

Selenium for preventing cancer (Review)

Dennert G, Zwahlen M, Brinkman M, Vinceti M, Zeegers MPA, Horneber M



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[Intervention Review]

Selenium for preventing cancer

Gabriele Dennert¹, Marcel Zwahlen², Maree Brinkman³, Marco Vinceti⁴, Maurice P A Zeegers⁵, Markus Horneber⁶

¹Institut für Transdisziplinäre Gesundheitsforschung, Berlin, Germany. ²Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland. ³Department of General Practice, Katholieke Universiteit Leuven, Leuven, Belgium. ⁴Department of Public Health Sciences, University of Modena and Reggio Emilia, Modena, Italy. ⁵Unit of Genetic Epidemiology, Department of Public Health & Epidemiology, Birmingham, UK. ⁶Medizinische Klinik 5-Schwerpunkt Onkologie/Haematologie, Klinikum Nord, Nuernberg, Germany

Contact address: Gabriele Dennert, Institut für Transdisziplinäre Gesundheitsforschung, Graefestrasse 16, Berlin, D-10967, Germany. dennert@diverse-health.de.

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ABSTRACT

Background

Selenium is a trace element essential to humans. Higher selenium exposure and selenium supplements have been suggested to protect against several types of cancers.

Objectives

Two research questions were addressed in this review: What is the evidence for

1. an aetiological relationship between selenium exposure and cancer risk in women and men?
2. the efficacy of selenium supplementation for cancer prevention in women and men?

Search strategy

We searched electronic databases and bibliographies of reviews and included publications.

Selection criteria

We included prospective observational studies to answer research question (a) and randomised controlled trials (RCTs) to answer research question (b).

Data collection and analysis

We conducted random effects meta-analyses of epidemiological data when five or more studies were retrieved for a specific outcome. We made a narrative summary of data from RCTs.

Main results

We included 49 prospective observational studies and six RCTs. In epidemiologic data, we found a reduced cancer incidence (summary odds ratio (OR) 0.69 (95% confidence interval (CI) 0.53 to 0.91) and mortality (OR 0.55, 95% CI 0.36 to 0.83) with higher selenium exposure. Cancer risk was more pronouncedly reduced in men (incidence: OR 0.66, 95% CI 0.42 to 1.05) than in women (incidence:

OR 0.90, 95% CI 0.45 to 1.77). These findings have potential limitations due to study design, quality and heterogeneity of the data, which complicated the interpretation of the summary statistics.

The RCTs found no protective efficacy of selenium yeast supplementation against non-melanoma skin cancer or L-selenomethionine supplementation against prostate cancer. Study results for the prevention of liver cancer with selenium supplements were inconsistent and studies had an unclear risk of bias. The results of the Nutritional Prevention of Cancer Trial (NPCT) and SELECT raised concerns about possible harmful effects of selenium supplements.

Authors' conclusions

No reliable conclusions can be drawn regarding a causal relationship between low selenium exposure and an increased risk of cancer. Despite evidence for an inverse association between selenium exposure and the risk of some types of cancer, these results should be interpreted with care due to the potential limiting factors of heterogeneity and influences of unknown biases, confounding and effect modification.

The effect of selenium supplementation from RCTs yielded inconsistent results. To date, there is no convincing evidence that selenium supplements can prevent cancer in men, women or children.

PLAIN LANGUAGE SUMMARY

Selenium for preventing cancer

Selenium is a trace element that is important for human health, but might also be harmful for humans when taken in excess.

Fifty-five studies with more than one million participants were included in this systematic review. Forty-nine studies observed and analysed whether healthy people with high selenium levels in blood or toenail samples or with a high selenium intake developed cancer more or less often than other people. We found that people with higher selenium levels or intake had a lower frequency of certain cancers (such as bladder or prostate cancer) but no difference for other cancers such as breast cancer. However, it was not possible to determine from these studies that selenium levels or selenium intake were really the reason for the lower risk of cancer in some people. Factors apart from higher selenium levels could also influence the cancer risk: They might have had a healthier nutritional intake or lifestyle, have had a more favourable job or overall living conditions.

Six randomised controlled trials (RCTs) assessed whether the use of selenium supplements might prevent cancer. In general, there are two types of selenium supplements: one type uses the salt of selenium as main ingredient, the other type uses organic selenium. These two types may act differently in the human body when ingested. We assessed the quality of each trial according to four established methodological criteria. The trials with the most reliable results found that organic selenium did not prevent prostate cancer in men and increased the risk of non-melanoma skin cancer in women and men. Other trials found that participants using selenium salt or organic supplements had a decrease in liver cancer cases. However, due to methodological shortcomings this evidence was less convincing. We advise further investigation of selenium for liver cancer prevention before translating results into public health recommendations. We also recommend that there should be further evaluation of the effects of selenium supplements in populations according to their nutritional status as they may differ between undernourished and adequately nourished groups of people.

To maintain or improve health, access to healthy food and a healthy diet is important. Currently, there is no convincing evidence that individuals, particularly those who are adequately nourished, will benefit from selenium supplementation with regard to their cancer risk.

BACKGROUND

Selenium

Selenium is a trace element essential to humans. Humans usually ingest selenium with crop and animal products and sometimes as functional foods or supplements. Speciation and concentration of

selenium in food sources vary considerably, depending on plant and animal metabolism and growth conditions or animal nutrition (Duffield 1999).

Selenium species can be classified into selenium-containing organic compounds (e.g. selenomethionine, selenocysteine) and inorganic forms (selenate, selenite) (Rayman 2008a). Selenium yeast refers to a selenium-enriched yeast medium which usually contains 80% to 90% organically bound selenium with a high proportion of selenomethionine (Rayman 2004). Whether selenium is linked to specific beneficial health effects in humans is suspected but unproven and the debate on those effects is controversial (Drake 2006; Rayman 2008a).

The recommended daily allowance differs between regulatory agencies. For example, the highest amount of daily intake (55 µg selenium for adults) has been recommended by the US Institute of Medicine (Institute of Medicine 2009), whereas the WHO (World Health Organization) recommendations range between 30 and 40 µg/day for men and women (WHO 2004).

To prevent the risk of developing selenosis, the US Institute of Medicine has set the tolerable upper intake level to 400 µg per day for adults (Office of Dietary Supplements 2009). Besides the acute and chronic toxicity of high selenium exposure, possible harmful effects of long-term intake of lower dosages have also been discussed. However, effects of long-term intake of lower dosages are not so well investigated or understood (Vinceti 2001) and there may be differences between organic and inorganic forms (Rayman 2008a). A recent publication has questioned the current upper limit of 'safe intake' and proposed a far lower 'safe level' for long-term usage (20 µg/day for organic selenium) and a differentiation between organic and inorganic selenium sources (Vinceti 2009). An accurate estimation of selenium exposure in epidemiological research presents a challenge. Individual exposure is often assessed as the concentration in blood specimens or toenail clippings (Longnecker 1996) or as estimated dietary or supplemental intake, but the validity of dietary logs and recall questionnaires has been questioned (Patterson 1998). For the measurement in blood specimens, either whole blood or blood fractions (plasma = blood without the cells; serum = plasma without the clotting factors) are used.

Selenium levels found in human specimens (Rayman 2008b) as well as the estimated intake of selenium (Alfthan 1996) show a high global variability. Different selenium levels within populations have been found to be related to ethnicity (Kant 2007), gender, age or smoking behaviour. Smoking tends to lower selenium biomarker concentrations despite being a source of selenium exposure (Kafai 2003). Globally, however, there are also inconsistencies as to how these factors are associated with selenium levels. For example, selenium levels increased with age in women, but not in men, in the French SU.VI.M.AX cohort study (Arnaud 2007), decreased with age in a female population in Ohio (Smith 2000) and two studies from Switzerland and Austria could not find an association between age and selenium status in either gen-

der (Burri 2008; Gundacker 2006). Gender-specific nutritional and health behaviours, as well as gender-specific differences in selenium metabolism, may contribute to the observed discrepancies in selenium levels between genders (Rodriguez 1995).

These global and within-population differences formed the early basis of investigations into the association of selenium exposure and cancer risk (Schrauzer 1977; Shamberger 1969).

The hypotheses about the potentially anticarcinogenic mechanisms of selenium include its effects on DNA stability, cell proliferation, necrotic and apoptotic cell death in healthy and malignant cells and its effects on the immune system (Whanger 2004). Selenium is involved in these processes as a source of selenometabolites and is part of selenium-containing enzymes (Hatfield 2001). The optimum level for the prevention and retardation of carcinogenesis in human cells has been discussed to be higher than the level commonly achieved under a diet not deficient in selenium (Whanger 2004). Gender differences regarding the effects of selenium on health, including cancer diseases, have been increasingly debated in recent years. Apart from gender differences in selenium levels, gender differences in selenium distribution in tissue or tumour biology might be involved in the differential health effects in women and men (Waters 2004).

However, selenium has also been shown to promote malignant cell transformation (Kandas 2009; Novoselov 2005; Su 2005) and protect cancer cells against stress-induced apoptosis (Sarada 2008) in animal and in-vitro studies and might therefore work as carcinogen.

Cancer

Cancer is a leading cause of death worldwide. According to WHO estimates, 11.3 million people developed and 7.9 million died of cancer in 2007, with more than half of all new cases occurring in middle-income or low-income countries (WHO 2008).

The role of diet and nutrition for carcinogenesis and, as a potentially modifiable factor, in cancer prevention is still under debate. The identification of a nutrient supplement with cancer preventive properties would be a major breakthrough for public health. However, cancer is not a uniform disease and the existence of such a nutrient, or combination of nutrients, has been debated.

Case-control studies as well as systematic and non-systematic reviews have found conflicting results on risks of specific cancers and selenium exposure. Zhuo 2004 found a summary risk estimate suggestive for a protective effect of higher selenium exposure against lung cancer in a systematic review and meta-analysis of epidemiological studies; Brinkman 2006 found similar results for prostate cancer. However, two other epidemiological reviews concluded that studies did not support an association between selenium status and breast cancer risk in women (Navarro Silvera 2007; Waters 2004).

Vinceti and colleagues observed an increased melanoma incidence (Vinceti 1998) and mortality from melanoma (Vinceti 2000a)

in both genders in a cohort of people from Northern Italy who where accidentally exposed to long-term consumption of drinking water with a high content of inorganic selenium. The standardised mortality ratio for melanoma in comparison to the non-exposed individuals in the municipality was 4.15 (95% CI 0.21 to 20.47) in women and 10.98 (95% CI 1.84 to 36.27) in men.

The first indication from an RCT that selenium supplements may reduce risk of gastrointestinal (GIT) cancers came from the General Population Trial in Linxian, China (Blot 1993; Dawsey 1994; Wang 1994). Study participants were living in regions with a very high rate of GIT cancers and subclinical deficiencies of several nutrients. The RCT investigated the efficacy of vitamin and mineral supplements to reduce cancer incidence and mortality, especially of oesophageal and gastric cancer, in middle-aged adults with four treatment factors for a period of 5.25 years. Participants receiving one study supplement (containing 50 µg selenised yeast, beta-carotene, alpha-tocopherol) had a reduced mortality from, but not incidence of, gastric cancer. Oesophageal cancer risk was not altered.

In the more recent French SU.VI.M.AX trial (Hercberg 2004), a supplementation with beta-carotene, vitamin C, vitamin E and 100 µg selenium-enriched yeast did not alter the incidence of cancer of the digestive tract after a median period of 7.5 years in women. In men, the incidence rate was lower in the intervention group than in the placebo group, but risk ratios (RRs) with confidence intervals (CIs) were not calculated because of low numbers. Bjelakovic 2006 conducted a Cochrane Review on antioxidant supplements for the prevention of gastrointestinal (GIT) cancers. Nine RCTs that investigated mono-selenium or selenium-containing supplements were included in this review. The authors concluded that selenium may potentially possess beneficial effects, but the results required further research before any recommendation could be made.

Why it is important to do this review

Selenium is suggested to be involved in central anti-carcinogenic processes. Selenium supplements are widely marketed with many health claims, the prevention of cancer being one of them. There is a worldwide debate about the association between selenium exposure and cancer risk or whether selenium supplements are effective in decreasing the incidence or mortality of cancer. Epidemiologic and other data suggest differential effects in men and women and there are hints that selenium supplements might even have harmful effects, this especially being the case in certain populations. This review is timely and important as several meta-analyses and systematic reviews have been published, but a comprehensive summary providing evidence from both prospective studies and intervention trials which a) include all types of cancer and b) look for gender-related differences does not exist.

OBJECTIVES

Two research questions were addressed in this review: What is the evidence for

1. an aetiological relationship between selenium exposure and cancer risk in women and men?
2. the efficacy of selenium supplementation for cancer prevention in women and men?

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) and prospective observational studies (cohort studies and nested case-control studies) were included, irrespective of publication year, publication status or language.

Types of participants

All adult participants (aged 18 years and over) at risk of malignant neoplastic diseases.

Types of interventions

We considered prospective observational studies (cohort studies including sub-cohort controlled studies and nested case-control studies) for inclusion if they assessed baseline exposure to selenium in apparently cancer-free individuals either as biochemical selenium status or estimated selenium intake at study inception. We considered RCTs for inclusion if they used selenium supplementation at any dose or route of administration for a minimum of four weeks versus placebo or no intervention. We excluded trials using selenium supplementation as part of a multi-component preparation, without a study arm using selenium monotherapy supplementation.

Types of outcome measures

The primary outcome measures were

1. the number of participants developing cancers (incidence of any cancer);
2. the number of participants dying from cancers (cancer-related mortality).

Search methods for identification of studies

We conducted electronic searches in the Cochrane Central Register of Controlled Trials (CENTRAL, *The Cochrane Library* Issue 1, 2011), MEDLINE (via PubMed, 1966 to February 2011), EMBASE (1980 to 2010 week 50), CancerLit (February 2004) and CCMed (February 2011). We conducted the initial search in 2004 and updates in July 2007, January 2009, October 2009, and February 2011. As MEDLINE now includes the journals indexed in CancerLit, no further searches were conducted in this database after 2004.

We also searched the following online clinical trials databases: Clinical Trials of the American Cancer Society (<http://www.cancer.gov>, February 2011), the metaRegister of Controlled Trials (mRCT, <http://www.controlled-trials.com>, February 2011) and the German Cancer Study Register (<http://www.studien.de>, February 2011). The search strategies are given in [Appendix 1](#).

We scanned conference abstracts to identify unpublished material and searched the database for grey literature SIGLE (February 2004). This electronic database was discontinued in 2005.

Data collection and analysis

Selection of studies

Two review authors independently checked all electronic search results for eligibility. When search results could not be rejected with certainty on the basis of title and/or abstract, we obtained full text material.

We scanned bibliographies of papers retrieved with the described search strategy, and included publications to identify additional studies. If additional information was necessary we tried to contact all the correspondent authors of the included studies and asked investigators for information about unpublished trials.

Two review authors (GD, MH) independently applied the inclusion and exclusion criteria, if necessary with the assistance of an interpreter. We resolved disagreements by discussion and with the involvement of a third review author.

Data extraction and management

We used pre-tested extraction forms for epidemiological studies and RCTs to document data from the original material and assess the quality of studies. GD and another review author independently extracted data unblinded. GD checked extracted data for discrepancies and any discrepancies were discussed between both extracting review authors. In a small number of cases, we sought the opinion of a third review author to reach a consensus. If several reports from the same study were available, we considered the most recent to be the primary publication, but study details available from other publications were also extracted if not reported in the primary study reference.

We entered data from the extraction forms into a Microsoft Access database by hand. GD double-checked completely for errors and MH and GD triple-checked using descriptive database methods and plausibility checks.

For comparisons of selenium exposure as measured in serum and plasma specimens, we converted all data into the unit µg/l. Results provided as ppm (parts per million) or µg/g were converted using the factor 1.026 g/ml (weight density of serum) and data provided as µmol/l using the factor 78.96 (molecular weight of selenium). In order to be included, prospective observational studies had to report estimates of relative risk (RR (e.g. odds ratio (OR)) for each selenium exposure level.

Assessment of risk of bias in included studies

Observational studies

The risk of bias in observational studies was assessed using an assessment form adapted from the Newcastle-Ottawa Quality Assessment Scale (NOS) for cohort and case-control studies ([Wells 2004](#)). The NOS was developed using a 'star system' in which cohort or case-control studies are judged on the selection and comparability of the study groups and the ascertainment of either the exposure or outcome of interest.

The NOS form for cohort studies was used for all included observational studies. In addition, we assessed the risk of bias of nested case-control studies with the NOS case-control form. Both forms must be adapted a priori for use in a systematic review according to the research question and the review topic. For each question within this standardised assessment procedure either a 'star' or 'no star' is assigned to a study. A 'star' indicates that study design was considered adequate and less likely to introduce bias.

We used the questions as reported in the appendices for study assessment; (*) means that for the corresponding item a 'star' according to the NOS was assigned to the study. Key domains are the selection and comparability of the exposed and non-exposed cohort, the ascertainment of exposure and outcome and the length of follow-up. A study could receive a maximum of 9 stars in the cohort assessment ([Appendix 2](#)) and 9 stars in the assessment of the case-control part ([Appendix 3](#)).

The risk of bias assessment was based on the data provided in the included publications. We did not check other, not included publications for details. If an included study encompassed more than one publication with divergent rating in the NOS, we used the highest score.

Randomised controlled trials

We categorised generation of allocation sequence, allocation concealment, blinding and completeness of outcome data as adequate (low risk of bias), inadequate (high risk of bias) or unclear following the criteria specified in the Cochrane Handbook of Review

of Interventions (Higgins 2009a). We considered these four items to be the key domains for bias risk assessment. Studies that were categorised as “adequate” in all four domains were considered to have a low risk of bias; studies with inadequate procedures in one or more key domains were considered to have a high risk of bias. Studies with unclear procedures in one or more key domains were considered to have an unclear risk of bias.

We assessed the fulfillment of ethical standards as follows:

- Was informed consent obtained from patients? (yes/no/unclear)
- Was approval obtained from an ethical board? (yes/no/unclear)

Dealing with missing data

When data were missing or discrepancies in study publications were found, we tried to make contact with the study investigators for further information. Contacting study authors helped to clarify discrepancies in several publications, e.g. differing data in text and tables within the same report, however, we retrieved no missing data or study details.

Data synthesis

Data synthesis and analysis

We performed data synthesis and analysis separately for RCTs and observational studies.

We restricted meta-analyses to cancers for which at least 5 studies were available. There were two reasons for this restriction. The first was practical and was to limit the number of analyses to be performed. The second was that we expected that results are heterogeneous, but heterogeneity cannot be described and quantified well if only very few studies are available (Higgins 2009b). Although the cut-off at 5 studies is somewhat arbitrary, this decision was made very early in the review process and was declared in the protocol.

Observational studies

This review includes only binary outcomes. If five or more studies were available for a specific type of cancer, we conducted a meta-analysis.

Study authors defined cancer cases either as diagnosis (i.e. cancer incidence) or death from cancer (i.e. cancer mortality) or as a combination of both. The term ‘cancer risk’ is used in this paper as a generic term and refers likewise to cancer incidence, cancer mortality and combined incidence/mortality data.

A meta-analysis of highest versus lowest selenium exposure category was performed using a random effects model and by analysing

the natural logarithm of the OR or RR, using the squared standard error of the natural logarithm of the OR or RR as weights. The latter was calculated from the reported upper and lower boundaries of the 95% CI of the OR or RR. If a 95% CI was not reported, we used the total number of cases and the total number of controls as well as the number of categories of selenium exposure to estimate the number of cases and controls per exposure category. We then used the standard normal approximation formula to calculate the standard error of the OR (comparing the highest versus the lowest exposure category ($\ln OR = (1/a + 1/b + 1/c + 1/d)$ where a, b, c, d are the four counts needed to calculate the OR via $(a*d)/(b*c)$).

We took the OR from the analysis that included the most extensive adjustment in the publication. For the calculation of the summary risk estimate, gender-aggregated data of mixed-gender studies were used when available.

We performed a χ^2 test for heterogeneity of study results. Additionally, we used I^2 statistics (Higgins 2003) to quantify inconsistency. Meta-analyses were conducted using STATA 10.0 and STATA 11.0 software. We repeated meta-analyses that were included in this review publication using the Review Manager 5 statistical tool; for this, logarithmic data for the OR and the standard error were copied from STATA into Review Manager 5 and results were double-checked for errors.

We conducted sensitivity analyses to assess the effect of the methods used to assess selenium status/intake. We used gender-disaggregated data from mixed-gender studies together with data from single-gender cohorts for subgroup analyses by gender. We conducted the latter subgroup analyses to account for potential gender differences in selenium health effects (see [Background](#)).

Randomised controlled trials

We did not perform a meta-analysis of summary statistics with RCT data in this review as the minimum number of five studies, required for meta-analysis according to our review protocol, was not reached for any type of cancer.

Risk ratios (RR) of intervention trials that were not reported in the original publication were calculated on the basis of the number of participants and cases using the statistical tool for meta-analysis included in Review Manager 5. We also calculated the RR of adverse outcomes and its 95% CI, if sufficient data were available.

RESULTS

Description of studies

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

Citation style: Please note that we reference the sources of relevant information in a certain way to increase traceability of our results for interested readers. When the source of information is not the primary publication of an included study, the specific publication of interest is also referenced. For example “Hakama 1990 in: [Knekt 1990](#)” indicates that the cited paper is “Hakama 1990” as part of the mentioned study.

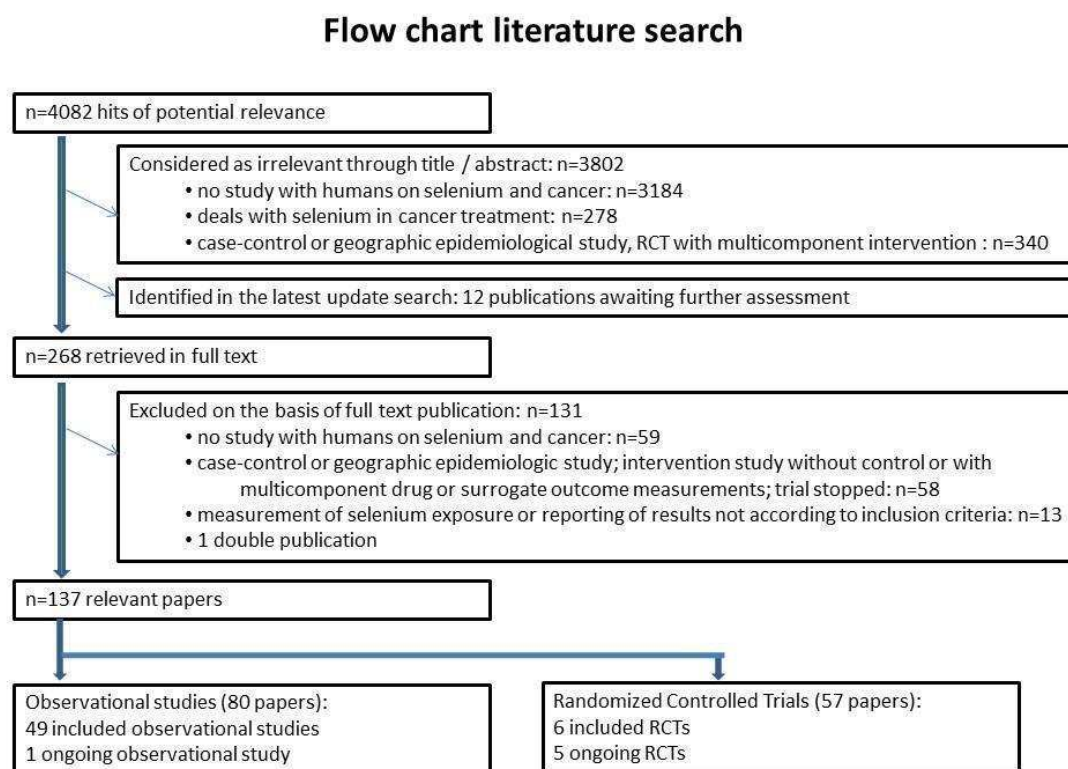
Three full text theses published in the US, could not be accessed (Coates 1987, in: [Coates 1988](#); Menkes 1986a, in: [Menkes 1986](#); Schober 1986, in: [Menkes 1986](#)). However, later journal publi-

cations were available and included in this review as main study publications (Coates 1988, in: [Coates 1988](#); Menkes 1986b, in: [Menkes 1986](#); Schober 1987, in: [Menkes 1986](#)). Thus the retrieval of the full text theses was considered to be unnecessary.

Results of the search

After excluding duplicates, the electronic search retrieved 4082 hits (flow chart of literature search: [Figure 1](#)). Of these, we excluded 3802 references as being clearly irrelevant due to title and abstract. The reasons for exclusion were:

Figure 1. Flow chart literature search



- the paper did not report a study on selenium and cancer with humans (n = 3184),
- the paper dealt with selenium in the treatment of cancer (n = 278),
- the study did not meet other inclusion criteria, e.g. retrospective case-control studies or RCTs using a multi

component vitamin/trace element supplement (n = 340).

Twelve publications of potential relevance were identified in the latest update search in February 2011. Due to time restrictions, these publications could not be included in the current review version and are listed in the section “Classification pending refer-

ences”.

The remaining 268 publications were considered of possible relevance and re-evaluated.

Included studies

One hundred and thirty-seven papers were identified for inclusion in this review: 80 papers referred to one ongoing and 49 completed observational studies. Fifty-seven papers referred to five ongoing and six completed randomised controlled trials.

A detailed description of the studies included is given in the table [Characteristics of included studies](#).

I. Observational studies

Forty-nine completed observational studies were included in this review. Thirty-six studies were nested case-control studies, the others were sub-cohort controlled or cohort studies and one study used a cohort together with a nested case-control design. Sub-cohort controlled studies used (random) samples of the cohort as controls. The original papers were published between 1983 and 2009. Five studies were conducted in Asia (China, Japan and Taiwan), one in Australia, 19 in Europe (including data from Belgium, Denmark, Germany, Greece, Italy, Netherlands, Norway, Spain, Sweden, Channel Islands, Finland, France and the UK) and 24 in the US. Overall, the studies included more than 1,078,000 participants. European study populations made up 45%, the US 45%, Asia 9.7%, and Australia 0.2% of all study participants. The median size of the study populations was 10,494. Twenty-six studies included men and women, one did not report gender, 17 included only men and five only women. For a substantial proportion of the study populations (38%), gender was not reported. Forty-one percent of participants were men, 21% were women. Six studies with gender-mixed populations reported results stratified by gender. The study populations were derived from 42 different cohorts. Twenty-three cohorts were non-randomly recruited, e.g. included volunteers, and 19 cohorts consisted of a random (or total) sample of the population of interest, which was either a specifically exposed population such as male tin-miners in China or the general population.

Thirty-seven studies specified the age range of their included participants, the majority of which included adults over 40 years.

Five studies investigated nutritional and/or supplemental selenium intake, using food-frequency questionnaires or interviews. Forty-three studies assessed biochemical selenium status:

- eight used toenail specimens,
- 11 plasma specimens,
- 23 serum specimens,
- and one used both serum and plasma specimens.

One study measured both serum selenium levels and intake.

The mean follow-up period was up to three years in five studies and longer than three years in the remaining studies. Generally, study authors grouped the cases following the ICD classification that was up-to-date at the inception of the cohort observation. The level of disaggregation of data varied remarkably between the studies. While some studies reported cancer risk according to organ systems (e.g. urinary tract, respiratory tract), others stratified their data by one or two organs (e.g. female breast, urinary bladder). Only in the case of skin cancer did studies also differentiate according to histological type (e.g. melanoma, basal cell carcinoma).

For the following outcomes, five or more studies were included in the review and observational data were meta-analysed:

- any cancer (15 studies)
- female breast cancer (7)
- urinary bladder cancer (5)
- lung cancer (13)
- prostate cancer (14)
- stomach cancer (5)
- colon/colorectal cancer (5)

[Table 1](#) provides an overview on the studies for each outcome. Five studies gave data for the group of “other” cancers, which encompassed any type of cancer not reported separately in the study publications. The definition of the group of “other” cancers varied between studies including predominantly rare cancers but also cancers of unknown origin. The results of the studies within the category “other cancers” are mentioned for the sake of completeness, however, due to the diversity of outcomes the results were not included in further analysis or discussion of this review.

Table 1. Included observational studies by outcome

Organ System	Outcome	Number of studies/case definition	Meta-analysis	Countries	Number of participants	Number of cases	Selenium assessment	Reporting study
Any cancer	Any cancer	Total: 15 incidence: 8 mortality: 6 incidence &	✓ yes	US Finland Netherlands	total: ~ 151,000	total: 3220 male: 1700 female: 736	serum: 11 plasma: 2 serum + plasma: 1	Knekt 1990 Coates 1988 Kok 1987

Table 1. Included observational studies by outcome (Continued)

		mortality combined: 1		Sweden Norway Belgium France			plasma sele- nium P: 1	Salonen 1984 Nomura 1987 Virtamo 1987 Willett 1983 Fex 1987 Ringstad 1988 Persson 2000 Salonen 1985 Peleg 1985 Kornitzer 2004 Akbaraly 2005 Bleys 2008
Gynecolog- ical cancer	Fe- male breast cancer	Total: 7 incidence: 7 mortality: 0 incidence & mortality combined: 0	✓ yes	US Finland Nether- lands Channel Is- lands	to- tal / female: > 155,000 (one study did not re- port cohort size)	total / fe- male: 992	serum: 2 plasma: 1 serum + plasma: 1 toenail: 3	Dorgan 1998 vd Brandt 1993 Coates 1988 Overvad 1991 Knekt 1990 Garland 1995 van Noord 1987
	Cervical cancer	Total: 2 incidence: 2 mortality: 0 incidence & mortality combined: 0	× no	US	to- tal / female: > 15,161 (one study did not re- port cohort size)	total / fe- male: 62	serum: 2	Menkes 1986 Coates 1988
	Uterine can- cer	Total: 1 incidence: 1 mortality: 0 incidence & mortality combined: 0	× no	US	to- tal / female: 62,641	total / fe- male: 91	toenail: 1	Garland 1995

Table 1. Included observational studies by outcome (Continued)

	Ovarian cancer	Total: 4 incidence: 4 mortality: 0 incidence & mortality combined: 0	× no	US Finland	total / female: ~ 214,000	total / female: 568	serum: 2 toenail: 1 supplemental intake: 1	Knekt 1990 Garland 1995 Menkes 1986 Thomson 2008
	Gynecological cancer (without breast cancer)	Total: 1 incidence: 1 mortality: 0 incidence & mortality combined: 0	× no	Finland	total / female: ~ 18,000	total / female: 86	serum: 1	Knekt 1990
Urological cancers	Urinary bladder cancer	Total: 5 incidence: 5 mortality: 0 incidence & mortality combined: 0	✓ yes	US/Hawaii Finland Netherlands	total: 279,100 female: 130,786 male: 128,009	total 965 female: 175 male 755	serum: 2 toenail: 3	Menkes 1986 Nomura 1987 Michaud 2002 vd Brandt 1993 Michaud 2005
	Urinary tract cancer	Total: 2 incidence: 2 mortality: 0 incidence & mortality combined: 0	× no	Netherlands Finland	total: 48,000	total: 104 male: 91 female: 13	serum: 1 plasma: 1	Knekt 1990 Persson 2000
Respiratory tract cancers	Lung cancer	Total: 13 incidence: 12 mortality: 1 incidence & mortality combined: 0	✓ yes	China Japan US Finland Netherlands	total: ~ 333,000 male: 125,341 female: 181,895	total: 1835 male: 1256 female: 333	serum: 8 serum + plasma: 2 toenail: 2 dietary intake: 1 (one study reported both serum levels and food intake)	Knekt 1990 Knekt 1998 Garland 1995 Coates 1988 Nomura 1987 vd Brandt 1993 Kabuto 1994 Menkes 1986 Goodman

Table 1. Included observational studies by outcome (Continued)

								2001 Comstock 1997 Kromhout 1987 Ratnasinghe 2000 Epplein 2009
	Oral / pharyngeal cancer	Total: 1 incidence: 1 mortality: 0 incidence & mortality combined: 0	× no	US	total: 25,804	total: 28	serum: 1	Menkes 1986
	Any cancer of the respiratory tract	Total: 1 incidence: 1 mortality: 0 incidence & mortality combined: 0	× no	Sweden	total / male: ~ 9500	total / male: 69	Plasma selenium P: 1	Persson 2000
Andrological cancers	Prostate cancer	Total: 14 incidence: 14 mortality: 0 incidence & mortality combined: 0	✓ yes	US Europe	total / male: > 416,500 (one study did not report cohort size)	total / male: 5249	serum: 6 plasma: 3 toenail: 3 dietary intake: 2	Hartman 1998 Helzlsouer 2000 Coates 1988 Brooks 2001 vd Brandt 1993 Nomura 2000 Goodman 2001 Yoshizawa 1998 Li 2004a Peters 2007 Peters 2008 Allen 2008 Epplein 2009

Table 1. Included observational studies by outcome (Continued)

Gastroin- testinal cancers	Oe- sophageal cancer	<i>Total: 2 incidence: 2 mortality: 1 incidence & mortality combined: 0</i>	× no	China US	total: 29,923	total: > 959	serum: 1 supplemen- tal intake: 1	Wei 2004 Dong 2008
	Oe- sophageal / stomach cancer	<i>Total: 1 incidence: 1 mortality: 0 incidence & mortality combined: 0</i>	× no	Netherlands	total: 36,265	total: 86 male: 51 female: 35	serum: 1	Knekt 1998
	Stomach cancer	<i>Total: 5 incidence: 5 mortality: 1 incidence & mortality combined: 0</i>	✓ yes	China Japan US/Hawaii Finland Netherlands	total: ~ 197,000 male: 86,311 female: 80,669	total: 955 male: 626 female: 329	serum: 4 toenail: 1	Knekt 1990 vd Brandt 1993 Nomura 1987 Kabuto 1994 Wei 2004
	Primary liver cancer	<i>Total: 2 incidence: 1 mortality: 1 incidence & mortality combined: 0</i>	× no	Taiwan	total: 46,404	total: 235 male: 223 female: 12	plasma: 1 toenail: 1	Yu 1999 Sakoda 2005
	Pancreatic cancer	<i>Total: 2 incidence: 2 mortality: 0 incidence & mortality combined: 0</i>	× no	US Finland	total: 65,072	total: 67 male: 31 female: 36	serum: 2	Menkes 1986 Knekt 1990).
	Colon/col- orectal can- cer	<i>Total: colon 2, col- orectum 3 incidence: 5 mortality: 0 incidence & mortality combined: 0</i>	✓ yes	US Nether- lands Finland	total: 255,425 male: 86,311 female: 143,310	total: 617 male: 285 female: 332	serum: 3 toenail: 2	vd Brandt 1993 Nomura 1987 Menkes 1986 Garland 1995 Knekt 1990
	Rectal can- cer	<i>Total: 2 incidence: 2</i>	× no	US/Hawaii Netherlands	total: 127,712	total: 145 male: 109	serum: 1 toenail: 1	vd Brandt 1993

Table 1. Included observational studies by outcome (Continued)

		mortality: 0 incidence & mortality combined: 0				female: 36		Nomura 1987
	All gastroin- testinal can- cers	Total: 2 incidence: 2 mortality: 0 incidence & mortality combined: 0	× no	US Sweden	total: > 9500 (one study did not re- port cohort size)	total: 143	plasma + serum: 1 plasma sele- nium P: 1	Coates 1988 Persson 2000
Skin cancer	Melanoma	Total: 3 incidence: 3 mortality: 0 incidence & mortality combined: 0	× no	US	total: ~ 158,000	total: 547	serum: 1 toenail: 1 supplemen- tal intake: 1	Garland 1995 Menkes 1986 Peters 2008
	Basal cell carcinoma	Total: 3 incidence: 3 mortality: 0 incidence & mortality combined: 0	× no	Australia US Finland	total: > 66,000	total: 292	serum: 3 dietary intake: 1	Knekt 1990 Menkes 1986 Mc- Naughton 2005
	Squamous cell carcinoma	Total: 4 incidence: 4 mortality: 0 incidence & mortality combined: 0	× no	Australia US	total: ~ 30,000	total: 488	serum: 2 plasma: 1 dietary intake: 1	Combs 1993 Karagas 1997 Menkes 1986 Mc- Naughton 2005
	Total non- melanoma skin cancer	Total: 1 incidence: 1 mortality: 0 incidence & mortality combined: 0	× no	US	total: 117	total: 19	plasma: 1	Clark 1985
Rare and other can- cers	Haemato- logical can- cers	Total: 1 incidence: 1 mortality: 0 incidence & mortality	× no	US	total: ~ 6,200	total: 12	serum + plasma: 12	Coates 1988

Table 1. Included observational studies by outcome (Continued)

		<i>combined: 0</i>					
Thyroid cancer	<i>Total: 1 incidence: 1 mortality: 0 incidence & mortality combined: 0</i>	× no	Norway	total: 100,000	total: 43 male: 12 female: 31	serum: 1	Glattre 1989
Other cancers	<i>Total: 5 incidence: 4 mortality: 1 incidence & mortality combined: 0</i>	× no	China US Finland Sweden		total: 573 male: 230 female: 285		Garland 1995 Coates 1988 Knekt 1990 Wei 2004 Persson 2000

Some studies did not report the gender of participants or cancer cases; consequently, figures for women and men not always sum up to the total number of participants or cancer cases.

2. Randomised controlled trials

Six randomised controlled trials with a total of 43,408 participants (94% men) were included in this review. All used parallel group designs with either two arms (Li 2000; NPCT 1996; Reid 2008; Yu 1991; Yu 1997) or four arms (SELECT 2009). Three were conducted in China (Li 2000; Yu 1991; Yu 1997), two in the US (NPCT 1996; Reid 2008) and one in the USA/Canada/Puerto Rico (SELECT 2009).

Selenium supplements and placebos were administered daily. As an active intervention, trials used 200 µg (NPCT 1996; Yu 1991; Yu 1997) or 400 µg (Reid 2008) selenium in the form of selenised yeast tablets. Li 2000 used 500 µg sodium selenite and SELECT 2009 used 200 µg L-selenomethionine.

2.1. Primary liver cancer

Three Chinese trials investigated the preventive efficacy of selenium supplementation against primary liver cancer in different high-risk populations. Participants were either carriers of the Hepatitis B surface antigen (HBs-Ag) with normal liver function or first-degree relatives of liver cancer patients. Two trials used selenised yeast (Yu 1991; Yu 1997) and one sodium selenite (Li 2000).

2.2. Non-melanoma skin cancer

The US Nutritional Prevention of Cancer Trial (NPCT) investigated the influence of selenium on the development of squamous and basal cell skin cancer in a high-risk group (NPCT 1996). Participants were men and women between 18 and 80 years. All had a history of two or more basal cell carcinomas or of one squamous cell carcinoma. All results were reported for two periods of follow-up: the intended study period (from 15 September 1983 to 31 December 1993; Clark 1996 see NPCT 1996) and the entire blinded intervention period (from 15 September 1983 to 31 January 1996; Duffield-Lillico 2002; Duffield-Lillico 2003 see NPCT 1996). A sub-study of the NPCT (Reid 2008) investigated the efficacy of a higher selenium dose, supplied as selenised yeast orally, in the prevention of non-melanoma skin cancer in one of the NPCT study sites. Study design was similar to the NPCT study, except that 423 participants at this study site were randomised to placebo or intervention with higher selenium content.

