Selenium and Lung Cancer: A Quantitative Analysis of Heterogeneity in the Current Epidemiological Literature

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Abstract

While numerous laboratory investigations have shown that selenium may have anticarcinogenic activity, the epidemiological data have been inconsistent. In this report, meta-analysis was used to quantitatively summarize the existing epidemiological evidence on selenium and lung cancer and identify sources of heterogeneity among studies. When all studies were combined, the summary relative risk (RR) for subjects with higher selenium exposures was 0.74 [95% confidence interval (CI) 0.57–0.97]. In subgroup analyses based on the average selenium level in the study population, the summary RR for areas where selenium levels were low was 0.72 (95% CI 0.45–1.16), while the RR for areas where selenium levels were higher was 0.86 (95% CI 0.61–1.22). In both studies in high selenium areas where RRs were markedly below 1.0, protective effects were only found when subjects in the lowest category of selenium exposure were used as referents. No clear protective effects were seen when highly exposed subjects were compared with those in the middle exposure categories. The summary RR was lower in studies assessing selenium exposure using toenails (RR 0.46, 95% CI 0.24–0.87) than in studies using serum selenium (RR 0.80, 95% CI 0.58–1.10) or studies assessing dietary intake (RR 1.00, 95% CI 0.77–1.30). Overall, these results suggest that selenium may have some protective effect against lung cancer in populations where average selenium levels are low. The evidence for these findings is greater in studies of toenail selenium than in studies involving other measures of exposure. (Cancer Epidemiol Biomarkers Prev 2004;13(5):771–8)

Introduction

Lung cancer is the most common cause of cancer death in the world (1), and an estimated 1.04 million new cases occur worldwide each year (2). Smoking is clearly the most common cause of this disease, but factors such as occupational exposures, household radon, and certain dietary constituents may also have important impacts on lung cancer risks (3). Selenium is a naturally occurring element in the environment and is an essential trace element in humans (4). Laboratory studies in animals have shown that selenium may help protect against the development of cancer (5). Some human ecological studies have also reported associations between low selenium intake and increased cancer mortality (6–8), and possible protective effects of selenium have been reported in studies of prostate cancer and Barrett's esophagus (9, 10).

Received 10/28/03; revised 12/30/03; accepted 1/8/04.

Grant support: National Institute of Environmental Health Sciences grants R01 ES011317 and K23 ES11133, California Cancer Research Program grant 99-00563V-10262, and University of California Center for Occupational and Environmental Health.

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Several case-control and cohort studies have reported reduced risks of lung cancer in people in the higher categories of selenium intake, although other studies have failed to confirm this association (11–18). For example, in a cohort study in the Netherlands, a relative risk (RR) of 0.50 [95% confidence interval (CI) 0.30–0.81] was reported for subjects in the highest quintile for toenail selenium (18). However, in a nested case-control (NCC) study in the United States, no association was found between serum selenium levels and lung cancer risks (RR 1.2, 95% CI 0.77–1.88; Ref. 19). In a large randomized trial of selenium supplements, an adjusted hazard ratio (HR) of 0.56 (95% CI 0.31–1.01) was initially reported after ~5 years of follow-up (20). However, in a subsequent report that included 3 additional years of follow-up, the adjusted HR increased to 0.74 (95% CI 0.44–1.24; Ref. 21).

Overall, the human epidemiological data on selenium exposure and lung cancer have been mixed. The reason for these inconsistencies could be related to differences in exposure assessment, control selection, follow-up period, study populations, or other differences in study design. The goal of this report is to use meta-analysis to summarize the existing epidemiological literature on selenium and lung cancer and to quantitatively evaluate sources of heterogeneity across studies. Identifying important sources of heterogeneity could help guide researchers in planning future studies and could provide

further insight into the possible mechanisms by which selenium may impact lung cancer risks. To our knowledge, this is the first meta-analysis to evaluate the role of selenium on human cancer risks.

Materials and Methods

Databases such as MEDLINE, CancerLit database, Cochrane Database of Systematic Reviews, Current Contents, and BIOSIS were searched for all epidemiological studies on selenium and lung cancer. The bibliographies of relevant articles and pertinent review articles were also searched. Meta-analyses were performed using case-control and cohort studies assessing selenium exposure by either dietary intake, serum, or toenail selenium levels. Ecological studies comparing selenium levels and cancer rates in large population areas were not included due to the wide ranges in selenium levels that can occur within a single population area. Cross-sectional studies were also excluded because of questions regarding the temporal relationship between exposure and disease in these studies (22).

