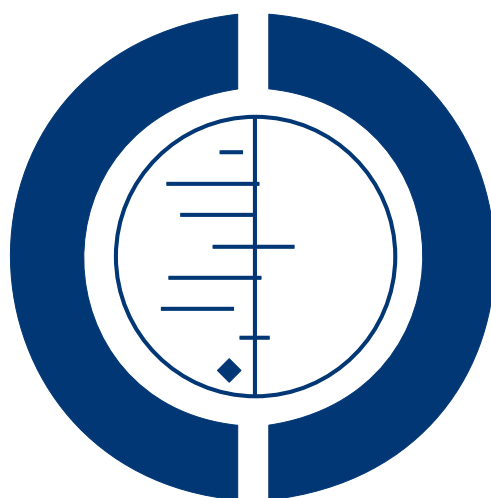


Selenium for alleviating the side effects of chemotherapy, radiotherapy and surgery in cancer patients (Review)

Dennert G, Horneber M



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[Intervention Review]

Selenium for alleviating the side effects of chemotherapy, radiotherapy and surgery in cancer patients

Gabriele Dennert¹, Markus Horneber²

¹Medizinische Klinik 5, Klinikum Nord, Nuernberg, Germany. ²Medizinische Klinik 5 - Schwerpunkt Onkologie/Haematologie, Klinikum Nord, Nuernberg, Germany

Contact address: Gabriele Dennert, Medizinische Klinik 5, Klinikum Nord, Prof.-Ernst-Nathan-Str. 1, Nuernberg, D-90419, Germany. Gabriele.Dennert@klinikum-nuernberg.de. (Editorial group: Cochrane Pain, Palliative and Supportive Care Group.)

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ABSTRACT

Background

This is an updated version of the original Cochrane review published in Issue 3, 2006. Selenium supplements are frequently used by cancer patients. Selenium is an essential trace element and is involved in antioxidant protection and the redox-regulation in humans. Several adverse effects of radiotherapy and chemotherapy in cancer patients as well as cellular processes that maintain chronic lymphoedema have been linked to oxidative cell processes in the human body. Selenium has been claimed to alleviate side effects of conventional cancer therapy and recently been investigated as a remedy against chemotherapy and radiotherapy-associated side effects and secondary lymphoedema.

Objectives

This review assessed the effects of supplementary selenium on adverse effects of conventional radiotherapy, chemotherapy, or surgery in oncology patients and on quality of life/performance status during and after oncological treatment.

Search strategy

The Cochrane Pain, Palliative & Supportive Care Trials Register, the Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects (DARE), CENTRAL, MEDLINE, EMBASE, SIGLE, Cancerlit, CCMed, the German online register for cancer trials, the ISRCTN, the mRCT, the NCI Clinical Trials register databases were searched and most updated in July 2007.

Selection criteria

Randomised controlled trials (RCTs) of selenium mono-supplements in cancer patients undergoing tumour specific therapy, such as chemotherapy, radiotherapy or surgery.

Data collection and analysis

Two review authors independently checked trials for eligibility, extracted data and assessed trial quality.

Main results

One new included study as well as further participants to a study already included was added to this update involving a further 39 participants. There were a total of three studies included involving 162 participants for this update.

For this review two RCTs were included investigating secondary lymphoedema in 60 women after breast cancer surgery and 20 men and women after head and neck cancer surgery. One ongoing trial with preliminary results of 82 participants was also identified studying radiotherapy induced diarrhoea as a secondary outcome. All studies had considerable drawbacks with regards to quality and reporting.

One study on secondary lymphoedema reported a decreased number of recurrent erysipela infections in the selenium supplementation group compared to placebo. The second study reported a decreased facial swelling in the selenium group in a two-week period following surgical tumour resection. However, results must be interpreted with caution and cannot be generalised to other populations.

The ongoing trial on radiotherapy associated diarrhoea preliminarily reported a lower incidence of diarrhoea in participants receiving selenium supplementation concomitant to pelvic radiation, however, no data were presented. We must await publication of final results to discuss these findings in detail.

No RCTs were found studying the effect of selenium supplementation on other therapy-associated toxicities or quality of life/performance status in cancer patients.

Authors' conclusions

There is insufficient evidence at present that selenium supplementation alleviates the side effects of tumour specific chemotherapy or radiotherapy treatments or that it improves the after-effects of surgery, or improves quality-of-life in cancer patients or reduces secondary lymphoedema. To date, research findings do not provide a basis for any recommendation in favour or against selenium supplementation in cancer patients. Potential hazards of supplementing a trace mineral should be kept in mind. Since the last version of this review, the one new additional study has not provided information to change the conclusions of the original review.

PLAIN LANGUAGE SUMMARY

Selenium supplements for alleviating the side effects of chemotherapy, radiotherapy and surgery in cancer patients

There is no evidence that selenium supplements reduce side effects of chemotherapy, radiotherapy or the effects of surgery in cancer patients. Selenium is a mineral necessary for human health. Selenium acts against cell damage in the body and might help to alleviate the side effects of therapies in cancer patients, such as nausea, diarrhoea or the lymph retention in limbs. Selenium supplements are frequently used by cancer patients. This systematic review looked at studies providing selenium supplements to cancer patients and found no clear evidence that selenium supplements improve side effects of cancer therapy. No adverse effects were reported in the studies, but evidence of overdosing, all be it unintentional and selenium intoxication has occurred in several selenium users. More research is needed to find out which doses of selenium supplements can be reasonably used by cancer patients and whether selenium supplements can affect the side effects of cancer therapy.

BACKGROUND

This review is an update of a previously published review in The Cochrane Database of Systematic Reviews (Issue 3, 2006) on 'Selenium for alleviating the side effects of chemotherapy, radiotherapy and surgery in cancer patients'.

Selenium is an essential trace element for humans. It is involved in antioxidant protection and redox regulation as a component of seleno-proteins and as a source of seleno-metabolites (Hatfield 2001). Adverse effects of radiotherapy and chemotherapy in cancer patients have been linked to the formation of free radicals and the related oxidative damage to normal cells (Weijl 1997). Lately, intervention strategies have been investigated to use biological response modifiers, such as selenium compounds, as toxicity antago-

nists for prevention of chemotherapy and radiotherapy associated side effects.

