Vitamin or antioxidant intake (or serum level) and risk of cervical neoplasm: a meta-analysis

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Background Case–control studies have reported the preventive effect of vitamin or antioxidant intake on cervical neoplasms such as cervical intraepithelial neoplasia (CIN) and invasive cervical cancer. However, the findings are inconsistent.

Objective To investigate quantitative effects of vitamin or antioxidant intake on cervical neoplasm using meta-analysis.

Search strategy We searched PubMed, EMBASE and the Cochrane Library in November 2008. All articles searched were independently reviewed and selected by two evaluators according to predetermined selection criteria.

Selection criteria We included case–control studies reporting an association between vitamin or antioxidant intake (or serum level) and cervical neoplasm risk and reporting the adjusted odds ratios (OR) and 95% confidence intervals (CI), whenever possible.

Data collection and analysis After retrieval of data from selected articles, we performed a meta-analysis using both fixed-effects and random- effects models.

Main results Of 274 articles meeting our initial criteria, we included 22 case–control studies involving a total of 10 073 participants. In meta-analyses by type of vitamin or antioxidant, a significant preventive effect on cervical neoplasm was found in intakes of vitamin B12 (OR 0.35, 95% CI 0.19–0.63; $n = 2$), vitamin C (OR 0.67, 95% CI 0.55–0.82; $n = 8$), vitamin E (OR 0.56, 95% CI 0.35–0.88; $n = 10$), and beta-carotene (OR 0.68, 95% CI 0.55–0.84; $n = 9$).

Authors' conclusions The findings of this meta-analysis indicate that overall, there were preventive effects of vitamin or antioxidant intake on cervical neoplasms in case–control studies.

Keywords Antioxidants, case–control studies, cervical neoplasm, meta-analysis, vitamins.

Introduction

Cervical cancer is one of the most important preventable cancers, as the second most common cancer in women worldwide, especially in developing countries, although its incidence and mortality rates have declined in developed countries, specifically in the USA.[1,2]

Besides human papillomavirus (HPV) infection, well-known as the most important risk factor for the development of cervical neoplasms such as cervical cancer or cervical intraepithelial neoplasia (CIN), epidemiological studies have reported other risk factors such as low socio-economic status, smoking, multiple sexual partners, and use of oral contraceptives.[3–6] The relationships between vitamin or antioxidant micronutrients and cervical neoplasms have been studied in case–control studies,[7–25] but neither cohort studies nor randomised controlled trials (RCTs) have been published.

However, the preventive effects of vitamin or antioxidant intake on cervical neoplasms have not been established and are controversial in the case–control studies, although potential biological mechanisms or hypotheses regarding these micronutrients' anti-cancer activities and antioxidant effects have been suggested by *in vitro* or *in vivo* studies.[26–29]

The purpose of this study was to examine the preventive effects of major vitamins or antioxidants such as carotenoids, vitamin A, vitamin C, vitamin E, folate, selenium and lycopene on cervical neoplasm using a meta-analysis of case–control studies.

Methods

Data sources and keywords

We searched MEDLINE (PubMed), EMBASE, and the Cochrane Library in November 2008 using selected common keywords regarding vitamin or antioxidant intake (or serum level) and cervical neoplasm (cervical dysplasia, carcinoma *in situ* [CIS], and cervical cancer) in case–control studies. We also scanned the bibliographies of relevant articles to identify additional studies. As the keywords for the literature search, we selected 'vitamin', 'antioxidant', 'retinol (vitamin A)', 'beta-carotene', 'carotenoids', 'ascorbic acid (vitamin C)', 'alpha-tocopherol (vitamin E)', 'folate', 'selenium' and 'lycopene' for the exposure factors; 'cervical cancer', 'cervical neoplasm' and 'cervical intraepithelial neoplasia', for the outcome factors; and 'case–control studies' for the study design.

Study selection

We included case–control studies reporting an association between vitamin or antioxidant intake (or serum level) and cervical neoplasm risk and reporting the adjusted odds ratios (ORs) and 95% CIs, whenever possible. We only selected articles written in English and excluded those studies with insufficient data or those reporting disease not confirmed by biopsy. When the study samples overlapped in two or more articles, we selected the article with the most comprehensive population.

