



The effects of dietary supplements in patients with cervical cancer: a comprehensive systematic review

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ABSTRACT

Background: Recent studies reported that complementary therapy including dietary supplements may have a beneficial role in cervical cancer. However, the results are inconsistent. This study aimed to investigate the association between cervical cancer and dietary supplements.

Methods: A systematic literature review was conducted to summarize and quantify the most recent findings on dietary supplement and cervical cancer. Several databases were checked for relevant publications published in English up to March 2023. Of the 32 articles identified, only 20 met the inclusion criteria and were included.

Results: Women with cervical intraepithelial neoplasia may benefit from folate supplementation against oxidative stress and inflammation. Vitamin D may reduce oxidative stress and may have a therapeutic effect. Zinc promotes the clearance of the human papilloma virus and reduces the chance of viral infection. The use of probiotic supplements may improve the complications associated with chemotherapy in patients with cervical cancer, such as diarrhea and abdominal pain. Radiotherapy and chemotherapy complications may also be reduced by omega-3 fatty acids.

Conclusion: Some dietary supplements including folate, vitamin D, zinc, probiotics, and omega-3 fatty acids may have beneficial effects in patients with cervical cancer. Further studies are warranted to confirm these results.

Introduction

Cervical cancer is the fourth most common cancer in women, and more than 500,000 women are diagnosed each year, causing more than 300,000 worldwide deaths [1]. About 85% of cervical cancers and 90% of related deaths occur in underdeveloped and developing countries.

Many cervical cancers and mortalities occur in Asian countries, especially in India and China, due to religious and cultural barriers and a lack of adequate education that have reduced screening in these countries [2]. Human papillomavirus (HPV) infection is the primary cause of cervical cancer, which is a preventable disease, and early detection improves survival rates [3]. Although safe sex education and

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vaccination have been established as effective prevention strategies against developing cervical intraepithelial neoplasia (CIN) and persistent HPV infection to cervical cancer, women in many developing countries do not have access to such services [4].

Previous studies indicated that the main cause of cervical cancer is infection with high-risk types or oncogenes of HPV, especially HPV 16 and 18 [5]. Other causes, such as smoking [6], sexual activity at a young age (especially under 16 years), poor economic status [7], excessive use of oral contraceptives [8] and deficiencies of dietary vitamins, minerals, and nutrients could lead to DNA damage and immune incompetence [9]. Many studies confirmed that most cancer patients use complementary therapies in which dietary supplements are common [10]. For example, one study showed that long-term folate supplementation could improve metabolic status in patients with cervical intraepithelial neoplasia [11]. Recently, some studies have suggested that polymorphisms in genes related to folate metabolism might be involved in cervical neoplasia [12, 11, 13, 14]. Folate and vitamin B12 deficiency are associated with a lower degree of long interspersed nucleotide element methylation, which might explain the risk of cervical cancer [15]. Previous evidence demonstrated the critical role of antioxidant supplementation on hematological toxicity, oxidative stress, and quality of life in cervical cancer patients [16]. Antioxidants help to stop or limit free radical harm to prevent DNA damage [17]. In addition, if the levels of free radicals and oxidants increase, the inflammatory processes caused by HPV infection can significantly harm DNA proteins. Some vitamins such as vitamin A (retinoic acid), C (ascorbic acid), D3, and E (tocopherol) may inhibit the proliferation of cancer cells, DNA damage, and diminish immunosuppression [18]. According to some studies, certain dietary patterns are associated with hrHPV infection and CC, and Mediterranean

diets are recommended over unhealthy eating habits and It has been suggested that pro-inflammatory diets increase the risk of CIN2 and more severe lesions [19, 20]. Other studies reported that probiotics and prebiotics might have an influential role in the management of cervical cancer patients by reducing complications of radiotherapy, such as diarrhea and proctitis [21, 22]. However, the results of the studies on the beneficial effects of supplements in managing cervical cancer have been conflicting [12, 23]. Therefore, this systematic study aimed to investigate the latest findings on the association between cervical cancer and dietary supplements.

Methods

A systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [24]. Based on PICO elements (i.e. population, intervention, comparison, and outcome), this study focused on women with cervical cancer (P) to determine the effects of dietary supplements (I) compared to the placebo group (C) on the treatment and management of the disease and related complications (O). We initially searched on March 2023 and included clinical trials, cohort, and case-control studies that evaluated the association of dietary supplements in adult women with cervical cancer. Fig. 1 shows the process of searching, screening, and excluding studies.

