Drugs for preventing lung cancer in healthy people (Review)

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TABLE OF CONTENTS

[Intervention Review]

Drugs for preventing lung cancer in healthy people

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ABSTRACT

Background

This is an updated version of the original review published in Issue 2, 2003. Some studies have suggested a protective effect of antioxidant nutrients on lung cancer. Observational epidemiological studies suggest an association between higher dietary levels of fruits and vegetables containing beta-carotene and a lower risk of lung cancer.

Objectives

To determine whether vitamins, minerals and other potential agents, alone or in combination, reduce incidence and mortality from lung cancer in healthy people.

Search methods

For this update we have used a search strategy adapted from the design in the original review. The following electronic databases have been searched up to December 2011: MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials (CENTRAL). References included in published studies and reviews were also screened.

Selection criteria

Included studies were randomised controlled clinical trials comparing different vitamins, mineral supplements or supplements with placebo, administered to healthy people with the aim of preventing lung cancer.

Data collection and analysis

Two authors independently selected the trials to be included in the review, assessed the methodological quality of each trial and extracted data using a standardised form. For each study, relative risk and 95% confidence limits were calculated for dichotomous outcomes and pooled results were calculated using the random-effect model.

Main results

In the first version of this review four studies were included; in this review update, an additional five studies have been included. Four studies included only males and two only females; two studies included only participants considered at high risk, namely smokers or exposed to asbestos, and one study included people deficient in many micronutrients. Six studies analysed vitamin A, three vitamin C, four vitamin E, one selenium supplements, and six studied combinations of two or more products. All the RCTs included in this review were classified as being of low risk of bias.

For people not at high risk of lung cancer and compared to placebo, none of the supplements of vitamins or minerals or their combinations resulted in a statistically significant difference in lung cancer incidence or mortality, except for a single study that included 7627 women and found a higher risk of lung cancer incidence for those taking vitamin C but not for total cancer incidence, but that effect was not seen in males or when the results for males and females were pooled.

For people at high risk of lung cancer, such as smokers and those exposed to asbestos and compared to placebo, beta-carotene intake showed a small but statistically significant higher risk of lung cancer incidence, lung cancer mortality and for all-causes mortality.

Authors' conclusions

There is no evidence for recommending supplements of vitamins A, C, E, selenium, either alone or in different combinations, for the prevention of lung cancer and lung cancer mortality in healthy people. There is some evidence that the use of beta-carotene supplements could be associated with a small increase in lung cancer incidence and mortality in smokers or persons exposed to asbestos.

PLAIN LANGUAGE SUMMARY

Antioxidant drugs for preventing lung cancer in healthy people

Lung cancer is among the leading causes of cancer death all over the world and its prevention has become a public health priority. It has been suggested that vitamin supplements may prevent lung cancer. In this new updated version of a previous review five additional studies have been added to the four previous ones. Updated analysis of the data shows that taking supplements of vitamins or minerals, either alone or combined, does not result in a reduction in either lung cancer incidence or lung cancer mortality, neither on males nor females. So current evidence does not support recommending the use of supplements of vitamins A, C and E or selenium, either alone or combined, for the prevention of lung cancer in healthy people. Indeed, in smokers and people exposed to asbestos the use of beta-carotene supplements should be avoided because it may be associated with a small increase in lung cancer incidence and mortality.

BACKGROUND

This review is an update of a previously published review in *The Cochrane Database of Systematic Reviews* Issue 2, 2003 (Caraballoso 2003). In 2008, lung cancer accounted for 13% (1.6 million) of the total cases and 18% (1.4 million) of the deaths (Jemal 2011), it was the most commonly diagnosed cancer as well as the leading cause of cancer death in males. Among females, it was the fourth most commonly diagnosed cancer and the second leading cause of cancer death. Lung cancer incidence rates and trends vary a lot across countries or between males and females within each country and largely reflect differences in the stage of the tobacco epidemic. Male lung cancer death rates are decreasing in many European countries, North America, and Australia and in contrast, lung cancer rates are increasing in countries such as China and other countries in Asia and Africa. Generally, lung cancer trends among females lag behind males because females started smoking in large numbers several decades later than males. In some countries, indoor air pollution from unventilated coal-fueled stoves and from cooking fumes accounts for an important part of lung cancer rates in women. Other known risk factors for lung cancer include exposure to several occupational and environmental carcinogens such as asbestos, arsenic, radon, and polycyclic aromatic hydrocarbons (Brown 2009, Luo 2011).

Approximately 20-30% of Americans consume multivitamin supplements daily, indicating high public interest in the prevention of cancer and other chronic diseases through a nutrition-based

approach. Although several bioactive food components, including vitamins and minerals, have been investigated for their ability to affect cancer risk, few large, randomised, placebo-controlled clinical trials of multivitamins with cancer as the primary endpoint have been performed (Greenwald 2007).

Advances in cell and molecular biology have increased understanding of the multiple events that lead to the development of lung cancer: the field cancerisation theory suggests that multiple genetic abnormalities occur throughout the respiratory epithelium as a result of long term carcinogen exposure (Gould 1997). Because of this diffuse injury throughout the lungs, systemic therapy, which could halt or reverse the development of cancerous changes, may be effective in preventing lung cancer.

Chemoprevention, especially for people exposed to risk factors of lung cancer, appears to be biologically feasible for certain cancers and has been proposed as a potential new strategy for blocking or reversing the carcinogenic process (Siegfried 1998; Vainio 1999; Whelan 1999). Chemoprevention is the use of specific agents to reverse, suppress, or prevent the process of carcinogenesis (Goodman 2008). A mechanism responsible for turning off a tumour-suppressing gene in many lung cancers has been described and it seems clear that cells need to inactivate many genes before they can become malignant. In the case of lung cancer, scientists have long known that retinoic acid plays an important role in lung development and differentiation, acting primarily via nuclear receptors encoded by the retinoic acid receptor-β (RAR-β) gene. Because receptor isoforms RAR-β2 and RAR-β4 are repressed in human lung cancers, studies have investigated whether methylation of the promoter of these receptor isoforms, P2, might lead to silencing of the RAR-β gene in human lung tumours and cell lines. These studies have concluded that chemical demethylation is a potential approach to lung cancer therapy (Arvind 2000).

It has been suggested that a number of vitamin supplements may prevent lung cancer and attention has focused on three in particular: (1) alpha-tocopherol, which is the most prevalent chemical form of vitamin E found in vegetable oils, seeds, grains, nuts, and other foods, and acts as an antioxidant; (2) beta-carotene, a violet to yellow plant pigment found in many yellow, orange and dark-green, leafy vegetables and many fruits; it acts as an antioxidant and can be converted to vitamin A by enzymes in the intestinal wall and liver; and (3) retinol, which is an alcohol chemical form of vitamin A (Weisburger 1991). Non-experimental studies suggest that individuals with higher selenium status are at decreased risk of cancer (Reid 2008).

Other vitamins, minerals and agents are also under investigation. Several trials have been undertaken in the last few decades to evaluate the potential prevention of initial cancers and of second primary tumours in patients previously treated for lung cancer and the possibility of reversal of premalignants lesions (Benner 1995).

Although folic acid has been investigated for its potential to inhibit carcinogenesis, few epidemiologic studies have assessed the effects of intake of thiamin, riboflavin, and niacin, which may reduce cancer risk by acting as cofactors in folate metabolism or by other mechanisms. Using data from a large cohort of Canadian women, it was examined the association of dietary intake of these nutrients, as well as intake of folate, methionine, and alcohol, with cancers of the breast, endometrium, ovary, colorectum, and lung ascertained during an average of 16.4 years of follow-up. Few significant associations of intake of individual B vitamins with the five cancers were observed. (Kabat 2008)

Carotenoids are thought to have anti-cancer properties, but findings from population-based research have been inconsistent (Gallicchio 2008). Beta-carotene and retinoids initially appeared to be promising at combating common cancers (Comstock 1992; Halliwell 1992; Peto 1981). To investigate their action, the National Cancer Institute mounted a substantial program of population-based trials in the early 1980s (Omenn 1996). However, the two major lung cancer chemoprevention trials not only showed no benefit of the agents (ATBC 1994; Omenn 1996), but Omenn 1996 (the CARET study) was terminated early after a 28% higher incidence and 17% higher mortality from lung cancer was observed in the intervention group compared with the placebo group (Patrick 2000). Equally, ATBC 1994 found that there was a 16% increase in lung cancer in those receiving either beta-carotene alone or in combination with alpha-tocopherol. In a third study that compared beta-carotene and aspirin separately and in combination, versus a placebo, no difference in either cancer mortality or incidence was found in the intervention groups (Hennekens 1996). In a fourth study, however, a 55% reduction in cancer incidence was observed for those receiving vitamins combined with minerals (beta-carotene + selenium + alpha-tocopherol), but this study had low statistical power (Patrick 2000).

A new generation of laboratory research, testing for example N-acetyl cysteine, has been identified and shows promise. Current public health recommendations support the need for multilevel research to develop and evaluate candidate chemoprevention agents to prevent lung and other common cancers (ATBC 1994; Omenn 1996). Given the continuing cancer burden, the relatively low impact of proven cancer treatment strategies in reducing lung cancer mortality, and the possibility that food-based or other components may have chemo preventive properties, it is essential to evaluate the use of these agents. Our purpose was to review the evidence for the effectiveness of chemoprevention in lung cancer in healthy population.

OBJECTIVES

To determine whether vitamins and minerals and other potential agents, natural or synthetic, such as retinoids, isothiocyanates, flavonoids, monoterpenes, or pharmaceuticals such as N-acetyl

cysteine, alone or in combinations, reduce lung cancer incidence and mortality in healthy populations.

METHODS

Criteria for considering studies for this review

Types of studies

Only randomised controlled trials (RCTs) comparing any eligible intervention with placebo were considered for inclusion.

Types of participants

Healthy males and females of all ages, independent of their smoking status or other risk factors for lung cancer.
Smokers and those exposed to asbestos were considered as people at high risk; people not known to have been exposed to such risk factors were considered as people at low risk.

Types of interventions

Dietary supplementation with specific vitamins, minerals (selenium, zinc or others) and other potential agents, natural or synthetic, such as isothiocyanates, flavonoids, monoterpenes, or pharmaceuticals such as N-acetyl cysteine, alone or in combinations, at any doses. Administration could be in capsule or tablet form to be consumed orally.

Types of outcome measures

The primary outcomes considered in this review are:

- lung cancer incidence, and
- lung cancer mortality.

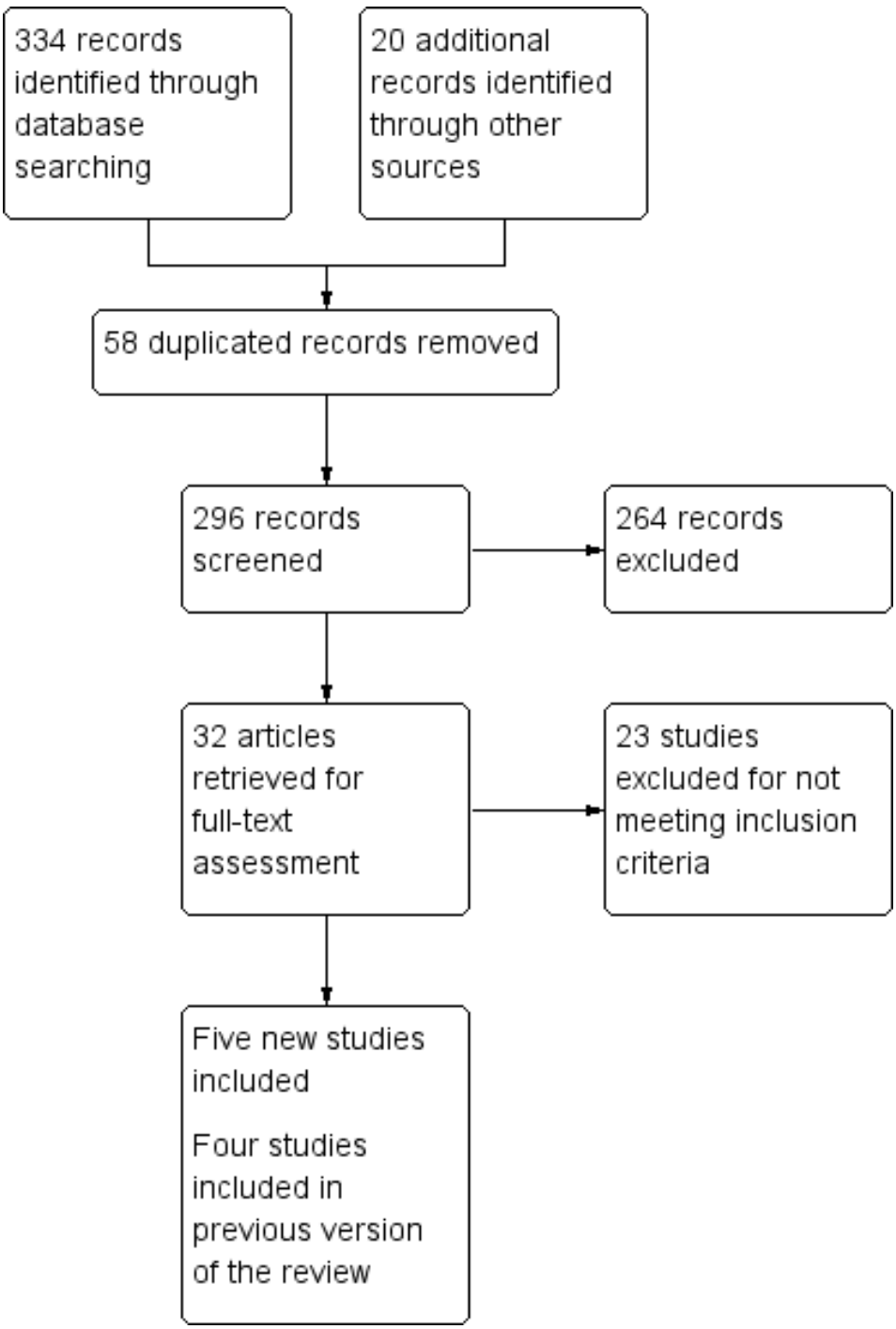
Since the role of the drugs included in this review could also have an impact on other cancers or diseases, the following secondary outcomes are also considered:

- total cancer incidence,
- total cancer mortality, and
- total mortality.

Search methods for identification of studies

We ran a search in December 2011 to update the original completed review. For this update we adapted the original searches to search the following databases: Cochrane Central Register of Controlled Trials (CENTRAL, *The Cochrane Library* 2011, Issue 11; MEDLINE (PubMed); and EMBASE (1974 to 2011). Published meta-analyses and recent reviews addressing the topic of our review were also searched and screened for RCTs.
We include in the Appendix 1 the search strategies and the results obtained in Figure 1.

Figure 1. Bibliographic searches. Flow diagram.



Data collection and analysis

In this update two (MC-J and JRR) searched independently the titles and abstracts obtained from the initial electronic search. The full text of provisionally included studies was assessed to determine whether the study met the inclusion criteria. There were no disagreements in this process. For the first published version of this review, data collection was done using a standardised form designed for the purpose of this review. Extracted data included details of randomisation methods, comparisons of interest, the number and type of people originally randomised in each arm of the study, any losses to follow-up and the outcomes of interest from each study arm. If information on any of these was incomplete, we attempted to obtain it by writing to the authors concerned. Authors who did not answer were sent a second follow-up letter. All except one provided additional information and data on their studies.

All the included studies have presented their results in several articles and in some cases post intervention follow-up data are also available. For all studies the most recently published data were used for each relevant outcome variable.

In this update of the review, data from the new included studies were extracted by two authors (MC-J and JRR) and the most relevant information about the study is presented in the Characteristics of included studies section. The same two reviewers have also extracted and analysed the most recent post intervention follow-up data of the trials included in the first published of this review.

For each study, relative risks and their 95% confidence limits were calculated for dichotomous outcomes. Where appropriate, results of comparable groups of trials were pooled, using the random effects model. The analysis was performed using the Cochrane Collaboration's statistical software, Review Manager 2011. Heterogeneity between trials was tested with the chi-squared heterogeneity test, using a P value of 0.40 as a cut-off point.

When available, subgroup analysis has been performed for high and low risk groups:

- High risk: those known to be smokers and/or those known to be exposed to occupational risk factors of lung cancer, such as asbestos.
- Low risk: those with no known risk factors for lung cancer such as smoking or asbestos.

Separate analysis for men and women are presented when available data allow it.

Assessment of risk of bias in included studies

Two review authors (MC-J and JRR) independently assessed the risk of bias for each study for the following domains: sequence generation, allocation concealment, blinding of participants, personnel and outcome assessment, incomplete outcome data and selective reporting. Judgement of the risk of bias for each domain has been assessed according to the criteria defined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Any disagreement was resolved by discussion and consensus.

Sequence generation (checking for possible selection bias)

The methods used to generate the allocation sequence should produce comparable groups.

- Low risk of bias. The investigators describe a random component in the sequence generation process (e.g. random number table; computer random number generator).
- High risk of bias. The investigators describe a non-random component in the sequence generation process (e.g. odd or even date of birth; hospital or clinic record number or by judgement of the clinician or preference of the participant).
- unclear. When we have insufficient information about the sequence generation process to permit judgement of 'low risk' or 'high risk'.

Allocation concealment (checking for possible selection bias)

The methods used to conceal the allocation sequence should prevent intervention allocation been foreseen in advance of, or during recruitment, or changed after assignment.

- Low risk of bias. e.g. central allocation; sequentially numbered of identical appearance; numbered, opaque, sealed envelopes.
- High risk of bias. e.g. open random allocation; unsealed or non-opaque envelopes, alternation; date of birth.
- Unclear. e.g. the method of concealment is not described or not described in sufficient detail to allow a definite judgement.

Blinding of participants and personnel (checking for possible performance bias)

We assessed the methods as:

- Low risk of bias. No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding or blinding of participants and key study personnel ensured,and unlikely that the blinding could have been broken.
- High risk of bias. No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding or blinding of key study participants and personnel attempted, but

likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding).

- Unclear. Insufficient information to permit judgement of 'low risk' or 'high risk' or the study did not address this outcome.

Blinding of outcome assessment (checking for possible performance bias)

- Low risk of bias. No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding or blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.

- High risk of bias. No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding or blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.

- Unclear. Insufficient information to permit judgement of 'low risk' or 'high risk' or the study did not address this outcome.

Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations)

- Low risk of bias. Any one of the following: no missing outcome data; missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate.

- High risk of bias. Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; 'as-treated' analysis done with substantial departure of the intervention received from that assigned at randomisations.

- Unclear. Insufficient reporting of attrition/exclusions to permit judgement of 'low risk' or 'high risk' (e.g. number randomised not stated, no reasons for missing data provided or the study did not address this outcome).

Selective reporting (checking for possible reporting bias)

- Low risk of bias. Any one of the following: the study protocol is available and all of the study prespecified (primary and secondary) outcomes that are of interest in the review have been reported in the prespecified way or the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were prespecified (convincing text of this nature may be uncommon).

- High risk of bias. Not all of the study prespecified primary outcomes have been reported or one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not prespecified; or one or more reported primary outcomes were not prespecified, unless clear justification for their reporting is provided, such as an unexpected adverse effect or one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; finally as the study report fails to include results for a key outcome that would be expected to have been reported for such a study.