All studies retrieved from databases and bibliographies were independently evaluated by two authors of this study (SKM and WJ). When there were disagreements between evaluators concerning the selected studies, they discussed the matter and reached consensus. Of the articles found in the three databases, duplicate articles and those that did not meet the selection criteria were excluded. We extracted the following data from the studies included in the final analyses: study name (first author, year of publication), journal name, country, years enrolled, participants' characteristics and range of participants' age, exposure, OR with 95% CI, and adjustments.

Statistical analyses

We used an adjusted OR with 95% CI of the highest intake (or serum level) group for the disease outcome variable compared with the lowest intake (or serum level) group reported in each study, whenever possible. The main analysis was to investigate the association between individual vitamin or antioxidant intake (or serum level) and risk of cervical neoplasm. We also conducted subgroup analyses by type of cervical neoplasm, i.e. CIS and invasive cervical cancer.

A summary OR with 95% CI was estimated by using both fixed-effects and random-effects models. For assessing heterogeneity, we used the Higgins I^2, which is calculated as follows:

$$I^2 = 100\% \times (Q - df)/Q,$$

where Q is Cochran's heterogeneity statistic and df is degrees of freedom.

Negative values of I^2 are considered as zero. Values of I^2 range from 0% (no heterogeneity) to 100% (maximal heterogeneity).[30] We considered an $I^2 > 50\%$ as having substantial heterogeneity.

Woolfe's method (inverse variance method) was used in a fixed-effects model and the DerSimonian and Laird[31] method was used in a random-effects model. We used STATA SE version 10.0 software package (StataCorp, College Station, TX, USA) for statistical analysis.

Results

Selected studies

Our study included a total of 22 case–control studies (15 hospital-based, four population-based, and three nested case–control studies), involving a total of 10 073 participants (3728 cervical neoplasms with 1597 CINs and 2131 invasive cervical cancers and 6345 controls), which were published between 1986 and 2008. We present a flow diagram of identification for the relevant studies in Figure 1. A total of 274 articles were obtained from the three databases and the bibliographies. After excluding the duplicates ($n = 34$), all the remaining articles were reviewed ($n = 240$) and 193 articles were excluded for not meeting the selection criteria. After we reviewed the full text for the remaining 47 articles, we included 22 articles in the final analysis. During the final selection process, the main reasons for
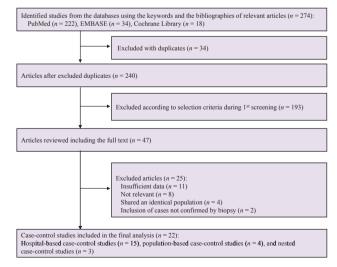

Identified studies from the databases using the keywords and the bibliographies of relevant articles ($n = 274$): PubMed ($n = 222$), EMBASE ($n = 34$), Cochrane Library ($n = 18$)

Excluded with duplicates ($n = 34$)

Articles after excluded duplicates ($n = 240$)

Excluded according to selection criteria during 1st screening ($n = 193$)

Articles reviewed including the full text ($n = 47$)

Excluded articles ($n = 25$):
Insufficient data ($n = 11$)
Not relevant ($n = 8$)
Shared an identical population ($n = 4$)
Inclusion of cases not confirmed by biopsy ($n = 2$)

Case-control studies included in the final analysis ($n = 22$):
Hospital-based case–control studies ($n = 15$), population-based case–control studies ($n = 4$), and nested case-control studies ($n = 3$)

Figure 1. Flow diagram of identification of relevant studies.

exclusion were as follows ($n = 25$): insufficient data ($n = 11$), not relevant ($n = 8$), sharing identical participants ($n = 9$), and inclusion of disease not confirmed by biopsy ($n = 2$).