Most studies we identified presented results as RRs. However, some studies presented results only as the difference in mean selenium levels between lung cancer cases and controls. Separate meta-analyses were performed for each outcome type. RR estimates and 95% CI or mean selenium levels and SE in cases and controls were abstracted from each article. In some studies, RRs were presented for several levels of selenium exposure. For these studies, the RR comparing the highest level to the lowest level was selected. In two of the three studies assessing dietary intake, data on vitamin supplement use were collected although neither article describes whether these data were used in categorizing subjects (23, 24). The other dietary intake study does not mention whether supplement data were collected (25). For all studies used in this meta-analysis, RR estimates were either adjusted for smoking or involved study designs that matched on smoking status. In one instance, RRs from the same cohort were presented for both dietary selenium intake and serum selenium (26, 27). In our meta-analysis, the results from this cohort for serum selenium were used in the analysis where we combined all studies and in the subgroup analysis where we combined only serum studies. The results from this cohort on dietary selenium intake were used in the subgroup analysis of studies involving dietary intake history.

To explore heterogeneity among studies, we performed subgroup analyses based on the type of selenium measurement (serum, toenail, or dietary intake), length of follow-up (greater or less than 10 years), average level of selenium in the study population, and several other factors. For studies assessing dietary intake, populations with low selenium levels were defined as those where the average dietary selenium intake in the controls was less than the U.S. Recommended Daily Amount of 55 μg/day (4). For studies assessing serum selenium, populations with low selenium levels were defined as those where the average serum selenium levels in the controls was <100 ng/ml. A value of 100 ng/ml was used because it was the approximate midpoint among the six serum studies used in this report. Separating studies at this level resulted in three serum studies in the high baseline selenium group and three studies in the low baseline selenium group. Too few studies were available to perform a similar analysis for toenail selenium.

One study reported an unusually narrow CI given the number of cases and controls reported by the authors. Zhou *et al.* (25) reported a smoking-adjusted odds ratio of 0.76, with 95% CI of 0.71–0.82 for subjects in the highest quartile of selenium intake compared with those in the lowest quartile. While the study involved a total of 290 cases, this particular odds ratio was based on 95 cases and 72 controls in the lowest tertile and 70 cases and 72 controls in the upper tertile. These data correspond to an unadjusted odds ratio and CI of 0.74 (95% CI 0.47–1.15). This CI is ~6 times wider than the reported CI. Using simple 2 × 2 table simulations, we estimated that roughly 30 times more subjects than were in the study would be needed to obtain the reported CI width of 0.11. We therefore used the recalculated CI in our meta-analysis.

The Nutritional Prevention of Cancer (NPC) trial is a randomized placebo-controlled trial of selenium supplementation and several health outcomes, including lung cancer (20, 21, 28, 29). This study design differs markedly from the designs of the other studies used in our meta-analysis. For this reason, we have performed separate analyses with and without the NPC study.

Summary RR estimates were calculated using both the fixed effects inverse variance weighting method (30) and the random effects method described by DerSimonian and Laird (31). Heterogeneity among studies was assessed using the general variance-based method as described by Petitti (32). If heterogeneity was present, CIs in the fixed effects model were adjusted to account for between-study variance using the method presented by Shore *et al.* (33). Publication bias was assessed by plotting the logarithm of the RR for each study by its SE (34). Publication bias was also assessed using the Egger *et al.* (35) and Begg *et al.* (36) tests.

In the meta-analysis of mean differences in selenium levels between controls and cases, summary results for serum and toenail selenium are reported separately. Selenium levels from each study were converted into ng/ml for serum selenium and mg/g for toenail selenium. For each study, the mean level in cases was subtracted from the mean level in controls, and this difference was weighed by the pooled SE for that study. Summary mean differences and 95% CIs were calculated using the method described by Petitti (32).

Results

A total of 16 studies meeting the inclusion criteria were identified. Five presented data only as RRs (12, 21, 23, 24, 37), three presented data only as mean differences (15, 16, 38), and eight studies presented both (11, 13, 18, 19, 25, 26, 39, 40). Descriptions of each study are provided in Tables 1 and 2. Studies that could not be included in the meta-analysis are described in Table 3.