- Unclear. Insufficient information to permit judgement of 'low risk' or 'high risk'.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

In the first version of this review four studies were included (ATBC 1994; Hennekens 1996; Lee 2005; Omenn 1996). In this new version five additional studies have been included (Gaziano 2009; Hercberg 2010; Kamangar 2006; Lin 2009; Lippman 2009). Two of the new studies were not included in the previous review since at that time disaggregated published data for lung cancer incidence or lung cancer mortality were not available.

Five studies were conducted in the United States (Gaziano 2009; Hennekens 1996; Lee 2005, Lin 2009; Omenn 1996), one in the USA, Canada and Puerto Rico (Lippman 2009), one in China (Kamangar 2006), and two in Europe (ATBC 1994; Hercberg 2010).

Four studies included only males (ATBC 1994; Gaziano 2009; Hennekens 1996; Lippman 2009) and two, only females (Lee 2005; Lin 2009). The age of participants at the start of treatment ranged from to 35 to 84 years.

Two studies included only participants considered at high risk, namely smokers or exposed to asbestos (ATBC 1994; Omenn 1996). One study included people deficient in many micronutrients (Kamangar 2006).

The type of supplements and doses varied across studies. Six studies analysed vitamin A, three vitamin C, four vitamin E, one selenium supplements, and six studies combinations of two or more products. Detailed data are presented in (Table 1).

The duration of treatments varied among the studies, ranging from two to twelve years and the length of follow-up ranged form

six to sixteen years (Table 2). Three studies were terminated prematurely, two of them when an interim analysis of ATBC 1994 and Omenn 1996 found a harmful effect associated with vitamins (beta-carotene + retinol) (Lee 2005; Omenn 1996), and the third one when the independent data and safety monitoring committee (Lippman 2009), after the second formal interim analysis, recommended the discontinuation of study supplements because the alternative hypothesis of no evidence of benefit from either study agent was convincingly demonstrated and there was no possibility of a benefit to the planned degree with additional follow-up (Table 2).

Risk of bias in included studies

The risk of bias can be considered as low for all the included studied. See individual and summarised results of risk of bias assessment in Characteristics of included studies, Figure 2 and Figure 3.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

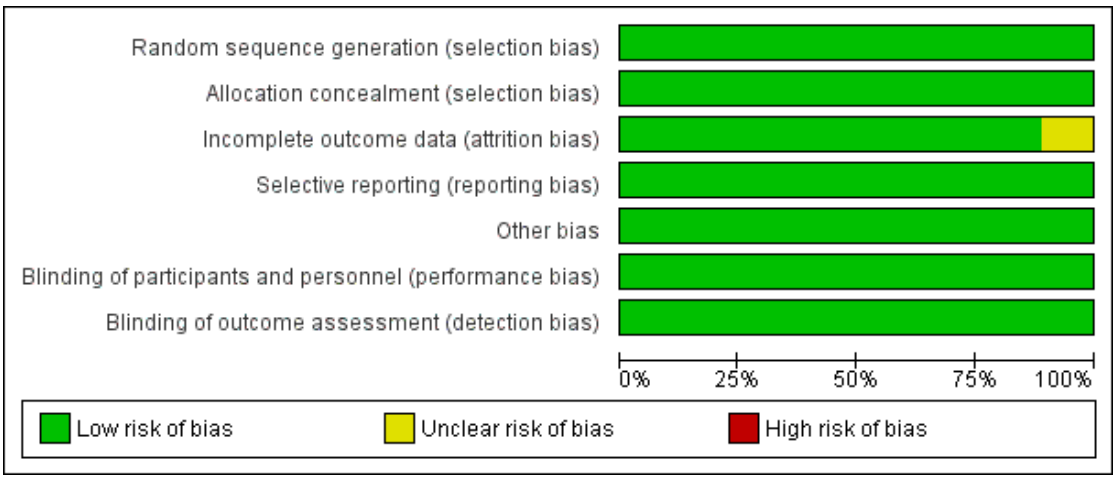
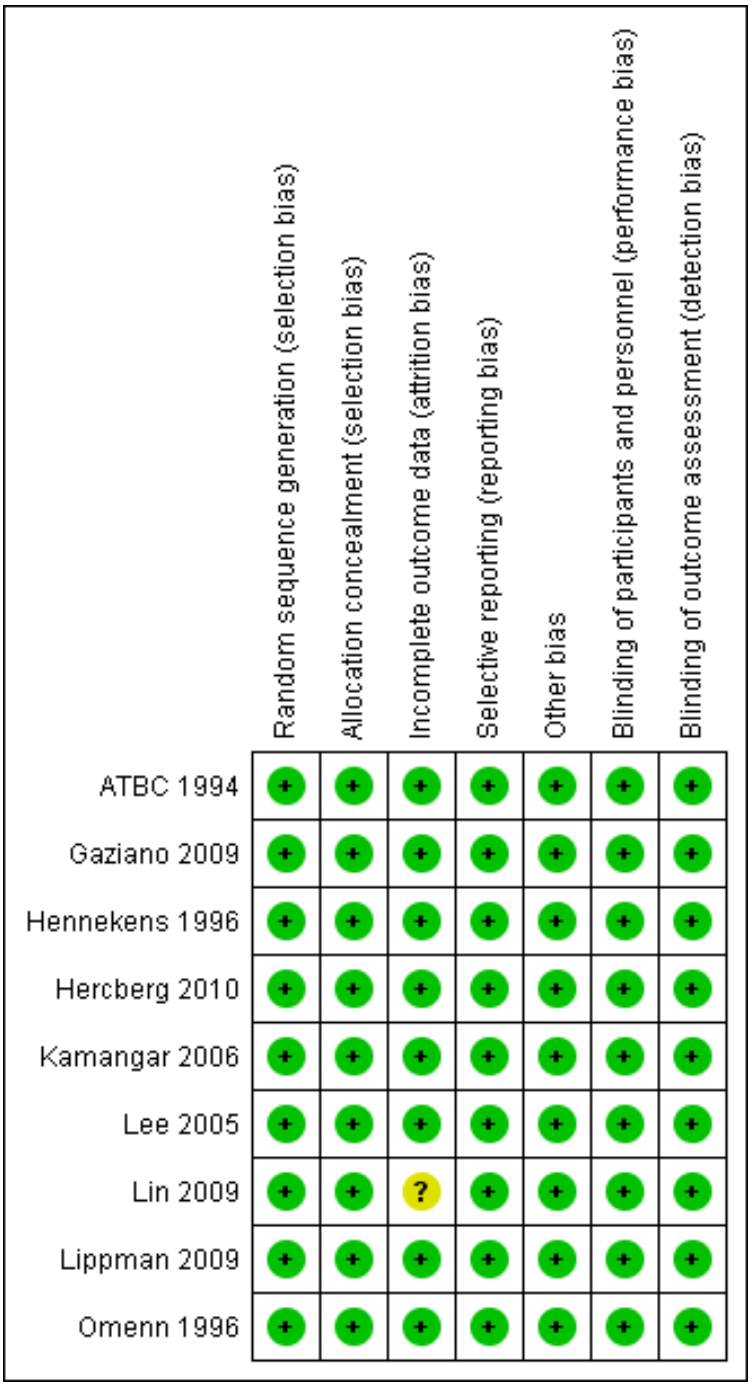


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

All studies have been classified as low risk since all reported adequate random sequence generation procedures. The allocation concealment process can be considered adequate since allocation to treatment was done centrally in all the studies.

Blinding

The risk of performance bias and detection bias is very low in the included studies. Studies were double-blinded and those bias are quite unlikely to happen since the primary outcomes of this review are incidence of cancer and mortality.

Incomplete outcome data

Only one study reported a relevant percentage of overall losses but they were evenly distributed across the randomised groups (ATBC 1994).

Selective reporting

Reporting bias risk has been considered as "low" for all the included studies, since all of them reported all the outcomes stated as relevant in the protocols or methods' sections of the publications.

Effects of interventions

Vitamin A (beta-carotene or retinol)

For people at high risk for lung cancer, smokers and those exposed to asbestos, compared to placebo, Vitamin A showed a statistically significant higher risk for lung cancer incidence (RR 1.11, 95% CI 1.01 to 1.21, I^2 = 0%, Analysis 1.1; data pooled from 4 studies and 49,230 participants; ATBC 1994; Hennekens 1996; Lee 2005; Omenn 1996), lung cancer mortality (RR 1.18, 95% CI 1.01 to 1.38, I^2 = 0%, Analysis 1.2; data pooled from 2 studies and 29,426 participants; ATBC 1994; Hennekens 1996) and for all causes mortality (RR 1.09, 95% CI 1.05 to 1.13, I^2 = 0%, Analysis 1.5; data pooled from 2 studies and 32,883 participants; ATBC 1994; Omenn 1996). The differences on total cancer incidence (data from one study and 14,569 participants; ATBC 1994) and total cancer mortality (data from one study and 22,071 participants; Hennekens 1996) were not statistically significant.

For people at no high risk there were not any statistically significant differences between placebo and Vitamin A for any of the outcomes measures, neither for males or females separately nor for both sexes pooled together [lung cancer incidence: 202,924 people from four studies (Hennekens 1996; Kamangar 2006; Lee 2005; Lin 2009); lung cancer mortality:160,692 participants from two studies (Hennekens 1996; Kamangar 2006); all cancers incidence: 7627 women from one study (Lin 2009).

Vitamin C (ascorbic acid)

Lin 2009 included 7627 women and found a statistically significant higher risk for lung cancer incidence for those taking vitamin C (RR 1.84; 95% CI 1.14 to 2.95), but not for total cancer incidence.

Gaziano 2009 included 14,641 men did not find significant differences between placebo and Vitamin C for any of the outcomes measures (lung cancer incidence, lung cancer mortality, total cancer incidence, total cancer mortality and all cause mortality).

Pooling data from both studies there were no statistically significant differences neither for lung cancer incidence nor for the incidence of all cancers.

Vitamin E (alpha-tocopherol)

No statistically significant difference was found in people taking Vitamin E compared with those taking placebo for any of the outcome measures, neither for high nor low risk risks groups, nor for sex or age groups nor after pooling data from different subgroups (data from five studies accounting overall for 94,141participants; ATBC 1994; Gaziano 2009; Lee 2005; Lin 2009; Lippman 2009).

Selenium

A single study with 17,448 male participants compared selenium versus placebo and did not find any statistically significant difference for any of the outcome measures (lung cancer incidence, lung cancer mortality, total cancer incidence, total cancer mortality and all-cause mortality) (Lippman 2009).

Vitamin A (beta-carotene) and Vitamin E (alpha-tocopherol) vs. placebo

One study with 14,565 participants, all of them male smokers (5+ cigarettes/day) or asbestos workers, did not find any statistically significant difference between placebo or Vitamin a + Vitamin E multivitamins in relation with lung or all cancer incidence or all-cause mortality (ATBC 1994).

Vitamin C and Vitamin E vs. placebo

One single study with 7328 male doctors did not find any statistically significant difference between placebo or Vitamin C and Vitamin E in relation with lung or all cancer incidence (Gaziano 2009).

Vitamin E (alpha-tocopherol) and selenium vs. placebo

One single study with 17,399 males did not find any statistically significant difference between placebo or Vitamin E + selenium for any of the outcome measures (lung cancer incidence, lung cancer mortality, total cancer incidence, total cancer mortality and all-cause mortality) (Lippman 2009).

Vitamins A, E and selenium vs. placebo

One single study compared with Vitamins A and E with selenium versus placebo, in a population with nutritional deficiencies, and did not find a statistically significant difference in lung cancer mortality but found such a difference for all-cancer mortality in women (RR 0.79, 95% CI 0.64 to 0.98) and for all-cause mortality (RR 0.95, 95% CI 0.91 to 0.99) (Kamangar 2006).

Vitamins A, C, E, selenium and zinc vs. placebo

A single study with 12,741 participants did not find statistically significant differences either for lung cancer incidence, all-cancer incidence and all-cause mortality, or for males or females or for both sexes pooled together (Hercberg 2010).

DISCUSSION

Summary of main results

Taking some supplements of vitamins or minerals, either alone or combined, does not result in a reduction in either lung cancer incidence or lung cancer mortality, neither for males nor females, and so their use is not justified for lung cancer prevention. These data come from RCTs with low risk of bias.

Moreover, for people at high risk for lung cancer, smokers and those exposed to asbestos, the available evidence shows that supplementation of vitamin A could result in a slightly higher risk of lung cancer incidence, lung cancer mortality and for all-cause mortality.

Overall completeness and applicability of evidence

For all the interventions addressed in this review there is information on relevant outcomes, lung cancer incidence and mortality, and the source of evidence is direct since studies were carried out in relevant population groups.

For vitamin A there is information from studies which separated people at high risk from those without relevant risk factors, information coming in both cases from more than one study: four studies for lung cancer incidence and two for lung cancer mortality.

For vitamin E there is information from studies which investigated males and females separately, information coming in both cases from two studies for lung cancer incidence. For lung cancer mortality data comes from two studies in the case of males and from a single study for females. There are also disaggregated data available for people at high risk, but these come from a single study.

For vitamin C, there is available information from studies which investigated males and females separately, but coming from separate single studies. One study that included 7627 women found a statistically significant higher risk for lung cancer incidence in those taking vitamin C (RR 1.84, 95% CI 1.14 to 2.95), but not for total cancer incidence (Lin 2009). However, those results should be taken with caution given that they come from a single study and that the differences were not statistically significant for males or for males and females pooled together.

For selenium and for all the combinations of two or more products evidence comes from a single and different study in each case.

Quality of the evidence

The studies included in this review were all of them RCTs and classified as being of low risk of bias.

In those cases in which there is information coming from several studies, consistency of results varies. For vitamin A in the case of high risk people and for lung cancer incidence, separate analysis of the data from each of the four studies found no statistically significant differences between placebo and active treatment but pooled results show a slightly higher risk for those taking vitamin A. Among the two studies that assessed lung cancer mortality, only one found significant differences between treatment and placebo (ATBC 1994). A possible explanation is that the second study included high-risk people who were smokers (Hennekens 1996), whereas in ATBC 1994 they also included people exposed to asbestos.

For vitamin E and for males, evidence for both incidence and lung cancer mortality comes from two studies with consistent results of no significant differences between placebo and active treatment; for women, incidence of lung cancer was assessed by two studies with consistent results.

Potential biases in the review process

Publication bias is unlikely to have happened in the review process given that the published studies found results that are unfavourable for active treatments compared with placebo, and it is quite unlikely that any relevant study had remained unpublished.

Agreements and disagreements with other studies or reviews

The previous version of this Cochrane review did not find a significantly higher risk of lung cancer incidence and lung cancer mortality for people at high risk (smokers or people exposed to asbestos) for those taking vitamin A as compared to placebo (Caraballoso 2003), taking into account pooled data from three studies (ATBC 1994; Hennekens 1996; Lee 2005). In this new updated review, we have included an additional study into the meta-analysis (Omenn 1996), which in the previous review was analysed separately. We have considered now that the active intervention (when that is vitamin A) could be included into the pooled analysis, given that the participants received beta-carotene plus retinol and that beta-carotene is a precursor of retinol. When pooling data from the four studies the results change and it appears that there is a small, but statistically significant increase in the risk of lung cancer incidence and lung cancer mortality for those taking vitamin A.

Also, the previous version of this Cochrane review (Caraballoso 2003), based on data from a single study (ATBC 1994), found that among people at high risk there was a statistically significant *higher* risk of both lung cancer incidence and mortality (1.45 and 1.75, respectively) for those who took the combination of beta-carotene and retinol. In this update we have included new available published data from a longer follow-up of participants in that study and now differences between active treatment and placebo are not statistically significant for lung cancer incidence (RR 1.10, 95% CI 0.97 to 1.24). For overall mortality differences remain statistically significant but the magnitude of the possible effect is small (RR 1.06, 95% CI 1.02 to 1.11), suggesting that the possible adverse effects of the combination of beta-carotene and retinol tend to diminish in the longer term.

Recently published systematic reviews on the effects of supplements of beta-carotene or antioxidants reach similar conclusions as ours about the ineffectiveness of using those supplements in preventing lung cancer compared to placebo (Druesne-Pecollo 2010; Myung 2010).

A recent review finds that consumption of vegetables and fruit is associated with a low risk of developing lung cancer (Wakai 2011), though this evidence comes from observational studies. Fruits and vegetables contain numerous components in addition to beta-carotene, and those observational studies generally evaluate foods rather than specific bioactive food components. It has been suggested that beta-carotene could be simply a marker for other protective dietary components and that a systematic approach is needed to determine how combinations of vitamins and minerals may interact to influence cancer risk and to increase our understanding of the potential benefits and risks of supplement use (Greenwald 2002; Greenwald 2007).

The story of antioxidants and cancer is a clear example of the need for translational research. At the time most RCTs started, there was an widespread belief in the scientific community that a diet high in fruits and vegetables, both of which are rich in antioxidants, may prevent cancer. That belief was based mainly on observational studies. Recently published basic research has cast doubts on the belief of the anticancer properties of antioxidants and has warned that in some cases their effect might in fact be carcinogenic (DeNicola 2011).

AUTHORS' CONCLUSIONS

Implications for practice

There is no evidence for recommending supplements of vitamins A, C, E, selenium, either alone or in different combinations, for the prevention of lung cancer and lung cancer mortality in healthy people. There is some evidence that the use of beta-carotene could be associated with a small *increase* in lung cancer incidence and mortality in smokers or people exposed to asbestos.

Implications for research

Main clinical trial registers do not include any new ongoing or planned RCT on supplementary vitamins, minerals and other antioxidants for the prevention of lung cancer in healthy people.