Acute mucositis is a severe condition seen frequently in patients undergoing radiotherapy. A recent review found that about 80% of ENT radiotherapy patients developed mucositis, about half of them experienced a severe form (grade three to four) which lead to treatment interruption or alteration in one in nine patients (Trotti 2003). Patients undergoing pelvic radiation for e.g. gynecological malignancies are at risk for developing acute intestinal mucositis, enteritis, and diarrhoea. Atrophy of the salivary glands and xerostomia are long-term sequelae of a radiogenic sialadenitis after ENT radiotherapy, which can only be controlled insufficiently by symptomatic interventions, such as saliva substitutes or stimulants

(Groetz 2003).

Both in acute and long-term side effects of radiotherapy, selenium has been discussed as a preventive agent. In vitro experiments found a cytoprotective effect of sodium selenite on human fibroblasts and endothelial cells without reducing radiotherapy activity against cancer cells (Rodemann 1999; Schleicher 1999). Sagowski 2004 showed that administration of parenteral sodium selenite reduced radiogenic damage to parotid glands in rats, which was confirmed by better gland function after irradiation.

A number of chemotherapy toxicities and adverse effects have been linked to the formation of free radicals by cytostatics (Weijl 1997). A protective effect of selenium against doxorubicin induced cell damage was seen in rat cardiomyocytes in vitro (Kotamraju 2000). Animal studies suggested that sodium selenite may decrease cisplatin induced nephrotoxicity (Baldev 1989; Francescato 2001; Yoshida 2000) and myelotoxicity (Ohkawa 1988) in rats and mice. Cardiac sensitivity to ischemia after adriamycin treatment was reduced by sodium selenite supplementation in rats (Boucher 1995).

Secondary lymphoedema is a common complication after surgical and radiological therapy of breast and ENT cancer (Dietz 1998; Erickson 2001). Patients with lymphoedema of the upper extremity and the head and neck region can experience a substantial degree of functional impairment and psychological morbidity. Endolaryngeal oedema and swelling may even lead to airway obstruction and require tracheostomy. The development of oedema is indicated by surgical or radiological damage to the lymphatic system resulting in fluid retention (Zimmermann 2005). Higher interstitial pressure lessens oxygen supply to oedematous tissue and chronic inflammatory processes lead to fibrosis of small lymph vessels. Highly reactive oxygen containing radicals (reactive oxygen species) are claimed to have a crucial role in development and maintenance of lymphoedema. Selenium compounds may improve redox balance in sparsely perfused oedematous tissue and, hence, be effective in control and therapy of secondary lymphoedema (Micke 2003; Zimmermann 2005).

The role of the complementary use of selenium in cancer patients is unclear. Some publications report a positive effect of selenium supplementation on radio/chemotherapy associated side effects and lymphoedema following surgical cancer treatment. However, trial evidence is inconsistent, and a systematic review on this topic has not been conducted.

Surveys in Canada, UK, Austria and Germany found that four to 12% of breast cancer and prostate cancer patients used selenium supplements during and after cancer therapy to alleviate adverse effects of conventional therapy and to improve quality of life (Cheetham 2001; Nam 1999; Petru 2001; Sehouli 2000). This high number of cancer patients using selenium supplements contrasts with the little clear evidence in this field thus justifying the need to update this Cochrane review.

OBJECTIVES

The aim of this review was to assess the effects of supplementary selenium, given at any dose, on:

- adverse effects of conventional radiotherapy, chemotherapy, and/or oncological surgery;
- quality of life and performance status during and after conventional oncological therapy.

A further aim was to make recommendations for future research.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised-controlled trials (RCTs) were included in this review which studied the efficacy of selenium supplementation as supplementary cancer treatment. No restriction was made regarding publication status, year or language of publication.

Types of participants

Study participants were patients of any age with malignant diseases (regardless of the stage of disease) who were undergoing tumour specific therapy (chemotherapy, radiotherapy or surgery).

Types of interventions

Studies that assessed selenium supplements or selenium preparations at any dose, duration, and route of administration compared with placebo or no intervention/routine care were eligible. Studies using selenium supplements as part of a multicomponent preparation in which there was no study arm testing for selenium supplements alone were not included in this review. Collateral interventions (e.g. manual therapy for lymphoedema) were allowed if adequately controlled for, and used in, all arms of the study.

Types of outcome measures

Data on the following outcomes were collected:

- the effect of selenium on the incidence and severity of chemotherapy or radiotherapy related toxicities if they were reported according to internationally accepted criteria for common toxicities (e.g. WHO, ECOG or NIH criteria for adverse effects; DCTD 2004; Miller 1981; Oken 1982);
- the effect of selenium on the incidence and severity of lymphoedema following surgical treatment or radiotherapy;

- patient-reported levels of physical and psychological indices of symptom distress (measured using reliable and valid assessment tools);
- quality of life, as measured by a validated instrument;
- incidence and type of adverse effects.

Search methods for identification of studies

Electronic searches

For this update we searched the following databases, sources of grey literature and registers of clinical trials with the reported search strategies:

- the Cochrane Pain, Palliative & Supportive Care Trials Register (July 2007),
- the Cochrane Database of Systematic Reviews (*The Cochrane Library*, Issue 2, 2007),
- the Database of Abstracts of Reviews of Effects (DARE) (*The Cochrane Library*, Issue 2, 2007),
- the Cochrane Central Register of Controlled Trials CENTRAL (*The Cochrane Library*, Issue 2, 2007),
- MEDLINE (1966 to July 2007),
- EMBASE (1980 to 2007 week 28),
- SIGLE (October 2004; database discontinued in 2005),
- Cancerlit (July 2007),
- CCMed (Clinical Contents in Medicine, German) (October 2004),
- the German online register for cancer trials (July 2007),
- the International Standard Randomised Controlled Trial Number Register ISRCTN (October 2004),
- the Meta-Register of Controlled Trials mRCT (October 2004),
- the NCI Clinical Trials register (October 2004).

The search for the original review was run in 2004, subsequent searches for the update were run in 2007. CCMed database - a database of German journals - search was omitted in 2007 as the relevant journals for this review are now indexed in MEDLINE, which they were not in 2004. ISRCTN, mRCT and NCI Clinical Trials are online registers for clinical studies and helpful to identify ongoing RCTs. We considered a time interval of three years too short for an update search in these online resources taking into account a reasonable balance of resources and expected outcome. We used the MEDLINE search strategy as outlined in [Appendix 1](#) (via PubMed - 1966 to July 2007), its strategy was adapted and developed for other databases searched which can be seen in [Appendix 2](#).

