Effectiveness of zinc supplementation on the incidence of oral mucositis during chemotherapy and radiation: A meta-analysis

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Abstract. Oral mucositis (OM) is a commonly observed and debilitating side effect of chemotherapy and radiation therapy in patients with cancer, especially head and neck cancer. Although there is no proven therapy for the prevention and treatment of OM, zinc supplementation effectively decreases the incidence of OM. This paper provides a current and comprehensive meta-analysis of the efficacy of zinc compared with placebo/control in OM. A systematic literature review was conducted using MEDLINE and Central databases for randomized control trials (RCTs) comparing zinc supplementation (oral or rinse) with placebo/control in patients with various types of cancer undergoing chemotherapy, radiation therapy or combined chemo-radiation. The outcome was OM incidence, independent of the severity. A random-effects model was used to calculate the pooled risk ratio and subgroup analyses were performed. A total of 12 RCTs were included, containing information from 783 patients. A decrease in OM incidence was observed overall when all cancer therapies were considered. However, subgroup analyses showed that zinc did not significantly decrease the incidence of OM when studies were stratified by cancer therapy or scale/criteria used to assess OM. The results of the meta-analysis support the use of zinc supplementation in decreasing OM incidence in patients with cancer receiving chemotherapy or radiation therapy. However, the high heterogeneity between studies and the small number of studies are limitations of the meta-analysis.

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Introduction

Globally, head and neck cancer accounts for ~900,000 cancer cases and >40,000 deaths annually (1). In the United States, head and neck cancer accounts for ~4% of all cancers and incidence varies depending on sex and ethnicity (2,3). Risk factors include alcohol and tobacco consumption and viral infections (4). Other than surgical treatment, chemotherapy and radiation therapy remain the mainstay treatment for patients diagnosed with head and neck cancer and can be used independently or in conjunction with surgery (5). Although chemotherapy and radiation therapy can be used for treatment of cancer, these are associated with side effects such as nausea, vomiting, hair loss, loss of appetite and oral mucositis (OM) (6,7). Cytotoxic effects of anticancer therapy cause inflammatory changes in the oral mucosal epithelial cells leading to painful, multiple lesions in the oral cavity (8,9). A total of 30-40% of patients with cancer treated with chemotherapy develop mucositis; this incidence increases to 90% for patients with head and neck cancer treated with radiotherapy + chemotherapy (10,11). Mucositis occurs during chemotherapy and lasts for a few weeks following the completion of the treatment (12,13). Physical discomfort during eating and drinking impairs nutritional status of patients, affecting their physical and psychological state, as well as their quality of life (14). OM is associated with bacteraemia, increased inpatient hospital duration and mortality (15,16). Keratinocyte growth factor was shown to be effective in decreasing the duration of radiation-induced OM (RIOM), prolonging the time to develop RIOM and decreasing the incidence of RIOM in patients with head and neck cancer (17).

The Multinational Association of Supportive Care in Cancer and the International Society for Oral Oncology (MASCC/ISOO) performed a systematic review to identify interventions found to be most effective for the prevention, treatment and alleviation of OM symptoms (18). Basic oral care, use of anti-inflammatory agents (such as benzydamine mouthwash), intraoral photobiomodulation using low-level laser therapy, anaesthetics, analgesics, vitamins, minerals and nutritional supplements (such as glutamine, zinc, supersaturated calcium phosphate rinse, vitamin E, selenium, folinic

acid and calcitriol) are recommended for mucositis (17). Several studies have showed the benefit of oral zinc supplementation in the prevention of OM in patients with cancer receiving chemotherapy and radiation (14,17,19,20).

