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Review

Vitamin A and risk of cervical cancer: A meta-analysis

Xingliang Zhang, Bingqin Dai, Bingzhen Zhang, Zhiping Wang *

Department of Epidemiology and Health Statistics, School of Public Health, Shandong University, Shandong, PR China

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ABSTRACT

Objective: To conduct a systematic review with meta-analysis of studies assessing the association of vitamin A (retinol, carotene and other carotenoids) intake or blood (serum or plasma) levels of vitamin A (retinol and carotene) with risk of cervical cancer.
Methods: We evaluated the studies published in English and Chinese on diet or blood vitamin A for the risk of cervical cancer. We also reviewed reference lists from retrieved articles. Meta-analysis was applied to calculate the combined effect values and their 95% confidence intervals. The risk of bias was assessed by the Egger regression asymmetry test.
Results: As many as 11 articles on dietary vitamin A and 4 articles on blood vitamin A were selected according to the eligibility criteria and were included in the meta-analysis, for a total of 12,136 participants. The pooled odds ratios (ORs) of cervical cancer were 0.59 (95% CI, 0.49–0.72) for total vitamin A intake and 0.60 (95% CI, 0.41–0.89) for blood vitamin A levels. The combined ORs of cervical cancer were 0.80 (95% CI, 0.64–1.00), 0.51 (95% CI, 0.35–0.73) and 0.60 (95% CI, 0.43–0.84) for retinol, carotene and other carotenoid intake, and 1.14 (95% CI, 0.83–1.56) and 0.48 (95% CI, 0.30–0.77) for blood retinol and carotene.
Conclusions: Vitamin A intake and blood vitamin A levels were inversely associated with the risk of cervical cancer in this meta-analysis.

Contents

* Corresponding author at: Department of Epidemiology and Health Statistics, School of Public Health, Shandong University, 44 Wenhua Xi Road, Jinan, Shandong, 250012, PR China. Fax: +86 531 88382128.
E-mail address: zhipingw@sdu.edu.cn (Z. Wang).

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Introduction

Although incidence and mortality from cervical cancer declined substantially from the 1950s onward in developed countries, cancer of the cervix remains the third most common cancer among women in the world, and the seventh overall, accounting for about 15% of all new female cancer cases in 2008 [1]. Approximately 530,000 cases are newly diagnosed and 275,000 women die each year from cervical cancer, about 88% of which occur in developing countries [1].

Overwhelming evidence now supports the role of human papillomaviruses (HPV) in cervical carcinogenesis [2]. HPV infection is a crucial factor in the onset of cervical lesions, and continued expression of viraltransforming genes causes neoplastic progression of the lesions. Persistent infection by certain HPV genotypes has been recognized as a necessary step for the development, maintenance and progression of cervical intraepithelial neoplasia (CIN) and cervical cancer [3]. Despite this, HPV infection is most likely not a sufficient cause of cervical cancer, since prospective studies consistently show that only a small fraction of infected women do eventually develop the disease [4]. Cervical cancer is believed to have a cofactorial etiology in which HPV interacts with other cofactors, including nutritional ones [5], that influence the risk of HPV persistence and progression to CIN. Deficiency of vitamin A is known to be associated with carcinogenesis in human beings [6]. Experiments in animals have also shown that vitamin A deficiency predisposes to the development of squamous intraepithelial lesions [7].

The hypothesis that the etiology of epithelial cancers might be related to a relative deficiency of dietary vitamin A was initially proposed in the late 1970s and has created considerable interest [8,9]. Findings from published studies that have examined the association between vitamin A intake or vitamin A levels in the blood and the risk of cervical cancer have been inconsistent. Some studies [10,11] revealed that vitamin A could decrease the risk of cervical cancer, however, another studies [12,13] did not find this effect. The aim of this study was to evaluate the evidence from studies on vitamin A intake or blood levels of vitamin A and the risk of cervical cancer by summarizing it quantitatively with a meta-analytic approach, and to provide evidence for the prevention and intervention of cervical cancer.