Searching other resources

We contacted the Chinese Cochrane Center and the Russian Branch of the Nordic Cochrane Center, but due to limited resources we were not able to have the Moscow Medical Library or the Chinese Biomedical Database searched for publications. Additionally, we checked the reference lists of retrieved publications for further studies and searched the archive of our work group. Manufacturers of selenium supplements and authors of publications were contacted and asked to contribute additional data.

Data collection and analysis

Selection of studies

Identified publications were checked for eligibility by both review authors. A publication was obtained in full text if it could not be rejected with certainty on the basis of its title or abstract. Studies of possible relevance were also obtained in full text for further evaluation. If inclusion or exclusion could not be assessed from the publication alone, first authors were contacted for additional information. Reasons for excluding trials from the review are reported in the '[Characteristics of excluded studies](#)' table. The review authors were not blinded to authors' names, institution and source of publication. Any disagreement was resolved by discussion between the review authors.

Data extraction and management

Both review authors independently extracted and documented data using a pre-tested extraction form. The following information was collected:

- study methods (randomisation, allocation concealment, blinding, eligibility criteria, follow-up);
- participants (patient characteristics, age, gender, cancer type, other cancer management/treatment, comorbidity) and additional treatments/medication;
- interventions (selenium dose, regimen, duration of treatment, route of administration) and placebo
- outcome measures;
- study withdrawals, drop-outs and protocol deviations;
- adverse effects;
- informed consent, ethic board approval.

Discrepancies were resolved by discussion between both review authors.

We contacted all primary study authors of included studies for additional information and data. Details of all eligible studies are summarised in the '[Characteristics of included studies](#)' table.

Methodological quality

Review authors assessed studies for methodological quality using a critical appraisal checklist according to [Juni 2001](#).

This checklist included the following aspects of methodological quality:

- randomisation, allocation concealment,
- blinding,
- specification of eligibility criteria,
- equal provision of care (apart from selenium supplementation) and equal follow-up,
- similarity of groups at baseline,
- reporting of protocol deviations, withdrawals and drop-outs,
- reporting of outcome measures and adverse effects,
- statistical procedures (intention-to-treat analysis).

Additionally, completed studies were rated according to the Oxford Quality Scale (Jadad 1996) and the Delphi list (Verhagen 1998).

Analysis

We planned to calculate a summary statistic and its 95% confidence interval (CI) for each outcome and to perform a meta-analysis of summary statistics if appropriate. Due to the small number of included studies, their methodological limitations and clinical heterogeneity, we considered summary statistics not to be appropriate. Study results are reported as presented in the original publication along with information on adverse effects.

RESULTS

Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#); [Characteristics of ongoing studies](#).

Results of the search

For this update review one new included study (Zimmermann 2005) was included and more participants were added to the Mücke 2007 study adding a further 39 participants to the total participants included within the review. The previous review identified an ongoing study which has been completed since the original publication of this review and is now excluded (Schumacher 2003). The total number of participants considered within the included studies is 162.

Our search returned 1981 studies of possible relevance. Of these, 1943 studies could be excluded based on title or abstract. The apparently high number of screened studies was due to our intensive literature search in databases that did not allow the use of a search strategy other than the main topic "selenium". After screening, the remaining 38 publications were obtained in full text. Following

the inclusion criteria of this review, a further 30 papers (representing 26 studies) had to be excluded. The main reasons for exclusion were that the publications described a non-randomised study or the study investigated laboratory parameters, e.g. the change of serum selenium status after supplementation. (see '[Characteristics of excluded studies](#)').

The remaining eight publications represented four studies (Büntzel 2004; Kasseroller 1998; Mücke 2007; Zimmermann 2005). Two of these studies were completed (Kasseroller 1998; Zimmermann 2005) and intermediate results have been published for one of the ongoing studies (Mücke 2007) (see '[Characteristics of included studies](#)'). One study is ongoing (Büntzel 2004) and no preliminary results have been published so far. All study authors were contacted and provided additional papers or information for this review.

All four studies were or are being conducted in Germany and Austria as a cooperation between different clinicians and one German pharmaceutical company, which manufactures sodium selenite products for clinical application.

Included studies

1) Effects on the incidence and severity of lymphoedema

Two completed RCTs could be identified for this outcome (Kasseroller 1998; Zimmermann 2005):

Kasseroller 1998 was described as a placebo-controlled randomised, double blind trial. Sixty female cancer patients were included in the study and results were presented for 57. The objective was to investigate the efficacy of sodium selenite application in combination with physical therapy to relieve secondary lymphoedemas after breast cancer surgery; recurrence of erysipela infection in the oedematous limb was reported as the primary outcome. Participants in the intervention group received sodium selenite per os for 15 weeks with a sum dose of 19.600 µg to 28.000 µg (19.6 mg to 28 mg, depending on body weight). All participants were treated with a combined physical congestion-relief programme.

Preliminary results of this study were published in 1996 giving data for 34 female cancer patients, including 25 women after breast cancer surgery and nine women after pelvic surgery. According to our correspondence with the author, all 25 breast cancer patients reported in 1996 were participants of this later study (Kasseroller 1998). We could not obtain additional information on the remaining participants with other gynecologic malignancies.

Zimmermann 2005 was also described as a placebo-controlled randomised, double-blind trial. Twenty participants (18 male, two female) with head-and-neck cancer undergoing curatively intended tumour resection were included. The objective was to investigate blood selenium concentration and different enzyme activities and postoperative lymphoedema. Only the latter outcome is of interest for this systematic review. Participants in the intervention

group received 3000 µg sodium selenite intravenously on the day of surgery and 1000 µg sodium selenite daily (i.v. or per os(p.o.)) on days one to 21 after surgery.

2) Effects on the incidence and severity of chemo- or radiotherapy related toxicities

One ongoing RCT with published preliminary results could be identified for this outcome:

Mücke 2007 investigated the use of sodium selenite supplements in female cancer patients during adjuvant radiotherapy in an ongoing randomised, unblinded two-armed multi-center study with a no-treatment control group. Study objectives were the assessment of the efficacy of sodium selenite p.o. for normalization of selenium deficiency during adjuvant radiotherapy (primary outcome) and, secondarily, its effect on the incidence and severity of radiotherapy toxicities (e.g. diarrhoea according to common toxicity criteria (CTC), changes in body weight and blood count). The intervention group received a sum dosage of approximately 15,900 to 18,000 µg sodium selenite p.o. (15.9 to 18 mg) during radiotherapy (ca. 5 weeks). According to the study protocol, the trial will randomise 200 participants to intervention and control group. Intermediate results have been published for 41 participants (Mücke 2004b) and 63 participants (Mücke 2004a), 77 participants (Mücke 2006b), 79 participants (Mücke 2006a), 80 participants (Mücke 2007), and 82 participants (Mücke 2007a; Mücke 2007b) (Mücke 2007).

