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Selenium and prostate cancer: systematic review and meta-analysis

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ABSTRACT

Background: Prostate cancer is a growing public health problem. Several human studies have shown a potentially protective effect of selenium, but the conclusions from published reports are inconsistent.

Objective: The objective was to examine the evidence for relations between selenium intake, selenium status, and prostate cancer risk.

Design: This was a systematic review and meta-analysis of randomized controlled trials, case-control studies, and prospective cohort studies. The World Cancer Research Fund/American Institute for Cancer Research Continuous Update Project database was searched up to September 2010. The studies included reported measurements of selenium intake or status (plasma, serum, or toenail selenium), assessments of prostate cancer cases

(number of events), and the RR in the adult population. Meta-analyses were performed, and study quality, heterogeneity, and small study effects were assessed. Dose-response meta-analyses were used, with restricted cubic splines and fractional polynomials for nonlinear trends, to investigate the association between selenium status and prostate cancer risk.

Results: Twelve studies with a total of 13,254 participants and 5007 cases of prostate cancer were included. The relation between plasma/serum selenium and prostate cancer in a nonlinear dose-response meta-analysis showed that the risk decreased with increasing plasma/serum selenium up to 170 ng/mL. Three high-quality studies included in the meta-analysis of toenail selenium and cancer risk indicated a reduction in prostate cancer risk (estimated RR: 0.29; 95% CI: 0.14, 0.61) with a toenail selenium concentration between 0.85 and 0.94 μg/g.

Conclusion: The relation between selenium status and decreased prostate cancer risk was examined over a relatively narrow range of selenium status; further studies in low-selenium populations are required.

Introduction

Prostate cancer is the most common cancer in men in the United Kingdom, Europe, and United States with >400,000 incident cases in Europe, 40,000 in the United Kingdom, and >200,000 in the United States in 2008 (1). More than one million new cases of prostate cancer are predicted worldwide for 2015 and with almost 100,000 predicted prostate cancer deaths in Europe alone (1), this is a growing public health problem. Several human studies have shown a potentially protective effect of selenium associated with prostate cancer risk reduction, particularly in relation to advanced or aggressive prostate cancer (2, 3). The systematic review and meta-analysis in the 2007 World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR)5 report (4) indicated a 10% decrease in the risk of advanced/aggressive prostate cancer for every 10-ng/mL increase in plasma/serum selenium (4). Other systematic reviews and meta-analyses have reported an inverse relation between selenium status and prostate cancer risk (5–7), but the dose response or beneficial range of intake or status associated with the risk reduction has not been established. Because low selenium status is estimated to be widespread in the United Kingdom and Europe (8–12), defining an optimal selenium intake or status range that may be associated with a reduction in risk of prostate cancer is important. A recent high-quality systematic review of selenium and several cancers suggested a reduced odds of prostate cancer for those with higher selenium status compared with those with lower selenium status (OR: 0.78; 95% CI: 0.66, 0.92) without notable heterogeneity (7), but higher supplemental intakes of selenium may not reduce prostate cancer risk (13, 14). Indeed, the US Selenium and Vitamin E Cancer Prevention Trial (SELECT) showed that a long term supranutritional supplemental dose of selenomethionine (200 μg/d) in a selenium-replete population did not significantly reduce the risk of developing prostate cancer (13).

The analysis used in the Cochrane review and previous reviews (4–7, 15, 16) assumed a linear dose-response relation, such that the slope of the change in risk with change in selenium status would be constant for any baseline selenium status. In biological systems we often see curvilinear relations, eg, a saturation curve (where at low baseline selenium status additional selenium would reduce risk, but as baseline selenium status increases a similar rise in selenium status would have no further effect on cancer risk). A further possibility is that as selenium status increases above a certain level, more selenium may increase the risk of prostate cancer relative to an optimum level, ie, a U-shaped relation as noted for plasma selenium and cancer mortality (17), alcohol and diabetes (18), and folate and pancreatic cancer (19). It is important to determine the shape of the dose-response curve because inconsistencies in the results between studies may relate to different exposure levels. It is possible that only those individuals with a low baseline selenium intake or status may benefit from higher selenium intake, and the implications for men with moderate or high selenium status or populations where selenium supplementation is common (20, 21) may be different. However, none of the previous reviews have investigated these issues. Thus, we conducted an updated systematic review to clarify the shape of the dose-response relation between selenium intake, selenium status, and risk of prostate cancer.