Zinc is naturally present in saliva, dental plaque and hard tissues. Supplementation with zinc is effective against oral conditions, for example, gingivitis, periodontitis, halitosis and others. Zinc deficiency is associated with poor oral and periodontal health (21-23). Zinc is involved in numerous processes associated with immunity, growth and development, and it is implicated in wound healing and has anti-inflammatory properties (23,24). Zinc is administered orally or parenterally as zinc sulphate (22.5 mg elemental zinc/100 mg), zinc acetate (30 mg elemental zinc/100 mg), or zinc oxide (80 mg elemental zinc/100 mg) for therapeutic purposes (25). A meta-analysis of five studies by Tian *et al* (26) showed that oral zinc sulphate failed to decrease the incidence of chemotherapy-induced OM or relieve the chemotherapy-induced OM grade. In addition, zinc sulphate did not show a beneficial effect in decreasing the incidence and grade of RIOM in a meta-analysis of four randomized controlled trials by Shuai *et al* (27). Chaitanya *et al* (28) conducted a meta-analysis with 10 studies to assess the effect of oral zinc on OM incidence and severity in patients undergoing chemotherapy, radiation therapy or combined chemo-radiation therapy (28); zinc did not decrease the prevent OM but decreased its severity.

The present study assessed evidence from available randomized controlled trials (RCTs) and prospective studies evaluating the effectiveness of zinc supplementation vs. placebo or control treatments on the incidence of OM in patients undergoing chemotherapy, radiation therapy or a combined approach.

Materials and methods

Search strategy. MEDLINE (PubMed; pubmed.ncbi.nlm.nih.gov and Cochrane Register of Controlled Trials (CENTRAL) databases (https://www.cochranelibrary.com/central/about-central) were searched in December 2021. Various search terms and associated Medical Subject Heading terms such as 'oral mucositis', 'chemotherapy', 'radiation', 'zinc', 'oral mucositis chemotherapy' and 'radiation-induced oral mucositis', were used and full-text versions of the articles were retrieved after screening the titles and abstracts. Additional studies were identified by cross-checking the reference lists of the relevant studies.

Study selection and inclusion/exclusion criteria. RCTs and prospective randomized studies that compared the use of zinc in any form (orally or as a rinse) with placebo or control in patients during cancer therapy were included in the present meta-analysis. All studies reporting OM incidence irrespective of the criteria or scale used to define mucositis were included.

Non-randomized, retrospective and cohort studies were excluded from the present meta-analysis.

Data extraction and quality assessment. Relevant data from studies such as first author(s), publication year, type of therapy, OM criteria/grading scale, type of carcinoma, intervention and control were abstracted onto data extraction forms.

The methodological quality of the included studies was assessed using the Cochrane Collaboration's risk of bias tool (methods.cochrane.org/bias/resources/rob-2-revised-cochrane-risk-bias-tool-randomized-trials) using the following criteria: Randomization; allocation concealment; blinding and completeness of follow-up (17). The risk of bias for each item was graded as high, low or unclear risk.

Quantitative data synthesis. Meta-analysis was performed using Review Manager 5 (training.cochrane.org/online-learning/core-software/revman). The risk ratios (RRs) and 95% CIs were used to construct forest plots. Meta-analysis was performed using a random-effects model (Mantel-Haenszel method) and heterogeneity was evaluated using I^2 statistic, with low heterogeneity for I^2 values of <25%, moderate heterogeneity for I^2 values of 25-50% and high heterogeneity for I^2 values >50% (18). Forest plots were constructed and $P<0.05$ was considered to indicate a statistically significant difference. Subgroup analysis was performed according to the type of cancer therapy and grading criteria for oral mucositis.

A funnel plot was used to assess publication bias in which the log(RR) for each study was plotted against its standard error.

Results

Identification of studies. A total of 151 records were identified by database searching, of which 53 were screened by title and abstract. Of the records, 44 RCTs were assessed for eligibility. However, 32 RCTs were excluded due to inappropriate comparator groups, irrelevant outcomes and inappropriate trial design. The preferred reporting items for systematic and meta-analysis diagrams for the process of selection are shown in Fig. 1.

Study characteristics. In total, 12 RCTs (13,18-20,29-36) totalling 783 participants met the inclusion criteria (397 and 386 participants for zinc intervention and control groups, respectively). These RCTs involved a comparison of zinc vs. control or placebo in patients with cancer undergoing chemotherapy or radiation. The studies included male and female participants undergoing chemotherapy or radiation therapy with various types of cancer with sample sizes ranging from 30-140 participants (Table I). Most studies involved oral zinc capsules in the intervention group and placebo capsules in the control group except for one study that involved the use of zinc chloride mouthwash (34) and one with oral polaprezinc rinse (36). OM was defined using different scales, with radiation therapy oncology group (RTOG) acute radiation morbidity scoring criteria and the World Health Organization (WHO) (18-20,31,34) toxicity scale being the most commonly used (Table II).