Risk of bias in included studies

Details of the methodological quality of included studies are given in an additional table (see Additional Table 1: 'Quality Assessment of Included Studies').

Table 1. Quality assessment of included studies

Study	Allocation	Concealment	Study groups	Eligibility	Blinding	Attrition	Delphi list	Jadad score	Comment
Kasseroller 1998	random allocation; method of sequence generation not reported	unclear	no information on comparability of study groups regarding risk factors at baseline	eligibility criteria specified; number of eligible patients not stated	patient: yes; care provider: yes; outcome assessor: yes - unblinding of treatment status after	3 dropouts	1-0-0-1-1-1-1-0-0	1-1-1	Selection bias possible: allocation concealment unclear, no information on distribution of risk

Table 1. Quality assessment of included studies (Continued)

					end of intervention				factors at baseline. Observer/detection bias possible: no control procedure reported whether blinding was successful, details on outcome assessment not reported Performance bias possible: concomitant treatment not sufficiently described
Mücke 2007	random allocation; method of sequence generation not reported	serially numbered, sealed, opaque envelopes	no information on comparability of study groups regarding risk factors at baseline	eligibility criteria specified; number of eligible patients not stated	patient: no; care provider: no; outcome assessor: no	dropouts / withdrawals not reported in most recent publications	--	--	Preliminary results of an ongoing study (Delphi List and Jadad Score will be given when final report is available) Selection bias unlikely, but possible: allocation con-

Table 1. Quality assessment of included studies (Continued)

									ceal- ment ade- quate, but no infor- mation on distribu- tion of risk factors for outcome. Observer/detection bias possi- ble: no blinding. Perfor- mance bias possible: concomi- tant treat- ment un- clear
Zimmerman 2005	random al- location; method of sequence gen- eration not reported	unclear	no infor- mation on compa- rabil- ity of study groups re- garding risk factors at baseline	eli- gibility cri- teria speci- fied; num- ber of eli- gible pa- tients not stated	pa- tient: un- clear; care provider: un- clear; out- come as- sessor: un- clear	no dropouts or with- drawals	1-0-0-1-0- 0-0-0-0	1-1-1	Selection bias possi- ble: alloca- tion con- cealment unclear, in- formation on distri- bution of risk factors at baseline. Observer/detection bias possi- ble: study was reported as double- blinded - informed consent form, how- ever, con- tained infor- ma-

Table 1. Quality assessment of included studies (Continued)

										tion on intervention status, reliability and validity of outcome assessment unclear. Performance bias possible: concomitant treatment not sufficiently described. Randomisation and blinding unclear: informed consent form for participants contains the sentence “you have been allocated to the group receiving selenium supplements”, while study is reported as double-blinded
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No study described the method of sequence generation for random allocation. Mücke 2007 reported an adequate procedure of allocation concealment (personal communication); methods of allocation concealment in Kasseroller 1998 and Zimmermann 2005 remained unclear. All studies specified criteria for inclusion and exclusion of participants, but information on intervention and control groups' characteristics at baseline was not provided. Therefore, unequal distribution of risk factors for the outcomes of in-

terests cannot be ruled out. Treatment allocation was described as blinded to participants, doctors, care-givers and outcome assessors in Kasseroller 1998, but a control procedure checker as to whether blinding was successful was not reported. Zimmermann 2005 was described as a double-blinded, placebo-controlled trial. However, the informed consent form for participants indicated that they had been allocated to the selenium group (see: Leonhardt 2002, p. 79 (Zimmermann 2005)). We were not able to clarify the actual pro-

cedure of treatment allocation and blinding with the investigators of this study. Mücke 2007 is an unblinded trial.

According to Kasseroller 1998, all participants received comparable physical treatment for lymphoedema. However, details on concomitant treatments such as high-voltage therapy and information on additional medication that might influence erysipela incidence (e.g. corticosteroids) were not provided. All participants in Zimmermann 2005 underwent curatively intended oral tumour surgery with bilateral neck dissection. Information on factors that might influence postsurgical local swelling, such as the extent of intraoperative tissue trauma, postoperative complications or comorbidity was not reported. In the ongoing trial by Mücke 2007, participants are excluded who receive specific medication at study commencement (antibiotics, antacids, adsorbents, 5-HT₃-antagonists). If started after study inclusion, concomitant intake of these drugs should be avoided according to the study protocol, but will not result in exclusion from the study group. Other drugs that might influence diarrhoea, especially opioid analgesics, are not mentioned in the study protocol and not reported in the preliminary data.

Kasseroller 1998 gave no details for methods of outcome assessment or criteria of erysipela diagnosis. Especially the assessment of erysipela infections after dismissal from hospital remained unclear. Zimmermann 2005 reported three distances in the face (tragus - nostril, tragus - tip of chin, tragus - corner of mouth), each distance measured both directly and circumferentially. The measurements were manually undertaken by one investigator before surgery and repeated immediately after, one and two weeks after tumour resection. Reliability of measurements was unclear. Study investigators equated the measurement of postsurgical face swelling within the first two weeks after surgery with the assessment of postoperative secondary lymphoedema. The validity of this procedure seems questionable as the short interval between surgery and outcome assessment does not allow for postsurgical traumatic swelling to disappear and for lymphoedema to develop. In addition, Zimmermann and colleagues themselves stated that the "measuring distances chosen only partly describe the extent of the lymphedema" (Zimmermann 2005, p. 199). Measurements of caudal to mandible, where lymphoedema would be most prominent according to Zimmermann and colleagues, were not conducted. In Mücke 2007, incidence and severity of diarrhoea are diagnosed by the radiologist on a weekly basis based on participants' self-reports.

Kasseroller 1998 reported findings for recurrence of erysipela infection. In contrast to the study objectives, results on the development of lymphoedema with and without selenium supplementation were not reported. Results of a data analysis (i.e. OR/CI or t-test/P) were not presented. Zimmermann 2005 reported the measurements for three distances in the face at four time points as raw data. Results were presented as graphs only; Cross-tables or absolute numbers of results were not provided. Results were

tested for differences between intervention and control group and significance levels were reported; the related test was not specified. Mücke 2007 reported preliminary data on incidence and severity of radiation-induced diarrhoea and chi-square test and t-test were performed to investigate differences in the occurrence of diarrhoea according to CTC.