2.3. Prostate cancer

The Selenium and Vitamin E Cancer Prevention Trial (SELECT) investigated the preventive potential of selenium, as selenomethionine, and vitamin E supplementation in men of diverse ethnic backgrounds against prostate cancer (SELECT 2009).

2.4. Other cancers

In 1990 additional secondary endpoints were identified post-hoc in [NPCT 1996](#) (total cancer mortality, total cancer incidence, incidence of lung, prostate, colorectal cancers). Furthermore, the incidences of female breast cancer, bladder cancer, oesophageal cancer, melanoma, haematological cancers and cancers of the head and neck were also reported in trial publications ([NPCT 1996](#)). [Reid 2008](#) reported the incidence of internal cancers. [SELECT 2009](#) investigated several pre-specified secondary outcomes, including the incidence of and deaths from any type of cancer, lung cancer, colorectal cancer and other cancers (excluding prostate, basal cell and squamous cell skin cancer).

Excluded studies

Of these, 131 papers did not fulfil the inclusion criteria. Eighty-eight of these publications were rejected on the basis of abstract and title in the second evaluation, 43 papers were retrieved as full-text and their reasons for exclusion are described in the table [Characteristics of excluded studies](#).

The main reasons for exclusion were:

- The publication was a review or comment.
- Cancer was not a study endpoint.
- Selenium was not the exposure/intervention of interest.
- The study was a retrospective case-control study.
- The RCT had not been started.
- A multi component supplement was used.
- A control group was not included in the trial.
- Observational studies did not report their results according to the inclusion criteria, e.g. only differences in the mean selenium exposure between cases and controls were provided.

Risk of bias in included studies

Observational studies

The median value of 'assigned stars' was seven in the cohort study assessment and eight in the (nested) case-control study assessment out of a maximum of nine stars each ([Figure 2](#) and [Figure 3](#)). A summary of the rating according to the Newcastle-Ottawa-Scale (NOS) is presented in [Table 2](#).

Figure 2. Newcastle-Ottawa-Scale: number of studies by number of “stars” assigned in the case-control part of studies

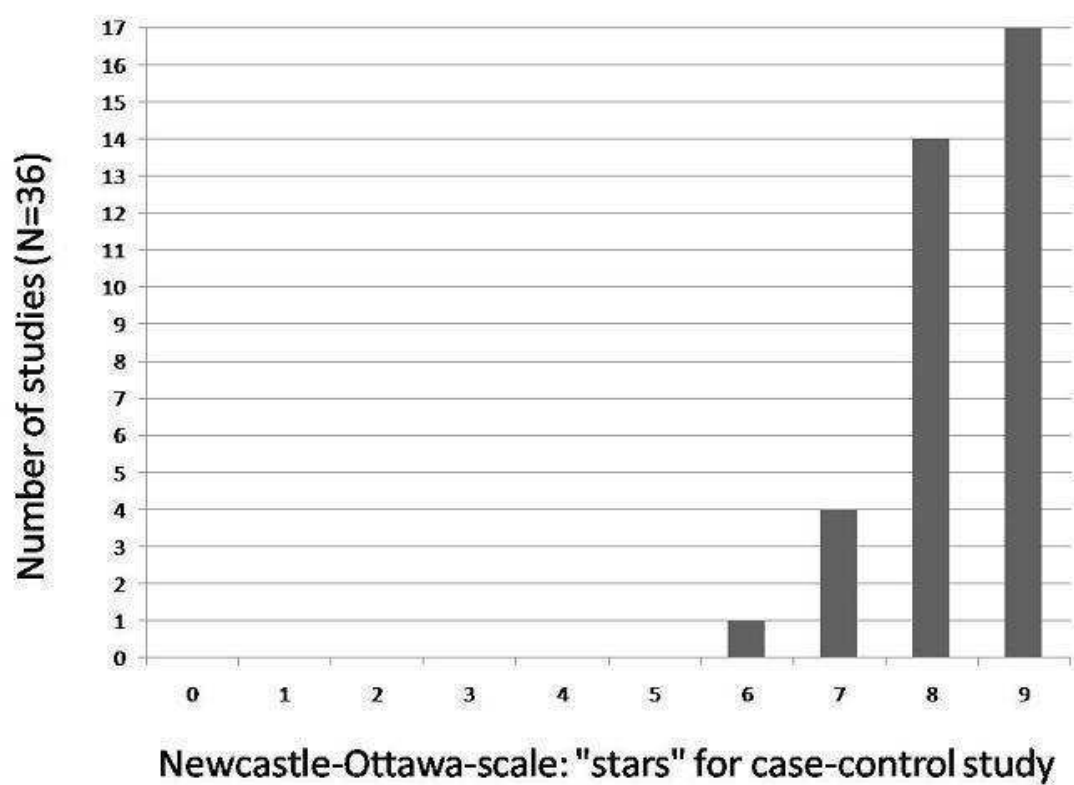


Figure 3. Newcastle Ottawa-Scale: number of studies by number of “stars” assigned in the cohort part of studies

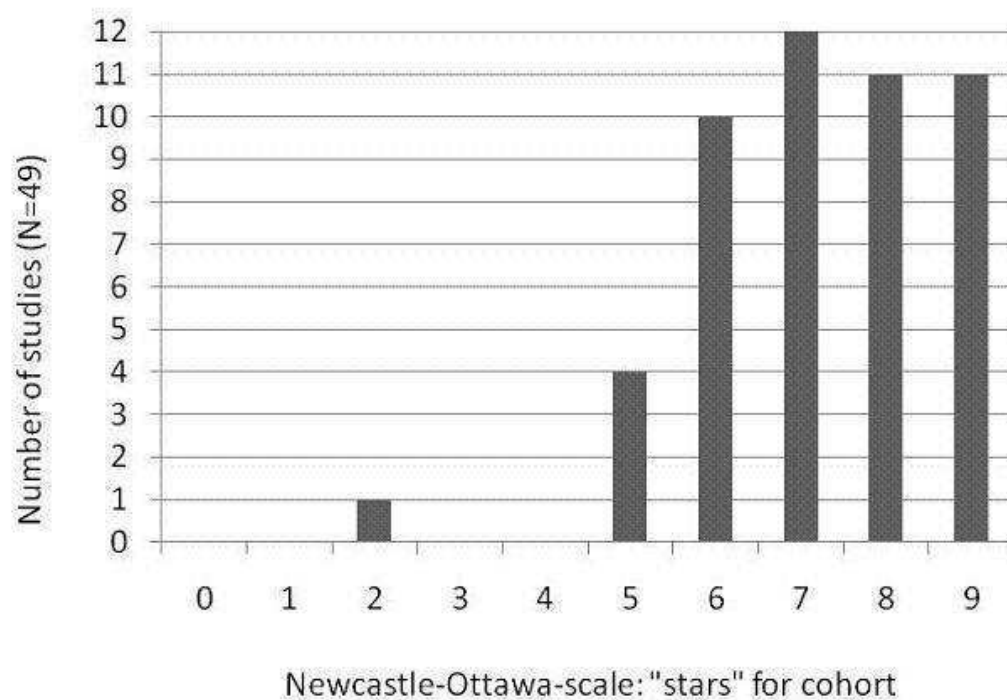


Table 2. Risk of bias: observational studies

Study	Publication	Newcastle Ottawa Scale (Cohort)				Newcastle Ottawa Scale (Case-Control)			
		Selection	Comparability	Outcome	Total	Selection	Comparability	Exposure	Total
Kabuto 1994	Kabuto 1994	0-1-1-1	2	1-1-0	7	0-1-1-1	2	1-1-1	8
Ratnasinghe 2000	Ratnasinghe 2000	1-1-1-1	2	1-0-0	7	0-0-1-1	2	1-1-1	7
Sakoda 2005	Sakoda 2005	0-1-1-0	1	1-1-0	5	1-1-1-1	1	1-1-1	8
Wei 2004	Wei 2004	1-1-1-1	1	1-1-1	8	
	Mark 2000	1-1-1-1	1	1-1-1	8	

Table 2. Risk of bias: observational studies (Continued)

Yu 1999	Yu 1999	0-1-1-1	2	1-1-0	7	1-1-1-1	2	1-1-1	9
Mc-Naughton 2005	Mc-Naughton 2005	1-1-1-1	1	1-1-0	7	1-1-1-1	1	1-1-1	8
	Heinen 2007	1-1-1-1	2	1-1-1	9	.-.-.-.		.-.-.	
	van der Pols 2009	1-1-1-1	2	1-1-0	8	.-.-.-.		.-.-.	
Akbaraly 2005	Akbaraly 2005	0-1-1-1	2	0-1-0	6	.-.-.-.		.-.-.	
Allen 2008	Allen 2008	1-1-1-1	2	1-1-0	8	1-1-1-1	2	1-1-1	9
Fex 1987	Fex 1987	1-1-1-0	2	1-1-1	8	1-0-1-1	2	1-1-1	8
Glattre 1989	Glattre 1989	0-1-1-0	1	1-1-1	6	1-1-1-1	1	1-1-1	8
Hartman 1998	Hartman 1998	1-1-0-1	2	1-1-0	7	.-.-.-.		.-.-.	
Knekt 1990	Knekt 1990	1-1-1-1	2	1-1-1	9	0-1-1-1	2	1-1-1	8
	Hakama 1990	1-1-1-1	2	1-1-1	9	0-1-1-1	2	1-1-1	8
	Knekt 1988	1-1-1-1	2	1-1-1	9	0-0-1-1	2	1-1-1	7
	Knekt 1996	1-1-1-1	1	1-1-1	8	0-1-1-1	1	1-1-1	7
	Knekt 1991	1-1-1-1	2	1-1-1	9	0-1-1-1	2	1-1-1	8
Knekt 1998	Knekt 1998	1-1-1-1	2	1-1-1	9	0-1-1-1	2	1-1-1	8
Kok 1987	Kok 1987b	1-1-1-1	2	1-1-1	9	1-0-1-1	2	1-1-1	8
	Kok 1987a	.-.-.-.		.-.-.		.-.-.-.		.-.-.	
Kornitzer 2004	Kornitzer 2004	1-1-1-0	1	1-1-1	7	1-1-1-1	1	1-1-1	8

Table 2. Risk of bias: observational studies (Continued)

Kromhout 1987	Kromhout 1987	1-1-1-0	2	1-1-1	8	
Michaud 2002	Michaud 2002	1-1-1-1	2	1-1-0	8	0-1-1-1	2	1-1-1	8
Overvad 1991	Overvad 1991	1-1-1-0	1	1-1-0	6	
Persson 2000	Persson- Moschos 2000	1-1-1-0	2	1-1-1	8	1-0-1-1	2	1-1-1	8
Ringstad 1988	Ringstad 1988	1-1-1-1	2	1-1-0	8	1-1-1-1	2	1-1-1	9
Salonen 1984	Salonen 1984	1-1-1-1	2	1-1-1	9	0-1-1-1	2	1-1-1	8
Salonen 1985	Salonen 1985	1-1-1-1	2	1-1-1	9	1-1-1-1	2	1-1-1	9
van Noord 1987	van Noord 1987	1-1-1-0	1	1-0-1	6	1-1-1-0	1	1-1-1	7
vd Brandt 1993	van den Brandt 1993	1-1-1-1	2	1-1-1	9	
	van den Brandt 1994	1-1-1-1	2	1-1-1	9	
	van den Brandt 1993	1-1-1-1	2	1-1-1	9	
	van den Brandt 2003	1-1-1-1	2	1-1-1	9	
	Zeegers 2002	1-1-1-1	2	1-1-1	9	
Virtamo 1987	Virtamo 1987	0-1-1-1	2	1-1-1	8	
Bleys 2008	Bleys 2008	1-1-1-1	2	1-1-1	9	

Table 2. Risk of bias: observational studies (Continued)

Brooks 2001	Brooks 2001	0-1-1-0	2	1-0-0	5	1-0-1-1	2	1-1-0	7
Clark 1985	Clark 1985	0-1-1-0	0	0-0-0	2	.-.-.-.		.-.-.	
Coates 1988	Coates 1988	0-1-1-0	1	1-1-0	5	1-0-1-0	1	1-1-1	6
	Coates 1987	.-.-.-.		.-.-.		.-.-.-.		.-.-.	
Combs 1993	Combs jr 1993	0-1-1-0	2	1-0-0	5	.-.-.-.		.-.-.	
Comstock 1997	Comstock 1997	0-1-1-0	2	1-1-0	6	1-1-1-1	2	1-1-1	9
Dong 2008	Dong 2008	1-1-1-1	2	1-1-1	9	.-.-.-.		.-.-.	
Dorgan 1998	Dorgan 1998	0-1-1-1	2	0-1-0	6	1-1-1-1	2	1-1-1	9
Epplein 2009	Epplein 2009	0-1-1-1	2	1-1-0	7	0-1-1-1	2	1-1-1	8
	Gill 2009	0-1-1-1	1	1-1-0	6	0-1-1-1	1	1-1-1	7
Garland 1995	Garland 1995	0-1-1-1	2	1-1-1	8	1-1-1-1	2	1-1-1	9
	Hunter 1990	0-1-1-1	2	1-1-1	8	1-1-1-1	2	1-1-1	9
Goodman 2001	Goodman 2001	0-1-1-0	2	1-1-0	6	1-1-1-1	2	1-1-1	9
Helzlsouer 2000	Helzlsouer 2000	0-1-1-1	1	1-1-0	6	1-1-1-1	1	1-1-1	8
Karagas 1997	Karagas 1997	0-1-1-1	2	1-1-1	8	1-1-1-1	2	1-1-1	9
Li 2004a	Li 2004	0-1-1-1	2	0-1-1	7	1-1-1-1	2	1-1-1	9
Menkes 1986	Menkes 1986	0-1-1-1	2	1-1-0	7	1-1-1-1	2	1-1-1	9

Table 2. Risk of bias: observational studies (Continued)

	Batieha 1993	0-1-1-1	2	1-1-0	7	1-1-1-1	2	1-1-1	9
	Breslow 1995	0-1-1-1	2	1-1-0	7	1-0-1-1	2	1-1-1	8
	Burney 1989	0-1-1-1	2	1-1-0	7	0-1-1-1	2	1-1-1	8
	Helzlsouer 1996	0-1-1-1	2	1-1-0	7	0-1-1-1	2	1-1-1	8
	Helzlsouer 1989	0-1-1-1	2	1-1-0	7	1-1-1-1	2	1-1-1	9
	Ko 1994	0-1-1-0	2	1-1-0	6	1-1-1-1	2	1-1-1	9
	Menkes 1986	.-.-.-.		.-.-.		.-.-.-.		.-.-.	
	Schober 1987	0-1-1-1	1	1-1-0	6	0-1-1-1	1	1-1-1	7
	Schober 1986	.-.-.-.		.-.-.		.-.-.-.		.-.-.	
	Zheng 1993	0-1-1-1	2	1-1-0	7	0-1-1-1	2	1-1-1	8
Michaud 2005	Michaud 2005	0-1-1-1	2	0-1-0	6	1-1-1-1	2	1-1-1	9
Nomura 1987	Nomura 1987	1-1-1-1	2	1-1-1	9	1-1-1-1	2	1-1-1	9
Nomura 2000	Nomura 2000	1-1-1-1	2	1-1-1	9	1-1-1-1	2	1-1-1	9
Peleg 1985	Peleg 1985	1-1-1-1	1	1-1-0	7	1-1-1-1	1	1-1-1	8
Peters 2007	Peters 2007	0-1-1-1	2	1-1-0	7	1-1-1-1	2	1-1-1	9
Peters 2008	Peters 2008	0-1-1-1	1	1-1-1	7	.-.-.-.		.-.-.	
	Asgari 2009	0-1-1-1	1	1-1-0	6	.-.-.-.		.-.-.	

Table 2. Risk of bias: observational studies (Continued)

Thomson 2008	Thomson 2008	0-1-1-1	2	0-1-0	6	.-.-.-.		.-.-.	
Willett 1983	Willett 1983	1-1-1-0	2	1-1-0	7	1-1-1-1	2	1-1-1	9
Yoshizawa 1998	Yoshizawa 1998	0-1-1-1	2	1-1-1	8	1-0-1-1	2	1-1-1	8

All but one cohort study received five to nine 'stars' in the NOS. The exception (two 'stars') was an early investigation, which was only available in abstract form for assessment (Clark 1985). For three items of the NOS cohort assessment, less than 70% of the included studies were considered adequate: representativeness of the cohort for the target population (51% of the studies received a 'star'), demonstration that cancer was not present at study commencement (69%) and completeness of follow-up data (49%).

The representativeness of the cohort for the target population is a matter of external validity and generalisability of study results, but a systematic deviation of participants from the target population might also introduce bias to study results. The target population of included studies depended on the study objectives and could have been the general population, but also special occupational groups. Studies that did not identify their target population or recruited volunteers were not assigned a 'star' to this question. Differential selection of study participants, e.g. volunteers, from the target population can lead to confounding by factors associated with selenium status and cancer incidence, e.g. nutritional behaviour or socio-economic position.

All included studies chose comparison groups (cases/controls or exposed/non-exposed) from the same study population. This approach increased the comparability between groups.

The presence of undiagnosed cancer at the beginning of the study, when specimens for selenium analysis were taken, might influence selenium levels. People with certain types of cancer have been found to have lower selenium levels than healthy controls. This might lead to an overestimation of the protective effect of higher selenium levels against cancer, if undiagnosed cancer cases are prevalent. Some studies tried to investigate this source of bias by excluding cases that occurred within a certain period from the beginning (mostly one or two years).

Follow-up data were considered either as complete or as missing data unlikely to introduce bias to study results in 50% of the included observational studies. In the other cohorts, losses to follow-

up were more than 5% and a description of losses to follow-up was not provided. A high attrition may alter the characteristics of the population under investigation and impede generalisability of study results to the intended target population (external validity). The presence of attrition does not necessarily mean that the study results are biased. However, given the possibility that selenium status may be linked to sociodemographic variables and socio-economic position which may also influence participation in follow-up procedures, a differential effect of attrition may introduce bias towards under- or over-estimation of the true exposure effect.

Thirty-six included observational studies were nested case-control studies and therefore additionally assessed using the NOS case-control form. The number of 'stars' in the NOS assessment of the case-control part of the studies ranged from six to nine, with more than 85% having received eight or nine 'stars'. Although the included prospective case-control studies were generally assessed as having a low risk of bias, in some studies concern arose due to case definition and the question of representativeness of the cases. Definition of cases was considered inadequate in 19% of the nested case-control studies as cases were identified by self-reporting, linkage to databases with unclear validity of data or procedures were not described. The magnitude and direction of bias that might have been introduced to the study results is unclear.

In 19% of studies, not all identified cases (or an appropriate sample of them) were included in the trial analyses or selection procedures for analysed cases were not reported. In some studies, blood specimens were lost due to technical problems (e.g. cooler breakdown in one study centre), others did not have enough material available for analysis or cases for analysis were otherwise selected in a non-random manner. This might bias the estimates of association in either direction.

There was no obvious asymmetry (as an indicator of publication bias) in the funnel plots of the studies on total and prostate cancer risk (Figure 4; Figure 5).

Figure 4. Funnel plot of comparison: I Highest versus lowest selenium exposure, outcome: I.17 Total cancer incidence and mortality.

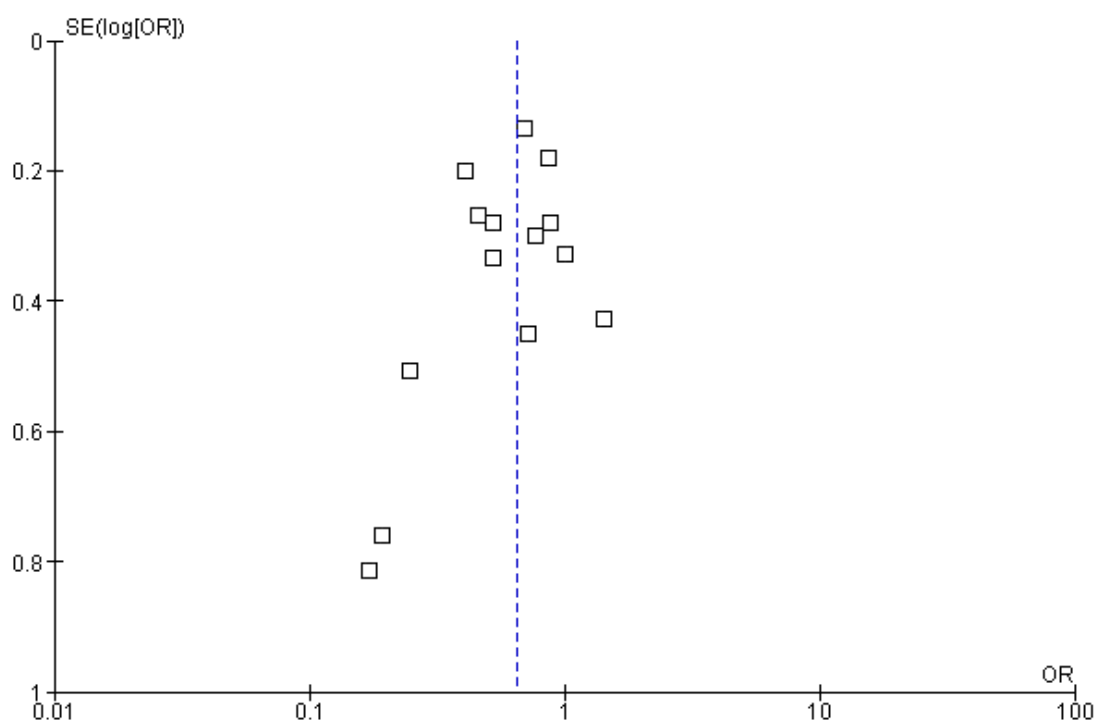
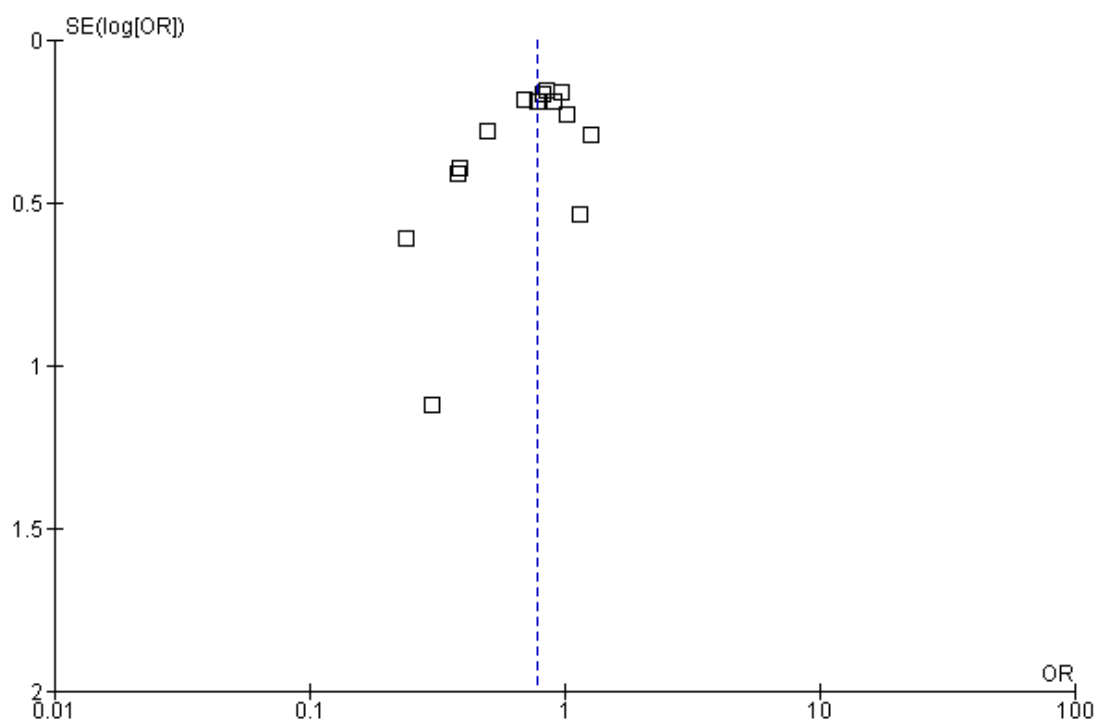


Figure 5. Funnel plot of comparison: I Highest versus lowest selenium exposure, outcome: I.7 Prostate cancer risk.



Randomised controlled trials

An overview of the risk of bias in the included randomised controlled trials is presented in [Table 3](#).

Table 3. Risk of bias: randomised controlled trials

Study	Sequence generation	Allocation concealment	Blinding	Completeness of outcome data	Risk of bias
NPCT 1996	adequate	adequate	adequate	adequate	low
Reid 2008	adequate	adequate	adequate	adequate	low
Li 2000	unclear	unclear	adequate	adequate	unclear
Yu 1997	unclear	unclear	adequate	unclear	unclear
Yu 1991	unclear	unclear	adequate	unclear	unclear
SELECT 2009	adequate	adequate	adequate	adequate	low

Primary liver cancer

All three trials on liver cancer risk (Li 2000; Yu 1991; Yu 1997) were considered to have an unclear risk of bias. In these trials, the generation of allocation sequence and the allocation concealment were not reported. One study mentioned that the drop-out rate was similar in the intervention and control group, the remaining two studies did not report the completeness of outcome data. Blinding was judged as adequate in all three studies as the use of placebo supplements was reported. We inferred from this procedure that at least the study participants and the physicians directly involved were blinded towards treatment status.

We would like to point out that we are not entirely convinced that Li 2000 is a randomised controlled trial. The study investigators used the term 'randomization based on the residence area' and did not describe the randomisation procedure any further. As participants were recruited from 17 villages, the villages and not the individual participants (stratified by village) could have been randomly assigned to the intervention and control group. However, we could not make contact with the study investigators and clarify these questions. A randomisation of villages instead of individuals would have introduced bias to the study results as the incidence of liver cancer is known to differ between areas as a result of environmental factors.

Studies with inadequate or unclear allocation concealment have been found to overestimate the benefit of interventions in RCTs, especially in trials with subjective outcomes (Pildal 2007; Wood 2008). In all three liver cancer RCTs, follow-up and case-detection procedures were not reported, so the influence of subjective factors on case detection, such as interpretation of bodily symptoms as trigger of further diagnostic tests, is unknown. Although we judged blinding as 'adequate' in all three liver cancer trials, we do not know whether it was successful in practice for patients, healthcare providers and outcome assessors.

These uncertainties about study methods seriously weaken our confidence in the reported RCT results on liver cancer risk.

Non-melanoma skin cancer

Both included RCTs on non-melanoma skin cancer (NPCT 1996; Reid 2008) were considered to have a low risk of bias with adequate generation of allocation sequence, allocation concealment, blinding and completeness of outcome data. Reid 2008 was a sub-study of NPCT 1996.

Both studies also reported data for several secondary outcomes that were introduced post-hoc, such as lung, prostate, colorectal cancer and total cancer incidence. Placebo and selenium groups were similar regarding the distribution of the risk factors smoking, age, gender and PSA levels at randomisation. New cases were identified in the biannual participants' interviews and by documenting cancer screening and diagnostic procedures from their medical files. Detection bias might have been introduced by a different use of diagnostic procedures in both groups: Men in the placebo group were, despite similar PSA levels, more likely to have undergone prostate biopsy (NPCT 1996) than men in the selenium group

(Duffield-Lillico 2003b see NPCT 1996) which might have led to an underestimation of prostate cancer incidence in the selenium group and an overestimation of the treatment effect. As the background of this difference is unclear, it cannot be ruled out that differential health behaviours and diagnostic activities in both study groups might have affected the detection of lung and colorectal cancer as well, at least in the 75% male participants.

Prostate cancer

SELECT 2009 was considered to have a low risk of bias with adequate generation of allocation sequence, allocation concealment, blinding and completeness of outcome data.

Placebo and selenium groups were similar regarding the distribution of age, education, smoking status, PSA levels and race/ethnicity at baseline. No inter-group differences were found in the utilisation of PSA tests, prostate biopsies or digital rectal examinations during the course of the study.

Ethical criteria

Informed consent and ethics board approval was fulfilled by NPCT 1996, Reid 2008 and SELECT 2009, but not mentioned in Li 2000, Yu 1997, and Yu 1991.

Effects of interventions

1. Observational studies

When comparing the risk of cancer in higher and lower levels of selenium exposure, a summary risk estimate of 1 suggests that there is no association between selenium exposure and cancer, a summary risk estimate below 1 suggests a possible protective effect of higher selenium exposure and a summary risk estimate above 1 suggests a possible harmful effect of higher selenium exposure.

1.1. Aetiological association: Results from meta-analyses

1.1.1. Any cancer

Results of 13 prospective observational studies on total cancer risk including data of more than 143,000 participants were meta-analysed. The cohorts of Salonen 1984 and Salonen 1985 overlapped. Hence, only data from Salonen 1985 were included in the meta-analysis. Fex 1987 had to be omitted as the CI value was not reported and could not be calculated from the available data.

In participants in the highest category of pre-diagnostic selenium exposure, the summary risk estimate was OR 0.69 (95% CI 0.53 to 0.91) for cancer incidence and OR 0.55 (95% CI 0.36 to 0.83) for cancer mortality in both genders (Analysis 1.17) when compared with participants in the lowest exposure category. Statistically significant heterogeneity was observed both among studies on incidence ($I^2 = 49\%$) and mortality ($I^2 = 58\%$).

Analyses by gender found the risk to be lower in men (incidence: OR 0.66 (95% CI 0.42 to 1.05), mortality 0.56 (95% CI 0.38 to 0.81)) (Analysis 1.20) than in women (incidence: OR 0.90 (95% CI 0.45 to 1.77), mortality: OR 0.92 (95% CI 0.79 to 1.07) (Analysis 1.19).

All studies used either serum or serum and plasma biomarker levels for the assessment of selenium status. Analysis 1.18 shows the results in ascending order of baseline exposure of those studies that reported their category borders. The graph does not reveal a clear pattern of a relationship between baseline biomarker level and cancer risk.

1.1.2. Female breast cancer

Seven studies were included in the meta-analysis. No association was seen between baseline selenium levels and incidence of breast cancer with an overall risk estimate of OR 1.00 (95% CI 0.78 to 1.29) (Analysis 1.1). The heterogeneity of trial results ($I^2 = 5.4\%$) was low and not statistically significant.

1.1.3. Bladder cancer

Meta-analysis of bladder cancer incidence in five observational studies found an inverse association with an overall risk estimate of 0.67 (95% CI 0.46 to 0.97) suggesting a protective effect of higher selenium levels against bladder cancer (Analysis 1.2) (overall heterogeneity: $I^2 = 30\%$).

Gender-disaggregated data were only available from Michaud 2005 indicating a protective effect in women, but not in men in this study. However, two studies (Michaud 2002; Nomura 1987) had only male participants and both found a non-significantly reduced bladder cancer risk for higher selenium exposure (Analysis 1.2). Heterogeneity was not reduced by gender stratification ($I^2 = 40\%$ in study results for men).

1.1.4. Lung cancer

Eleven studies were included in this meta-analysis. Data from Menkes 1986 and Knekt 1990 were not meta-analysed as the study population of the former overlapped with another meta-analysed study (Comstock 1997) and results of the latter were presented in insufficient detail.

The summary risk estimate for lung cancer incidence in both genders was 0.75 (95% CI 0.54 to 1.03) (Analysis 1.3). Statistically significant moderate heterogeneity was seen between study results ($I^2 = 54\%$).

In the meta-analysis according to gender using gender-stratified study results (Analysis 1.4), the summary risk estimate for women was OR 0.83 (95% CI 0.43 to 1.61) and for men OR 0.88 (95% CI 0.61 to 1.28). Heterogeneity among study results was not reduced by stratification. However, we expected the results for gender-combined data to be more or less a combination of the separate results for women and men. This was not the case here with 'gender-neutral' data suggesting a larger protective effect than gender-stratified data. This discrepancy might relate to differences in study designs or populations.

In Knekt 1998, 95% of the lung cancer cases occurred in men. We repeated the meta-analysis of gender-disaggregated data categorising Knekt 1998 as 'men-only' study and found a slightly changed summary risk estimate for men (OR 0.81 (95% CI 0.56 to 1.18)). The only study using nutritional intake assessment for exposure classification (Kromhout 1987) found no association with lung cancer risk (Analysis 1.6). Two studies measured selenium content in toenails with inconsistent results: Participants of the (all women) Nurses' Health Study (Garland 1995) showed an increased lung cancer risk with higher selenium toenail levels, while an inverse association was observed in the Netherlands' Cohort Study (vd Brandt 1993). The remaining eight studies used serum or plasma selenium levels. The summary OR was 0.84 (95% CI 0.66 to 1.06) with low heterogeneity ($I^2 = 3.5\%$).

We plotted the studies using serum/plasma in ascending order of baseline exposure level (Analysis 1.5). No clear pattern of a relationship between baseline exposure levels and lung cancer risk could be seen in this graph. The two studies, which suggested the largest protective effect of higher selenium levels, were Knekt 1998 and Kabuto 1994. However, two other studies with quite similar biomarker levels found discrepant results (Nomura 1987; Ratnasinghe 2000).

1.1.5. Prostate cancer

Fourteen epidemiological studies on prostate cancer incidence were included in the meta-analysis. The summary risk estimate for higher selenium exposure was OR 0.78 (95% CI 0.66 to 0.92) (heterogeneity: $I^2 = 37\%$) (Analysis 1.7).

Stratification by the method of selenium assessment showed a reduction in prostate cancer risk for higher baseline biochemical markers (OR 0.74 (95% CI 0.61 to 0.88)), but not for higher estimated selenium intake (OR 1.00 (95% CI 0.73 to 1.36)) (Analysis 1.8). The inverse association between selenium biomarkers and prostate cancer incidence was stronger for toenail levels (OR 0.53 (95% CI 0.35 to 0.81)) than for blood levels (OR 0.81 (95% CI 0.68 to 0.97)) (Analysis 1.9). Heterogeneity among study results was slightly reduced with these stratifications.

Stratification by country and continent found the risk reduction more pronounced in the US than in Europe (Analysis 1.10; Analysis 1.11).

Overall, the strongest inverse associations were seen in studies from the US published before 2001. These findings cannot be explained by differences in baseline selenium levels alone. Analysis 1.12 shows the results for studies using serum or plasma measurements in ascending order of selenium levels. For quite similar categories of selenium concentration, studies indicated different effects (Goodman 2001 versus Clark 1985; Nomura 2000 versus Peters 2007 and Gill 2009 see Epplein 2009).

1.1.6. Stomach cancer

Five observational studies were included in the meta-analysis of gastric cancer incidence. The summary risk estimate for both genders was OR 0.66 (95% CI 0.43 to 1.01) in the highest exposure

category when compared with the lowest ($I^2 = 50.8\%$) ([Analysis 1.13](#)). However, in this meta-analysis one cohort (Mark 2000 in: [Wei 2004](#)) is included twice because the results were reported stratified according to cardia and non-cardia gastric cancer.

We repeated the meta-analyses including alternately the results of Mark 2000 (see [Wei 2004](#)) for cardia and non-cardia gastric cancer. The summary OR was 0.75 (95% CI 0.47 to 1.21) when data for non-cardia cancer were included and OR 0.59 (95% CI 0.38 to 0.93) when data for cardia cancer were included.

Using the available gender-stratified results for meta-analysis, the risk estimate for men was OR 0.43 (95% CI 0.14 to 1.32) ($I^2 = 56.1\%$) and for women OR 0.73 (95% CI 0.12 to 4.35) ($I^2 =$

62.3%) ([Analysis 1.14](#)).

1.1.7. Colon/colorectal cancer

Five observational studies reported data on colon or colorectal cancer incidence. The summary risk estimate was OR 0.89 (95% CI 0.65 to 1.23) for both genders ($I^2 = 3.8\%$) ([Analysis 1.15](#)), OR 0.69 (95% CI 0.42 to 1.12) for men and OR 1.06 (95% CI 0.57 to 2.00) for women ([Analysis 1.16](#)).

1.2. Aetiological association: other results

Results of the observational studies, which were not included in meta-analyses, are reported in [Table 4](#).

Table 4. Results of observational studies not included in meta-analysis

Organ system	Cancer	Case definition	Relative risk estimate (highest versus lowest exposure category)	95% CI	Selenium marker	Gender	Study
Gynecologic	Cervix	Incidence	0.89	0.40 to 2.00	serum	women	Menkes 1986 (Batieha 1993)
			1.10	n.r.	serum		Coates 1988
	Gynaecologic (without breast)	Incidence	0.96	n.r.	serum		Knekt 1990
	Ovary	Incidence	0.87	0.25 to 5.26	serum		Knekt 1990 (Knekt 1996)
			1.22	0.44 to 3.38	toenail		Garland 1995
			0.58	0.2 to 1.7	serum		Menkes 1986 (Helzlsour 1996)
			1.00 (HR)	0.73 to 1.37	suppl. intake		Thomson 2008
	Uterus	Incidence	1.38	0.62 to 3.08	toenail		Garland 1995
Gastrointestinal	Gastrointestinal tract (all)	Incidence	1.00	n.r.	serum/plasma	both	Coates 1988
			0.29	0.10 to 0.91	plasma	men	Persson 2000
	Oesophagus	Incidence	0.56	0.44 to 0.71	serum	both	Wei 2004 (Mark 2000)
		Mortality	0.62	0.44 to 0.89	serum		

Table 4. Results of observational studies not included in meta-analysis (Continued)

		Mortality	0.35	0.16 to 0.81	serum	both	Wei 2004 (Wei 2004)
		Incidence	0.27	0.03 to 2.21	suppl. intake	both	Dong 2008
	Oesophages and stomach	Incidence	0.45	n.r.	serum	men	Knekt 1990 (Knekt 1988)
		Incidence	0.67	n.r.	serum	women	
	Liver	Incidence	0.62	0.21 to 1.86	plasma	men	Yu 1999
		Incidence	0.50	0.28 to 0.90	toenail	both	Sakoda 2005
		Mortality	0.50	0.28 to 0.90		both	
			0.57	0.31 to 1.05		men	
			0.18	0.03 to 1.13		women	
		Pancreas	Incidence	0.08	0.01 to 0.56)	men	Menkes 1986 (Burney 1989)
				0.83	0.4 to 1.67	women	
				0.58	n.r.	men	Knekt 1990
				3.49	n.r.	women	
			1.05	0.54 to 2.03	toenail	both	vd Brandt 1993
			0.91	0.41 to 2.00		men	
			1.58	0.59 to 4.22		women	
Urinary tract	Urinary tract (all)	Incidence	5.0	0.71 to	plasma	men	Persson 2000
			0.81	n.r.	serum	men	Knekt 1990
			4.12	n.r.		women	
Respiratory tract	Cavum oris/pharynx	Incidence	5.43	n.r.	serum	both	Menkes 1986 (Zheng 1993)
	Respiratory tract (all)	Incidence	6.0	1.5 to 24.2	plasma	men	Persson 2000
			0.90	0.30 to 2.50	serum	both	Menkes 1986 (Breslow 1995)
			0.98	0.69 to 1.41	suppl. intake	both	Peters 2008 (Asgari 2009)

Table 4. Results of observational studies not included in meta-analysis (Continued)

	Any non-melanoma cancer	Incidence	0.77	n.r.	plasma	both	Clark 1985
	Basal cell car-	Incidence	0.54	n.r.	serum	men	Knekt 1990
			1.55	n.r.		women	
			0.80	0.10 to 4.5	serum	both	Menkes 1986 (Breslow 1995)
			0.86	0.38 to 1.96	serum	both	McNaughton 2005
			0.95	0.59 to 1.50	nutritional intake		
	Squamous cell	Incidence	0.69	0.51 to 0.92	plasma	both	Combs 1993
			0.60	0.20 to 1.50	serum	both	Menkes 1986 (Breslow 1995)
			0.86	0.47 to 1.58	plasma	both	Karagas 1997
			1.30	0.77 to 2.3	nutritional intake	both	McNaughton 2005
			0.49	0.24 to 0.99	serum		
Other	Hematologic	Incidence	0.60	n.r.	serum/plasma	both	Coates 1988
	Thyroid	Incidence	0.15	0.0 to 5.0	serum	men	Glattre 1989
			0.12	0.01 to 1.11		women	
			0.13	0.02 to 0.77		both	

n.r. not reported

2. Randomised controlled trials

2.1. Preventive efficacy: main outcomes

2.1.1. Primary liver cancer

Three RCTs investigated the efficacy of selenium supplementation for liver cancer prevention. All RCTs were conducted in China and with participants of different high-risk groups in the Qidong province.