Methods

Data sources and searches

We carried out a systematic search according to the published search strategy and protocol as detailed previously (4); the updated PubMed search up to November 2010 was completed as described in the continuous update protocol, and a copy of the full electronic search is available at http://dietandcancerreport.org/downloads/cu/cu_prostate_cancer_protocol.pdf. Our systematic review was conducted according to standard criteria and guidelines (22).

Study selection

Study data were included from articles published in English language when full-print articles were available. As part of the updated systematic review search from 2005 to 2010, Epub ahead of print and In Press articles were not included (the data from these articles were extracted once the final definitive version of the article was released). We excluded literature reviews, animal or cell model studies, and cross-sectional studies. For inclusion, the study design had to be either case-control, nested case-control, prospective cohort, or randomized controlled trial (RCT). Criteria for inclusion were an adult population, assessment of selenium intake or status (plasma/serum or toenail selenium) as an exposure with >2 categories, assessment of total or advanced prostate cancer cases (number of events), and RR (with 95% CI) as an outcome. The definition of advanced cancer for inclusion included advanced or metastatic cancer, fatal cancer, high-stage, or grade of prostate cancer, including Gleason grade ≥7, stage 3–4 on the American Joint Committee on Cancer classification scale, and stage C or D on the Whitmore / Jewett scale (http://dietandcancerreport.org/downloads/cu/cu_prostate_cancer_protocol.pdf).

Data extraction and study quality assessment

The search, study selection, and data extraction were conducted by several reviewers at the University of Bristol, United Kingdom, up to June 2006 [search in Medline (using Ovid, www.ovid.com/site/catalog/DataBase/901.jsp, or PubMed, http://www.ncbi.nlm.nih.gov/pubmed/), Embase, BIOSIS and ISI (through Web of Knowledge, http://apps.webofknowledge.com/), Cochrane Central (www.thecochranelibrary.com/), LILACS (http://lilacs.bvsalud.org/en/), and DARE (http://onlinelibrary.wiley.com/o/cochrane/cochrane_cldare_articles_fs.html)] and by 2

reviewers at Imperial College London from June 2006 to November 2010 (search in Medline by using PubMed as interface because most relevant articles in the search before 2006 were referenced in Medline). We also hand-searched reference lists from retrieved articles, reviews, and meta-analysis articles. When multiple articles on the same study were found, the selection of results for the meta-analysis was based on longer follow-up, more cases identified, and completeness of the information required to do the meta-analysis. For articles published after 2006, case-control studies were not extracted into the WCRF/AICR continuous update database. The search results highlighted that 4 case-control studies were published on selenium and prostate cancer from 2006 up to September 2010; therefore, these articles were assessed separately for data extraction. On the basis of the inclusion criteria for the nonlinear dose-response meta-analysis, no further case-control studies (from 2006 onward) were eligible for inclusion (for the reasons why, see Supplemental Table S1 under "Supplemental data" in the online issue).

Study quality was assessed by using the Newcastle-Ottawa scoring system (23). Small study effects were assessed by using a contour-enhanced funnel plot and Egger test (24), including recommendations for interpretation by Sterne et al 2011 (25).

Statistical analysis

Generalized least-squares trend estimation and meta-analysis trend estimation from the data were carried out as described by Greenland and Longnecker (26), Berlin et al (27), and Orsini et al (28). The nonlinear dose-response meta-analyses were conducted when there were ≥3 studies with relevant data. To maximize relevant data inclusion for the meta-analysis, when data were not reported for the mean or midpoint of the categories, the midpoint was estimated assuming that the width of the upper category was the same as the adjacent category (29). To

investigate the association between selenium status and prostate cancer risk, dose-response meta-analyses were used, with fractional polynomials for nonlinear trends (30, 31) and restricted cubic splines combined by using multivariate meta-analysis (32). Both methods were used to investigate the shape of the dose-response plot for each relation (plasma/serum selenium and total/advanced prostate cancer plus toenail selenium and prostate cancer risk) to investigate whether the results were sensitive to the method. When both methods were in good agreement, the best-fitting cubic spline plots are presented. For the toenail selenium dataset, as there were only 3 studies included, both plots are presented for comparison. For the plasma/serum selenium and prostate cancer risk data set, sensitivity analyses investigated nonlinear dose-response plots from nested case-control studies alone compared with data included from all relevant case-control and nested case-control studies in the main analysis. STATA version 11.1 (StataCorp) was used for the statistical analysis.