Table S1 shows the main characteristics of all 22 studies included in the final analysis. The countries in which the studies were conducted were as follows: USA ($n = 12$), UK ($n = 2$), Japan ($n = 2$), Poland ($n = 2$), four Latin American countries ($n = 2$), Finland and Sweden ($n = 1$), and Thailand ($n = 1$). Overall, the range of enrolment periods for participants was 1975–1998. In studies in which the age was reported, the mean age was 42.2 years (range 18–90 years).

Preventive effects of vitamin or antioxidant intake (or serum level) on cervical neoplasm by type of vitamin or antioxidant

As shown in Figure 2, meta-analyses by type of vitamin or antioxidant showed significant preventive effects on cervical neoplasm (cervical dysplasia, CIS and invasive cancer) in the highest intake (or serum level) group of vitamin B12 (OR 0.35, 95% CI 0.19–0.63, $I^2 = 0.0\%$, $n = 2$), vitamin C (OR 0.67, 95% CI 0.55–0.82, $I^2 = 13.6\%$, $n = 8$), vitamin E (OR 0.56, 95% CI 0.35–0.88, $I^2 = 66.1\%$, $n = 10$), beta-carotene (OR 0.68, 95% CI 0.55–0.84, $I^2 = 32.1\%$, $n = 9$), folate (OR 0.60, 95% CI 0.41–0.88, $I^2 = 59.8\%$, $n = 9$) and lycopene (OR 0.54, 95% CI 0.39–0.75, $I^2 = 4.4\%$, $n = 5$), compared with the lowest intake (or serum level) group. However, these preventive effects were not found for vitamin A (OR 1.05, 95% CI 0.76–1.46, $I^2 = 52.0\%$, $n = 12$) and selenium (OR 0.82, 95% CI 0.57–1.18, $I^2 = 0.0\%$, $n = 3$).

Preventive effects of vitamin or antioxidant intake (or serum level) on cervical neoplasm by type of neoplasm

Table 1 shows preventive effects of vitamin or antioxidant intake (or serum level) on cervical neoplasm by type of neoplasm such as CIN and invasive cancer. The highest intake (or serum level) of vitamin B12, vitamin C, vitamin E and lycopene was significantly associated with a decreased risk of CIN compared with the lowest intake (or serum level), whereas no association was observed for vitamin A, beta-carotene, folate and selenium.

Also, the intake (or serum level) of vitamin C, folate and lycopene was associated with a decreased risk of invasive cancer, whereas no preventive effect was found in vitamin A, vitamin E, beta-carotene and selenium.

Subgroup meta-analysis by adjustment for HPV infection

As shown in Table 2, when using data from the studies with adjustment for HPV infection, preventive effects on cervical neoplasm were found in intakes of vitamin B12, vitamin C, vitamin E and lycopene, but no preventive effect was found in vitamin A, beta-carotene, folate and selenium.

Discussion

In the current meta-analysis of case–control studies, we found that the preventive effect on cervical neoplasm was found in the high intake (or serum level) of vitamins or antioxidants such as vitamin B12, vitamin C, vitamin E, beta-carotene, folate and lycopene, whereas no preventive effect was observed for vitamin A and selenium. In subgroup meta-analyses by type of cervical neoplasm, the highest intake (or serum level) of vitamin C and lycopene decreased a risk for both CIN and invasive cervical cancer. Furthermore, when using data from the studies with adjustment for HPV infection, preventive effects on cervical neoplasm were found for intakes of vitamin B12, vitamin C, vitamin E and lycopene.

Our findings support the possible protective role of various vitamins and antioxidants on cervical cancer suggested in previous literature. Folate is generally known to be required for DNA synthesis, repair and methylation, and low folate status might facilitate the incorporation of HPV into the host genome.[24,32,33] Vitamin B12 is associated with cellular folate uptake.[10,23] Also, vitamin B12 and folate are both cofactors for methionine synthase, which catalyses the conversion of homocysteine, and are inversely associated with homocysteine levels.[23,34,35] Homocysteine could be associated with increased risk of cervical cancer as a marker of low folate and vitamin B12 levels.[23,34] However, more research is required to confirm the protective role of vitamin B12 because only two case–control studies were included in our study through a paucity of individual studies.

