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Selenium and bladder cancer risk: a meta-analysis

André F. S. Amaral[1], **Kenneth P. Cantor**[2], **Debra T. Silverman**[3], **Núria Malats**[1]

[1]Spanish National Cancer Research Centre (CNIO), Genetic and Molecular Epidemiology Group, Madrid, Spain

[2]formerly of the National Cancer Institute; currently KP Cantor Environmental LLC, Silver Spring, MD, USA

[3]National Cancer Institute (NCI), Division of Cancer Epidemiology & Genetics, Bethesda, MD, USA

Abstract

Background—Selenium is considered to be an anti-oxidant, and its high levels have been inversely associated with cancer risk of several sites. This meta-analysis examined the relationship between levels of selenium measured in serum and toenails and the risk of bladder cancer.

Methods—A meta-analysis using data from seven published epidemiologic studies (three case-control, three nested case-control, one case-cohort) published before March 2010 was performed to examine the association between levels of selenium and bladder cancer. Fixed- and random-effects analyses were performed to calculate meta-odds ratio (mOR) and 95% confidence intervals (CI). Heterogeneity among studies was measured by the I^2 statistic.

Results—Overall, the risk of bladder cancer was inversely associated with elevated levels of selenium according to a random-effects model (mOR = 0.61; 95% CI, 0.42–0.87). The mORs were 0.95 (95% CI, 0.69–1.27) and 0.55 (95% CI, 0.32–0.95) among men and women, respectively. Sex, type of sample specimen, smoking status, and study design were found to be potential sources of heterogeneity.

Conclusions—A significant protective effect of selenium, observed mainly among women, may result from gender-specific differences in its accumulation and excretion. The heterogeneity found among studies was mainly linked to the different biological sample specimens used to measure the selenium concentrations and the small size of the studies. While these results suggest a protective effect of selenium for bladder cancer risk, additional large studies are warranted to support these preliminary evidences.

Impact—The present results suggest a beneficial effect of high selenium intake for bladder cancer risk.

Corresponding Author: Núria Malats, Spanish National Cancer Research Centre (CNIO), Genetic and Molecular Epidemiology Group, C/ Melchor Fernández Almagro, 3, 28029 Madrid, Spain, Phone: +34-912-246-900 (ext. 3330), Fax: +34-912-246-911, nmalats@cnio.es.

Disclosure of Potential Conflict of Interests

No potential conflicts of interest were disclosed.

Keywords

bladder cancer; selenium; meta-analysis

Introduction

Worldwide, bladder cancer is one of the most common types of cancer, especially among men. The highest incidence is observed in Spain and Italy. The established risk factors for bladder cancer are smoking, which accounts for 60% of cases in men and 35% in women, occupational exposure to aromatic amines, high levels of arsenic intake, and schistosomiasis infection (1). Bladder cancer is a complex disease, and polymorphisms in low penetrance genes are also involved in the development of this neoplasm. There is consistent evidence that NAT2 slow acetylator and GSTM1 null genotypes increase the risk of bladder cancer. Furthermore, NAT2 slow acetylator has been found to modulate the effect of smoking on bladder cancer, which represents one of the few known gene-environment interactions involved in carcinogenesis (2). While these factors explain more than half of the etiological scenario of bladder cancer (3), a substantial fraction of the disease remains unexplained. The risk factors that remain may include a complex pattern of environmental exposures, difficult to measure with questionnaires. The increasing evidence of a role for trace metals and other environmental exposures in cancer acting through oxidative stress mechanisms (4, 5), suggests their further exploration in relation to bladder and other cancers.

Although the mechanism(s) by which selenium may act as an anti-carcinogen are not fully known, several studies have observed an inverse association between selenium status and cancer, such as gastrointestinal, lung and prostate cancers (6–9). However, for prostate cancer there have been some conflicting results reported by clinical trials (10–12).

The present meta-analysis was conducted to summarize the association between high levels of selenium as measured in biological sample specimens and bladder cancer risk, and examine the possible causes of heterogeneity among published studies on this topic.

Materials and Methods

Study Selection

Studies were identified by searching PubMed, ISI Web of Knowledge, Scopus, Cochrane Library, and Google Scholar databases before March 2010 for the terms “selenium” and “bladder cancer”. References from relevant articles were also used to identify studies that were not found in the database search.