Materials and methods

Literature searches

Studies published in English and Chinese were considered in this study. Studies in English were identified through Pub Med, Medline, Elsevier Science, and Springer Link cochrane database from their earliest available date to Jun 1st, 2011. Reports in Chinese were found through China National Knowledge Infrastructure (CNKI), Database of Chinese Scientific and Technical Periodicals (VIP) and China biology medical literature database (CBM), three commonly used databases, which were searched from 1979, 1989, 1970, respectively, to Jun 1st, 2011. Key words ('uterine cervical neoplasm') and ('vitamin A' or 'beta carotene' or 'carotenoids' or 'diet' or 'nutrition status') were used in combination to retrieve the relevant literatures in all these databases. Moreover, we reviewed the reference lists from retrieved articles to search for further relevant studies. This systematic review was planned, conducted, and reported in adherence to standards of quality for reporting meta-analyses [14].

Eligibility criteria

Studies were included in the meta-analysis if they met the following criteria: (1) the exposure of interest was intake of vitamin A (retinol, carotene or other carotenoids) or blood (plasma or serum) levels of vitamin A; (2) the outcome of interest was cervical cancer; (3) analytical study (case–control study or cohort study) or experimental study; (4) the number of high and low dietary or blood vitamin A in cases and controls can be obtained; and (5) odds ratio (OR) estimates with 95% confidence intervals (CIs) (or data to calculate these) were reported. If data were duplicated in more than 1 study, we included the study with the largest number of cases.

Data extraction

The following data were extracted from each study: the first author's last name, publication year, country where the study was performed, study period, range of age, research contents, the type and clinical stage (FIGO) of cancer in cases and sample size (cases and controls size). If one study did not mention the total vitamin A levels but included several kinds, we defined the study as −1, −2 and so on. The study quality was assessed using the 9-star Newcastle-Ottawa Scale (Wells GA et al., Oxford). Data extraction was conducted independently by 2 authors (Zhang and Wang), with disagreements resolved by consensus.

Statistical analysis

Data were abstracted from all the studies that met our eligibility criteria. The homogeneity of the data was tested by RevMan 5.1.2 which was downloaded from Cochrane Collaboration. We used the OR with 95% CI of the highest intake (or blood level) group for cervical cancer compared with the lowest intake (or blood level) group reported in each study. A summary OR with 95% CI was estimated by using both fixed-effects and random-effects models. If the data were homogeneous, fixed effect model would be applied and if the data were heterogeneous, random effect model would be adopted. Since most statistical tests for heterogeneity are not very sensitive, a $P = 0.10$ was employed as the threshold of P-values for the analysis. Sensitivity analysis was performed to strengthen the result of the meta-analysis. We also conducted the subgroup analyses based on the geographic region of studies, the kind of vitamin A, the type of cancer and the clinical stage of cancer in cases. We defined the clinical stage as early stage cervical cancer when at least 80% of the cases were in FIGOII and earlier stage. Publication bias was evaluated with the funnel plot and the use of the Egger regression asymmetry test [15].

Results

Literature search

The detailed steps of our literature search are shown in Fig. 1. Briefly, we identified 21 potentially relevant articles concerning vitamin A intake and blood vitamin A levels in relation to risk of cervical cancer. One article on vitamin A intake was excluded because of duplicate report from the same study population and 7 articles were excluded because of not meeting the eligibility criteria (4). The remaining articles, including 11 on vitamin A intake and 4 on blood vitamin A levels (1 article reported both vitamin A intake and blood vitamin A levels) were included in the meta-analysis. No cohort study or randomized controlled trials (RCT) were included in our meta-analysis based on the criteria.

Study characteristics

The 11 articles [10–13,16–22] on vitamin A intake were published between 1983 and 2010 (Table 1) and involved a total of 3108 cases and 5574 controls. Five studies were conducted in the United States, 4 in Asia, 1 in Europe, and 1 in Latin America. Only 2 articles reported total vitamin A intake, 7 studies included retinol and carotene intake, and 3 studies involved other carotenoid intake. The 4 case–control