The results of the meta-analysis are shown in Table 4. Overall, the pooled RR estimate for all studies is 0.74 (95% CI 0.57–0.97). No single study received more than 14% of the total weight applied in this analysis. The χ^2

Table 1. Characteristics of the studies on selenium and lung cancer included in the pooled analysis of RRs

Author	Study design	Assessment method	Gender	Location	Years of follow-up	No. of cases	RR (95% CI)	*P* for dose-response trend	%W
Comstock *et al.* (11)	NCC	Serum	All	Maryland	15–18	258	0.65 (0.41–1.02)	0.08	12.8
Goodman *et al.* (19)	NCC	Serum	All	Multicenter, United States	5–14	356	1.20 (0.77–1.88)	0.49	13.3
Kabuto *et al.* (12)	NCC	Serum	All	Japan	11–13	77	0.56 (0.20–1.43)	NA	2.7
Knekt *et al.* (26)	NCC	Serum	Male	Finland	8–12	153	0.66 (0.37–1.19)	0.001	7.8
Knekt *et al.* (13)	NCC	Serum	All	Finland	16–19	77	0.41 (0.17–0.94)	0.46	3.6
Ratnasinghe *et al.* (37)	NCC	Serum	Male	China	4–5	108	1.20 (0.60–2.40)	0.52	5.5
Reid *et al.* (21)	Randomized clinical trial	Plasma	All	Eastern United States	5–13	60	0.74 (0.44–1.24)	NA	9.9
Garland *et al.* (39)*	NCC	Toenail	Female	Multicenter, United States	3.5	47	4.33 (0.54–34.60)	0.17	0.6
Hartman *et al.* (40)†	NCC	Toenail	Male	Finland	5–8	NA	0.20 (0.09–0.44)	NA	4.2
Hartman *et al.* (40)†	NCC	Toenail	Male	Finland	5–8	NA	0.61 (0.27–1.41)	NA	3.9
van den Brandt *et al.* (18)	Cohort	Toenail	All	Netherlands	3.3	317	0.50 (0.30–0.81)	0.006	10.8
Hu *et al.* (23)	Case-control	Diet/FFQ	All	China	–	227	1.30 (0.70–2.20)	0.48	8.1
Kromhout (24)	Cohort	Diet/FFQ	Male	Netherlands	25	63	0.98 (0.41–2.36)	>0.01	3.5
Zhou *et al.* (25)‡	Case-control	Diet/FFQ	Female	China	–	290	0.76 (0.47–1.15)	0.11	13.3

Note: NA, not available; %W, percentage of the total weight applied to the study in the fixed effects model.
*Based on conditional logistic regression with 47 matched pairs. The unadjusted RR reported by the authors was 0.46 (95% CI 0.15–1.44; Ref. 39).
†Results presented separately by randomization period.
‡CI calculated from data given in the publication.

test statistic shows evidence of substantial heterogeneity in the study results (χ^2 = 28.9, P < 0.01). Using the random effects model, the pooled RR estimate was 0.72 (95% CI 0.54– 0.96). Addition of the NPC trial had little impact on the overall summary RR (0.74, 95% CI 0.58–0.94) or the heterogeneity statistic (χ^2 = 28.9, P < 0.01).

Few differences were seen in subgroup analyses based on study design, gender, smoking status, and follow-up time. However, in the subgroup analyses based on assessment method, the summary RR was lower for the three studies of toenail selenium (RR 0.46, 95% CI 0.24–0.87) than for the six studies of serum selenium (RR 0.80, 95% CI 0.58–1.10) or the four studies of dietary selenium (RR 1.00, 95% CI 0.77–1.30). In addition, the RR estimate for studies in populations with low average selenium levels (RR 0.72, 95% CI 0.45–1.16) is below the estimate for studies involving populations with higher average selenium levels (RR 0.86, 95% CI 0.61–1.22). Using the random effects model, the RR estimate for studies in populations with lower selenium levels was 0.66 (95% CI 0.41–1.08), while the RR estimate for studies in populations with higher average selenium levels was 0.85 (95% CI 0.59–1.24).