Effects of interventions

After a comprehensive literature search, we located two completed studies investigating the effect of selenium supplementation on secondary lymphoedema. Another ongoing study examines radiotherapy-associated diarrhoea as a secondary outcome; with the primary objective being the evaluation of sodium selenite supplementation for compensation of pre-existing selenium deficiency. We could not identify trials covering other outcomes of this review, such as quality of life or chemotherapy toxicities.

1) Effects of selenium with physical therapy on the incidence and severity of lymphoedema

Kasseroller 1998 measured the recurrence of erysipela infections of lymphoedematous upper limbs after breast cancer treatment. During the three-week treatment in the hospital no erysipela occurred in the intervention group, and one erysipela occurred in the control group. During the entire intervention and follow-up period of 15 weeks no participant in the intervention group developed recurrent erysipela while in the placebo group 14 participants (50 % of n = 28) were diagnosed with erysipela infections. These findings suggest that there might be a lower incidence of recurrent erysipela infections in the selenium group compared to placebo in the 15 weeks' period. However, this study has severe methodological limitations, as described earlier in this review. Due to these methodological problems, no conclusions on the effect of selenium supplementation on the recurrence of erysipelas in the intervention group can be drawn and generalisations to other cancer patients seem questionable.

Zimmermann 2005 reported the extent of facial swelling after oral tumour surgery for head and neck cancer. The control group showed the peak in facial swelling at the measuring point one week after surgery. In the selenium group, the maximum swelling was seen directly after surgery. The circumferential distance tragus/tip of chin was significantly shorter one week and two weeks after surgery in the intervention group, indicating a lesser facial swelling than in the control group. Taking into consideration the low number of participants and the limitations in methodology and reporting, both internal validity of results and external generalisability to other patients seems questionable.

2) Effects of selenium on the incidence and severity of chemo- or radiotherapy related toxicities

Mücke 2007 investigated radiotherapy associated diarrhoea as a secondary outcome in selenium deficient women undergoing pelvic radiation. The latest publication of this study provided data on 82 female participants with a median age of 66 years (range 31

to 80). Authors reported a statistically significant lower incidence and severity of diarrhoea in weeks four to six of radiotherapy in the intervention group. The overall incidence of radiation-induced diarrhoea grade CTC two or higher was 21% in the selenium group compared to 47% in the control group. Further data on incidence or severity of diarrhoea, cross-tables, additional data analysis (e.g. OR with CI) or results (e.g. blood count) have not yet been presented. Also, distribution of risk factors for diarrhoea at baseline and concomitant medication that might influence diarrhoea have not been reported. A conclusive discussion of this trial will need to await the publication of detailed final results. In all three studies, no adverse effects of selenium supplementation were observed.

DISCUSSION

After a comprehensive literature search, we were able to locate only two completed RCTs (Kasseroller 1998; Zimmermann 2005) that fulfilled the inclusion criteria of this review and another ongoing study (Mücke 2007) with published preliminary results. All three included studies used inorganic sodium selenite as medication. Another study not included within the included studies is currently ongoing (Büntzel 2004).

Due to methodological limitations it is not possible to draw conclusions on the effect of selenium supplementation on the recurrence of erysipela infections in women with secondary lymphoedema in the Kasseroller 1998 study. This study has been included in another Cochrane Review assessing the efficacy of anti-inflammatories for reducing acute inflammatory episodes in lymphoedema of the limbs (Badger 2004), which came to a similar conclusion regarding trial quality and the subsequent limitations in the interpretation of trial results. However, Badger 2004 reported two publications of Kasseroller 1996 and Kasseroller 1998 as two distinct studies. Having been able to make contact with Kasseroller, it was confirmed that the publication Kasseroller 1996 reported preliminary results of Kasseroller 1998.

Zimmermann 2005 reported a lesser facial swelling after head and neck tumour resection in one (of three) measurements in a two week follow-up in a group of 20 participants. Considering the unclear reliability and validity of outcome measurements, it is unclear whether the measured differences really reflect a reduction in postoperative lymphoedema in the selenium group. Generalisation to other cancer patients seems questionable. Furthermore, the clinical relevance of these measurements remained unclear.

The findings of Kasseroller have been cited in a number of secondary publications and non-systematic reviews. In 2000 Kasseroller/Schrauzer published an overview with pooled results from different studies that investigated the efficacy of selenium supplementation in female breast cancer patients with secondary

lymphoedema (Kasseroller 2000). We obtained confirmation from Kasseroller that his study data (Kasseroller 1998) were included in this summary report, but could not clarify where the remaining data stemmed from. It is doubtful that all data in this overview originated from RCTs. Kasseroller/Schrauzer inferred that clinical “studies with lymphedema of the arm after breast cancer surgery document that sodium selenite increases the efficacy of physical decongestion therapy and prevents erysipela infections” (Kasseroller 2000). Another summary of current treatment options for secondary lymphoedema (Bruns 2003) arrived at a similar positive conclusion regarding selenium supplementation: “Present data demonstrate that selenium can enhance the benefits of physical therapy in radiation-induced lymphedemas. The very low toxicity profile of selenium and its cost effectiveness are further arguments for its use in lymphedema treatment” (Bruns 2003). Authors backed their approval with a reference to the Kasseroller 1998 study and asserted that “Kasseroller [...] reported promising results of a placebo-controlled, double-blind study of selenium in 179 postmastectomy patients”. However, the Kasseroller 1998 study included only 60 participants and the above described overview by Kasseroller/Schrauzer (Kasseroller 2000), which reported data of 179 participants altogether, did not describe a RCT, but pooled data of predominantly unknown origin.

More recent publications also referred to Zimmermann 2005 to back their approval of selenium supplementation (Beuth 2007) claiming that “[r]andomized controlled clinical trials have demonstrated significant benefits for cancer patients receiving Se during chemo and radiotherapy, such as reduction of lymphedema in head and neck” cancer patients (p. 427).

Considering the lack of evidence from studies with a design that aimed to minimise possible sources of bias and the low quality of reporting in the two completed trials, this systematic review does not support the conclusions in the above cited secondary publications on the efficacy of selenium supplementation in patients with secondary lymphoedema.