Yu 1997 investigated a 4-year supplementation period with 200 µg selenium yeast/day in 226 male and female hepatitis B-surface antigen (HBs-Ag) carriers. Eleven cases (person-time incidence rate: 1573.03/100,000) were detected in the placebo group and four cases in the selenium group (RR 0.36 (95% CI 0.12 to 1.11))

during the 8-year follow-up period. The mean blood selenium level was 152 ng/ml in the intervention group and 107 ng/ml in the control group (during the intervention period).

Yu 1991 reported on a trial with 2474 male and female first-degree relatives of liver cancer patients who also received 200 µg selenium yeast/day. During the study period of two years, 10 cases in the selenium and 13 cases in the placebo group were observed (RR 0.55 (95% CI 0.24 to 1.25)).

Li 2000 randomised 2065 male HBs-Ag carriers receiving 0.5 mg sodium selenite daily for 3 years. Thirty four cases of liver cancer occurred in the 1112 subjects receiving selenium and 57 cases in the 953 placebo subjects (RR 0.51 (95% CI 0.34 to 0.77)).

2.1.2. Non-melanoma skin cancer

2.1.2.1. Total non-melanoma skin cancer

A higher risk for non-melanoma skin cancer was seen in the 200 µg/day selenium supplementation group of the NPCT (RR 1.27 (95% CI 1.11 to 1.45)) (Duffield-Lillico 2003 see NPCT 1996). The increase remained statistically significant after multivariate adjustment (HR 1.17 (95% CI 1.02 to 1.34)). No variation in this effect by age, gender or smoking status was statistically significant. Mean selenium plasma concentration of the participants was 114 ng/ml at the time of randomisation. An increased risk for total non-melanoma skin cancer was seen in all tertiles of baseline plasma levels (Reid 2008 see NPCT 1996). The increased risk could be observed more pronouncedly at one study centre (Macon, Georgia) than at the other study sites. The percentage of female participants was higher in Macon, but distribution of other factors, in particular baseline selenium levels, was similar to the other sites and the reason for the different effect, if not due to chance alone, remained unclear.

In the sub-study with 400 µg/day selenium supplementation (Reid 2008), no alteration of non-melanoma skin cancer risk was seen (HR 0.91 (95% CI 0.69 to 1.20)). Gender-stratified analyses found a decreased risk in women (RR 0.40 (95% CI 0.20 to 0.80)) and a non-statistically significant increased risk in men (exact data not reported). Distribution of baseline plasma selenium levels was similar in this sub-study to the participants of the NPCT main study and we found no evidence for an effect modification according to baseline selenium exposure.

Neither the intervention with 200 µg/day nor with 400 µg/day found evidence that supported a preventive efficacy of selenium yeast supplementation against non-melanoma skin cancer in these populations. The results of the NPCT raised concerns about harmful effects of selenium yeast supplementation.

The comparison of the results of both investigations did not show a dose-response relationship between the amount of supplemental selenium intake and outcome: While a harmful effect on non-

melanoma skin cancer risk was seen with the 200 µg/day supplement, the 400 µg/day supplement showed a decreased risk in women and no effect in men. This might indicate differential biological mechanisms and health effects of selenium at different levels of supplemental intake by gender. The 400 µg/day supplemental intake led to a mean selenium level of approximately 250 ng/ml while 200 µg/day supplemental intake increased plasma levels to approximately 200 ng/ml.

2.1.2.2. Basal cell carcinoma

At the end of the total blinded treatment period in the NPCT, the RR 1.17 (95% CI 1.02 to 1.35) for basal cell carcinoma (BCC) was increased in the 200 µg/day selenium group. Multivariate adjustment attenuated the effect to a HR of 1.09 (95% CI 0.94 to 1.26). Eliminating the cases that occurred within the first two years of supplementation had no further effect on the RR. We found no statistically significant variations in effects according to age, gender or smoking status.

Reid 2008 found an adjusted HR of 0.95 (95% CI 0.69 to 1.29) in the 400 µg/day selenium sub-study.

2.1.2.3. Squamous cell carcinoma

In the NPCT, selenium supplementation increased both the (unadjusted) risk for squamous cell carcinoma (SCC) (RR 1.32 (95% CI 1.09 to 1.60)) and the multivariate-adjusted HR 1.25 (95% CI 1.03 to 1.51). After exclusion of the cases that occurred within the first two years, a slight decline in the effect of selenium supplementation was seen (leading to statistical non-significance). We found no statistically significant variations in effects according to age, gender or smoking status. The adverse effect of selenium supplementation on SCC risk seemed to increase with increasing plasma selenium levels at baseline. A higher risk of non-melanoma skin cancer incidence was seen only in participants with baseline plasma levels in the highest two tertiles of baseline exposure (greater or equal to 105.6 ng/ml), which suggested a possible interaction between supplementation and baseline exposure.

In the 400 µg/day selenium sub-study (Reid 2008), we found no alteration of SCC risk by selenium supplementation (HR 1.05 (95% CI 0.71 to 1.56)).

2.1.3. Prostate cancer

In the SELECT trial, we found no evidence of benefit of L-selenomethionine supplementation (compared to placebo) for a median of 5.5 years on prostate cancer incidence (HR 1.04, (95% CI 0.90 to 1.18), (99% CI 0.87 to 1.24)) (SELECT 2009). The adjusted HR for prostate cancer in the selenium plus vitamin E group compared to placebo was HR 1.05 ((95% CI 0.91 to 1.20), (99% CI 0.88 to 1.25)).

SELECT was terminated early in 2008 following the recommendation of the data and safety monitoring committee. The committee had some concern over a statistically non-significant increase in prostate cancer in the vitamin E-alone group (HR 1.13, (95% CI 0.99 to 1.29), (99% CI 0.95 to 1.35)).

SELECT failed to replicate the findings of the NPCT, which observed a reduction in prostate cancer incidence in the selenium yeast group (adjusted HR 0.48 (95% CI 0.28 to 0.80)), and found no evidence for a statistically significant cancer preventive efficacy of selenium supplements. NPCT investigators argued that as randomisation worked, bias seemed unlikely to explain the positive findings for some cancers including prostate cancer in their trial. Regarding prostate cancer, however, a differential participation of men with elevated PSA levels in prostate biopsies was observed in the selenium and placebo group (35% versus 14%; Duffield-Lillico 2003 see NPCT 1996). This may have occurred by chance and could have contributed to an overestimation of the effect of selenium supplementation in the NPCT.

2.2. Preventive efficacy: secondary and other outcomes

The NPCT (NPCT 1996) reported on a number of secondary outcomes identified post-hoc and other cancers, which had occurred in the trial population.

The total cancer incidence was reduced in the selenium group (adjusted HR 0.75 (95% CI 0.58 to 0.97)) after a mean follow-up of 7.4 years (Duffield-Lillico 2002 see NPCT 1996). Cancer mortality was also reduced (adjusted HR 0.59 (95% CI 0.39 to 0.87)). A gender-stratified analysis revealed that any possibly protective effect on total cancer incidence in the NPCT was confined to men (adjusted HR 0.67 (95% CI 0.50 to 0.89)). The adjusted HR for women was 1.20 (95% CI 0.66 to 2.2). Because of the predominance of male participants, these gender-differential effects added up to a net benefit for the total study population.

The observed risk of specific cancers in the selenium group was lower than in the placebo group for lung cancer (adjusted HR 0.74 (95% CI 0.44 to 1.24)), colorectal cancer (adjusted HR 0.46 (95% CI 0.21 to 1.02)), oesophageal cancer (adjusted HR 0.40 (95% CI 0.08 to 2.07)) and prostate cancer, as mentioned above. On the contrary, it was higher in the selenium group than in the placebo group for melanoma (adjusted HR 1.18 (95% CI 0.49 to 2.85)), bladder cancer (adjusted HR 1.28 (95% CI 0.50 to 3.25)), breast cancer (adjusted HR 1.89 (95% CI 0.69 to 5.14)), head and neck cancer (adjusted HR 1.27 (95% CI 0.47 to 3.42)) and lymphoma/leukaemia (adjusted HR 1.25 (95% CI 0.43 to 3.61)). Reid 2008 found no evidence that selenium supplementation altered total cancer incidence (RR 1.10 (95% CI 0.57 to 2.17)).

2.3. Adverse effects

NPCT 1996 and SELECT 2009 reported on adverse effects of selenium supplements.

In the NPCT, 35 participants had withdrawn from the study because of adverse effects, mainly gastrointestinal upset. The RR for adverse events in the selenium group was 1.51 (95% CI 0.74 to 3.11) (own calculation, based on the number of all randomised participants).

In SELECT, men in the selenium group had an increased risk of alopecia (RR 1.28 (99% CI 1.10 to 1.62)) and dermatitis (grade 1 to 2) (RR 1.17 (99% CI 1.00 to 1.35)), but not of halitosis, nail changes, fatigue, nausea or dermatitis (grade 3 to 4). A statistically non-significant increase in diabetes mellitus type II in the selenium-alone group (HR 1.07 (99% CI 0.94: 1.22)) was seen.

An increased risk for diabetes mellitus type II was also observed in the NPCT (Stranges 2007 in: NPCT 1996). A secondary analysis of participants who did not have diabetes at the start of the study revealed an excess risk in the selenium group (adjusted HR 1.55 (95% CI 1.03 to 2.33)). We found no statistically significant interactions with age, gender, smoking status and BMI. The RR for developing type II diabetes mellitus was higher in participants in the upper two tertiles of plasma selenium levels, indicating a possible interaction with baseline exposure status.

Both the SELECT and the NPCT results suggest that long-term supplementation with selenium may adversely affect glucose metabolism and increase the risk for diabetes mellitus type II.

The three trials on liver cancer and Reid 2008 did not mention the occurrence of adverse effects. One paper stated that no case of selenosis had been observed during the trial.

DISCUSSION

Summary of main results

The aims of this review were to examine the efficacy of selenium supplements in preventing cancer and possible associations between selenium exposure and the risk of cancer incidence and mortality.

Observational studies and aetiological association

From our meta-analyses of 13 prospective observational studies on total cancer risk, we found a reduced cancer incidence and mortality with higher selenium exposure. The risk of cancer disease was 31% (95% CI 9% to 47%) lower in the highest category of selenium exposure than in the lowest, the risk of death from cancer was 45% (95% CI 17% to 64%) lower. Subgroup analyses by gender suggested that a beneficial effect of higher selenium exposure, if existent, could be higher in men than in women.

The risk of developing bladder cancer was reduced by 33% (95% CI 3% to 54%) and that of prostate cancer by 22% (95% CI 8% to 44%). The risk of lung, gastric or colorectal cancers were also

found to be reduced with higher selenium exposure; however the confidence intervals of the summary risk estimates overlapped the 1.

No association was seen between selenium and the risk of breast cancer.

For all other types of cancer, data were only available from less than five epidemiological studies; thus results were narratively summarised. None of the study results supported an association between selenium exposure and gynaecological cancer risk, while results for cancers of the gastrointestinal, respiratory or urological tract were inconsistent. For respiratory and urological cancers (other than bladder, prostate or lung cancer), studies reported either no associations or increased risks for participants with a higher selenium exposure. For gastrointestinal cancers, studies found either no associations or reduced risks with a higher selenium exposure.

As is the case with all meta-analyses of epidemiological data, our findings have potential limitations resulting from study design as well as quality and heterogeneity of the data. These limitations can complicate the interpretation of the summary statistics.

RCTs and preventive efficacy

We identified six randomised controlled trials, which investigated mono-selenium supplements in the prevention of non-melanoma skin cancer, liver cancer and prostate cancer. There was no convincing evidence that selenium supplementation can prevent non-melanoma skin cancer or liver cancer in women or men or prostate cancer. The results of the Nutritional Prevention of Cancer Trial (NPCT) raised concerns about possible harmful effects of selenium supplements.

The NPCT was considered to have a low risk of bias and found a statistically significant increase in the incidence of squamous cell carcinoma as well as a trend towards an increased basal cell carcinoma incidence with selenium yeast supplementation. The RR increase was 17% for total non-melanoma skin cancer and 25% for squamous cell carcinoma in both genders after a mean follow-up of 7.4 years. The number needed to harm in the study population was 19 (95% CI 10 to 143) after a duration of five years selenium supplementation. A sub-study of the NPCT, which used supplements with a higher selenium content, found no differences in non-melanoma skin cancer risk between the active and the control group in both genders combined (HR 0.91, 95% CI 0.69 to 1.20), but an indication of a possible modification of effect by sex or gender, which was not seen in the main part of the NPCT.

Secondary outcomes of the NPCT indicated a lower total cancer incidence and mortality in the selenium group in men, but not in women. Analyses stratified according to cancer type found a statistically significantly reduced risk for prostate cancer. These results were not seen in the sub-study of the NPCT and could not be replicated in the SELECT trial, although it should be noted

that this trial used a different intervention.

The SELECT trial was a large prostate cancer prevention trial in the general population of North America. It was considered to have a low risk of bias and found no alteration of prostate cancer incidence by L-selenomethionine supplements after a median follow-up of 5.5 years (HR 1.04, 95% CI 0.90 to 1.18).

One out of three liver cancer prevention trials reported a statistically significantly reduced risk of liver cancer (RR 0.51 (95% CI 0.34 to 0.77)) for male carriers of the hepatitis B surface antigen taking inorganic selenium supplements (sodium selenite) for three years. This was in contrast to the other two studies reporting no statistically significant effect of organic selenium supplements (selenium yeast) for the same cancer site. Due to several methodological concerns relating to randomisation and completeness of outcome data, the risk of bias was unclear for all three RCTs. Therefore, we cannot conclude that there is strong support for selenium supplements as agents for the prevention of liver cancer.

Overall completeness and applicability of evidence

Observational studies and aetiological association

We reviewed data from prospective observational studies, where selenium exposure was measured in populations without evidence of cancer, and which were then followed-up for a specified period of time. This approach minimised the risk of reverse causality if an association between selenium exposure and cancer was observed in the study.

The included studies differed in terms of selenium exposure measurement, types of outcomes, study designs and study populations. The low number of studies for most of the meta-analysed types of cancers prevented a thorough investigation of the sources of heterogeneity between study results. In particular, we could not explore the influence of specific sources of bias or the methodological quality of epidemiological studies on heterogeneity.

The investigations included over 1,078,000 individuals from diverse study populations predominantly from Europe and the USA and to a lesser extent, Asia and Australia) (also see: [Dennert 2008](#)). No prospective observational study on selenium and cancer risk could be identified from Africa or South America. This regional distribution reflects the under-representation of non-Western and resource-poor countries in epidemiological research ([Pearce 2004](#)). Differential regional representation in epidemiological studies is of special interest for this review, as selenium levels in humans vary significantly around the world. The selenium levels measured in the included cohorts reflect a broad range of naturally occurring selenium exposure as measured in cross-sectional studies worldwide. However, some of the lowest as well as the highest selenium levels in humans were reported in literature from South American

populations (Jaffé 1992), a region which was not investigated in any of the reviewed observational studies.

More than half of the studies included mixed gender populations, but the majority of them did not report gender-disaggregated data. In the available gender-specific results, men are over-represented, which inhibits the further understanding of a possible gender-specific association between selenium exposure and cancer risk in epidemiological data. This also limits the generalisability of the review results that evidence for a clinically relevant sex or gender-differential effect exists.

RCTs and preventive efficacy

This review investigated a diverse range of cancers, but cancer is not a uniform condition and malignant neoplasms show great differences in tumour biology. Only non-melanoma skin cancer, liver cancer and prostate cancer were investigated in the included prevention trials as primary outcomes. The results cannot be generalised to other types of cancers.

Regarding the three main outcomes, specific characteristics of the study populations may also limit the generalisability of the results to non-participants. Participants of the included RCTs on skin and liver cancer belonged to populations with a high risk for the outcome under investigation. The participants of the NPCT were mostly older and white, predominantly male inhabitants of the US. Mean plasma selenium concentration was in the lower range of U.S. levels, but still well above the average selenium level of Europeans. A possible interaction with baseline selenium levels was found resulting in an increased risk for developing squamous cell cancer and diabetes mellitus type II in participants receiving the selenium supplement who had higher baseline levels. An indication of interaction and modification of effect was also found for gender regarding some of the study results. When applying the study results to other populations, characteristics of the population regarding gender and selenium exposure should be considered.

Apparently healthy men over 50 years of age from the general population of North America participated in the SELECT trial on prostate cancer prevention. The large sample size and the inclusion of non-white participants from different socio-economic backgrounds supported the generalisability of study findings to other adequately nourished populations.

Selenium supplements contain either organic or inorganic species of selenium or a mixture of both, e.g. in the form of selenised yeast. The different species of selenium may exhibit differential effects on human health. Four included RCTs used selenised yeast supplements and found either a harmful or no effect of supplementation on the main study outcome. The SELECT trial used L-selenomethionine supplements, which is the major component of selenium yeast, and also found no preventive efficacy. The only RCT investigating sodium selenite supplements found a protective effect against liver cancer, but was considered to have an unclear risk of bias. It is also unclear how applicable these results are in

other settings and populations with a different nutritional status.

Interpretation of the results of clinical trials using selenium supplements should consider the different biological forms as well as their potential differential health effects when supplemented.

Quality of the evidence

Observational studies and aetiological association

The 49 observational studies were heterogeneous, not only regarding methodology, but also in the quality and level of detail of reporting. The publications included ranged from a congress abstract to a full-text dissertation.

Bias and confounding

Selenium measurement and categorical exposure classification

Five observational studies measured nutritional or supplemental selenium intake using questionnaires or interviews. Most studies, however, relied on selenium biomarkers such as toenail, serum or plasma selenium levels. Percentile borders, for example quartiles or quintiles, were usually applied as cut-off points for exposure categories. Our analyses were based on the comparison of highest versus lowest baseline exposure category. In our meta-analyses, different methods of selenium measurement and different numbers of exposure categories covering different absolute selenium levels were combined.

Assessment of total selenium intake with food-frequency questionnaires (FFQ) or interviews has proven difficult in other investigations because of the lack of food composition data which adequately reflects regional and seasonal variations in selenium concentration. The Duffield 1999 trial compared duplicate diet collections, dietary logs, FFQ and biomarkers as measurements for selenium intake and status in New Zealand men and women. The FFQ overestimated the mean selenium intake in study participants when compared with laboratory analyses of duplicate meals. The ranking in quartiles according to intake for both dietary logs and FFQ differed from the results from duplicate meals. Correlation between all three dietary measurements and selenium biomarkers (whole blood and plasma) were modest ($r = 0.1$ to 0.4) at the best. Also Karita 2003 found only a modest correlation between selenium intake as estimated from FFQ and from a 7-day dietary log in Japanese men and women. In the same study, a correlation between both estimates of dietary intake and serum selenium levels could not be seen.

Validity problems, possibly leading to exposure misclassification, have also been reported when questionnaires are used to assess supplement use (Murphy 2002).

Regarding biomarkers for selenium measurement, Ashton 2009 showed in a systematic review that plasma and whole-blood selenium concentrations increased with higher selenium intake in supplementation studies. Plasma, whole-blood and presumably serum selenium levels, although Ashton 2009 could not identify serum studies for their systematic review, were therefore considered by the authors to adequately reflect a short-term increase in supplemental selenium intake in healthy adults. However, authors also found significant, unexplained heterogeneity in the reaction of participants' plasma selenium levels to selenium supplementation.

Concerning the estimation of long-term nutritional intake with biomarkers, Longnecker 1996 demonstrated a high correlation between long-term selenium intake as estimated from duplicate food portions and single measurements from whole blood, serum and toenail specimens.

These findings support the concern that the ranking of selenium exposure differs according to the instruments used to assess intake and also between intake assessment and biomarkers. Exposure misclassification may have biased the results of individual studies and a meta-analysis of observational data is likely to reflect these biases. Non-differential exposure misclassification might have occurred in all included studies due to measurement errors or as a result of the gap between the theoretical definition of selenium exposure and the measurement thereof, which served as a proxy. Non-differential misclassification might lead to an under- as well as over-estimation of an effect in the presence of more than two exposure categories. Our approach of a meta-analysis covering different methods of selenium assessment might have introduced additional heterogeneity to review results.

A concern, which we cannot clarify to date, is that biomarkers do not adequately reflect intake of both organic and inorganic selenium species. Animal studies indicate that selenium from inorganic sources is not retained so well in the body as organic selenium. Selenium from organic sources led to higher blood selenium levels and a higher activity of glutathione peroxidase than equal doses of inorganic supplements in veterinary studies (Slavik 2008; Steen 2008). However, symptoms of acute toxicity were observed in animals with a lower intake of inorganic than organic selenium species (Kim 2001; Tiwary 2006). Hall 2008 found an increased genotoxic effect in human cell lines by sodium selenite in comparison to organic selenium. When considering the possibly differential effects of selenium species on human health, an adequate interpretation of the biomarkers representing selenium exposure would require knowledge of the selenium sources of the individual.

The observation in our review that cancer risks only show an association with biomarker levels, but not with nutritional intake might therefore be a consequence of an invalid measurement of

nutritional intake, which biased the results towards the null. Alternatively, it might likewise reflect that there truly is no association and that the findings from the biomarker studies were the result of chance and measurements of nutritional intake may provide better estimates of the exposure situation than do biomarkers, which may misclassify the exposure to inorganic selenium sources.

Furthermore, the comparison of risks between the highest and the lowest exposure category is most suitable to identify an effect when there is a consistent decrease or increase across absolute exposure levels. Other associations (e.g. threshold effects or U-shaped relationships) may be missed by this method of meta-analyses or the true effect might be diminished.

Comparability of cases and controls and detection of cancer

All included studies recruited participants pre-diagnostically and cases and control subjects stemmed from the same population. This approach decreased potential differences between both groups, which could have influenced cancer disease or death due to factors other than selenium exposure. We included the results from each study in meta-analyses which were adjusted for the highest number of additional variables.

Any cancer

All studies on total cancer risk identified cases by using registry links or a combination of several methods and losses to follow-up were low. Two studies on cancer incidence and two studies on cancer mortality analysed less than 80% of all identified cases (incidence: Persson 2000: 76%; Coates 1988: 79%; mortality: Kok 1987: 71%; Kornitzer 2004: 57%). The main reason for this was samples missing for selenium measurement. Not all studies that assessed mortality as a measure of cancer risk excluded participants with cancer disease at study inception. This might have led to an overestimation of a protective effect when selenium levels were lowered by the presence of cancer.

We therefore consider the results for cancer incidence to provide the more valid estimation for the relationship between selenium exposure and cancer risk than the mortality data.

Prostate cancer

All but two of the studies on prostate cancer risk identified cases by using links to cancer registries or a combination of personal follow-up interviews with PSA screening. Two studies with health professionals used self-reporting for case identification, followed by confirmation through medical records. The number of people lost to follow-up was low in all studies included. Two studies, however, included less than 80% of all identified cases in their analyses (Brooks 2001: 39%; van den Brandt 2003 in: vd Brandt 1993: 77%) because samples were not available for selenium measurement or diagnosis was not confirmed. In Brooks 2001, bias might have been introduced to the results to some extent, as the

demographic variables differed between the identified and analysed cases.

Bladder cancer

Losses to follow-up were low in three studies (Michaud 2002; Nomura 1987; Zeegers 2002 in: vd Brandt 1993) and unclear in two on bladder cancer risk (Helzlsouer 1986 in: Menkes 1986; Michaud 2005). Endpoints were ascertained in elaborate ways in four studies including linkages to registries and regional and national databases; one study relied on the self-reporting of study participants (Michaud 2005). The latter investigation compared bladder cancer in the Nurses' Health Study (women) and the Health Professionals Follow-Up Study (men) and was the only one to report gender disaggregated data. A gender-differential association between selenium exposure and bladder cancer risk was found, but the role of potential biases due to possible different self-reporting behaviour in these two distinct cohorts remained unclear.

The second study which found a statistically inverse association between selenium exposure and bladder cancer risk was Zeegers 2002, which could only analyse 70% of the identified bladder cancer cases as specimens for selenium measurement were not available for the remainder.

Residual confounding and effect modification

Most of the studies included controls for smoking and age, either by matching or by using multivariate techniques. However, only a few considered the potential effect of other factors. Possible confounding factors could be another food nutrient or a certain behaviour, which exhibits cancer protective effects and is associated with higher intake of selenium-rich foods. Furthermore, intake of heavy metals and other dietary factors may modify selenium health effects or the relationship between selenium exposure and biomarker concentration (overview in: Vinceti 2000). Metabolic interactions, for example, are known for arsenic (Zeng 2005).

Even in studies that considered the influence of a specific factor, validity of the assessment of the potential confounder can be challenging and is not commonly reported in study publications. For example, control for smoke exposure as a known risk factor for several types of cancer seems a crucial issue in epidemiologic studies on cancer risk. Cigarette smokers, for example, tend to have lower selenium biomarker levels, though cigarette smoking is a source of selenium exposure itself. Therefore an inverse association between selenium and lung cancer risk might also be the result of residual confounding and effect modification by smoking. Exposure to environmental and household smoking, which has been shown to be associated with increased risks of cancer (Gorlova 2006; Nishino 2001), might also be associated with selenium status due to differential nutritional behaviours or other mechanisms. We are not aware of any study that investigated this issue. Unknown factors may influence an observed selenium - cancer association and thus pose a challenge as to causal inferences.

Some of these factors cluster in population groups according to

socio-economic position (SEP). Only a few studies attempted to control for indicators of adult SEP as potential confounders, e.g. education, occupation or income. None used a composite index of indicators or considered childhood SEP. Some studies restricted their cohorts to certain subgroups of a population, such as occupational groups, and were likely only to include people of a similar adult socio-economic background.

It has been claimed that associations between vitamins and diseases are the result of confounding by social and behavioural factors acting over the course of a lifetime (Lawlor 2004). Lawlor 2004 argued that the divergent results from epidemiological and randomised controlled studies on the prevention of cardiovascular diseases can be explained by unmeasured confounding due to SEP. Risk of most cancers is - like cardiovascular morbidity - known to decrease with higher SEP. Research also indicated a positive association between higher SEP and selenium biomarkers (Barany 2002; Niskar 2003). However, other investigations did not confirm these findings: Kant 2007, for example, did not find an association between a measure of household poverty and selenium status.

The hypothesis of possible confounding due to SEP leading to an indirect association between selenium and cancer in epidemiological research would be consistent with the results for all types of cancers in this review - including the null association with breast cancer - with the exception of prostate cancer findings. Prostate cancer has been found to be more often diagnosed in men of a higher SEP (Dalton 2008) while we saw a protective association with higher selenium exposure. However, it remains unclear whether the more frequent diagnoses of prostate cancer in men with higher SEP reflects an excess of prostate cancer incidence in this population. It might also result from differential health and screening behaviours leading to a detection of otherwise symptom-free cases while men with a lower SEP tend to be overrepresented in diagnoses of advanced stages of the disease (Rapiti 2009). More information on screening and diagnostic behaviour of the male cohort participants would be necessary to further elucidate these findings.

For prostate cancer, studies published before 2000 and especially those from the US found a larger protective effect with higher selenium levels than did later studies. We consistently observed this in the studies on lung cancer.

This might be attributable to differences in study design or populations (with the later studies being the larger studies including the general population) or changing health and screening behaviours over time in the case of prostate cancer studies. It could also reflect publication bias in earlier years favouring positive results.

An alternative explanation could be a 'threshold' effect for a possible protective effect of selenium against prostate cancer around

a certain level, which has been diminishing due to the increasing use of selenium supplements in the US. Brooks 2001 reportedly observed results consistent with a threshold effect at a level of 108 µg/l serum selenium. Conversely, a threshold effect was not seen in another study with almost the same percentile limits (Goodman 2001) in a population of asbestos workers, who may have had other sources of selenium exposure than the participants of Brooks 2001 from the general population. It has been frequently suggested that an increase in selenium intake might be beneficial only for men with lower selenium levels as glutathione peroxidase activity reaches a plateau above approximately 95 (range 89 to 114) µg/l (Rayman 2000).

We found no clear indication of a threshold effect in either lung or prostate cancer in the overview of study results. Heterogeneity between studies might therefore not reflect a consistent biological threshold effect of baseline selenium exposure levels, but a cluster of known and unknown influences of factors related to study design, population and potential biases.

The role of chance

Large epidemiological studies are not designed to test for a specific aetiological hypothesis, but enable research to investigate a large number of possible associations. Given the multiplicity of possible comparisons, associations between selenium exposure and cancer endpoints may have resulted from chance alone.

Summary

Factors which seemed to account partially for the inter-study heterogeneity were type of outcome measure (incidence or mortality), assessment of exposure and gender.

Considering the possible influences of bias, residual confounding and modifying factors on the selenium-cancer relationship, the summary estimates from meta-analyses should be interpreted with caution. Meta-analyses of spurious findings in observational studies increase the precision of a summary risk estimate, which does not itself get nearer to the true value and may suggest a non-existent association (Egger 1998).

RCTs and preventive efficacy

The NPCT, its sub-study and the SELECT trial were considered to have a low risk of bias with adequate sequence generation, allocation concealment, blinding and reporting of findings. In the three trials on liver cancer prevention, quality of reporting was an issue and they were considered to have an unknown risk of bias. The individual trials were - in some cases discrepantly - reported in several papers and essential questions regarding sequence generation, allocation concealment, handling of drop-outs and withdrawals and detection of outcomes remained unanswered. This might be due to inadequate reporting, but might also hint

to flaws in trial design and implementation. We were uncertain that the only trial which found positive results for selenium supplements in liver cancer prevention randomised participants individually. A cluster randomisation of participants who lived in the same area/village, which may have been the procedure in this investigation, might have introduced additional bias to the study results, e.g. due to different environmental factors contributing to liver cancer development or detection, and might have led to an overestimation of the protective efficacy of selenium. A duplication of results with a rigorous study design would be necessary to assess the effect of sodium selenite on liver cancer incidence.

Potential biases in the review process

RCTs and preventive efficacy & observational studies and aetiological association

The literature search included the major international databases in the English and German language and we applied a broad search strategy supplemented by hand searching for references. We assume that we identified all randomised controlled studies and prospective observational studies relevant to our review questions. As we did not search databases in other languages, e.g. Chinese or Russian, we cannot rule out that we missed smaller studies which were not published in international journals. There is also a chance that we might have missed observational studies whose results on selenium exposure and cancer were reported in the body of a paper but not mentioned in the paper's title or abstract, even if the paper is indexed in the searched databases.

Although we tried to contact all investigators for missing or additional data on their studies, we were unable to retrieve answers to questions we had regarding methodology or outcomes in some studies. This applied particularly to earlier epidemiological studies where primary investigators may have relocated, died, or where data were not available in a current electronic format. Similarly, we could not make contact with the primary investigators of the Chinese RCTs.

The risk of bias assessment was based on the included publications. The risk of bias of studies that did not adequately describe the study design in the included publication but gave a reference to another paper, might therefore have been overestimated in this review.

Another concern, especially with the epidemiological studies, is publication bias. Cohort and nested case-control studies are not exclusively designed to test for a specific exposure-outcome association, but enable researchers to investigate a range of questions. It is conceivable that unfavourable results were less likely to be published.

We decided a priori to conduct meta-analyses only when five or more studies were available for a study outcome. As a result of this

cut-off, we did not conduct meta-analyses for a number of observational study outcomes with two to four studies available (see: [Table 1](#)). Our primary intention was to facilitate the investigation of heterogeneity between studies that were included in meta-analyses, in order to avoid producing more precise, but still unexplainably biased results. However, results of this review revealed that the cut-off at five studies did not guarantee this possibility and could therefore be reconsidered in future updates.

Regarding the question of the efficacy of selenium for cancer prevention, the cut-off point led to the situation that no meta-analytic procedures were conducted for RCTs. Looking out our results, however, only liver cancer results would have pooled without the cut-off. Results for this meta-analysis of liver cancer have already been published in another systematic review ([Bjelakovic 2008](#)) and were included in the discussion here. Replicating the meta-analysis of liver cancer trials would not have changed the results of this systematic review.

The authors of this review came from different disciplines and have different focuses, e.g. epidemiology, clinical medicine and nutrition. We consider this internal variety of expertise to be a strength of this review and made use of it by applying double-checking procedures during the entire review process whenever possible.

Agreements and disagreements with other studies or reviews

The idea of selenium supplementation for cancer prevention received broad support following the NPCT and the publication of several large epidemiological studies which supported the hypothesis of an aetiological relationship between low selenium status and cancer development. [Combs 2005](#) stated that “the hypothesis that Se (selenium) can affect cancer risk is supported by a remarkably consistent body of scientific evidence” ([Combs 2005](#), p346). These ideas stimulated the largest ever cancer prevention trial SELECT, which failed to provide support for this hypothesis. Disagreement between the results of this systematic review and other publications may partly be explained by the differentiation between aetiology and efficacy in the research questions of this review.

Observational studies and aetiological association

A number of systematic reviews with and without meta-analyses have been conducted on selenium and the risk of different types of cancer. Overall, our combined risk estimates are consistent with their results and slight discrepancies in numbers are attributable to different inclusion criteria. However, some of the previous publications arrived at more favourable conclusions regarding a possible protective association of higher selenium exposure against cancer. Our meta-analyses of epidemiological studies suggested an inverse association between selenium exposure and risk of several cancers

in men, which was reflected in a reduced overall cancer incidence and mortality. Associations with toenail selenium levels tended to be larger than with serum or plasma levels and in general no associations were seen with selenium intake. These findings were consistent with the secondary outcomes of the NPCT, which suggested a preventive efficacy of selenium supplements against several types of cancers in men, the strongest of which was prostate cancer. However, the large-scale SELECT trial failed to confirm any beneficial effects of supplemental selenium intake on prostate cancer risk. An earlier ecological analysis of a nationwide program to increase selenium intake with fortification in Finland also found no evidence of any protective effect against prostate cancer ([Vinceti 2000](#)).

Overall, there is little evidence for an association between selenium exposure and cancer risk in women and, if existent, it is likely to be small. Our meta-analyses do not support a protective association between higher selenium exposure and breast or colorectal cancer in women. These findings are consistent with the results of the NPCT trial, where all protective effects of selenium yeast supplementation were confined to men.

It has been argued that gender-related outcomes may reflect different exposure levels at baseline possibly related to gender-specific nutritional behaviour, which might be true for comparisons of distinct women-only and men-only cohorts ([Michaud 2005](#)). However, comparisons by gender within studies also pointed to a differential effect at similar exposure levels. We cannot rule out that sex or gender differences are observed by chance only, but laboratory and animal research have suggested sex differences in selenium metabolism and biology. Also sex-specific tumour biology and the predominance of specific cancer types may contribute to differential health outcomes in women and men. However, we cannot estimate the magnitude sex or gender differences possibly contribute to the observed differential health outcomes in men and women.

These considerations are of special interest as selenium supplements are aggressively marketed especially to women with regard to breast cancer prevention and treatment, which is not supported by data from observational or clinical investigations.

Heterogeneity between studies was not largely reduced by gender stratification in our meta-analyses. Furthermore, we expected that non-gender stratified data from observational studies would more or less reflect a combination of gender-stratified results for a specific tumour type, which was not always the case. In lung cancer meta-analysis, for example, the risk reduction by higher selenium levels seems to be larger in data for both genders combined than it was in data for women and men separately. This underlines the influence of other sources of heterogeneity on study outcomes. Reporting of gender-stratified results in mixed-gender cohort studies, which has become increasingly common over the years, might therefore reflect other factors related to study design, such as a better evaluation of possible confounders in more recently published studies. Socioeconomic position could be one such possible

confounder, leading to an overestimation of a protective effect of selenium. Several studies have found selenium levels to be positively associated with adult socioeconomic position in both men and women (Gundacker 2006; Niskar 2003).

Doubts seem therefore justified that the observed associations point to a causal relationship between selenium biomarker levels and cancer risk.

RCTs and preventive efficacy

Non-melanoma skin cancer

The risk increase in non-melanoma skin cancer by selenium supplements in the NPCT raises concerns about the safety of selenium yeast supplementation in both men and women.

The overall lack of a protective effect of selenium yeast against non-melanoma skin cancer is consistent with the results of the French SU.VI.M.AX trial. However, an increased risk (non-statistically significant) of non-melanoma skin cancer was only seen in women in the SU.VI.M.AX trial, not in men. These discrepancies between the results of both trials might relate to differences in intervention and characteristics of the study populations. Increased risk of non-melanoma skin cancer could be more pronounced in or restricted to high-risk populations or observable only at certain selenium levels.

Liver and other gastrointestinal cancers

Bjelakovic 2008 conducted a systematic review of antioxidant supplements for the prevention of gastrointestinal (GIT) cancers. They meta-analysed RCT data for liver cancer prevention with selenium-containing supplements and reported a protective effect in both genders (RR 0.56 (95% CI 0.42 to 0.76)). Three of the four trials in their meta-analysis were also included in this systematic review (Li 2000; Yu 1991; Yu 1997). The remaining RCT (Li 2004b) used a combination of selenium with allitridum, a synthetic garlic extract, in the intervention and therefore did not meet our inclusion criteria. Li 2004b found a preventive efficacy of high-dose allitridum/100 µg sodium selenite supplementation on total and gastric cancer incidence in men, but not in women. No effect on liver cancer was seen in either gender. Allitridum was considered the main intervention by Li and colleagues in their paper and the contribution of selenium to the overall effect remained unclear. The more recent RCT by Qu 2007 found no effect of 50 µg selenium yeast in combination with beta-carotene and alpha-tocopherol on liver cancer mortality.

We did not calculate a summary risk estimate for the included RCTs on liver cancer in this review. The minimum number of studies required for meta-analyses was set a priori to five in the

protocol because we expected large heterogeneity between interventions and study populations and a high risk of bias in studies using selenium supplements. Considering the methodological constraints of the studies, the summary risk estimate of Bjelakovic 2008 may have overestimated the preventive efficacy of selenium against liver cancer.

We could not identify RCTs that investigated other GIT cancers as primary outcomes. The NPCT reported a (statistically non-significant) reduced risk of colorectal and oesophageal cancer as a secondary outcome in the selenium group. Other studies using multi-component selenium-containing supplements found divergent results, which also indicated potential sex or gender differences (Blot 1993; Hercberg 2004; see Background)

We consider that a replication of study results in adequately conducted randomised controlled trials is necessary before the preventive efficacy of selenium supplements against liver or other gastrointestinal cancers can be further evaluated or any recommendation made regarding supplements for GIT cancer prevention. However, the indication that nutritional supplements may prevent GIT cancers in borderline nutrient-deficient populations of developing countries should not be ignored in future research. Special consideration should be given to sex or gender-specific effects, selenium specification and possible interactions with other nutrients and the presence of risk factors for gastrointestinal cancers.