Nowadays it is not advisable to prioritise research on the effect of vitamins, minerals and other antioxidants in lung cancer prevention on healthy people, given that available evidence does not support their use and that causes of lung cancer are well known and there are effective interventions for them.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

ATBC 1994

Methods	Alpha-Tocopherol Beta-Carotene Cancer Prevention (ATBC) Study Randomised, double-blind, placebo-controlled trial. Objective: to evaluate the effectiveness of alpha-tocopherol or beta-carotene supplements for the prevention of lung cancer. Southwestern Finland, period 1985-1993.
Participants	29,133 male smokers. 50-69 years of age. Excluded those with previous cancer or other serious illness, users of vitamin E, vitamin A, or beta-carotene supplements in excess of predefined doses, or treatment with anti-coagulants Smoking status definition criteria: 5+ cigarettes/day. Median of 20 cigarettes smoked daily and duration of smoking prior to study entry 36 years
Interventions	Four intervention groups: a) alpha-tocopherol (50 mg/day), n: 7286. b) beta-carotene (20 mg/day), n: 7282. c) alpha-tocopherol (50 mg/day) + beta-carotene (20 mg/day), n: 7278. d) placebo, n: 7287. Comparisons: 1) alpha-tocopherol (a+c) vs no alpha- tocopherol (b+d), n: 14564 vs 14569) 2) beta-carotene (b+c) vs no beta- carotene (a+d), n: 14560 vs 14573. 3) alpha-tocopherol (a+c) vs placebo (d), n: 14564 vs 7287. 4) beta-carotene (b+c) vs placebo (d), n: 14560 vs 7287. 5) alpha-tocopherol + beta-carotene (c) vs placebo (d), n: 7278 vs 7287. All doses were administered daily. Duration of treatment: for five to eight years, median 6.1 years
Outcomes	Lung cancer incidence. Lung cancer mortality. Total cancer mortality. All-cause mortality. Follow up: trial period 29133 participants (8 years: median, 6.1), total of 169,751 participants-years. Post-trial period another 3 years 25283 participants, and another 3 years more 22838 participants; six years for cancer incidence and mortality and eight years for total mortality
Notes	Comparisons 1 and 2: intention to treat analysis. Comparisons 3, 4 and 5: not intention to treat analysis. Information on cancer incidence and mortality was mainly taken from the cancer registry Trial Registration Identifier: NCT00342992. Funding: supported by Public Health Service of Finland contracts N01-CN-45165 and N01-RC-45035 from the US National Cancer Institute, National Institutes of Health,

ATBC 1994 (*Continued*)

	Department of Health and Human Services	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Mentioned as "randomly assigned" but sequence generation process is not explained in a detailed way, but probably done centralised, given that: Quote "A coded reserve supply of capsule packs was maintained centrally in the event of lost capsules requiring replacement."
Allocation concealment (selection bias)	Low risk	Randomisation was probably done centralised. Quote "A coded reserve supply of capsule packs was maintained centrally in the event of lost capsules requiring replacement."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Causes for withdrawal from the study well reported. Quote: "The chest film at study exit was available for all but 494 surviving men, yielding a 98% success rate that was equal across the supplementation groups". Quote: "The dropout rate varied only slightly across the randomised groups"
Selective reporting (reporting bias)	Low risk	Authors present results on all outcome measures that were prespecified as relevant
Other bias	Low risk	The study appears to be free of other sources of bias.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Stated as "double-blind. Quote: A coded reserve supply of capsule packs was maintained centrally in the event of lost capsules requiring replacement. All formulation were Coloured with quinoline yellow"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Participants and all study staff involved in the ascertainment of end points and the assignment of final diagnoses remained blinded to the participants' treatment assignment throughout the trial"

Gaziano 2009

Methods	Physicians' Health Study II (PHS II) Randomised in blocks of 16 and stratified by age, double blind, placebo-controlled, 2 x 2 x 2 x 2 factorial trial Objective: To evaluate whether long-term vitamin E or C supplementation decreases risk of prostate and total cancer events among men. Period: Began in 1997 and continued until its scheduled completion on August 31, 2007. Analysis will be in terms of number of events per participant-years of follow-up for each study agent, and will be conducted on intent to treat basis
Participants	14,641 male physicians (7641 from PHS I and 7000 new physicians) Mean age 64.3 years; 56,4% never smokers, 40% former smokers, 3.6% current smokers Inclusion criteria: 50 years and older; no history of cancer (except non-melanoma skin cancer), myocardial infarction, stroke or transient cerebral ischemias; no current liver or renal disease, peptic ulcer, gout, and will be required to indicate their willingness to avoid the use of non study vitamin supplements Smoking status definition criteria: none explicit. Categories: never, former, current
Interventions	1) Vitamin E (400 IU) every other day. 2) Vitamin C (500 mg) daily. 3) Multivitamin, daily. 4) Placebo daily. Duration of treatment: six years.
Outcomes	Prostate and total cancer. Mean follow -up 8 years, median 7.6.
Notes	PHS I participants who enrolled in PHS II (approximately 7500) continued on their original randomised beta-carotene treatment assignment and also be randomised to vitamin C, vitamin E, and a multivitamin, or their placebos. New physician participants in PHS II (approximately 7500), identified from a roster of all potentially eligible U. S. male physicians provided by the American Medical Association, randomised to beta-carotene, vitamin E, vitamin C, and a multivitamin, or their placebos Included 1307 men with a history of prior cancer at randomisation For analyses of the secondary end points of total mortality, any cancer mortality, and site-specific cancer deaths, we included all participants Trial Registration, ClinicalTrials.gov Identifier: NCT00270647 Funding. Sponsors and Collaborators Brigham and Women's Hospital and National Cancer Institute

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Randomised according to a two-by-two factorial design, with use of a computer-generated list of random numbers" Quote: "will be stratified according to age (55-59, 60-64, 65-69, 70-74, and 751 years) in blocks of sixteen."

Gaziano 2009 (*Continued*)

Allocation concealment (selection bias)	Low risk	Central provision of active drugs and placebo. Quote: "The participants were sent monthly calendar packs"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Very small percentage of losses in follow-up (0.01% of participants-years of follow-up)
Selective reporting (reporting bias)	Low risk	The study protocol is available and published reports include all prespecified outcomes
Other bias	Low risk	The study appears to be free of other sources of bias.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: Blinding of participants and physicians.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "reported diagnoses were confirmed after examination of all available information by a committee of physicians..., all blinded to treatment assignment"

Hennekens 1996

Methods	Physicians' Health Study (PHS) Randomised controlled trial. Double-blind Objective: to evaluate the effectiveness of beta-carotene supplements for preventing cancer. Harvard Medical School and Brigham and Women's Hospital, Boston, USA. Period: 1982-1995. Intention to treat analysis.
Participants	22,071 male healthy physicians (11,112 smokers and 10,919 non-smokers), selected from the American Medical Association; Aged 40-84; no history of cancer (except non-melanoma skin cancer), myocardial infarction, stroke or transient cerebral ischemias; no current liver or renal disease, peptic ulcer, gout, No contraindications to aspirin, or use of aspirin, other platelet active drugs, nonsteroidal antiinflammatory agents or vitamin A supplements; no side-effects to aspirin. High compliance, measured in a run-in-phase Smoking status definition criteria: none explicit. Categories: never, former, current
Interventions	1) Intervention: beta-carotene (50 mg on alternate days), n=11,036. 2) placebo, n=11,035. Duration of treatment: average 12 years (range, 11.6 to 14.2)

Hennekens 1996 (*Continued*)

Outcomes	Incidence of cancer (except non-melanoma skin cancer); histopathologically confirmed; only the first diagnosed cancer during follow-up was counted. Lung cancer mortality. Total mortality, total cancer mortality. Follow-up: average 12 years (from randomisation).
Notes	The study tested two hypotheses: 1) aspirin (325 mg alternate days) reduces cardiovascular mortality; 2) beta-carotene reduces incidence of cancer. Only data on objective 2 were included in this review. The aspirin component was terminated early, on 1988, due to a statistically extreme reduction in incidence of first myocardial infarction 5% of participants did not give consent to confirm their potential events and were not included in the analysis Trial Registration, ClinicalTrials.gov Identifier: NCT00005252 Funding. Sponsors and Collaborators: National Heart, Lung, and Blood Institute (NHLBI)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Randomised according to a two-by-two factorial design, with use of a computer-generated list of random numbers" Quote: "The Physicians' Health Study is a randomised, double-blind, placebo-controlled trial with a two-by-two factorial design."
Allocation concealment (selection bias)	Low risk	Central provision of active drugs and placebo. Quote: "The participants were sent monthly calendar packs"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: Data on all 22,071 participants were analysed according to their treatment assignment, 0.3% were lost to follow-up. The data were analysed according to intention to treat
Selective reporting (reporting bias)	Low risk	The study protocol is available and published reports include all prespecified outcomes (mortality of cardiovascular disease and lung cancer incidence)
Other bias	Low risk	The study appears to be free of other sources of bias.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: Blinding of participants and physicians.

Hennekens 1996 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "reported diagnoses were confirmed after examination of all available information by a committee of physicians..., all blinded to treatment assignment"

Hercberg 2010

Methods	Trial Registration: "Primary Prevention Trial of the Health Effects of Antioxidant Vitamins and Minerals." Randomised, placebo-controlled trial Objective: assess the efficacy of nutritional doses of supplementation with a combination of antioxidant vitamins and minerals in reducing the incidence of cancer and ischemics cardiovascular disease in the general population France.
Participants	Inclusion criteria: women in the range of 35-60 and men in the age range of 45-60 from all over France At randomisation 6364 placebo and 6377 supplemented group. 60.5% women; mean age 49 years. Women: 54.1% non-smokers, 28.9% former smokers, 17% current smokers; men: 32.3% non-smokers, 46,2% former smokers, 21.5% current smokers Smoking status definition criteria: none explicit.
Interventions	1) Intervention:combination of antioxidants (120 mg of ascorbic acid, 30 mg of vitamin E, 6 mg of beta-carotene, 100 μg of selenium [as selenium-enriched yeast], and 20 mg of zinc [as gluconate]) in a single daily capsule 2) Placebo in a single daily capsule. Duration of treatment: 8 years.
Outcomes	Primary outcomes: major fatal and nonfatal ischemics cardiovascular events and cancer of any kind, except for basal cell carcinoma of the skin Secondary outcome:all-cause mortality. Follow-up period 12,5 years.
Notes	Trial Registration, ClinicalTrials.gov Identifier: NCT00272428 The SU.VI.MAX project received public and private support form the following several companies or subsidiaries, all located in France: Institut National de la Santé Et de la Recherche Médicale, Fruit d'Or Recherche, Lipton, Cereal, Candia, Kellogg's, CERIN, LU/Danone, Sodexho, L'Oréal, Estée Lauder, Peugeot, Jet Service, RP Scherer, France Telecom, Becton Dickinson, Fould Springer, Boehringer Diagnostic, Seppic Givaudan Lavirotte, Le Grand Canal, Air Liquide, Carboxyque, Klocke, Trophy Radio, Jouan, and Perkin Elmer

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Hercberg 2010 (*Continued*)

Random sequence generation (selection bias)	Low risk	Random treatment allocation was performed by block-sequence generation stratified by sex, age group, smoking habits, and residence area
Allocation concealment (selection bias)	Low risk	Capsules were prepared in 52 weekly packages of 7 capsules and delivered each year in a box labelled with the participant's number and a 10-digit lot number
Incomplete outcome data (attrition bias) All outcomes	Low risk	At the end of the supplementation period remained 5501 participants in the intervention group and 5553 in the placebo group. Losses in the post-intervention period explained
Selective reporting (reporting bias)	Low risk	Authors present results on all outcome measures that were prespecified as relevant
Other bias	Low risk	The study appears to be free of other sources of bias.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Randomisation was concealed from subjects and all investigators except for the few who were in charge of capsule labelling.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Randomisation was concealed from subjects and all investigators except for the few who were in charge of capsule labelling

Kamangar 2006

Methods	Linxian General Population Nutrition Intervention Trial Randomised, double-blind, placebo-controlled trial. Objective: to evaluate the effectiveness of daily vitamin and mineral supplements for the prevention of cancer and mortality for all causes. Four communes (Yaocun, Rencun, Donggang and Hengshui) in northern Linxian, China
Participants	29,584 adults Median age 52 years; 55% female; 30% smoked tobacco; 23% reported alcohol use the past year, and 32% had a family history of oesophageal or stomach cancer Inclusion criteria: 40 to 69-year-old adults, with no history of malignancy. Smoking status definition criteria: ever smoking cigarettes for 6 o more months

Interventions	Five groups: a) retinol (as palmitate 5000 IU) and zinc (as zinc oxide 22.5 mg) daily b) riboflavin (3.2 mg) and niacin (40 mg) daily c) vitamin C (ascorbic acid 120 mg) and molybdenum (as molybdenum yeast complex 30 ug) daily d) beta-carotene (15 mg), vitamin E (a-tocopherol 30 mg) and selenium (as selenium yeast 50 ug) daily e) placebo daily Doses for those daily supplements ranged from 1 to 2 times United States Recommended Daily Allowances. Duration of treatment: 5.25 years
Outcomes	- Cancer incidence - Cancer mortality - Total mortality Follow-up: 15 years. Intervention 5,2 years and post -intervention follow-up ten years
Notes	Quote: "The people of Linxian are deficient in many micronutrients, which may limit the generalization of these results. Nevertheless, the results of this study are similar to other chemoprevention studies, which did not find benefit from vitamins in reducing lung cancer incidence or mortality." In Linxian area oesophageal and gastric cardia cancer mortality were among the highest in the world Trial Registration, ClinicalTrials.gov Identifier: NCT00342654 Funding. Sponsors and Collaborators: National Cancer Institute

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Computer-generated random numbers".
Allocation concealment (selection bias)	Low risk	Central allocation.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "case ascertainment was considered complete and loss to follow-up minimal (n = 276, or <1%)"
Selective reporting (reporting bias)	Low risk	Authors present results on all outcome measures that were prespecified as relevant
Other bias	Low risk	The study appears to be free of other sources of bias.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Stated as "double-blind or "double masked". Coded pill bottles kept in the central study management centre and available only to the study data manager

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Stated as "double-blind or "double masked".

Lee 2005

Methods	Women's Health Study (WHS) Randomised, double-blind, placebo controlled trial, using a 2 x 2 x 2 factorial design. Objective: to test the balance of benefits and risks of aspirin, vitamin E, and beta-carotene in the primary prevention of cancer and cardiovascular disease Brigham and Women's Hospital and Harvard Medical School, Boston, USA. Period: 1993-1998. Intention to treat analysis
Participants	39,876 female health professionals; aged 45 or older. No history of cancer (except non-melanoma skin cancer), coronary heart disease or cerebrovascular disease. 13% (2635) of women assigned to beta-carotene and 13% (2635) of placebo group were cigarette smokers at baseline Smoking status definition criteria: none explicit. Categories: current, past or never
Interventions	Eight treatment groups: all three active agents, three groups of two active agents and one placebo, three groups of one active agent and two placebo, or all three placebos. Comparisons: - beta-carotene (50 mg alternate days) groups (n=19939) or vs placebo groups (n=19937) - vitamin E (600 IU every other day) vs placebo groups Duration of treatment: 2.1 years.
Outcomes	Primary endpoint: invasive cancer, cardiovascular events (nonfatal myocardial infarction non fatal stroke and death). Follow-up after completion of treatment (median) = 4.1 years
Notes	The beta-carotene component was terminated early because of harmful results of an interim analysis in the CARET study for beta-carotene Trial Registration, ClinicalTrials.gov Identifier: NCT00000479 Sponsors and Collaborators: National Heart, Lung, and Blood Institute (NHLBI)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Insufficient information in publications to permit judgement, but probably done using a "computer-generated list of random numbers" since some of the members of the team were the same of the Physicians Health Study. Quote: "Is a randomised study, with a two-by-two factorial design."

Lee 2005 (*Continued*)

Allocation concealment (selection bias)	Low risk	Quote: "Study agents provided in convenient monthly calendar packs."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Only three losses were reported among the 39,876 participants."
Selective reporting (reporting bias)	Low risk	The study protocol is available and published reports include all prespecified outcomes
Other bias	Low risk	The study appears to be free of other sources of bias.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Participants and investigators will be blinded to treatment groups."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Reported diagnoses will be confirmed by an End points Committee of physicians (all of whom will be blinded to participant´ s treatment assignments)."

Lin 2009

Methods	Women's Antioxidant and Cardiovascular Study (WACS) Randomised, double-blind, placebo-controlled, 2 × 2 × 2 factorial trial. Objective: to evaluated the individual and combined effects of three antioxidant supplements, ascorbic acid, vitamin E, and beta-carotene, in the prevention of cardiovascular diseases USA.
Participants	7627 US female health professionals. Median age 60.4 years; 77% Postmenopausal, 77% overweight or obese, 27% reported having taken multivitamins at baseline Inclusion criteria: At least 40 years-old; were postmenopausal or not intending to become pregnant; and had known CVD or at least three of the following cardiac risk factors: hypertension, high cholesterol level, diabetes, parental history of myocardial infarction, or obesity (i.e., body mass index $\geq$ 30 kg/m 2) Exclusion criteria: self-reported history of cancer (except non melanoma skin cancer) within the past 10 years, had active liver disease or cirrhosis, had chronic kidney failure, were current users of anticoagulants, or were unwilling to avoid out-of study use of vitamins A, C, and E and beta-carotene at intakes exceeding the recommended daily allowance during the trial Smoking status definition criteria: none explicit. Categories: never, past, current
Interventions	WACS was designed as a 3 group trial: a) vitamin C (500 mg of ascorbic acid) vs. placebo daily. b) vitamin E (600 IU of α -tocopherol) vs. placebo every other day c) beta-carotene (50 mg of Lurotin) vs. placebo every other day

	Duration of treatment: average 9.2 years.
Outcomes	Primary outcomes: Incidence and total cancer mortality, and specific cancers (Breast, Lung, Colorectal, Pancreas, Uterine, Ovary, Non-Hodgkin Lymphoma and other cancers) Average duration of follow-up from random assignment to the end of the trial was 9.4 years
Notes	The trial was conducted as a companion to the Women's Health Study (WHS) Quote: "This study had very limited statistical power to investigate any effect of dietary antioxidants on the risk of specific cancers." Trial Registration, clinicaltrials.gov Identifier: NCT00000541 Funding. Sponsors and Collaborators: National Heart, Lung, and Blood Institute (NHLBI)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Subjects were randomised in a 2 x 2 x 2 factorial design to 500 mg of vitamin C or placebo daily, 600 mg of vitamin E or placebo on alternate days and/or 50 mg of beta-carotene or placebo on alternate days. There was a three month run-in phase in which eligible patients received placebo caplets. Subjects were randomised only if they reported good compliance, willingness to continue in the trial, had no history of cancer, active liver disease, or use of coumadin, and expressed continued willingness to forego the use of beta-carotene and vitamin A, C, or E supplements. In 1998, participants were further randomised to the B-vitamin intervention (folic acid, vitamin B6, vitamin B12)
Allocation concealment (selection bias)	Low risk	Central allocation.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No detailed information published on losses in follow-up.
Selective reporting (reporting bias)	Low risk	Authors present results on all outcome measures that were prespecified as relevant
Other bias	Low risk	The study appears to be free of other sources of bias.

Lin 2009 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Stated as "double-blind".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Stated as "double-blind".