Results

Twelve studies with a total of 13,254 participants and 5007 cases of prostate cancer were included in the dose-response meta-analysis (Table 1). As summarized in Figure 1 and elsewhere (see Supplemental Figure S1 under "Supplemental data" in the online issue), 9 studies were included in the meta-analysis of plasma/serum selenium and prostate cancer [2 case-control (33, 34) and 7 nested case-control (2, 3, 11, 35–38) studies)] in which data reported prostate cancer risk of quantiles of plasma/serum selenium status. There were 11,229 participants and 4507 incident cases of prostate cancer included in the meta-analysis of the plasma/serum selenium data from 7 studies in the United States of America and 2 in Europe. Of the 9 studies that reported the incidence of total prostate cancer (2, 3, 11, 33–38), 6 also reported advanced prostate cancer incidence (2, 3, 11, 35–37) (Table 2). For the meta-

analysis of toenail selenium and prostate cancer risk, 3 studies were included (39–41), as discussed in more detail below.

Other studies that were included but did not meet the criteria for nonlinear dose-response meta-analysis are summarized below, including 9 studies (13, 42–51) in the selenium intake and prostate cancer data set and 2 studies (41, 52) in the toenail selenium and advanced prostate cancer risk data set. The reasons for lack of suitability of the studies for use in the nonlinear dose-response meta-analysis are detailed elsewhere (see Supplemental Table S1 under "Supplemental data" in the online issue). In brief, the main reasons included presentation of data as mean exposure in cases and controls in <3 categories of exposure, correlation data, or continuous exposure data or study design that did not meet the inclusion criteria (53–79), missing key data (eg, numbers of cases/controls and 95% CI data) required for the dose-response analysis (80, 81), or lack of data on selenium status biomarkers, including selenoprotein P (82), fingernail selenium (83), erythrocyte glutathione peroxidase (75), and prostate cancer risk.

Plasma/serum selenium concentration and risk of total prostate cancer

The relation between plasma/serum selenium and prostate cancer risk, representing data from 3579 cases and 4510 controls (detailed in Table 1) in 9 studies (2, 3, 11, 33–38) is shown in Figure 2A. A gradual decrease in prostate cancer risk was found over the range of selenium exposures (plasma/serum selenium range from 60 to 170 ng/mL), with relatively wide 95% CIs. As an example of the data from the estimated RR in Figure 2A, at 135 ng/mL the RR was 0.85 (95% CI: 0.74, 0.97) and at 170 ng/mL the RR was 0.75 (95% CI: 0.65, 0.86). Sensitivity analysis with removal of the 2 case-control studies (33, 34) from the nonlinear meta-analysis resulted in a remarkably similar relation; the best-fitting cubic spline plot,

shown elsewhere (see Supplemental Figure S1 under "Supplemental data" in the online issue), was in good agreement with the nonlinear dose-response meta-analysis presented in Figure 2A.

Plasma/serum selenium concentration and risk of advanced prostate cancer

The relation between plasma/serum selenium and advanced prostate cancer risk is shown in Figure 2B. There were 876 cases of advanced cancer and 2116 controls (detailed in Table 1) in the 6 nested case-control studies included (2, 3, 11, 35–37). There was a gradual reduction in risk indicated with the nonlinear dose-response plot over the plasma/serum selenium status range investigated, with relatively wide 95% CIs, eg, at 135 ng/mL the RR was 0.60 (95% CI: 0.45, 0.81) and at 170 ng/mL the RR was 0.50 (95% CI: 0.36, 0.68).