Prostate cancer

The SELECT trial failed to provide evidence for the preventive efficacy of oral L-selenomethionine and alpha-tocopherol either alone or in combination against prostate cancer.

The SELECT results contrasted with findings of the NPCT on prostate cancer. This might have occurred because of an overestimation of the real effect in the NPCT, where prostate cancer was not the primary outcome. It has also been argued that selenomethionine was the wrong supplement to replicate the NPCT results (Goossens 2009; El-Bayoumy 2009) and future trials should investigate selenium yeast as the active intervention.

SELECT participants had a higher selenium level at randomisation than men in the NPCT. While the mean plasma selenium concentration was 113 to 114 µg/l in the NPCT, median serum concentration was 135 to 138 µg/l in the different study arms in SELECT. Lower prostate cancer incidence in the NPCT trial was confined to men with baseline selenium levels in the lower two thirds (below 121 µg/l). Subgroup analyses of the SELECT trial are underway to investigate a possible modification by pre-intervention selenium levels.

The SU.VI.M.AX trial, which used a multivitamin and mineral supplement containing 100 µg selenised yeast, found a reduction in the rate of prostate cancers only in men with normal PSA levels at baseline (HR 0.52 (95% CI 0.29 to 0.92)), but an increased risk in men with elevated PSA (> 3 ng/ml) (HR 1.54 (95% CI 0.87 to 2.72) (Meyer 2005). There was no interaction with serum sele-

niium levels at baseline in this study and authors hypothesised that their multi component supplement might be beneficial in healthy men, but might promote prostate cancer development in men at higher risk. However, an interaction with baseline PSA levels was not seen in the NPCT. In SELECT, only men with normal PSA levels (less than 4 ng/ml) were eligible for participation.

Other cancers and diseases

Data for a variety of other cancers were reported in the NPCT trial. Notably, the results for the primary outcome of the NPCT, i.e. the incidence of non-melanoma skin cancer, received less attention in the public debate than those for secondary outcomes, especially those in favour of selenium supplementation. As they were based on a post-hoc analysis, the question of confounding and bias arose. Also the role of chance was unclear because of the uncontrolled procedures for detection of secondary outcomes. Under-representation of women in the NPCT decreased the power to detect sex-/gender-specific effects (Duffield-Lillico 2002, in: NPCT 1996) and is a concern as the highest hazard ratio for a single cancer type in the selenium group was seen for breast cancer (HR 1.89 (95% CI 0.69 to 5.14), non-statistically significant). All possible beneficial effects on cancer incidence were confined to men in this study.

In the SU.VI.M.AX trial, the selenium yeast-containing supplement did not alter breast cancer risk in female participants (Hercberg 2004). Overall, the SU.VI.M.AX trial detected no effect on total cancer incidence by its multivitamin/nutrient supplement in both genders combined (RR 0.90 (95% CI 0.76 to 1.06). Gender-stratified analyses showed a protective efficacy in men (RR 0.60 (95% CI 0.53 to 0.91), but not in women (RR 1.04 (95% CI 0.85 to 1.29)), with a reduction of cases mainly seen in gastrointestinal and respiratory cancers in men. Women had the higher baseline levels of antioxidants and study authors hypothesised that differences in outcomes between men and women may be attributable to gender differences in nutritional behaviour and consequent antioxidant status.

Also the Linxian General Population Trial (Blot 1993) found no statistically significant protective effect of the selenium containing supplement on total cancer incidence in either gender (RR 0.93 (95% CI 0.83 to 1.03); gender stratified results were not reported). Cancer deaths were marginally significantly reduced (RR 0.87 (95% CI 0.75 to 1.00)) in participants receiving the selenium/beta-carotene/vitamin E supplement.

For lung cancer, the Linxian trial found no alteration in mortality by selenium-containing study supplements (RR 0.98 (95% CI 0.71 to 1.35); Kamangar 2006).

One study currently in progress investigates the efficacy of selenium for the recurrence of early stage non-small cell lung cancer after initial surgery (RCT-ECOG 2002).

The SELECT trial reported a slightly elevated risk (statistically non-significant) for diabetes mellitus type II in the selenium group

(RR 1.07 99% CI (95% CI 0.94 to 1.22)). Secondary analysis of the NPCT also indicated that long-term selenium supplementation may increase the risk for developing type II diabetes mellitus (Stranges 2007).

AUTHORS' CONCLUSIONS

Implications for practice

For women, there is little evidence for lower or higher nutritional intake of selenium exhibiting a major impact on cancer risk. The only RCT results that have a low risk of bias support concerns of an increased risk of non-melanoma skin cancer by selenium yeast supplements in women who had already suffered from this disease.

For men, there is evidence for an inverse association between higher selenium biomarker levels and cancer risk. However, we cannot exclude that this effect may well be the result of other factors related to higher selenium biomarker levels than caused by selenium exposure itself. Results from two randomised controlled trials (NPCT and SELECT) have failed to provide evidence that non-melanoma skin cancer or prostate cancer can be prevented by selenium supplementation in men.

Additionally, concerns have been raised about possible toxicities from long-term intake of supplemental selenium.

Currently, regular intake of selenium supplements for cancer prevention cannot be recommended to either the selenium-replete or deficient populations.

Implications for research

Selenium may have different effects on specific types of cancer. The results from randomised controlled trials for the prevention of liver cancer need to be replicated in studies with a rigorous design.

Potential differential effects of sex or gender and the use of selenium supplements in populations with a high burden of specific types of cancer diseases and differing selenium exposure levels, e.g. known low nutritional selenium intake, require further examination.

Future prospective epidemiological studies as well as intervention trials should be adequately designed to detect sex or gender differences on specific types of cancer. Results of gender-stratified analyses should be reported even when statistically significant differences cannot be found.

Further research should aim to clarify why biomarkers of selenium exposure failed to reliably predict the results of RCTs with low risk of bias.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Akbaraly 2005

Methods	Cohort/sub-cohort controlled cohort study <i>Country:</i> France
Participants	<i>Name of parent cohort:</i> Etude du Vieillissement Antérieur Study (EVA study) <i>Participants:</i> 1389 participants (41% male, 59% female) <i>Inclusion criteria:</i> 59 to 71 years of age; residents of Nantes; able to undergo examination at study centre <i>Recruitment:</i> 1991 to 1993 <i>Outcome assessment:</i> December 2001 <i>Number of cases:</i> Any cancer: 45 (male/female: n.r.) <i>Case definition:</i> mortality <i>Years of follow-up:</i> 9.0 years <i>Type of selenium marker:</i> plasma
Interventions	d.n.a.
Outcomes	<i>Statistical methods:</i> Cox proportional hazard model <i>Variables controlled in analysis:</i> gender, smoking, alcohol intake, medication use, obesity, diabetes mellitus, hypertension, CVD, age, education, dyslipidaemia, low cognitive function
Notes	

Allen 2008

Methods	Matched, nested case-control study <i>Countries:</i> Denmark, Germany, Greece, Italy, the Netherlands, Spain, Sweden, the UK
Participants	<i>Participants:</i> approximately 130,000 men <i>Inclusion criteria:</i> male participants of the EPIC study <i>Name of parent cohort:</i> European Prospective Investigation into Cancer and Nutrition (EPIC) <i>Recruitment:</i> 1992 to 2000 <i>Outcome assessment:</i> at each country's study closure date (between June 1999 and January 2003) <i>Number of cases:</i> Prostate cancer: 959 (male/female: 959/0) <i>Case definition:</i> incidence <i>Years of follow-up:</i> median 2.6 years (Greece) to 9.2 years (Sweden) <i>Type of selenium marker:</i> plasma
Interventions	d.n.a.
Outcomes	<i>Statistical methods:</i> conditional logistic regression <i>Variables controlled in analysis:</i> BMI, smoking, alcohol consumption, physical activity, marital status, education <i>Variables controlled by matching:</i> age, study centre, time of day of blood collection, time between blood collection and

Allen 2008 (Continued)

	last meal, sex
Notes	

Bleys 2008

Methods	Cohort Study <i>Country:</i> US
Participants	<i>Participants:</i> 13,887 men and women <i>Inclusion criteria:</i> male and female adults, aged 20 to 90 years, participating in the NHANES III: “stratified, multistage probability cluster to provide data representing the noninstitutionalized US population” (Bleys 2008, p. 404) <i>Name of parent cohort:</i> Third National Health and Nutrition Examination Survey (NHANES III) <i>Recruitment:</i> 1988 to 1994 <i>Outcome assessment:</i> 15 December 2000 <i>Number of cases:</i> Cancer deaths: 457 (male/female: n.r.) <i>Case definition:</i> mortality <i>Years of follow-up:</i> 6 to 12 years <i>Type of selenium marker:</i> serum
Interventions	d.n.a.
Outcomes	<i>Statistical methods:</i> Cox proportional hazard regression <i>Variables controlled in analysis:</i> age, sex, race, education, annual family income, post-menopausal status (women), cigarette smoking, serum cotinine level, alcohol consumption
Notes	

Brooks 2001

Methods	Matched, nested case-control study <i>Country:</i> US
Participants	<i>Name of parent cohort:</i> Baltimore Longitudinal Study of Aging <i>Participants:</i> 1555 men <i>Inclusion criteria:</i> n.r. <i>Recruitment:</i> n.r. <i>Outcome assessment:</i> n.r. <i>Number of cases:</i> prostate cancer: 52 (male/female: 52/0) <i>Case definition:</i> incidence <i>Years of follow-up:</i> n.r. <i>Type of selenium marker:</i> plasma
Interventions	d.n.a.

Brooks 2001 (Continued)

Outcomes	<i>Analysed cases:</i> analysis for 52 of 133 cases (reason for non-inclusion: plasma and/or histological confirmation of diagnosis not available) <i>Statistical methods:</i> logistic regression <i>Variables controlled in analysis:</i> years between blood donation and diagnosis/follow-up, age, age by years before diagnosis interaction, BMI, smoking history, alcohol use <i>Variables controlled by matching:</i> age
Notes	

Clark 1985

Methods	Cohort/sub-cohort-controlled cohort study <i>Country:</i> US
Participants	<i>Participants:</i> 177 participants; no information on gender <i>Inclusion criteria:</i> persons at high risk of non-melanoma skin cancer <i>Recruitment:</i> n.r. <i>Outcome assessment:</i> n.r. <i>Number of cases:</i> skin (non-melanoma): 19 (male/female: n.r.) <i>Case definition:</i> incidence <i>Years of follow-up:</i> mean: 3.0 years <i>Type of selenium marker:</i> plasma
Interventions	d.n.a.
Outcomes	<i>Statistical methods:</i> Cox proportional hazard model
Notes	

Coates 1988

Methods	Matched, nested case-control study <i>Country:</i> US
Participants	<i>Participants:</i> number of participants n.r.; both genders <i>Inclusion criteria:</i> employees of two Seattle companies <i>Recruitment:</i> 1972 to 1973 and 1976 <i>Outcome assessment:</i> not stated <i>Number of cases:</i> Any cancer: 154 (male/female: n.r.) Gastrointestinal cancer: 28 (male/female: n.r.) Breast cancer: 20 (male/female: 0/20) Prostate cancer: 13 (male/female: 13/0) Haematological cancers: 12 (male/female: n.r.) Cervical cancer: 12 (male/female: 0/12) Lung cancer: 11 (male/female: n.r.)

Coates 1988 (Continued)

	Other: 58 (male/female: n.r.) Case definition: incidence Years of follow-up: n.r. Type of selenium marker: serum and plasma
Interventions	d.n.a.
Outcomes	Analysed cases: 154 (133 serum, 21 plasma) of 195 cases analysed (reason for non-inclusion: no sample available for analysis or no control available) Statistical methods: conditional logistic regression Variables controlled by matching: age, gender, race/ethnicity, year/month of sample collection, employer, plasma or serum sample
Notes	Primary publication: Coates 1988 Secondary publication: Coates 1987

Combs 1993

Methods	Cohort/sub-cohort-controlled cohort study Country: US
Participants	Participants: 1239 men and women Inclusion criteria: participants of the NPCT with valid selenium measurement at baseline Name of parent cohort: Nutritional Prevention of Cancer Trial (NPCT) Recruitment: see: Nutritional Prevention of Cancer Trial Outcome assessment: not stated Number of cases: Squamous cell cancer: 204 (male/female: n.r.) Case definition: incidence Years of follow-up: 2.0 years Type of selenium marker: plasma
Interventions	d.n.a.
Outcomes	Statistical methods: Cox proportional hazard model Variables controlled in analysis: age, gender, current smoking, alcohol drinking
Notes	

Comstock 1997

Methods	Matched, nested case-control study Country: US
Participants	Participants: number of participants n.r.; both genders Inclusion criteria: residents of Washington County Name of parent cohort: CLUE I and II Cohort Recruitment: 1974/75 or 1989

Comstock 1997 (Continued)

	<i>Outcome assessment:</i> n.r. <i>Number of cases:</i> Lung cancer: 258 (male/female: 157/101) <i>Case definition:</i> incidence <i>Years of follow-up:</i> n.r. <i>Type of selenium marker:</i> serum/plasma
Interventions	d.n.a.
Outcomes	<i>Statistical methods:</i> conditional logistic regression <i>Variables controlled by matching:</i> age, gender, race/ethnicity, year and month of sample collection, participant of Clue I or Clue II cohort
Notes	

Dong 2008

Methods	Cohort study Country: US
Participants	<i>Participants:</i> 339 participants (275 men; 64 women) <i>Inclusion criteria:</i> participants of a surveillance programme for men and women with Barrett's oesophagus, no prior history of oesophageal cancer or diagnosis of cancer within first three months of baseline <i>Name of parent cohort:</i> Seattle Barrett's Esophagus Program <i>Recruitment:</i> 1983 to 2004, baseline assessment for this study: 1 February 1995 to 1 July 2004 <i>Outcome assessment:</i> n.r. <i>Number of cases:</i> oesophageal adenocarcinoma: 37 (32 men, 5 women) <i>Case definition:</i> incidence <i>Years of follow-up:</i> mean: 5 years <i>Type of selenium marker:</i> intake of selenium supplements (self administered food frequency questionnaire)
Interventions	d.n.a.
Outcomes	<i>Statistical methods:</i> Cox proportional hazards regression <i>Variables controlled in analysis:</i> age, sex, fruit and vegetable consumption, percent energy from fat, waist-hip ratio, cigarette smoking, non-steroidal anti-inflammatory drug use
Notes	

Dorgan 1998

Methods	Matched, nested case-control study Country: US
Participants	<i>Participants:</i> 6426 women <i>Inclusion criteria:</i> female volunteers with serum available at the Breast Cancer Serum Bank in Columbia (Missouri)/ U.S.A; no history of cancer at baseline; missing serum sample for analysis excluded <i>Recruitment:</i> 1987 to 1997

Dorgan 1998 (Continued)

	<i>Outcome assessment:</i> 1982 to 1983, 1989 <i>Number of cases:</i> Breast cancer: 105 (male/female: 0/105) <i>Case definition:</i> incidence <i>Years of follow-up:</i> median: 2.7 years <i>Type of selenium marker:</i> serum
Interventions	d.n.a.
Outcomes	<i>Statistical methods:</i> conditional logistic regression <i>Variables controlled in analysis:</i> serum cholesterol, packs of cigarettes / day, BMI <i>Variables controlled by matching:</i> age, year and month of sample collection, diagnosis of benign breast disease within two years prior to study enrolment, “sequence number of blood draw” for women who donate blood more than one time
Notes	

Epplein 2009

Methods	Matched, nested case-control study (Epplein 2009 , Gill 2009) <i>Country:</i> US
Participants	<i>Inclusion criteria:</i> participants of the Multiethnic Cohort, aged 45 to 75 years (native Hawaiians: aged 42 years and older), blood sample provided before cancer diagnosis between 1997 and 2006 <i>Name of parent cohort:</i> Multiethnic Cohort <i>Recruitment:</i> 1993 to 1996 <i>Case definition:</i> incidence <i>Type of selenium marker:</i> serum Epplein 2009: <i>Participants:</i> 67,594 (male: 29,009 / female: 38,585) men and women <i>Outcome assessment:</i> 2006 <i>Number of cases:</i> Lung cancer: 207 (male/female: 136/71) <i>Years of follow-up:</i> 0 to 10 years Gill 2009: <i>Participants:</i> 29,009 men <i>Outcome assessment:</i> n.r. <i>Number of cases:</i> Prostate cancer: 467 (male/female: 467/0) <i>Years of follow-up:</i> n.r.
Interventions	d.n.a.
Outcomes	<i>Statistical methods:</i> conditional logistic regression Epplein 2009: <i>Variables controlled in analysis:</i> age, fasting hours, pack-years, pack-years squared, years of schooling, family history of lung cancer <i>Variables controlled by matching:</i> age, sex, race/ethnicity, date of sample collection, time of day of sample collection, fasting status, smoking

Epplein 2009 (Continued)

	<u>Gill 2009:</u> <i>Analysed cases:</i> 450 of 467 cases analysed <i>Variables controlled in analysis:</i> age, fasting hours, BMI, family history of prostate cancer, education <i>Variables controlled by matching:</i> age, race/ethnicity, date of sample collection, geographic site (California, Hawaii), time of day of sample collection, fasting status
Notes	<i>Primary publication:</i> Epplein 2009 <i>Other publications:</i> Gill 2009

Fex 1987

Methods	Matched, nested case-control study <i>Country:</i> Sweden
Participants	<i>Participants:</i> 7935 men <i>Inclusion criteria:</i> 46 to 48 years of age; residents of Malmo/Sweden; no restriction regarding malignant disease at baseline (11 of 35 cases were diagnosed with cancer at baseline screening examination and/or died during first year of follow-up) <i>Name of parent cohort:</i> Malmo Preventive Programme <i>Recruitment:</i> 1975 to 1979 <i>Outcome assessment:</i> June 1981 <i>Number of cases:</i> Any cancer: 35 (male/female: 35/0) <i>Case definition:</i> mortality <i>Years of follow-up:</i> 3.5 to 8.0 years <i>Type of selenium marker:</i> plasma
Interventions	d.n.a.
Outcomes	<i>Analysed cases:</i> 35 of 61 cases analysed (reason for non-inclusion: no plasma sample available) <i>Statistical methods:</i> logistic regression, Mantel-Haenszel <i>Variables controlled by matching:</i> age, month of sample collection
Notes	

Garland 1995

Methods	Matched, nested case-control study <i>Country:</i> US
Participants	<i>Participants:</i> 62,641 women <i>Inclusion criteria:</i> female registered nurses in 11 U.S. states; aged 30 to 55 years at baseline; completed questionnaire in 1976 and provision of toenail sample in 1982; no history of cancer at baseline <i>Name of parent cohort:</i> Nurses' Health Study (NHS) <i>Recruitment:</i> 1976 (toenail sample collection in 1982) <i>Outcome assessment:</i> 1 June 1986 <u>Garland 1995:</u> <i>Number of cases:</i>

Garland 1995 (Continued)

	<p>Any cancer (without breast): 503 (male/female: 0/503) Colon and rectal cancer: 89 (male/female: 0/89) Melanoma: 63 (male/female: 0/63) Ovarian cancer: 58 (male/female: 0/58) Lung cancer: 47 (male/female: 0/47) Other: 155 (male/female: 0/155) Uterine cancer: 91 (male/female: 0/91) <u>Hunter 1990:</u> <i>Number of cases:</i> Breast cancer: 434 (0/434) <i>Case definition:</i> incidence <i>Years of follow-up:</i> 2.0 to 4.4 years <i>Type of selenium marker:</i> toenail</p>
Interventions	d.n.a.
Outcomes	<p><i>Statistical methods:</i> logistic regression, conditional logistic regression <i>Variables controlled in analysis:</i> smoking status <i>Variables controlled by matching:</i> age, year and month of sample collection <u>Hunter 1990</u> additionally controlled in analysis for: age at first birth, age at menarche, alcohol use, history of benign breast disease, menopausal status, maternal breast cancer, breast cancer in sister(s), oral contraceptive use, parity, relative weight</p>
Notes	<p><i>Primary publication:</i> Garland 1995 <i>Other publications:</i> Hunter 1990</p>

Glattre 1989

Methods	<p>Matched, nested case-control study <i>Country:</i> Norway</p>
Participants	<p><i>Participants:</i> 100,000 men and women <i>Inclusion criteria:</i> serum available at Janus serum bank (Norwegian serum bank which is consolidated from several sources and maintained by the Norwegian Cancer Society for research purposes) <i>Recruitment:</i> 1972 to 1985 <i>Outcome assessment:</i> end of 1985 <i>Number of cases:</i> thyroid cancer: 43 (male/female: 12/31) <i>Case definition:</i> incidence <i>Years of follow-up:</i> 0.0 to 14.0 years <i>Type of selenium marker:</i> serum</p>
Interventions	d.n.a.
Outcomes	<p><i>Statistical methods:</i> conditional logistic regression <i>Variables controlled by matching:</i> age, gender, year of sample collection, county of residence</p>
Notes	

Goodman 2001

Methods	Matched, nested case-control study <i>Country:</i> US
Participants	<i>Participants:</i> 18,314 men and women <i>Inclusion criteria:</i> asbestos workers: 45 to 74 years of age; smokers > 20 pack-years: 50 to 69 years of age; cohort of a RCT for lung cancer prevention in high risk populations <i>Name of parent cohort:</i> Caret (Carotene and Retinol Efficacy Trial) <i>Recruitment:</i> 1988 to 1994 <i>Outcome assessment:</i> April 1999 <i>Number of cases:</i> Lung cancer: 235 (male/female: n.r.) Prostate cancer: 356 (male/female: 356/0) <i>Case definition:</i> incidence <i>Years of follow-up:</i> 6.0 to 12.0 years <i>Type of selenium marker:</i> serum
Interventions	d.n.a.
Outcomes	<i>Analysed cases:</i> 235 of 236 prostate cancer cases analysed (reason for non-inclusion: no sample available for analysis or no control available); 356 of 385 lung cancer cases analysed (reason for non-inclusion: missing selenium values for case-control pairs) <i>Statistical methods:</i> conditional logistic regression <i>Variables controlled by matching:</i> age, smoking status at randomisation, year of randomisation, year of sample collection, treatment arm, exposure population
Notes	

Hartman 1998

Methods	Cohort/sub-cohort-controlled cohort study <i>Country:</i> Finland
Participants	<i>Participants:</i> 29,133 men <i>Inclusion criteria:</i> 50 to 69 years of age; smokers; no history of cancer (other than non-melanoma skin cancer) at baseline; no severe physical or psychiatric illness; intake of vitamin E/A/beta-carotene supplements in excess of defined amounts <i>Name of parent cohort:</i> Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study <i>Recruitment:</i> 1985 to 1988 <i>Outcome assessment:</i> 30 April 1993 <i>Number of cases:</i> Prostate cancer: 302 (male/female: 302/0) <i>Case definition:</i> incidence <i>Years of follow-up:</i> 5.0 to 8.0 years <i>Type of selenium marker:</i> intake (food use questionnaire)
Interventions	d.n.a.

Hartman 1998 (Continued)

Outcomes	<p><i>Analysed cases:</i> 302 of 317 cases included in analysis (reason for non-inclusion: no dietary information available) analysis stratified by randomisation status according to active interventions or placebo interventions in the RCT results reported separately for total selenium intake and non-supplemental selenium intake</p> <p><i>Statistical methods:</i> Cox regression</p> <p><i>Variables controlled in analysis:</i> age, living in urban area, beta-carotene intervention, total energy, BPH</p>
Notes	

Helzlsouer 2000

Methods	<p>Matched, nested case-control study</p> <p><i>Country:</i> US</p>
Participants	<p><i>Participants:</i> 10,456 men</p> <p><i>Inclusion criteria:</i> residents of Washington county; cases with second malignancy or missing pathologic confirmation excluded</p> <p><i>Name of parent cohort:</i> CLUE II Cohort</p> <p><i>Recruitment:</i> 1989</p> <p><i>Outcome assessment:</i> September 1996</p> <p><i>Number of cases:</i> prostate cancer: 117 (male/female: 117/0)</p> <p><i>Case definition:</i> incidence</p> <p><i>Years of follow-up:</i> 6.8 to 7.8 years</p> <p><i>Type of selenium marker:</i> toenail</p>
Interventions	d.n.a.
Outcomes	<p><i>Analysed cases:</i> 117 of 145 cases analysed (reason for non-inclusion: no toenail clipping available)</p> <p><i>Statistical methods:</i> conditional logistic regression</p> <p><i>Variables controlled in analysis:</i> BMI at age 21, education, hours since last meal</p> <p><i>Variables controlled by matching:</i> age, race/ethnicity, year and month of sample collection, size of toenail clipping</p>
Notes	

Kabuto 1994

Methods	<p>Matched, nested case-control study</p> <p><i>Country:</i> Japan</p>
Participants	<p><i>Participants:</i> 20,000 men and women</p> <p><i>Inclusion criteria:</i> survivors of the atomic bomb in Hiroshima or Nagasaki; serum available for analysis</p> <p><i>Name of parent cohort:</i> Adult Health Study Hiroshima and Nagasaki</p> <p><i>Recruitment:</i> 1960 (blood samples drawn in 1970 to 1972)</p> <p><i>Outcome assessment:</i> 1983</p> <p><i>Number of cases:</i> Stomach cancer: 201 (male/female: 113/88) Lung cancer: 77 (male/female: 43/34)</p>

Kabuto 1994 (Continued)

	<i>Case definition:</i> incidence <i>Years of follow-up:</i> 12.0 to 14.0 years <i>Type of selenium marker:</i> serum
Interventions	d.n.a.
Outcomes	<i>Statistical methods:</i> conditional logistic regression <i>Variables controlled in analysis:</i> radiation dose, smoking, age, gender <i>Variables controlled by matching:</i> age, gender, year/month of sample collection, city
Notes	

Karagas 1997

Methods	Matched, nested case-control study <i>Country:</i> US
Participants	<i>Participants:</i> 1805 men and women <i>Inclusion criteria:</i> at least one basal cell or squamous cell cancer before study entry; participants of an RCT for non-melanoma skin cancer prevention with oral beta-carotene supplementation <i>Name of parent cohort:</i> Skin Cancer Prevention Study <i>Recruitment:</i> February 1983 to February 1986 <i>Outcome assessment:</i> 30 September 1989 <i>Number of cases:</i> Squamous cell cancer: 131 (89% male/11% female) <i>Case definition:</i> incidence <i>Years of follow-up:</i> 3.0 to 5.0 years <i>Type of selenium marker:</i> plasma
Interventions	d.n.a.
Outcomes	<i>Statistical methods:</i> conditional logistic regression <i>Variables controlled in analysis:</i> cigarette smoking <i>Variables controlled by matching:</i> age, gender, study centre of RCT, time in study (diagnosis date)
Notes	

Knekt 1990

Methods	Matched, nested case-control study (Knekt 1990 , Hakama 1990 , Knekt 1988 , Knekt 1996) Cohort study (Knekt 1991) <i>Country:</i> Finland
Participants	<i>Inclusion criteria:</i> no history of cancer at baseline <i>Name of parent cohort:</i> Social Insurance Institution's Mobile Clinic Health Examination Survey <i>Recruitment:</i> 1968 to 1972 Knekt 1990: <i>Participants:</i> 39,268: 21,172 men and 18,096 women

Knekt 1990 (Continued)

	<p><i>Outcome assessment:</i> 31 December 1980</p> <p><i>Number of cases:</i></p> <p>Any cancer: 1096 (male/female: 597/499)</p> <p>Stomach cancer: 95 (male/female: 58/37)</p> <p>Colon and rectal cancer: 91 (male/female: 32/59)</p> <p>Lung cancer: 198 (male/female: 189/9)</p> <p>Prostate cancer: 51 (male/female: 51/0)</p> <p>Urinary tract cancer: 47 (male/female: 34/13)</p> <p>Pancreatic cancer: 45 (male/female: 22/23)</p> <p>Breast cancer: 90 (male/female: 0/90)</p> <p>Gynaecological cancer (without breast): 86 (male/female: 0/86)</p> <p>Basal cell carcinoma (skin): 126 (male/female: 64/62)</p> <p>Other: 267 (male/female: 147/120)</p> <p><u>Hakama 1990:</u></p> <p><i>Participants:</i> number of participants n.r.; both genders</p> <p><i>Inclusion criteria:</i> aged 15 years and older</p> <p><i>Outcome assessment:</i> 1977</p> <p><i>Number of cases:</i></p> <p>Any cancer: 766 (male/female: n.r.)</p> <p>Lung cancer: 151 (male/female: 151/0)</p> <p>Breast cancer: 67 (male/female: 0/67)</p> <p>Stomach cancer: 76 (male/female: n.r.)</p> <p>Prostate cancer: 37 (male/female: 37/0)</p> <p><u>Knekt 1988:</u></p> <p><i>Participants:</i> 36,265: 21,172 men and 15,093 women</p> <p><i>Outcome assessment:</i> 31 December 1977</p> <p><i>Number of cases:</i></p> <p>Oesophageal and stomach cancer: 86 (male/female: 51/35)</p> <p>Colon and rectal cancer: 57 (male/female: 21/36)</p> <p><u>Knekt 1991:</u></p> <p><i>Participants:</i> 4538 men</p> <p><i>Inclusion criteria:</i> aged 20 to 69 years, with dietary history taken</p> <p><i>Outcome assessment:</i> 1986</p> <p><i>Number of cases:</i></p> <p>Lung cancer: 117 (male/female: 117/0)</p> <p><u>Knekt 1996:</u></p> <p><i>Participants:</i> 1896 women</p> <p><i>Outcome assessment:</i> 1980</p> <p><i>Number of cases:</i></p> <p>Ovarian cancer: 24 (male/female: 0/24)</p> <p><i>Case definition:</i> incidence</p> <p><i>Years of follow-up:</i> 9 to 20 years</p> <p><i>Type of selenium marker:</i> serum (Knekt 1990, Hakama 1990, Knekt 1988, Knekt 1996), intake (Knekt 1991; dietary history)</p>
Interventions	d.n.a.
Outcomes	<p><u>Knekt 1990:</u></p> <p><i>Statistical methods:</i> conditional logistic regression</p> <p><i>Variables controlled in analysis:</i> smoking</p>

Knekt 1990 (Continued)

	<p><i>Variables additionally controlled in analysis of highest four quintiles versus lowest quintile:</i> occupation, BMI, parity, cholesterol, haematocrit</p> <p><i>Variables controlled by matching:</i> age, gender, municipality, time of baseline examination, duration of storage of sample</p> <p><u>Hakama 1990:</u></p> <p><i>Analysed cases:</i> 766 of 864 cases analysed (reason for non-inclusion: no serum sample)</p> <p><i>Statistical methods:</i> conditional logistic regression</p> <p><i>Variables controlled in analysis:</i> smoking</p> <p><i>Variables additionally controlled in analysis of highest four quintiles versus lowest quintile:</i> retinol level, alpha-tocopherol level</p> <p><i>Variables controlled by matching:</i> age, gender, municipality, time of baseline examination, duration of storage of sample</p> <p><u>Knekt 1988:</u></p> <p><i>Statistical methods:</i> n.r.</p> <p><i>Variables controlled in analysis:</i> smoking, serum cholesterol</p> <p><i>Variables controlled by matching:</i> age, gender, municipality, time of baseline examination, duration of storage of sample</p> <p><u>Knekt 1991:</u></p> <p><i>Statistical methods:</i> Cox-proportional hazards model</p> <p><i>Variables controlled in analysis:</i> age, smoking (data stratified according to smoking status)</p> <p><u>Knekt 1996:</u></p> <p><i>Statistical methods:</i> conditional logistic regression</p> <p><i>Variables controlled by matching:</i> age, gender, municipality, time of baseline examination, duration of storage of sample</p>
Notes	<p><i>Primary publication:</i> Knekt 1990</p> <p><i>Other publications:</i> Hakama 1990, Knekt 1988, Knekt 1991, Knekt 1996</p>

Knekt 1998

Methods	<p>Matched, nested case-control study</p> <p><i>Country:</i> Finland</p>
Participants	<p><i>Participants:</i> 9101 men and women</p> <p><i>Inclusion criteria:</i> 19 years or older; no history of cancer at baseline; serum sample available for analysis</p> <p><i>Name of parent cohort:</i> Social Insurance Institution's Mobile Clinic Health Examination Survey</p> <p><i>Recruitment:</i> 1973 to 1976</p> <p><i>Outcome assessment:</i> end of 1991</p> <p><i>Number of cases:</i></p> <p>Lung cancer: 91 (male/female: approximately 95%/5%)</p> <p><i>Case definition:</i> incidence</p> <p><i>Years of follow-up:</i> 16.0 to 19.0 years</p> <p><i>Type of selenium marker:</i> serum</p>
Interventions	d.n.a.
Outcomes	<p><i>Analysed cases:</i> 91 of 95 (male/female: 90/5) cases analysed</p> <p><i>Statistical methods:</i> conditional logistic regression</p> <p><i>Variables controlled in analysis:</i> smoking, alpha-tocopherol, serum cholesterol, copper, orosomucoid, BMI</p> <p><i>Variables controlled by matching:</i> age, gender, municipality, season of sample collection, length of storage of sample</p>
Notes	

Kok 1987

Methods	Matched, nested case-control study <i>Country:</i> the Netherlands
Participants	<i>Participants:</i> 10,532 men and women <i>Inclusion criteria:</i> inhabitants of Zoetermeer; 5 years or older <i>Name of parent cohort:</i> EPOZ Cohort (Epidemiologisch onderzoek naar risico-indicatoren voor hart- en vaatziekten) <i>Recruitment:</i> 1975 to 1978 <i>Outcome assessment:</i> 31 December 1983 <i>Number of cases:</i> Any cancer: 69 (male/female: 40/29) <i>Case definition:</i> mortality <i>Years of follow-up:</i> 6.0 to 9.0 years <i>Type of selenium marker:</i> serum
Interventions	d.n.a.
Outcomes	<i>Analysed cases:</i> 69 of 114 cases analysed (reason for non-inclusion: serum or baseline data not available, deaths in first year of follow-up excluded) <i>Statistical methods:</i> not specified <i>Variables controlled in analysis:</i> age, smoking, serum cholesterol, serum vitamin A and E, systolic and diastolic blood pressure, BMI, week of blood collection, years of education, gender (in group of both genders) <i>Variables controlled by matching:</i> age, gender, smoking status
Notes	<i>Primary publication:</i> Kok 1987b <i>Other publication:</i> Kok 1987a

Kornitzer 2004

Methods	Matched, nested case-control study <i>Country:</i> Belgium
Participants	<i>Participants:</i> cohort size not reported; men and women <i>Inclusion criteria:</i> 25 to 74 years of age <i>Name of parent cohort:</i> Belgian Interuniversity Study on Nutrition and Health <i>Recruitment:</i> 1980 to 1984 <i>Outcome assessment:</i> n.r. <i>Number of cases:</i> Any cancer: 193 (male/female: 143/50) <i>Case definition:</i> mortality <i>Years of follow-up:</i> 10.0 years <i>Type of selenium marker:</i> serum
Interventions	d.n.a.
Outcomes	<i>Analysed cases:</i> 143 male/50 female cases analysed from 252 male/91 female cases (reason for non-inclusion: no selenium measurement available) <i>Statistical methods:</i> not specified <i>Variables controlled in analysis:</i> BMI, total energy, total fat, saturated fat, alcohol intake, fibre, retinol, vitamin C, smoking, beta-carotene

Kornitzer 2004 (Continued)

	Variables controlled by matching: age, gender
Notes	

Kromhout 1987

Methods	Cohort/sub-cohort-controlled cohort study Country: the Netherlands
Participants	Participants: 878 men Inclusion criteria: 40 to 59 years of age; random sample of general male population at specific age in Zutphen Name of parent cohort: Zutphen Study Recruitment: 1960 Outcome assessment: 1985 Number of cases: lung cancer: 63 (male/female: 63/0) Case definition: mortality Years of follow-up: 25.0 years Type of selenium marker: intake (interview)
Interventions	d.n.a.
Outcomes	Statistical methods: Cox proportional hazard model Variables controlled in analysis: age, pack years of smoking
Notes	

Li 2000

Methods	Randomised controlled trial Allocation: randomised, "based on their residence area" Sequence generation: unclear, not described Concealment: unclear, not described Blinding: of participants: adequate (placebo), of investigators and doctors: unclear, not described Dropouts/withdrawals: no significant difference between percentage of drop-outs in intervention and control group (absolute numbers not reported) Intention-to-treat-analysis: unclear Recruitment period: unclear, not described Observation period: 3 years, started in 1996 Study period: unclear, not described Detection of cases: unclear, the study followed the diagnostic menu published by the National Cancer Control and Prevention Center, follow-up procedures not described Informed consent: unclear, not described
Participants	Country: China Number of participants: 2065 (selenium group: 1112; placebo group: 953) Condition: HBsAg carriers with negative AFP and normal ALT living in Qidong, Jiangsu province Demographics: men only; aged 20 to 65 years (screening group)

Li 2000 (Continued)

	<i>Recruitment and setting:</i> recruitment of 2065 HBsAg carriers from 17 villages out of a screening group of 18,000 men
Interventions	<i>Intervention:</i> 0.5 mg sodium selenite p.o. daily for 3 years <i>Control:</i> placebo
Outcomes	<i>Primary outcome measure:</i> incidence of primary liver cancer <i>Other:</i> blood selenium levels, activity of glutathione peroxidase <i>Results:</i> person-year incidence rate (number of cases/total number of persons) in intervention and control group: 1st year of follow-up: selenium group 899.25/100,000 (10/1112); placebo group: 1,888.77/100,000 (18/953) 2nd year of follow-up: selenium group 1,708.60/100,000 (19/1112); placebo group: 4,302.20/100,000 (41/953) 3rd year of follow-up: selenium group 3,057.55/100,000 (34/1112); placebo group: 5,981.11/100,000 (57/953)
Notes	adverse effects were not mentioned

Li 2004a

Methods	Matched, nested case-control study <i>Country:</i> US
Participants	<i>Participants:</i> 14,916 men <i>Inclusion criteria:</i> participants of Physicians' Health Study who provided blood sample (healthy male physicians); no history of cancer at baseline; several physical conditions excluded at baseline: chronic renal failure, unstable angina pectoris, liver disease, peptic ulcer, history of TIA/stroke/myocardial infarction/gout; no use of vitamin A or beta-carotene supplements <i>Name of parent cohort:</i> Physicians' Health Study <i>Recruitment:</i> 1982 <i>Outcome assessment:</i> 1995 <i>Number of cases:</i> Prostate cancer: 586 (male/female: 586/0) <i>Case definition:</i> incidence <i>Years of follow-up:</i> 13.0 years <i>Type of selenium marker:</i> plasma
Interventions	d.n.a.
Outcomes	<i>Statistical methods:</i> logistic regression <i>Variables controlled in analysis:</i> age at baseline, smoking status, duration of follow-up <i>Variables controlled by matching:</i> age, smoking status
Notes	