Lippman 2009

Methods	Selenium and Vitamin E Cancer Prevention Trial (SELECT). Phase III randomised, placebo-controlled trial. Objective: to determine whether selenium, vitamin E, or both could prevent prostate cancer and other diseases with little or no toxicity in relatively healthy men
Participants	35 533 men from 427 participating sites in the United States, Canada, and Puerto Rico Median age 62.4 years; 78%, White 20% African Americans, 3% Hispanics, 1% Asians and 17% had a family history of prostate cancer Inclusion criteria: age 50 years or older for African American men and 55 years or older for all other men, no prior prostate cancer diagnosis, 4 ng/mL or less of PSA in serum, and a digital rectal examination (DRE) not suspicious for cancer. No current use of anticoagulant therapy other than 175 mg/d or less of acetylsalicylic acid or 81 mg/d or less of acetylsalicylic acid with clopidogrel bisulphate, no history of hemorrhagic stroke, and normal blood pressure Smoking status definition criteria: none explicit. Categories: never, current, former, ever (unknown status), unknown
Interventions	SELECT was designed as a 4 group trial with 5 prespecified comparisons: a) Selenium (200 μg) vs placebo daily b) Vitamin E (400 IU) vs placebo daily c) Selenium (200 μg) and vitamin E (400 IU) vs placebo daily d) selenium(200 μg) vs selenium(200 μg) and vitamin E(400 IU) daily e) vitamin E(400 IU) vs selenium and vitamin E(400 IU) daily Duration of treatment: seven years.
Outcomes	Prostate cancer survival and prespecified secondary outcomes, including lung, colorectal, and overall primary cancer incidence and survival Duration of follow-up: seven years (planned follow-up of minimum of 7 years and a maximum of 12 years)
Notes	Quote: "On September 15, 2008, the independent data and safety monitoring committee met, reviewed data as of August 1, 2008, for the second formal interim analysis, and recommended the discontinuation of study supplements because the alternative hypothesis of no evidence of benefit from either study agent was convincingly demonstrated (P.0001) and there was no possibility of a benefit to the planned degree with additional follow-up. Study sites were notified to discontinue supplements on October 23, 2008, and the data presented in this article are current as of this date." Trial Registration, ClinicalTrials.gov Identifier: NCT00006392

	Funding. Sponsors and Collaborators: Southwest Oncology Group, National Cancer Institute, National Center for Complementary and Alternative Medicine (NCCAM), Eastern Cooperative Oncology Group Cancer and Leukemia Group B, NCIC Clinical Trials Group

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: Participants were randomised in a randomised block scheme, in which the block was the study site. This ensured a balance of the 4 intervention groups within each study site
Allocation concealment (selection bias)	Low risk	Central randomisation.
Incomplete outcome data (attrition bias) All outcomes	Low risk	The authors' detailed information published on losses in follow-up. Quote: "All analyses were performed by using an intention-to-treat analysis in which men were classified according to the group to which they were randomised."
Selective reporting (reporting bias)	Low risk	Authors present results on all outcome measures that were prespecified as relevant
Other bias	Low risk	Monitoring policy for stopping the trial and interim analyses previously defined
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Doble-blind and main outcome measures assessments are not likely to be biassed by lack of blinding. Quote: "To ensure the quality Supplement Quality Control and Quality Assurance of the blind was maintained, capsules received in each subsequent lot were compared with the previous lot and with matching capsules in the current shipment for their characteristics of weight, shape and size, colour and external marking, odour, and comparability of contents of opened capsules."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Doble-blind and main outcome measures assessment are not likely to be biassed by lack of blinding

Omenn 1996

Methods	Carotene and Retinol Efficacy Trial (CARET) Randomised, double-blind, placebo-controlled trial. Objective: to evaluate the effectiveness of retinol and beta-carotene supplements for the prevention of lung cancer. Seattle, Portland, San Francisco, Baltimore, Conneticut, Irvine (USA). Period: pilot study: 1985-1988; efficacy cohort: 1989 and 1991 recruitment of additional study centres, follow-up until 1995 and 2000. Intention to treat analysis.
Participants	1) 4,060 male workers exposed to asbestos; Aged 45-69 (45-74 in pilot study), 15 years. previous exposure to asbestos, and asbestos related disease or workers in high risk trades for 5 years, current non- smokers or smoking in previous 15 years. Smoking status definition criteria: none explicit. 2) 14,254 male and female smokers recruited from health care organisations; Aged 50-69 years, heavy current or ex-smokers (previous 6 years) of 20 or more pack-years cigarettes Inclusion Criteria: - Asbestos-exposed men who were:current smokers or quit within 15 years prior to enrolment had first exposure to asbestos on the job at least 15 years prior to enrolment had chest X-ray positive for changes compatible with asbestos exposure according to ILO. criteria; or had been employed in a protocol-defined high-risk trade for at least 5 years, at least 10 years prior to enrolment - Heavy Smokers, men and women:cigarette smoking history of 20+ pack-years either current smokers or had quit within previous 6 years Exclusion Criteria: - Premenopausal women. - History or cirrhosis or hepatitis within 12 months prior to enrolment - Taking > 5500 IU daily vitamin A supplement. - Taking any beta-carotene supplement. - History of cancer within 5 years prior to enrolment. - SGOT > than 2.5x upper limit of normal, or alkaline phosphatase > 1.5x upper limit of normal - taking less than 50% of study vitamins during the enrolment period between the First and Second Visit
Interventions	Intervention: 30 mg/day beta-carotene + 25,000 IU/day retinol Comparison: two placebos, one each/day. Duration of treatment: planned for eight years but stopped ahead schedule after interim analysis
Outcomes	Lung cancer incidence. Incidence of other cancers. Cancer mortality. The During the post-intervention phase primary endpoints were incidences of lung cancer, all-cause mortality, and mortality from cardiovascular disease Duration of follow-up: stopped ahead schedule after interim analysis
Notes	Information on cancer incidence and mortality was obtained from clinical records. The CARET intervention was stopped 21 months early because of clear evidence of no benefit and substantial evidence of possible harms. Because the CARET Steering Committee decided to end active intervention on January 11,1996, all participants were asked to stop taking the intervention agents and to return them to their study centre,

	where a final blood sample was collected from each participant and written informed consent was obtained for post-intervention follow-up A total of 1174 participants who were enrolled in CARET did not contribute participant-years of follow-up to this post-intervention analysis; of these, 1092 (93%) died during the intervention phase and 82 (7%) were lost to follow-up. In the ongoing postintervention follow-up in CARET, 93% of the living participants are being followed actively through mailed questionnaires; the remainder (including those considered lost to follow-up during the intervention phase) are being followed passively through searches of local cancer registries and the National Death Index Trial Registration Identifier: NCT00712647. Funding:Sponsors and Collaborators Fred Hutchinson Cancer Research Center and national Cancer Institute

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: Randomization is based on a permuted blocks algorithm with random block size and equal allocation to the two arms, stratified by study centre and exposure population.The unit of randomizations is the household to guard against household members taking the wrong vitamin type
Allocation concealment (selection bias)	Low risk	Central allocation.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "As of December 15, 1995, ascertainment of vital status was more than 98 percent complete"
Selective reporting (reporting bias)	Low risk	Authors present results on all outcome measures that were prespecified as relevant
Other bias	Low risk	Monitoring policy for stopping the trial and interim analyses previously defined
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Stated as "double-blind or "double masked".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Stated as "double-blind or "double masked".

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Arnold 1992	Randomised placebo-controlled trial of chemoprevention in healthy smokers, but outcome measure was changes in sputum atypia (intermediate endpoint)
Ayoub 1999	Randomised controlled trial of chemoprevention in healthy smokers, but outcome measure was abnormalities in the expression of RAR beta (intermediate endpoint)
Bolla 1994	Randomised controlled trial of chemoprevention in patients with squamous cell carcinoma of the head and neck (non-healthy participants)
Clark 1996	Randomised controlled trial of chemoprevention in patients with squamous cell carcinoma of the skin (non-healthy participants)
De Klerk 1998	Clinical controlled trial of chemoprevention. Intervention and control groups not randomly selected, though participants in the intervention group were randomised to receive either beta-carotene or retinol
de Vries 1991	Randomised controlled trial of chemoprevention in patients with non-small cell lung cancer
Heimburger 1988	Randomised, double-blind trial of chemoprevention in patients with bronchial squamous metaplasia and outcome measures were changes in metaplasia index (intermediate endpoint)
Hong 1990	Randomised controlled trial of chemoprevention in patients with squamous cell cancers of the larynx, pharynx or oral cavity (non-healthy participants)
Kato 1997	Randomised controlled trial of chemoprevention in patients with bronchial squamous metaplasia. The effect was estimated with a scoring system of cell atypia (intermediate endpoint)
Kurie 2000	Randomised, double-blind, placebo-controlled trial of chemoprevention in healthy smokers, but the outcome measure was changes in bronchial epithelium (intermediate endpoint)
Lee 1994	Randomised placebo-controlled trial of chemoprevention of lung cancer in healthy smokers, but the outcome measure was changes in bronchial metaplasia index (intermediate endpoint)
Lee 1998	Comparative study with placebo-controlled group in healthy smokers, but was not randomised and the outcome was oxidative DNA and protein (globin) damage) (intermediate endpoint)
Lippman 2001	Randomised controlled trial of chemoprevention in patients with squamous adenocarcinoma, large-cell or bronchioalveolar non-small cell lung cancer
Lonn 2005	Participants were not healthy participants.
Mayne 2001	Randomised controlled trial of chemoprevention in patients with squamous cell carcinoma of the oral cavity, pharynx or larynx, or carcinoma in situ (non-healthy participants)

(*Continued*)

McLarty 1995	Randomised, placebo-controlled trial of chemoprevention in healthy asbestos workers, but the outcome measure was the reduction in the incidence and prevalence of sputum atypia (intermediate endpoint)
NCT00008385	On-going randomised controlled trial of chemoprevention in patients with non-small cell lung cancer
NPC trial 2002	The study was originally designed to test the efficacy of selenium supplementation in preventing non melanoma skin cancer recurrence in men and women with a history of two or more basal cell carcinoma or one squamous cell carcinoma of the skin (non-healthy participants)
Pastorino 1993	Randomised controlled trial of chemoprevention in patients with non-small cell lung cancer
Van Poppel 1997	Randomised controlled trial of chemoprevention in healthy smokers, but the outcome were sputum cytology (intermediate endpoint)
Veronesi 1999	Randomised controlled trial of chemoprevention in patients with breast cancer (non-healthy participants)
Wang 1989	Randomised controlled trial of chemoprevention in patients with moderate or severe atypical hyperplasia cells in the sputum, compared two different regimens of chemoprevention
Willett 1984	Randomised placebo-controlled trial of chemoprevention in healthy female workers, but the outcome was plasma retinol level (intermediate endpoint)
Yun 2010	Randomised, double-blinded, placebo-controlled trial on 643 chronic atrophic gastritis patients (non-healthy participants)

DATA AND ANALYSES

Comparison 1. Vitamin A (beta-carotene or retinol) vs. placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incidence lung cancer	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 High risk people (smokers and asbestos workers)	4	49230	Risk Ratio (M-H, Random, 95% CI)	1.11 [1.01, 1.21]
1.2 Low risk people (non-smokers or mixed population)	4	202924	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.76, 1.42]
2 Mortality lung cancer	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 High risk people (smokers)	2	29426	Risk Ratio (M-H, Random, 95% CI)	1.18 [1.01, 1.38]
2.2 Low risk people (non-smokers or mixed population)	2	160692	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.35, 1.44]
3 Incidence all cancers	3	44267	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.97, 1.07]
3.1 High risk people (smokers and asbestos workers)	1	14569	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.98, 1.12]
3.2 Low risk people (non-smokers or mixed population)	1	7627	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.86, 1.16]
3.3 Global PHS study population	1	22071	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.92, 1.06]
4 Mortality all cancers	1	22071	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.88, 1.17]
5 Mortality all causes	2	32883	Risk Ratio (M-H, Random, 95% CI)	1.09 [1.05, 1.13]
5.1 High risk people (smokers and asbestos workers)	2	32883	Risk Ratio (M-H, Random, 95% CI)	1.09 [1.05, 1.13]

Comparison 2. Vitamin C vs. placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incidence lung cancer	2	22268	Risk Ratio (M-H, Random, 95% CI)	1.29 [0.67, 2.49]
1.1 Males	1	14641	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.64, 1.38]
1.2 Females	1	7627	Risk Ratio (M-H, Random, 95% CI)	1.84 [1.14, 2.95]
2 Mortality lung cancer	1	14641	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.53, 1.24]
2.1 Males	1	14641	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.53, 1.24]
3 Incidence all cancers	2	22268	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.94, 1.13]
3.1 Males	1	14641	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.92, 1.09]
3.2 Females	1	7627	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.95, 1.29]
4 Mortality all cancers	1	14641	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.89, 1.24]
4.1 Males	1	14641	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.89, 1.24]
5 Mortality all causes	1	14641	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.97, 1.16]

5.1 Males	1	14641	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.97, 1.16]

Comparison 3. Vitamin E (alpha-tocopherol) vs. placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incidence lung cancer	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 High risk people (smokers and asbestos workers)	1	14573	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.89, 1.15]
1.2 Males 50 years or older	2	32074	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.73, 1.21]
1.3 Women	2	47503	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.90, 1.43]
2 Mortality lung cancer	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 High risk people (male smokers)	1	14573	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.73, 1.19]
2.2 Males 50 years or older	2	32074	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.72, 1.32]
3 Incidence all cancers	5	94141	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.97, 1.04]
3.1 High risk people (smokers and asbestos workers)	1	14564	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.91, 1.05]
3.2 Males 50 years or older	2	32074	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.97, 1.10]
3.3 Women	2	47503	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.93, 1.06]
4 Mortality all cancers	2	54517	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.99, 1.24]
4.1 Males	1	14641	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.92, 1.29]
4.2 Females	1	39876	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.95, 1.32]
5 Mortality all causes	4	86523	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.98, 1.06]
5.1 High risk people (smokers and asbestos workers)	1	14573	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.98, 1.07]
5.2 Males 50 years or older	2	32074	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.91, 1.09]
5.3 Females	1	39876	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.93, 1.15]

Comparison 4. Selenium vs. placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incidence lung cancer	1	17448	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.80, 1.54]
1.1 Males	1	17448	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.80, 1.54]
2 Mortality lung cancer	1	17448	Odds Ratio (M-H, Fixed, 95% CI)	1.09 [0.71, 1.67]
2.1 Males	1	17448	Odds Ratio (M-H, Fixed, 95% CI)	1.09 [0.71, 1.67]
3 Incidence all cancers	1	17448	Odds Ratio (M-H, Fixed, 95% CI)	1.01 [0.91, 1.12]
3.1 Males	1	17448	Odds Ratio (M-H, Fixed, 95% CI)	1.01 [0.91, 1.12]
4 Mortality all cancers	1	17448	Odds Ratio (M-H, Fixed, 95% CI)	1.02 [0.79, 1.30]
4.1 Males	1	17448	Odds Ratio (M-H, Fixed, 95% CI)	1.02 [0.79, 1.30]
5 Mortality all causes	1	17448	Odds Ratio (M-H, Fixed, 95% CI)	0.98 [0.85, 1.14]
5.1 Males	1	17448	Odds Ratio (M-H, Fixed, 95% CI)	0.98 [0.85, 1.14]

Comparison 5. Vitamin A (beta-carotene)+ Vitamin E (alpha-tocopherol) vs. placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incidence lung cancer	1	14565	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.97, 1.24]
1.1 High risk people (smokers and asbestos workers)	1	14565	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.97, 1.24]
2 Incidence all cancers	1	14565	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.97, 1.11]
2.1 High risk people (smokers and asbestos workers)	1	14565	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.97, 1.11]
3 Mortality all causes	1	14565	Risk Ratio (M-H, Random, 95% CI)	1.06 [1.02, 1.11]
3.1 High risk people (smokers and asbestos workers)	1	14565	Risk Ratio (M-H, Random, 95% CI)	1.06 [1.02, 1.11]

Comparison 6. Vitamin C + Vitamin E vs. placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incidence lung cancer	1	7328	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.50, 1.39]
1.1 Males	1	7328	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.50, 1.39]
2 Incidence all cancers	1	7309	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.91, 1.16]
2.1 Males	1	7309	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.91, 1.16]

Comparison 7. Vitamin E (alpha-tocopherol) + selenium vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incidence lung cancer	1	17399	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.84, 1.61]
1.1 Males	1	17399	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.84, 1.61]
2 Mortality lung cancer	1	17399	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.61, 1.47]
2.1 Males	1	17399	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.61, 1.47]
3 Incidence all cancers	1	17399	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.94, 1.12]
3.1 Males	1	17399	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.94, 1.12]
4 Mortality all cancers	1	17399	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.73, 1.20]
4.1 Males	1	17399	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.73, 1.20]
5 Mortality all causes	1	17399	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.82, 1.08]
5.1 Males	1	17399	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.82, 1.08]

Comparison 8. Vitamins A, C, E + selenium + zinc vs. Placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incidence lung cancer	1	12741	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.28, 1.48]
1.1 Males (65% exposed to tobacco or asbestos)	1	5028	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.22, 1.64]
1.2 Females (45% exposed to tobacco or asbestos)	1	7713	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.17, 3.37]
2 Incidence all cancers	1	12741	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.83, 1.10]
2.1 Males	1	5028	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.74, 1.06]
2.2 Females	1	7713	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.87, 1.20]
3 Mortality all causes	1	12741	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.70, 1.11]
3.1 Males	1	5028	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.60, 1.05]
3.2 Females	1	7713	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.72, 1.40]

Comparison 9. Vitamins A and E + selenium vs. placebo

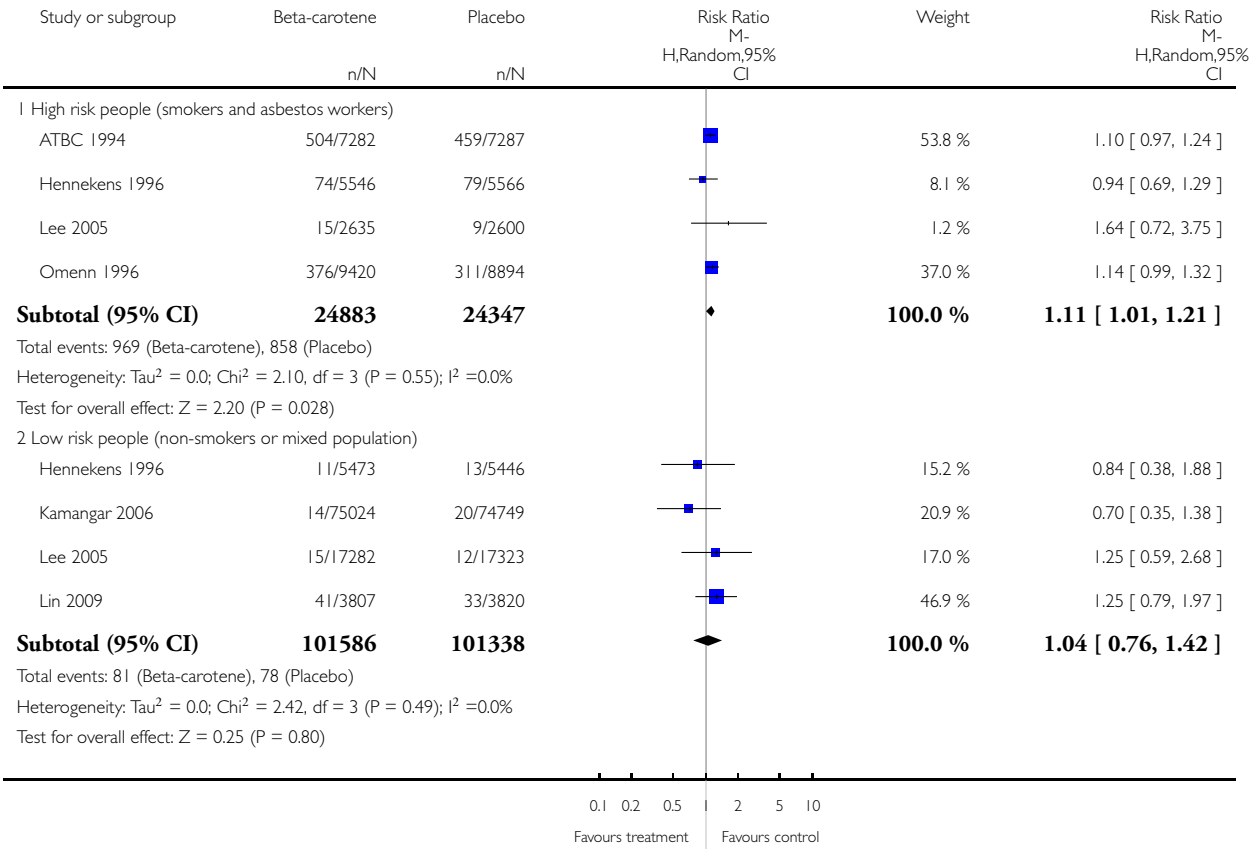
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality lung cancer (intervention period)	1	149773	Risk Ratio (M-H, Random, 95% CI)	0.55 [0.26, 1.14]

Analysis 1.1. Comparison 1 Vitamin A (beta-carotene or retinol) vs. placebo, Outcome 1 Incidence lung cancer.

