15) for cohort studies. When histological types were considered, no significant association was found for either intestinal type (pooled RR = 1.06, 95% CI: 0.89–1.26) or diffuse type (pooled RR = 1.15, 95% CI: 0.93–1.42) of gastric cancer. The heterogeneity could be explained partially by region (see Table 2).

3.5. Association between blood retinol level and gastric cancer risk

Five studies (4 case-control studies and 1 cohort study) evaluating blood retinol level were included, as detailed in Table S1. The pooled RRs of gastric cancer for the highest versus lowest categories of blood retinol level was 0.87 (95% CI: 0.73–1.05), as shown in Fig. 3. Non-significant heterogeneity across studies was observed ($I^2 = 47.4\%$, $p = 0.107$). The result of dose–response analysis indicated an approximately U-shaped relationship between the dose of blood retinol level and gastric cancer risk, as shown in Fig. 4C. No significant publication bias for blood retinol level was indicated ($P_{Egger} = 0.866$), as shown in Fig. S1C.

Table 2
Subgroup analysis of the association between retinol intake and gastric cancer risk.

Factor	Number of study	RR	95% CI	*P* for trend	Heterogeneity	
					P	I^2
Region						
Asia	2	0.91	0.66–1.25	0.564	0.195	40.40%
Europe and USA	16	0.91	0.79–1.06	0.229	0.013	49.60%
Design						
Case-control	15	0.96	0.88–1.05	0.411	0.038	43.20%
Cohort	4	0.78	0.53–1.15	0.203	0.082	55.20%
Histological type						
Intestinal type	2	1.06	0.89–1.26	0.502	0.254	23.30%
Diffuse type	2	1.15	0.93–1.42	0.204	0.228	31.10%

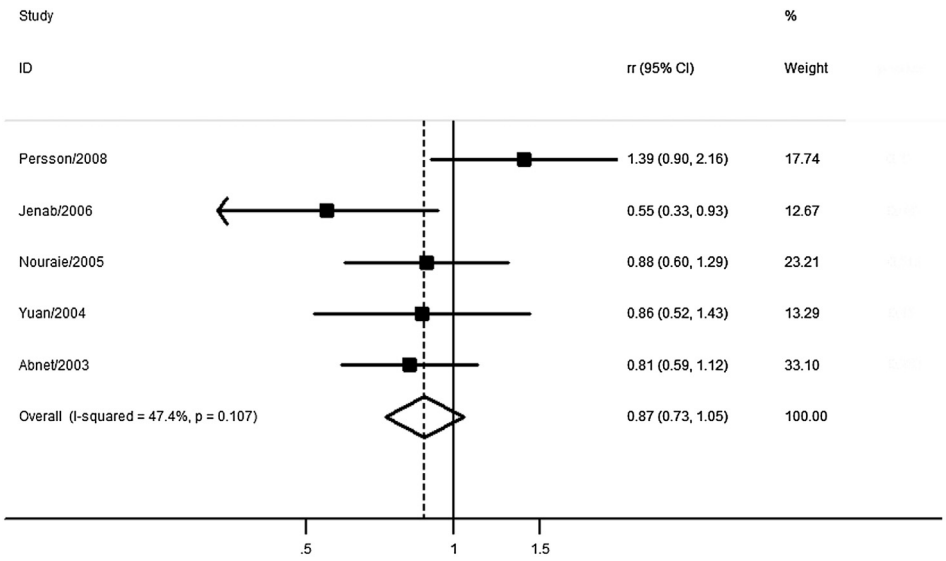

Fig. 3. Forest plot of the association between blood retinol level and gastric cancer risk.

The results of subgroup analyses were shown in Table 3. Significant association between blood retinol level and gastric cancer risk was found in Western countries (pooled RR = 0.61, 95% CI: 0.45–0.97), but not in Asian countries (pooled RR = 0.95, 95% CI: 0.76–1.20). Three studies provided data stratified by anatomical subsite, and the pooled RRs were 0.78 (95% CI, 0.58–1.05) for cardial gastric cancers and 0.84 (95% CI, 0.59–1.17) for noncardial gastric cancers, neither of which was significant. The heterogeneity could be explained by region and design.

3.6. Dose-response of vitamin A, retinol intake and blood retinol level

As shown in Fig. 4, the dose–response analysis of vitamin A intake showed that the gastric cancer risk might decrease with the dose increasing from 500 to 6000 μg RE/d, and the effect would be significant at dose ranged from 500 to 1000 μg RE/d. The results of retinol intake and blood retinol level indicated that the risk of gastric cancer would decrease with increasing doses. But after a certain dose point (2300 μg/d for retinol intake and 65 μg/dl for blood retinol level), the risk would be increased with the dose continuing to rise.

