Authors' objectives
To review the study designs and results of randomised controlled trials of cancer prevention. The authors do, however, mention findings from non-randomised studies. The authors also report data from trials on cardiovascular disease whose main aim was not to evaluate the effect of treatments on cancer, but which report end points that may be relevant to the review.

Searching
MEDLINE (1975-Feb 1993) was searched electronically. Additional studies were located through reviewing the main epidemiology and cancer journals from Feb 1993 to Apr 1993. Ongoing studies were identified through searching the Directory of On-going Research in Cancer Epidemiology, various conference proceedings and lists of cancer prevention trials supplied by the National Cancer Institute and the European Community programme: 'Europe Against Cancer'.

Study selection
Study designs of evaluations included in the review
All published and ongoing randomised controlled trials (RCTs) (phase III studies).

Specific interventions included in the review
Chemoprevention (e.g. beta-carotene, vitamins, minerals, tamoxifen, fenretidine, NSAIDs, other local natural products), life-style modification (e.g. anti-smoking advice, diet modification) and immunisation (e.g. hepatitis B vaccination for liver cancer).

Participants included in the review
Members of the general population and individuals at high risk of developing any type of cancer, including patients with pre-cancerous lesions and previous primary cancer.

Outcomes assessed in the review
Early markers of cellular damage, incidence of pre-cancerous and cancerous lesions, and cancer mortality rates.

How were decisions on the relevance of primary studies made?
The author does not state how the papers were selected for the review, or how many of the reviewers performed the selection.

Assessment of study quality
The authors do not report a method for assessing validity. The validity of individual studies was not formally assessed but general issues of quality were discussed (study population, treatment characteristics, study end-points and outcomes, participant compliance, and ethical issues of study design).

Data extraction
Not stated how many individuals were involved. However, tables reported in the review include the following data: bibliographic details, participant characteristics, numbers of participants, treatment characteristics, length of follow-up, number of cancer deaths in each study group, and details of end-points/outcomes.

Methods of synthesis
How were the studies combined?
A narrative summary was used.

**How were differences between studies investigated?**

No formal assessment of study heterogeneity was reported, however some differences between the studies were discussed in the text of the review.

**Results of the review**

Ninety trials were identified. The number of participants was not always reported in the studies. Twenty-seven of the studies were published and 63 were on-going.

**Colorectal cancer (5 published, 19 ongoing studies):**

Published studies evaluated calcium, anti-oxidant micronutrients and fibre supplementation as treatments. All had small sample sizes and most considered indirect and early indicators (such as labelling index) of colon cancers as outcomes. One study looked at individuals with high fat diets, two at individuals with familial adenomatous polyposis, one at patients with previous adenomas and one at colectomy patients. Ongoing studies were mainly of chemoprevention (different doses of calcium or fibres, different types of fibres, prostaglandin inhibitors and trace elements). In general the ongoing studies included populations with pre-cancerous lesions, with the outcome of polyp recurrence (secondary prevention). Only one ongoing study looked at healthy participants (primary prevention). There was little published or ongoing evidence to suggest that any of the treatments had significant effects long term.

**Oral cancer (6 published, 4 ongoing studies):**

Both published and unpublished studies aimed to achieve chemoprevention of early markers of oral carcinogenesis (micronuclei) or treatment of oral leukoplakias (secondary prevention) mainly using retinoid-related chemicals (vitamin A, 13-cis-retinoic acid, beta-carotene) in very high risk groups or people already suffering from leukoplakia. The evidence in favour of vitamin A and cis-retinoic acid was quite strong in terms of the frequency of micronuclei and recurrence or development of leukoplakias. A less conspicuous effect was obtained with beta-carotene, which was the least toxic of the three treatments.

**Oesophageal cancer (3 published, 5 ongoing studies):**

The studies mainly focused on Asian populations, which generally have a higher risk of developing oesophageal cancer. None of the studies looked at high-risk Western populations. Published trials suggested a possible protective effect of combinations of vitamins and trace elements (zinc) on chronic oesophagitis with or without hyperplasia and dysplasia (thought to be pre-cancerous lesions). The ongoing studies should provide more information concerning cancer incidence and mortality.