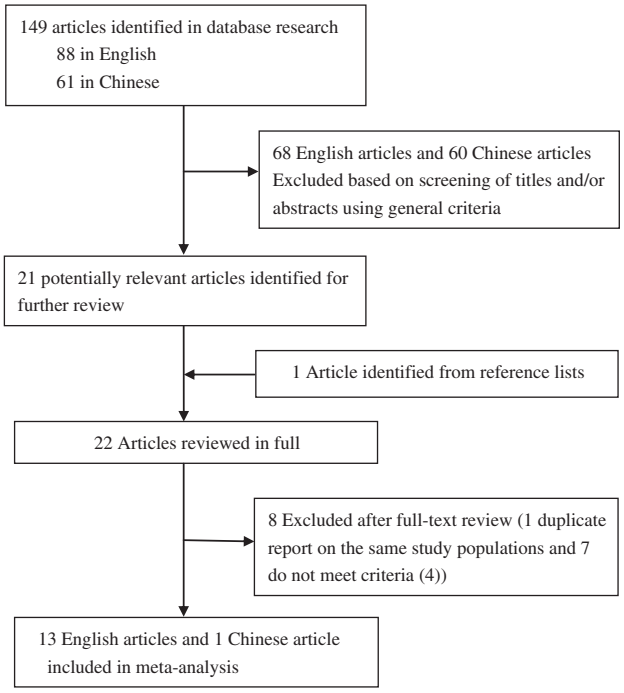

Fig. 1. Selection of studies for inclusion in meta-analysis.

studies [20,23–25] on blood vitamin A levels (comprising a total of 1070 cases and 1697 controls) were published between 1986 and 2010. Among them, 2 were conducted in Latin America, 1 in England, and measured serum retinol and carotene levels, and 1 was conducted in Australia and measured plasma levels (Table 1). The quality score of studies ranged from 6 stars to 8 stars according to the 9-star Newcastle-Ottawa Scale.

High vs low vitamin A intake or blood vitamin A levels

The ORs for each study and all studies combined for the highest vs lowest categories of vitamin A intake or blood vitamin A level are shown in Figs. 2 and 3. Results from studies on total vitamin A intake in relation to cervical cancer risk were inconsistent, with both inverse and positive associations reported (Fig. 2). All studies on the association of blood retinol levels with cervical cancer risk showed no association, and the studies on blood carotene showed an inverse association, which was statistically significant in 5 studies (Fig. 3). The pooled ORs of cervical cancer for the highest vs lowest categories of vitamin A intake and blood vitamin A level were, respectively, 0.59 (95% CI, 0.49–0.72) and 0.60 (95% CI, 0.41–0.89).

Subgroup analyses

When we stratified the analysis by the kind of vitamin A, the combined ORs of cervical cancer for the highest vs lowest category of retinol, carotene and other carotenoid intake were 0.80 (95% CI, 0.64–1.00), 0.51 (95% CI, 0.35–0.73) and 0.60 (95% CI, 0.43–0.84), respectively (Fig. 4). The combined ORs of cervical cancer for the highest vs lowest category of blood retinol and carotene were 1.14 (95% CI, 0.83–1.56) and 0.48 (95% CI, 0.30–0.77). There was heterogeneity among studies of carotene intake ($\chi^2 = 38.76$, $P < 0.01$) but not among studies of retinol intake ($\chi^2 = 11.91$, $P = 0.10$) and other carotenoid intake ($\chi^2 = 4.12$, $P = 0.13$). There was heterogeneity among studies of blood carotene level ($\chi^2 = 13.10$, $P = 0.01$) but not among studies of blood retinol ($\chi^2 = 0.08$, $P = 0.96$).

In addition, stratifying by clinical stage of cancer in cases, the pooled ORs of early stage cervical cancer for the highest vs lowest

Table 1
Characteristics of studies on vitamin A and cervical cancer.

Source	Location	Period	Age (y)	No. of participants		Cancer type	Clinical stage of cancer	Parameters examined	Study quality
				Cases	Controls				
Ghosh et al. [10], 2008	United States	1982–1998	21–90	239	979	SCC	None[a]	Diet: retinol, α-carotene, β-carotene, vitamin A	6
Kim et al. [11], 2010	Korea	2006–2007	20–75	144	288	None[a]	None[a]	Diet: retinol, β-carotene, vitamin A, total vitamin A	7
Herrero et al. [12], 1991	Colombia, Costa Rica, Mexico, Panama	1986–1987	<70	748	1411	SCC + AC + ASC	All[b]	Diet :retinol, β-carotene, carotenoids	7
Ziegler et al. [13], 1990	United States	1982–1983	19–74	271	502	SCC	All[b]	Diet: vitamin A, carotenoids	8
Verreault et al. [16], 1989	United States	1979–1983	20–74	189	297	SCC + AC + ASC	All[b]	Diet :retinol, carotene	8
Marshall et al. [17], 1983	United States	1957–1965	–	513	490	None[a]	None[a]	Diet: vitamin A	6
Ziegler et al. [18], 1990	United States	1982–1983	20–74	229	502	CIS	0	Diet :vitamin A, carotenoids	8
Vecchia et al. [19], 1988	Italy	1981–1986	22–74	392	392	None[a]	All[b]	Diet :retinol, β-carotene	6
Brock et al. [20], 1988	Australia	1980–1983	18–65	117	196	CIS	0	Diet :retinol, carotene Plasma: retinol, β-carotene, carotenoids	8
Shannon et al. [21], 2002	Thailand	1991–1993	<63	134	384	None[a]	None[a]	Diet: retinol, β-carotene, total vitamin A	6
Ma et al. [22], 2004	China	2004	–	132	133	None[a]	None[a]	Diet retinol	6
Potischman et al. [23], 1991	Colombia, Costa Rica, Mexico, Panama	1986–1987	<70	387	670	SCC + AC + ASC	All[b]	Serum: retinol, α-carotene, β-carotene,	7
Harris et al. [24], 1986	England	1975–1979	–	113	226	None[a]	None[a]	Serum: retinol, β-carotene	6
Tomita et al. [25], 2010	Brazil	2003–2005	21–65	453	605	SCC + AC + ASC	None[a]	Serum: carotene	6