Review: Drugs for preventing lung cancer in healthy people

Comparison: 1 Vitamin A (beta-carotene or retinol) vs. placebo

Outcome: 1 Incidence lung cancer

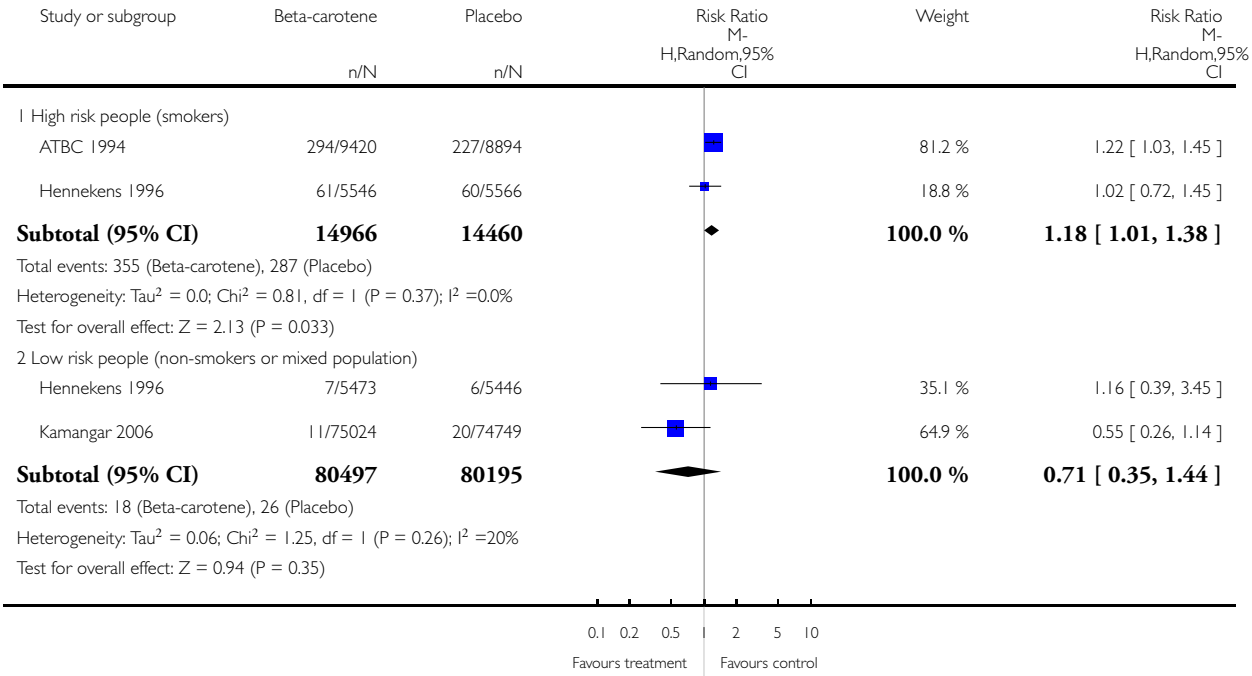


Analysis 1.2. Comparison 1 Vitamin A (beta-carotene or retinol) vs. placebo, Outcome 2 Mortality lung cancer.

Review: Drugs for preventing lung cancer in healthy people

Comparison: 1 Vitamin A (beta-carotene or retinol) vs. placebo

Outcome: 2 Mortality lung cancer



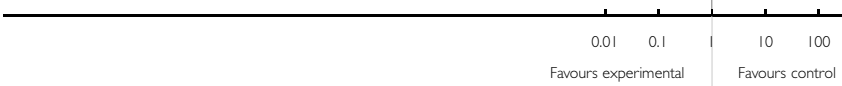
Analysis 1.3. Comparison 1 Vitamin A (beta-carotene or retinol) vs. placebo, Outcome 3 Incidence all cancers.

Review: Drugs for preventing lung cancer in healthy people

Comparison: 1 Vitamin A (beta-carotene or retinol) vs. placebo

Outcome: 3 Incidence all cancers

Study or subgroup	Beta-carotene n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 High risk people (smokers and asbestos workers)					
ATBC 1994	1392/7282	1327/7287		48.2 %	1.05 [0.98, 1.12]
Subtotal (95% CI)	**7282**	**7287**		**48.2 %**	**1.05 [0.98, 1.12]**
Total events: 1392 (Beta-carotene), 1327 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.40 (P = 0.16)					
2 Low risk people (non-smokers or mixed population)					
Lin 2009	311/3807	313/3820		9.8 %	1.00 [0.86, 1.16]
Subtotal (95% CI)	**3807**	**3820**		**9.8 %**	**1.00 [0.86, 1.16]**
Total events: 311 (Beta-carotene), 313 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.04 (P = 0.97)					
3 Global PHS study population					
Hennekens 1996	1273/11036	1293/11035		41.9 %	0.98 [0.92, 1.06]
Subtotal (95% CI)	**11036**	**11035**		**41.9 %**	**0.98 [0.92, 1.06]**
Total events: 1273 (Beta-carotene), 1293 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.42 (P = 0.67)					
Total (95% CI)	**22125**	**22142**		**100.0 %**	**1.02 [0.97, 1.07]**
Total events: 2976 (Beta-carotene), 2933 (Placebo)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 1.67, df = 2 (P = 0.43); I^2 =0.0%					
Test for overall effect: Z = 0.69 (P = 0.49)					
Test for subgroup differences: Chi^2 = 1.67, df = 2 (P = 0.43), I^2 =0.0%					



Analysis 1.4. Comparison 1 Vitamin A (beta-carotene or retinol) vs. placebo, Outcome 4 Mortality all cancers.

Review: Drugs for preventing lung cancer in healthy people

Comparison: 1 Vitamin A (beta-carotene or retinol) vs. placebo

Outcome: 4 Mortality all cancers

Study or subgroup	Beta-carotene n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Hennekens 1996	386/11036	380/11035		100.0 %	1.02 [0.88, 1.17]
Total (95% CI)	**11036**	**11035**		**100.0 %**	**1.02 [0.88, 1.17]**

Total events: 386 (Beta-carotene), 380 (Placebo)

Heterogeneity: not applicable

Test for overall effect: Z = 0.22 (P = 0.83)

Test for subgroup differences: Not applicable

Analysis 1.5. Comparison 1 Vitamin A (beta-carotene or retinol) vs. placebo, Outcome 5 Mortality all causes.

Review: Drugs for preventing lung cancer in healthy people

Comparison: 1 Vitamin A (beta-carotene or retinol) vs. placebo

Outcome: 5 Mortality all causes

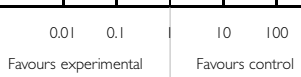
Study or subgroup	Beta-carotene n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 High risk people (smokers and asbestos workers)					
ATBC 1994	2819/7282	2605/7287		77.0 %	1.08 [1.04, 1.13]
Omenn 1996	1225/9420	1047/8894		23.0 %	1.10 [1.02, 1.19]
Total (95% CI)	**16702**	**16181**		**100.0 %**	**1.09 [1.05, 1.13]**

Total events: 4044 (Beta-carotene), 3652 (Placebo)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.20$, df = 1 (P = 0.65); $I^2 = 0.0\%$

Test for overall effect: Z = 4.46 (P < 0.00001)

Test for subgroup differences: Not applicable

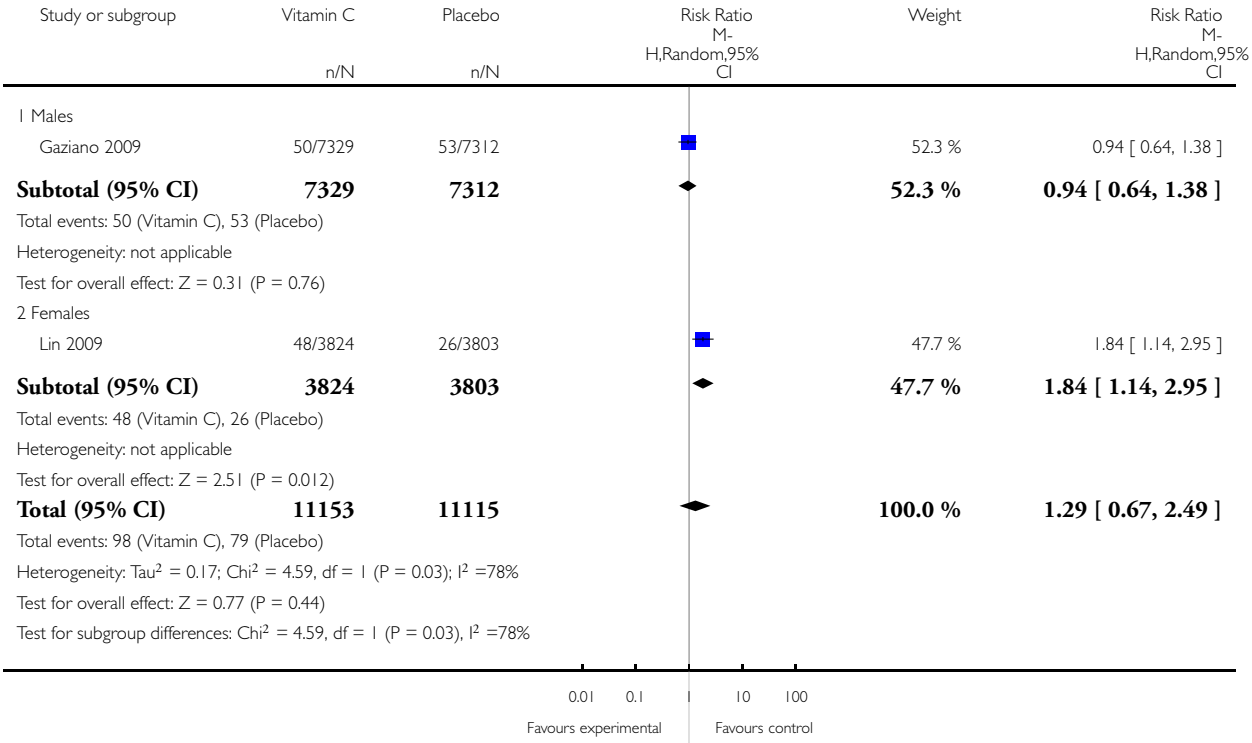


Analysis 2.1. Comparison 2 Vitamin C vs. placebo, Outcome 1 Incidence lung cancer.

Review: Drugs for preventing lung cancer in healthy people

Comparison: 2 Vitamin C vs. placebo

Outcome: 1 Incidence lung cancer

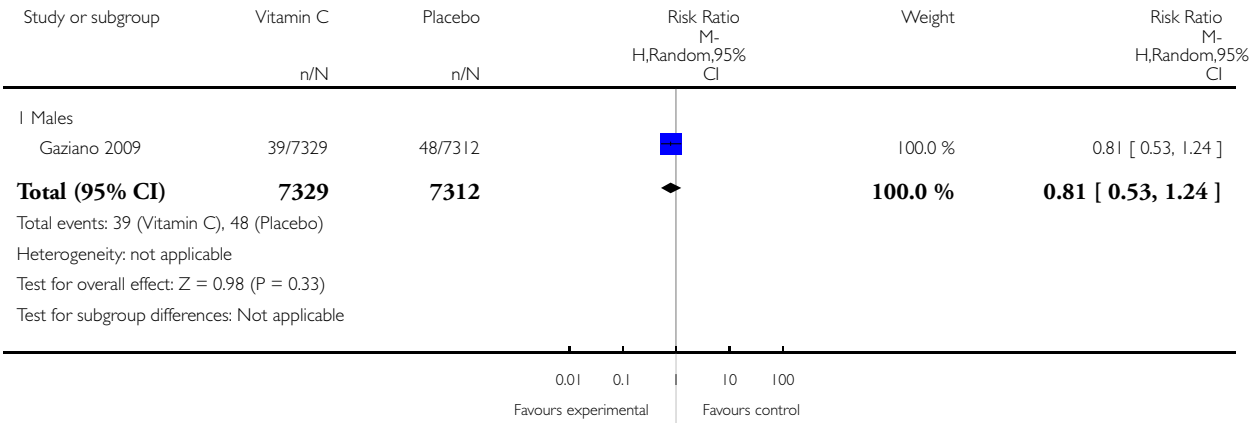


Analysis 2.2. Comparison 2 Vitamin C vs. placebo, Outcome 2 Mortality lung cancer.

Review: Drugs for preventing lung cancer in healthy people

Comparison: 2 Vitamin C vs. placebo

Outcome: 2 Mortality lung cancer

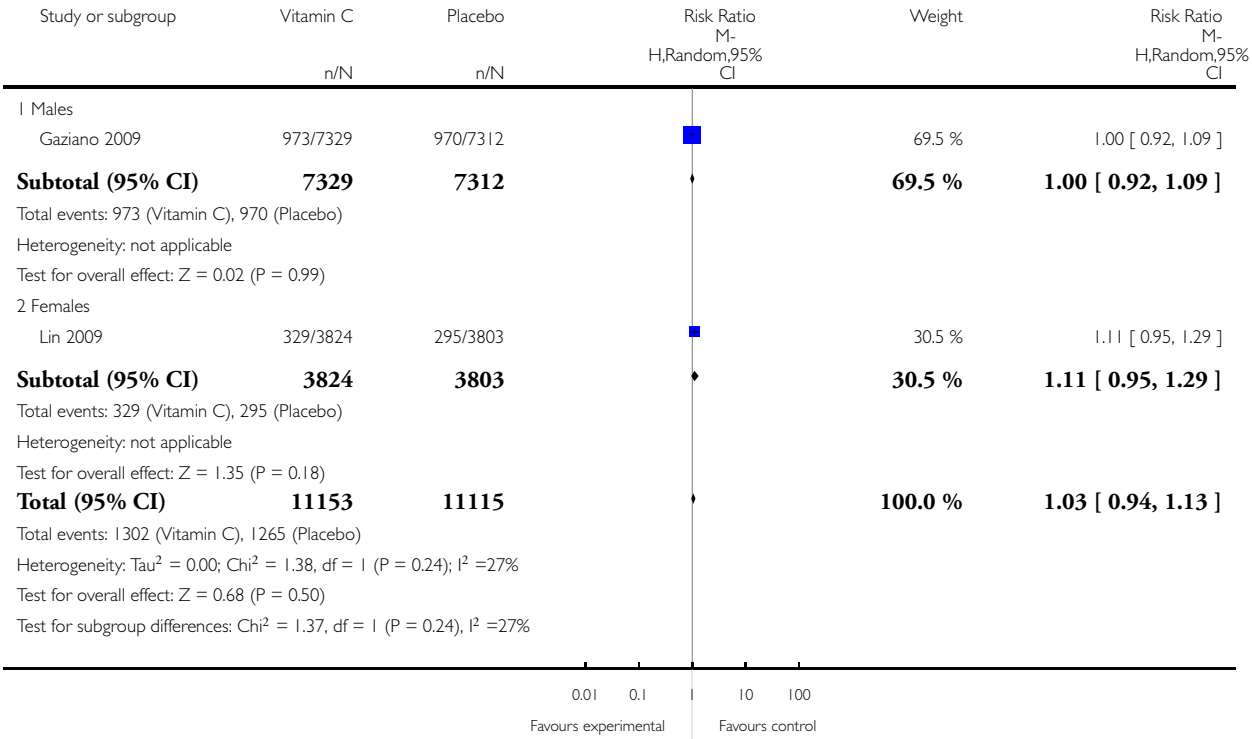


Analysis 2.3. Comparison 2 Vitamin C vs. placebo, Outcome 3 Incidence all cancers.

Review: Drugs for preventing lung cancer in healthy people

Comparison: 2 Vitamin C vs. placebo

Outcome: 3 Incidence all cancers

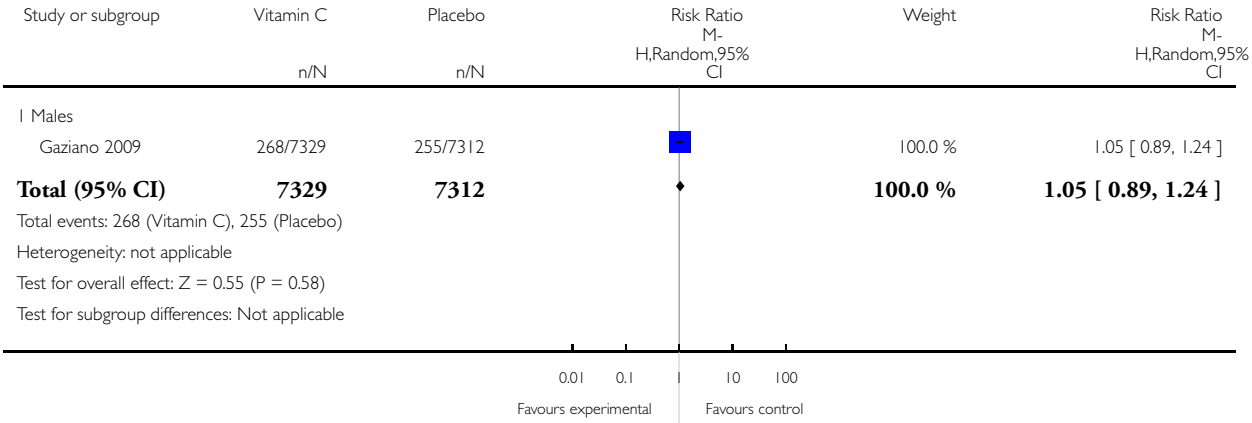


Analysis 2.4. Comparison 2 Vitamin C vs. placebo, Outcome 4 Mortality all cancers.

Review: Drugs for preventing lung cancer in healthy people

Comparison: 2 Vitamin C vs. placebo

Outcome: 4 Mortality all cancers

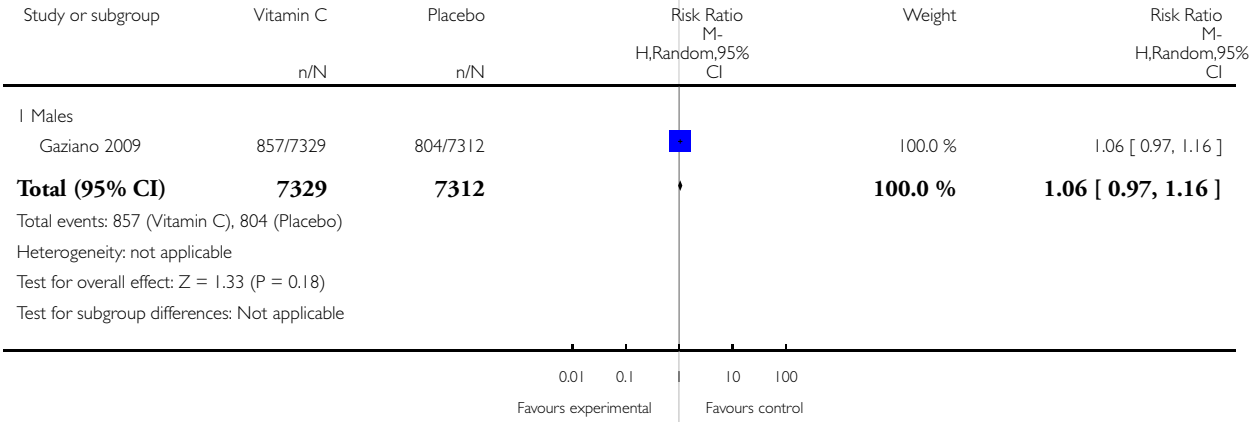


Analysis 2.5. Comparison 2 Vitamin C vs. placebo, Outcome 5 Mortality all causes.