To date no completed RCT is available that investigates the efficacy of selenium supplements to ameliorate side effects of conventional cancer chemo- or radiotherapy. Intermediate results from one study using sodium selenite to diminish diarrhoea in women undergoing pelvic radiation were included in this review, but have not yet been published in sufficient detail for a conclusive discussion (Mücke 2007). Another study is currently ongoing with toxicities of conventional therapy as outcomes of interest: Büntzel 2004 has a design comparable to that of Mücke 2007 and includes participants with a pre-existing selenium deficiency who are undergoing radiotherapy for ENT-malignancies. This study has been recruiting since 2000 and aims to include 200 participants randomly allocated to intervention (oral administration of sodium selenite) or control group (without selenium supplementation). Primary outcome measure is the normalisation of selenium deficiency in the blood, and secondary outcomes include radiotherapy

toxicities.

In contrast to the complete lack of evidence from RCTs regarding the efficacy of selenium supplements against radio-/chemotherapy associated side-effects, selenium supplements are frequently recommended for this indication in secondary publications (Arnold 2001; Beuth 2002) and claimed that “a protective effect against chemotherapy toxicities” has been proven in clinical studies and observations (Sill-Steffens 2003). Considering the lack of evidence, no recommendation can currently be given regarding the use of selenium supplements to ameliorate radio- or chemotherapy associated side effects.

Authors of secondary publications frequently emphasize that selenium supplementation seems to be a safe intervention as no side effects have been reported in clinical studies. In both RCTs that are included in this review no side effects attributable to selenium supplementation were reported at average dosages between 100 to 1000 µg sodium selenite daily over a period of five to 15 weeks. Inorganic selenium compounds have known acute and chronic toxicities (selenosis) at high dosages. The recommended daily allowance for adults varies between 30 to 100 µg daily depending on country and gender. 200 µg to 300 µg are considered the maximally safe daily intake over longer periods (Baehr 1999), but dosages of 1000 µg daily have been used in clinical investigations with sepsis patients for up to four weeks without signs of selenosis (Zimmermann 1997).

A few cases of acute and chronic selenosis in patients due to accidental overdosage of selenium-containing medication have been reported in the literature. In the year 2000 two severe incidents occurred in Germany and Austria when physicians mistakenly prescribed milligrams of sodium selenite instead of micrograms causing one death in Austria after parenteral administration of about 200 mg selenium (Pfeffer 2002). In 2006, the case of an Australian man with an adenocarcinoma of the prostate was published, who ingested 10 g of sodium selenite after reading on the internet about selenium as putative treatment for prostate cancer. He died some hours later of selenium intoxication (See 2006). Several cases of chronic selenosis have been reported in persons using non-prescribed nutritional supplements with inaccurate specification of selenium content. Individuals had a daily intake of ca. 1000 µg/d selenium up to 27,000 µg/d in the form of organic or inorganic selenium compounds over several weeks resulting in chronic selenium intoxication with partly severe symptoms (nausea, vomiting, loss of nails and hair, and halitosis) (Helzlsouer 1985; Jensen 1984).

Apart from acute and chronic toxicity of selenium, long-term effects of selenium supplementation are still controversially discussed (Vinceti 2001). Evidence from observational and intervention trials regarding the effect of selenium on cancer incidence and mortality is contradictory; a Cochrane review on the cancer-preventive efficacy of selenium is in process (Dennert 2005). In

Germany, inorganic selenium compounds are currently classified as potential workplace cancerogenics (Greim 1999; Greim 2003). Whether short or long-term selenium supplementation bears any protective or harmful effect on cancer diseases, is still open to question.

To summarise, the current evidence is insufficient to provide guidelines for clinical practice. The lack of primary study data contrasts remarkably with the amount of secondary publications and the proportion of cancer patients using selenium supplements, especially in German-speaking countries. It remains to be seen whether the ongoing studies will be able to add substantially to the current body of evidence.

AUTHORS' CONCLUSIONS

Implications for practice

The currently available evidence is insufficient to assess reliably the possible role of selenium supplementation on toxicities related to oncology treatments, on the development and severity of secondary lymphoedema and on quality of life during antineoplastic treatments. The quality of the studies prohibits us from extrapolating any effects observed to the general population level. Currently, research findings do not provide a basis for any recommendation in favour or against selenium supplementation in cancer patients. Nevertheless, the potential hazards of supplementing a trace mineral should always be kept in mind.

Since the last version of this review the additional participants have not provided additional information to change the conclusions.

Implications for research

As it is likely that a considerable number of cancer patients will seek “complementary” treatments to alleviate adverse effects connected with conventional therapy, further research is desirable.

Supplementation with sodium selenite is currently under investigation in RCTs and robust and sound replication of the existing trial might be useful. However, no systematic dosage-finding study has been reported so far. An adequate dosage-finding study seems as desirable as adequate reporting of completed, ongoing and future trials.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Kasseroller 1998

Methods	Randomised placebo-controlled, double-blind trial with two parallel arms Recruitment period: July 1994 - September 1995 Observation period: 15 weeks Ethical approval: yes
Participants	Number of patients: eligible/accrued: unclear - included: 60 - reported: 57 Drop Outs: "During the treatment, some of the patients were excluded from the study since they did not meet the criteria for study inclusion, namely, too short a period of stay." (Kasseroller 1998, p. 2228) Inclusion criteria: female cancer patients with one-sided secondary lymphoedema (arm) after mastectomy with axillar dissection and recurrent erysipela infections (> = 3 in the year before admission) who were admitted to the hospital for lymphoedema treatment Exclusion criteria: current treatment with antibiotics, NSAIDs or antioxidant medication Demographics: women, average age = 60.5 years Recruitment and setting: patients admitted to Wittlinger's therapy center, Walchsee, Austria (private rehab clinic) for lymphoedema treatment Informed consent: yes
Interventions	Intervention: week 1: sodium selenite solution 1000 µg/d p.o.; week 2-3: 300 µg/d p.o.; week 4-15: 200 µg/d p.o. (body weight > 70 kg), 100 µg/d p.o. (body weight < 70 kg) Control: identically looking placebo (sodium chloride p.o.) Concomitant treatment: combined physical congestion-relief program (manual lymph drainage twice daily, compressive bandages, high-voltage therapy, therapeutic exercise, meticulous skin care)
Outcomes	Primary outcome measure: incidence of recurrent erysipelas in a 15-week follow-up period Outcome assessment: diagnosis of erysipela infection based on clinical examination, blood sedimentation rate and CRP titer
Notes	Post-marketing surveillance study in Austria Participants: no data on stage of lymphoedema, comorbidity given Number of participants: inconsistent data: results reported for n = 57 participants in text, but for n = 60 participants in table Intervention: application of 1000 mg sodium selenite reported (misprint instead of 1000 µg) Outcomes: criteria for erysipela diagnosis unclear, diagnosis might differ between in-hospital treatment and follow-up after dismissal Investigator provided additional information on study methods