McNaughton 2005

Methods	<p>Matched, nested case-control study (McNaughton 2005b)</p> <p>Cohort study (Heinen 2007, van der Pols 2009)</p> <p>Country: Australia</p>
Participants	<p><i>Name of parent cohort:</i> Nambour Skin Cancer Study</p> <p><i>Recruitment:</i> 1992 to 1996</p> <p><i>Case definition:</i> incidence</p> <p>McNaughton 2005b :</p> <p><i>Participants:</i> approximately 1000 men and women</p> <p><i>Inclusion criteria:</i> randomly selected adults, aged 20 to 69 years; recruited for participation in a randomised controlled trial for skin cancer prevention with beta-carotene supplements and sunscreen application in 1992; living in the Nambour community; free of SCC at baseline; with blood sample and FFQ provided in 1996; participants with extreme energy intakes in FFQ excluded</p> <p><i>Outcome assessment:</i> December 2001</p> <p><i>Number of cases:</i></p> <p>Basal cell carcinoma of the skin: 90 (male/female: 39/51)</p> <p><i>Years of follow-up:</i> 5.5 years</p> <p><i>Type of selenium marker:</i> serum and nutritional intake (FFQ)</p> <p>Heinen 2007:</p> <p><i>Participants:</i> 1001 men and women</p> <p><i>Inclusion criteria:</i> randomly selected adults, aged 20 to 69 years; recruited for participation in randomised controlled trial for skin cancer prevention with beta-carotene supplements and sunscreen application in 1992; living in the Nambour community; with blood sample and FFQ provided in 1996; participants with extreme energy intakes in FFQ and missing consumption frequencies for more than 10% of food items excluded</p> <p><i>Outcome assessment:</i> 31 December 2004</p> <p><i>Number of cases:</i></p> <p>Basal cell carcinoma of the skin: 149 (male/female: 87/62) participants with 321 BCC tumours</p> <p>Squamous cell carcinoma of the skin: 116 (male/female: 70/46) participants with 221 SCC tumours,</p> <p><i>Case definition:</i> incidence (tumour-based incidence and person-based incidence)</p> <p><i>Years of follow-up:</i> 8 years</p> <p><i>Type of selenium marker:</i> nutritional intake (FFQ)</p> <p>van der Pols 2009:</p> <p><i>Participants:</i> 485 (male/female: 223/262) men and women</p> <p><i>Inclusion criteria:</i> randomly selected adults, aged 20 to 69 years; recruited for participation in randomised controlled trial for skin cancer prevention with beta-carotene supplements and sunscreen application in 1992; randomised to placebo in the intervention trial; living in the Nambour community; free of SCC at baseline; with blood sample and FFQ provided in 1996; participants with extreme energy intakes in FFQ excluded</p> <p><i>Outcome assessment:</i> 31 December 2004</p> <p><i>Number of cases:</i></p> <p>Basal cell carcinoma of the skin: 77 (male/female: 46/31) participants with 173 BCC tumours</p> <p>Squamous cell carcinoma of the skin: 59 (male/female: 38/21) participants with 124 SCC tumours,</p> <p><i>Years of follow-up:</i> 8 years</p> <p><i>Type of selenium marker:</i> serum</p>
Interventions	d.n.a.
Outcomes	<p>McNaughton 2005b :</p> <p><i>Statistical methods:</i> conditional logistic regression</p> <p><i>Variables controlled in analysis:</i> age, gender</p> <p><i>Variables controlled by matching:</i> age, gender</p>

McNaughton 2005 (Continued)

	<p>Heinen 2007: <i>Statistical methods:</i> generalised linear models <i>Variables controlled in analysis:</i> age, sex, intervention arm in RCT, energy intake, skin colour, elastosis of the neck, smoking, use of dietary supplements, history of skin cancer</p> <p>van der Pols 2009: <i>Statistical methods:</i> generalised linear models <i>Variables controlled in analysis:</i> age, sex, pack-years of smoking, alcohol intake, time spent outdoors on weekdays, history of skin cancer before 1996</p>
Notes	<p><i>Primary publication:</i> McNaughton 2005b <i>Other publication:</i> Heinen 2007, van der Pols 2009 tumour-based incidence: number of newly developed histologically confirmed BCC or SCC divided by the person-years of follow-up accumulated over follow-up period person-based incidence: number of persons newly affected by BCC or SCC during the same person-years of follow-up time as calculated for the tumour-based analysis</p>

Menkes 1986

Methods	<p>Matched, nested case-control study <i>Country:</i> US</p>
Participants	<p><i>Participants:</i> 25,804 men and women <i>Inclusion criteria:</i> female and male inhabitants of Washington county/Maryland; history of cancer at baseline excluded <i>Name of parent cohort:</i> CLUE I Cohort <i>Recruitment:</i> September to November 1974 <u>Menkes 1986b:</u> <i>Outcome assessment:</i> 1983 <i>Number of cases:</i> Lung cancer: 99 (69% male/31% female) <u>Helzlsour 1996:</u> <i>Inclusion criteria:</i> women only; women who used hormones at baseline excluded <i>Outcome assessment:</i> 1989 <i>Number of cases:</i> Ovarian cancer: 35 (male/female: 0/35) <u>Breslow 1995:</u> <i>Outcome assessment:</i> 1994 <i>Number of cases:</i> Melanoma: 23 (male/female: n.r.) Basal cell carcinoma (skin): 17 (male/female: n.r.) Squamous cell cancer: 37 (male/female: n.r.) <u>Zheng 1993:</u> <i>Outcome assessment:</i> 1990 <i>Number of cases:</i> Oral and pharyngeal: 28 (male/female: n.r.) <u>Batieha 1993:</u> <i>Inclusion criteria:</i> 15,161 women <i>Outcome assessment:</i> 31 May 1990 <i>Number of cases:</i></p>

Menkes 1986 (Continued)

	<p>Cervical cancer: 50 (male/female: 0/50)</p> <p><u>Helzlsour 1989:</u></p> <p><i>Inclusion criteria:</i> 20,305 men and women</p> <p><i>Outcome assessment:</i> 1986</p> <p><i>Number of cases:</i></p> <p>Bladder cancer: 35 (male/female: n.r.)</p> <p><u>Burney 1989:</u></p> <p><i>Outcome assessment:</i> 1986</p> <p><i>Number of cases:</i></p> <p>Pancreatic cancer: 22 (male/female: 9/13)</p> <p><u>Ko 1994:</u></p> <p><i>Outcome assessment:</i> 25 September 1991</p> <p><i>Number of cases:</i></p> <p>Colon cancer: 121 (male/female: 50/71)</p> <p><i>Case definition:</i> incidence</p> <p><i>Years of follow-up:</i> 8.0 to 16.8 years</p> <p><i>Type of selenium marker:</i> serum</p>
Interventions	d.n.a.
Outcomes	<p><u>Menkes 1986b:</u></p> <p><i>Statistical methods:</i> conditional logistic regression</p> <p><i>Variables controlled by matching:</i> age, gender, race/ethnicity, smoking status, year and month of sample collection</p> <p><u>Helzlsour 1986:</u></p> <p><i>Statistical methods:</i> conditional logistic regression</p> <p><i>Variables controlled by matching:</i> Age, race/ethnicity, day time of blood sample collection, hours since last meal, time since last menstrual period (post-menopausal: years, pre-menopausal: days)</p> <p><u>Breslow 1995:</u></p> <p><i>Statistical methods:</i> conditional logistic regression</p> <p><i>Analysed cases:</i> 17 of 98 basal cell carcinoma cases, and 23 of 30 melanoma cases (and all squamous cell carcinoma cases) included in analysis</p> <p><i>Variables controlled by matching:</i> age, gender, race/ethnicity</p> <p><u>Zheng 1993:</u></p> <p><i>Statistical methods:</i> n.r.</p> <p><i>Variables controlled in analysis:</i> smoking</p> <p><i>Variables controlled by matching:</i> age, gender, race/ethnicity, year and month of sample collection, hours between previous meal and blood collection</p> <p><u>Batieha 1993:</u></p> <p><i>Statistical methods:</i> conditional logistic regression</p> <p><i>Analysed cases:</i> 50 of 60 cases (CIS and invasive cervical cancer) analysed (reason for non-inclusion: no matched control available)</p> <p><i>Variables controlled by matching:</i> age, race/ethnicity, year and month of blood collection, hours since last meal, time since last menstrual period</p> <p><u>Helzlsour 1989:</u></p> <p><i>Statistical methods:</i> n.r.</p> <p><i>Variables controlled in analysis:</i> cigarette smoking, use of vitamin supplements</p> <p><i>Variables controlled by matching:</i> age, gender, race/ethnicity, hours since last meal (all samples collected in same year)</p> <p><u>Burney 1989:</u></p> <p><i>Statistical methods:</i> n.r.</p>

Menkes 1986 (Continued)

	<p><i>Variables controlled by matching:</i> age, gender, race/ethnicity, hours since last meal</p> <p><u>Ko 1994:</u></p> <p><i>Analysed cases:</i> 121 of 154 cases analysed (reason for non-inclusion: no serum sample available, tumour pathology or localisation unclear)</p> <p><i>Statistical methods:</i> conditional logistic regression</p> <p><i>Variables controlled by matching:</i> age, gender, race/ethnicity, year and month of sample collection, hours since last meal, women: time since last menstrual period, women: use of hormones/hormonal contraceptives</p>
Notes	<p><i>Primary publication:</i> Menkes 1986b</p> <p><i>Other publications:</i> Helzlsour 1996, Breslow 1995, Zheng 1993, Batieha 1993, Helzlsour 1989, Burney 1989, Ko 1994, Schober 1987 (cases included in Ko 1994), Menkes 1986a (cases included in Menkes 1986b)</p>

Michaud 2002

Methods	<p>Matched, nested case-control study</p> <p><i>Country:</i> Finland</p>
Participants	<p><i>Participants:</i> 29,133 men</p> <p><i>Inclusion criteria:</i> 50 to 69 years of age; smokers; no history of cancer (other than non-melanoma skin cancer) at baseline; no severe physical or psychiatric illness; intake of vitamin E/A/beta-carotene supplements in excess of defined amounts</p> <p><i>Name of parent cohort:</i> Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study</p> <p><i>Recruitment:</i> 1985 to 1988</p> <p><i>Outcome assessment:</i> 30 April 1993</p> <p><i>Number of cases:</i></p> <p>Bladder cancer: 133 (male/female: 133/0)</p> <p><i>Case definition:</i> incidence</p> <p><i>Years of follow-up:</i> 5.0 to 8.0 years</p> <p><i>Type of selenium marker:</i> toenail</p>
Interventions	d.n.a.
Outcomes	<p><i>Statistical methods:</i> conditional logistic regression</p> <p><i>Variables controlled in analysis:</i> smoking dose and duration</p> <p><i>Variables controlled by matching:</i> age, year/month of sample collection, intervention group status in RCT (only male smokers included in cohort)</p>
Notes	

Michaud 2005

Methods	<p>Matched, nested case-control study</p> <p><i>Country:</i> US</p>
Participants	<p><i>Participants:</i> 101,950: 33,737 men, 68,213 women</p> <p><i>Inclusion criteria:</i> cohort of HPFS (men) and NHS (women); no history of cancer at baseline</p> <p><i>Name of parent cohort:</i> Health Professional Follow-Up Study (HPFS) and Nurses' Health Study (NHS)</p> <p><i>Recruitment:</i> 1987 (HPFS), 1983 (NHS)</p>

Michaud 2005 (Continued)

	<i>Outcome assessment:</i> 2000 <i>Number of cases:</i> Bladder cancer: 337 (male/female: 221/116) <i>Case definition:</i> incidence <i>Years of follow-up:</i> 13.0 to 17.0 years <i>Type of selenium marker:</i> toenail
Interventions	d.n.a.
Outcomes	<i>Statistical methods:</i> conditional logistic regression <i>Variables controlled in analysis:</i> pack-years of smoking, heavy smoking at baseline <i>Variables controlled by matching:</i> age, gender, smoking status, month of sample collection
Notes	

Nomura 1987

Methods	Unmatched, nested case-control study <i>Country:</i> US
Participants	<i>Participants:</i> 6860 men <i>Inclusion criteria:</i> born 1900 to 1919; Japanese ancestry; inhabitants of Oahu/Hawaii; participants in the Honolulu Heart Program (1965 to 68) <i>Name of parent cohort:</i> Honolulu Heart Program <i>Recruitment:</i> 1971 to 1975 <i>Outcome assessment:</i> n.r. <i>Number of cases:</i> Any cancer: 280 (male/female: 280/0) Stomach cancer: 66 (male/female: 66/0) Rectal cancer: 32 (male/female: 32/0) Lung cancer: 71 (male/female: 71/0) Colon cancer: 82 (male/female: 82/0) Bladder cancer: 29 (male/female: 29/0) <i>Case definition:</i> incidence <i>Years of follow-up:</i> 11.0 years <i>Type of selenium marker:</i> serum
Interventions	d.n.a.
Outcomes	<i>Statistical methods:</i> proportional hazards regression/Cox regression <i>Variables controlled in analysis:</i> age at examination, cigarettes/day (any cancer, lung cancer, bladder cancer) age at examination (stomach, rectum, colon)
Notes	N.B.: "Any cancer" in this study comprises all cancer cases for stomach, rectal, lung, colon and bladder cancer.

Nomura 2000

Methods	Matched, nested case-control study <i>Country:</i> US
Participants	<i>Participants:</i> 9345 men <i>Inclusion criteria:</i> no cancer diagnosis at baseline, blood sample available for analysis, men from two cohorts: sub-cohort one: participants of Nomura 1987; sub-cohort 2: brothers of participants in Nomura 1987 <i>Recruitment:</i> 1971 to 1977 <i>Outcome assessment:</i> 1995 <i>Number of cases:</i> Prostate cancer: 249 (male/female: 249/0) <i>Case definition:</i> incidence <i>Years of follow-up:</i> 19.0 to 25.0 years <i>Type of selenium marker:</i> serum
Interventions	d.n.a.
Outcomes	<i>Analysed cases:</i> random sample of 249 (out of 360) cases analysed because of limited resources <i>Statistical methods:</i> generalised linear model <i>Variables controlled in analysis:</i> cigarette smoking history, age <i>Variables controlled by matching:</i> age, year/month of sample collection, recruitment in sub-cohort 1 or 2
Notes	

NPCT 1996

Methods	<p>Randomised controlled trial</p> <p>Nutritional Prevention of Cancer Trial (NPCT)</p> <p><i>Allocation:</i> random, block/stratified by clinic</p> <p><i>Sequence generation:</i> computer generated random numbers</p> <p><i>Concealment:</i> central assignment (sealed pill bottles)</p> <p><i>Blinding:</i> participant blinded, doctor blinded, outcome assessor/pathologist unclear, review/coding of medical records blinded</p> <p><i>Dropouts/withdrawals:</i> "9 patients (5 in the selenium group and 4 in the placebo group) declined to provide additional illness information" (Clark 1996, p. 1959) - 0 participants lost to vital follow-up</p> <p><i>Intention-to-treat-analysis:</i> yes</p> <p><i>Recruitment period:</i> 1983 to 1991</p> <p>End of predefined study period: 31 December 1993</p> <p>Blinded intervention continued until the end of the blinded period: 31 January 1996</p> <p><i>Intervention duration:</i></p> <p>31 December 1993 (end of study period): mean = 4.5 years</p> <p>31 January 1996 (end of blinded period): mean = 7.9 years</p> <p><i>Observation period/dermatologic follow-up:</i></p> <p>31 December 1993 (end of study period): mean = 6.4 years</p> <p>31 January 1996 (end of blinded period): mean = 7.4 years</p> <p><i>Detection of cases:</i> dermatologic examination and interview every 6 months during follow-up; incident BCC and SCC were diagnosed by biopsy and confirmed by another dermatopathologist</p> <p><i>Informed consent:</i> written informed consent forms, approval by institutional review board of participating institutions</p>
Participants	<p><i>Country:</i> US</p> <p><i>Number of participants:</i> 1312 (randomised to selenium group: 653, to placebo group: 659)</p> <p><i>Condition:</i> male and female participants with history of 2 or more squamous cell or basal cell skin cancers</p> <p><i>Demographics:</i> mean age 63.4 years (selenium)/63.0 years (placebo); 73.8% men (selenium). 75.6% men (placebo)</p> <p><i>Recruitment and setting:</i> seven dermatological clinics (three academic units, four private practices) in the US</p>
Interventions	<p><i>Intervention:</i> 200 µg selenium supplied as 500 mg selenium yeast tablets p.o./daily.</p> <p><i>Control:</i> placebo</p>
Outcomes	<p><i>Primary outcome measure:</i> incidence of basal and squamous cell carcinoma of the skin: all analyses were based on 1250 participants with initial blood collection within four days after randomisation (621 in the selenium group and 629 in the placebo group)</p> <p><i>Other reported outcomes and secondary outcome measures:</i></p> <p>Reported in Clark 1996: Incidence of lung cancer, prostate cancer, colorectal cancer, any cancer, head and neck cancer, bladder cancer, oesophageal cancer, breast cancer, melanoma, haematologic cancer,</p> <p>Reported in Duffield-Lillico 2002: Overall cancer mortality</p>
Notes	<p>Adverse effects: Clark 1996: 35 participants (21 in selenium and 14 in control group) complained of adverse effects, mostly involving gastrointestinal upset, and withdrew treatment.</p> <p>Post-hoc introduced secondary outcomes were: all-cause mortality, total cancer mortality, total cancer incidence and incidence of lung / prostate / colorectal cancers</p> <p>HR: adjusted for sex, age, smoking status, clinic site, plasma selenium concentration, clinical sun damage, sunscreen use at baseline and number of BCCs/SCCs/NMSCs in the 12 months before randomisation</p>

Overvad 1991

Methods	Cohort/sub-cohort-controlled cohort study <i>Country:</i> Channel Islands
Participants	<i>Participants:</i> 5162 women <i>Inclusion criteria:</i> ≥ 35 years of age; ostensibly healthy inhabitants of Guernsey <i>Name of parent cohort:</i> Channel Island Cohort <i>Recruitment:</i> 1967 to 1976 <i>Outcome assessment:</i> end of 1985 <i>Number of cases:</i> Breast cancer: 46 (male/female: 0/46) <i>Case definition:</i> incidence <i>Years of follow-up:</i> mean: 11 years for cases <i>Type of selenium marker:</i> plasma
Interventions	d.n.a.
Outcomes	<i>Analysed cases:</i> 46 of 88 cases analysed (reason for non-inclusion: no plasma available) <i>Statistical methods:</i> logistic regression <i>Variables controlled in analysis:</i> age, age at menarche, age at first baby, parity, BMI
Notes	

Peleg 1985

Methods	Matched, nested case-control study <i>Country:</i> US
Participants	<i>Participants:</i> 2530 men and women <i>Inclusion criteria:</i> 15 years of age and older; residents of Evans county; cases within first two years of follow-up excluded <i>Name of parent cohort:</i> Evans County Study <i>Recruitment:</i> 1967 to 1969 <i>Outcome assessment:</i> January 1981 <i>Number of cases:</i> Any cancer: 130 (male/female: 78/52) <i>Case definition:</i> incidence <i>Years of follow-up:</i> 11.0 to 14.0 years <i>Type of selenium marker:</i> serum
Interventions	d.n.a.
Outcomes	<i>Statistical methods:</i> n.r. <i>Variables controlled by matching:</i> age, gender, race/ethnicity, year/month of sample collection
Notes	

Persson 2000

Methods	Matched, nested case-control study <i>Country:</i> Sweden
Participants	<i>Participants:</i> approximately 9500 men (exact figure not reported) <i>Inclusion criteria:</i> 46 to 48 years; residents of Malmo/Sweden <i>Name of parent cohort:</i> Malmö Preventive Programme <i>Recruitment:</i> 1974 to 1982 <i>Outcome assessment:</i> end of 1988 <i>Number of cases:</i> Any cancer: 302 (male/female: 302/0) Gastrointestinal cancer: 115 (male/female: 115/0) Respiratory tract cancer: 69 (male/female: 69/0) Other: 61 (male/female: 61/0) Urinary tract cancer: 57 (male/female: 57/0) <i>Case definition:</i> incidence <i>Years of follow-up:</i> 6.0 to 15.0 years <i>Type of selenium marker:</i> plasma selenium P
Interventions	d.n.a.
Outcomes	<i>Analysed cases:</i> 302 of 400 cases analysed (reason for non-inclusion: no sample available) <i>Statistical methods:</i> logistic regression, Mantel-Haenszel <i>Variables controlled in analysis:</i> smoking <i>Variables controlled by matching:</i> age, year/month/date of sample collection
Notes	Arbitrary unit: Concentration of selenoprotein P was expressed in arbitrary units (AU) relative to a standard of pooled plasma. 0.3 AU equal one standard deviation.

Peters 2007

Methods	Matched, nested case-control study <i>Country:</i> US
Participants	<i>Participants:</i> 26,975 white non-Hispanic men <i>Inclusion criteria:</i> 55 to 74 years of age; excluded: no baseline questionnaire/informed consent/blood sample, no further contact after screening <i>Name of parent cohort:</i> Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial <i>Recruitment:</i> September 1993 to June 2001 <i>Outcome assessment:</i> 1 October 2001 <i>Number of cases:</i> Prostate cancer: 724 (male/female: 724/0) <i>Case definition:</i> incidence <i>Years of follow-up:</i> 0.3 to 8.0 years <i>Type of selenium marker:</i> serum
Interventions	d.n.a.

Peters 2007 (Continued)

Outcomes	<p><i>Analysed cases:</i> 724 of 803 cases included in analysis (reason for non-inclusion: no selenium measurement available)</p> <p><i>Statistical methods:</i> n.r.</p> <p><i>Variables controlled in analysis:</i> age, time since initial screening, year of blood collection, study centre</p> <p><i>Variables controlled by matching:</i> age, month of sample collection, time since initial screening</p>
Notes	

Peters 2008

Methods	<p>Cohort study</p> <p>Country: US</p>
Participants	<p><i>Inclusion criteria:</i> aged 50 to 76 years, participants recruited from subscribers of commercial mailing list, residents of western Washington state, non-whites excluded, no malignant disease at baseline</p> <p><i>Name of parent cohort:</i> Vitamins and lifestyle (VITAL) study</p> <p><i>Recruitment:</i> 1 October 2000 to 31 December 2002</p> <p><i>Type of selenium marker:</i> supplemental intake (questionnaire: use of supplements over the last 10 years, mean supplemental intake / day calculated)</p> <p><i>Case definition:</i> incidence</p> <p><u>Peters 2008:</u></p> <p><i>Participants:</i> 35,242 men</p> <p><i>Outcome assessment:</i> 31 December 2004</p> <p><i>Number of cases:</i></p> <p>Prostate cancer: 818 (male/female: 818/0)</p> <p><i>Years of follow-up:</i> 2 to 4 years</p> <p><u>Asgari 2009:</u></p> <p><i>Participants:</i> 69,671 men and women</p> <p><i>Outcome assessment:</i> 31 December 2006</p> <p><i>Number of cases:</i></p> <p>Melanoma: 461 (male/female: n.r.)</p> <p><i>Years of follow-up:</i> 4 to 5 years</p>
Interventions	d.n.a.
Outcomes	<p><u>Peters 2008:</u></p> <p><i>Analysed cases:</i> 818 of 830 cases analysed (reason for non-inclusion: not reported)</p> <p><i>Statistical methods:</i> Cox proportional hazard regression analysis</p> <p><i>Variables controlled in analysis:</i> age, family history of prostate cancer, BPH, income, multivitamin use</p> <p><u>Asgari 2009:</u></p> <p><i>Analysed cases:</i> one case not analysed (reason for non-inclusion: not reported)</p> <p><i>Statistical methods:</i> Cox proportional hazard regression</p> <p><i>Variables controlled in analysis:</i> age, sex, education, family history of melanoma, personal history of non-melanoma skin cancer, mole removal, freckles, sunburns, hair colour, reaction to sunlight exposure</p>
Notes	

Ratnasinghe 2000

Methods	Matched, nested case-control study <i>Country:</i> China
Participants	<i>Participants:</i> 9143 men <i>Inclusion criteria:</i> 35 years or older; tin miners employed by the Yunnan Tin Corporation; 10 or more years of underground mining / smelting; no history of cancer at baseline <i>Recruitment:</i> 1992 to 1997 <i>Outcome assessment:</i> 1997 <i>Number of cases:</i> Lung cancer: 108 (male/female: 108/0) <i>Case definition:</i> incidence <i>Years of follow-up:</i> 3 years <i>Type of selenium marker:</i> serum
Interventions	d.n.a.
Outcomes	<i>Analysed cases:</i> plasma was available for 108 of a total of 339 identified cases <i>Statistical methods:</i> logistic regression, conditional logistic regression, Wilcoxon rank sum test <i>Variables controlled in analysis:</i> radon exposure, smoking <i>Variables controlled by matching:</i> age, year and month of sample collection
Notes	

Reid 2008

Methods	Randomised controlled trial Sub-study of the Nutritional Prevention of Cancer Trial (NPCT 1996) <i>Allocation:</i> random <i>Sequence generation:</i> computer generated random numbers <i>Concealment:</i> central assignment (sealed pill bottles) <i>Blinding:</i> participant blinded, doctor blinded, outcome assessor/pathologist unclear, review/coding of medical records blinded <i>Dropouts/withdrawals:</i> two participants declined to provide additional illness information, no participant lost to vital follow -up <i>Intention-to-treat-analysis:</i> yes <i>Recruitment period:</i> 1989-1992 <i>Treatment duration:</i> Blinded intervention continued until the end of the blinded period; 1 February 1996. <i>Observation period/dermatologic follow-up:</i> 1 February 1996 <i>Detection of cases:</i> dermatological examination and interview every 6 months during follow-up; incident BCC and SCC were diagnosed by biopsy and confirmed by another dermatopathologist <i>Informed consent:</i> written informed consent forms, approval by institutional review board of participating institutions
Participants	423 male and female participants with prior non-melanoma skin cancer <i>Country:</i> US <i>Number of patients:</i> 423 (randomised to selenium group: 210, to placebo group: 213) <i>Condition:</i> male and female patients with history of 2 or more squamous cell or basal cell skin cancers <i>Demographics:</i> mean age 63.8 years (selenium)/63.8 years (placebo); 66.2% men (selenium). 68.2% men (placebo)

Reid 2008 (Continued)

	<i>Recruitment and setting:</i> dermatologic clinic in Macon, Georgia
Interventions	<i>Intervention:</i> 400 µg selenium supplied as selenium yeast tablets p.o./daily. Control: placebo 400 µg/day of selenium yeast or identical-appearing low selenium yeast placebo <i>Recruitment:</i> 12 September 1989 to 3 April 1992 <i>End of the blinded treatment period:</i> 2 February 1996
Outcomes	<i>Primary outcome measure:</i> incidence of basal and squamous cell carcinoma of the skin: all analyses were based on n = 423 participants with initial blood collection within 4 days after randomizations <i>Other reported outcomes:</i> total internal cancer incidence
Notes	Information on study design, which was not reported in Reid 2008, was taken from the information available on the Nutritional Prevention of Cancer Trial. Adverse effects: not reported HR: adjusted for: age (continuous), smoking status (never, former, current), gender

Ringstad 1988

Methods	Matched, nested case-control study <i>Country:</i> Norway
Participants	<i>Participants:</i> 9364 men and women <i>Inclusion criteria:</i> 20 to 54 years of age (men), 20 to 49 years of age (women); inhabitants of Tromsø; blood sample provided in 1979; no history of cancer at baseline <i>Name of parent cohort:</i> Tromsø Heart Study II <i>Recruitment:</i> 1979 to 1980 <i>Outcome assessment:</i> 1985 <i>Number of cases:</i> Any cancer: 60 (male/female: 26/34) <i>Case definition:</i> incidence <i>Years of follow-up:</i> 5.0 to 7.0 years <i>Type of selenium marker:</i> serum
Interventions	d.n.a.
Outcomes	<i>Analysed cases:</i> 60 of 72 cases analysed (reason for non-inclusion: no sample available) <i>Statistical methods:</i> n.r. <i>Variables controlled by matching:</i> age, gender, smoking status, month of sample collection, place of residence (district of Tromsø)
Notes	

Sakoda 2005

Methods	Matched, nested case-control study <i>Country:</i> China
Participants	<i>Participants:</i> 41,563 men and women <i>Inclusion criteria:</i> inhabitants of Haiman city of Chinese origin; written consent; toenail clipping available <i>Recruitment:</i> January 1993 to December 1993 <i>Outcome assessment:</i> 30 September 2000 <i>Number of cases:</i> Primary liver cancer: 166 (male/female: 154/12) <i>Case definition:</i> mortality <i>Years of follow-up:</i> 6.8 to 7.8 years <i>Type of selenium marker:</i> toenail
Interventions	d.n.a.
Outcomes	<i>Analysed cases:</i> 166 of 455 observed cases included in analysis (only cases with questionnaire, blood sample and toenail specimen analysed after 2000 due to different methods of selenium analysis) <i>Statistical methods:</i> not specified <i>Variables controlled in analysis:</i> both genders: age, gender, HBsAg-status, alcohol intake, history of acute hepatitis, occupation men: age, HBsAg-status, alcohol intake, history of acute hepatitis, family history of HCC, occupation women: HBsAg-status, age, history of acute hepatitis <i>Variables controlled by matching:</i> age, gender, township of residence
Notes	

Salonen 1984

Methods	Matched, nested case-control study <i>Country:</i> Finland
Participants	<i>Participants:</i> 8113 men and women <i>Inclusion criteria:</i> 31 to 59 years of age; random sample of inhabitants of two Finnish provinces; initially free of cancer <i>Name of parent cohort:</i> North Karelia Project <i>Recruitment:</i> February to April 1972 <i>Outcome assessment:</i> 31 December 1978 <i>Number of cases:</i> Any cancer: 128 (male/female: n.r.) <i>Case definition:</i> incidence <i>Years of follow-up:</i> 8.5 years <i>Type of selenium marker:</i> serum
Interventions	d.n.a.
Outcomes	<i>Statistical methods:</i> logistic regression / paired-sample OR <i>Variables controlled in analysis:</i> tobacco consumption, serum cholesterol, beer consumption, dietary saturated fats, years of education, study area <i>Variables controlled by matching:</i> age, gender, smoking (tobacco use/day), total serum cholesterol

Salonen 1984 (Continued)

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Salonen 1985

Methods	Matched, nested case-control study <i>Country:</i> Finland
Participants	<i>Participants:</i> 12,155 men and women <i>Inclusion criteria:</i> 30 to 64 years of age; random sample of residents of two Finnish provinces; initially free of cancer <i>Name of parent cohort:</i> North Karelia Project <i>Recruitment:</i> January to March 1977 <i>Outcome assessment:</i> 31 December 1980 <i>Number of cases:</i> Any cancer: 51 (male/female: 30/21) <i>Case definition:</i> mortality <i>Years of follow-up:</i> 3.7 years <i>Type of selenium marker:</i> serum
Interventions	d.n.a.
Outcomes	<i>Analysed cases:</i> 51 out of 56 cases (reason for non-inclusion: no serum sample available) <i>Statistical methods:</i> logistic regression <i>Variables controlled by matching:</i> age, gender, smoking (tobacco use/day)
Notes	

SELECT 2009

Methods	<p>Randomised controlled trial</p> <p>SELECT (Selenium and Vitamin E Cancer Prevention Trial)</p> <p><i>Allocation:</i> random, block/stratified by clinic</p> <p><i>Sequence generation:</i> computer-generated random numbers</p> <p><i>Concealment:</i> central assignment (pill bottles)</p> <p><i>Blinding:</i> participant blinded, doctor blinded, outcome assessor/pathologist blinded, review/coding of medical records blinded</p> <p><i>Dropouts/withdrawals:</i> of 35,533 randomised participants, 645 were excluded from analysis because they had prior prostate cancer, did not give informed consent or participated at two study sites, which were excluded due to management and regulatory issues</p> <p><i>Intention-to-treat-analysis:</i> yes</p> <p><i>Recruitment period:</i> 22 August 2001 to 24 June 2004</p> <p><i>End of study period:</i> 1 August 2009</p> <p>Blinded intervention was discontinued on 23 October 2008 following the recommendation of the data safety and monitoring committee after the second formal interim analysis in September 2008</p> <p><i>Detection of cases:</i> Participants had clinic visits once every 6 months and reported prostate cancers to the study staff. Study staff obtained medical records to verify the diagnosis. Tissue and the corresponding pathology report were sent to the central pathology laboratory for confirmation.</p> <p><i>Informed consent:</i> yes</p>
Participants	<p><i>Countries:</i> US, Canada, Puerto Rico</p> <p><i>Number of participants:</i> 34,888 men, randomised to four groups: placebo (8696), vitamin E (8737), selenium (8752), selenium + vitamin E (8703)</p> <p><i>Condition:</i> healthy men, aged 50 years or older (African American) or 55 years or older (all other), no prior diagnosis of prostate cancer, 4 ng/ml or less of PSA in serum, a digital rectal examination not suspicious for cancer, no current use of anticoagulant therapy other than 175 mg/day or less of acetylsalicylic acid or 81 mg/day or less of acetylsalicylic acid with clopidogrel bisulphate, no history of haemorrhagic stroke, normal blood pressure.</p> <p><i>Demographics:</i> median age: 62.3-62.6 years in all four intervention groups, 79% white in all four intervention groups</p> <p><i>Recruitment and setting:</i> 427 participating sites</p>
Interventions	<p>Group 1: placebo + placebo</p> <p>Group 2: 400 IU/day all rac-alpha-tocopheryl acetate + placebo</p> <p>Group 3: 200 µg/day L-selenomethionine + placebo</p> <p>Group 4: 400 IU/day all rac-alpha-tocopheryl acetate + 200 µg/day L-selenomethionine</p>
Outcomes	<p><i>Primary outcome:</i> incidence of prostate cancer as determined by routine clinical management</p> <p><i>Secondary outcomes:</i> incidence of any cancer / lung cancer / colorectal cancer, diabetes mellitus, cardiovascular events, death from any cause</p>
Notes	<p>Adverse effects:</p> <p>alopecia RR 1.28, (99% CI 1.01 to 1.62)</p> <p>dermatitis grade 1-2 RR 1.17, (99% CI 1.00 to 1.35)</p> <p>dermatitis grade 3-4 RR 1.74, (99% CI 0.56 to 5.44)</p> <p>halitosis RR 1.17, (99% CI 0.99 to 1.38)</p> <p>nail changes RR 1.04, (99% CI 0.94 to 1.16)</p> <p>fatigue grade 1-2 RR 1.09, (99% CI 0.95 to 1.26)</p> <p>fatigue grade 3-4 RR 0.87, (99% CI 0.40 to 1.88)</p> <p>nausea grade 1-2 RR 1.19, (99% CI 0.94 to 1.52)</p> <p>nausea grade 3 RR 0.99, (99% CI 0.30 to 3.34)</p>

Thomson 2008

Methods	Cohort Study Country: US
Participants	<i>Participants:</i> 133,614 women <i>Inclusion criteria:</i> post-menopausal participants (aged 50 to 79 years) of the WHI clinical trial and observational study <i>Name of parent cohort:</i> Women's Health Initiative (WHI) <i>Recruitment:</i> n.r. <i>Outcome assessment:</i> December 2004 <i>Number of cases: ovarian cancer:</i> 451 (0/451) <i>Case definition:</i> incidence <i>Years of follow-up:</i> mean: 7 years <i>Type of selenium marker:</i> supplemental selenium intake (food frequency questionnaire)
Interventions	d.n.a.
Outcomes	<i>Statistical methods:</i> Cox logistic regression <i>Variables controlled in analysis:</i> participation in observational or intervention study, age, log calories, number of relatives with breast/ovarian cancer, dietary modification randomisation arm, hysterectomy, minority race, pack-years of smoking, physical activity, NSAID use, parity, infertility, duration of oral contraceptive use, number of lifetime ovulatory cycles, partial oophorectomy, age at menopause, hormone therapy at study entry
Notes	

van Noord 1987

Methods	Matched, nested case-control study Country: the Netherlands
Participants	<i>Participants:</i> 8760 women <i>Inclusion criteria:</i> 42 to 52 years of age; pre-menopausal; inhabitants of Utrecht <i>Name of parent cohort:</i> DOM (Diagnostic onderzoek mammacarcinoom) Study <i>Recruitment:</i> n.r. <i>Outcome assessment:</i> 1 February 1986 <i>Number of cases:</i> Breast cancer (pre-menopausal): 27 (male/female: 0/27) <i>Case definition:</i> incidence <i>Years of follow-up:</i> 0.6 to 3.5 years, mean: 2.1 years <i>Type of selenium marker:</i> toenail
Interventions	d.n.a.
Outcomes	<i>Analysed cases:</i> 7 cases were detected in the initial mammography screening in this study and not included in the analysis of incident cases <i>Statistical methods:</i> n.r. <i>Variables controlled by matching:</i> age, date of birth, pre-menopausal status
Notes	

vd Brandt 1993

Methods	Cohort/sub-cohort-controlled cohort study <i>Country:</i> the Netherlands
Participants	<p><i>Name of parent cohort:</i> Netherlands Cohort Study (NLCS) <i>Recruitment:</i> 1986 <u>van den Brandt 1993b:</u> <i>Participants:</i> 120,852: 58,279 men and 62,573 women; aged 55 to 69 years; returned baseline questionnaire; no history of cancer at baseline <i>Outcome assessment:</i> n.r. <i>Number of cases:</i> Stomach cancer: 104 (male/female: 84/20) Colon cancer: 234 (male/female: 121/113) Rectal cancer: 113 (male/female: 77/36) <u>van den Brandt 1993a:</u> <i>Participants:</i> 120,852: 58,279 men and 62,573 women; age 55 to 69 years; returned baseline questionnaire; no history of cancer at baseline <i>Outcome assessment:</i> n.r. <i>Number of cases:</i> Lung cancer: 370 (male/female: 335/35) <u>van den Brandt 1994:</u> <i>Participants:</i> 62,573 post-menopausal women <i>Outcome assessment:</i> 1989 <i>Number of cases:</i> Breast cancer (post-menopausal): 355 (male/female: 0/355) Breast cancer (post-menopausal), multivariate analysis: 270 (male/female: 0/270) <u>Zeegers 2002:</u> <i>Participants:</i> 120,852: 58,279 men and 62,573 women <i>Outcome assessment:</i> December 1992 <i>Number of cases:</i> Bladder cancer: 431 (male/female: 372/59) <u>van den Brandt 2003:</u> <i>Participants:</i> 58,279 men <i>Outcome assessment:</i> n.r. (probably December 1992) <i>Number of cases:</i> Prostate cancer: 540 (male/female: 540/0) <i>Case definition:</i> incidence <i>Years of follow-up:</i> 3.3 years (Brandt 1993a; Brandt 1993b; Brandt 1994), 6.3 years (Zeegers 2002; Brandt 2003) <i>Type of selenium marker:</i> toenail</p>
Interventions	d.n.a.
Outcomes	<p><u>van den Brandt 1993b:</u> <i>Analysed cases:</i> 234 of 351 colon cancer cases / 104 of 176 stomach cancer cases / 113 of 185 rectal cancer cases analysed (reasons for non-inclusion: history of cancer at baseline not available, no pathological confirmation or CIS, no toenail clipping available) <i>Statistical methods:</i> Mantel-Haenszel <i>Variables controlled in analysis:</i> age, gender <u>van den Brandt 1993a:</u></p>

vd Brandt 1993 (Continued)