The addition of NPC data had little impact on the subgroup analyses of assessment method, smoking status, or follow-up time. When results from the NPC trial were added to the analysis of average population selenium levels based on the subjects prestudy baseline selenium status, the summary RR for populations with low average selenium levels was 0.69 (95% CI 0.45–1.07), while the summary RR for populations with higher average selenium levels was 0.89 (95% CI 0.67–1.19).

The summary estimates of mean differences between selenium levels in cases and controls are also shown in Table 4. The pooled estimate of mean toenail selenium was slightly higher in controls than in cases (mean difference 0.02 μg/g, 95% CI 0.01–0.04 μg/g). In the subgroup analysis including only those studies assessing serum selenium, levels were also slightly higher in controls (mean difference 1.02 ng/ml, 95% CI −0.47 to 2.51 ng/ml), although the CI included the null value. For the five serum studies in populations with low selenium levels, the summary mean difference was 3.90 ng/ml (95% CI 1.84–5.96 ng/ml). In contrast, the summary mean difference for serum studies in populations with high selenium levels was −1.69 ng/ml (95% CI −3.84 to 0.46 ng/ml).

Five of the study results used in the analysis of mean differences in serum levels were also used in the analyses combining RRs. When these studies were excluded, the summary mean difference in the remaining three studies was 1.31 ng/ml (95% CI −1.92 to 4.54 ng/ml; Refs. 15, 16, 38). Two of these three studies were in low selenium populations (summary mean difference 3.63 ng/ml, 95% CI −0.32 to 7.59 ng/ml) and one was in a high selenium population (mean difference −0.5 ng/ml; P > 0.50).

Five studies reported both smoking-adjusted RRs and either nonadjusted RRs or crude data that could be used to calculate them (12, 13, 23, 25, 39). As shown in Table 4, little difference was seen in the summary RR estimates of crude and adjusted data.

Table 3 presents the six studies not included in the meta-analysis. Five of the six studies reported either RRs below 1.0 or lower mean selenium levels in cases than in controls, although only one of these is statistically significant. In the study by Peleg *et al.* (41) that included only 16 lung cancer cases, the mean serum selenium levels were about the same in cases and controls (118 *versus* 115 ng/ml, respectively; P not given).

Figure 1 presents the publication bias funnel plot for the individual studies that presented data as RRs. No clear asymmetry indicative of publication bias is seen. In the Egger *et al.* test, the coefficient for bias was −0.23 (P = 0.87). In the Begg *et al.* test, no correlation was found between SE and the logarithm of the odds ratio (P = 0.66).

Table 2. Characteristics of the studies on selenium and lung cancer included in the pooled analysis of mean differences

Author	Study design	Assessment method	Gender	Location
Goodman *et al.* (19)	NCC	Serum	All	Multicenter, United States
Knekt *et al.* (26)	NCC	Serum	Male	Finland
Knekt *et al.* (26)	NCC	Serum	Female	Finland
Knekt *et al.* (13)	NCC	Serum	All	Finland
Menkes *et al.* (14)	NCC	Serum	All	Maryland
Nomura *et al.* (15)	NCC	Serum	Male	Hawaii
Salonen *et al.* (16)	NCC	Serum	All	Finland
Virtamo *et al.* (38)	Cohort	Serum	Male	Finland
Garland *et al.* (39)	NCC	Toenail	Female	Multicenter, United States
Hartman *et al.* (40)	NCC	Toenail	Male	Finland
van den Brandt *et al.* (18)	Cohort	Toenail	Male	Netherlands
van den Brandt *et al.* (18)	Cohort	Toenail	Female	Netherlands
Zhou *et al.* (25)	Case-control	Diet/FFQ	Female	China

*Units for toenail selenium are μg/g; units for serum selenium are ng/ml; and units for diet/FFQ are μg/day.
†Mean difference calculated as the mean selenium level in controls minus the mean selenium levels in cases.
‡P of the mean difference. If P not presented in the article, it was estimated using an unpaired t test (two-sided).

Discussion

The findings of this study suggest that selenium may have some protective effect against lung cancer. In both the analysis of mean differences and the analysis of RRs, protective effects appear to be greater in areas where average selenium levels are low than in areas where average levels are higher. This may indicate that a threshold exists for the effects of selenium, such that only those subjects in the lower categories of selenium exposure will benefit from increased selenium intake.