4. Discussion

The present meta-analysis assessed the association between dietary vitamin A, retinol intake and blood retinol level and the risk of gastric cancer. The results indicated that comparing the highest with the lowest categories, vitamin A intake showed a significant protective effect (pooled RR = 0.66, 95% CI: 0.52–0.84) for gastric cancer risk, whereas a marginally inverse association was found between retinol intake (pooled RR = 0.94, 95% CI: 0.87–1.03) or blood retinol level (pooled RR = 0.87, 95% CI: 0.73–1.05) and gastric cancer risk. The inconsistence of vitamin A and retinol might be explained partly by the other sources of vitamin A in the food. For instance, β-carotene and α-carotene (two types of provitamin A) showed a significantly protective effect in another independent study by us, with the pooled RRs of 0.59 (95% CI: 0.49–0.70) and 0.69 (95% CI: 0.52–0.93) for β-carotene and α-carotene respectively [23]. Further observational and mechanistic are warranted to explain this issue. The results of dose–response analysis suggested an inverse association between vitamin A intake and gastric cancer risk, in contrast to the U-shaped correlation of retinol intake or blood retinol level with gastric cancer risk.

Of note, the results of subgroup analysis indicated that there was no significant association between gastric cancer risk and vitamin A intake or blood retinol level for Asian population, while a significant effect was shown in Western countries. In addition, the results of retinol intake analysis also showed a marginally inverse association with gastric cancer risk in Western countries. One possible explanation could be the different prevalence of *Helicobacter pylori* infection in people from different regions. Asia population has a high prevalence of *H. pylori* infection [40]. It has been reported that *H. pylori* infection modifies the pH level of stomach, thus reduces the bioavailability of vitamin A and influences vitamin A intake [41]. Some other possible explanations might be the small sample size and inconsistent ranges of vitamin A or retinol levels in the studies included.

Vitamin A, composed of provitamin A (beta-carotene, alpha-carotene and so on) and retinoid (retinol, retinal and retinoic acid) [20], was indicated to be involved in gastric carcinogenesis through multiple pathways. Carotenes function through several mechanisms, including protection against oxidative DNA damage as an antioxidant factor [42,43], induction of apoptosis [44] and influence on immune response [45]. On the other hand, retinol can be irreversibly oxidized to retinoic acid in vivo, and as a signaling molecule it can participate in the regulation of certain cellular functions including growth, proliferation, and differentiation [46]. Retinoid functions through two types of nuclear receptors: retinoic acid receptors (RARs) and retinoid X receptors (RXRs), which are important for gene transcription as ligand-activated transcription factors [46,47]. Previous reports also revealed that RARα and RXRα play vital roles in regulating cell growth and proliferation in gastric cancer cell [46,48,49].

RARα is the receptor of all-trans retinoic acid (ATRA). ATRA can increase RARα expression, suppress AP-1 (activator protein-1) activity and inhibit the growth of gastric cancer cell lines (MGC80-3, BGC-823 and SGC-7901) [22]. On the other hand, it is proven that suppressing the RARα expression leads to the cell losing function of anti-proliferation [22,49].

Interestingly, RXRα expression can't be induced by ATRA directly [22,49]. Instead, after treated with 9-cis retinoid acid, RXRα assists