	<p><i>Analysed cases:</i> 370 of 617 cases analysed (reasons for non-inclusion: history of cancer at baseline not available, no toenail clipping, no pathological confirmation, problems with selenium measurement)</p> <p><i>Statistical methods:</i></p> <p><i>Statistical methods:</i> Mantel-Haenszel</p> <p><i>Variables controlled in analysis:</i> age, gender</p> <p><u>van den Brandt 1994:</u></p> <p><i>Analysed cases:</i> 355 of 553 cases analysed (reasons for non-inclusion: history of cancer at baseline not available, CIS, no toenail sample or problems with selenium detection)</p> <p><i>Statistical methods:</i> multivariate case-cohort analysis</p> <p><i>Variables controlled in analysis:</i> age, history of benign breast disease, maternal breast cancer, breast cancer in sister(s), age at menarche, age at menopause, oral contraceptive use, parity, age at first birth, body mass index, education, current cigarette smoking, alcohol intake, energy intake</p> <p><u>Zeegers 2002:</u></p> <p><i>Analysed cases:</i> 431 of 619 cases analysed (reason for non-inclusion: no toenails available)</p> <p><i>Statistical methods:</i> exponentially distributed failure time regression models</p> <p><i>Variables controlled in analysis:</i> age, gender, number of cigarettes/day, years of cigarette smoking</p> <p><u>van den Brandt 2003:</u></p> <p><i>Analysed cases:</i> 540 of 704 cases analysed (reason for non-inclusion: no toenail samples or selenium detection not possible)</p> <p><i>Statistical methods:</i> exponentially distributed failure time regression models</p> <p><i>Variables controlled in analysis:</i> age, family history of prostate cancer, number of cigarettes/day, years of cigarette smoking, level of education</p>
Notes	<p><i>Primary publication:</i> van den Brandt 1993b</p> <p><i>Other publications:</i> Zeegers 2002, van den Brandt 1993a, van den Brandt 1994, van den Brandt 2003</p>

Virtamo 1987

Methods	<p>Cohort/sub-cohort-controlled cohort study</p> <p><i>Country:</i> Finland</p>
Participants	<p><i>Participants:</i> 1110 men</p> <p><i>Inclusion criteria:</i> 55 to 74 years of age; inhabitants of Finnish rural areas; participants of prior study on CHD; serum sample available: cases within first year of follow-up excluded</p> <p><i>Name of parent cohort:</i> Men in rural East and West Finland</p> <p><i>Recruitment:</i> 1974</p> <p><i>Outcome assessment:</i> 31 December 1983</p> <p><i>Number of cases:</i></p> <p>Any cancer: 109 (male/female: 109/0)</p> <p><i>Case definition:</i> incidence</p> <p><i>Years of follow-up:</i> 10.0 years</p> <p><i>Type of selenium marker:</i> serum</p>
Interventions	d.n.a.
Outcomes	<p><i>Statistical methods:</i> conditional logistic regression</p> <p><i>Variables controlled in analysis:</i> age, area of residence, smoking, serum cholesterol, alcohol intake</p>

Notes	
Wei 2004	
Methods	Frequency-matched cohort controlled study <i>Country:</i> China
Participants	<p><i>Participants:</i> Mark 2000: 29,584 men and women; Wei 2004: 1103 people who were originally selected as disease-free controls in Mark 2000</p> <p><i>Inclusion criteria:</i> 40 to 69 years of age; healthy inhabitants of 4 Linxian communities; participants of a randomised controlled trial</p> <p><i>Name of parent cohort:</i> General Population Trial Linxian</p> <p><i>Recruitment:</i> 1985</p> <p><i>Outcome assessment:</i> May 1991 (Mark 2000); n.r. (Wei 2004)</p> <p><i>Number of cases:</i></p> <p>Wei 2004:</p> <p>oesophageal cancer: 75 (male/female: 49/26) mortality</p> <p>stomach, cardia cancer: 36 (male/female: 22/14) mortality</p> <p>stomach, non-cardia cancer: 24 (male/female: 20/4) mortality</p> <p>other: 32 (male/female: 22/10) mortality</p> <p>Mark 2000:</p> <p>oesophageal cancer: 590 (male/female: 286/304) incidence</p> <p>oesophageal cancer: 332 (male/female: n.r.) mortality</p> <p>stomach, cardia cancer: 402 (male/female: 239/163) incidence</p> <p>stomach, cardia cancer: 232 (male/female: n.r.) mortality</p> <p>stomach, non-cardia cancer: 87 (male/female: 66/21) incidence</p> <p>stomach, non-cardia cancer: 68 (male/female: n.r.) mortality</p> <p><i>Case definition:</i> mortality, incidence</p> <p><i>Years of follow-up:</i> unclear/approximately 9 years (Wei 2004), 6 years (Mark 2000)</p> <p><i>Type of selenium marker:</i> serum</p>
Interventions	d.n.a.
Outcomes	<p><i>Statistical methods:</i> cox-proportional hazard model</p> <p><i>Variables controlled in analysis:</i> Wei 2004: age, cholesterol, smoking, alcohol intake, BMI; Mark 2000: age</p> <p><i>Variables controlled by matching:</i> age category, gender</p>
Notes	<p><i>Primary publication:</i> Wei 2004</p> <p><i>Other publication:</i> Mark 2000</p> <p>Remark:</p> <p>Wei 2004 measured serum selenium in a sub-cohort derived from 29,584 male and female participants of the Linxian Population Trial. The earlier publication of this study, Mark 2000 reported 332 fatal cases and 590 incident cases. The later publication, Wei 2004 reported deaths from oesophageal cancer in the disease-free controls of Mark 2000 and analysed 75 fatal cases.</p>

Willett 1983

Methods	Matched, nested case-control study <i>Country:</i> US
Participants	<i>Participants:</i> 10,940 men and women <i>Inclusion criteria:</i> 30 to 69 years of age; serum sample available (only 4480 samples of cohort were available because of freezer breakdown); participants of an RCT on hypertension; institutionalised and bedfast people were excluded <i>Name of parent cohort:</i> Hypertension Detection Follow-Up Programme (HDFP) <i>Recruitment:</i> 1973 to 1974 <i>Outcome assessment:</i> n.r. <i>Number of cases:</i> Any cancer: 111 (male/female: 60/51) <i>Case definition:</i> incidence <i>Years of follow-up:</i> 5.0 years <i>Type of selenium marker:</i> serum
Interventions	d.n.a.
Outcomes	<i>Statistical methods:</i> logistic regression of unmatched data <i>Variables controlled by matching:</i> age, gender, race/ethnicity, smoking status, year/month of sample collection, initial blood pressure, use of antihypertensive medication, randomisation group in women: parity, menopausal status
Notes	

Yoshizawa 1998

Methods	Matched, nested case-control study <i>Country:</i> US
Participants	<i>Participants:</i> 33,737 men <i>Inclusion criteria:</i> 40 to 75 years of age; physicians from all 50 U.S. states; provision of toenails in 1987 and completed baseline questionnaire in 1986; exclusion of histologically confirmed prostate cancer at baseline and cases within first 2 years of follow-up <i>Name of parent cohort:</i> Health Professionals Follow-Up Study (HPFS) <i>Recruitment:</i> 1986 to 1987 <i>Outcome assessment:</i> 1994 <i>Number of cases:</i> Prostate cancer: 181 (male/female: 181/0) <i>Case definition:</i> incidence <i>Years of follow-up:</i> 8.0 to 9.0 years <i>Type of selenium marker:</i> toenail
Interventions	d.n.a.
Outcomes	<i>Statistical methods:</i> logistic regression, conditional logistic regression <i>Variables controlled in analysis:</i> quintiles of lycopene, saturated fat, calcium, family history of prostate cancer, BMI, vasectomy <i>Variables controlled by matching:</i> age, smoking status, year/month of sample collection

Notes	
Yu 1991	
Methods	<p>Randomised controlled trial</p> <p><i>Allocation:</i> random</p> <p><i>Sequence generation:</i> unclear, not described</p> <p><i>Concealment:</i> unclear, not described</p> <p><i>Blinding:</i> described as double-blind; <i>blinding of participants:</i> adequate, placebo tablets; <i>blinding of investigators and doctors:</i> unclear</p> <p><i>Dropouts/withdrawals:</i> unclear, not described</p> <p><i>Intention-to-treat-analysis:</i> unclear, not described</p> <p><i>Recruitment period:</i> unclear, not described</p> <p><i>Observation period:</i> 2 years</p> <p><i>Study period:</i> 2 years</p> <p><i>Detection of cases:</i> unclear, use of “national standards” for the diagnosis of liver cancer</p> <p><i>Informed consent:</i> unclear, not described</p>
Participants	<p><i>Country:</i> China</p> <p><i>Number of participants:</i> 2,474</p> <p><i>Condition:</i> first-degree relatives within three generations of families with 2 or more cases of liver cancer during the period 1972 to 1985</p> <p><i>Demographics:</i> gender distribution not reported; age: 15 to 75 years</p> <p><i>Recruitment and setting:</i> participants were residents in Qidong province</p>
Interventions	<p><i>Intervention:</i> 200 µg selenium as selenised yeast p.o. daily, intervention period unclear</p> <p><i>Control:</i> placebo</p>
Outcomes	<p><i>Primary outcome measure:</i> incidence of primary liver cancer within 2 years after start of intervention</p> <p><i>Results:</i></p> <p>13 cases in 1030 placebo subjects</p> <p>10 cases in 1444 selenium subjects</p>
Notes	<p>Data were extracted from Yu 1991.</p> <p>We identified two later publications (Li 2002, Yu 1993), which we assumed to report on the same trial as Yu 1991. However, total number of participants differed from the initial report (N = 3849 in the later publications with 1485 receiving placebo and 2364 receiving selenium). The total number of cases was not reported in either Li 1992 or Yu 1993.</p> <p>The reported results were:</p> <p><i>Li 1992:</i></p> <p>person-year incidence rate in intervention and control group:</p> <p>within one year of follow-up: selenium group 175.36/100,000; placebo group: 414.65/100,000</p> <p>within two years of follow-up: selenium group 219.37/100,000; placebo group: 553.15/100,000</p> <p><i>Yu 1993:</i></p> <p>cumulated incidence:</p> <p>after one year: selenium group 1.75/1000; placebo group: 4.15/1000</p> <p>after two years: selenium group 2.19/1000; placebo group: 5.53/1000</p> <p>We could not make contact with the study investigators to clarify these discrepancies. As we could not clarify the</p>

Yu 1991 (Continued)

	actual number of liver cancer cases in the later publications, we decided to use the data of Yu 1991 for this review. Adverse effects were not mentioned in Yu 1991 or Li 1992. Yu 1993 stated that no cases of selenosis were observed in the trial.
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Yu 1997

Methods	Randomised controlled trial <i>Allocation:</i> random <i>Sequence generation:</i> unclear, not described <i>Concealment:</i> unclear, not described <i>Blinding: of participants:</i> adequate (placebo), <i>of investigators and doctors:</i> unclear, not described <i>Dropouts/withdrawals:</i> unclear, not described <i>Recruitment period:</i> unclear, not described <i>Intention-to-treat-analysis:</i> unclear, not described <i>Observation period:</i> 1987 to 1994 <i>Intervention period:</i> 1987 to 1990 <i>Detection of cases:</i> unclear, monthly blood sample during follow-up for liver enzymes (SGPT, ZnTT), use of “national standards” for the diagnosis of liver cancer <i>Informed consent:</i> unclear, not described
Participants	<i>Country:</i> China <i>Number of participants:</i> 226 (selenium group: 113; placebo group 113) <i>Condition:</i> HBs-antigen carriers with normal liver function <i>Demographics:</i> 95 men, 131 women; age: 21 to 63 years <i>Recruitment and setting:</i> recruitment “through screening in a village in the city Qidong” (Li 1992)
Interventions	<i>Intervention:</i> 200 µg selenium as selenised yeast p.o. daily for 4 years <i>Control:</i> placebo
Outcomes	<i>Primary outcome measure:</i> incidence of primary liver cancer (defined as increase of SGPT and ZnTT) <i>Results: at the end of the intervention period:</i> 0 cases in the selenium group; 7 cases in the placebo group in a total of 445 person years of observation (person-time incidence rate: 1,573.03/100,000)
Notes	<i>Adverse effects:</i> “No side effects have been found in these trials.” (Yu 1997, p124) <i>further data reported in:</i> Li 1992 (Chinese, translated); Yu 1991 In Yu 1991 a different incidence in the selenium group was reported (5 cases). We could not clarify this discrepancy to the later papers Li 1992 and Yu 1997.

Yu 1999

Methods	Matched, nested case-control study <i>Country:</i> China (Taiwan)
Participants	<i>Participants:</i> 4841 men <i>Inclusion criteria:</i> 30 to 65 years of age; HBsAg-positive or/and HCV-positive; recruited at two centres: Government Employee Central Clinics or Liver Unit of Chang-Gung Memorial Hospital <i>Recruitment:</i> August 1988 to June 1992 <i>Outcome assessment:</i> 31 December 1996

Yu 1999 (Continued)

	<i>Number of cases:</i> Primary liver cancer: 69 (male/female: 69/0) <i>Case definition:</i> incidence <i>Years of follow-up:</i> 4.5 to 8.3 years <i>Type of selenium marker:</i> plasma
Interventions	d.n.a.
Outcomes	<i>Analysed cases:</i> 69 of 73 cases analysed (reason for non-inclusion: no sample available) <i>Statistical methods:</i> conditional logistic regression <i>Variables controlled in analysis:</i> age, cigarette smoking, alcohol intake, plasma levels of retinol/alpha-tocopherol/alpha-carotene/beta-carotene/lycopene <i>Variables controlled by matching:</i> age, year and season of sample collection, recruitment clinic
Notes	

(lower border; upper border) lower and upper border of the 95% CI (if not otherwise specified)

μ	micro
AFP	alpha-fetoprotein
ALT	alanine aminotransferase
ATBC	Alpha-tocopherol, beta-carotene cancer prevention study
AU	arbitrary unit
BCC	basal cell carcinoma
BMI	body-mass-index
BPH	benign prostate hyperplasia
CARET	Carotene and Retinol Efficacy Trial
CHD	coronary heart disease
CI	confidence interval
CIS	carcinoma in situ
CVD	cardiovascular disease
dl	deciliter
d.n.a.	does not apply
DOM	Diagnostisch onderzoek mammacarcinoom
EVA	Etude du Vieillissement Antérieur
EPOZ	Epidemiologisch onderzoek naar risico-indicatoren voor hart- en vaatziekten
FFQ	food-frequency questionnaire
g	gram
HBsAg	Hepatitis B surface antigen
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HPFP	Hypertension Detection Follow-up Programme
HPFS	Health Professionals Follow-up Study
HR	hazard ratio
IU	international unit
l	litre
m	milli
max. adj.	maximally adjusted
MHC	Mobile Health Clinic

n nano
 NHS Nurses' Health Study
 NLCS Netherlands Cohort Study
 NMSC non-melanoma skin cancer
 NPCT Nutritional Prevention of Cancer Trial
 n.r. not reported
 NSAID non-steroidal antiinflammatory drugs
 OR Odds ratio
 p. page
 p.o. per os
 ppm parts per million
 PSA prostate-specific antigen
 RCT randomised controlled trial
 RR relative risk
 SCC squamous cell carcinoma
 SGPT alanine aminotransferase
 TIA transient ischemic attack
 UK United Kingdom
 US United States of America
 VITAL Vitamins and Lifestyle Study
 ZnTT zinc turbidity test

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

Study	Reason for exclusion
Bostick 1993	Cohort study: Iowa Women's Health Study Cohort. Selenium exposure not assessed according to eligibility: only intake of selenium supplements yes/no in questionnaire assessed
Brock 1991	Case-control study with pre-cancerous condition (carcinoma in situ of the cervix)
Chen 1988	Case-control study
Chen 2003	Case-control study
Connelly-Frost 2009	Case-control study
Costello 2001	APPOSE (Australian Prostate Cancer Prevention Trial Using Selenium): publication describes study design, trial was not started
Criqui 1991	Population-based prospective case-control study: Lipid Research Clinic Prevalence and Follow-Up Study Results not reported according to inclusion criteria: differences in mean selenium levels were reported
Cui 2007	Nested case-control study Selenium exposure not assessed according to eligibility: selenium measurement was conducted in tissue of benign breast diseases

(Continued)

Davies 2002	Nested case-control study: EPIC Norfolk Study Cohort Results not reported according to inclusion criteria: RR estimate per unit increase in selenium level reported
Fleshner 2003	Randomised Study of Vitamin E, Selenium, and Soy Protein Isolate in Patients with High-Grade Prostatic Intraepithelial Neoplasia: Multicomponent intervention
Hagmar 1992	Historical cohort study
Hartman 2002	Nested case-control study: ATBC Cohort Results not reported according to inclusion criteria: differences in mean selenium levels reported; OR reported as graph and could not be calculated from reported data
Huzarski 2006	Interventional study without control group with 1489 female participants with BRCA1 mutation who received a selenium-containing nutritional supplement
Joniau 2007	Intervention study without control group with male participants with high-grade intraepithelial neoplasia of the prostate who received a selenium-containing nutritional supplement
Kellen 2008	Case-control study
Kilander 2001	Cohort study in Uppsala/Sweden Results not reported according to inclusion criteria: RR estimate per unit increase in selenium level reported
Knekt 1988a	Nested case-control study: Mobile Health Clinic Cohort Results not reported according to inclusion criteria: differences in mean selenium levels reported
Knekt 1988c	Nested case-control study: Mobile Health Clinic Cohort Results not reported according to inclusion criteria: differences in mean selenium levels reported
Knekt 1991b	Nested case-control study: Mobile Health Clinic Cohort Results not reported according to inclusion criteria: differences in mean selenium levels reported
Kok 1987c	Nested case-control study: Zoetermeer Cohort Results not reported according to inclusion criteria: differences in mean selenium levels reported
Kune 2006	Case-control study
Kuroda 1988	Case-control study
Lawson 2007	Cohort study on multivitamin use and risk of prostate cancer
Le Marchand 2006	Case-control study
Li 2004b	RCT for gastric cancer prevention with multi component intervention (200 mg synthetic allitridum and 100 µg selenium per day)

(Continued)

Limburg 2005	Randomised controlled trial: primary endpoint in this 2 by 2 factorial design trial with selenomethionine 200 µg daily and/or celecoxib 200 mg twice daily was the per-subject change (regression, stable, progression) of pre-existing oesophageal dysplasia - cancer incidence or mortality were not endpoints in this study
Linxian Pilot 2000	Randomised controlled trial with selenium supplements and celecoxib in participants with oesophageal squamous dysplasia in Linxian, China Endpoint was "regression of disease", cancer was not an endpoint in this investigation
Neuhouser 2009	Cohort study (Women's Health Initiative) on multivitamin use and risk of cancer and cardiovascular disease. No data for selenium and cancer risk reported.
Ray 2006	Cohort study (Women's Health and Aging Studies I and II) on selenium and carotenoid serum levels and mortality. No data for selenium and cancer mortality reported
Rayman 2001	PRECISE trial (Prevention of Cancer by Intervention with Selenium): trial has been stopped
Rendon	Randomised controlled trial: Vitamin E, Selenium, and Soy Protein in Preventing Cancer in Patients with High-Grade Prostate Neoplasia. Multicomponent intervention
Thompson 2009	Cohort study: Iowa Women's Health Study Cohort. Selenium exposure not assessed according to eligibility: only intake of selenium supplements yes/no in questionnaire assessed
Tsugane 1996	Case-control and cross-sectional studies
Ujiie 2002	A part of this study is a prospective cohort study in Miyagi/Japan Results not reported according to inclusion criteria: differences in mean selenium levels reported
van Noord 1992	Nested case-control study: DOM Cohort Results not reported according to inclusion criteria: differences in mean selenium levels reported
van Noord 1993	Nested case-control study: DOM II Cohort Results not reported according to inclusion criteria: RR estimate per unit increase of selenium level reported
van't Veer 1996	Case-control study
Wallace 2009	Case-control study
Watters 2009	Cohort study on smoking and prostate cancer risk. Selenium not reported as independent variable.
Wright 2004	Cohort study: ATBC Cohort Exposure to antioxidants was assessed using a self-developed index
You 2005	Randomised controlled trial to test retardation of the progression of pre-cancerous gastric lesions among 3400 adults in Shandong, China. Intervention: vitamin C, vitamin E, selenium, garlic preparation. Multicomponent intervention.

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Yuan 2006	Nested case-control study: Shanghai Cohort Study No data on selenium and cancer risk reported
Zeegers 2009	Cohort study on factors influencing recurrence or progression of bladder cancer: West Midlands Bladder Cancer Prognosis Programme

μ	micro
APPOSE	Australian Prostate Cancer Prevention Trial Using Selenium
ATBC	Alpha-tocopherol, beta-carotene cancer prevention study
BRCA	breast cancer
DOM	Diagnostic onderzoek mammacarcinoom
EPIC	European Prospective Investigation of Cancer
m	milli
g	gram
OR	Odds ratio
PRECISE	Prevention of Cancer by Intervention with Selenium
RCT	randomised controlled trial

Characteristics of studies awaiting assessment [ordered by study ID]

Characteristics of ongoing studies [ordered by study ID]

Epi' Nomura 2002

Trial name or title	Cancer Sero Epidemiology Among the Japanese in Hawaii
Methods	This is a sero-epidemiologic prospective study to identify biochemical markers related to common cancers. Among the aims are: (a) to see if low serum selenium levels increase prostate cancer risk (b) to determine whether low serum selenium levels increase urinary bladder cancer risk in men
Participants	9,345 male American Japanese subjects, examined in Hawaii
Interventions	d.n.a.
Outcomes	risk of prostate and urinary bladder cancer
Starting date	Project Start: 15 September 1983, Project End planned for: 30 June 2004
Contact information	Abraham M. Nomura Kuakini Medical Center 347 N Kuakini St Honolulu, HI 96817

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RCT Cheng 2003

Trial name or title	Selenium supplementation for the prevention of hepatocellular carcinomas in HBsAg positive patients (pilot study)
Methods	Randomised controlled trial
Participants	Men aged 45 to 64 years with positive HBsAg test, negative AFP test and normal ALT values
Interventions	Placebo or 200 mg (sic!)/day selenium as selenised yeast
Outcomes	Primary liver cancer
Starting date	2003
Contact information	Prof Kar Keung Cheng, University of Birmingham, UK
Notes	Author contacted for further information, but no reply received. Should probably say 200 µg/day selenium yeast as intervention in the publication.

RCT Cheng 2006

Trial name or title	
Methods	Double-blinded, placebo-controlled, 2 by 2 factorial, randomised controlled trial (SELENIB), nested within a prospective observational cohort study (Bladder Cancer Prognosis Programme BCPP)
Participants	1200 participants of the Bladder Cancer Prognosis Programme in the United Kingdom Inclusion criteria: Histopathologically confirmed non-muscle invasive transitional cell carcinoma. Solitary grade 1 pTa larger than 3 cm and all other stage pTa, pT1 or pTcis Exclusion criteria: 1. Disease characteristics - solitary grade 1 pTa < 3 cm or stage pT2 and above 2. Patients that are pregnant or breastfeeding 3. Patients diagnosed with human immunodeficiency virus (HIV) infection 4. Patients who are on immunosuppressive therapy following organ transplantation 5. Patients taking cyclosporin 6. Any condition, which, in the opinion of the local investigator, might interfere with the safety of the patient or evaluation of the trial objectives
Interventions	Four study arms: 1) selenium 2) alpha-tocopherol 3) selenium and alpha-tocopherol 4) placebo

RCT Cheng 2006 (Continued)

Outcomes	Primary outcomes: recurrence-free survival, progression-free survival SELENIB trial - secondary outcomes 1. All cause mortality 2. Incidence of transitional cell carcinoma (TCC) outside the bladder 3. Incidence of all other malignancies clinically diagnosed 4. Incidence of cardiovascular events: myocardial infarction, stroke, death from cardiovascular causes, 5. Quality of life - as assessed by the quality of life instruments: European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30, QLQ-BLS24 and QLQ-BLM30
Starting date	
Contact information	
Notes	Ongoing trial Contact details: Prof K. K. Cheng The Public Health Building University of Birmingham Edgbaston Birmingham United Kingdom B15 2TT http://www.bcpp.bham.ac.uk

RCT ECOG 2002

Trial name or title	Phase III Randomised Chemoprevention Study of Selenium in Participants With Previously Resected Stage I Non-Small Cell Lung Cancer
Methods	Randomised controlled trial
Participants	Disease Characteristics: Histologically confirmed, completely resected stage IA (pT1, N0) or IB (pT2, N0) non-small lung cancer (except carcinoid) Completion of treatment for stage I lung cancer within the past 6 to 36 months and currently disease free At least one mediastinal lymph node sampled at resection Age: 18 years and over Performance status: ECOG 0-1 A total of 1,960 participants (980 per arm) will be accrued for this study within 4 years.
Interventions	Arm I: Participants receive oral selenium yeast daily for 6 months. Treatment repeats every 6 months for 8 courses for a total of 4 years in the absence of unacceptable toxicity Arm II: Participants receive an oral yeast placebo as in arm I Participants are followed annually
Outcomes	Second incidence/recurrence of primary lung tumours Toxicity Incidence of specific cancers, mortality from cancer, and overall survival

RCT·ECOG 2002 (Continued)

Starting date	October 2000
Contact information	Eastern Cooperative Oncology Group Daniel Karp, MD, Protocol chair Phone: 713-745-7398; 800-392-1611 Southwest Oncology Group Omer Kucuk, MD, Protocol chair Phone: 313-576-8739; 800-527-6266 Email: kucuko@karmanos.org
Notes	Recruiting

RCT·HGPIN·Marshall 2006

Trial name or title	L-selenium-based chemoprevention of prostate cancer among men with high-grade prostatic intraepithelial neoplasia (HGPIN)
Methods	Randomised controlled trial
Participants	Country: US 465 men, age 40 years and over with diagnosis of HGPIN with no evidence of cancer
Interventions	Placebo or 200 µg/day selenium
Outcomes	Incidence of prostate cancer
Starting date	February 2000
Contact information	James R. Marshall, Roswell Park Cancer Institute, Buffalo, New York, US
Notes	No longer recruiting

RCT·NBT·Stratton 2003

Trial name or title	Negative Biopsy Trial (NBT)
Methods	The study is a Phase III cancer chemoprevention study among men at high risk of prostate cancer because of a persistent elevation in PSA above 4 ng/ml and a negative initial biopsy.
Participants	The trial will randomise at least 700 patients with persistently elevated PSA levels (greater 4 ng/ml) and at least one negative biopsy for prostate cancer. The principal purpose of this trial is to assess the potential for treatment with the essential trace element selenium (Se) to prevent prostate cancer (PCa).
Interventions	The trial will randomise patients to either placebo or one of two selenium dosages, 200 µg/day or 400 µg/day.
Outcomes	The primary endpoints for the trial are the incidence of PCa and the velocity of the primary serum marker of prostate cancer progression, prostate specific antigen (PSA). Safety endpoints for the trial include onset of

RCT·NBT·Stratton 2003 (Continued)

	mild symptoms of selenium toxicity as well as significant changes in liver and kidney enzyme levels.
Starting date	30 September 1999
Contact information	M. Suzanne Stratton, Ph.D. Research Assistant Professor Arizona Cancer Center Prostate Cancer Prevention Program 2504 E Elm Street. Tucson, AZ 85716 http://www.selenium.arizona.edu
Notes	

μ	micro
AARP	American Association of Retired Persons
AFP	alpha-fetoprotein
ALT	alanine aminotransferase
BCC	basal cell carcinoma
BCPP	Bladder Cancer Prognosis Programme
BRCA	breast cancer
cm	centimeter
d.n.a.	does not apply
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organisation for Research and Treatment of Cancer
EPIC	European Prospective Investigation of Cancer
g	gram
HBsAg	Hepatitis B surface antigen
HGPIN	high-grade prostatic intraepithelial neoplasia
HIV	human immunodeficiency virus
iU	international unit
l	liter
m	milli
n	nano
n.r.	not reported
NHANES	National Health and Nutrition Examination Survey
NIH	National Institute of Health
p.	page
PSA	prostate specific antigen
pT	tumour after pathological assessment, according to the tumour/nodules/metastases TNM-staging system
QLQ	Quality of Life Questionnaire
RCT	randomised controlled trial
SCC	squamous cell carcinoma
SELECT	Selenium and Vitamin E Cancer Prevention Trial
SELENIB	(randomised controlled trial of selenium and vitamin E in the recurrence and progression of non muscle invasive bladder cancer)
TCC	transitional cell carcinoma

UK	United Kingdom
US	United States of America
WHAS	Women's Health and Aging Study
WHI	Women's Health Initiative
WHO	World Health Organization

DATA AND ANALYSES

Comparison 1. Highest versus lowest selenium exposure

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Breast cancer risk (women)	7		Odds Ratio (Random, 95% CI)	1.00 [0.77, 1.29]
1.1 Breast cancer (all)	6		Odds Ratio (Random, 95% CI)	1.01 [0.74, 1.36]
1.2 Breast cancer (premenopausal)	1		Odds Ratio (Random, 95% CI)	1.10 [0.46, 2.65]
2 Bladder cancer risk	5		Odds Ratio (Random, 95% CI)	0.67 [0.46, 0.97]
2.1 all (male + female)	2		Odds Ratio (Random, 95% CI)	0.65 [0.46, 0.92]
2.2 male	3		Odds Ratio (Random, 95% CI)	0.82 [0.41, 1.62]
2.3 female	1		Odds Ratio (Random, 95% CI)	0.36 [0.14, 0.92]
3 Lung cancer risk (gender-aggregated data)	11		Odds Ratio (Random, 95% CI)	0.76 [0.57, 1.03]
3.1 incidence	10		Odds Ratio (Random, 95% CI)	0.75 [0.54, 1.03]
3.2 mortality	1		Odds Ratio (Random, 95% CI)	0.98 [0.41, 2.35]
4 Lung cancer risk (gender-disaggregated data)	11		Odds Ratio (Random, 95% CI)	0.77 [0.60, 0.98]
4.1 all (female + male)	4		Odds Ratio (Random, 95% CI)	0.58 [0.39, 0.86]
4.2 female	4		Odds Ratio (Random, 95% CI)	0.83 [0.43, 1.61]
4.3 male	6		Odds Ratio (Random, 95% CI)	0.88 [0.61, 1.28]
5 Lung cancer risk (ascending order of selenium levels)	7	1756	Odds Ratio (Random, 95% CI)	0.90 [0.69, 1.16]
6 Lung cancer risk	11		Odds Ratio (Random, 95% CI)	0.76 [0.57, 1.03]
6.1 intake	1		Odds Ratio (Random, 95% CI)	0.98 [0.41, 2.35]
6.2 serum or plasma	8		Odds Ratio (Random, 95% CI)	0.84 [0.66, 1.06]
6.3 toenail	2		Odds Ratio (Random, 95% CI)	1.05 [0.11, 10.36]
7 Prostate cancer risk	14		Odds Ratio (Random, 95% CI)	0.78 [0.66, 0.92]
8 Prostate cancer risk (by selenium measurement)	14		Odds Ratio (Random, 95% CI)	0.78 [0.66, 0.92]
8.1 biochemical selenium level	12		Odds Ratio (Random, 95% CI)	0.74 [0.61, 0.88]
8.2 estimated selenium intake	2		Odds Ratio (Random, 95% CI)	1.00 [0.73, 1.36]
9 Prostate cancer risk (by exposure assessment)	14		Odds Ratio (Random, 95% CI)	0.78 [0.66, 0.92]
9.1 intake	2		Odds Ratio (Random, 95% CI)	1.00 [0.73, 1.36]
9.2 serum or plasma	9		Odds Ratio (Random, 95% CI)	0.81 [0.68, 0.97]
9.3 toenail	3		Odds Ratio (Random, 95% CI)	0.53 [0.35, 0.81]
10 Prostate cancer risk (by continent)	14		Odds Ratio (Random, 95% CI)	0.78 [0.66, 0.92]
10.1 Europe	4		Odds Ratio (Random, 95% CI)	0.91 [0.70, 1.17]
10.2 North America	10		Odds Ratio (Random, 95% CI)	0.71 [0.58, 0.88]
11 Prostate cancer risk (by country)	14		Odds Ratio (Random, 95% CI)	0.78 [0.66, 0.92]
11.1 Several European countries	1		Odds Ratio (Random, 95% CI)	0.96 [0.70, 1.31]
11.2 Finland	2		Odds Ratio (Random, 95% CI)	1.24 [0.75, 2.05]
11.3 The Netherlands	1		Odds Ratio (Random, 95% CI)	0.69 [0.48, 0.99]

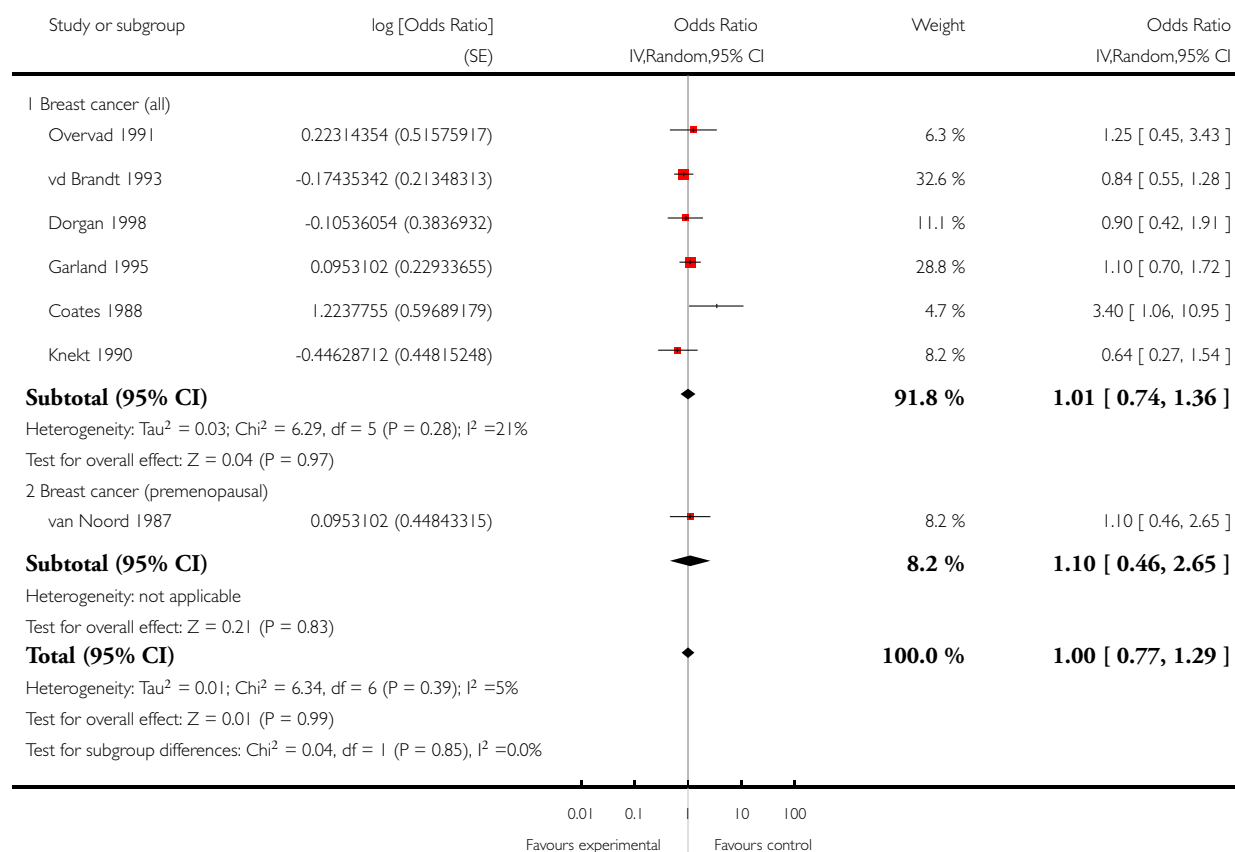
11.4 U.S.A.	10		Odds Ratio (Random, 95% CI)	0.71 [0.58, 0.88]
12 Prostate cancer risk (ascending order of selenium levels)	9	2112	Odds Ratio (Random, 95% CI)	0.81 [0.68, 0.97]
13 Stomach cancer risk	5		Odds Ratio (Random, 95% CI)	0.66 [0.43, 1.01]
13.1 stomach	4		Odds Ratio (Random, 95% CI)	0.65 [0.35, 1.19]
13.2 stomach: cardia cancer	1		Odds Ratio (Random, 95% CI)	0.47 [0.33, 0.66]
13.3 stomach: non-cardia cancer	1		Odds Ratio (Random, 95% CI)	1.07 [0.55, 2.08]
14 Stomach cancer risk (by gender)	5		Odds Ratio (Random, 95% CI)	0.66 [0.42, 1.04]
14.1 all (female + male)	2		Odds Ratio (Random, 95% CI)	0.75 [0.41, 1.36]
14.2 female	2		Odds Ratio (Random, 95% CI)	0.73 [0.12, 4.35]
14.3 male	3		Odds Ratio (Random, 95% CI)	0.43 [0.14, 1.32]
15 Colorectal cancer risk	5		Odds Ratio (Random, 95% CI)	0.89 [0.65, 1.23]
15.1 colon and rectal cancer	2		Odds Ratio (Random, 95% CI)	1.11 [0.50, 2.46]
15.2 colon cancer	3		Odds Ratio (Random, 95% CI)	0.80 [0.56, 1.15]
16 Colorectal cancer risk (by gender)	5		Odds Ratio (Random, 95% CI)	0.89 [0.65, 1.23]
16.1 all (female + male)	1		Odds Ratio (Random, 95% CI)	1.22 [0.52, 2.86]
16.2 female	3		Odds Ratio (Random, 95% CI)	1.06 [0.57, 2.00]
16.3 male	3		Odds Ratio (Random, 95% CI)	0.69 [0.42, 1.12]
17 Total cancer incidence and mortality	13		Odds Ratio (Random, 95% CI)	Subtotals only
17.1 incidence	8		Odds Ratio (Random, 95% CI)	0.69 [0.53, 0.91]
17.2 mortality	5		Odds Ratio (Random, 95% CI)	0.55 [0.36, 0.83]
18 Total cancer incidence and mortality (ascending order of selenium levels)	11		Odds Ratio (Random, 95% CI)	Subtotals only
18.1 incidence	6	1297	Odds Ratio (Random, 95% CI)	0.69 [0.52, 0.91]
18.2 mortality	5	1032	Odds Ratio (Random, 95% CI)	0.55 [0.36, 0.83]
19 Total cancer incidence and mortality (women)	5		Odds Ratio (Random, 95% CI)	Subtotals only
19.1 incidence	2		Odds Ratio (Random, 95% CI)	0.90 [0.45, 1.77]
19.2 mortality	3		Odds Ratio (Random, 95% CI)	0.92 [0.79, 1.07]
20 Total cancer incidence and mortality (men)	8		Odds Ratio (Random, 95% CI)	Subtotals only
20.1 incidence	5		Odds Ratio (Random, 95% CI)	0.66 [0.42, 1.05]
20.2 mortality	3		Odds Ratio (Random, 95% CI)	0.56 [0.38, 0.81]

Analysis 1.1. Comparison 1 Highest versus lowest selenium exposure, Outcome 1 Breast cancer risk (women).