Abbreviation:SCC: squamous cell cervical cancer, AC: adenocarcinoma, ASC: adenosquamous cancer, CIS: carcinoma in situ.
[a] Not mentioned in the article.
[b] Include all stages of cancer.

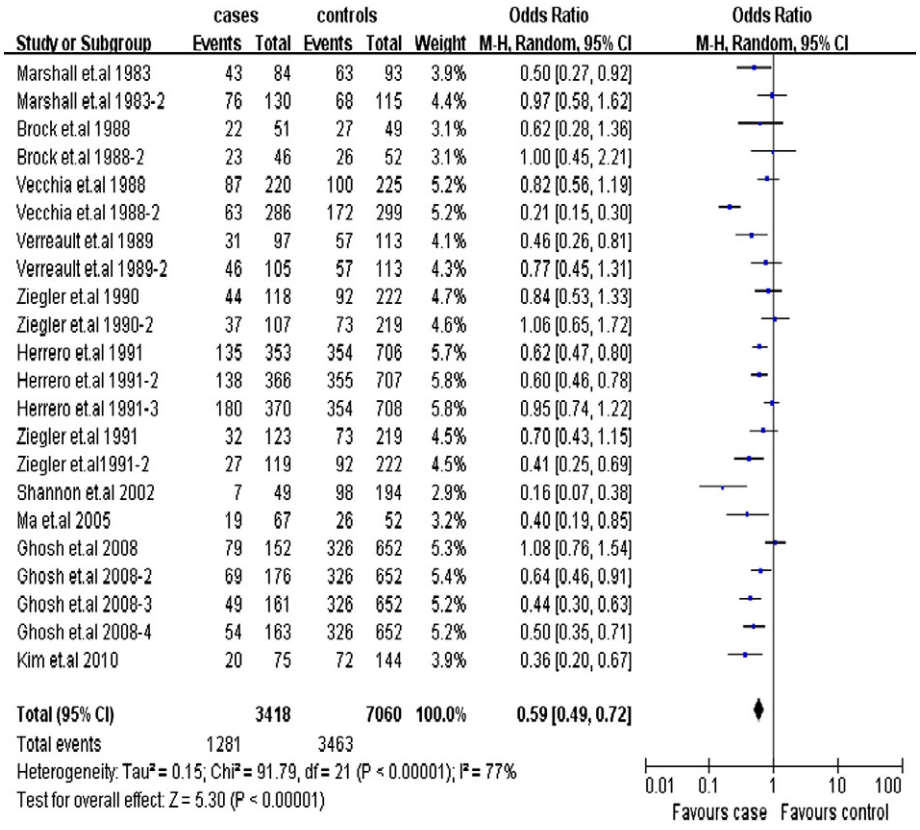

Fig. 2. The pooled odds ratios of cervical cancer for the highest vs lowest categories of total vitamin A intake.CI indicates confidence interval. The forest plot shows the odds ratio (OR) and its 95% confidence interval (95% CI) for each of the studies included, the total OR and its 95% CI, and the results of the homogeneity test. The graph was produced by RevMan 5.1.2.

categories of vitamin A intake were 0.58 (95% CI, 0.37–0.92) (Fig. 5), but the ORs of advanced cervical cancer could not be got from the original articles. We can't stratify by the type of cancer because most of the studies did not mention the proportion of type of the cancer. And, stratifying by geographic region, the ORs for total vitamin A intake were 0.66 (95% CI, 0.54–0.81) for studies conducted in the United States, and 0.43 (95% CI, 0.25–0.74) for studies in Asia.