Eligible studies included epidemiologic manuscripts reporting measures of association between selenium and bladder cancer risk by measuring selenium in any of the following biological sample specimens: blood/serum, nails, hair, and saliva. Studies were excluded if they were not written in English, Spanish or Portuguese, if they presented insufficient data, if they were reviews or if they were not epidemiologic studies. Furthermore, duplicate articles were excluded (Figure 1).

From the selected articles, the following information was extracted: (i) first author's last name, year of publication, and country of the population studied; (ii) study design; (iii) sample size; (iv) odds ratio (OR) or relative risk (RR) estimates with 95% confidence interval (CI), and adjustments for potential confounding factors, if applicable. Information on sex and type of sample specimen was also extracted from all the eligible publications, whenever possible. Relative risk was treated as if it was OR.

The corresponding authors of the selected studies were contacted if pertinent information on relevant study data was not available in the published article. In order to assess the quality of each study, the criteria used by Flores-Mateo et al. (13) were adapted (Supplementary Table 1). These major criteria include, for example, the assessment of exposure at the individual level, data collection in a similar manner for all participants and the use of incident cases only.

Statistical Analysis

The OR or RR and 95% CI for highest (exposed) versus lowest (reference) levels of selenium groups were extracted from the selected manuscripts. To obtain the suitable weight of each study related to the summary OR, the standard error (SE) for each logarithm of the OR was calculated by using the 95% CI. The square of the SE was used as the estimated variance of the logarithm of the OR. Both fixed and random effects models were assessed, but the latter was preferentially used when heterogeneity was detected.

The I^2 statistic, representing the proportion of total variation across study estimates due to heterogeneity, was used to determine the level of heterogeneity (14). Potential sources of heterogeneity were explored using stratified meta-analysis to check the influence of the following determinants: sex, type of sample specimen, smoking status, and study design. Additionally, the relative influence of each study on pooled estimates was assessed by omitting one study at a time. Publication bias was explored by analyzing funnel plots and Egger's regression asymmetry test. Statistical calculations were performed with STATA/SE 10.1 (StataCorp, Texas, USA).

Results

The initial literature search identified 172 publications. After excluding duplicates and other publications according to selection criteria (Supplementary Table 2), three case-control, three nested case-control, and one case-cohort studies that examined the association between selenium status and bladder cancer risk were identified and used in the present analysis (Table 1). A nested case-control study of a Finnish population met almost all the inclusion criteria but could not be included because it lacked an adequate definition of referent and exposed groups (15). The total number of cases and controls/cohort members in the identified studies was 1,910 and 17,339, respectively. Four studies were performed in the USA and three in Northern Europe. In four studies, selenium status was based on analysis of toenails, while in the remaining three, serum was the sample specimen used. The two oldest and smallest studies of the seven reported non-significant inverse associations (16, 17) (Table 1). Three other studies reported the same tendency. Only two showed a significant decrease in the risk of bladder cancer among individuals with higher selenium levels (18–22)

(Table 1). In two case-control studies, toenail selenium concentrations were inversely associated with bladder cancer risk only among women, moderate smokers, and p53-positive cancers (19, 22) (Table 1). Using a random effects model, the overall OR of bladder cancer risk for the highest compared with the lowest selenium status was 0.61 (95% CI, 0.42–0.87). A comparable result was found when using a fixed effects model (OR = 0.70; 95% CI, 0.58–0.84) (Figure 2).

Among the pooled studies, a moderate level of heterogeneity was detected (χ^2 = 15.32; degrees of freedom = 6; P = 0.018; I^2 = 60.8%) (Figure 2).

In the analysis stratified by gender, only women yielded significant decreased risk associated with selenium (OR = 0.55; 95% CI, 0.32–0.95) with a non-significant I^2 of 23.7% (Table 2). The sample specimen where selenium was determined (serum or toenails) was found to be a source of heterogeneity (Table 2). Although selenium in toenails and in serum provided significant results, serum levels of selenium showed a stronger protective effect (OR = 0.33; 95% CI, 0.21–0.51). Stratifying the analysis according to smoking status, decreased the heterogeneity found in the overall analysis and results became similar between never and ever smokers (Table 2). As for the type of study, the stratified results were consistent with the pooled overall estimate. Moreover, heterogeneity increased in the stratum of case-control studies (χ^2 = 13.13; degrees of freedom = 2; P = 0.001; I^2 = 84.8%) (Table 2).

Publication bias was not detected in the meta-analysis (coefficient = −1.84, P = 0.357), even when stratifying by the several study determinants (Table 2). As expected, the most influential studies in the analysis were found to be the largest ones (18, 19, 22).

