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Higher serum zinc levels may reduce the risk of cervical cancer in Asian women: A meta-analysis

Yueying Xie[1], Junjie Wang[2], Xiaoya Zhao[1], Xuli Zhou[1], Xiaohui Nie[2], Chuncheng Li[1], Fulian Huang[2] and Haibin Yuan[3]

Abstract

Objective: This meta-analysis was conducted to examine the possible association between serum zinc concentration and cervical cancer risk.

Methods: PubMed, WanFang, China National Knowledge Infrastructure, and SinoMed databases were searched for relevant articles published between January 1980 and September 2017. Results were combined using a random-effects model, and pooled standardized mean differences (SMD) and 95% confidence intervals (CI) were calculated to compare serum zinc levels in patients with cervical cancer versus controls. Publication bias was evaluated using Begg's funnel plot and Egger's regression asymmetry test.

Results: Twelve articles regarding serum zinc levels and cervical cancer were included in this meta-analysis. Combined results showed that serum zinc levels in cervical cancer cases were significantly lower than in controls without cervical cancer (summary SMD −1.379, 95% CI −1.527, −1.231), with high heterogeneity ($I^2 = 98.8\%$). Analysis of data stratified by geographic location showed a significant association between serum zinc levels and cervical cancer risk in Asian populations (summary SMD −1.391, 95% CI −1.543, −1.239).

Conclusions: Higher serum zinc levels may be a protective factor for cervical cancer in Asian women.

[1]Department of Pathology, the Maternal and Child Health Care Hospital of Xiangtan City, Hunan Province, China
[2]Department of Gynaecology, the Maternal and Child Health Care Hospital of Xiangtan City, Hunan Province, China
[3]Department of Paediatrics, the Maternal and Child Health Care Hospital of Xiangtan City, Hunan Province, China

Corresponding author:
Haibin Yuan, Department of Paediatrics, the Maternal and Child Health Care Hospital of Xiangtan City, 295 East Lake Road, Xiangtan, Hunan Province, 411104, China.
Email: yuan_hb2017@sina.com

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Introduction

In 2016, cervical cancer was rated as one of the most common gynaecological cancers worldwide and the third leading cause of cancer-related death among women in developing countries.[1] Although cervical cancer incidence and mortality rates have decreased due to improvements in diagnostic techniques and treatment strategies, the overall prognosis of patients with cervical cancer remains poor, particularly in developing countries.[2,3]

Studies have suggested that cervical cancer is related to genetic factors,[4,5] and that micronutrients also play a role in the development of cervical cancer.[6,7] Zinc is used for cell growth and is also useful in maintaining the integrity of cell membranes, therefore, cancer cells may absorb zinc from the circulation to maintain cancer growth and membrane integrity.[8] Zinc ions (Zn^{2+}) have also been suggested to inhibit viral replication and various other viral functions in many viruses.[9,10] However, to the best of the present authors' knowledge, there is no published comprehensive meta-analysis specifically concerning the association between serum zinc levels and cervical cancer risk. Thus, the aim of the present study was to clarify potentially inconsistent results and compare serum zinc levels between patients with cervical cancer and controls without cervical cancer.

Materials and methods

Literature search

The PubMed, WanFang, China National Knowledge Infrastructure (CNKI) and SinoMed databases were searched for pertinent studies published between January 1980 and September 2017, using the following search terms: ('zinc concentration' OR 'zinc level' OR 'zinc' OR 'Zn' OR 'trace element') AND 'cervical' AND ('cancer' OR 'tumor' OR 'carcinoma'). References cited in the retrieved articles were also manually searched to find any additional relevant articles. Titles and abstracts of articles retrieved from the database search were initially screened for eligibility by two independent investigators (YX and JW) according to the inclusion criteria. The remaining articles then underwent full paper review, and data were extracted from articles that still met the inclusion criteria and were included for meta-analyses.