Sensitivity analyses

To explore the heterogeneity among studies of vitamin A intake and blood vitamin A level and cervical cancer, we performed sensitivity analyses. A sensitivity analysis omitting 1 study at a time and calculating the pooled ORs for the remainder of the studies showed that 2 studies by Vecchia et al. [19], and Shannon et al. [21] substantially influenced the pooled OR for carotene intake and 1 study by Tomita et al. [25] influenced the pooled OR for blood carotene. After excluding the 2 studies, there was no study heterogeneity ($\chi^2 = 2.98$, P = 0.70), and the OR for the highest vs lowest category of carotene intake was 0.53 (95% CI, 0.45–0.62). The OR for the highest vs lowest category of blood carotene was 0.60 (95% CI, 0.42–0.86) after excluding 1 study ($\chi^2 = 5.27$, P = 0.15).

Estimation of publication bias

The results of publication bias in the studies evaluated with Egger's test indicated that there was a very low possibility of publication bias on vitamin A intake (P = 0.393) and blood vitamin A level (P = 0.249). And the funnel plot showed the low possible publication bias (S1).

Discussion

The findings from this meta-analysis indicate that increased total vitamin A intake are associated with a reduced risk of cervical cancer. And among them, retinol intake has a weak inverse association with the risk of cervical cancer, but carotene and carotenoid intake have a strong inverse association with the risk of cervical cancer. Moreover, the blood total vitamin A levels have a significantly association with the risk of cervical cancer, and the effect of reducing the risk of mainly comes from carotene, but the blood retinol level has no significant association with cervical cancer.

In a recent meta-analysis [26], the authors also found that carotene levels were inversely associated with the risk of invasive cervical cancer (OR = 0.68, 0.55–0.84). The effect value in the study came from two parts, the diet intake and serum levels, and we could not indentify how big each of the two parts devoted. In our study, we found both carotene intake (OR = 0.51, 0.35–0.73) and blood carotene levels (OR = 0.48, 0.30–0.77) had moderate association with cervical cancer, and the effect was consistent. However, the results of the study [26] showed that retinol had no preventive effect for cervical cancer, maybe because the study involved less participants (4234 women), different from ours. Our meta-analysis' results revealed that retinol intake was weakly associated with cervical cancer (OR = 0.80, 0.64–1.00, 6105 participants), and a recent prospective study [27] involving 299,649 women also found retinol had a weak inverse association with invasive cervical cancer (OR = 0.81, 0.62–1.06).

In the similar meta-analysis [26], the authors did not extract some data describing the extent of disease (clinical stage) in invasive cervical cancer cases. If cases were at advanced stage, one might a priori expect nutritional deficiencies in those patients, and it would be harder to verify the hypothesis that vitamin A intake or levels have