Search strategy

A comprehensive search was conducted in PubMed, Scopus, ISI Web of Science, and Cochrane library. The merger of MeSH and non-MeSH

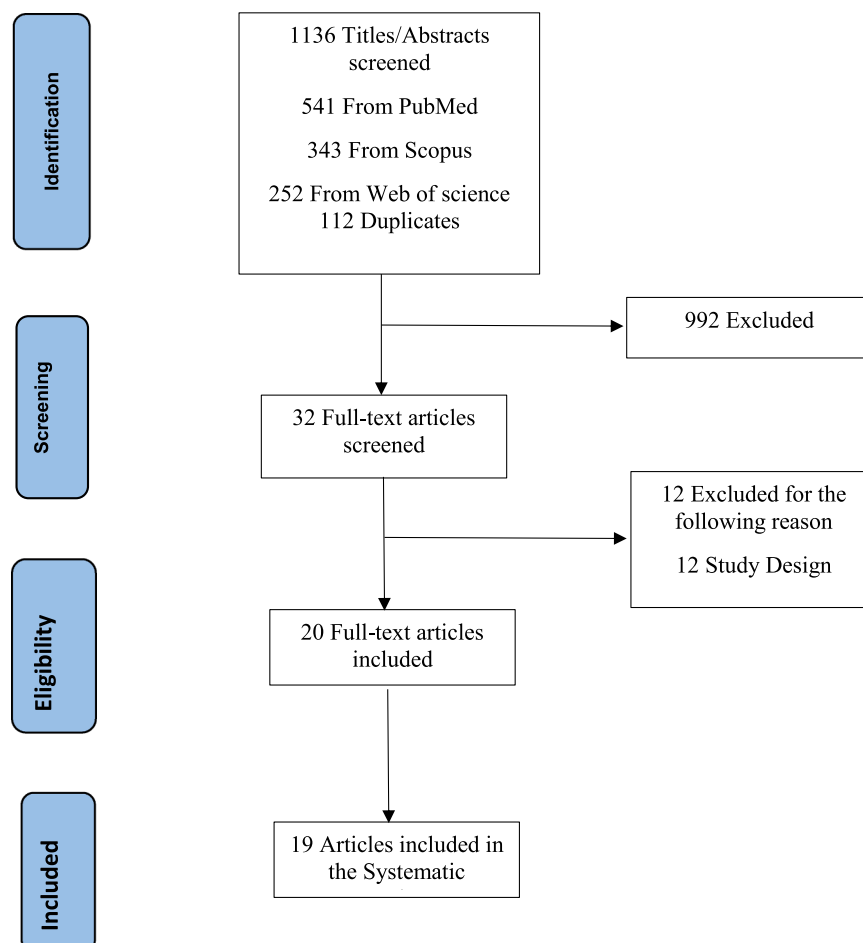


Fig. 1. PRISMA flowchart of the search results and the included studies.

terms were composed by experts in the field and included the following terms: "multivitamin" OR "multi-vitamin" OR "multimineral" OR "multi-mineral" OR "antioxidative" OR "antioxidant" OR "anti-oxidant" OR "antioxidants" OR "Vitamin A" OR "retinol" OR "beta carotene" OR "β carotene" OR "vitamin C" OR "ascorbic acid" OR "ascorbate" OR "Vitamin E" OR "alpha tocopherol" OR "α tocopherol" OR "Selenium" OR "Zinc" OR "Lycopene" OR "Lutein" OR "Dietary Supplements" OR "supplement" OR "Vitamin D" OR "Ergocalciferols" OR "Cholecalciferol" OR "vitamin D2" OR "vitamin D3" OR "calciferol" AND "Vitamin B" to prevent missing any related studies. We also hand-searched all reference lists of eligible studies, related reviews, and systematic reviews.

Eligibility criteria

Based on the PICOS elements [25], the eligible studies were included in this systematic review. Search terms included controlled vocabulary and text terms describing dietary supplements' effect on cervical cancer.

Several bibliographic databases were searched (Embase, Cochrane Reviews and Trials, PubMed) as well as gray literature (ClinicalTrials.gov, Google Scholar). To identify additional relevant studies, we

screened the references of all included studies. Studies with the following conditions were included in this study: (a) clinical trials and cohort or case-control studies, (b) performed on individuals over 18 years of age infected with cervical cancer, (c) assessed the effects of dietary supplements, (d) outcomes included cervical intraepithelial neoplasia and/or cervical cancer, (E) published in English, and (F) availability of full text.