Although the differences we identified between studies in high and low selenium areas could be due to chance, there are several pieces of evidence to suggest that the protective effects of selenium are truly greater in populations where average selenium levels are low. First, in the NPC trial, significant protective effects from selenium supplementation on lung cancer incidence were found only in those subjects who started the study in the lowest tertile of baseline plasma selenium (HR 0.42, 95% CI 0.18–0.96; $P = 0.04$). This HR is based on an analysis comparing selenium supplementation with placebo in all study subjects who began the study in the lowest tertile of selenium exposure. Similar effects were not identified in subjects who began the study in the middle (HR 0.91, 95% CI 0.33–2.52; $P = 0.86$) or higher (HR 1.25, 95% CI 0.49–3.21; $P = 0.64$; Ref. 21) tertiles of baseline selenium levels. The importance of baseline selenium status was also seen in the analysis of NPC data on prostate cancer (9). In the NPC study, the prostate cancer HR for subjects receiving selenium supplements compared with placebo was 0.14 (95% CI 0.03–0.61) for subjects in the lowest tertile of preintervention baseline serum selenium and 1.14 (95% CI 0.51–2.59) for subjects in the highest tertile.

Second, in both of the studies in high selenium areas where RRs were substantially below 1.0, the protective effects that are identified do not increase above a certain level of exposure. In the Comstock *et al.* study (11), the odds ratios for the five quintiles of serum selenium (lowest to highest) were 1.00 (referent), 0.68, 0.53, 0.76, and 0.65. In the Kabuto *et al.* study (12), the odds ratios in each quartile (lowest to highest) were 1.0 (referent), 0.33, 0.55, and 0.55. Thus, in both studies, protective effects appeared in the second to the lowest selenium category, and there was little change with increasing selenium levels beyond that. This leveling off suggests that above a certain level of selenium exposure, increasing selenium intake has little effect at decreasing lung cancer risk.

In our analysis, protective effects were observed in studies assessing toenail selenium. Protective associations were identified when both RRs and mean differences were analyzed, and the 95% CI excluded the null value in both analyses. It should be noted that the actual mean difference between controls and cases is small, and the biological significance of this difference is unknown. In addition, data from only three individual studies were used in these calculations. In two of these studies, both the RR estimate and the mean difference were consistent with protective effects (18, 40). In the other study, controls had higher selenium levels than cases (mean difference 0.09 μg/g; $P = 0.03$), but the smoking-adjusted RR for those in the highest tertile of toenail selenium was 4.33 (95% CI 0.54–34.60; Ref. 39). Interestingly, the reported unadjusted RR for these same subjects was only 0.46 (95% CI 0.15–1.44). The unusually large change in both the RR and the width of the CI following adjustment raises questions about the validity of the adjusted estimate. Imprecision could have been caused by the use of conditional logistic regression and the small number of matched pairs (47 matched pairs). However, similar changes in precision were not seen following adjustment for the other cancer types studied in this investigation. In addition, large changes in RR or precision were not seen when adjusted and unadjusted results from other studies are compared. In our meta-analysis, summary RR estimates and CIs differed only slightly when smoking-adjusted and crude data were analyzed separately (Table 4). Using the unadjusted instead of the adjusted result for the Garland *et al.* study

Table 2. Characteristics of the studies on selenium and lung cancer included in the pooled analysis of mean differences (Cont'd)

Years of follow-up	No. of cases/controls	Mean (SD) selenium*		Mean difference†	P‡
		Controls	Cases		
5–14	356/356	117.7 (18.5)	119.1 (19.6)	−1.4	0.33
8–12	189/378	61.0 (13.5)	57.0 (16.7)	4.0	<0.01
8–12	9/18	63.4 (13.8)	62.8 (17.9)	0.6	>0.05
16–19	91/177	57.8 (16.9)	53.2 (24.3)	4.6	0.14
9	99/196	110 (16.0)	113 (18.0)	−3	0.16
11	71/293	124.9 (19.4)	125.4 (22.1)	−0.5	>0.50
6	23/23	52.4 (11.5)	49.0 (9.6)	3.4	0.28
9	38/964	55.3 (15.5)	51.5 (16.0)	3.8	0.16
3.5	47/47	0.90 (0.31)	0.81 (0.17)	0.09	0.03
5–8	250/250	0.55 (0.13)	0.54 (0.13)	0.01	>0.05
3.3	335/1211	0.55 (0.13)	0.53 (0.21)	0.02	0.13
3.3	35/1248	0.58 (0.11)	0.54 (0.08)	0.04	0.01
–	290/290	39.80 (33.00)	36.10 (16.00)	3.70	0.08