OM incidence. The incidence of OM is shown in Table III. The OM incidence rates were 0.00-86.7% in the zinc intervention group and 4-100% in the control group. The overall incidence of (OM) was 30.5% in the zinc intervention group and 51.3% in the control group.

The results of the risk of bias evaluation are shown in Fig. 2. Overall, there was a moderate to high risk of bias due

Table I. Characteristics of the studies included in the present meta-analysis.

First author/s, year	Treatment	Treatment regimen and duration	Type of cancer	No. of patients	(Refs.)
Anandhi *et al*, 2020	Chemotherapy and radiation	Chemotherapy, weekly cisplatin (40 mg/m^3) Radiation, cumulative radiation dose 69.5 Gy over 28 days	Oropharyngeal and hypopharyngeal	120	(29)
Arbabikalati *et al*, 2012	Chemotherapy	Cyclophosphamide, doxorubicin, dacarbazine, gemcitabine, methotrexate, 5-fluorouracil over 20 weeks	Nasopharyngeal carcinoma	50	(19)
Ertekin *et al*, 2004	Radiation	Median radiation dose, 6,400 cGy (4-7 weeks)	Head and neck	30	(13)
Gholizadeh *et al*, 2017	Chemotherapy	Chemotherapy for acute myeloid leukaemia (4 weeks)	Acute myeloid leukaemia	140	(20)
Gorgu *et al*, 2013	Radiation	Median radiation dose, 6440 cGy	Head and neck	40	(30)
Mansouri *et al*, 2012	Chemotherapy	High-dose chemotherapy conditioning regimen	Hematological malignancy	60	(31)
Mosalaei *et al*, 2010	Radiation	Total radiation dose, 6,000 cGy	Head and neck	58	(32)
Moslemi *et al*, 2014	Radiation	Total radiation dose, 6,000-7,000 cGy (30-35 treatment sessions)	Head and neck	40	(33)
Oshvandi *et al*, 2021	Chemotherapy	Daunorubicin and cytarabine	Stage 1 or 2 liver, stomach, colon, uterus, breast, kidney, bladder and lung	70	(34)
Rambod *et al*, 2018	Chemotherapy	Not specified	Leukaemia	72	(18)
Sangthawan *et al*, 2013	Radiation	Total radiation dose, 50-70 Gy (5-7 weeks)	Head and neck	140	(35)
Watanabe *et al*, 2010	Chemotherapy and radiation	Total radiation dose, 50-60 Gy (37-45 days)	Head and neck	31	(36)

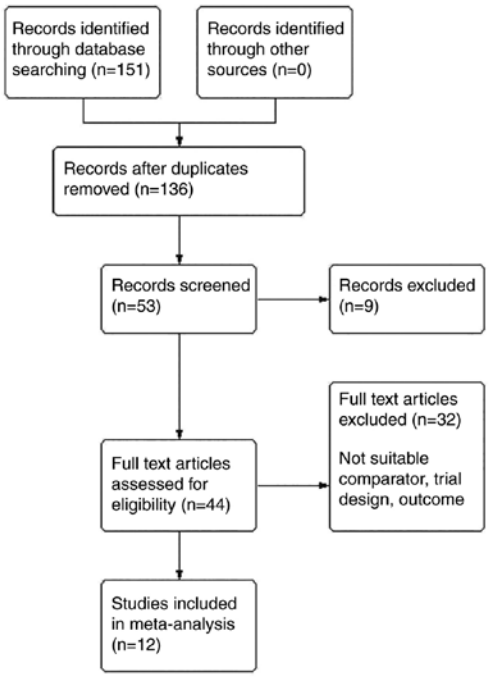

Figure 1. Flow chart for identification and inclusion of studies in the present meta-analysis according to preferred reporting items for systematic and meta-analyses (PRISMA).

to unclear or high risk related to randomization, blinding, and selective reporting domains. Possibility of publication bias was observed in the asymmetry of the funnel plot Fig. 3.