Excluded criteria

Studies with, at most, one of the following conditions were excluded: (a) studies that did not provide sufficient information for the outcomes of interest, (b) studies with less than one-week follow-ups, and (c) studies that were conducted before 2000.

Data extraction

Two researchers (M Gh and M B) independently conducted the study selection, while a chief investigator (SD) was also present to resolve any disagreements. The following data were recorded from each study: first

Table 1
Association between dietary consumption and cervical cancer.

Ref.	Study design	Country	Supplement	Sample characteristic	Results
Sanusi (2019)	Clinical Trial	Indonesia	Vitamin A supplementation	15 Treatment group/15 Placebo	When treated with neoadjuvant chemotherapy, vitamin A supplementation had no significant effect in the treatment of cervical cancer.
K A Keefe et al. (2001)	Clinical Trial	USA	Beta-carotene supplementation	103 women with cervical intraepithelial neoplasia	β-carotene does not promote the regression of high-grade cervical intraepithelial neoplasia, especially in HPV-positive patients
Sima Sabihi et al. (2022)	Clinical Trial	Iran	Folate supplementation	30 Treatment group/30 Placebo	Supplementation with folate for 12 weeks reduced recurrence of CIN2/3 among and improved insulin sensitivity, inflammation, and markers of oxidative stress.
Nazlı Yenigul et al. (2020)	Cohort trial	Turkey	Folate and B12 supplementation	100 Treatment group/100 Placebo	Women with ASCUS who are positive for HPV have low levels of vitamin B12 and folate in their serum
Asemi et al. (2016)	Clinical Trial	Iran	Folate supplementation	29 Treatment group/29 Placebo	Folate supplementation reversed CIN1 in women, decreased MDA levels, decreased insulin levels, and increased plasma GSH levels in women with CIN1.
Shikany et al. (2004)	Clinical Trial	USA	folic acid fortification	77 Smoker women at high risk for cervical cancer	Subjects who were fortified with folic acid consumed more folate
Fuchs-Tarlovsky et al. (2012)	Clinical Trial	México	B carotene, vitamin C y vitamin E	Antioxidants 49 / Placebo 54	the antioxidant supplement, maintained hemoglobin levels, decreased oxidative stress, and improved quality of life
Álvarez-Altamirano et al. (2016)	Clinical trial	mexico	Antioxidant supplementation	Antioxidants 49 / Placebo 54	After 4 years of follow-up, antioxidant supplementation did not prevent cervical cancer recurrence.
Muecke et al. (2014)	Clinical Trial	Germany	Antioxidant supplementation	Antioxidants 39 / Placebo 42	In patients undergoing pelvic radiation therapy who are deficient in Se, Se supplementation is an effective adjuvant treatment.
Aredes et al. (2019)	Clinical Trial	Brazil	Fatty acids supplementation	Supplements 20 / Placebo 20	The 2.5 g ω3 capsules was effective in maintaining skeletal muscle quality, nutritional status, and reduced symptoms of chemoradiotherapy and chemotherapy toxicity occurrence compared to the control group.
Wuryanti et al. (2015)	Clinical Trial	Indonesia	Fatty acids supplementation	Supplements 16 / Placebo 15	In patients with advanced cervical cancer, PUFA-enriched diets can reduce inflammation. PGE2 levels that are reduced will lower cancer cell survival;
Vahedpoor et al. (2017)	Clinical Trial	Iran	Vitamin D supplementation	Supplements 29 / Placebo 29	Women with CIN1 who were given vitamin D3 for six months had their condition improve, while markers of insulin metabolism, plasma NO levels, TAC levels, and GSH levels also improved.
Vahedpoor et al. (2018)	Clinical Trial	Iran	Vitamin D supplementation	Supplements 29 / Placebo 29	Supplementing women with vitamin D3 for 6 months reduced the risk of recurrence of CIN1/2/3 and improved their metabolic status.
Yanazume et al. (2021)	Clinical Trial	Japan	Zinc supplementation	Supplements 40 / Placebo 40	It is likely that zinc supplementation will prevent the alteration in taste perception as it increases serum levels rapidly and without major complications.
Ayatollahi et al. (2022)	Clinical Trial	Iran	Zinc supplementation	Supplements 28 / Placebo 28	Zinc sulfate was found to improve HPV clearance and resolve predisposed cervical lesions in the following study.
Chitapanarux et al. (2019)	Clinical Trial	Thailand	Arginine, glutamine, and fish oil supplementation	Supplements 20 / Placebo 20	As a result of arginine, glutamine, and fish oil supplementation during CCRT, severe hematologic toxicities were significantly reduced.
Modarres Gilani et al. (2021)	Clinical Trial	Iran	Multivitamins, Minerals, and Q10	Supplements 60 / Placebo 60	The multi-mineral and Q10 supplements lead to a 30% improvement in Pap smear test results ($P < 0.001$) and may reduce the risk of cervical cancer in women with abnormal Pap smear
Sasidharan et al. (2019)	Clinical Trial	India	Resistant starch and digestible starch	Supplements 50 / Placebo 50	There was no significant advantage in administering resistant starch over a usual diet to patients undergoing pelvic radiotherapy
Linn YH et al. (2019)	Clinical Trial	Myanmar	Probiotics	Supplements 27 / Placebo 27	There was a significant reduction in the incidence of diarrhea, diarrhea severity, in women with cervical cancer