in the meta-analysis of toenail selenium changes the summary estimate from 0.46 (95% CI 0.24–0.87) to 0.43 (95% CI 0.27–0.67) and the heterogeneity statistic from 9.25 (P = 0.03) to 4.63 (P = 0.20). Thus, the RR changes only slightly, but the consistency of findings from one study to the next is increased.

The main evidence of protective effects was found in studies involving toenail selenium and not in studies using serum selenium or food frequency questionnaires (FFQ). This could be an indication that toenail selenium is a better measure of relevant exposure than a single serum measurement or data from FFQs. Selenium measurement based on FFQs can be inaccurate because the selenium content of particular foods varies markedly with the selenium concentration in the soil where the food is produced (42–44). The RR of 1.00 we identified for studies using FFQs could be an indication that such methods cannot adequately assess dietary intake of selenium.

Both serum and toenail selenium levels have been shown to correlate well with selenium intake measured using duplicate plate food collection studies (45–47). However, there is some evidence that toenail selenium may be a more accurate reflection of true long-term average exposure. In a study of 77 subjects from South Dakota and Wyoming, between-person and within-person variances were calculated on serum and toenail selenium samples provided over a 6–12-month period (45). For both toenails and serum, between-person variance was substantially larger than within-person variance. However, relative to the mean value of each measure, within-person variance was roughly three times greater in serum samples than in toenail samples. This suggests that less short-term fluctuation occurs in toenail selenium than in serum selenium. If this is true, nondifferential misclassification of exposure and a resultant bias toward the null may be less likely in selenium studies using toenail levels than in studies using a single serum sample. Toenail selenium also appears to reflect selenium intake from the more distant past than serum selenium. In a study in which subjects were given high selenium bread for a 1-year period, serum selenium levels increased after about 2 weeks on the high selenium bread and returned to baseline about 12–24 weeks after the bread was discontinued. In contrast, toenail selenium levels did not increase until week 30 and had not returned to baseline up to 1 year after the bread was stopped (48).

The long-term reproducibility of toenail selenium levels has been assessed. In a study of 127 women in the United States, the Spearman correlation coefficient for measurements in paired samples taken 6 years apart was 0.48 (P < 0.001; Ref. 49). This finding shows that toenail selenium levels remain relatively stable in many subjects. However, it should be noted that this correlation is over a limited time period and is only moderate. Substantial misclassification can occur in subjects who change their selenium intake over time. This is especially important if the latency of effects is long and the impact of selenium exposure on cancer risks is not seen for

Table 3. Selenium and lung cancer studies excluded from the meta-analysis

Author	Study design	No. of cases	Result	Reason not used
Coates *et al.* (64)	NCC	11	RR = 0.8, P for trend = 0.73	CI not given
Criqui *et al.* (65)	NCC	21	2 ng/ml lower in cases; P > 0.1	SD not given
Peleg *et al.* (41)	NCC	16	118 ng/ml (cases); 115 ng/ml (controls)	SD not given
Ringstad *et al.* (66)	NCC	7	123.97 ng/ml (cases); 135.02 ng/ml (controls); P = 0.25	SD not given
Salonen *et al.* (17)	NCC	15	52.6 ng/ml (cases); 62.0 ng/ml (controls); P < 0.05	SD not given
Willett *et al.* (56)	NCC	18	122 ng/ml (cases); 131 ng/ml (controls); P = 0.21	SD not given