Inclusion and exclusion criteria

Inclusion criteria for this study were as follows: (1) observational studies or randomized controlled trials; (2) studies that investigated the association between serum zinc concentration and cervical cancer; (3) availability of data regarding study group numbers, and mean ± SD serum zinc levels for cases and controls; (4) human studies; and (5) studies published in English or Chinese language.

Articles were excluded if they: (1) reported on animal or cell (*in vitro*) studies; (2) were reviews, letters to the editor or comments; (3) contained insufficient data for statistical analyses; and (4) were overlap studies.

Data extraction

The following data were extracted by two independent investigators (YX and JW) according to a predefined standardized form: the first author's last name; publication year; geographical region for the study; study type; mean age or age range; follow-up duration if available; study group numbers; mean ± SD serum zinc levels for cases (data for zinc levels following diagnosis and before receiving treatment were extracted) and controls; and adjustment for covariates. Any disagreements were resolved by a third reviewer (XZhao).

Statistical analyses

Standardized mean differences (SMD) and corresponding 95% confidence intervals (CI) were pooled to evaluate the association between serum zinc levels and cervical cancer risk.[11] Heterogeneity was evaluated using the I^2 statistic,[12] where I^2 values $< 25\%$ indicated low heterogeneity, I^2 values 25–50% indicated moderate heterogeneity, and I^2 values $> 75\%$ indicated high heterogeneity.[13] Due to a high level of between-study heterogeneity in the present meta-analysis, the random-effects model was used to combine the results. Meta-regression analysis was used to explore the high level of between-study heterogeneity.[14] Sensitivity analysis was performed to evaluate the potential effects of individual studies on the overall results when a single study was removed.[15] Publication bias was evaluated using Begg's funnel plot and Egger's regression asymmetry test.[16] All analyses were two sided, and a P value < 0.05 indicated statistical significance. Statistical analyses were performed using Stata statistical software, version 12.0 (StataCorp LP, College Station, TX, USA).

Results

Included studies

The initial database search resulted in 521 articles (169 articles from PubMed, 112 articles from WanFang, 131 articles from CNKI and 109 articles from SinoMed databases), and an additional two articles were found through other sources (Figure 1). Following removal of duplicates, 393 articles remained for initial title and abstract screening. Forty-two articles remained after screening and underwent full text review, which resulted in exclusion of a further 30 articles due to the following: 15 were review articles, five articles did not report mean ± SD serum zinc levels, nine were animal studies, and there was one letter to the editor. Hence, 12 articles[17–28] were suitable for inclusion in the present study (Figure 1). All the included articles reported case–control studies. Nine studies came from China, two from India and one from the United Kingdom. In total, the studies comprised 591 patients with cervical cancer and 946 controls, and the study and population characteristics are shown in Table 1.

Serum zinc levels and risk of cervical cancer

In the overall meta-analysis, patients with cervical cancer were found to have significantly lower zinc levels compared with controls without cervical cancer (summary SMD –1.379, 95% CI –1.527, –1.231; Z score = 18.27, $P < 0.001$), with significant evidence of between-study heterogeneity ($I^2 = 98.8\%$, $P < 0.001$) (Figure 2). There were 11 studies from Asia and one study from Europe (UK). In the analysis stratified by geographic location, a significant association was found between serum zinc levels and cervical cancer risk in Asian populations (summary SMD –1.391, 95% CI