author's name, year of publication, study location, study duration, gender, mean age, study design, the health status of the study population, kind of dietary supplementation, and dose of dietary supplementation. The full texts of potentially eligible articles were reviewed to identify relevant studies for inclusion.

Results

We identified 1136 manuscripts with the initial systematic literature search. After duplicate removal and title and abstract screening, we revised the full text of 32 manuscripts. 12 studies were excluded due to study design. Finally, 19 papers were included in the final review (Fig. 1).

A summary of the studies conducted on the effect of nutritional supplements on cervical cancer is presented in Table 1. The main studies were on the effects of vitamin A, vitamin D, folate and B12, zinc, antioxidants, and omega-3 fatty acids on cervical cancer which are described below.

Vitamin A and β -carotene

The association between vitamin A and β -carotene supplemental use and cervical carcinoma was examined in two Randomized Double-Blind Clinical Trial (RCT) studies. Sanusi (2019) [26] conducted a double-Blind Clinical Trial study to compare the effects of treatment with neo adjuvant chemotherapy (NAC) and added vitamin A (NAC + vitamin A) in 30 patients (with 15 patients in each treatment arm) with advanced cervical carcinoma. The addition of vitamin A was associated with a better clinical response in advanced cervical carcinoma treatment, although it was not statistically significant. Keefe et al. (2001) examined the effect of daily β -carotene (30 mg) versus placebo over two years on 103 women with cervical intraepithelial neoplasia (CIN) 2 and 3 lesions and found that regression of CIN was negatively associated with retinol levels. In fact, there was a higher (though not significant) regression rate in the placebo group (38%) than in the β -carotene group (25%), especially in HPV-positive subjects in this trial. Consequently, β -carotene does not promote the regression of high-grade CIN, especially in HPV-positive patients [27]. Therefore, no proven beneficial role of vitamin A supplementation was reported in cervical carcinoma treatment so far and further studies are required in this regard.

Folic Acid and B12

A total of four studies investigated the association between folic acid supplement intake and cervical cancer risk, and one of them also examined the association of vitamin B12 with cervical cancer [12,11,13,14].

In the Asemi et al. (2016) [12] double-blind, placebo-controlled trial study, 58 women with CIN1, aged 18–55, were randomly assigned into two groups to receive either daily placebo (n = 29) or five mg/d folate supplements (n = 29) for six months. A more significant percentage of women in the folate group had significantly regressed CIN1 (83.3 versus 52.0%) than those in the placebo group (P = 0.019). Consequently, folate supplementation among women with CIN1 resulted in its regression, reduction of plasma MDA, serum insulin, and HOMA-B, and enhancement of plasma GSH levels. Sabihi et al. (2021) [11] performed a double-blind (RCT) study to evaluate the effects of daily folate (5 mg) supplementation versus placebo over 12 weeks on 60 overweight/obese women with CIN2/3 (n = 30 in each group). Folate supplementation did not significantly decrease the recurrence of CIN2/3 (P = 0.08) but had significant beneficial effects on metabolic factors (insulin sensitivity, inflammation, and oxidative stress markers). In the Nazli Yenigul et al. (2020) [14] cohort trial, 200 women aged 30–65 who had Papanicolaou (PAP) smear test were divided into atypical squamous cells of undetermined significance (ASCUS) group (n:100) and women who did not have intraepithelial neoplasia as a control group (n:100). In ASCUS women

with positive HPV, serum folate and vitamin B12 levels were significantly lower than HPV negative patients with or without ASCUS (P < 0.01). There was no statistically significant difference between folate levels in patients with different types of HPV (P > 0.05), and vitamin B12 levels were significantly lower in patients with other types of high-risk HPV than in patients with positive HPV (p = 0.01). HPV positivity in women with ASCUS is associated with low serum vitamin B12 and folate levels.