Toenail selenium and risk of prostate cancer

The relation between toenail selenium and prostate cancer risk by using restricted cubic spline and fractional polynomial plots is shown in Figure 3, A and B, respectively. There were 500 cases of prostate cancer and 1525 controls overall (39–41). The best-fitting polynomial model (Figure 3B) with powers 2 and 3 included data from only 3 high-quality (see Supplemental Table S2 under "Supplemental data" in the online issue) studies available (39–41); therefore, the nonlinear plot must be interpreted with caution. With this caveat in mind, the best-fitting polynomial model is shown in Figure 3B. The relation between toenail selenium and prostate cancer risk was U-shaped, with the risk decreasing to ~30% (estimated RR: 0.29; 95% CI: 0.14, 0.61) with toenail selenium ranging from 0.85 to 0.94 μg/g. Restricted cubic spline analysis (Figure 3A) showed that the shape of the relation and the estimated RR were very similar (RR: 0.32; 95% CI: 0.24, 0.45), with toenail selenium ranging from 0.85 to 0.94 μg/g (Figure 3A).

For toenail selenium and advanced prostate cancer, 2 nested case-control studies reported on this association (41, 52): 1 from the Netherlands and 1 from the United States. It was not reasonable to complete a meta-analysis on these studies because there were only 2 studies for the advanced prostate cancer data set. Compared with the lowest quintiles, a >30% reduction in RR was observed in both studies, with toenail selenium ranging from 0.514 to >0.672 (41) and 0.73 to 0.85 μg/g (52)—similar to the range of toenail selenium status associated with reduction in risk in the fractional polynomial and cubic spline dose-response plots (Figure 3, A and B).

Selenium intake and risk of prostate cancer (all grades) and advanced prostate cancer

There were 8 studies in total that were considered for inclusion in the meta-analysis of selenium intake and prostate cancer risk: 2 RCTs (13, 42, 49, 50), 3 case-control studies (44, 47, 48), and 3 prospective cohort studies (43, 45, 46). Selenium intake was measured by using a food-frequency questionnaire (n = 3) (13, 47, 48), dietary-history questionnaire (n = 1) (44), and detailed supplement-use questionnaire (n = 3) (43, 45, 46). For the 2 RCTs (13, 49) and 1 cohort (45), only the supplemental intake of selenium was reported, whereas the habitual intake of the participants was not given (13, 42, 45, 49). Lawson et al in 2007 (46) described the frequency of intake of supplements containing selenium but not dietary selenium intake, and Gonzalez et al in 2009 (43) reported the average intake over 10 y estimated from a questionnaire. Only 2 case-control studies (44, 48) presented total selenium intake from the diet in >2 categories of exposure, which was an inclusion criterion; therefore, it was not possible to investigate the effect of total dietary selenium intake and prostate cancer risk from these studies by using the dose-response meta-analysis. Similarly, for selenium intake and advanced prostate cancer we were not able to undertake a dose-response

analysis because only 2 of the included studies reported on selenium intake and advanced prostate cancer (42, 46).

The results from RCTs on selenium intake and prostate cancer included in this review were inconsistent. The large SELECT trial (13) demonstrated that selenium (as 200 μg/d L-selenomethione) did not reduce prostate cancer risk (HR: 1.04; 99% CI: 0.87, 1.24), but this study was carried out in a selenium-replete US population (median baseline serum selenium: 136 ng/mL) with no history of cancer (13). The Nutritional Prevention of Cancer (NPC) trial (49) showed a significant decrease in prostate cancer risk (HR: 0.33; 95% CI: 0.13, 0.82), but only for those men who had a history of cancer and lower selenium status (<123.2 ng/mL) at the start of the trial (42, 49). In the remaining 2 case-control studies, selenium intake was significantly associated with prostate cancer risk, and the effects were dose specific. In the study described by Jain et al in 1999 (44), a significant decrease in prostate cancer risk by ~30% (OR: 0.69; 95% CI: 0.52, 0.92) was observed in the participants who had selenium intakes between 88 and 119 μg/d compared with those with lower or higher intakes. Data from West et al in 1991 (48) showed that an increased RR of prostate cancer (RR: 1.6; 95% CI: 0.9, 2.8) was associated with selenium intakes ranging from 139 to 227 μg/d in men aged 68–74 y from the United States—all results indicating that the total daily intake of selenium is a critical factor.