Meta-analysis results. The results of the meta-analysis for all the included studies stratified by type of cancer treatment showed there was no significant difference between the zinc intervention and control groups (RR 0.91; 95% CI, 0.65-1.29; P=0.60; I^2=54% for radiation therapy; RR 0.49; 95% CI, 0.19-1.26; P=0.14; I^2=84% for chemotherapy; RR 0.50; 95% CI, 0.14-1.76; P=0.28; I^2=97% for chemotherapy and radiation; Fig. 4). In addition, there was no significant difference between the subgroups, indicating that zinc supplementation was not beneficial in patients receiving any type of cancer treatment (P=0.35). Moderate to high heterogeneity in the subgroups could be attributed to different patient characteristics, methods of assessing OM and type of cancer. However, when the results for OM incidence for all types of cancer therapies were grouped, a beneficial effect of zinc vs. control groups was observed (RR 0.67; 95%, 0.47-0.95; P=0.03; I^2=84%; Fig. 4).

Stratification of the results by criteria used to assess OM showed no significant decrease in favour of the zinc intervention group when the RTOG and WHO scales were used (RR 0.77; 95% CI, 0.36-1.64; P=0.49; I^2=93% for the RTOG scale;

Table II. Interventions included in studies in meta-analysis.

First author/s, year	Intervention	Control	Scoring criteria	(Refs.)
Anandhi *et al*, 2020	Oral zinc sulfate (150 mg), twice daily	Placebo, twice/day	RTOG	(29)
Arbabi-kalati *et al*, 2012	Oral zinc sulfate capsule (220 mg), three times/day	Placebo capsule, three times/day	WHO	(19)
Ertekin *et al*, 2004	Oral zinc sulfate capsule (50 mg), three times/day	Placebo capsule, three times/day	RTOG	(13)
Gholizadeh *et al*, 2017	Oral zinc sulfate capsule (220 mg), three times/day	Placebo capsule, three times/day	WHO	(20)
Gorgu *et al*, 2013	Oral zinc tablet (25 mg), four times/day	No treatment	RTOG	(30)
Mansouri *et al*, 2012	Oral zinc sulfate capsule (220 mg), twice daily	Placebo capsule, twice daily	WHO	(31)
Mosalaei *et al*, 2010	Oral zinc sulfate capsule (220 mg), three times/day	Placebo capsule, three times/day	RTOG	(32)
Moslemi *et al*, 2014	Oral zinc sulfate capsule (30 mg), three times/day	Placebo capsule	Oral mucositis assessment scale	(33)
Oshvandi *et al*, 2021	Zinc chloride mouthwash, three times/day	Placebo mouthwash	WHO	(34)
Rambod *et al*, 2018	Zinc sulfate capsule (50 mg), three times/day	Placebo capsule, three times/day	WHO	(18)
Sangthawan *et al*, 2013	Zinc sulfate capsule, three times/day	Placebo capsule, three times/day	Not specified	(35)
Watanabe *et al*, 2010	Oral polaprezinc rinse, four times a day	Azulene rinse, four times/day	Common terminology criteria for adverse events	(36)

RTOG, radiation therapy oncology group acute radiation morbidity scoring criteria; WHO, World Health Organization.

Table III. Oral mucositis incidence in studies included in the meta-analysis (n=12).

	Oral mucositis, %		
First author/s, year	Intervention	Control	(Refs.)
Anandhi *et al*, 2020	30.00	100.00	(29)
Arbabi-kalati *et al*, 2012	0.00	4.00	(19)
Ertekin *et al*, 2004	86.67	100.00	(13)
Gholizadeh *et al*, 2017	7.14	28.57	(20)
Gorgu *et al*, 2013	81.25	50.00	(30)
Mansouri *et al*, 2012	83.33	76.67	(31)
Mosalaei *et al*, 2010	31.03	37.93	(32)
Moslemi *et al*, 2014	40.00	70.59	(33)
Oshvandi *et al*, 2021	4.44	12.00	(34)
Rambod *et al*, 2018	25.00	52.78	(18)
Sangthawan *et al*, 2013	17.14	23.26	(35)
Watanabe *et al*, 2010	81.25	100.00	(36)

RR 0.49; 95% CI, 0.19-1.26; P=0.14; I^2=84% for WHO scale; Fig. 5). High heterogeneity could be attributed to different follow-up times used to assess OM and differences in patient characteristics between studies.