Antioxidants

The association between cervical cancer and antioxidant supplementation was examined in three studies [28–30]. In the Fuchs-Tarlovsky et al. (2012) single-blinded controlled trial study, six weeks of the antioxidant supplementation in 103 women with cervical cancer aged 29–73 maintained hemoglobin levels, decreased oxidative stress, and improved quality of life (p < 0.025) in the supplemented group compared to the placebo group [29]. In the Álvarez-Altamirano et al. (2016) RCT entitled antioxidant supplementation and cervical cancer recurrence, 88 treated patients in clinical stages IIB and IIIB of cervical cancer were randomized into the treatment (daily combination of β -carotene, selenium, yeast, zinc oxide, Ginkgo biloba extract, Panax ginseng extract, vitamin C and E) or placebo (Granulated sugar) groups. With four years of follow-up, antioxidant supplementation has no significant treatment effect on cervical cancer recurrence [28]. In the Muecke et al. (2014) study, 81 patients aged 31–80 were randomized to the case (Se supplementation) and the control group (without Se supplementation). After a median follow-up of 70 months, no significant association was found between Se supplementation and the effectiveness of the anticancer irradiation therapy. Also, no effects on patients' long-term survival were observed. Due to its positive effects on RT-induced diarrhea, Se supplementation was considered a meaningful and valuable adjuvant therapy in Se-deficient cervical and uterine cancer patients while undergoing pelvic radiation therapy [30].

Fatty acids

Two clinical trial studies examined the association between cervical cancer and fatty acids consumption [31,32]. Wuryanti et al. (2015) examined the supplementation with iso-protein, iso-caloric, and PUFA containing with a ratio of ω -6: ω -3 fatty acids = 1.27:1 versus supplementation without PUFA in patients with advanced cervical cancer. No significant difference was found on prostaglandin E2 (PGE2) level between the treatment and control groups at baseline (P = 0.127). However, PGE2 levels were reduced by 8.9% in the treatment group, while in the control group the PGE2 level increased by 28.1%. High-PUFA dietary supplementation may diminish inflammatory status in women with advanced cervical cancer and may ameliorate tumor response to radiation by reducing the survival of cancer cells [32]. Aredes et al. (2019) performed a randomized, triple-blinded, placebo-controlled clinical trial study on 40 females with cervical cancer and reported that 45-day use of 2.5 g ω -3 capsules was effective in maintaining skeletal muscle quality, nutritional status, and reduced symptoms of chemoradiotherapy and chemotherapy toxicity occurrence compared to the control group that received the same number of capsules with olive oil [31].

Vitamin D

The association between vitamin D supplementation and cervical cancer was reported in two double-blind RCTs [33,34]. In the Vahedpoor et al. (2017) study, 58 women aged 18–55 years with CIN1 were randomized to receive either 50,000 IU vitamin D3 supplements or placebo every two weeks for six months. Administration of vitamin D had a significant effect on CIN1 regression (84.6% vs. 53.8%, P = 0.01) and had beneficial effects on insulin metabolism, total antioxidant

capacity (TAC), total glutathione (GSH), plasma nitric oxide (NO), and malondialdehyde (MDA) levels [33]. In the study of Vahedpoor et al. (2018) on 58 women diagnosed with CIN2/3, supplementation with 50,000 IU vitamin D3 for six months did not affect CIN2/3 (recurrence (recurrence rate 18.5% vs. 48.1% vitamin D vs. placebo, $p = 0.15$); however, vitamin D3 had beneficial effects on CIN1/2/3 recurrence ($p = 0.02$) and metabolic status compared with the placebo [34].