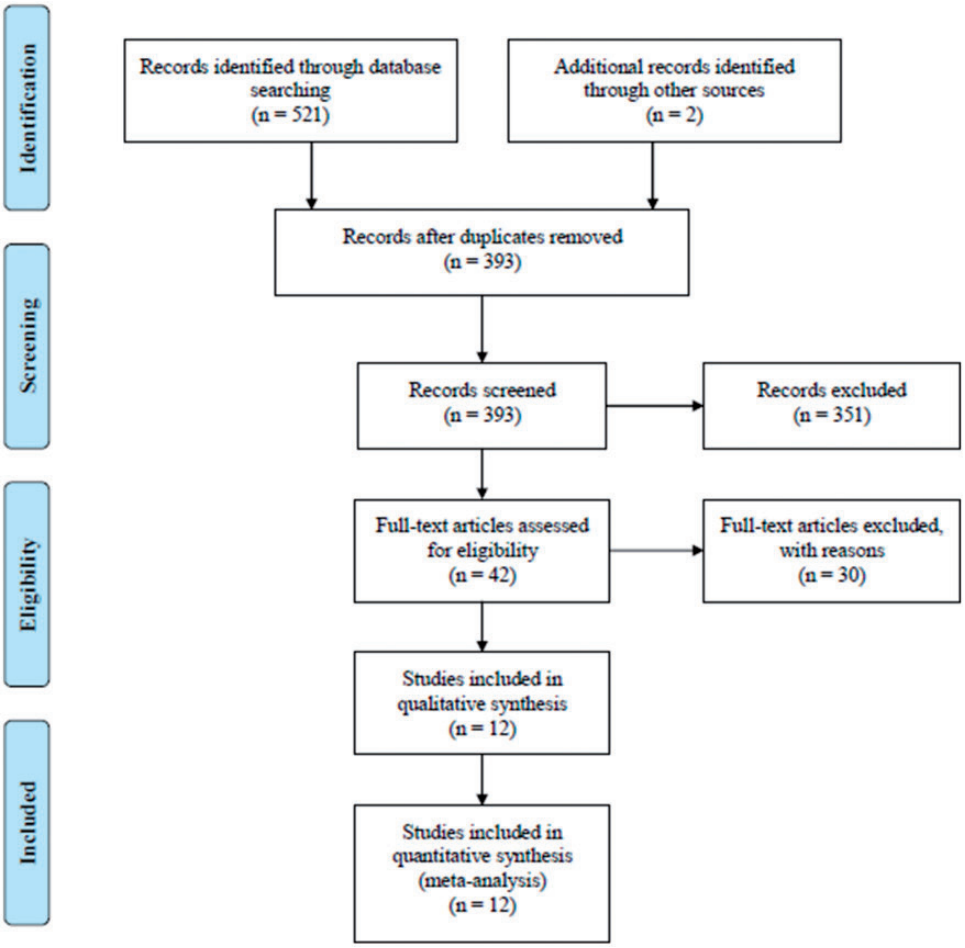

Figure 1. Flow diagram and results of the literature search for published studies relating to serum zinc levels and cervical cancer

–1.543, –1.239; Z score = 17.92, $P < 0.001$). The results for the European population was not further analysed as only one relevant study was included.

Between-study heterogeneity

Significant evidence of between-study heterogeneity appeared when the overall data were pooled. Therefore, univariate meta-regression, with publication year, geographic location and case numbers as covariates, was performed to explore the reason for high heterogeneity. None of the investigated covariates were found to have contributed to the high heterogeneity level (publication year, $P = 0.231$; geographic location, $P = 0.237$; and case numbers, $P = 0.291$).

Publication bias and sensitivity analysis

Egger's regression asymmetry test indicated significant publication bias in the overall analysis ($P = 0.025$). When a trim and fill method was used to adjust for the

Table 1. Characteristics of 12 published studies included in a meta-analysis of the association between serum zinc level and cervical cancer risk