Risk of bias

Item	Authors' judgement	Description
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Kasseroller 1998 (Continued)

Allocation concealment?	Unclear	B - Unclear
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Mücke 2007

Methods	Ongoing randomised placebo-controlled, open label trial with 2 parallel arms Recruitment period: December 2000 - ongoing Observation period: December 2000 - ongoing most recent publication reports on December 2000 to May 2007 Ethical approval: yes
Participants	Number of patients eligible: unclear - blood tested for selenium deficiency: unclear - selenium deficiency in blood: unclear - included: unclear reported: 82 Drop Outs: unclear Inclusion criteria: female cancer patients with cervical or endometrial cancer after surgery and with pre-existing selenium deficiency in whole blood/serum receiving adjuvant percutaneous radiotherapy Exclusion criteria: distant metastases; patients receiving combined radio-/ chemotherapy; patients with prior pelvic/ abdominal radiation; current diarrhea; use of antibiotics, antacids, astringents, adsorbents, intestinal disinfectants or 5-HT3-antagonists at the beginning of the study; use of selenium supplements; use of cytoprotectants Demographics: women, age 31 to 80 years (median: 66 years). Recruitment and setting: multicenter study, Germany Informed consent: yes
Interventions	Intervention: sodium selenite solution 500 µg/d for two days before start of radiotherapy, 500 µg/d on days of radiation, 300 µg/d on days without radiation (weekend) Control: no supplementation all patients: percutaneous adjuvant radiotherapy with total doses between 45 to 50 Gy and single doses between 1.8 to 2.0 Gy supportive medication: not reported
Outcomes	Primary outcome measure: compensation of selenium deficiency as measured in whole blood other: incidence and severity of diarrhoea Outcome assessment: weekly examination by physician; blood tests; participants' diary of well-being and physical problems
Notes	Post-marketing surveillance study in Germany Intervention: concomitant medication with influence on diarrhea (opioids etc.) not reported Investigators provided a study plan and additional information on study methods Actual intervention deviated from study protocol: sodium selenite prior to radiotherapy was omitted in a number of patients (see: recent publications, confirmed by investigators)

Risk of bias

Mücke 2007 (Continued)

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Zimmermann 2005

Methods	Randomised placebo-controlled, double-blind trial with 2 parallel arms Recruitment period: unclear Observation period: 2 weeks (for postoperative face swelling) Ethical approval: yes
Participants	Number of patients: eligible: unclear - included: unclear - reported: 20 Drop outs: unclear Inclusion criteria: female and male patients, age >18, with carcinoma of the tongue or floor of the mouth (clinical stage T3 or T4) Exclusion criteria: clinical tumour stage T1 or T2; second malignancy; cardiac oedema; hypoproteinic oedema; acute infections during the past 6 months; regular intake of antioxidants; chronic renal failure; intellectual disability; pregnant women; prison inmates; participants of other clinical studies. Demographics: 18 men - 2 women; age 30 - 74 (mean: 57) years; all patients had histologically confirmed squamous cell cancer (2 pT2, 7 pT3, 8 pT4) Recruitment and setting: monocenter study, Dresden, Germany Informed consent: yes
Interventions	Intervention: 3000 µg sodium selenite solution i.v. on day of surgery; 1000 µg sodium selenite solution i.v. or p.o. on days 1 to 21 after surgery Control: placebo (0.9% sodium chloride solution) all patients: surgical tumour resection in curative intention with bilateral neck dissection
Outcomes	Primary outcome measures: three defined distances and circumferences in the face; selenium levels in whole blood and several other laboratory parameters Assessment of outcome of interest: manual measurement by one investigator at four time points (prior to, immediately after, one week after and two weeks after surgical intervention)
Notes	Intervention: concomitant surgical and non-surgical interventions with influence on lymphoedema not reported Investigators provided additional information on their interpretation of study results All patients who refused the continuation of study medication due to perceived adverse effects would have been excluded from the final study report according to Leonhardt 2002; according to personal communication no drop-outs occurred.

Risk of bias

Item	Authors' judgement	Description
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Zimmermann 2005 (Continued)

Allocation concealment?	Unclear	B -Unclear
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CRP: C-reactive protein

d: day

Gy: Gray

µg: microgram

NSAID: non-steroidal antiinflammatory drugs

p.o.: per os

Characteristics of excluded studies [ordered by study ID]

Asfour 2006	RCT, outcome:apoptosis in polymorphonuclear leucocytes; also infections in selenium and control group reported, authors contacted. Study excluded because assessment is not possible on the basis of available information
Badger 2004	Cochrane Review: includes patients with malignant and non-malignant diseases
Büntzel 1999	Case series
Elango 2006	Clinical trial; outcome:plasma selenium level and activity of selenium-dependent enzymes
Fakih 2006	Phase I clinical trial to determine the maximum tolerated dose of irinotecan in combination with a fixed dose of selenomethionine
Federico 2001	RCT, zinc/selenium combination supplement
Fraunholz 2001	Non-randomized clinical trial
Hoerjett 2005	RCT with multi component supplement; only non-clinical outcomes
Hu 1997	RCT, outcome: treatment toxicities of chemotherapy; data not presented according to toxicity scale; author contacted, but no reply obtained
Kasseroller 1995	RCT, participants with malignant and non-malignant diseases
Kiremidjian 2000	RCT, outcome: reaction of peripheral lymphocytes to mitogen stimulation after selenium supplementation
Kreienberg 2003	Study title mentioned in University of Heidelberg' s trials' register of the year 2003; hospital contacted, but no answer obtained

(Continued)

Lasch 1999	Clinical controlled trial: study not described as randomized, allocation to study and control group was performed according to date of birth
Schumacher 2003	Planned RCT, so far not recruiting patients
Sieja 2000	Multi component drug, study not described as randomised
Sundström 1984	No RCT, outcome: change in selenium-related biomarkers
Sundström 1989	No RCT, outcome: change in selenium-related biomarkers
Wagler 2000	RCT, outcome: change in selenium-related biomarkers - author contacted, but no reply obtained
Xu 1990	RCT, outcome: change of chemiluminescence measurement after selenium supplementation
Xu 1999	RCT, outcome: immunomodulation following selenium supplementation
Yu 1996	Outcome: selenium-related biomarkers; author contacted, but no answer obtained