Zinc

A total of two studies determined the association between zinc supplement intake and cervical cancer [35,36]. In a single-arm, prospective interventional study by Yanazume et al. (2021) with 28 gynecological malignancies, females with zinc deficiency consumed 167.8 mg/day of oral zinc acetate hydrate for three weeks before chemotherapy. Taking zinc supplements promptly increased serum zinc levels regardless of chemotherapy but did not alter taste perception for zinc deficiency during chemotherapy [36]. In Ayatollahi et al. (2022) study, 80 zinc-sufficient women with positive HPV, and abnormal cervical cytology, aged 21–55 years, were randomized to receive oral zinc sulfate tablets (220 mg, every 12 hrs) for three months ($N = 40$) or control group received no treatment. After three months of follow-up, the risk of HPV infection persistence (CI 95% 0.04–0.381; $p < 0.001$) and progression from baseline cytology (95% CI 0.777–0.116; $p = 0.012$) was significantly reduced, and pre-existing cervical lesion and HPV clearance rates increased [35].

Other dietary components

Probiotic

One randomized, double-blind, placebo-controlled study reported the association between probiotics and cervical cancer, including 54 patients with cervical cancer who were randomly divided to intake probiotics (receiving capsules containing 1.75 billion lyophilized live bacteria three times daily) or placebo (received capsules containing starch). There was a significant reduction in the incidence of diarrhea ($P < 0.05$), diarrhea severity ($P < 0.01$), Loperamide consumption ($P < 0.01$), and episodes of abdominal pain per day ($P < 0.001$) was observed in the treatment group compared to the placebo group [37].

Arginine, glutamine, and fish oil

One study by Chitapanarux et al. (2019) included 20 cervical cancer patients who were randomized into a regular diet and a regular diet plus 250 mL twice a day of arginine, glutamine, and fish oil supplements during their concurrent chemoradiotherapy (CCRT) course. The occurrence of high-grade toxicities and hematologic toxicities was significantly lower in patients who received glutamine, arginine, and fish oil supplements ($P = 0.03$). The CCRT completion rate and two-year overall survival were lower in the supplemented group, but the results were not significant [38].

Resistant starch and digestible starch

In a double-blind RCT performed by Sasidharan et al. (2019), 100 women with cervical cancer were randomized to receive either daily 30 gm of resistant starch ($N = 50$) or digestible starch ($N = 50$) during the course of radiotherapy. After six weeks of intervention follow-up, both groups reported similar toxicity and occurrence of grade 2 and higher diarrhea. Therefore, there was no significant advantage in administering resistant starch over a usual diet to patients undergoing pelvic radiotherapy [39].

Multivitamins, minerals, and Q10

In the RCT of Modarres Gilani et al. (2021) entitled "Multivitamins, Minerals, and Q10 supplementation on precancerous Lesions of the Cervix", 120 participants with abnormal Pap smear test results, aged 20–40 years or older were randomized into the treatment (multi-mineral

and Q10 supplements at a dose of 30 mg daily) or placebo arms for three months. It was found that short-term use of multi-mineral and Q10 supplements lead to a 30% improvement in Pap smear test results ($P < 0.001$) and may reduce the risk of cervical cancer in women with abnormal Pap smear [40].

Totally, this is the first comprehensive study on the effects of dietary supplements on cervical cancer. The results indicated that some dietary supplements including folate, vitamin D, zinc, probiotics, and omega-3 fatty acids may have beneficial effects in patients with cervical cancer. However, this study has some limitations. First, most findings are derived from epidemiological or retrospective studies, and only a few randomized controlled trials are available in the literature. In retrospective studies, possible biases may be due to selective recall or changes in metabolism and food habits after disease diagnosis. In addition, regarding dietary intake, a non-negligible part of data derived from food frequency questionnaires was exposed to methodological biases and difficulties in accurately obtaining data on patients' dietary intake. Furthermore, the estimation of micronutrient amounts from food consumption does not consider food preparation, food processing, and the freshness of the food products. Moreover, using different doses of dietary supplements in different studies may influence the obtained results. Finally, the assessment methods in different studies were variable and also the measurement of serum levels of nutrients was rarely done which makes it difficult to integrate the results and draw definitive conclusions.

Conclusion

This study pooled results from 20 studies that evaluated the effect of different dietary supplements on cervical cancer. The results showed that some dietary supplements including folate, vitamin D, zinc, probiotics, and omega-3 fatty acids may have beneficial effects in patients with cervical cancer. There is a variety of populations, study designs, and assessment methods in the included studies. Further clinical studies are needed to confirm these findings and to discover the underlying mechanisms of the effects of dietary supplements on cervical cancer.

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CRediT authorship contribution statement

NHA, MGH, ZAN, ZS, NM, MM, FB, MA, SHT, AA, SKH, SM, NK and SD designed the study, involved in the data collection, analysis, and drafting of the manuscript. All authors read and approved the final manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

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