The results were also sub-grouped by the type of cancer for which zinc supplementation was given. There was no significant difference in the incidence of OM between the zinc and control group in patients with head and neck cancer (RR 0.89; 95% CI, 0.70-1.13; P=0.35; I^2=45%). However, zinc supplementation significantly decreased the incidence of OM in patients with leukaemia (RR 0.37; 95% CI, 0.20-0.70; P=0.002; I^2=23%) and pharyngeal cancer (RR 0.31; 95% CI, 0.21-0.45; P<0.00001; I^2=0%). The test for subgroup effects was significant indicating that the effect of zinc on OM was affected by the type of cancer (P<0.00001).

Discussion

OM is a serious and common side effect of chemotherapy and radiation therapy and it is reported to affect ~40% of patients receiving chemotherapy and 100% of patients treated with radiation therapy (37,38). Pain, physical and psychological distress, reduced nutritional intake and decreased quality of life are negative outcomes associated with OM along with increased hospital stay and medical expenditure (33). Despite the high occurrence of OM in patients with cancer, specifically

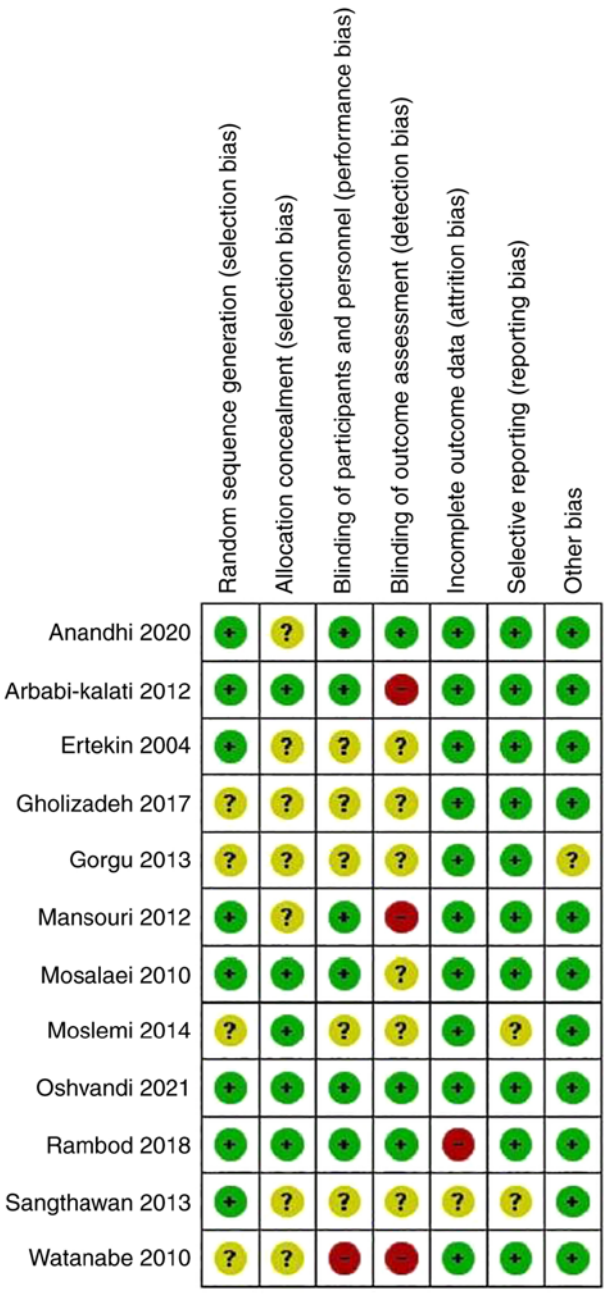

Figure 2. Risk of bias summary for trials included in the present meta-analysis (n=12). Red means a high risk of bias, yellow means an unclear risk of bias, and green means a low risk of bias.