				Study population			
				Cervical cancer cases		Controls	
Study, year	Country	Age, years	Study type	*n*	Serum zinc level	*n*	Serum zinc level
Cunzhi et al., 2003[17]	China	30–65	case-control	40	14 ± 5 (μmol/l)	50	17 ± 7 (μmol/l)
Fu et al., 2009[18]	China	31–70	case-control	74	12.74 ± 2.38 (μmol/l)	180	17.25 ± 4.35 (μmol/l)
Grail et al., 1986[19]	United Kingdom	25–60	case-control	24	0.73 ± 0.12 (mg/l)	21	1.02 ± 0.34 (mg/l)
Naidu et al., 2007[20]	India	25–65	case-control	30	87.4 ± 11.91 (μg%)	30	97.6 ± 8.71 (μg%)
Shi et al., 2011[21]	China	38.4 ± 6.12	case-control	15	7.45 ± 1.04 (μmol/l)	30	13.73 ± 2.72 (μmol/l)
Subramanyam et al., 2013[22]	India	30–75	case-control	104	56.32 ± 0.43 (μg/dl)	50	89.45 ± 0.32 (μg/dl)
Wang et al., 2010[23]	China	25–60	case-control	41	5.74 ± 2.11 (μmol/l)	260	7.25 ± 6.73 (μmol/l)
Xin et al., 2011[24]	China	38.4 ± 6.12	case-control	20	7.69 ± 1.09 (ng/l)	30	13.73 ± 2.72 (ng/l)
Xu et al., 2013[25]	China	25–60	case-control	60	0.81 ± 0.167 (mg/ml)	60	1.12 ± 0.131 (mg/ml)
Yu et al., 2016[26]	China	36–65	case-control	70	23.51 ± 3.5 (μmol/l)	150	104.36 ± 9.21 (μmol/l)
Zhang et al., 1996[27]	China	32–61	case-control	55	13.54 ± 2.01 (μmol/l)	35	17.83 ± 2.63 (μmol/l)
Zhang et al., 2015[28]	China	32–70	case-control	58	22.3 ± 1.7 (μmol/l)	50	133.9 ± 1.4 (μmol/l)

Data presented as range or mean ± SD.

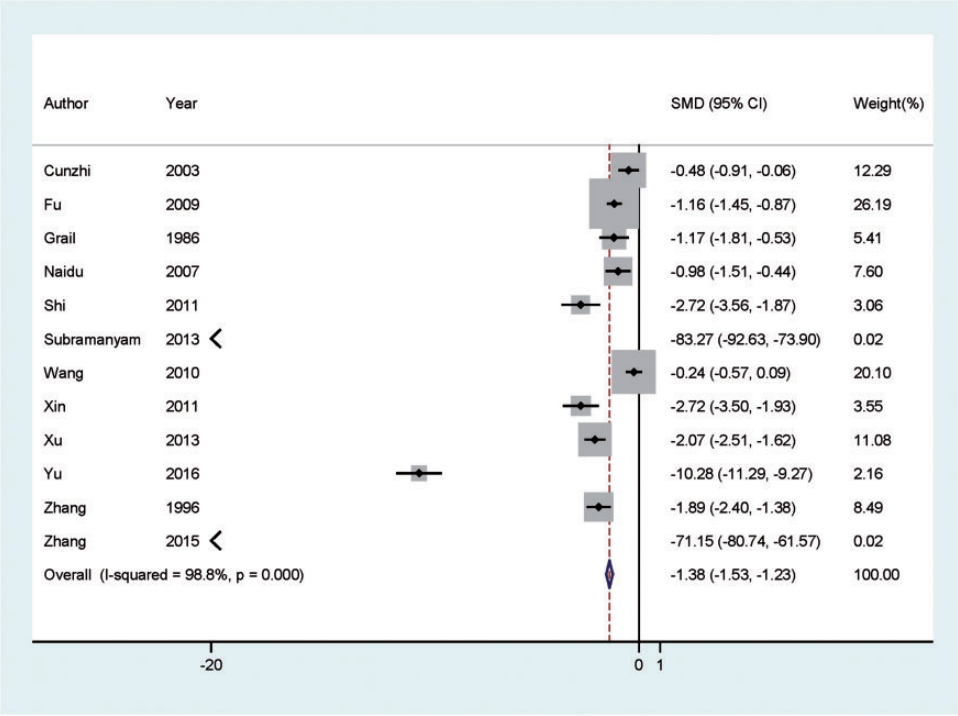

Figure 2. Forest plot showing meta-analysis of published studies regarding the association between serum zinc levels and cervical cancer risk. Data presented as standardized mean difference (SMD) with corresponding 95% confidence intervals (CI); The size of the grey square for each study is proportional to the sample size, and the horizontal line represents the 95% CI of the SMD

significant publication bias, the pooled result remained significant (SMD –1.281, 95% CI –1.436, –1.116; *P* for Egger's regression asymmetry test = 0.191).