Review: Drugs for preventing lung cancer in healthy people

Comparison: 2 Vitamin C vs. placebo

Outcome: 5 Mortality all causes

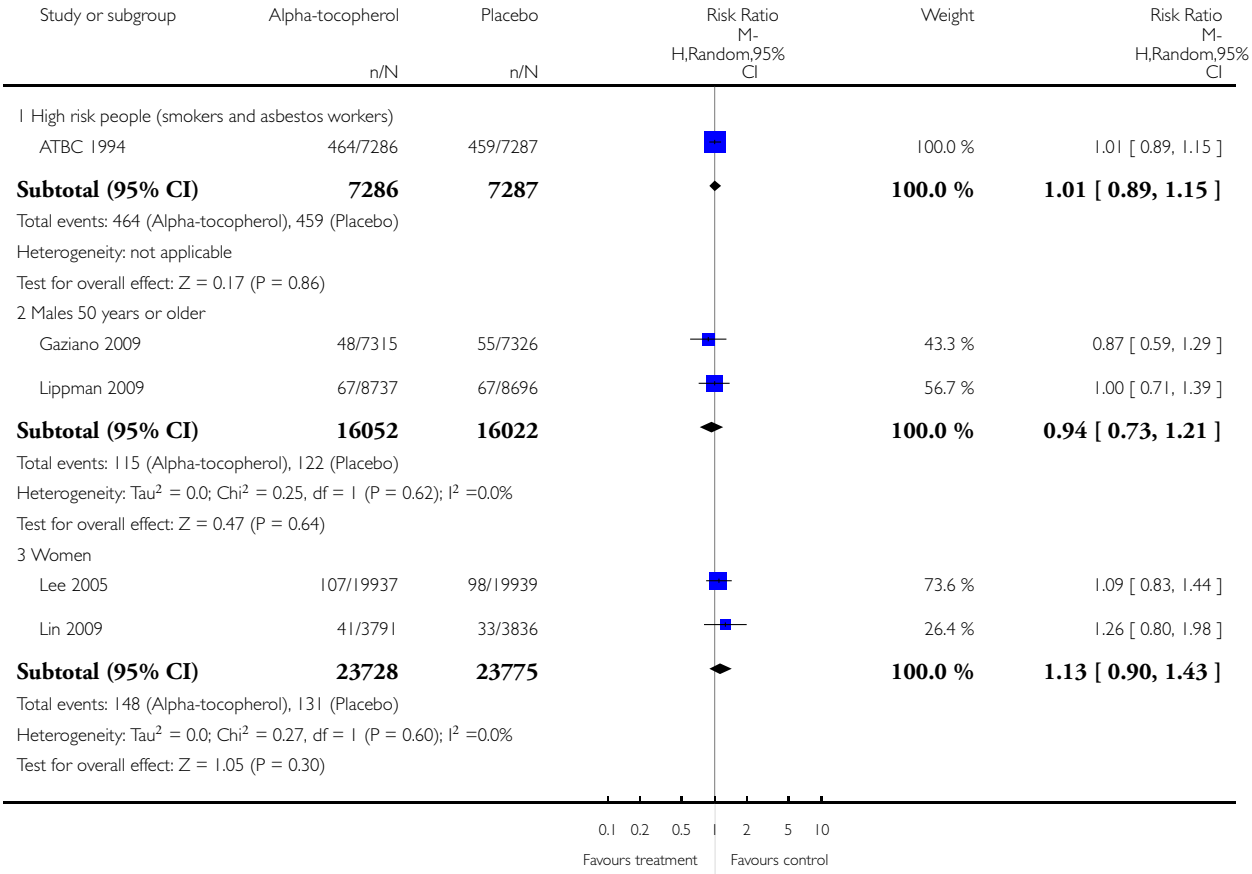


Analysis 3.1. Comparison 3 Vitamin E (alpha-tocopherol) vs. placebo, Outcome 1 Incidence lung cancer.

Review: Drugs for preventing lung cancer in healthy people

Comparison: 3 Vitamin E (alpha-tocopherol) vs. placebo

Outcome: 1 Incidence lung cancer

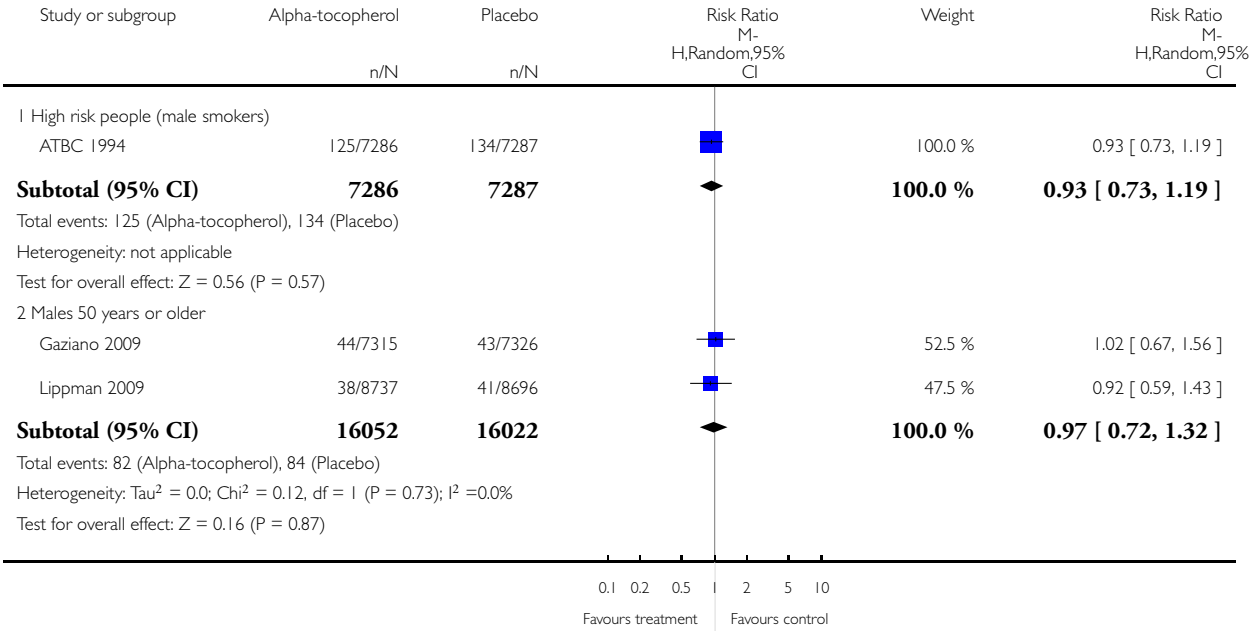


Analysis 3.2. Comparison 3 Vitamin E (alpha-tocopherol) vs. placebo, Outcome 2 Mortality lung cancer.

Review: Drugs for preventing lung cancer in healthy people

Comparison: 3 Vitamin E (alpha-tocopherol) vs. placebo

Outcome: 2 Mortality lung cancer



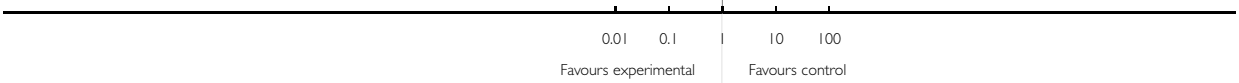
Analysis 3.3. Comparison 3 Vitamin E (alpha-tocopherol) vs. placebo, Outcome 3 Incidence all cancers.

Review: Drugs for preventing lung cancer in healthy people

Comparison: 3 Vitamin E (alpha-tocopherol) vs. placebo

Outcome: 3 Incidence all cancers

Study or subgroup	Alpha-tocopherol n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 High risk people (smokers and asbestos workers)					
ATBC 1994	1296/7286	1327/7278		28.9 %	0.98 [0.91, 1.05]
Subtotal (95% CI)	**7286**	**7278**		**28.9 %**	**0.98 [0.91, 1.05]**
Total events: 1296 (Alpha-tocopherol), 1327 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.70 (P = 0.48)					
2 Males 50 years or older					
Gaziano 2009	984/7315	959/7326		20.2 %	1.03 [0.95, 1.12]
Lippman 2009	856/8737	824/8696		16.8 %	1.03 [0.94, 1.13]
Subtotal (95% CI)	**16052**	**16022**		**37.0 %**	**1.03 [0.97, 1.10]**
Total events: 1840 (Alpha-tocopherol), 1783 (Placebo)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.01, df = 1 (P = 0.92); I^2 =0.0%					
Test for overall effect: Z = 0.96 (P = 0.34)					
3 Women					
Lee 2005	1437/19937	1428/19939		27.9 %	1.01 [0.94, 1.08]
Lin 2009	300/3791	324/3836		6.1 %	0.94 [0.81, 1.09]
Subtotal (95% CI)	**23728**	**23775**		**34.0 %**	**0.99 [0.93, 1.06]**
Total events: 1737 (Alpha-tocopherol), 1752 (Placebo)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.71, df = 1 (P = 0.40); I^2 =0.0%					
Test for overall effect: Z = 0.20 (P = 0.84)					
Total (95% CI)	**47066**	**47075**		**100.0 %**	**1.00 [0.97, 1.04]**
Total events: 4873 (Alpha-tocopherol), 4862 (Placebo)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 2.17, df = 4 (P = 0.71); I^2 =0.0%					
Test for overall effect: Z = 0.09 (P = 0.93)					
Test for subgroup differences: Chi^2 = 1.44, df = 2 (P = 0.49), I^2 =0.0%					



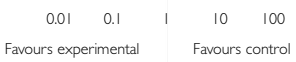
Analysis 3.4. Comparison 3 Vitamin E (alpha-tocopherol) vs. placebo, Outcome 4 Mortality all cancers.

Review: Drugs for preventing lung cancer in healthy people

Comparison: 3 Vitamin E (alpha-tocopherol) vs. placebo

Outcome: 4 Mortality all cancers

Study or subgroup	Alpha-tocopherol n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Males					
Gaziano 2009	273/7315	250/7326		47.9 %	1.09 [0.92, 1.29]
Subtotal (95% CI)	**7315**	**7326**		**47.9 %**	**1.09 [0.92, 1.29]**
Total events: 273 (Alpha-tocopherol), 250 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.04 (P = 0.30)					
2 Females					
Lee 2005	308/19937	275/19939		52.1 %	1.12 [0.95, 1.32]
Subtotal (95% CI)	**19937**	**19939**		**52.1 %**	**1.12 [0.95, 1.32]**
Total events: 308 (Alpha-tocopherol), 275 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.38 (P = 0.17)					
Total (95% CI)	**27252**	**27265**		**100.0 %**	**1.11 [0.99, 1.24]**
Total events: 581 (Alpha-tocopherol), 525 (Placebo)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.04$, df = 1 (P = 0.84); $I^2 = 0.0\%$					
Test for overall effect: Z = 1.71 (P = 0.086)					
Test for subgroup differences: $Chi^2 = 0.04$, df = 1 (P = 0.84), $I^2 = 0.0\%$					



Analysis 3.5. Comparison 3 Vitamin E (alpha-tocopherol) vs. placebo, Outcome 5 Mortality all causes.

Review: Drugs for preventing lung cancer in healthy people

Comparison: 3 Vitamin E (alpha-tocopherol) vs. placebo

Outcome: 5 Mortality all causes

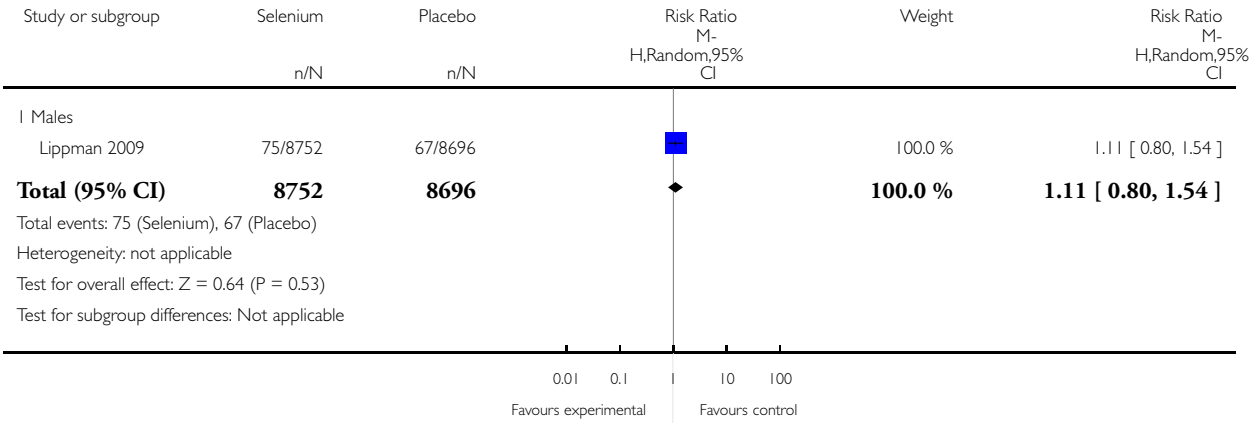
Study or subgroup	Alpha-tocopherol n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 High risk people (smokers and asbestos workers)					
ATBC 1994	2671/7286	2605/7287		67.7 %	1.03 [0.98, 1.07]
Subtotal (95% CI)	**7286**	**7287**		**67.7 %**	**1.03 [0.98, 1.07]**
Total events: 2671 (Alpha-tocopherol), 2605 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.14 (P = 0.25)					
2 Males 50 years or older					
Gaziano 2009	841/7315	820/7326		15.3 %	1.03 [0.94, 1.12]
Lippman 2009	358/8737	382/8696		6.3 %	0.93 [0.81, 1.07]
Subtotal (95% CI)	**16052**	**16022**		**21.7 %**	**0.99 [0.91, 1.09]**
Total events: 1199 (Alpha-tocopherol), 1202 (Placebo)					
Heterogeneity: Tau^2 = 0.00; Chi^2 = 1.27, df = 1 (P = 0.26); I^2 =21%					
Test for overall effect: Z = 0.12 (P = 0.90)					
3 Females					
Lee 2005	636/19937	615/19939		10.6 %	1.03 [0.93, 1.15]
Subtotal (95% CI)	**19937**	**19939**		**10.6 %**	**1.03 [0.93, 1.15]**
Total events: 636 (Alpha-tocopherol), 615 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.61 (P = 0.55)					
Total (95% CI)	**43275**	**43248**		**100.0 %**	**1.02 [0.98, 1.06]**
Total events: 4506 (Alpha-tocopherol), 4422 (Placebo)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 1.69, df = 3 (P = 0.64); I^2 =0.0%					
Test for overall effect: Z = 1.12 (P = 0.26)					
Test for subgroup differences: Chi^2 = 0.43, df = 2 (P = 0.81), I^2 =0.0%					

Analysis 4.1. Comparison 4 Selenium vs. placebo, Outcome 1 Incidence lung cancer.

Review: Drugs for preventing lung cancer in healthy people

Comparison: 4 Selenium vs. placebo

Outcome: 1 Incidence lung cancer

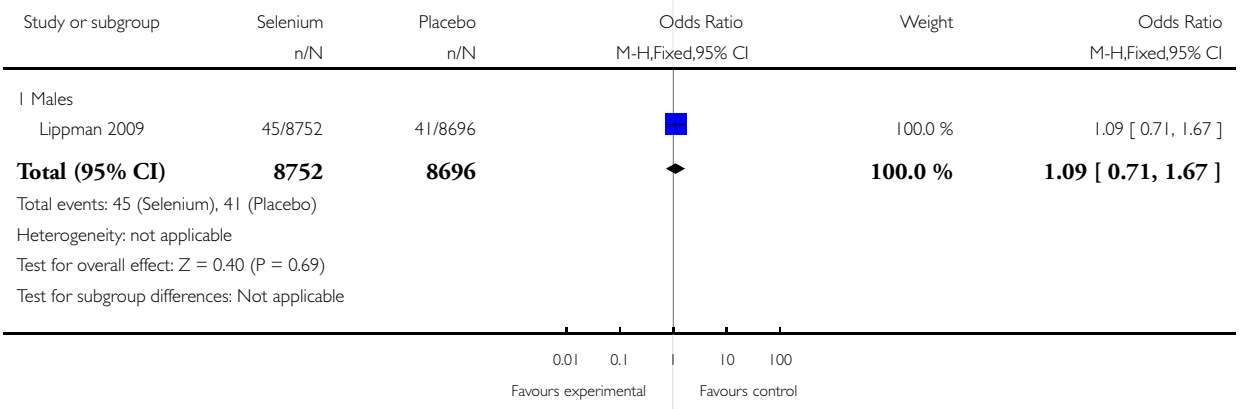


Analysis 4.2. Comparison 4 Selenium vs. placebo, Outcome 2 Mortality lung cancer.

Review: Drugs for preventing lung cancer in healthy people

Comparison: 4 Selenium vs. placebo

Outcome: 2 Mortality lung cancer



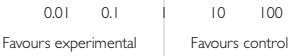
Analysis 4.3. Comparison 4 Selenium vs. placebo, Outcome 3 Incidence all cancers.

Review: Drugs for preventing lung cancer in healthy people

Comparison: 4 Selenium vs. placebo

Outcome: 3 Incidence all cancers

Study or subgroup	Selenium n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 Males					
Lippman 2009	837/8752	824/8696		100.0 %	1.01 [0.91, 1.12]
Total (95% CI)	**8752**	**8696**		**100.0 %**	**1.01 [0.91, 1.12]**
Total events: 837 (Selenium), 824 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.20 (P = 0.84)					
Test for subgroup differences: Not applicable					

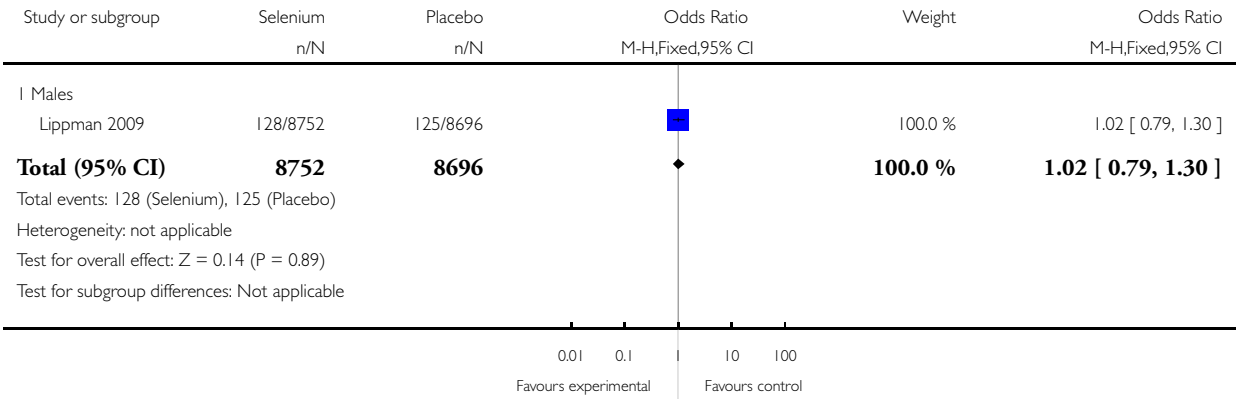


Analysis 4.4. Comparison 4 Selenium vs. placebo, Outcome 4 Mortality all cancers.