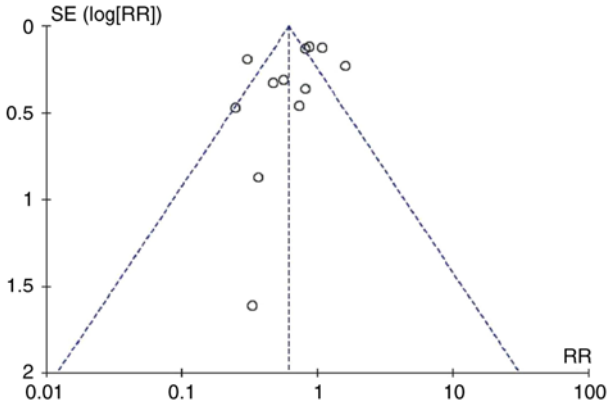

Figure 3. Funnel plot to assess publication bias in the present meta-analysis with oral mucositis incidence outcome. RR, risk ratio.

those with head and neck cancer, there is no specific treatment available for the prevention and treatment of OM. Antioxidant agents (amifostine, glutamine, oral zinc supplements, vitamin E and N-acetyl-cysteine), inhibitors of inflammation and cytokine production (turmeric, clonidine tablets, benzydamine oral rinses and pentoxifylline), natural agents (honey, manuka oils, aloe vera gel, chamomile mouthwash, and Chinese traditional herbs), probiotics and physical interventions (low-level laser therapy, oral cryotherapy and Oral hygiene care) are some therapies that are under investigation for mucositis prevention (11).

The present study aimed to provide an up-to-date meta-analysis of the effect of oral zinc supplementation on the incidence of OM in patients undergoing chemotherapy, radiation therapy and combined chemoradiation therapy. The current results indicated that oral zinc administration caused a significant decrease in incidence of OM in patients receiving cancer therapy. However, when stratified by the type of cancer therapy (chemotherapy, radiation or a combinatorial approach), zinc supplementation did not cause a significant decrease in OM incidence. The present results were in agreement with the results of Tian *et al* (26), which was conducted on patients undergoing chemotherapy only, and meta-analysis by Shuai *et al* (27) on patients receiving chemotherapy. Favourable effects of zinc when all studies were pooled could be attributed specifically to the studies by Gholizadeh *et al* (20) and Anandhi *et al* (29) that enrolled a higher number of patients. The high heterogeneity of the overall meta-analysis and subgroups can be attributed to differences in methodology, such as dose of chemotherapy and radiation, patient baseline characteristics, such as sex and age, zinc dose, type and severity of cancer and follow-up times. The type of anticancer agent, doses and number of cycles and treatment timing are known to influence mucositis incidence and severity (11). A total of four studies in the current meta-analysis (18,20,29,36) showed a significant decrease in OM incidence following zinc supplementation compared with the placebo or control group. These studies were performed on patients receiving chemotherapy or combined chemoradiotherapy across different types of cancer including head and neck cancer and leukaemia. Results in favour of zinc in studies by Gholizadeh *et al* (20) and Rambod *et al* (18) can also be attributed to normal dose chemotherapy in these studies whereas in the study by Mansouri *et al* (31) a high-dose chemotherapy regimen was used, which may have led to the lack of effect of zinc supplementation. Results in favour of the control group were also observed in the study by Gorgu *et al* (30), which could be associated with lower zinc dosage (25 mg four times/day) compared with other studies in which the dose of zinc was 15-220 mg two or three times per day. Watanabe *et al* (36) used polaprezinc (zinc-L-carnosine) in the treatment group, which has been shown to improve 5-fluorouracil-induced OM and mucosal ulceration in animal models (39,40). It is important to note that only two studies with patients with