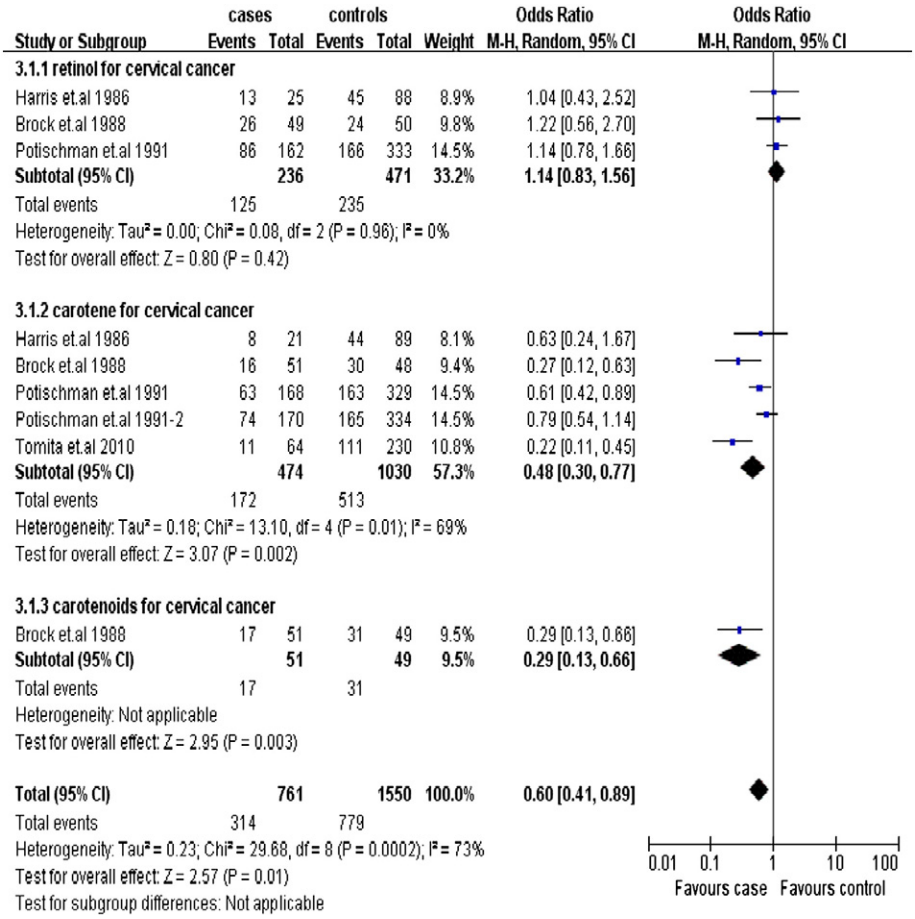

Fig. 3. The pooled odds ratios of cervical cancer for the highest vs lowest categories of blood vitamin A levels.CI indicates confidence interval. The forest plot shows the odds ratio (OR) and its95%confidence interval (95% CI) for each of the studies included, the total OR and its 95% CI, and the results of the homogeneity test.

a causative role. In order to further verify the association between vitamin A and cervical cancer, we stratified by clinical stage of cancer in cases and found that high vitamin A levels decreased the risk of early stage cervical cancer, and the ORs were similar to the effects of vitamin A for all stages of cervical cancer. Our study may explain the association between vitamin A and the risk of cervical cancer better. Moreover, several in vitro studies [28,29] found that retinoids can inhibit the growth of human cervical cancer HeLa cells. The effect of retinol on cervical cancer needs to be further studied.

In our study, we got an interesting result that blood retinol levels were not associated with the risk of cervical cancer. A nested case–control study [30] conducted in Finland and Sweden within a joint cohort of 405,000 women found that levels of retinol in the blood were not risk factors for cervical cancer. However, joint-effect analysis of low levels of retinol disclosed statistically significant synergistic interaction with HPV (HPV16, HPV18, or HPV33) seropositivity. It revealed that retinol might act as an effect modifier of the HPV-associated risk for cervical cancer. In another prospective Finnish study [31], high plasma retinol levels and presence of type-common HPV antibodies appeared to jointly protect against cervical neoplasia.

Two prospective studies suggest a protective effect of dietary beta-carotene [32,33] against HPV persistence. A study [34] also found that cases with cervical cancer were more likely to have a total dietary vitamin A intake below the pooled median and/or a β-carotene intake below the pooled median than were normal controls. The association between blood carotene level and risk of cervical cancer has been assessed in several studies [35–37], and the mean level was significantly lower in women with cervical cancer.

The observed heterogeneity among studies of the carotene intake or the carotene in blood and cervical cancer risk seemed to be explained by 2 studies by Vecchia et al. [19], and Shannon et al. [21]. The disparate results for the 2 studies may be due to the very narrow range of exposure in the studies (about 2.9-mg difference in median carotene intake between the highest and lowest categories) compared with the other studies (about 3.7-mg difference).

Although vitamin A is found in a wide variety of foods, many people don't obtain an adequate intake of this nutrient. In China, the prevalence of inadequate vitamin A intake is 9.3% for children aged 3 to 12 years old [38]. In the United States, the prevalence of inadequate vitamin A intake is 44% overall, and for women aged 14–18, 19–30, and 31–50 is 54%, 58% and 48% [39], respectively. Vitamin A is crucial for normal growth, vision, maintenance of many tissues, reproduction, metabolism, tissue differentiation, haemopoiesis, bone development, spermatogenesis, embryogenenesis, and overall survival [40]. Therefore, deficiency of vitamin A can lead to various unwanted biological effects. Almost all epithelial tissues contain receptors for retinoic acid, and a deficiency of vitamin A has consistently been implicated as an important causal factor in cancers in human beings.