Vitamin C, vitamin E, beta-carotene and lycopene, known as potent antioxidants that can prevent reactive oxygen species from oxidising cellular proteins and DNA, are considered to have anti-neoplastic effects in the cervix.[20,36] Selenium has also been known to have antioxidant properties and chemopreventive effects on cancer in animal studies *in vivo* and in laboratory studies *in vitro*.[37–39] However, the role of selenium in cervical neoplasm development remains unclear, and only a few case–control studies have been published on this issue. We are therefore unable to draw a definite conclusion regarding the effect of selenium on cervical neoplasm, and further research is required.

Retinol, the animal form of vitamin A, and its metabolites (retinoids) play an important role in cell proliferation and differentiation, and have also been known to modulate immune responses.[40] In our study, however, unlike other
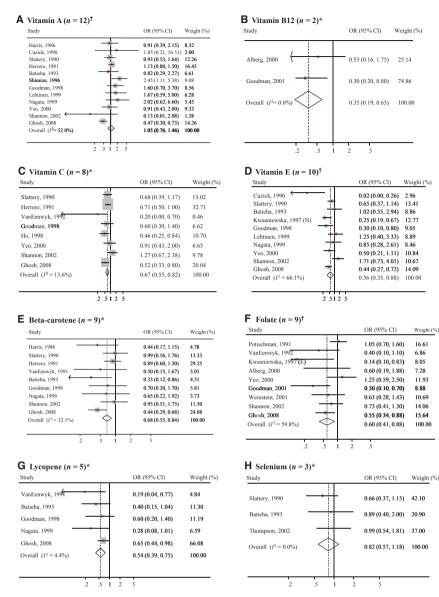
Figure 2. Association between vitamin and an antioxidant intake and cervical neoplasm (dysplasia, carcinoma *in situ*, and invasive cancer) risk by type of vitamin or antioxidant. *Fixed effects model; †random effects model; OR, odds ratio; 95% CI, 95% confidence interval.

vitamins or antioxidants, there was no significant association between intake or serum level of vitamin A and cervical neoplasm, although a few studies, up to 12 articles, have been published and were included in our analysis.

Our study has several limitations. First, it does not provide a high level of evidence because we only included case–control studies because of the paucity of data from prospective cohort studies or RCTs. Generally, case–control studies have two main biases, recall and selection. As for recall bias, women with cervical cancer might recall their dietary habits towards an unhealthy diet, differently from healthy people, who may report a healthy diet.[41,42] In

addition, it is known that the accuracy of recalling past dietary habits is influenced by current dietary habits.[43] Both cases and controls could not represent the whole population because they were a non-random sample of a population, which causes some members of the population to be more likely to be included than others. For example, the association between green tea consumption and risk of stomach cancer might be an example of the distinct discrepancy in findings between case–control studies and cohort studies. Myung et al.[44] reported that unlike the case–control studies (relative risk [RR] 0.73; 95% CI 0.64–0.83; *n* = 8), no preventive effect on stomach cancer was

Table 1. Preventive effects of vitamin or antioxidant intake on cervical neoplasm by type of neoplasm

Category	No. of studies	Summary OR (95% CI)	Heterogeneity, I^2 (%)	Model used
CIN				
Vitamin A	7	0.88 (0.34–2.27)	82.8	Random-effects
Vitamin B12	1	0.30 (0.20–0.80)	n.a.	n.a.
Vitamin C	5	0.67 (0.46–0.98)	43.6	Fixed-effects
Vitamin E	6	0.40 (0.19–0.85)	65.2	Random-effects
Beta-carotene	5	0.64 (0.39–1.04)	0.0	Fixed-effects
Folate	5	0.47 (0.21–1.09)	71.8	Random-effects
Lycopene	3	0.38 (0.19–0.74)	0.0	Fixed-effects
Selenium	1	0.61 (0.20–1.85)	n.a.	n.a.
Invasive cancer				
Vitamin A	5	0.74 (0.40–1.35)	74.5	Random-Effects
Vitamin C	3	0.67 (0.52–0.86)	20.1	Fixed-Effects
Vitamin E	3	0.87 (0.35–2.14)	70.6	Random-Effects
Beta-carotene	4	0.68 (0.44–1.05)	51.5	Random-Effects
Folate	4	0.75 (0.57–0.98)	33.7	Fixed-Effects
Lycopene	1	0.65 (0.44–0.98)	n.a.	n.a.
Selenium	1	0.99 (0.54–1.81)	n.a.	n.a.

n.a., not available.