**Cervical cancer (2 published, 4 ongoing studies):**

All of the studies deal with chemoprevention of precancerous lesions with vitamins or related compounds (oral or topical). No study took into account cervical cancer as an end point. The only study for which results have been published was negative; therefore the studies showed no evidence of efficacy.

**Lung cancer (4 published, 11 ongoing studies):**

The ongoing studies varied greatly from the published studies in terms of size, study design and end points. The published studies suggested some evidence of a possible positive effect of beta-carotene, selenium, folate+vitamin B12 on some early indicators of DNA damage in bronchial cells or on squamous metaplasia. The ongoing studies aim to evaluate the effect of treatment on lung cancer incidence in high-risk groups using mainly vitamin A (including its precursors and derivatives).

**Non-melanoma skin cancer (3 published, 7 ongoing studies):**

Results from two small randomised trials and several non-randomised clinical studies support the hypothesis that some
carotenoids can reduce the development of non-melanoma skin cancer in very high-risk groups affected by xeroderma pigmentosum, actinic keratosis or previous primary skin cancer itself. The most promising of these agents were certain synthetic derivatives of vitamin A. The preliminary results from one beta-carotene trial were non-significant, and the effect of selenium was unknown, although two ongoing trials were noted.

Head and neck cancer (1 published, 2 ongoing studies):

These were multi end point studies aimed at preventing new primary cancers in individuals previously affected by head and neck cancers. Treatment with 13-cis-retinoic acid seems to be protective, but toxicity is very high. New strategies in ongoing trials included lower doses of retinoic acid or identification of alternative treatments and less toxic treatments using other retinoid-related chemicals.

Breast cancer (1 published, 6 ongoing studies):

Six out of the seven trials (1 prevention, 6 chemoprevention) used treatments based on the proposed link between estrogenic activity/metabolic activity and breast cancer. Final results were not available from many of the studies as they were large and still on going.

Stomach cancer (0 published, 3 ongoing studies):

All of the studies were based on the chemoprevention of pre-cancerous lesions with anti-oxidants plus, in one, anti-Helicobacter treatment. There was no evidence of effectiveness as all of the trials were still on going.

Liver cancer (2 published, 2 ongoing studies):

Both published studies were chemoprevention RCTs looking at the protective effect on primary liver cancer of selenium in high-risk individuals. No comment was made as to the significance of the findings, which generally showed fewer incidences of cancer in the treatment as compared to control groups. There was evidence available from the ongoing studies. One looked at the affect of hepatitis B vaccine in childhood for preventing the incidence of cancer, and the other (a RCT) at the affect of green tea and radix salvia miltiorrhizae herb in preventing primary liver cancer in a Chinese population.

Authors' conclusions
The authors summarised the findings of studies for individual cancers, but failed to state any overall conclusions.

CRD commentary
This review looks at a broad question. A reasonable search of both published and unpublished literature was performed, although only MEDLINE was searched and not the Cancerlit database. The impact of this omission is unclear as the authors did search a number of other non-electronic sources. The criteria used to select studies for inclusion were broad and little information was provided as to how many reviewers were involved in the process of study selection and data extraction. The authors aim was to review evidence from phase III randomised controlled studies and the inclusion criteria reflect this. However, the findings from non-randomised studies, phase I and phase II studies were discussed on occasions (i.e. for skin cancer). The quality of the studies was not assessed on an individual basis however a number of methodological issues were raised and discussed. The broad range of studies included in the review precluded the pooling of data and consequently a narrative summary was used. This was clearly divided in sections dependent on the type of cancer and whether studies were published or not. The text was also supplemented with useful data tables. However, for certain groups of studies (colorectal and liver cancer studies), little attempt was made to synthesise the outcome data and the review also lacked overall concluding statements across the range of different cancers and treatments. In conclusion, it is difficult to assess the overall findings of the review and whether the evidence presented supports those findings.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.
Research: The authors stated that 'there is a need to develop large trials with cancer as an end-point, and possibly comparing more than one treatment in one trial'.

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.