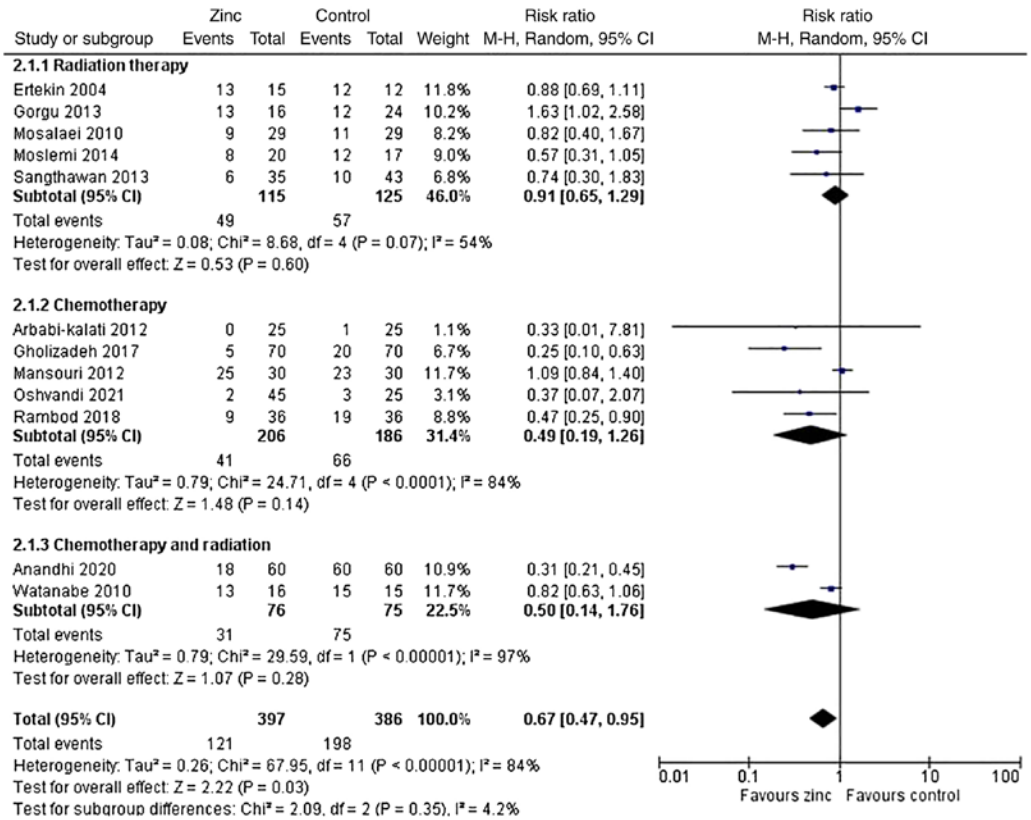

Figure 4. Forest plot of trials included in the present meta-analysis (n=12) using a random effects model with oral mucositis outcome stratified by type of cancer therapy. df, degrees of freedom.