Table 2. Preventive effects of vitamin or antioxidant intake on cervical neoplasm in subgroup meta-analysis of case-control studies by adjustment for HPV infection

Category	No. of studies	Summary OR (95% CI)	Heterogeneity, I^2 (%)	Model used
Vitamin A				
Unadjusted	8	0.96 (0.58–1.58)	60.5	Random-effects
Adjusted	4	1.18 (0.90–1.54)	0.0	Fixed-effects
Vitamin B12 (All studies adjusted)				
Unadjusted	n.a.			
Adjusted	2	0.35 (0.19–0.63)	0.0	Fixed-effects
Vitamin C				
Unadjusted	4	0.68 (0.51–0.92)	48.4	Fixed-effects
Adjusted	4	0.66 (0.51–0.86)	0.0	Fixed-effects
Vitamin E				
Unadjusted	7	0.58 (0.31–1.07)	75.7	Random-effects
Adjusted	3	0.49 (0.28–0.86)	0.0	Fixed-effects
Beta-carotene				
Unadjusted	6	0.60 (0.46–0.78)	44.5	Fixed-effects
Adjusted	3	0.83 (0.60–1.17)	0.0	Fixed-effects
Folate				
Unadjusted	4	0.45 (0.25–0.80)	59.8	Random-effects
Adjusted	5	0.86 (0.64–1.16)	45.7	Fixed-effects
Lycopene				
Unadjusted	3	0.57 (0.40–0.81)	34.3	Fixed-effects
Adjusted	2	0.45 (0.21–0.98)	0.0	Fixed-effects
Selenium				
Unadjusted	2	0.73 (0.46–1.16)	0.0	Fixed-effects
Adjusted	1	0.99 (0.54–1.81)	n.a.	n.a.

n.a., not available.

seen for the highest green tea consumption in the meta-analysis of the recent cohort studies (RR 1.04; 95% CI 0.93–1.17; *n* = 7). Therefore, further research providing a higher level of evidence such as prospective cohort studies or RCTs is needed to confirm the protective effect of vitamin or antioxidant intake on cervical neoplasm.

Second, many of the individual studies included in our analysis did not consider HPV infection in their individual analyses. However, when subgroup meta-analyses by adjustment for HPV infection were performed, similar findings were observed in subgroup meta-analyses of both studies with and without adjustment for HPV infection.

Last, we were unable to evaluate the dose–response relationship between vitamin or antioxidant intake and the risk of cervical neoplasm because we used only the extreme categories, highest versus lowest intake (or serum level). Also, we could not provide appropriate intake levels of vitamins or antioxidants for the prevention of cervical neoplasm. Those should be evaluated in the future research.

In conclusion, we found that there were significant protective effects of some vitamin or antioxidant intake on cervical neoplasm in the meta-analysis of case–control studies. However, given that case–control studies have potential biases, our findings and explanations should be confirmed in further research, such as prospective cohort studies and RCTs providing the highest level of evidence.

Disclosure of interests

Contribution to authorship

SKM and WJ were responsible for the conception and design, analysis and interpretation, and for final approval of the article. They also held overall responsibility. All four authors (SKM, WJ, SCK and HSK) were responsible for data collection, writing the article, critical revision of the article, and statistical analyses.

Details of ethics approval

Not applicable.

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Supporting information

The following supplementary materials are available for this article:

Table S1. Characteristics of the studies included in the final analysis (*n* = 22).

Additional Supporting Information may be found in the online version of this article.

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