Discussion

In the present meta-analysis, we observed a significant 39% decreased risk of bladder cancer associated with high levels of selenium by combining results from seven epidemiologic studies, conducted in different populations, which applied individual levels of selenium measured in serum or toenails. While little is known on the role of selenium in bladder cancer, several systematic reviews and meta-analysis, both on observational (6–9) and interventional studies (10–12) have reported on the protective effect of selenium on cancer. The few clinical trials on selenium supplementation have reported conflicting and not yet conclusive results, with the National Prevention of Cancer (NPC) and the Supplémentation en Vitamines et Minéraux Antioxydants (SU.VI.MAX) showing an inverse association between selenium and prostate cancer, and the Selenium and Vitamin E Cancer Prevention (SELECT) trial reporting non-significant increased risk of prostate cancer among those selenium supplemented individuals (8, 10–12).

The abovementioned high selenium status refers to concentrations of selenium in toenails of around 0.9 μg/g and in serum of approximately 100 μg/L, or higher. Toenail and serum selenium levels have been shown to be correlated[1] (23, 24). Furthermore, a level of about

[1]Behne D. (personal communication) calculated from the data of the 22 test persons investigated in “Behne D, Alber D, Kyriakopoulos A. Long-term selenium supplementation of humans: Selenium status and relationships between selenium concentrations in skeletal muscle and indicator materials. J. Trace Elem. Med. Biol., *24*: 99–105. 2010”

80–95 μg/L of selenium in serum is considered optimal for the maximization of glutathione peroxidases and selenoprotein P activities (25).

Selenium may exert anticarcinogenic effects mainly through selenoproteins, though the specific mechanisms are not yet fully known. Aberrant expression patterns of glutathione peroxidases and selenoprotein P, found in colorectal cancer, show that the antioxidant properties of selenoenzymes are relevant in carcinogenesis and tumor progression (26), particularly by scavenging reactive oxygen species and diminishing further oxidative damage. The protection of selenium against cancer is also linked to the activities of hydrogen selenide and selenomethionine present in cells, which may be responsible for modifying protein thiols and mimicking methionine, leading to higher methylating efficiency of RNA and thiols (27). Some studies suggest that this essential dietary trace element has antioxidant properties, and that it produces effects on apoptosis, DNA repair and carcinogen metabolism. In order to decrease the oxidative stress caused by exposure to arsenic, cadmium or lead, the selenium requirement increases (28) as these metals act as selenium antagonists (29). Moreover, both organic and inorganic forms of selenium may enhance p53 activity towards either DNA repair or apoptosis (30). If selenium is in the form of seleno-L-methionine, the DNA repair branch of the p53 pathway is preferentially induced, which also involves Ref1 and Brca1 in a protein complex (31).

Stratified analyses by type of sample specimen (serum and toenails), smoking status, and study design also found that higher levels of selenium lead to a lower risk of bladder cancer, although each was identified as a potential source of heterogeneity. Serum and toenail measurements are both accepted as biomarkers of exposure to assess the exposure to selenium in the organism (32, 33), but they provide information on different time frames with toenail selenium reflecting longer-term exposure (34, 35). Part of the heterogeneity found in the pooled overall analysis was also explained by the smoking status, which may be due to different ways of assessing that status and different definitions of smoking groups among studies. While published evidence between selenium and smoking is not clear, several studies on healthy individuals show that smokers have lower levels of selenium (36, 37). Though study design explained some of the heterogeneity, more diversity was found among the case-control studies, which is probably the result of different criteria for selection of controls.

The summary effects for the two sexes were not similar in that a significant inverse association was observed for women but not men. An opposite gender pattern, with protective effects in men and not in women, was reported in a meta-analysis on selenium supplementation and primary cancer incidence and mortality (6). However, the trials in that meta-analysis were not specific for the effects of selenium on bladder cancer risk, two of the four trials that provided sex-specific data used a mix of compounds rather than selenium alone, and the effects of selenium on cancer incidence and mortality were based on levels of supplementation instead of internal levels of selenium. Moreover, only one of them assessed the internal levels of selenium of the individuals, and this showed that men had higher levels of selenium at baseline, which could perhaps explain the higher protection from cancer in those. While no accepted explanation for these sex-specific differences exist, there are some

hypotheses indicating different excretion rates, half-lives, and also sensitivity to potential toxic effects of selenium between genders (38, 39).