Review: Selenium for preventing cancer

Comparison: 1 Highest versus lowest selenium exposure

Outcome: 1 Breast cancer risk (women)

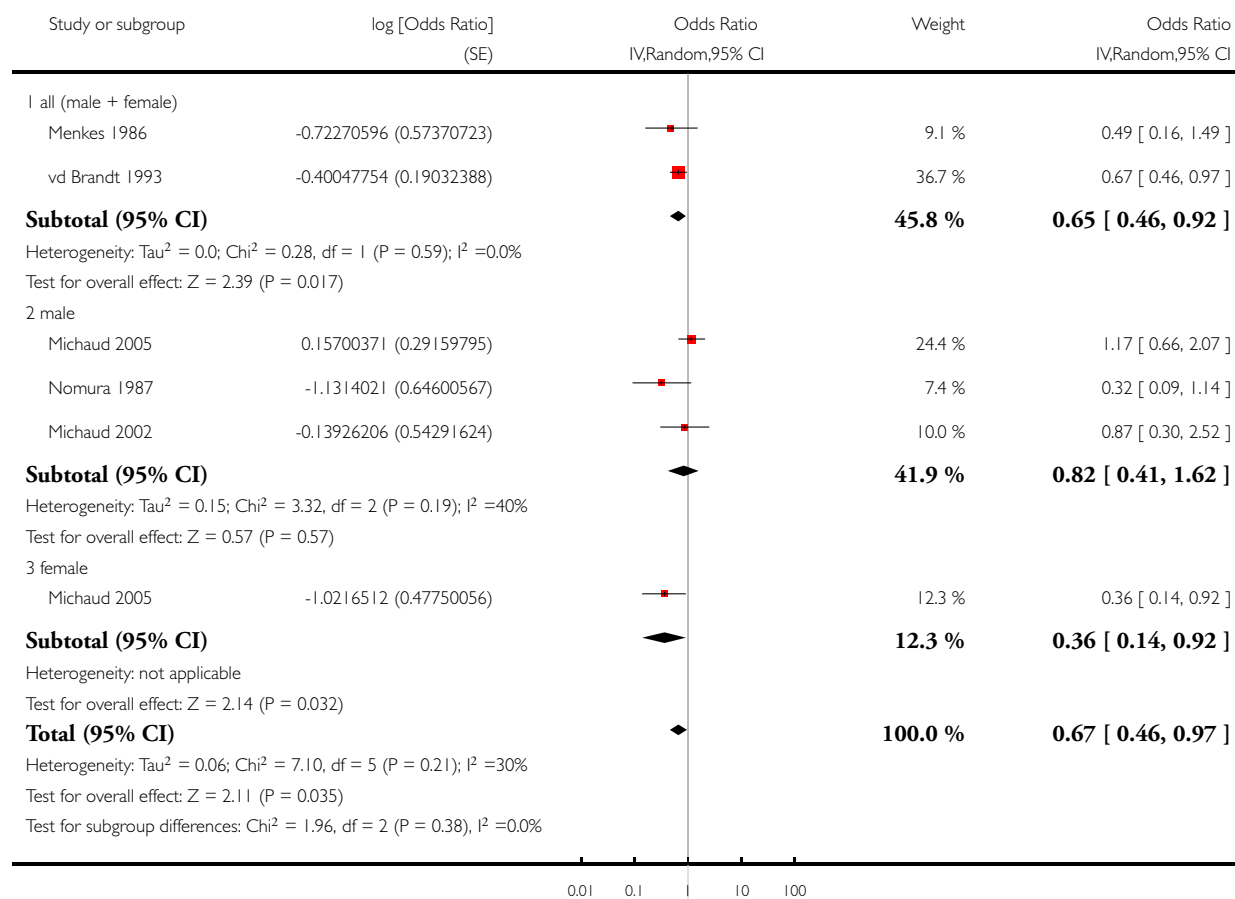


Analysis 1.2. Comparison 1 Highest versus lowest selenium exposure, Outcome 2 Bladder cancer risk.

Review: Selenium for preventing cancer

Comparison: 1 Highest versus lowest selenium exposure

Outcome: 2 Bladder cancer risk

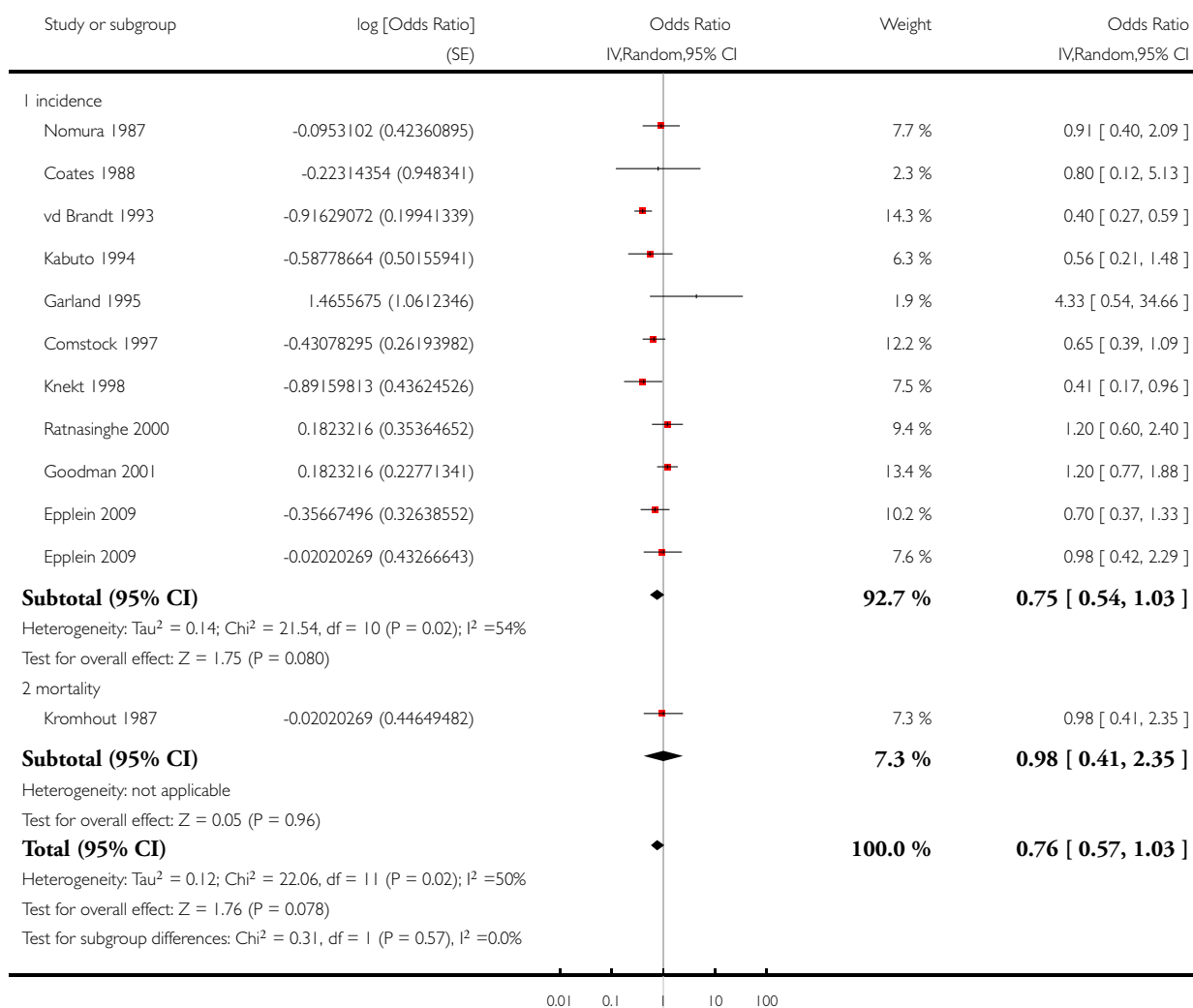


Analysis 1.3. Comparison 1 Highest versus lowest selenium exposure, Outcome 3 Lung cancer risk (gender-aggregated data).

Review: Selenium for preventing cancer

Comparison: 1 Highest versus lowest selenium exposure

Outcome: 3 Lung cancer risk (gender-aggregated data)

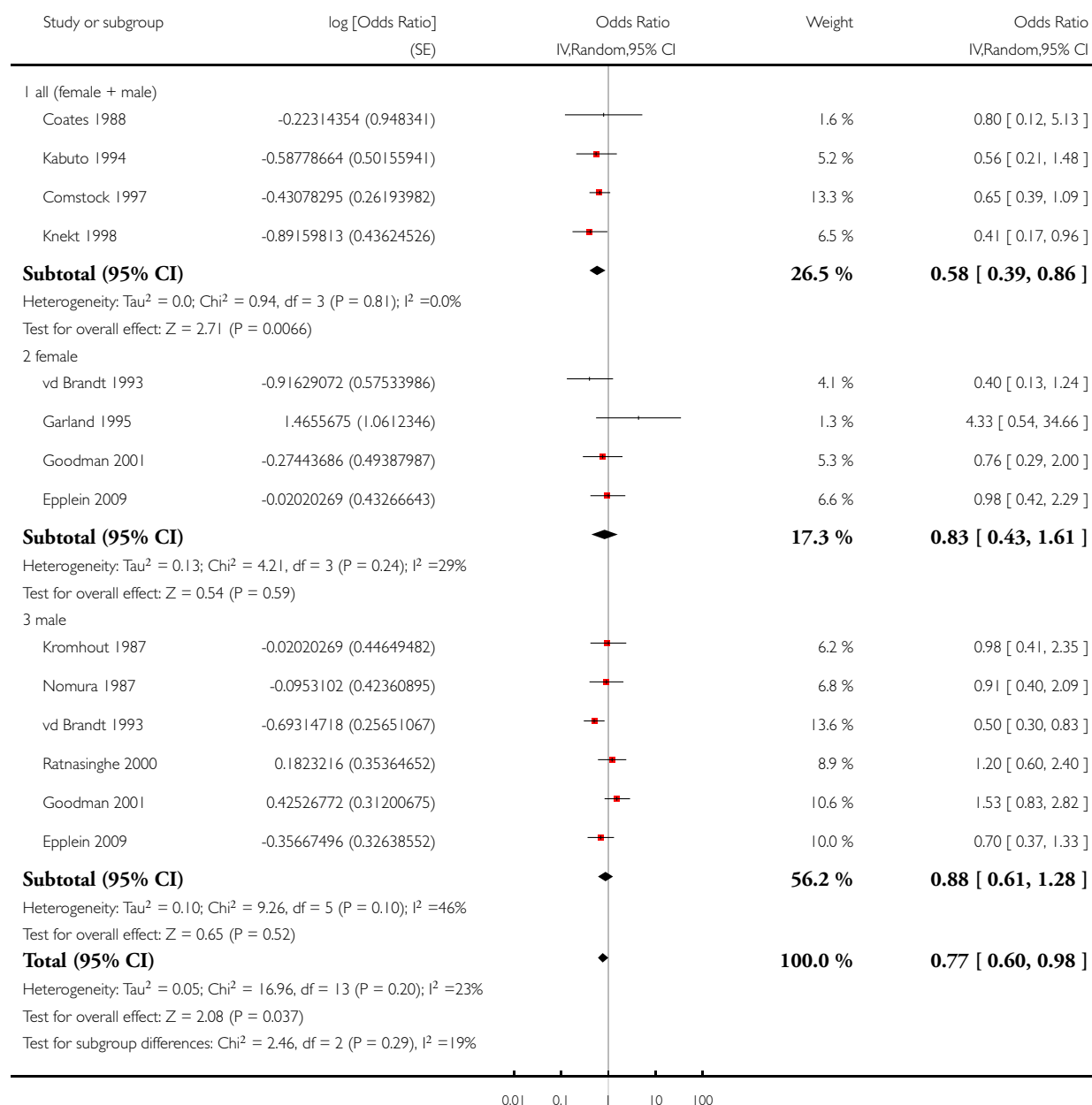


Analysis 1.4. Comparison 1 Highest versus lowest selenium exposure, Outcome 4 Lung cancer risk (gender-disaggregated data).

Review: Selenium for preventing cancer

Comparison: 1 Highest versus lowest selenium exposure

Outcome: 4 Lung cancer risk (gender-disaggregated data)

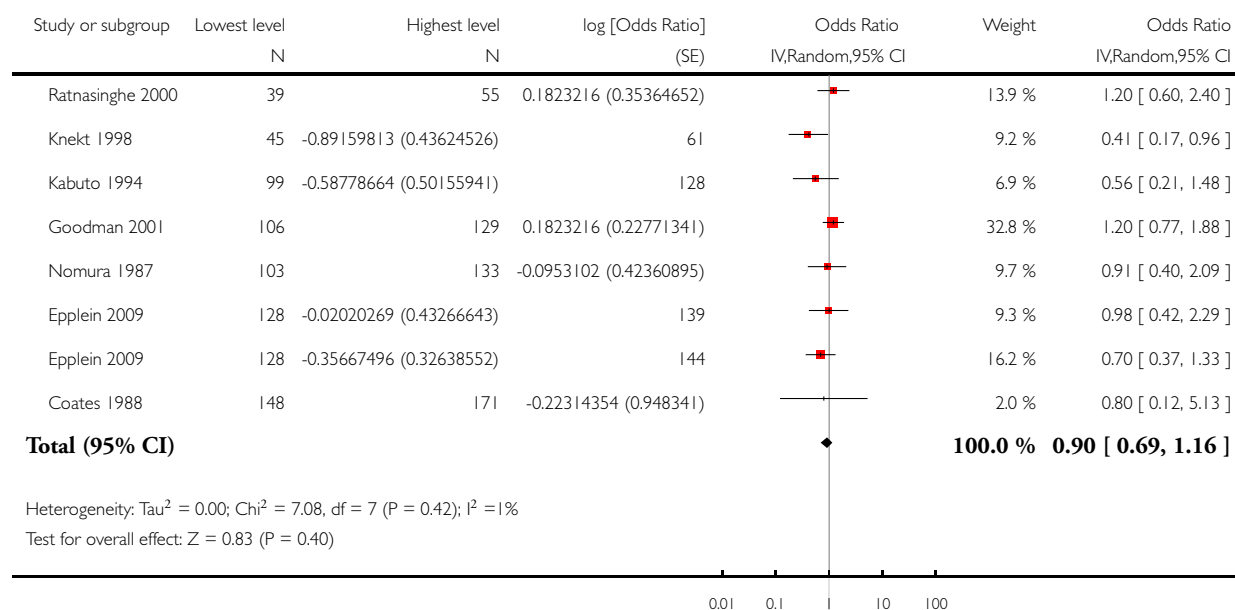


Analysis 1.5. Comparison 1 Highest versus lowest selenium exposure, Outcome 5 Lung cancer risk (ascending order of selenium levels).

Review: Selenium for preventing cancer

Comparison: 1 Highest versus lowest selenium exposure

Outcome: 5 Lung cancer risk (ascending order of selenium levels)

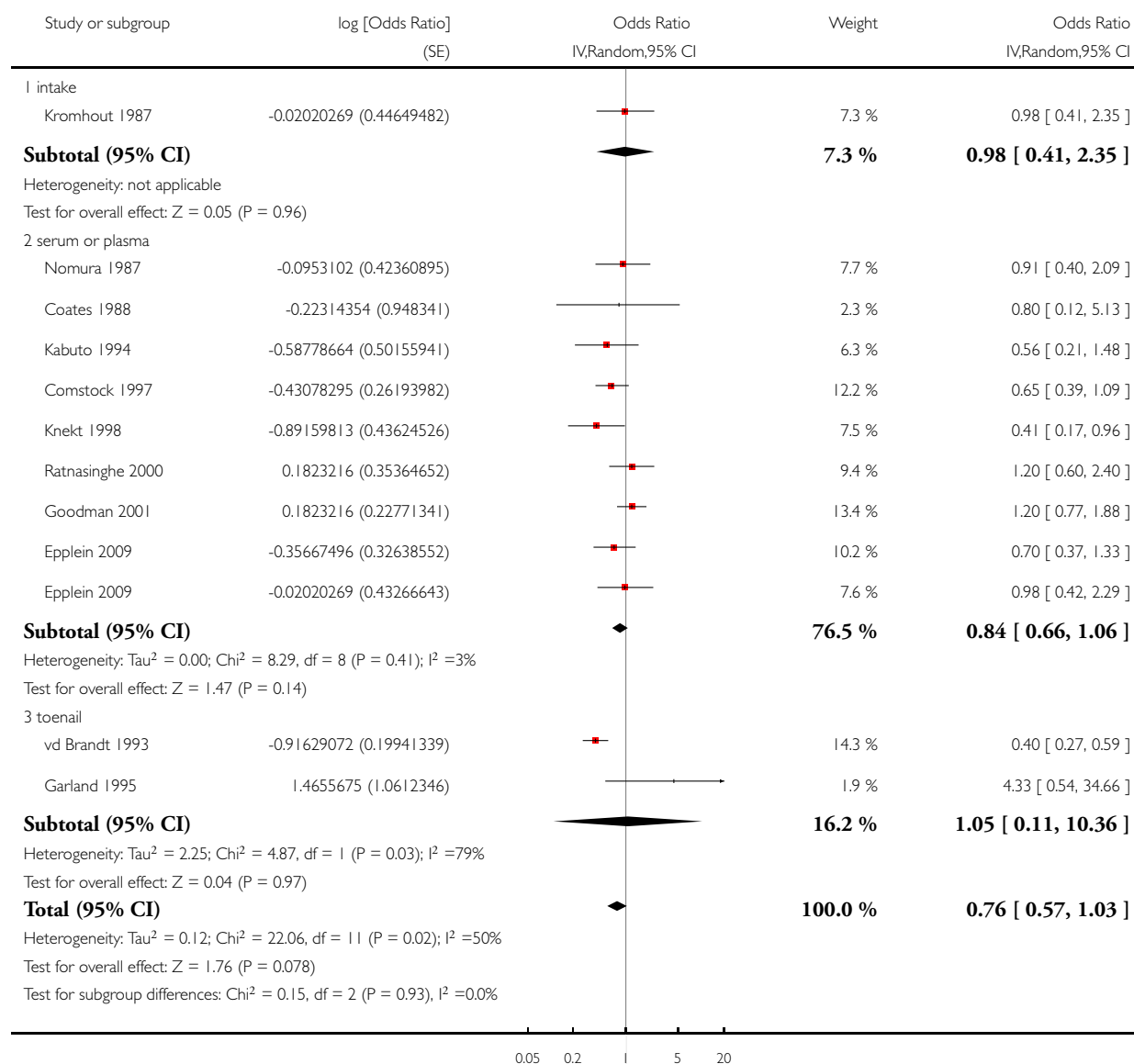


Analysis 1.6. Comparison 1 Highest versus lowest selenium exposure, Outcome 6 Lung cancer risk.

Review: Selenium for preventing cancer

Comparison: 1 Highest versus lowest selenium exposure

Outcome: 6 Lung cancer risk

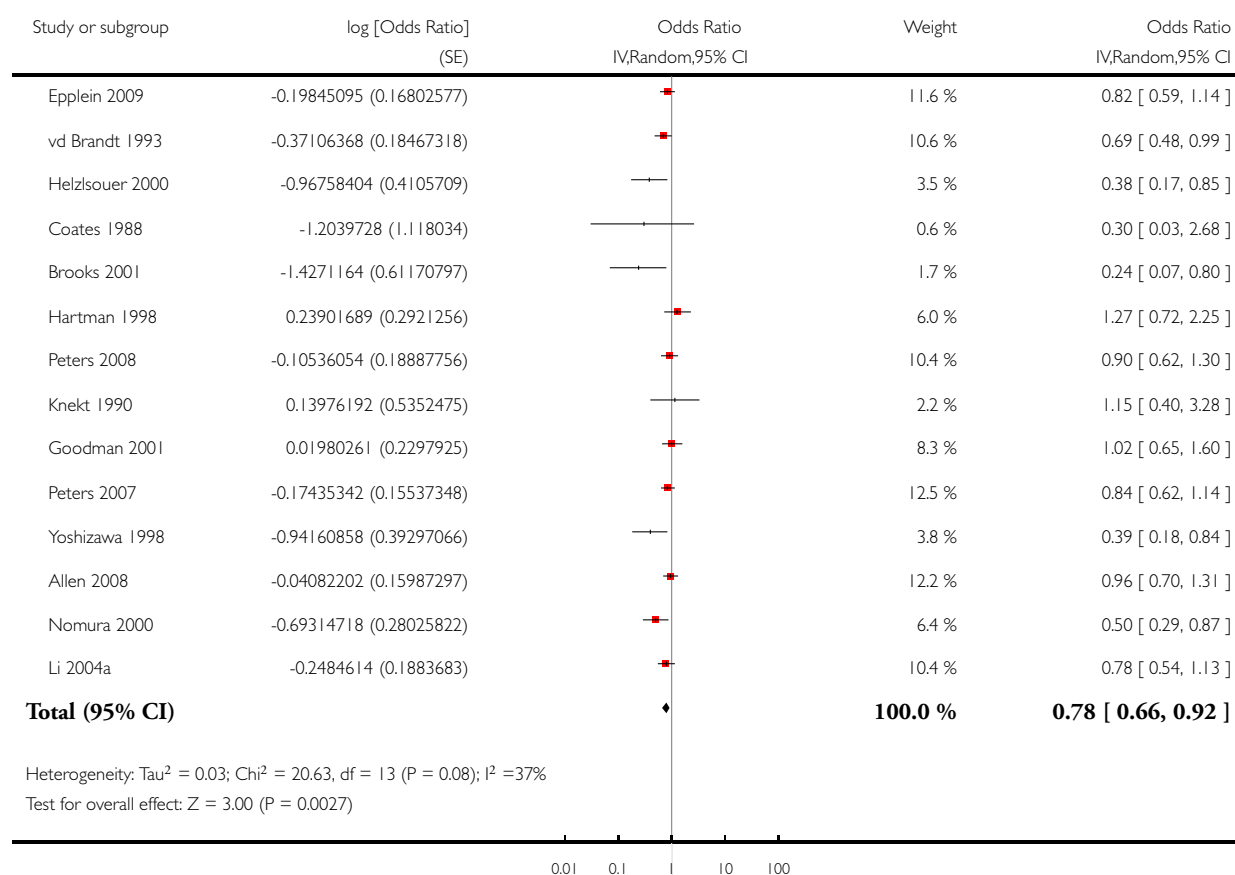


Analysis 1.7. Comparison 1 Highest versus lowest selenium exposure, Outcome 7 Prostate cancer risk.

Review: Selenium for preventing cancer

Comparison: 1 Highest versus lowest selenium exposure

Outcome: 7 Prostate cancer risk

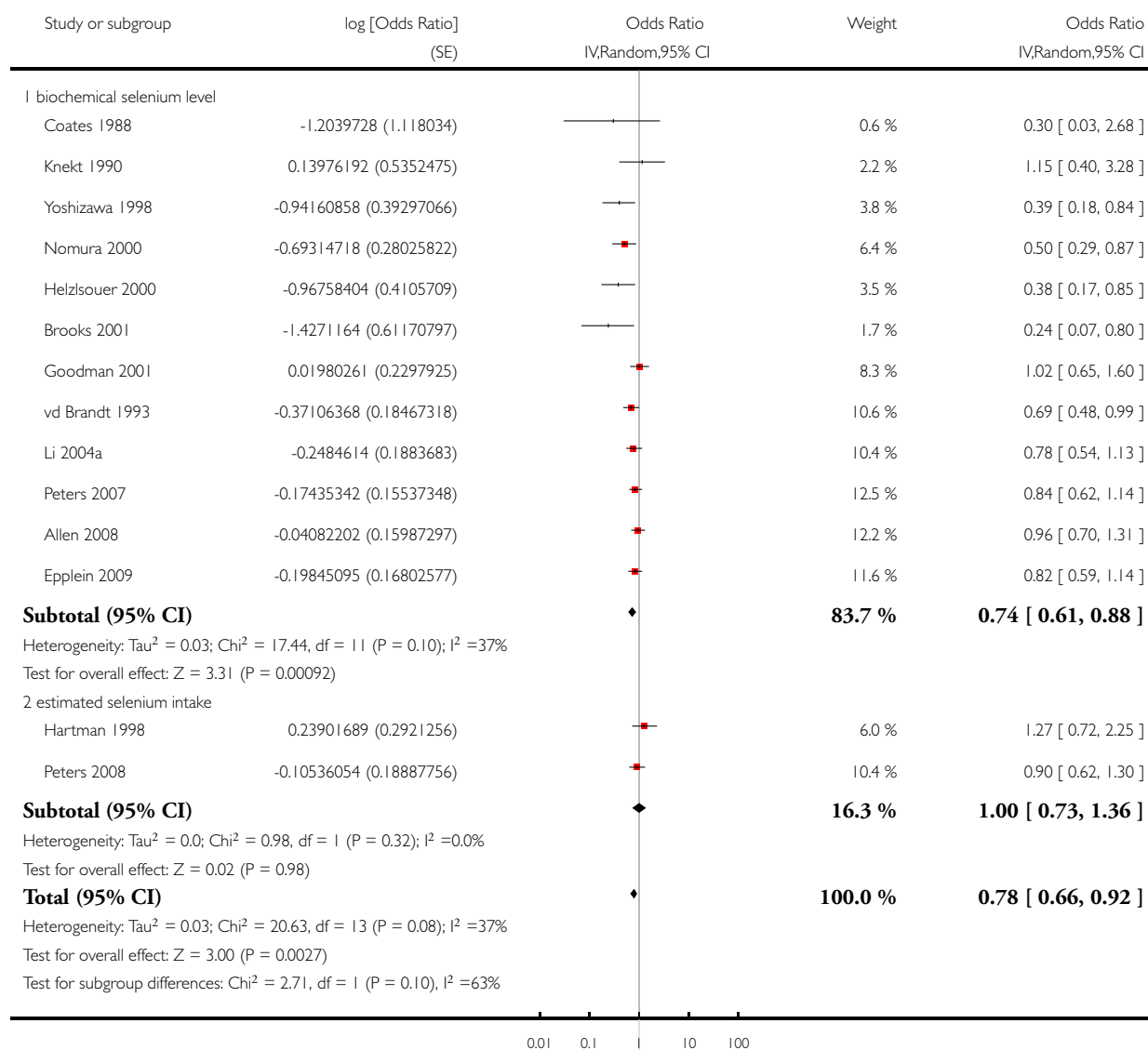


Analysis 1.8. Comparison 1 Highest versus lowest selenium exposure, Outcome 8 Prostate cancer risk (by selenium measurement).

Review: Selenium for preventing cancer

Comparison: 1 Highest versus lowest selenium exposure

Outcome: 8 Prostate cancer risk (by selenium measurement)

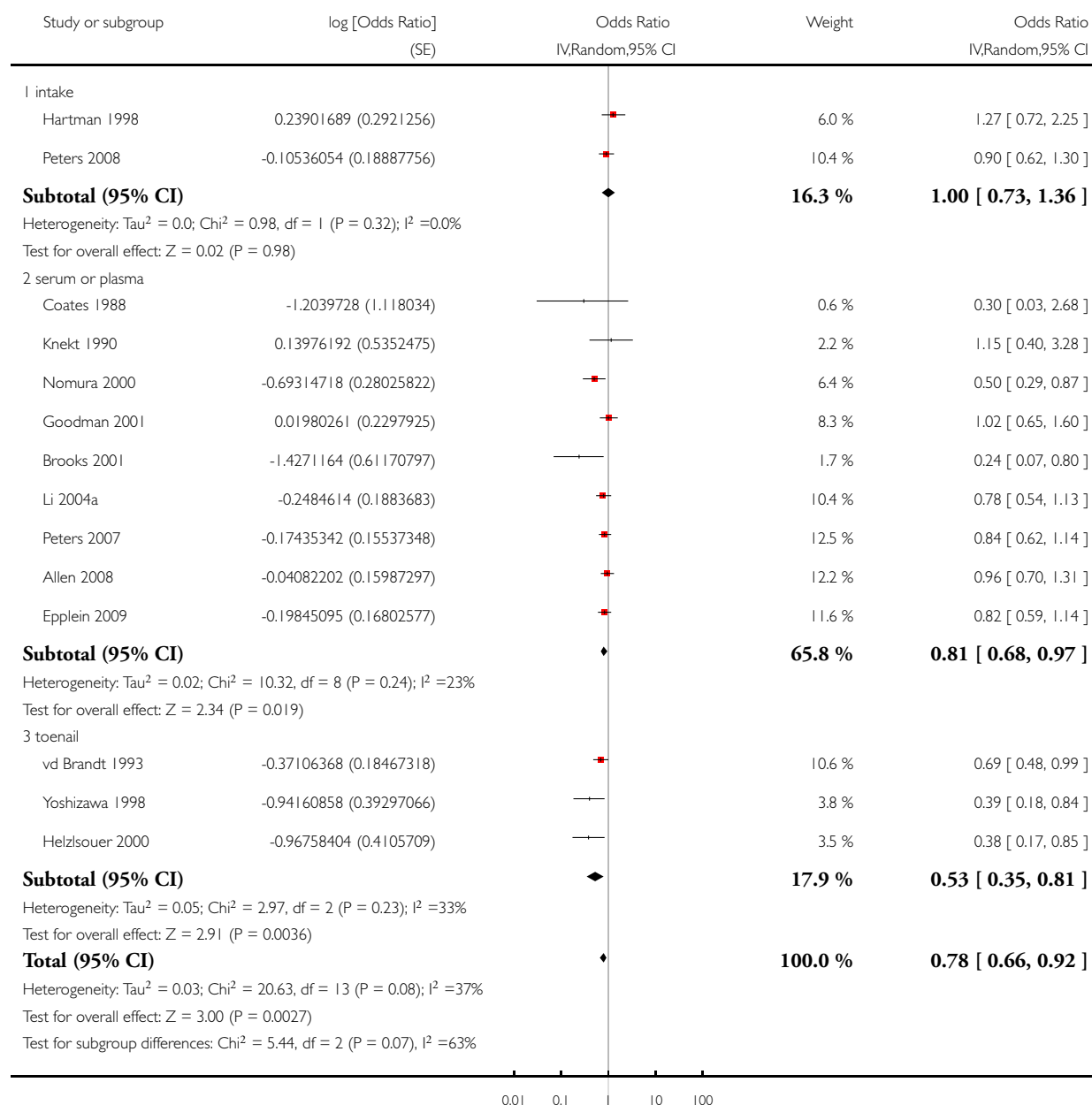


Analysis 1.9. Comparison 1 Highest versus lowest selenium exposure, Outcome 9 Prostate cancer risk (by exposure assessment).

Review: Selenium for preventing cancer

Comparison: 1 Highest versus lowest selenium exposure

Outcome: 9 Prostate cancer risk (by exposure assessment)

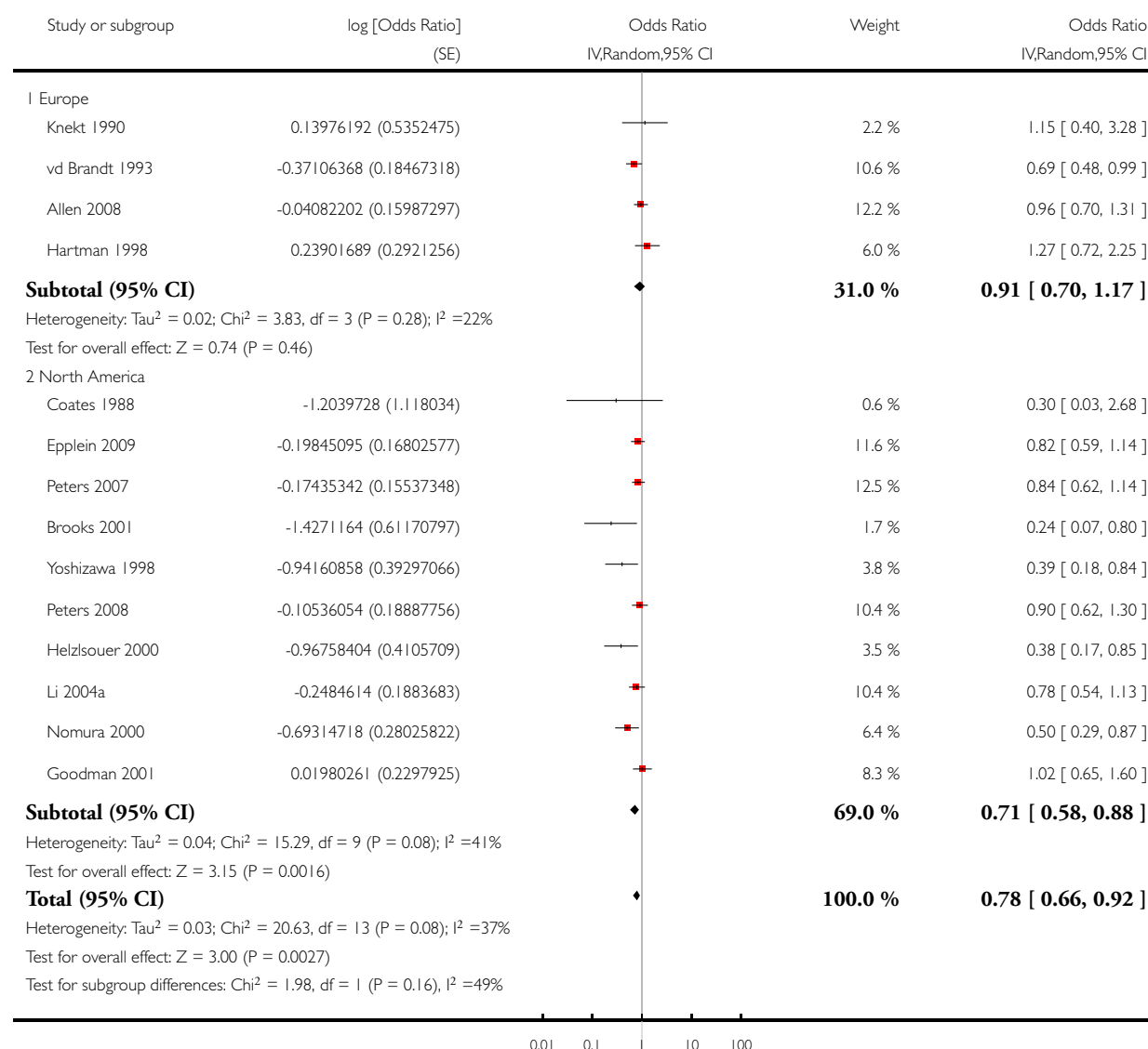


Analysis 1.10. Comparison 1 Highest versus lowest selenium exposure, Outcome 10 Prostate cancer risk (by continent).

Review: Selenium for preventing cancer

Comparison: 1 Highest versus lowest selenium exposure

Outcome: 10 Prostate cancer risk (by continent)

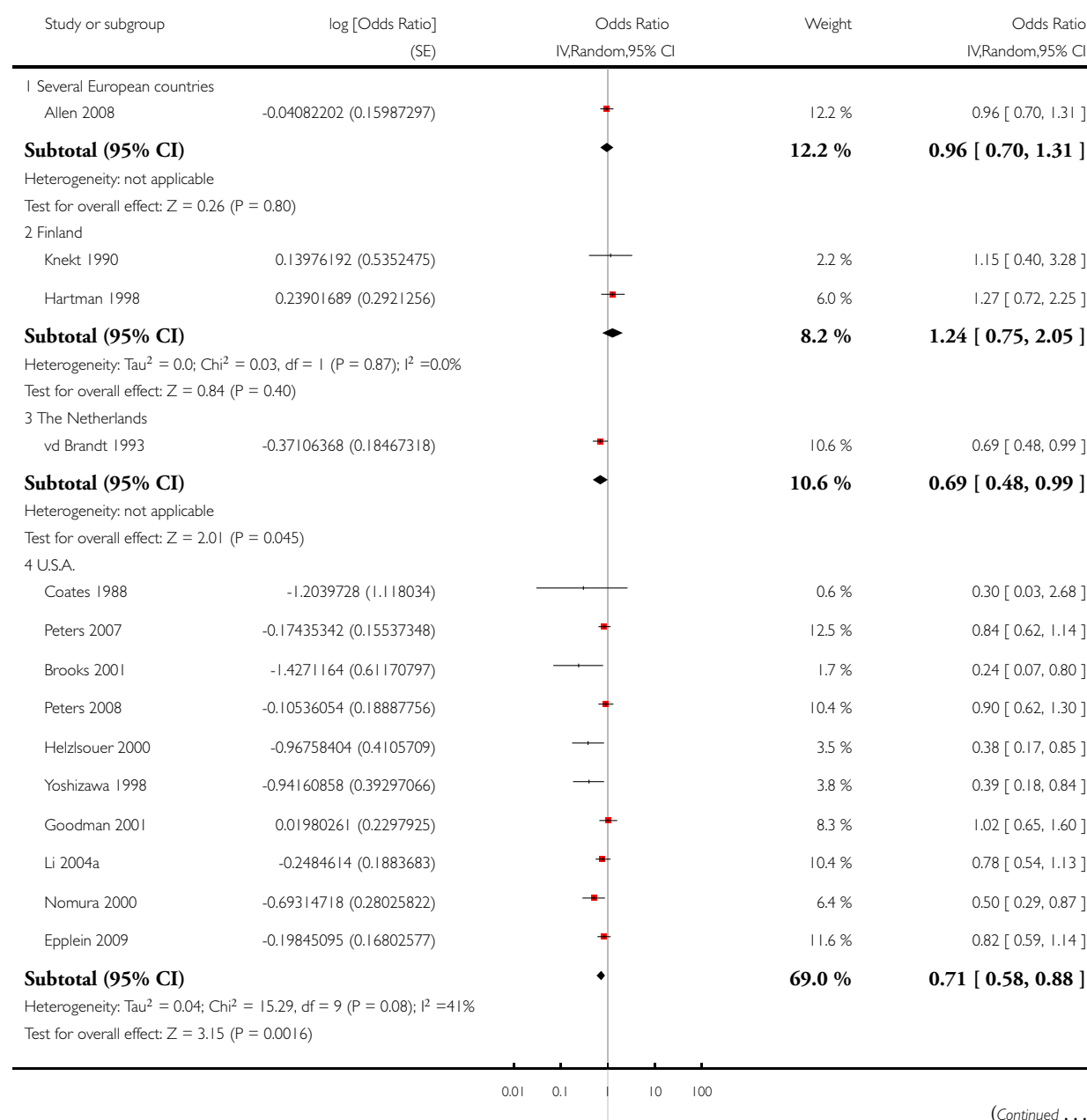


Analysis 1.11. Comparison 1 Highest versus lowest selenium exposure, Outcome 11 Prostate cancer risk (by country).

Review: Selenium for preventing cancer

Comparison: 1 Highest versus lowest selenium exposure

Outcome: 11 Prostate cancer risk (by country)



Study or subgroup	log [Odds Ratio] (SE)	Odds Ratio IV,Random,95% CI	Weight	(... Continued) Odds Ratio IV,Random,95% CI
Total (95% CI)			100.0 %	0.78 [0.66, 0.92]
Heterogeneity: $\tau^2 = 0.03$; $\chi^2 = 20.63$, $df = 13$ ($P = 0.08$); $I^2 = 37\%$				
Test for overall effect: $Z = 3.00$ ($P = 0.0027$)				
Test for subgroup differences: $\chi^2 = 6.00$, $df = 3$ ($P = 0.11$), $I^2 = 50\%$				

0.01 0.1 1 10 100

Analysis 1.12. Comparison 1 Highest versus lowest selenium exposure, Outcome 12 Prostate cancer risk (ascending order of selenium levels).