Table 4. Summary of pooled RRs for selenium and subgroup analyses

Groups	No. of results	No. of cases*	RR	95% CI	Adjusted 95% CI	Heterogeneity *P*
RRs						
Overall	13	1973	0.74	0.62–0.88	0.57–0.97	<0.01
Overall with NPC study	14	2033	0.74	0.63–0.87	0.58–0.94	<0.01
Study design†						
Cohort	4	501	0.81	0.60–1.10	0.51–1.30	0.07
NCC	9	1076	0.72	0.58–0.90	0.50–1.04	<0.01
Case-control	2	517	0.93	0.65–1.33	0.56–1.55	0.15
Gender						
Men	8	912	0.68	0.54–0.86	0.46–1.02	<0.01
Women	5	572	0.74	0.53–1.04	NA	0.41
Assessment†						
Diet history/FFQ	5	701	1.00	0.77–1.30	NA	0.47
Serum selenium	6	1029	0.80	0.63–1.03	0.58–1.10	0.13
Toenail selenium	4	364	0.46	0.32–0.66	0.24–0.87	0.03
Smoking status						
Current smokers	7	620	0.56	0.42–0.77	0.33–0.98	<0.01
Noncurrent smokers‡	5	274	0.72	0.46–1.12	NA	0.74
Former smokers	2	223	0.73	0.42–1.26	0.34–1.55	0.17
Follow-up time§						
<10 years	12	762	0.70	0.55–0.90	0.43–1.15	<0.01
≥10 years	6	596	0.79	0.60–1.03	0.57–1.09	0.21
Population selenium level‖						
High	4	754	0.86	0.65–1.15	0.61–1.22	0.22
Low	6	855	0.72	0.56–0.93	0.45–1.16	<0.01
Smoking adjustment						
Crude	5	718	0.79	0.60–1.05	0.52–1.21	0.06
Smoking adjusted	5	718	0.82	0.61–1.12	0.53–1.28	0.08
Mean differences						
Serum selenium‖	8	876	1.02 ng/ml¶	−0.47 to 2.51		0.05
High	3	526	−1.69 ng/ml¶	−3.84 to 0.46		0.75
Low	5	350	3.90 ng/ml¶	1.84–5.96		0.99
Toenail selenium	4	667	0.02 μg/g¶	0.01–0.04		0.31

Note: NA, not applicable.
*The actual numbers maybe higher because the Hartman *et al.* study did not provide case numbers.
†Total number of studies and cases is greater than the number of studies and cases in the overall analysis because one cohort study assessing diet history of selenium and one NCC study assessing serum selenium were done in the same cohort (26, 27). Only the NCC study was included in the overall analysis, but diet history and serum results were included in the appropriate subgroup analyses. In the cohort study involving diet history, results were presented separately for smokers and nonsmokers.
‡Includes never smokers and former smokers.
§Total number of studies is greater than the number of studies in the overall analysis because some studies presented data for more than one follow-up period.
‖Mean selenium levels in the controls. Classified as ''high'' if serum selenium ≥ 100 ng/ml or daily dietary selenium intake ≥ 55 μg. Classified as ''low'' if serum selenium < 100 ng/ml or daily dietary selenium intake < 55 μg.
¶Mean difference defined as mean selenium level in controls minus mean selenium level in cases.

many years. Currently, the latency of effects of selenium is unknown. In our analysis, no substantial differences were seen when studies were separated based on the length of follow-up.

Another factor that can impact studies of lung cancer and selenium is confounding. Several dietary factors, such as vitamin C, β-carotene, and vegetable consumption, have been associated with lung cancer risks and could be associated with selenium intake (50). These factors would not be expected to cause substantial confounding in selenium studies because the magnitude of the association between these variables and cancer is generally small and the correlation between these dietary variables and selenium intake is weak (11, 15). For example, in the study by Comstock *et al.* (11), correlation coefficients of serum selenium with serum β-carotene and vitamin C were 0.01 and 0.09, respectively. Vegetable intake would not be expected to cause substantial confounding, and selenium levels in vegetables can vary considerably depending on the selenium level of the soil where the vegetables were grown (51–54). Several

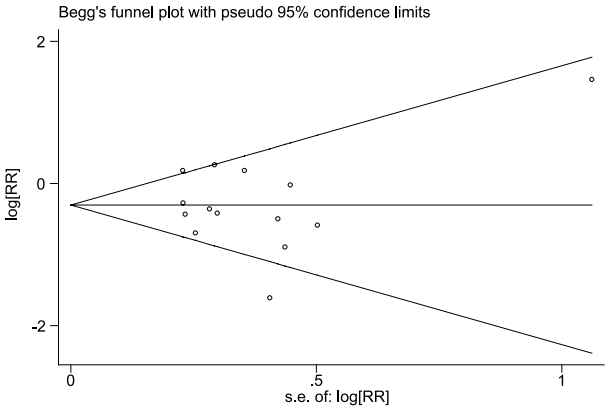

Figure 1. Logarithm of the RR *versus* SE for each individual study included in the meta-analysis of RRs.