The sensitivity analysis, in which one study was removed at a time, showed that no single study was responsible for the overall result. Summarized SMDs remained statistically significant, and ranged from –1.665 (95% CI –1.831, –1.500) to –1.182 (95% CI –1.331, –1.032) when one study was removed at a time.

Discussion

A total of 12 case–control studies were identified that investigated the association between serum zinc levels and cervical cancer risk. Results from the present meta-analysis suggested that serum zinc levels in patients with cervical cancer were significantly lower compared with controls. Sub-analysis of studies in Asian populations revealed the identical result.

A previously published meta-analysis of six studies indicated that serum folate deficiency may increase cervical cancer risk among Asian populations.[7] Other studies have suggested that serum vitamin A levels and serum vitamin E levels were also inversely associated with cervical cancer risk.[29,30] In addition, a study that investigated the association between trace elements and cervical cancer risk concluded that serum selenium exposure may be a protective factor for cervical cancer.[6]

The results obtained in the present meta-analysis of serum zinc levels were consistent with these published studies.

The role of zinc in cell growth and division, as well as in basal homeostasis is of key importance.[31] Zinc deficiency has adverse consequences, particularly on immune functioning, and zinc is one of the rare elements whose serum level changes are effective in oxidation and regeneration processes, as well as in carcinogenesis.[32] Moreover, zinc may directly prevent DNA damage and eventually gene mutation, and in this way, the element is thought to decrease the risk of cancer.[33]

In the present meta-analysis, a high level of between-study heterogeneity was found regarding the association between serum zinc levels and cervical cancer risk. Between-study heterogeneity in meta-analyses is said to be a common phenomenon,[34] and it is essential to explore any existing heterogeneity between the studies. In the present study, meta-regression was used to explore the causes of heterogeneity, however, none of the covariates investigated (publication year, geographic location and case numbers) were found to have contributed to the observed heterogeneity. A sensitivity analysis was subsequently conducted to evaluate the stability of pooled results, in which one study was removed at a time, and revealed that no individual study had potential effects on the overall result. It should be noted, however, that genetic or environmental factors would also affect the occurrence of cervical cancer.

A highlight of the present study is that to the best of the authors' knowledge, this was the first meta-analysis concerning the association between serum zinc levels and cervical cancer risk. Secondly, a positive result was found, which may provide data to support further studies regarding cervical cancer prevention. Thirdly, although the number of cervical cancer patients and controls in each study was relatively small, these studies were pooled to obtain a more comprehensive result using meta-analysis. In addition, no single study was found to have a key impact on the whole pooled result, and although evidence of significant publication bias was found, no bias was observed when using the trim and fill analysis to adjust for the high publication bias.

Some limitations regarding the present results should be mentioned. First, all the included studies were case–control studies, which may produce selection bias and recall bias. Case–control studies are an important observational research method, however, further studies with a prospective design would be of benefit to confirm the present result. Secondly, almost all of the included studies were from Asia, and only one study came from Europe (UK). Therefore, the present result is more representative of Asian populations. Further studies in other countries are warranted to confirm the present results in terms of the wider population. Thirdly, only studies that were published in English or Chinese language were included, and evidence of publication bias was found, however, as mentioned above, the bias was not significant when the trim and fill method was used to adjust for this high bias, and the pooled outcome was not changed. Fourthly, only one article (Naidu et al., 2007)[20] presented detailed data on cervical cancer stages (stage I, II, III and IV). Some articles reported the cervical cancer grade in patients, but did not report detailed data on the grade. Therefore, more studies are required that report detailed data regarding stage, grade, and type of cervical cancer in order to further assess the association between serum zinc levels and cervical cancer risk.

In conclusion, higher serum zinc levels may be a protective factor for cervical cancer in Asian women. Further studies that include populations from other

countries and ethnic backgrounds are required to validate the present results.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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