Review: Selenium for preventing cancer

Comparison: 1 Highest versus lowest selenium exposure

Outcome: 12 Prostate cancer risk (ascending order of selenium levels)

Study or subgroup	Upper border/lowest level N	Lower border/highest level N	log [Odds Ratio] (SE)	Odds Ratio IV,Random,95% CI	Weight	Odds Ratio IV,Random,95% CI
Knekt 1990	49	78	0.13976192 (0.5352475)		2.7 %	1.15 [0.40, 3.28]
Allen 2008	62	-0.04082202 (0.15987297)	84		19.6 %	0.96 [0.70, 1.31]
Li 2004a	92	124	-0.2484614 (0.1883683)		15.8 %	0.78 [0.54, 1.13]
Goodman 2001	101	126	0.01980261 (0.2297925)		11.8 %	1.02 [0.65, 1.60]
Brooks 2001	107	133	-1.4271164 (0.61170797)		2.1 %	0.24 [0.07, 0.80]
Nomura 2000	119	-0.69314718 (0.28025822)	147		8.6 %	0.50 [0.29, 0.87]
Peters 2007	127	-0.17435342 (0.15537348)	158		20.4 %	0.84 [0.62, 1.14]
Epstein 2009	127	-0.19845095 (0.16802577)	159		18.4 %	0.82 [0.59, 1.14]
Coates 1988	148	171	-1.2039728 (1.118034)		0.6 %	0.30 [0.03, 2.68]
Total (95% CI)					100.0 %	0.81 [0.68, 0.97]
Heterogeneity: $\tau^2 = 0.02$; $\chi^2 = 10.32$, $df = 8$ ($P = 0.24$); $I^2 = 23\%$						
Test for overall effect: $Z = 2.34$ ($P = 0.019$)						

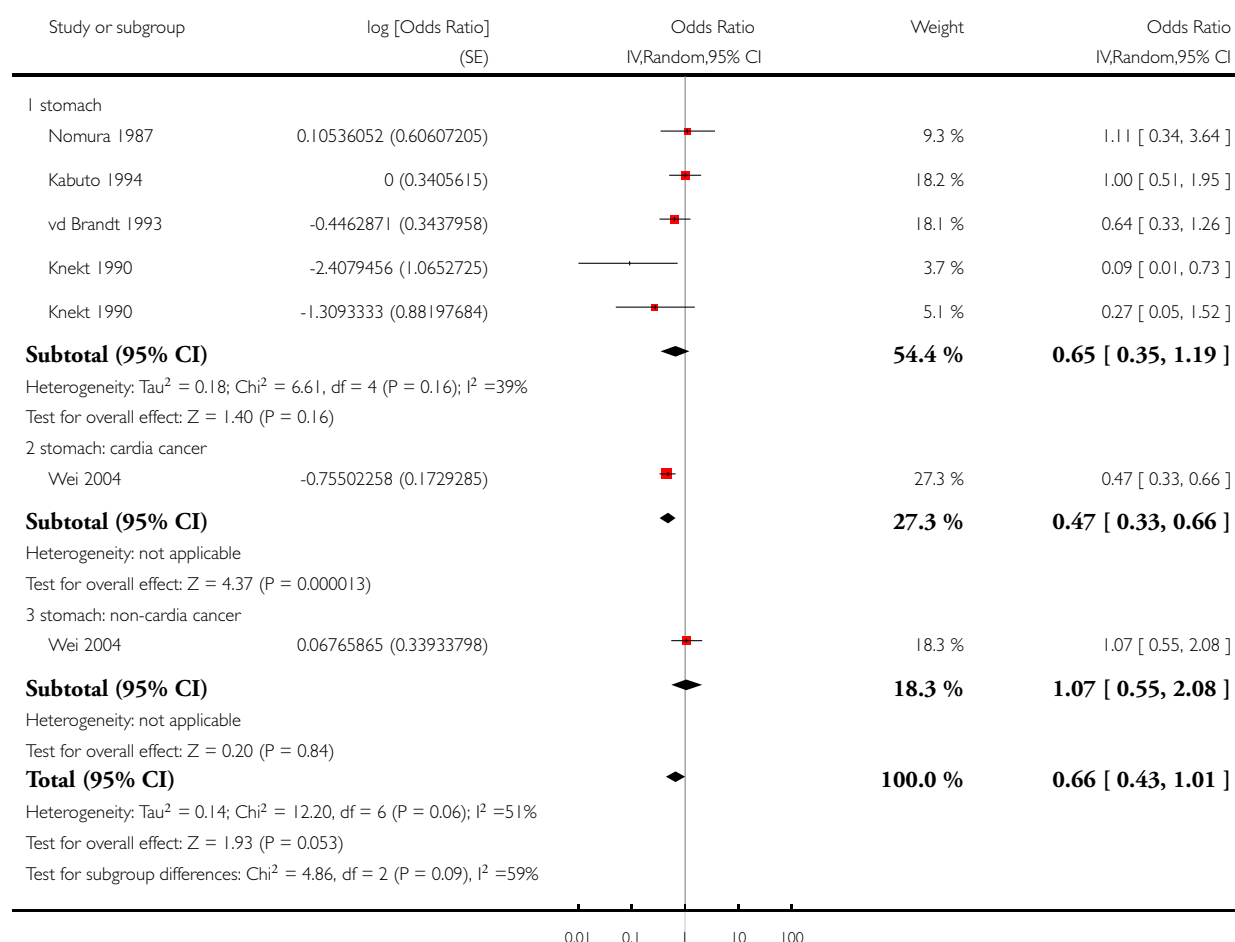
0.01 0.1 1 10 100

Analysis 1.13. Comparison 1 Highest versus lowest selenium exposure, Outcome 13 Stomach cancer risk.

Review: Selenium for preventing cancer

Comparison: 1 Highest versus lowest selenium exposure

Outcome: 13 Stomach cancer risk

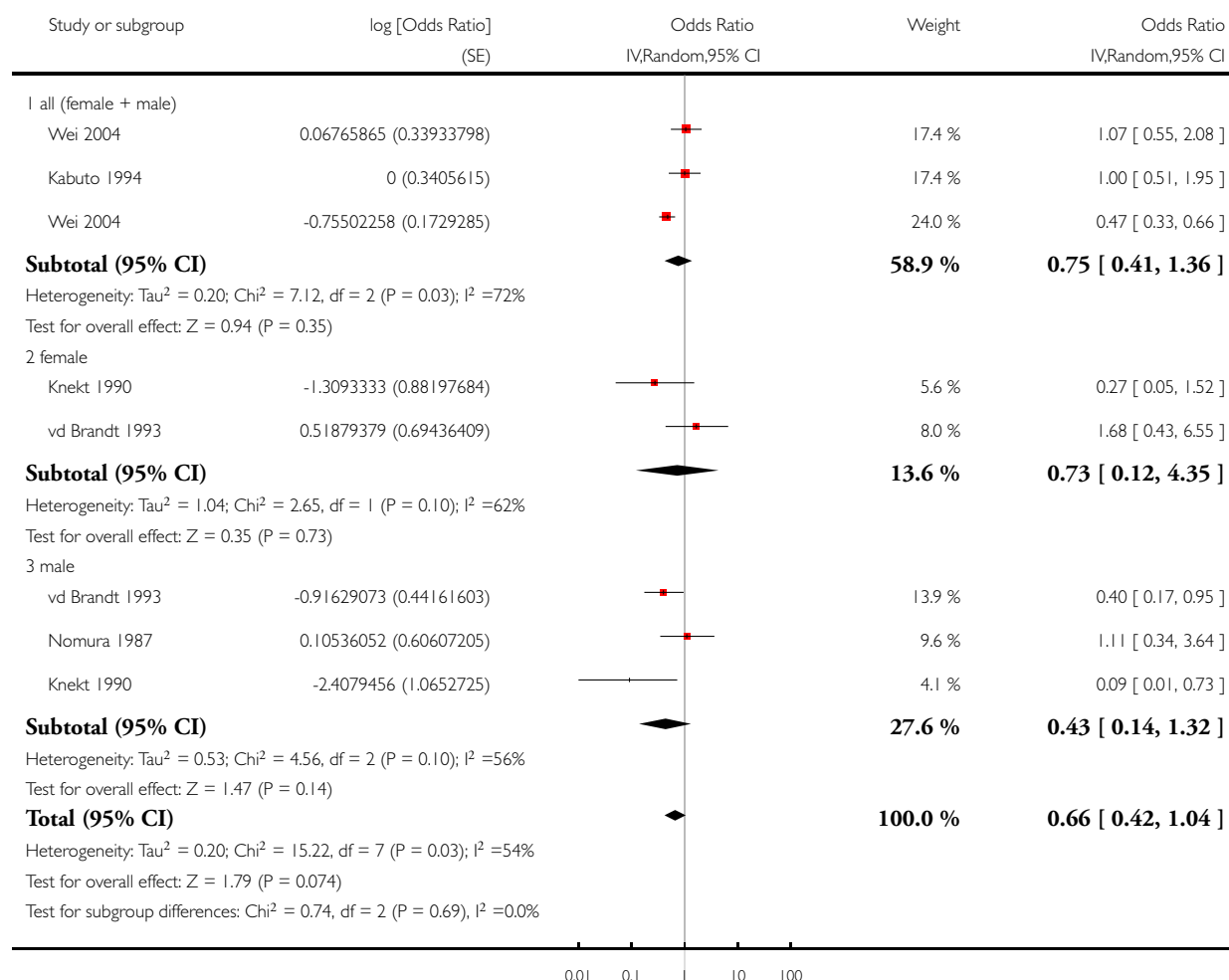


Analysis 1.14. Comparison 1 Highest versus lowest selenium exposure, Outcome 14 Stomach cancer risk (by gender).

Review: Selenium for preventing cancer

Comparison: 1 Highest versus lowest selenium exposure

Outcome: 14 Stomach cancer risk (by gender)

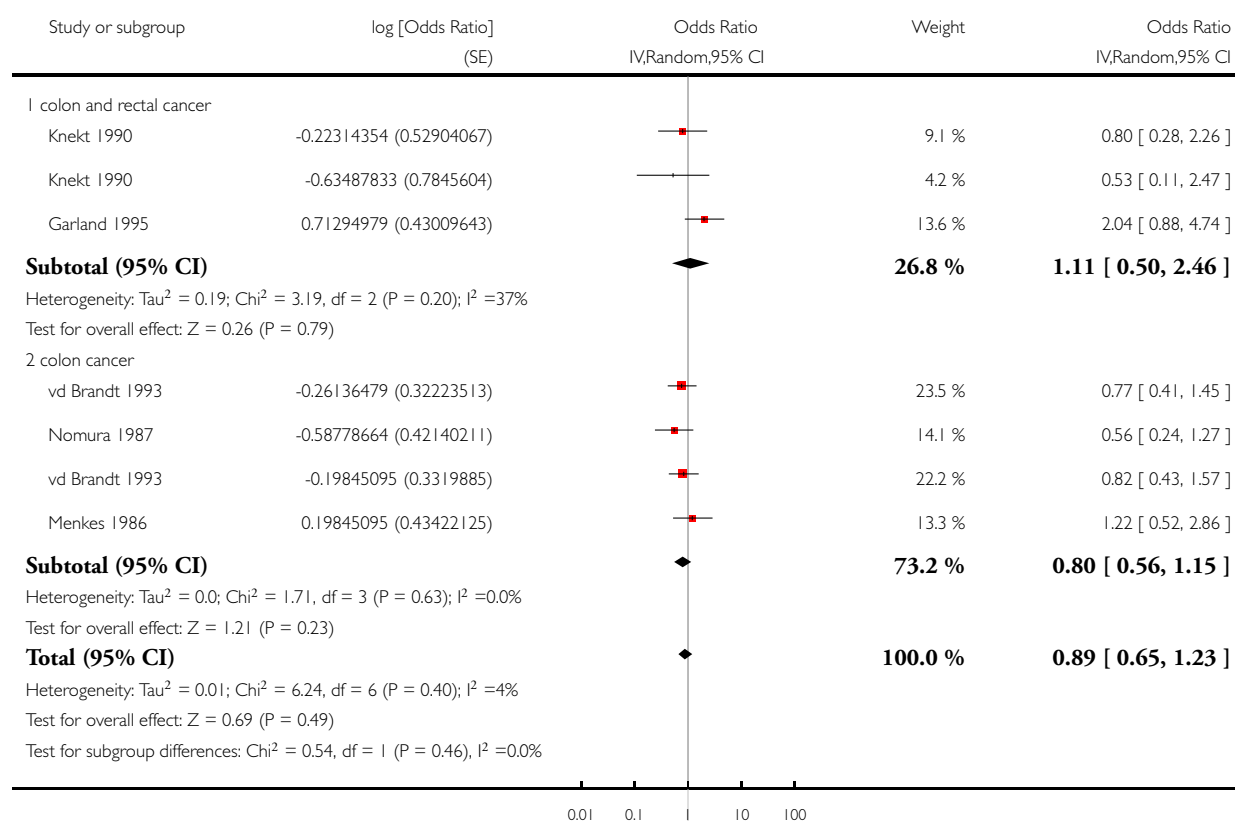


Analysis 1.15. Comparison 1 Highest versus lowest selenium exposure, Outcome 15 Colorectal cancer risk.

Review: Selenium for preventing cancer

Comparison: 1 Highest versus lowest selenium exposure

Outcome: 15 Colorectal cancer risk

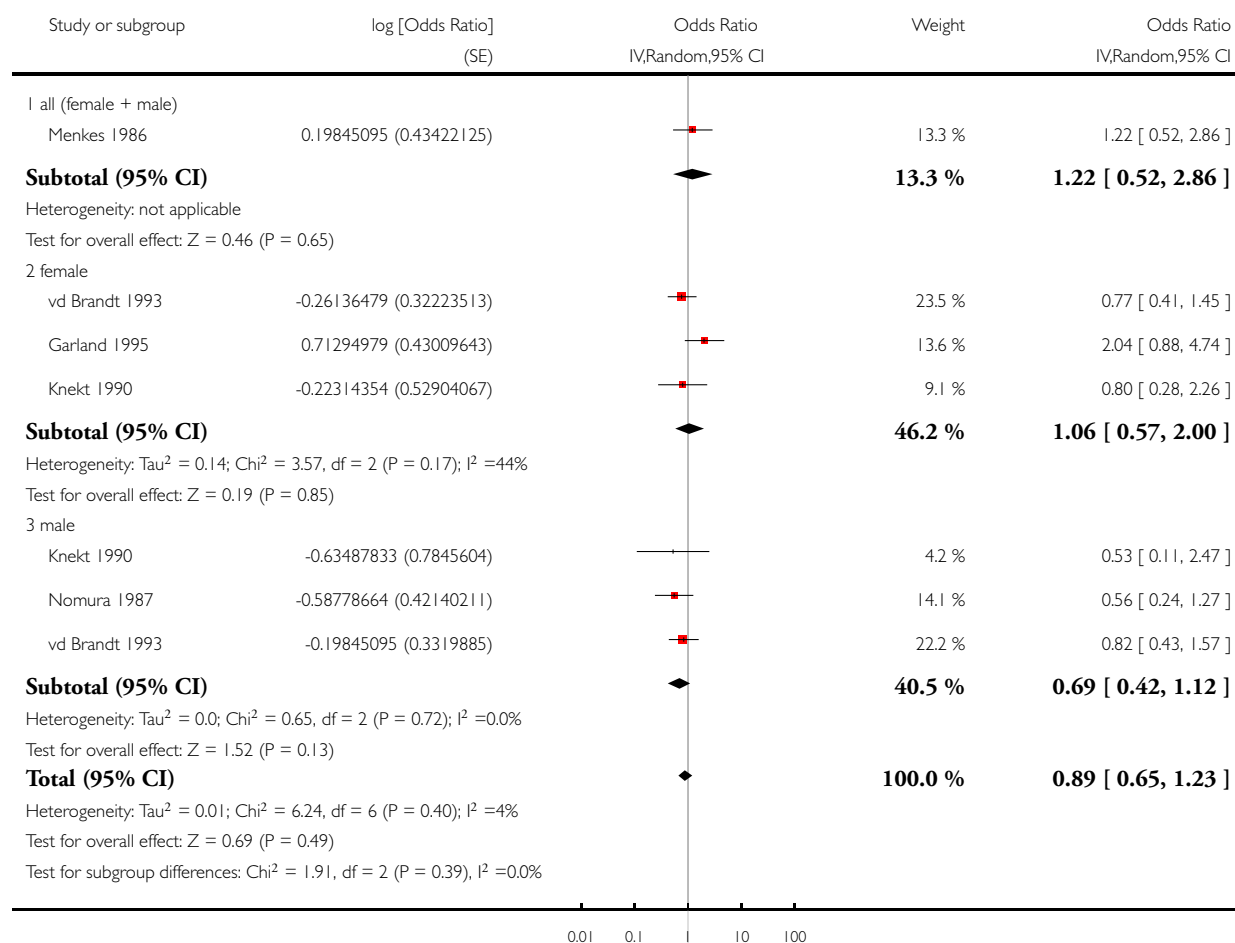


Analysis 1.16. Comparison 1 Highest versus lowest selenium exposure, Outcome 16 Colorectal cancer risk (by gender).

Review: Selenium for preventing cancer

Comparison: 1 Highest versus lowest selenium exposure

Outcome: 16 Colorectal cancer risk (by gender)

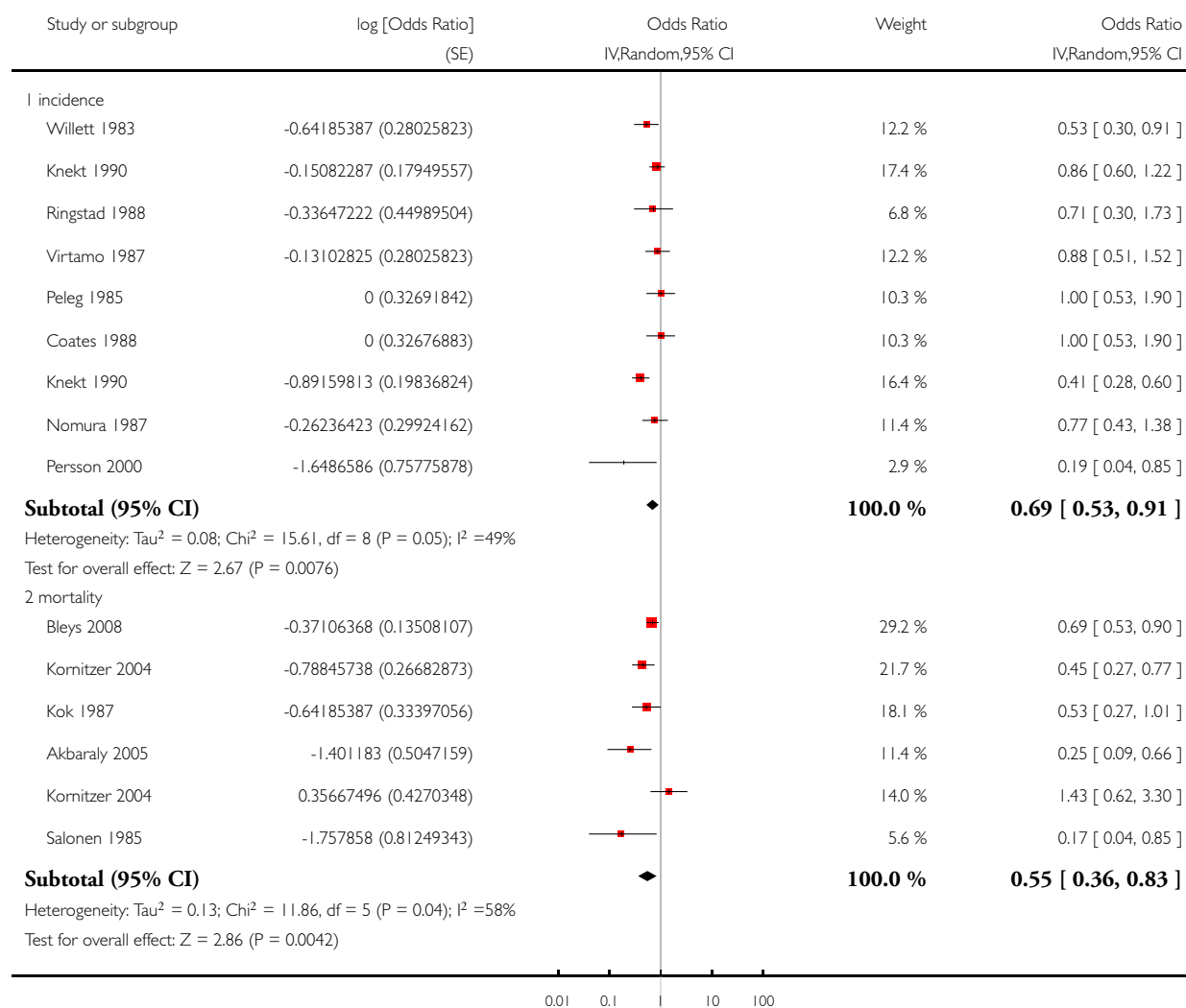


Analysis 1.17. Comparison 1 Highest versus lowest selenium exposure, Outcome 17 Total cancer incidence and mortality.

Review: Selenium for preventing cancer

Comparison: 1 Highest versus lowest selenium exposure

Outcome: 17 Total cancer incidence and mortality

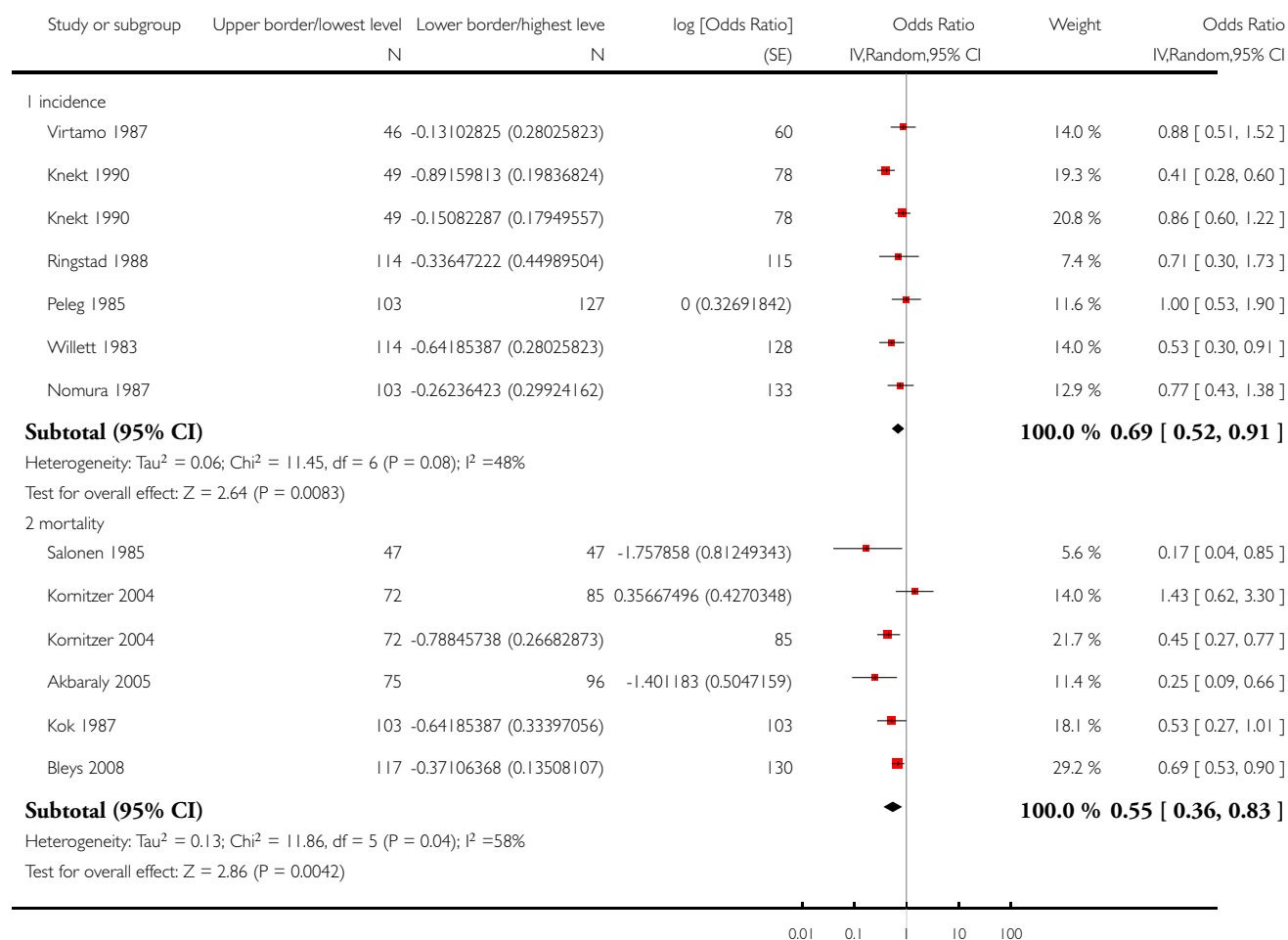


Analysis 1.18. Comparison 1 Highest versus lowest selenium exposure, Outcome 18 Total cancer incidence and mortality (ascending order of selenium levels).

Review: Selenium for preventing cancer

Comparison: 1 Highest versus lowest selenium exposure

Outcome: 18 Total cancer incidence and mortality (ascending order of selenium levels)

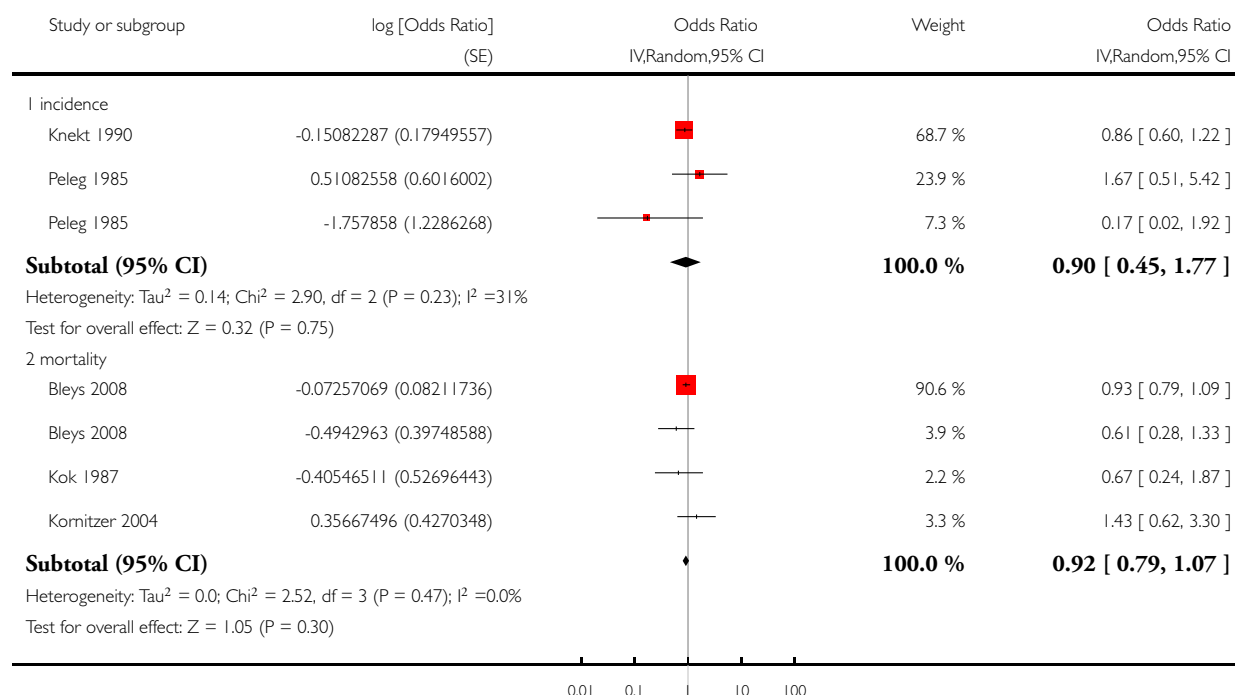


Analysis 1.19. Comparison 1 Highest versus lowest selenium exposure, Outcome 19 Total cancer incidence and mortality (women).

Review: Selenium for preventing cancer

Comparison: 1 Highest versus lowest selenium exposure

Outcome: 19 Total cancer incidence and mortality (women)

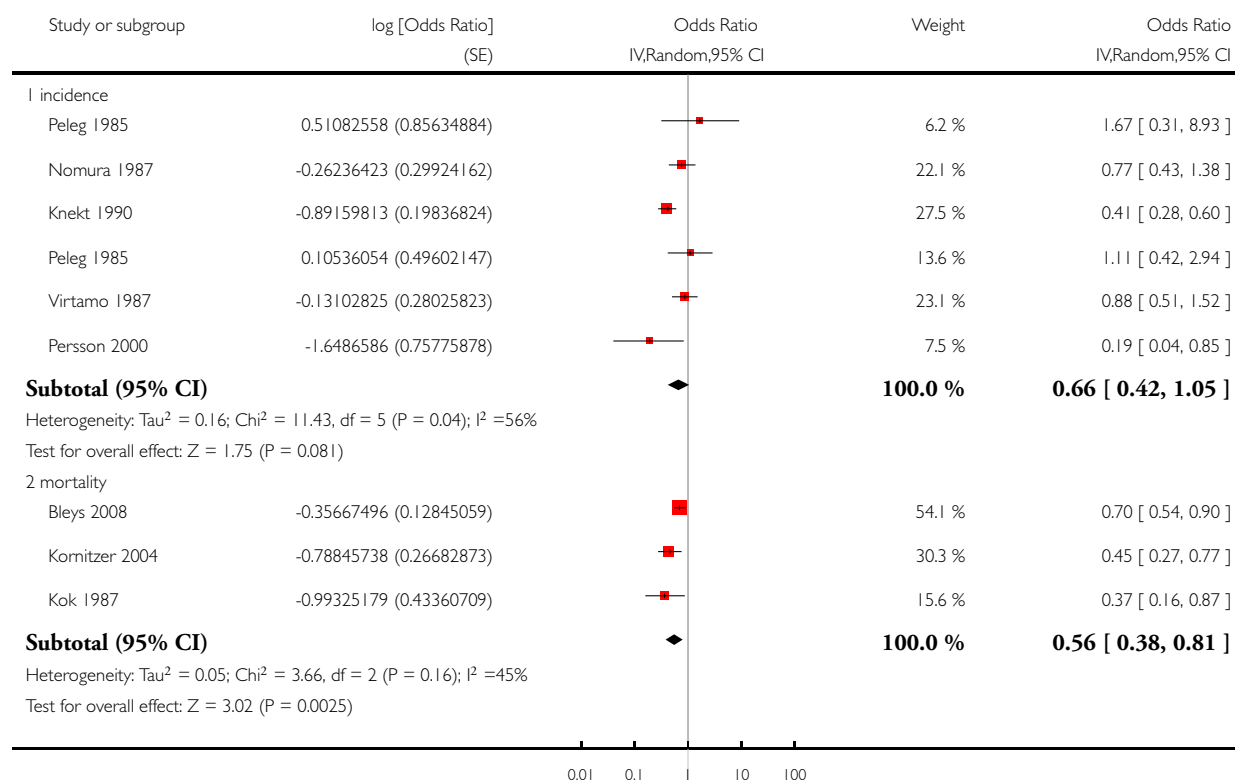


Analysis 1.20. Comparison 1 Highest versus lowest selenium exposure, Outcome 20 Total cancer incidence and mortality (men).

Review: Selenium for preventing cancer

Comparison: 1 Highest versus lowest selenium exposure

Outcome: 20 Total cancer incidence and mortality (men)



APPENDICES

Appendix I. Electronic search strategies

Database	Date of most recent literature search	Search strategy	Comment
www.cancer.gov	4 Feb 2011	medication: selenium indication: prevention	
Cancerlit	Oct 2004	1 selen* OR organoselen* OR natriumselen* 2 random* OR placebo* OR clinical trial* OR controlled trial* OR controlled clinical trial* OR double blind* OR single blind* 3 epidemiologic stud* OR co- hort OR case-control stud* OR nested case-control* OR case- control design* OR prospectiv* 4 2 OR 3 5 1 AND 4	now included in Medline database
Clinical Contents in Medicine (CCMed)	4 Feb 2011	selen* OR organoselen* OR na- triumselen*	
CENTRAL	Issue 1 2011	selen*	
Cochrane Library	Issue 1 2011	selen*	
metaRegister of Controlled Tri- als (mRCT, www.controlled- trials.com)	4 Feb 2011	selen AND cancer	
EMBASE	2010 week 50	1 selenium/ or selen\$.mp. 2 exp Clinical Study/ 3 exp NEOPLASM/ 4 1 and 2 and 3 5 Selenium 75/ 6 4 not 5 7 limit 6 to human (707) 8 exp Selenium Derivative/ (765) 9 methylseleninic acid/ or methylselenium.mp. 10 exp Organoselenium Derivative/ 11 1 or 8 or 9 or 10	

(Continued)

		12 11 and 2 and 3 13 12 not 5 15 limit 13 to human	
German Cancer Study Register: www.studien.de	4 Feb 2011	selen	
Medline (via Pubmed)	4 Feb 2011	<p>#1 Search selen* OR seleno* OR selenium[mesh] OR selen- nium compounds[mesh] OR organoselen- nium compounds[mesh]</p> <p>#2 Search randomized-con- trolled-trial[pt] Or controlled- clinical-trial[pt] OR clinical- trial[pt]</p> <p>#3 Search randomized-controlled- trials OR random-allocation OR double-blind-method OR single-blind-method OR place- bos OR research-design OR follow-up-studies OR prospec- tive-studies</p> <p>#4 Search epidemiologic study characteristics[mesh]</p> <p>#5 Search clinic*[tiab] NEAR trial*[tiab]</p> <p>#6 Search placebo*[tiab] OR random*[tiab]</p> <p>#7 Search clinical trial[tiab]</p> <p>#8 Search (singl*[tiab] OR doubl*[tiab] OR trebl*[tiab] OR tripl*[tiab]) NEAR (blind*[tiab] OR mask*[tiab])</p> <p>#9 Search control*[tiab] OR prospect*[tiab] OR volun- teer*[tiab]</p> <p>#10 Search #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9</p> <p>#11 Search neoplasms[mesh]</p> <p>#12 Search cancer* OR can- cers* OR cancro* OR carcino* OR carcinom* OR carcinog* OR malignan* OR neoplasm* OR tumor* OR tumori* Or tu- mors OR tumour*</p>	

(Continued)

		#13 Search melanoma* OR sarcoma* OR adenoma* OR adenosarcoma* OR adenocar- cinoma* OR carcinosarcoma* OR chondrosarcoma* OR fibrosar- coma* OR dermatofibrosar- coma* OR neurofibrosarcoma* OR hemangiosarcoma* OR leiomyosarcoma* OR liposar- coma* OR myosarcoma* OR rhabdomyosarcoma* OR myx- osarcoma* OR osteosarcoma* OR lymphoma* #14 Search #11 OR #12 OR # 13 #15 Search animals[mh] NOT human[mh] #16 Search #1 AND #10 AND #14 #17 Search #16 NOT #15	
SIGLE	Oct 2004	?selen?	database discontinued in 2005

Appendix 2. Newcastle-Ottawa-Scale for Cohort Studies

((*) means that a 'star' was assigned to the study for the corresponding item)

1) SELECTION

1.1) representativeness of the exposed cohort

- a) truly representative of the average (target population) in the community (*)
- b) somewhat representative of the average (target population) in the community (*)
- c) selected group of users, e.g. volunteers / nurses
- d) no description of the derivation of the cohort

1.2) selection of the non-exposed cohort

- a) drawn from the same community as the exposed cohort (*)
- b) drawn from a different source
- c) no description

1.3) ascertainment of selenium exposure

- a) secure record (biochemical records) (*)
- b) structured interview (*)
- c) written self report or medical record only
- d) no description

1.4) demonstration that outcome of interest was not present at start of study

- a) no history of disease or exclusion of cases that occurred in the first 12 months (*)
- b) not stated

2) COMPARABILITY

2.1.) comparability of cohorts on the basis of the design or analysis

- a) study controls for AGE (*)
- b) study controls for SMOKING (*)

3) OUTCOME

3.1) assessment of outcome

- a) independent blind validation (> 1 person/record/time/process to extract information or reference to primary source such as X-rays/hospital records) (*)
- b) record linkage (e.g. ICD codes in databases) (*)
- c) self report
- d) no description

3.2) Was follow-up long enough for outcomes to occur?

- a) yes (> 3 years)
- b) no

3.3) adequacy of follow up of cohorts

- a) complete follow-up of all subjects (*)

OR

- b) subjects lost to follow-up unlikely to introduce bias (< 5% lost to follow-up or description provided of lost people) (*)
- c) follow-up-rate < 95% and no description of those lost
- d) no statement

Appendix 3. Additional Newcastle-Ottawa-Scale for Nested Case-Control Studies

((*) means that a 'star' was assigned to the study for the corresponding item)

1) SELECTION

1.1) case definition

- a) independent validation (> 1 person/record/time/process to extract information or reference to primary source such as X-rays/hospital records) (*)
- b) record linkage (e.g. ICD codes in databases) or self-report with no reference to primary record
- c) no description

1.2) representativeness of cases:

- a) all eligible cases with outcome of interest over a defined period, cases in a defined catchment area/hospital etc. or an appropriate/random sample of those cases (*)
- b) not satisfying requirements in part (a) or not stated

1.3) selection of controls:

- a) community controls (same community and would be cases if had outcome) (*)
- b) hospital controls (within the same population e.g. city as cases)
- c) no description

1.4) definition of controls

- a) cases had no history of outcome controls had no history of outcome OR case had new (not necessarily first) occurrence of outcome controls with previous occurrence of outcome should not be excluded (*)
- b) no mention of history of outcome

2) COMPARABILITY

(validated in cohort assessment in question 2 - number of stars was copied)

3) EXPOSURE

3.1) ascertainment of selenium exposure:

(validated in cohort assessment in question 1.3 - number of stars was copied)

3.2) Same method of ascertainment for cases and controls

- a) yes (*)
- b) no

3.3) non-response rate

- a) same rate for both groups (*)
- b) non-respondents described
- c) rate different and no designation

HISTORY

Protocol first published: Issue 2, 2005

Review first published: Issue 5, 2011

CONTRIBUTIONS OF AUTHORS

GD is the primary author and co-ordinator of the authors' group and was involved in all steps of realising the protocol and the review.

MZw commented on the protocol, extracted data from papers, conducted the data analyses in STATA and commented on the review and provided a methodological perspective.

MB commented on the protocol, assisted by checking the original literature search and inclusion criteria, providing a brief and early background on urological cancer and provided feedback at various stages of the review.

MV commented on the protocol, screened search results, extracted data from papers, provided an early version of the background and feedback on the review text at various stages of the review.

MZe commented on the protocol, screened search results, extracted data from papers and provided feedback on the review text

MH commented on the protocol, screened search results, extracted data from papers, designed the Access database for data management, provided support for securing funding for the review, supported data management and commented on the review text at various stages of the review.

DECLARATIONS OF INTEREST

GD: None known

MZw: None known

MB: None known

MV: None known

MZe: Maurice Zeegers is the first investigator of one included observational study and one ongoing randomised controlled trial. He is second author of another included observational study.

MH: None known

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External sources

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- Deutsche Krebshilfe (German Cancer Aid), Germany.

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- NCCAM, USA.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We adapted the risk of bias assessment for RCTs, which was introduced by The Cochrane Collaboration after the publication of our protocol. According to our protocol, we also used the Jadad score and the Delphi list to assess the quality of RCTs. As the results of these checklist assessments are of no relevance for this review, we have omitted them.