Study quality, sensitivity analyses and small study effects

Study quality was assessed by using the Newcastle-Ottawa scale (23) (see Supplemental Table S2 under "Supplemental data" in the online issue). Of the studies included in the dose-response meta-analysis of plasma/serum selenium and prostate cancer risk, 2 studies (33, 34) were rated as of moderate quality and 7 studies (2, 3, 11, 35–38) as of high quality (see

Supplemental Table S2 under "Supplemental data" in the online issue). All studies included in the dose-response meta-analysis of the relation between toenail selenium and prostate cancer risk were of high quality (39–41) as assessed by using the Newcastle-Ottawa scale. Sensitivity analyses were carried out when there were >5 studies included in the dose-response meta-analysis by removing 1 study from the analysis at each time; the shape of the dose-response plot for the relation between plasma/serum selenium and prostate cancer risk was consistent regardless of study exclusion. For the dose-response meta-analysis, there were a maximum of 9 studies included in Figure 2A, which may have been underpowered to properly assess small study effects. However, the contour-enhanced funnel plot with regard to the studies included in Figure 2A does not appear to indicate bias or any asymmetry (see Supplemental Figure S2A under "Supplemental data" in the online issue), and there was moderate heterogeneity (I2 = 45%). When only nested case-control studies were included in the dose-response plot (see Supplemental Figure S1 under "Supplemental data" in the online issue), there was limited evidence of bias and asymmetry (I2 = 22%) as indicated in the contour-enhanced funnel plot (see Supplemental Figure S2B under "Supplemental data" in the online issue). Removal of the small nested case-control study of Brooks et al (38) resulted in I2 = 0%.

DISCUSSION

Evaluation of the association between selenium intake, status and prostate cancer

We showed in our dose-response meta-analysis that a decreased risk of prostate cancer appears to be associated with a relatively narrow range of selenium status. This evidence comes from high-quality case-control and nested case-controlled studies and is supported by data from 2 high-quality RCTs (13, 42, 49). On the basis of an expected U-shaped response and narrow range for a potentially protective action, accurate assessment of sensitive

biomarkers of selenium exposure and status in at-risk populations are of paramount importance. The novel dose-response analysis in this systematic review provides justification for further studies on selenium status and prostate cancer risk to firmly establish the optimal range of selenium intake and status associated with a reduced risk of prostate cancer, particularly in populations with low to moderate selenium status. This can then provide the basis for future public health policies and the derivation of reference values and dietary recommendations for selenium.

Comparison with other studies – selenium intake data

An overview of the selenium intake and prostate cancer data as part of this review was in accord with a recent Cochrane review on selenium intake and cancer (7) in that both suggest that selenium supplements do not, in general, prevent prostate cancer as the effects of selenium supplement are likely to be dependent on the form of selenium in the supplement, habitual baseline selenium intake and baseline selenium status and health of the population. Dennert et al (7) also concluded that, although the results need to be interpreted with care, there was evidence for an inverse association between selenium intake and risk of cancer in men (OR: 0.66; 95% CI: 0.42, 1.05) and, in particular, for prostate cancer (7). The systematic review by Etminan et al 2005 (5) showed that a high selenium intake was associated with a nonsignificant reduction in risk of early (RR: 0.87; 95% CI: 0.68, 1.12) and advanced prostate cancer (RR: 0.69; 95% CI: 0.48, 1.01), although it was not possible to determine the range of intakes associated with risk reduction. Two RCTs with selenium supplements, the SELECT study (13) and the NPC trial (49, 50) demonstrated that supplements of 200–400 μg/d in a selenium replete population did not reduce prostate cancer risk (13, 14, 42, 49). The NPC trial only showed a protective effect of 200 μg/d in a selenium deficient at risk group of

men who had a history of cancer (42), indicating that the total intake of selenium in the key target population is a critical factor.