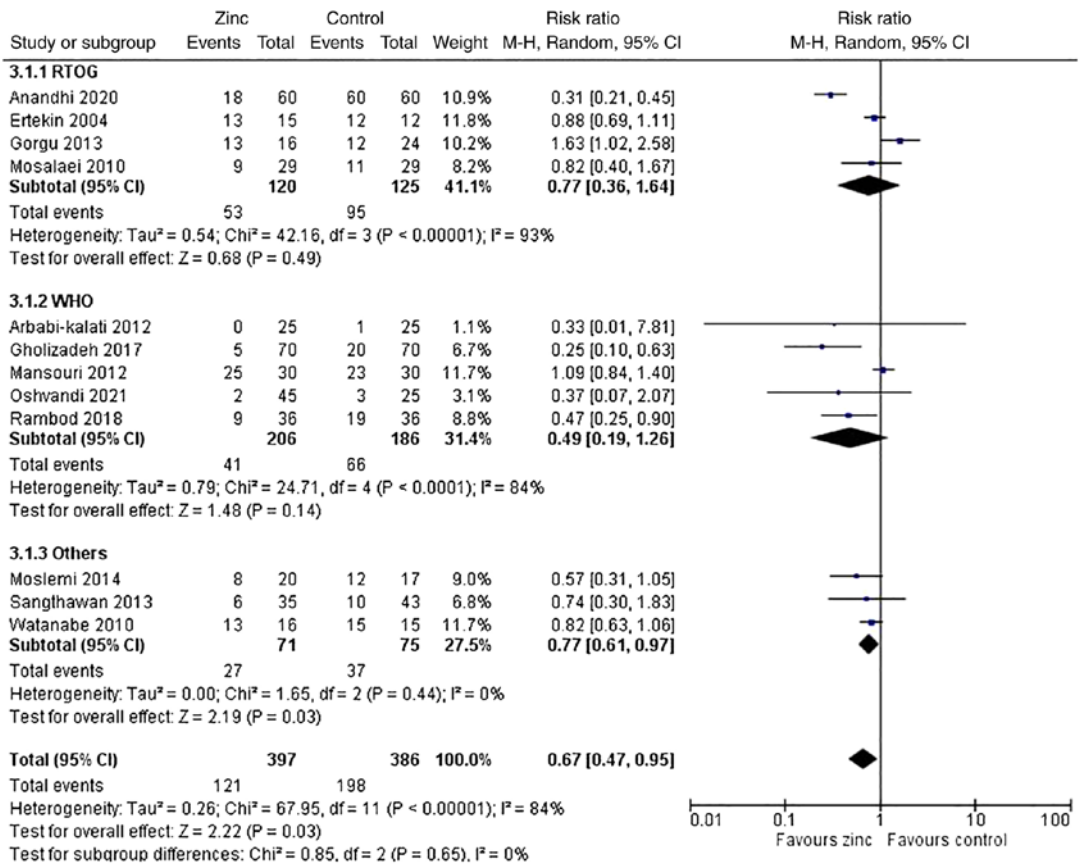

Figure 5. Forest plot of trials included in the present meta-analysis (n=12) using a random effects model with oral mucositis outcome stratified by scale or criteria used for oral mucositis incidence. df, degrees of freedom; RTOG, radiation therapy oncology group acute radiation morbidity scoring criteria; WHO, World Health Organization.

leukaemia and pharyngeal cancer were included in the present meta-analysis. The present study showed a significant benefit of zinc supplementation in decreasing incidence of OM compared with an active comparator, azulene oral rinse, which could be attributed to both the form of zinc used and the mode of administration (oral rinse as compared with the majority of other studies in which capsules of zinc salts were given). No definite conclusions on the effectiveness of zinc supplementation on OM incidence could be drawn from the studies that showed the positive effects of zinc. The dose of zinc was 30-220 mg three times daily and the radiation dose was 60-70 Gy with various chemotherapeutic agents and lengths of treatment ranging from 2 to 9 weeks. This makes it difficult to determine the dose or regimen of zinc supplementation that should be used concurrently with radiation treatment or chemotherapy, indicating that the response of patients to the beneficial effects of zinc varies based on the type of cancer, its location and antineoplastic agents used, and does not depend only upon the zinc form, dosage or duration of treatment.

Criteria/scale to assess OM differed between the studies, with the RTOG and WHO scale being the most widely used. Meta-analysis showed that the type of scale used did not have any effect on results obtained in favour of zinc. The high heterogeneity in each subgroup was attributed to methodological differences between the studies. However, there is no standard scale to assess the incidence or grade of the severity of OM. The commonly used WHO scale is based on objective assessment, such as the presence of erythema or ulceration and the OM assessment scale is based on quantitative assessment of ulceration dimension (11). The absence of a standardized scale makes it difficult to compare the severity of OM. Although OM incidence is judged by trained individuals, assessment may differ between the studies and therefore results should be interpreted with caution. The absence of a high number of trials in patients with cancer other than head and neck cancer limits the ability to understand the effects of zinc supplementation on different types and stages of cancer.

Limitations of the present meta-analysis are associated with the low number of eligible studies and small patient population size, making it difficult to assess the effect of zinc dose, chemotherapy and radiation dose and duration of treatment on OM outcome. Furthermore, the lack of details provided on the chemotherapeutic regimens or radiation doses and duration of treatments in the majority of the included trials makes it difficult to draw a definitive conclusion regarding circumstances in which zinc supplementation would be beneficial.

Further studies with larger sample sizes are needed to confirm the effectiveness of zinc supplementation in decreasing the incidence of OM. The studies published and included in the present meta-analysis are too heterogeneous to make any definite conclusion on the effectiveness of oral zinc. Additionally, since the effects of zinc supplantation were highly variable between the studies, it is important to investigate other therapies that may consistently alleviate the suffering of patients with cancer undergoing chemotherapy.

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Availability of data and materials

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

XL and WZ conceived and designed the study. YC and SR analysed data and drafted the manuscript. RC and WZ collected the data and contributed to the data analysis. SR and RC confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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