factors also argue against smoking as an important confounding variable. First, all of the studies used in the meta-analyses either matched on smoking status or adjusted for smoking in the statistical analysis. Second, although smoking is highly correlated with lung cancer risk, its association with selenium is less clear. Several studies have reported finding higher selenium levels in nonsmokers compared with smokers, but these effects have been small and have not been found in all studies (11, 12, 16, 18, 19, 27, 37, 39, 44, 55–57). Despite these factors, residual confounding from incomplete or inaccurate assessment of smoking is still possible. Previous analyses on studies of fruit, vegetables, and β-carotene have shown that residual confounding from incomplete smoking assessment could have important effects in lung cancer studies (58–60). However, these analyses also suggest that a strong correlation between smoking and the dietary variable being studied is needed for substantial bias to occur. Correlation coefficients for smoking and selenium levels between −0.10 and −0.30 have been reported (44, 61). These are not of sufficient magnitude to result in the odds ratios we identified for studies in low selenium populations or studies involving toenail selenium (59). In addition, in our comparison of crude and smoking-adjusted data (Table 4), the summary RR estimate changed only slightly with smoking adjustment. While this may not completely rule out any impact of residual confounding, it appears very unlikely that a more refined analysis of smoking would completely eliminate the protective effects identified in this analysis.

Publication bias can also bias the results of meta-analyses. This is the tendency of editors or authors to publish articles containing positive results (32). The prevailing theory on selenium is that it has anticarcinogenic potential and may prevent cancer (62). This raises the concern that studies showing protective effects might be more likely to be published than null findings or results consistent with causal associations. One method of assessing publication bias is the funnel plot. This is a graphical presentation of effect size *versus* an estimate of precision, such as the logarithm of the SE (34). In the absence of publication bias, studies should be symmetrically distributed around the summary estimate of effect size. This plot should appear in a funnel shape because the scattering of effect sizes should decrease as the precision of the studies increases. If there is bias against publication of smaller studies with null or unexpected results, the funnel shape will be distorted. In our analysis, no obvious asymmetry was identified in the funnel plot. In the Egger *et al.* test, asymmetry in the funnel plot can be formally tested by performing a simple linear regression of the effect size divided by its SE on the inverse of the SE (35). In the Begg *et al.* test, Kendall's rank order test is used to assess the correlation between the studies' effect sizes and their SE (36). In our analysis, no evidence of publication bias was seen in the Egger *et al.* ($P = 0.87$) or Begg *et al.* ($P = 0.66$) tests. However, it should be noted that several factors other than publication bias can affect the outcome of these tests and their validity and interpretation has been debated (63).

Importantly, most of the individual study results included in this analysis were not statistically significant. For example, in the overall meta-analysis involving RRs, only 3 of 14 individual results (21%) had CIs that excluded 1.0. This small proportion suggests that any bias resulting from a tendency to publish significant results did not play a major role in this meta-analysis. This finding, combined with the results of the funnel plot, as well as the Egger *et al.* and Begg *et al.* tests, provides some evidence that publication bias did not have a substantial impact on the results presented here. However, our findings regarding publication bias are somewhat imprecise and may been caused by other factors (63). For this reason, the presence of publication bias cannot be completely ruled out.

As a possible chemoprevention agent, the effect of selenium has been widely studied. Overall, the epidemiological data on selenium and lung cancer are mixed. We found evidence that selenium could have protective effects; however, based on this analysis and other evidence, these effects apparently occur primarily in populations where overall selenium levels are low. The results of this review also suggest that toenail selenium may be a better indicator of relevant selenium exposure than assessments based on a single serum selenium measurement or dietary intake. Potential bias from factors such as publication bias or confounding due to smoking or diet appear unlikely but cannot be completely ruled out. Despite the abundant laboratory and animal data on the anticarcinogenic effects of selenium, the exact role of selenium in cancer development in humans is still unclear. The results of this analysis, however, suggest that future studies may benefit by focusing on populations with generally low selenium levels and incorporating study designs that include toenail selenium or other more accurate measures of long-term selenium exposure.

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