Review: Drugs for preventing lung cancer in healthy people

Comparison: 4 Selenium vs. placebo

Outcome: 4 Mortality all cancers

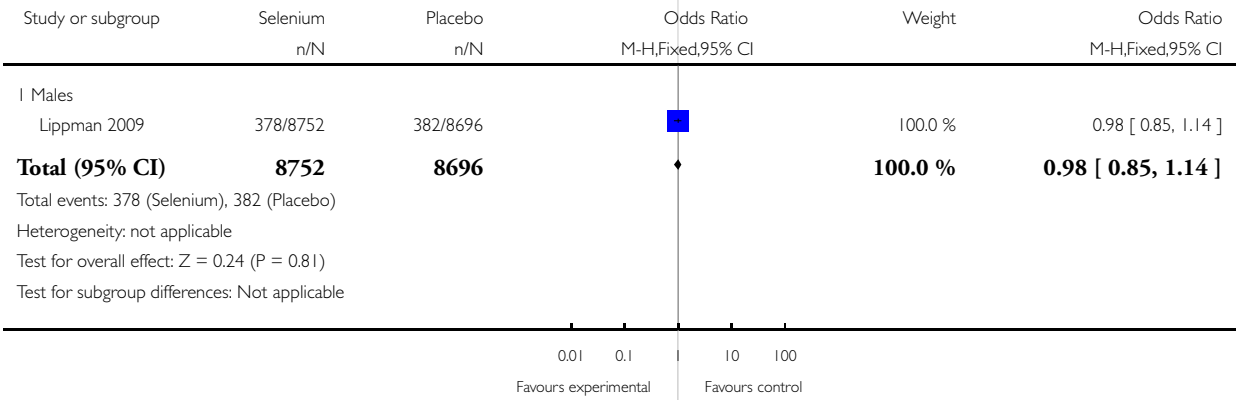


Analysis 4.5. Comparison 4 Selenium vs. placebo, Outcome 5 Mortality all causes.

Review: Drugs for preventing lung cancer in healthy people

Comparison: 4 Selenium vs. placebo

Outcome: 5 Mortality all causes

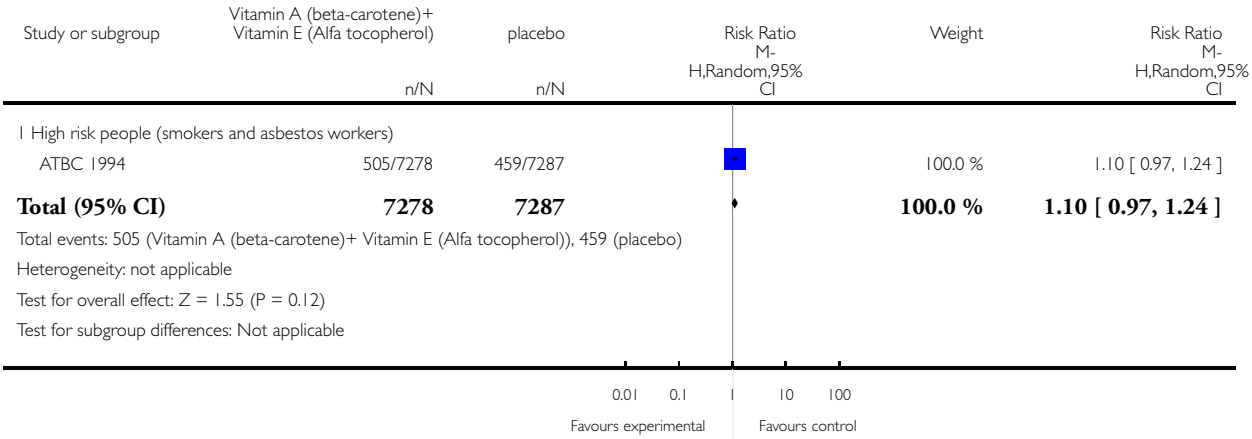


Analysis 5.1. Comparison 5 Vitamin A (beta-carotene)+ Vitamin E (alpha-tocopherol) vs. placebo, Outcome 1 Incidence lung cancer.

Review: Drugs for preventing lung cancer in healthy people

Comparison: 5 Vitamin A (beta-carotene)+ Vitamin E (alpha-tocopherol) vs. placebo

Outcome: 1 Incidence lung cancer

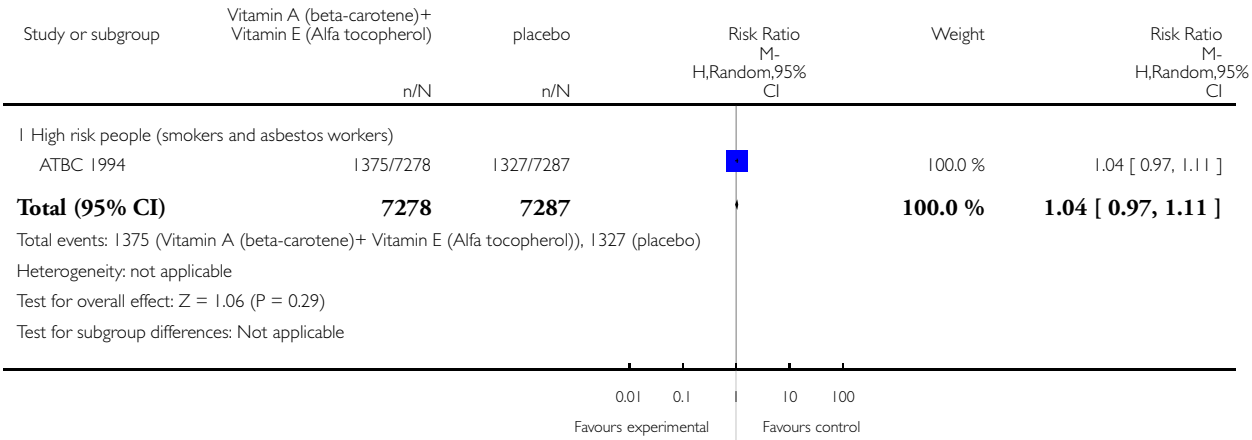


Analysis 5.2. Comparison 5 Vitamin A (beta-carotene)+ Vitamin E (alpha-tocopherol) vs. placebo, Outcome 2 Incidence all cancers.

Review: Drugs for preventing lung cancer in healthy people

Comparison: 5 Vitamin A (beta-carotene)+ Vitamin E (alpha-tocopherol) vs. placebo

Outcome: 2 Incidence all cancers

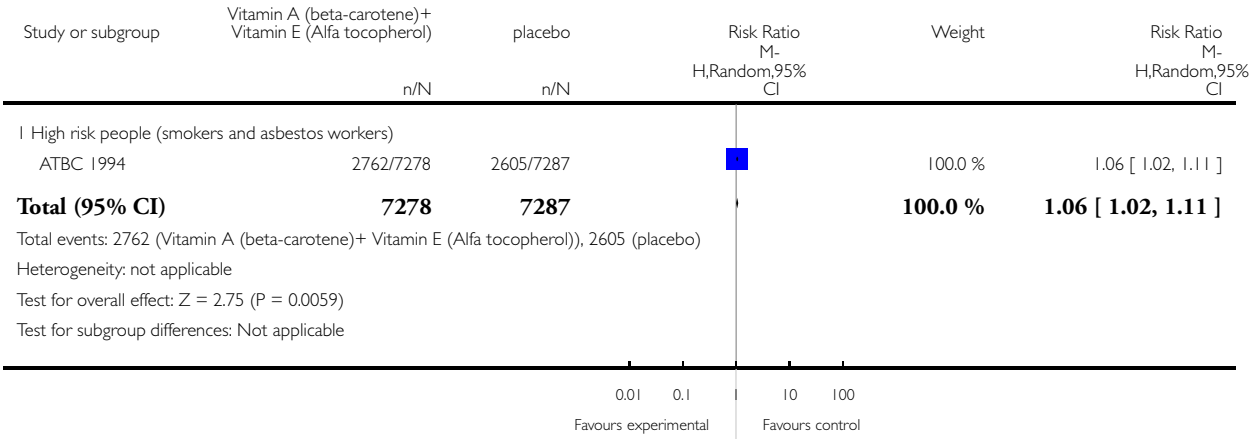


Analysis 5.3. Comparison 5 Vitamin A (beta-carotene)+ Vitamin E (alpha-tocopherol) vs. placebo, Outcome 3 Mortality all causes.

Review: Drugs for preventing lung cancer in healthy people

Comparison: 5 Vitamin A (beta-carotene)+ Vitamin E (alpha-tocopherol) vs. placebo

Outcome: 3 Mortality all causes

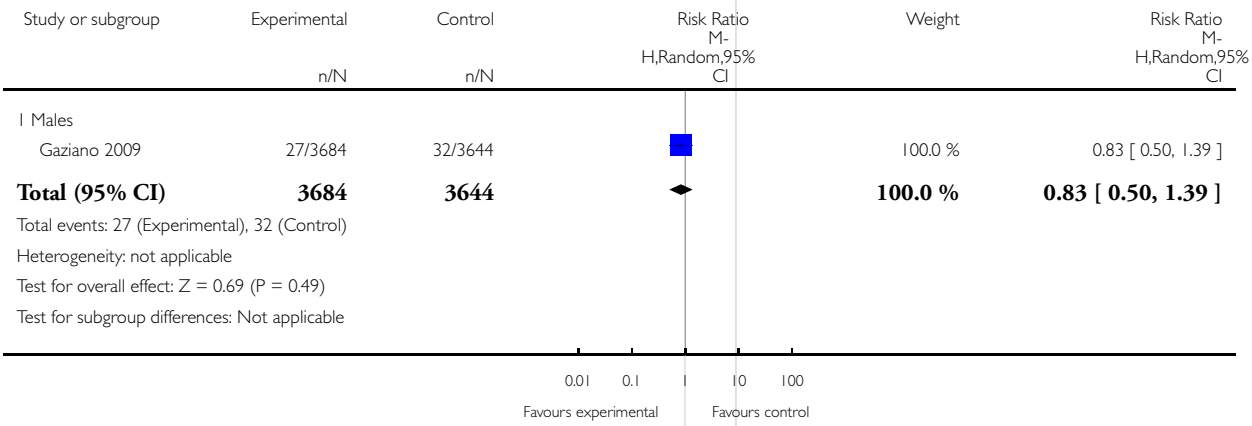


Analysis 6.1. Comparison 6 Vitamin C + Vitamin E vs. placebo, Outcome 1 Incidence lung cancer.

Review: Drugs for preventing lung cancer in healthy people

Comparison: 6 Vitamin C + Vitamin E vs. placebo

Outcome: 1 Incidence lung cancer

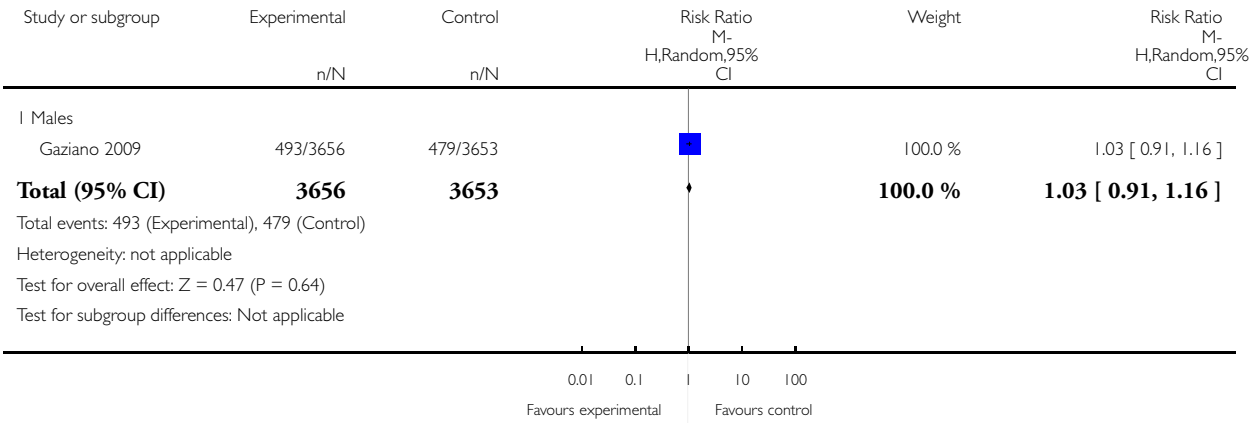


Analysis 6.2. Comparison 6 Vitamin C + Vitamin E vs. placebo, Outcome 2 Incidence all cancers.

Review: Drugs for preventing lung cancer in healthy people

Comparison: 6 Vitamin C + Vitamin E vs. placebo

Outcome: 2 Incidence all cancers

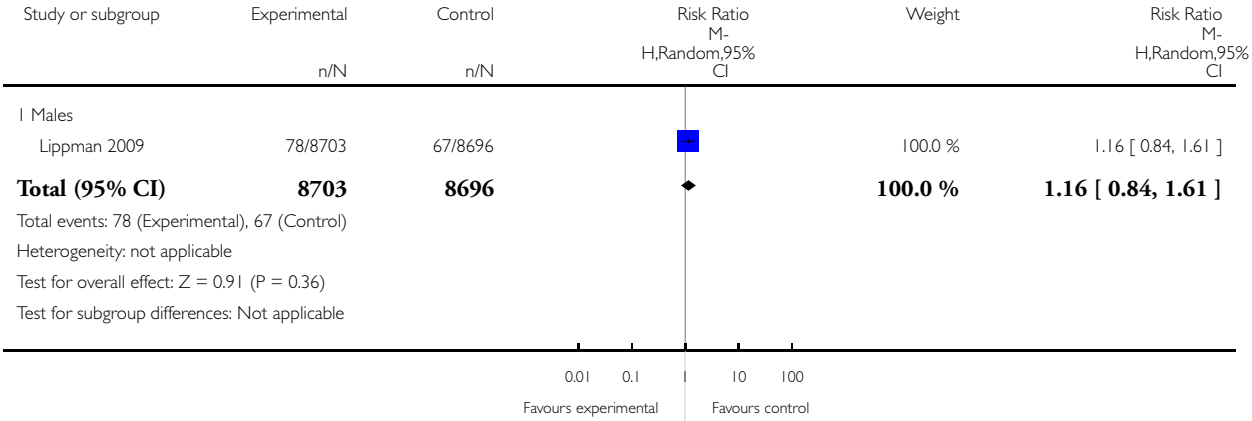


Analysis 7.1. Comparison 7 Vitamin E (alpha-tocopherol) + selenium vs placebo, Outcome 1 Incidence lung cancer.

Review: Drugs for preventing lung cancer in healthy people

Comparison: 7 Vitamin E (alpha-tocopherol) + selenium vs placebo

Outcome: 1 Incidence lung cancer

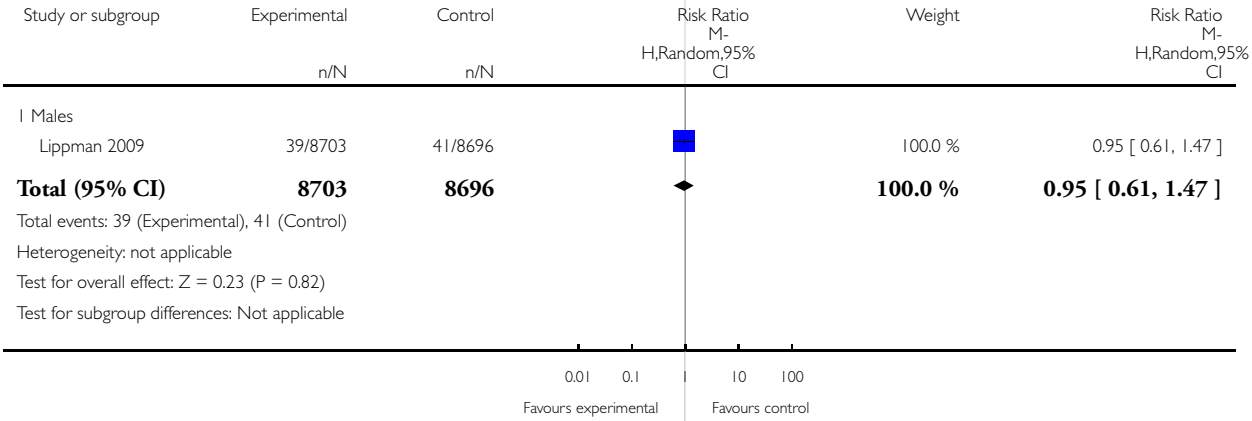


Analysis 7.2. Comparison 7 Vitamin E (alpha-tocopherol) + selenium vs placebo, Outcome 2 Mortality lung cancer.

Review: Drugs for preventing lung cancer in healthy people

Comparison: 7 Vitamin E (alpha-tocopherol) + selenium vs placebo

Outcome: 2 Mortality lung cancer

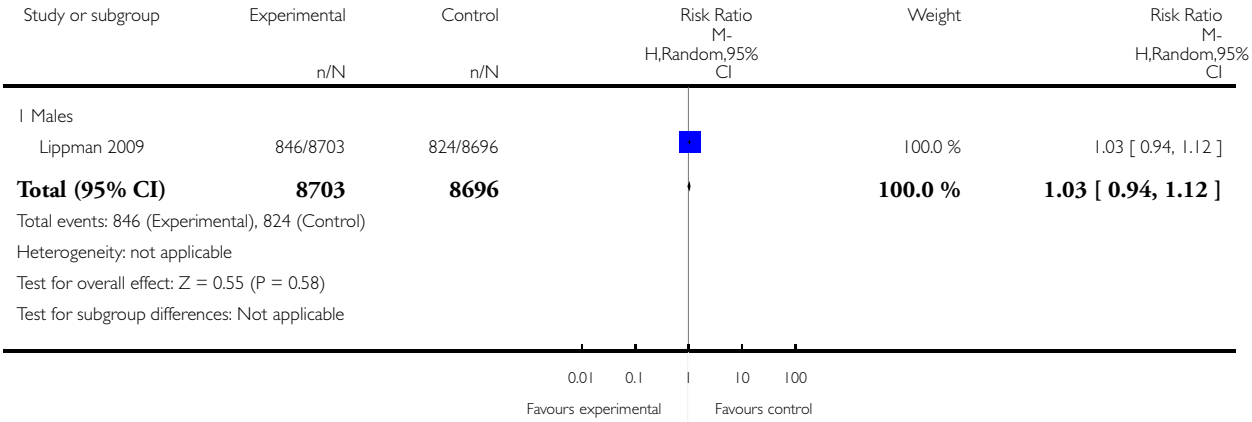


Analysis 7.3. Comparison 7 Vitamin E (alpha-tocopherol) + selenium vs placebo, Outcome 3 Incidence all cancers.

Review: Drugs for preventing lung cancer in healthy people

Comparison: 7 Vitamin E (alpha-tocopherol) + selenium vs placebo

Outcome: 3 Incidence all cancers



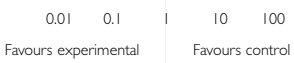
Analysis 7.4. Comparison 7 Vitamin E (alpha-tocopherol) + selenium vs placebo, Outcome 4 Mortality all cancers.

Review: Drugs for preventing lung cancer in healthy people

Comparison: 7 Vitamin E (alpha-tocopherol) + selenium vs placebo

Outcome: 4 Mortality all cancers

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Males					
Lippman 2009	117/8703	125/8696		100.0 %	0.94 [0.73, 1.20]
Total (95% CI)	**8703**	**8696**		**100.0 %**	**0.94 [0.73, 1.20]**
Total events: 117 (Experimental), 125 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.52 (P = 0.60)					
Test for subgroup differences: Not applicable					



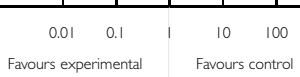
Analysis 7.5. Comparison 7 Vitamin E (alpha-tocopherol) + selenium vs placebo, Outcome 5 Mortality all causes.