Characteristics of ongoing studies [ordered by study ID]

Büntzel 2004

Trial name or title	Einsatz von selenase als Zusatztherapie zur Radiotherapie bei Tumoren im Hals-Nasen-Ohrenbereich. [Use of selenase as complementary therapy for radiotherapy in ENT tumours)
Methods	
Participants	200 female and male patients with selenium deficiency in whole blood receiving radiotherapy for ENT carcinomas
Interventions	Supplementation of sodium selenite solution p.o. Intervention: 500 µg/d for two days before start of radiotherapy, 500 µg/d on days of radiation, 300 µg/d on days without radiation (weekend) Control: no supplementation all patients: percutaneous adjuvant radiotherapy with total doses between 45 to 50 Gy and single doses between 1.8 and 2.0 Gy
Outcomes	Primary outcome measure: normalisation of pre-existing selenium deficiency in whole blood other: radiotherapy toxicities
Starting date	01.09.2000

Büntzel 2004 (Continued)

Contact information	Dr Jens Büntzel, Südharzkrankenhaus Nordhausen, Klinik für HNO-Erkrankungen, Dr.-Robert-Koch-Str. 29, 99734 Nordhausen, Germany
Notes	Information taken from study protocol version 1.4/01.03.2004 Study is recruiting according to authors

DATA AND ANALYSES

This review has no analyses.

APPENDICES

Appendix 1. MEDLINE search strategy

1. selen* OR seleno* OR selenium[mesh] OR selenium compounds[mesh] OR organoseleno compounds[mesh]
2. epidemiologic study characteristics[mesh] OR random* OR placebo* OR clinical trial* OR double blind method OR single blind method
3. neoplasms[mesh] OR stem cell transplantation[mesh] OR therapeutics[mesh] OR antineoplastic agents[mesh] OR quality of life[mesh]
4. cancer* OR malignan* OR carcino* OR neoplasm* OR tumor* OR tumour*
5. radioth* OR radiat* OR irradiat* OR radiochemo* OR radio-chemo* OR chemotherap*
6. melanoma* OR sarcoma* OR adenoma* OR adenosarcoma* OR adenocarcinoma* OR carcinosarcoma* OR chondrosarcoma* OR fibrosarcoma* OR dermatofibrosarcoma* OR neurofibrosarcoma* OR hemangiosarcoma* OR leiomyosarcoma* OR liposarcoma* OR myosarcoma* OR rhabdomyosarcoma* OR myxosarcoma* OR osteosarcoma* OR lymphoma* OR stem cell transplant* OR stem-cell transplant* OR bone marrow transplant*
7. lymphedem* OR lymphoedem* OR cardiotox* OR nausea* OR vomit* OR hair loss* OR leukopenia* OR neutropenia* OR thrombopenia* OR anemia*
8. #3 OR #4 OR #5 OR #6 OR #7
9. #1 AND #2 AND #8
10. animals[mh] NOT humans[mh]
11. #9 NOT #10

Appendix 2. Additional search strategies

Database	Time	Search Strategy
EMBASE	1980 - 2007 week 28	1 selenium/ or selen\$.mp. 2 exp Selenium Derivative/ 3 methylseleninic acid/ or methylselenium.mp. 4 exp Organoselenium Derivative/ 5 exp Clinical Study/ 6 exp NEOPLASM/ 7 Selenium 75/ 8 1 or 2 or 3 or 4 9 8 and 5 and 6 10 9 not 7 11 limit 10 to human

(Continued)

SIGLE [www.fiz- informationsdienste.de] [the database was discontinued]	October 2004	?selen? with restriction to subject group "06 Biological and Medical Sciences (without Botantics, Zoology, Biophysics)"
Cancerlit	July 2007	1 random* OR placebo* OR clinical trial* OR randomized controlled trial* OR controlled clinical trial* OR double blind OR single blind 2 selen* OR organoselen* 3 1 AND 2
Clinical Contents in Medicine CCMed	October 2004	selen* OR organoselen* OR natriumselen*
NCI Clinical Trials [www.cancer.gov]	October 2004	medication=selenium
ISRCTN and mRCT [www.controlled-trials.com]	October 2004	selenium AND cancer
German Register of Cancer Studies [www.studien.de]	July 2007	selen
Cochrane Pain, Palliative & Supportive Care Trials Register	July 2007	selen*
The Cochrane Database of Systematic Reviews; The Database of Abstracts of Reviews of Effects (DARE); The Cochrane Central Register of Controlled Trials (CENTRAL)	Issue 2, 2007	selen*

WHAT'S NEW

Last assessed as up-to-date: 16 February 2009.

17 February 2009	New search has been performed	For this update review one new included study (Zimmermann 2005) was included adding a further 20 participants of head and neck cancer patients to the total participants included within the review. The Mücke 2007 latest data included a further 19 participants. The previous review identified an ongoing study which has been completed since the original publication of this review and is now excluded (Schumacher 2003). The list of excluded studies, background and discussion chapter was also revised. The search for this update was run in July 2007. The new included and excluded studies did not change the original conclusions of this review.
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HISTORY

Protocol first published: Issue 4, 2004

Review first published: Issue 3, 2006

22 April 2008	Amended	Converted to new review format.
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CONTRIBUTIONS OF AUTHORS

GD, MH: protocol development, study assessment, data extraction, data analysis, discussion.

GD: literature search, data management, review coordination, contact with first authors, writing, review update.

DECLARATIONS OF INTEREST

None known

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Dr Ernst and Anita Bauer Stiftung, Germany.
- EU Project: Concerted action for complementary and alternative medicine in the cancer field (EU CAM-Cancer) (contract no.: QLG4-CT-2002-00786), Not specified.

INDEX TERMS

Medical Subject Headings (MeSH)

Antineoplastic Agents [adverse effects]; Antioxidants [*therapeutic use]; Diarrhea [*prevention & control]; Lymphedema [*prevention & control]; *Neoplasms [drug therapy; radiotherapy; surgery]; Postoperative Complications [prevention & control]; Radiotherapy [adverse effects]; Randomized Controlled Trials as Topic; Sodium Selenite [*therapeutic use]

MeSH check words

Humans