Our study has a few limitations. First, our quantitative assessment study was based on case–control studies, so we can't consider the deficiency of vitamin A as an etiology of cervical cancer from our results, because the level of vitamin A after the diagnosis cannot reflect the real level before suffering cervical cancer. Moreover, the intake of vitamin A was obtained by recalling the previous intake from food frequency questionnaire (FFQ), and the studies were conducted in different countries, people had their own diet habits and behaviors and were susceptible differently to cervical cancer. So, there was the possibility that our results had recalling or selection bias, which could be of concern. Second, a meta-analysis is not able to solve

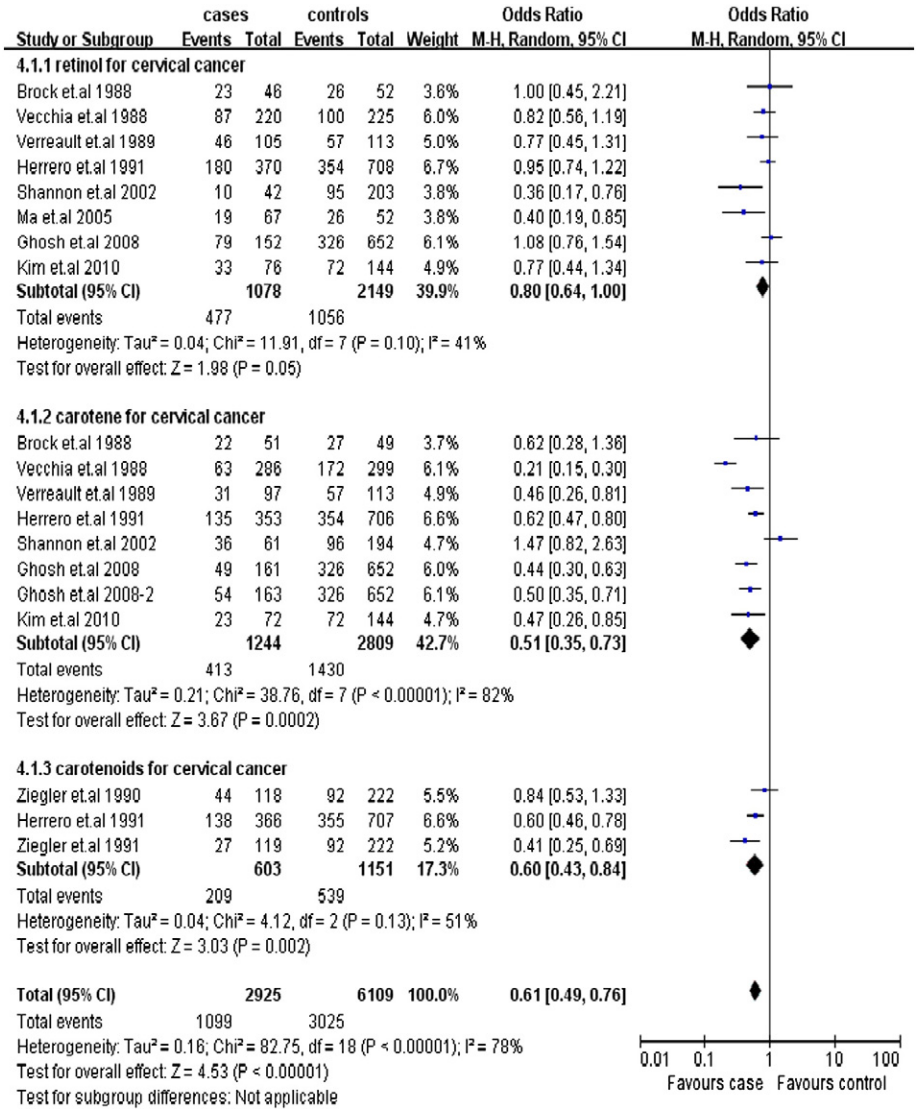

Fig. 4. The pooled odds ratios of cervical cancer for the highest vs lowest categories of retinol, carotene and carotenoid intake.CI indicates confidence interval. The forest plot shows the odds ratio (OR) and its 95% confidence interval (95% CI)for each of the studies included, the total OR and its 95% CI, and the results of the homogeneity test.

problems with confounding factors that could be inherent in the included studies. Inadequate control for confounders may bias the results in either direction, toward exaggeration or underestimation of risk estimates. Residual or unknown confounding cannot be excluded as a potential explanation for the observed findings. Vitamin A intake tends to be associated with healthy behaviors that may be protective against cervical cancer, such as better educational background, less smoking, and less parity. A third limitation is that our results are likely to be affected by some degree of misclassification of exposure. Misclassification of vitamin A intake may lead to an underestimation of the OR estimates. The associations between blood carotene level and cervical cancer were stronger than those between vitamin A intake and cervical cancer. This may be because of measurement error in the assessment of vitamin A intake, leading to an attenuation of the observed association between vitamin A intake and cervical cancer risk. Fourth, heterogeneity may be introduced because of methodological differences among studies, including different ranges of exposure. Finally, in a meta-analysis of published studies, publication bias could be of concern because small studies with null results tend not to be published. In this meta-analysis, we found no evidence of publication bias.