Review: Drugs for preventing lung cancer in healthy people

Comparison: 7 Vitamin E (alpha-tocopherol) + selenium vs placebo

Outcome: 5 Mortality all causes

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Males					
Lippman 2009	359/8703	382/8696		100.0 %	0.94 [0.82, 1.08]
Total (95% CI)	**8703**	**8696**		**100.0 %**	**0.94 [0.82, 1.08]**
Total events: 359 (Experimental), 382 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.87 (P = 0.38)					
Test for subgroup differences: Not applicable					

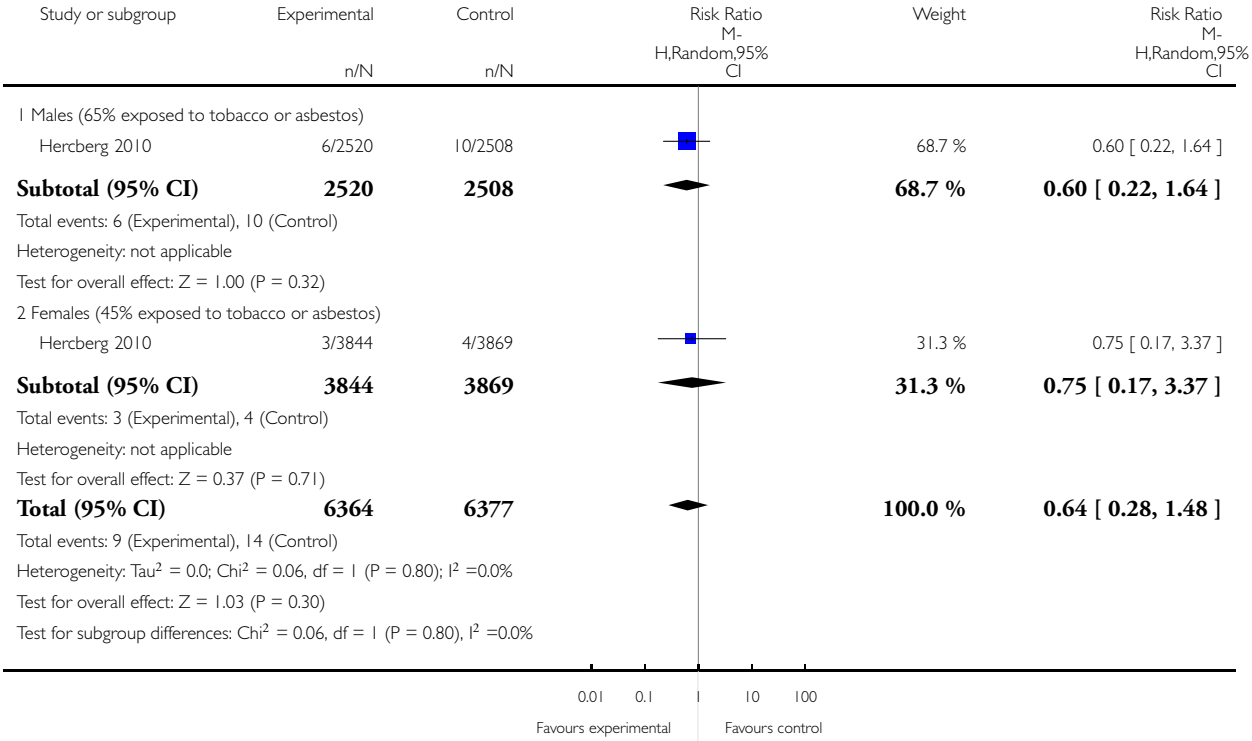


Analysis 8.1. Comparison 8 Vitamins A, C, E + selenium + zinc vs. Placebo, Outcome 1 Incidence lung cancer.

Review: Drugs for preventing lung cancer in healthy people

Comparison: 8 Vitamins A, C, E + selenium + zinc vs. Placebo

Outcome: 1 Incidence lung cancer



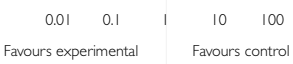
Analysis 8.2. Comparison 8 Vitamins A, C, E + selenium + zinc vs. Placebo, Outcome 2 Incidence all cancers.

Review: Drugs for preventing lung cancer in healthy people

Comparison: 8 Vitamins A, C, E + selenium + zinc vs. Placebo

Outcome: 2 Incidence all cancers

Study or subgroup	Experimental n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Males					
Hercberg 2010	207/2508	235/2520		45.8 %	0.89 [0.74, 1.06]
Subtotal (95% CI)	**2508**	**2520**		**45.8 %**	**0.89 [0.74, 1.06]**
Total events: 207 (Experimental), 235 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.34 (P = 0.18)					
2 Females					
Hercberg 2010	283/3869	276/3844		54.2 %	1.02 [0.87, 1.20]
Subtotal (95% CI)	**3869**	**3844**		**54.2 %**	**1.02 [0.87, 1.20]**
Total events: 283 (Experimental), 276 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.23 (P = 0.82)					
Total (95% CI)	**6377**	**6364**		**100.0 %**	**0.96 [0.83, 1.10]**
Total events: 490 (Experimental), 511 (Placebo)					
Heterogeneity: Tau^2 = 0.00; Chi^2 = 1.33, df = 1 (P = 0.25); I^2 =25%					
Test for overall effect: Z = 0.65 (P = 0.51)					
Test for subgroup differences: Chi^2 = 1.33, df = 1 (P = 0.25), I^2 =25%					

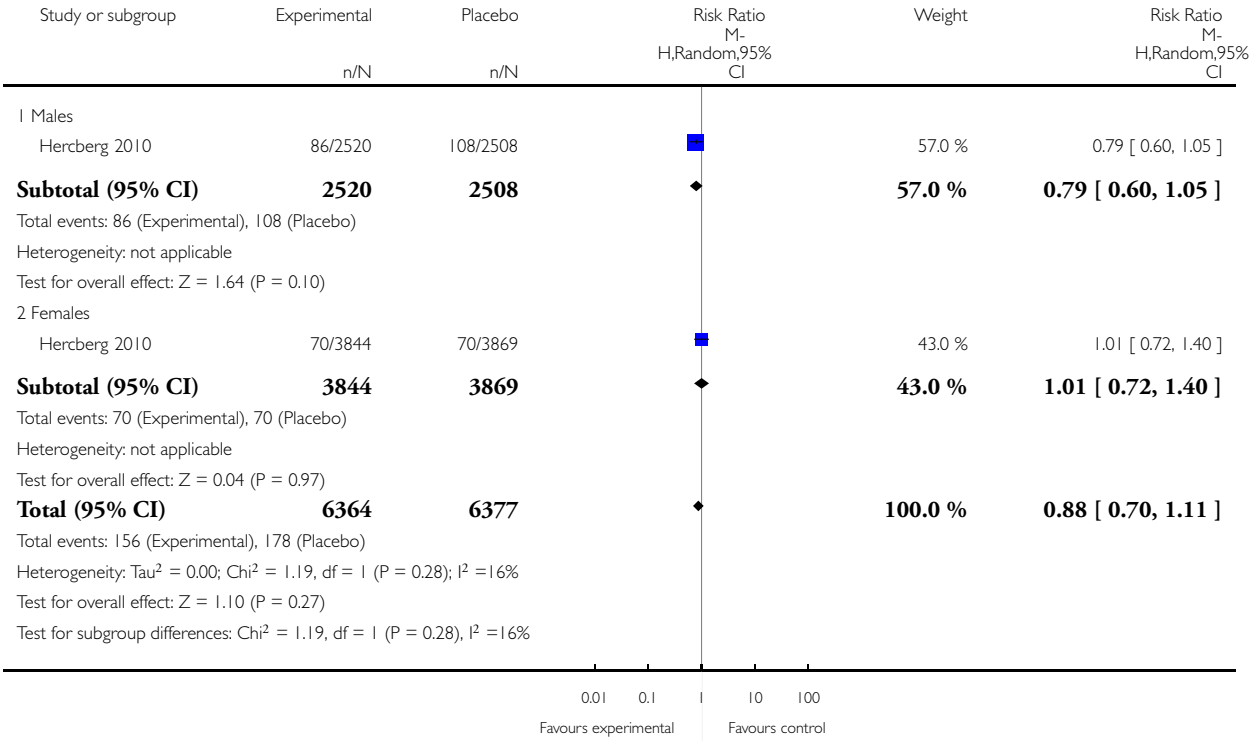


Analysis 8.3. Comparison 8 Vitamins A, C, E + selenium + zinc vs. Placebo, Outcome 3 Mortality all causes.

Review: Drugs for preventing lung cancer in healthy people

Comparison: 8 Vitamins A, C, E + selenium + zinc vs. Placebo

Outcome: 3 Mortality all causes

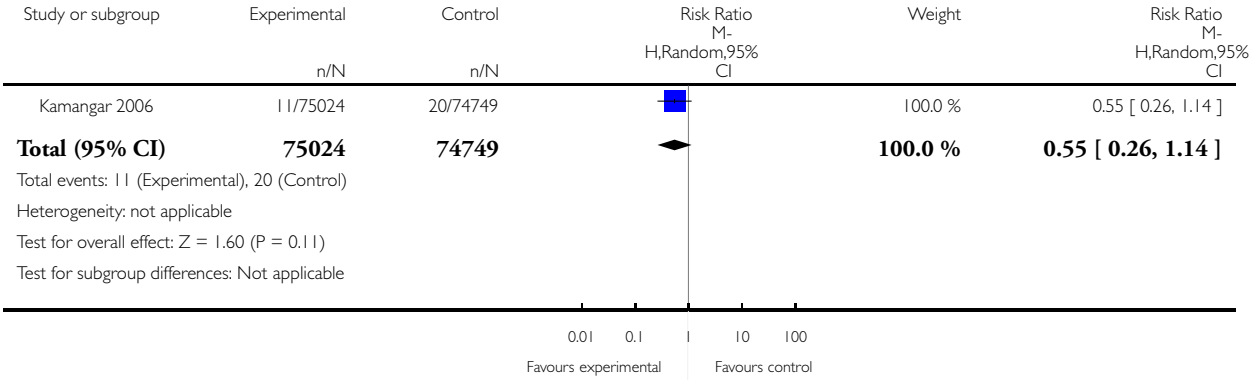


Analysis 9.1. Comparison 9 Vitamins A and E + selenium vs. placebo, Outcome 1 Mortality lung cancer (intervention period).

Review: Drugs for preventing lung cancer in healthy people

Comparison: 9 Vitamins A and E + selenium vs. placebo

Outcome: 1 Mortality lung cancer (intervention period)



ADDITIONAL TABLES

Table 1. Active intervention compared to placebo

Study	Vitamin A (Beta-carotene or retinol)	Vitamin C (Ascorbic acid)	Vitamin E (alpha-tocopherol)	Selenium	Other combinations of two or more products
ATBC 1994	20 mg daily		50 mg daily		Alpha-tocopherol (50 mg) + Beta-carotene (20 mg), daily
Gaziano 2009 (PHS II)		500 mg daily	400 IU every other day		Vitamin E 400 IU every other day + Vitamin C 500 mg daily
Hennekens 1996 (PHS)	50 mg every other day				
Hercberg 2010 (SU.VI.MAX)					Combination of antioxidants (120 mg of ascorbic acid, 30 mg of vitamin E, 6 mg of beta-carotene, 100 μg of selenium [as sele-

Table 1. Active intervention compared to placebo (*Continued*)

					nium-enriched yeast], and 20 mg of zinc [as gluconate]) in a single daily capsule
Kamangar 2006 (LINXIAN)	retinol (as palmitate 5000 IU) and zinc (as zinc oxide 22.5 mg) daily	120 mg and molybdenum (yeast complex 30 ug) daily			- beta-carotene (15 mg), vitamin E (a-tocopherol 30 mg) and selenium (as selenium yeast 50 ug) daily - riboflavin B2 (3.2 mg) and niacin B3 (40 mg) daily
Lee 2005 (WHS)	50 mg every other day		600 IU every other day		
Lin 2009 (WACS)	50 mg every other day	500 mg daily	600 IU every other day		
Lippman 2009 (SELECT)			400 IU daily	200 μg daily	Selenium 200 μg + vitamin E 400 IU daily
Omenn 1996 (CARET)	30 mg + 25,000 IU retinol daily				

Table 2. Length of treatment and follow-up period

Study	Lenght of treatment	Follow-up
ATBC	5 to 8 years	16 years
Gaziano 2009 (PHS II)	6 years	8 years
Hennekens 1996 (PHS)	12 years	12 years
Hercberg 2010 (SU.VI.MAX)	8 years	12 years
Kamangar 2006 (LINXIAN)	5 years	15 years
Lee 2005 (WHS)	2 years	6 years
Lin 2009 (WACS)	9 years	9 years
Lippman 2009 (SELECT)	7 years	7 years
Omenn 1996 (CARET)	4 years	12 years

APPENDICES

Appendix 1. Updated search strategy to December 2011

MEDLINE (PubMed; 07 December 2011)		
1	lung neoplasms[mh]	149424
2	carcinoma non small cell lung[mh]	24323
3	carcinoma small cell[mh]	15962
4	(lung*[tiab] OR pulmon*[tiab]) AND (tumor[tiab] OR tumors[tiab] OR tumour*[tiab] OR carcinoma*[tiab] OR oncolog*[tiab] OR cancer[tiab] OR neoplas*[tiab])	167588
5	1 OR 2 OR 3 OR 4	224420
6	carotenoids[mh]	59344
7	antioxidants[mh]	69715
8	vitamins[mh]	21266
9	glutathione[mh]	40841
10	diet[mh]	165781
11	dietary supplements[mh]	29093
12	micronutrients[mh]	33448
13	minerals[mh]	96677
14	plants medicinal[mh]	48045
15	6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14	499036
16	protective agents[mh]	118927
17	((risk*[tiab] AND modif*[tiab]) OR (risk*[tiab] AND reduc*[tiab]) OR (risk*[tiab] AND decreas*[tiab]))	316742
18	(protect*[tiab] OR prevent*[tiab])	1170528

(*Continued*)

19	16 OR 17 OR 18	1477848
20	15 AND 19	118380
21	chemoprevention[mh]	10277
22	anticarcinogenic agents[mh]	7415
23	((chem*[tiab] AND (prevent*[tiab] OR protect*[tiab])) NOT chemotherap*[tiab])	31878
24	anticarcinogenic propert*[tiab]	309
25	21 OR 22 OR 23 OR 24	48926
26	20 AND 25	5825
27	5 AND 26	408
28	5 AND 26 Limits: Publication Date from 2006	97
EMBASE (1974 to 2011 December 06; 07 December 2011)		
1	exp lung tumor/	207052
2	((lung$ or pulmon$) adj25 (tumor$ or tumour$ or cancer$ or onco$ or carcinoma or neoplas$)).ti,ab	178775
3	1 or 2	256913
4	((lung$ or pulmon$) adj25 (tumor$ or tumour$ or cancer$ or onco$ or carcinoma or neoplas$) adj10 prevent$).ti,ab	2339
5	cancer prevention/	23709
6	4 or 5	25630
7	3 and 6	4562
8	exp antioxidant/	77886
9	exp vitamin/	410942
10	exp nutrient/	684353

(*Continued*)

11	exp mineral/	19421
12	vitamin-supplementation/	15536
13	exp dietary intake/	278344
14	exp diet/	165547
15	8 or 9 or 10 or 11 or 12 or 13 or 14	1092755
16	7 and 15	1233
17	exp carotenoids/	96823
18	exp antioxidants/	77886
19	exp vitamins/	410942
20	exp glutathione/	52933
21	exp diet/	165547
22	exp dietary supplements/	50111
23	micronutrients/	19311
24	exp minerals/	19421
25	exp plants medicinal/	112682
26	17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25	806388
27	protective agents/	4358
28	risk$ modif$ or risk$ reduc$ or risk$ decras$).ti,ab.	13293
29	(protect$ or prevent$).ti,ab.	1390184
30	27 or 28 or 29	1399067
31	26 and 30	109566
32	exp chemoprevention/	14485
33	exp anticarcinogenic agents/	1191801

(*Continued*)

34	((chem$ adj25 (prevent$ or protect$)) not chemotherap$).ti,ab	25921
35	anticarcinogenic propert$.ti,ab.	361
36	32 or 33 or 34 or 35	1224280
37	31 or 36	1315882
38	16 or 26 or 37	1929017
39	7 and 38	2421
40	7 and 38	2421
41	limit 40 to yr="2006 -Current"	1078
42	random:.tw. or placebo:.mp. or double-blind:.mp.	881158
43	41 and 42	187
CENTRAL (*The Cochrane Library 2011, issue 11; 07 December 2011)*		
1	MeSH descriptor Lung Neoplasms explode all trees	3948
2	MeSH descriptor Carcinoma, Non-Small-Cell Lung explode all trees	1811
3	MeSH descriptor Small Cell Lung Carcinoma explode all trees	40
4	((lung* OR pulmon*) AND (tumor OR tumors OR tumour* OR carcinoma* OR oncolog* OR cancer OR neoplas*)):ti,ab	7058
5	(#1 OR #2 OR #3 OR #4)	7749
6	MeSH descriptor Carotenoids explode all trees	2413
7	MeSH descriptor Antioxidants explode all trees	9212
8	MeSH descriptor Vitamins explode all trees	10001

(*Continued*)

9	MeSH descriptor Glutathione explode all trees	451
10	MeSH descriptor Diet explode all trees	9865
11	MeSH descriptor Dietary Supplements explode all trees	5058
12	MeSH descriptor Micronutrients explode all trees	13238
13	MeSH descriptor Minerals explode all trees	2412
14	MeSH descriptor Plants, Medicinal explode all trees	849
15	(#6 OR #7 OR #8 OR #9 OR #10 OR # 11 OR #12 OR #13 OR #14)	33374
16	MeSH descriptor Protective Agents explode all trees	18601
17	((risk* AND modif*) OR (risk* AND reduc*) OR (risk* AND decreas*)):ti,ab	29386
18	(protect* OR prevent*)	115641
19	(#16 OR #17 OR # 18)	142778
20	(#15 AND # 19)	15505
21	MeSH descriptor Chemoprevention explode all trees	1235
22	MeSH descriptor Anticarcinogenic Agents explode all trees	358
23	((chem* AND (prevent* OR protect*)) NOT chemotherap*)	9350
24	anticarcinogenic propert*	21

(*Continued*)

25	(#21 OR #22 OR #23 OR #24)	10593
26	(#20 AND #25)	1657
27	(#5 AND #26)	79
28	(#5 AND #26), from 2006 to 2011	9

WHAT'S NEW

Last assessed as up-to-date: 7 December 2011.

Date	Event	Description
31 July 2012	New citation required but conclusions have not changed	Change in first author and list of authors
7 December 2011	New search has been performed	A search has been run and five new studies have been included in this update. For studies included in the previous review, in the cases in which there were newly-available post-intervention follow-up data, those data have been included in the analysis

HISTORY

Protocol first published: Issue 2, 2000

Review first published: Issue 2, 2003

Date	Event	Description
19 April 2012	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

MC-J and JRR screened the search results, assessed risk of bias data for trials included in the original version of the review, extracted data of new included studies, interpretation of the results, and drafted the manuscript. MC helped with the screening of the search results and drafted the background. GC and CF-C screened the search results and helped with interpretation of the results.

All authors commented on the manuscript. MC and XB developed the original version of the review.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Iberoamerican Cochrane Centre, Spain.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

None.

INDEX TERMS

Medical Subject Headings (MeSH)

*Dietary Supplements; Ascorbic Acid [therapeutic use]; Health Status; Lung Neoplasms [mortality; *prevention & control]; Minerals [*therapeutic use]; Randomized Controlled Trials as Topic; Selenium Compounds [therapeutic use]; Vitamin A [therapeutic use]; Vitamins [*therapeutic use]; alpha-Tocopherol [therapeutic use]; beta Carotene [therapeutic use]

MeSH check words

Female; Humans; Male