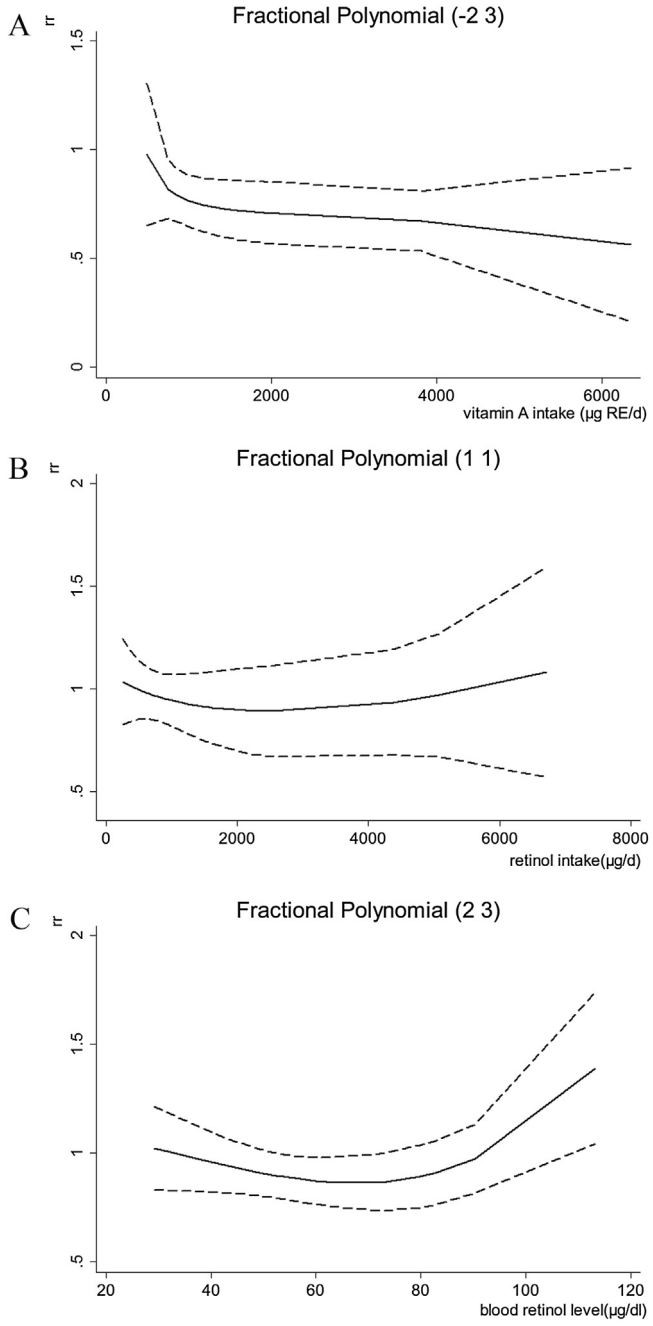

Fig. 4. Dose–response relationship between vitamin A intake (A), retinol intake (B), blood retinol level (C) and gastric cancer risk.

Table 3
Subgroup analysis of the association between blood retinol level and gastric cancer risk.

Factor	Number of study	RR	95% CI	*P* for trend	Heterogeneity	
					P	I^2
Region						
Asia	3	0.95	0.76–1.20	0.667	0.135	50.00%
Europe and USA	2	0.61	0.45–0.97	0.002	0.615	0.00%
Anatomical subsite						
Cardial gastric cancers	3	0.78	0.58–1.05	0.106	0.774	0.00%
Noncardial gastric cancers	3	0.84	0.59–1.17	0.301	0.684	0.00%

TR3 in translocation from the nucleus to cytoplasm and localization in the mitochondria to induce apoptosis thus it could inhibit gastric oncogenesis [46,49]. Taken together, all these studies supported the protective effect of vitamin A and retinol, although the detailed molecular mechanism still needs further investigation.

Explanation of heterogeneity is also a vital component of meta-analysis. As the subgroup analysis showed, the region and design of the studies contributed partially to the heterogeneity. For example, in the studies of vitamin A intake, the USA/Europe subgroup and case-control subgroup analyses decreased the heterogeneity from 64.6% to 47.9% and 56.1%, respectively; while in the studies of retinol intake, the Asia subgroup and case-control subgroup analyses decreased the heterogeneity from 45.3% to 40.4% and 43.2%, respectively. Furthermore, the USA/Europe subgroup analysis reduced the heterogeneity from 47.4% to 0.0% in the studies of blood retinol level.

Our meta-analysis had several strengths. First, this was the first meta-analysis to evaluate the relationship between vitamin A intake, retinol intake, blood retinol level and the risk of gastric cancer. Second, the number of participants and cases was sufficient. Third, most of the studies included were of high methodological quality. Fourth, no publication bias was observed. Finally, we conducted substantial subgroup analysis and showed that difference effects exist for population residing in different regions.

This meta-analysis also had several limitations. First, the heterogeneity of some results was significant and we could not be completely explained. Second, the detailed data on vitamin A, retinol intake and blood retinol level were not available from each study which might reduce the accuracy of our results. Finally, the studies included in some specific subgroup analysis were insufficient.

5. Conclusion

The present meta-analysis confirmed a statistically inverse association between dietary vitamin A intake and the risk of gastric cancer, while a marginally inverse association was found with retinol intake or blood retinol level.

Conflict of interest

The authors declare that they have no conflict of interest.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.clnu.2014.06.007.

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