In summary, findings from this meta-analysis indicate that vitamin A intake is inversely associated with risk of cervical cancer. There was no significant association between blood retinol level and cervical cancer risk. The findings from these observational studies need to be confirmed in large randomized clinical trials of vitamin A supplementation.

Supplementary materials related to this article can be found online at doi:10.1016/j.ygyno.2011.10.012.

Disclosure of interest

None.

Contribution to authorship

Xingliang Zhang and Zhiping Wang formulated the idea for conducting a systematic review; Xingliang Zhang and Zhiping Wang performed literature searches, study selection, data extraction, risk of bias assessment, meta-analysis, and wrote the initial draft; Bingqin Dai and Bingzhen Zhang solved disagreements regarding study selection and risk of bias assessment, and critically revised the article.

Details of ethics approval

Ethics approval was not required for this research.

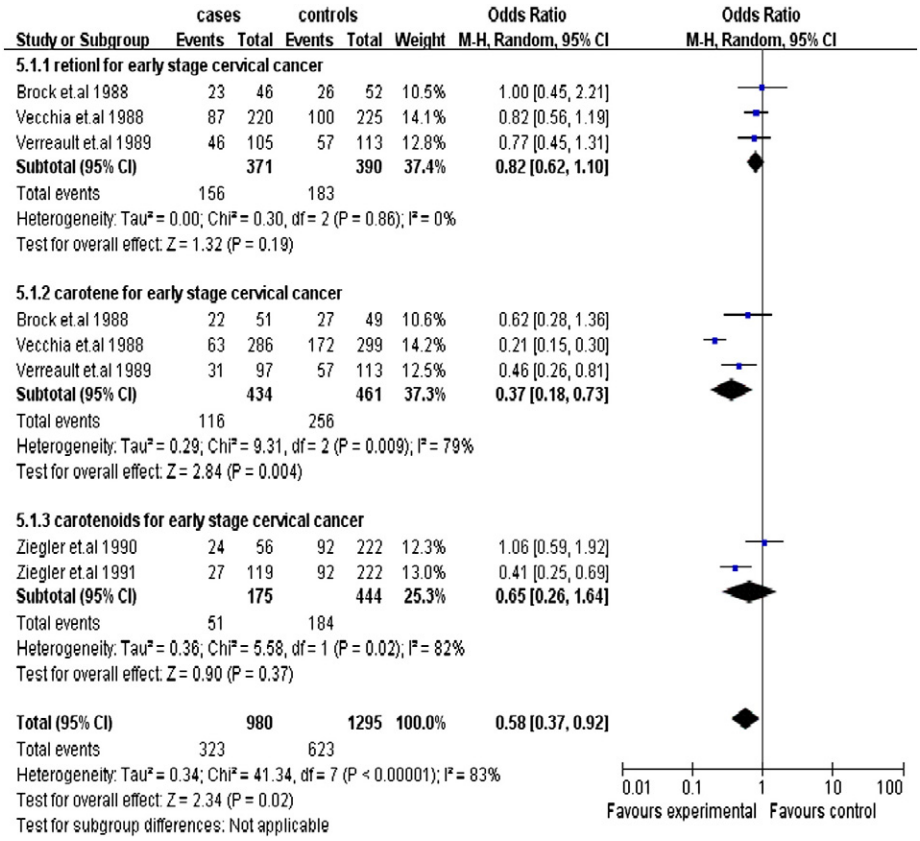

Fig. 5. The pooled odds ratios of early stage cervical cancer for the highest vs lowest categories of retinol, carotene and carotenoid intake.CI indicates confidence interval. The forest plot shows the odds ratio (OR) and its 95% confidence interval (95% CI) for each of the studies included, the total OR and its 95% CI, and the results of the homogeneity test.

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None.

Conflict of interest statement

The authors declare that there are no conflict of interest.

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None.

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