Publication bias was not evident in this meta-analysis. However, a note of caution is warranted since only seven epidemiologic studies were included in this meta-analysis and because they presented some heterogeneity. Nevertheless, the results of this meta-analysis and the heterogeneity found among studies are informative in the sense they emphasize the input of each study to the existing literature and the topics that entail further research.

In conclusion this meta-analysis supports an inverse association between selenium concentration and bladder cancer risk. To further elucidate this relationship, efforts to quantify selenium and other trace metals in biological sample specimens at the individual level in large observational studies or randomized trials are needed. These are fundamental steps before suggesting selenium supplementation to bladder cancer patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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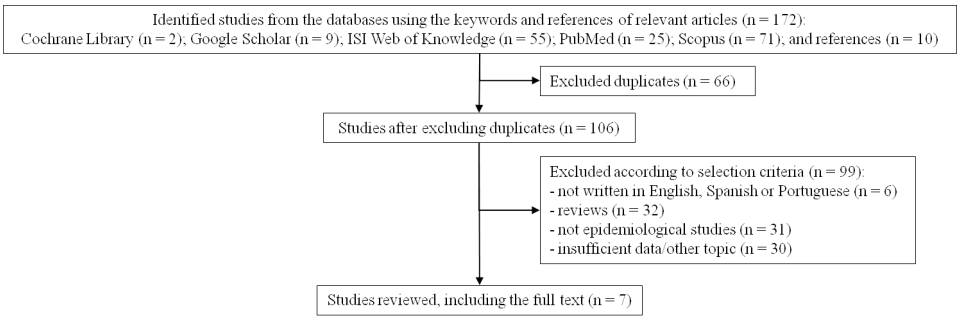

Inclusion criteria

1. Epidemiological studies
2. Reporting measures of association between selenium and bladder cancer risk
3. Measurements of selenium in any of the following biological samples: blood/serum, nails, hair, and saliva

Exclusion criteria

1. Not written in English, Spanish or Portuguese
2. Reviews
3. Not epidemiological studies
4. Insufficient data/other topic

Figure 1.

Selection process of eligible publications on selenium and bladder cancer risk.

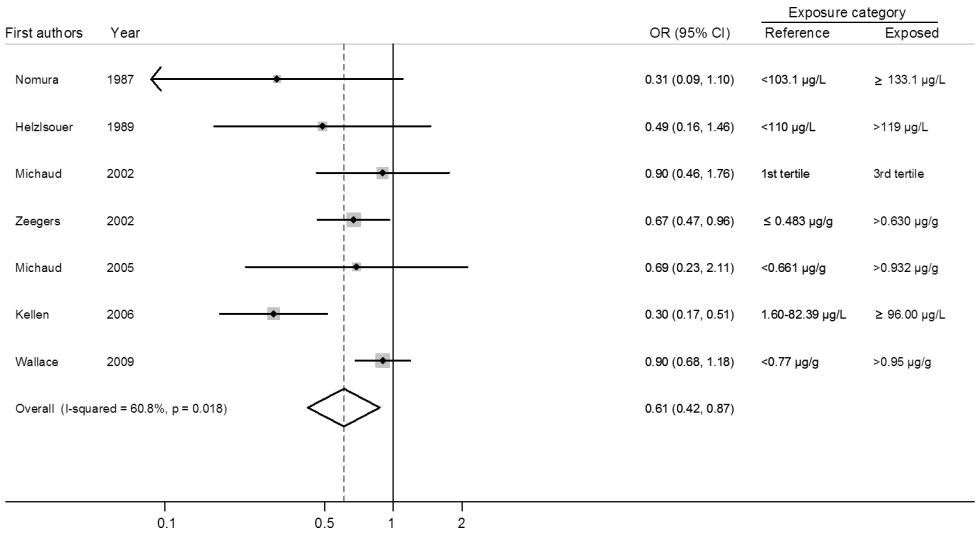

Figure 2.

Meta-analysis of the association of selenium with bladder cancer risk. Odds ratios (OR) regard to comparisons of extreme categories of exposure in each study. The area of each square is proportional to the percentage weight of each individual study in the meta-analysis. Horizontal lines represent 95% confidence intervals (95% CI). The diamond represents the meta-OR from a random-effects model.

Table 1.

Summary of results from the seven eligible studies on selenium and bladder cancer risk.

First author, year	Country	Matrix	Sex	Cases	Controls	Selenium concentration	OR	95% CI	*P*-trend	Smoker	Adjustment
Case-control											
Helzlsouer, 1989 (17)	U.S.A.	Serum	Combined sexes	14	23	<110 μg/L	1.00		0.03	Undefined	Age, sex, race, blood collection, previous meal
				14	23	110–119 μg/L	0.51	0.15–1.75			
				7	24	>119 μg/L	0.49	0.16–1.49			
Kellen, 2006 (18)	Belgium	Serum	Combined sexes	109	120	1.60–82.39 μg/L	1.00		<0.001	Undefined	Age, sex, smoking, occupation, PAHs or AA
				41	120	82.40–95.99 μg/L	0.48	0.29–0.79			
				28	122	≥96.00 μg/L	0.30	0.17–0.51			
Wallace, 2009 (22)	U.S.A.	Toenails	Combined sexes	245	280	<0.77 μg/g	1.00		0.15	Undefined	Age, sex, smoking
				217	275	0.77–0.86 μg/g	1.04	0.79–1.35			
				138	276	0.87–0.95 μg/g	0.73	0.55–0.98			
				167	277	>0.95 μg/g	0.90	0.68–1.19			
			Men	n.a.	n.a.	<0.77 μg/g	1.00		0.35	Undefined	Age, smoking
				n.a.	n.a.	0.77–0.86 μg/g	1.27	0.93–1.71			
				n.a.	n.a.	0.87–0.95 μg/g	0.83	0.59–1.16			
				n.a.	n.a.	>0.95 μg/g	0.97	0.70–1.36			
			Women	n.a.	n.a.	<0.77 μg/g	1.00		0.11	Undefined	Age, smoking
				n.a.	n.a.	0.77–0.86 μg/g	0.53	0.30–0.93			
				n.a.	n.a.	0.87–0.95 μg/g	0.50	0.29–0.84			
				n.a.	n.a.	>0.95 μg/g	0.66	0.40–1.10			
			Combined sexes	n.a.	n.a.	<0.77 μg/g	1.00		0.12	Never	Age, sex
				n.a.	n.a.	0.77–0.86 μg/g	1.05	0.59–1.88			
				n.a.	n.a.	0.87–0.95 μg/g	0.53	0.29–1.00			
				n.a.	n.a.	>0.95 μg/g	0.78	0.44–1.37			
				n.a.	n.a.	<0.77 μg/g	1.00		0.004	Moderate	Age, sex
				n.a.	n.a.	0.77–0.86 μg/g	0.85	0.56–1.31			
				n.a.	n.a.	0.87–0.95 μg/g	0.45	0.28–0.72			

First author, year	Country	Matrix	Sex	Cases	Controls	Selenium concentration	OR	95% CI	*P*-trend	Smoker	Adjustment
				n.a.	n.a.	>0.95 μg/g	0.61	0.39–0.96			
				n.a.	n.a.	<0.77 μg/g	1.00		0.009	Heavy	Age, sex
				n.a.	n.a.	0.77–0.86 μg/g	1.09	0.73–1.64			
				n.a.	n.a.	0.87–0.95 μg/g	1.30	0.83–2.01			
				n.a.	n.a.	>0.95 μg/g	1.44	0.91–2.27			
Nested case-control											
Nomura, 1987 (16)	U.S.A.	Serum	Men	6	26	<103.1 μg/L	1.00		0.12	Undefined	Age, smoking
				6	50	103.1–112.0 μg/L	0.53	0.15–1.81			
				5	76	112.1–123.0 μg/L	0.91	0.26–3.24			
				7	59	123.1–133.0 μg/L	0.53	0.16–1.73			
				5	82	≥133.1 μg/L	0.31	0.09–1.10			
Michaud, 2002 (20)	Finland	Toenails	Men	44	43	1st tertile	1.00		0.79	Ever	Age, nail collection, intervention group
				47	43	2nd tertile	0.88	0.47–1.68			
				42	47	3rd tertile	0.90	0.45–1.78			
Michaud, 2005 (19)	U.S.A.	Toenails	Men	52	55	0.660 μg/g	1.00		0.61	Undefined	Age, sex, smoking, nail collection
				54	57	0.765 μg/g	1.09	0.59–2.01			
				53	55	0.863 μg/g	1.09	0.59–2.00			
				62	56	0.990 μg/g	1.17	0.66–2.07			
			Women	37	28	0.626 μg/g	1.00		0.02	Undefined	Age, sex, smoking, nail collection
				35	31	0.716 μg/g	0.73	0.35–1.55			
				23	29	0.800 μg/g	0.49	0.21–1.16			
				21	29	0.933 μg/g	0.36	0.14–0.91			
Case-cohort											
Zeegers, 2002 (21)	The Netherlands	Toenails	Combined sexes	114	2986	≤0.483 μg/g	1.00		<0.01	Undefined	Age, sex, smoking
				116	3022	0.483–0.530 μg/g	1.09	0.80–1.48			
				78	3031	0.531–0.573 μg/g	0.55	0.38–0.79			
				62	2993	0.574–0.630 μg/g	0.63	0.43–0.91			
				61	3001	>0.630 μg/g	0.67	0.46–0.97			
				n.a.	n.a.	≤0.483 μg/g	1.00		0.62	Never	Age, sex, smoking

First author, year	Country	Matrix	Sex	Cases	Controls	Selenium concentration	OR	95% CI	*P*-trend	Smoker	Adjustment
				n.a.	n.a.	0.483–0.530 μg/g	2.69	1.02–7.09			
				n.a.	n.a.	0.531–0.573 μg/g	1.37	0.50–3.79			
				n.a.	n.a.	0.574–0.630 μg/g	1.09	0.38–3.14			
				n.a.	n.a.	>0.630 μg/g	1.36	0.50–3.69			
				n.a.	n.a.	≤0.483 μg/g	1.00		<0.01	Former	Age, sex, smoking
				n.a.	n.a.	0.483–0.530 μg/g	0.74	0.46–1.19			
				n.a.	n.a.	0.531–0.573 μg/g	0.48	0.28–0.81			
				n.a.	n.a.	0.574–0.630 μg/g	0.49	0.29–0.83			
				n.a.	n.a.	>0.630 μg/g	0.44	0.26–0.75			
				n.a.	n.a.	≤0.483 μg/g	1.00		0.25	Current	Age, sex, smoking
				n.a.	n.a.	0.483–0.530 μg/g	1.36	0.86–2.14			
				n.a.	n.a.	0.531–0.573 μg/g	0.45	0.24–0.86			
				n.a.	n.a.	0.574–0.630 μg/g	0.76	0.39–1.47			
				n.a.	n.a.	>0.630 μg/g	1.13	0.56–2.27			

n.a. = not available

Table 2.

Stratified summary odds ratios (ORs) and corresponding 95% confidence intervals (95% CI) for the association between selenium concentrations and bladder cancer risk (random effects model).

	OR (95% CI)		I^2 (p-value)	Publication bias[b] (p-value)
	Reference	Exposed[a]		
Sex[c]				
Men (n = 4)	1	0.95 (0.69–1.27)	16.2% (0.311)	−1.56 (0.314)
Women (n = 2)	1	0.55 (0.32–0.95)	23.7% (0.252)	---
Sample specimen				
Toenails (n = 4)	1	0.81 (0.66–1.00)	0.0% (0.617)	−0.38 (0.751)
Serum (n = 3)	1	0.33 (0.21–0.51)	0.0% (0.728)	0.77 (0.576)
Smoking status[d]				
Never (n = 2)	1	0.89 (0.55–1.44)	0.0% (0.333)	---
Ever (n = 3)	1	0.85 (0.54–1.34)	0.0% (0.861)	−1.84 (0.507)
Study design				
Case-control (n = 3)	1	0.53 (0.23–1.20)	84.8% (0.001)	−3.07 (0.518)
Nested case-control (n = 3)	1	0.70 (0.40–1.21)	6.2% (0.344)	−2.62 (0.323)
Case-cohort (n = 1)	1	0.67 (0.47–0.96)	---	---

n, number of studies considered.

I^2, degree of heterogeneity.

[a] top category of exposure to selenium presented in each study, according to each stratum of sex, matrix, smoking status, and study design.

[b] coefficient from Egger's test for publication bias.

[c] Studies with specific data for men: Nomura et al. 1987 (16), Michaud et al. 2002 (20), Michaud et al. 2005 (19), Wallace et al. 2009 (22); studies with specific data for women: Michaud et al. 2005 (19), Wallace et al. 2009 (22).

[d] Studies with specific data for never smokers: Zeegers et al. 2002 (21), Wallace et al. 2009 (22); studies with specific data for ever smokers: Michaud et al. 2002 (19), Zeegers et al. 2002 (21), Wallace et al. 2009 (22).