Because there were insufficient data to complete an in-depth dose-response analysis with the intake data from this meta-analysis, coupled with the fact that 2 recent reviews have investigated selenium intake and cancer risk (5, 7), the main focus for this review was to investigate the association between selenium status biomarkers and prostate cancer risk to identify the concentration range of selenium status biomarkers that are associated with risk reduction. Another reason why the focus of this review was on biomarkers of selenium status rather than selenium intake is that long-term dietary intakes of selenium cannot be accurately estimated via food-frequency questionnaire, diet records, or diet history because of the variations in the selenium content of soil and concomitant variability in the selenium content of foods.

Comparison with other studies – plasma/serum selenium status data

In relation to selenium status data, a meta-analysis presented in the WCRF/AICR report highlighted that a 10% decrease in risk was observed for every 10-ng/mL increase in plasma/serum selenium (4), but it was not possible to determine the exact range of status associated with the decreased risk. In our dose-response meta-analysis, we observed that a decreased risk of total and advanced prostate cancer was estimated with plasma/serum concentrations of ~135 ng/mL, up to the upper range investigated (170 ng/mL), and the relation with advanced prostate cancer was more pronounced (eg, at a plasma selenium concentration of 135 ng/mL, the estimated RRs for total and advanced prostate cancer were as follows: 0.85 (95% CI: 0.74, 0.97) and 0.60 (95% CI: 0.45, 0.81), respectively. Above this selenium status range, increased plasma/serum selenium concentrations (resulting from

selenium supplementation) up to 230–250 ng/mL were found not to be protective in US selenium-replete populations (13, 14, 42), and higher plasma/serum selenium concentrations (>160–200 ng/mL) have been associated with an increased risk of diabetes (84, 85). Data on serum selenium and total cancer mortality from NHANES showed that the association was nonlinear, and lower mortality was associated with serum selenium concentrations of 120 to 160 ng/mL (17), again in agreement with the status range observed in this meta-analysis.

Critical reviews, including a review of the NPC selenium-enriched yeast supplementation trial data, have suggested that there may be an optimal selenium status level, in the plasma/serum selenium range of 120 ng/mL or above (86–88); however, until now, a dose-response meta-analysis has not been undertaken to investigate the range based on the latest data from human studies.

In summary, several published systematic reviews and meta-analyses on selenium and prostate cancer to date have indicated a significant inverse association between selenium intake, plasma/serum selenium, and prostate cancer (4–7). We completed an updated dose-response analysis to investigate selenium status, for which protective effects were observed. We also analyzed the nonlinear dose-response relation for toenail selenium data and prostate cancer risk, and, on the basis of 3 high-quality studies, a U-shaped relation was observed; however, further high-quality data are required to accurately assess the relation for toenail selenium and risk.

Comparison with other studies –toenail selenium data

To our knowledge, there has been no nonlinear dose-response meta-analysis published of the association of toenail selenium with prostate cancer risk. Estimated decreases of 9% (RR:

0.91; 95% CI: 0.81, 1.02) and 20% (RR: 0.80; 95% CI: 0.69, 0.91) in total and advanced/aggressive prostate cancer, respectively, per 0.1-μg/g toenail selenium was estimated in the WCRF/AICR report, 2007 (4) based on data from 3 cohort studies (40, 41, 52); however, it was not possible to identify the range of toenail concentrations associated with decreased risk. In this dose-response meta-analysis, the fractional polynomial analysis indicated a U-shaped response, and both the cubic spline and fractional polynomial analyses indicated greater risk reduction at toenail selenium concentrations in the range of 0.85 to the upper range investigated, ~1.0 μg/g. This range of toenail selenium concentrations was estimated to be equivalent to 120–150 ng/mL plasma selenium by using the method described by Waters et al 2005 (89), which is in good agreement with the independent dose-response plots and meta-analysis of plasma/serum selenium data also presented in this review. Interestingly, a U-shaped response for toenail selenium and prostate DNA damage was observed in a canine model (88, 89), and the protective range of toenail selenium associated with reduced prostatic DNA damage was between 0.9 and 1.0 μg/g (plasma selenium ~110–150 ng/mL) (88), also in comparable ranges with the U-shaped dose response plot from the human toenail data.

In a population-based cohort in Canada, toenail selenium was inversely correlated with colon and lung cancer in males; however, no significant inverse association was observed for prostate cancer over the mean range of 0.875 to 0.94 ppm (55). Also, data from a population-based case-control study of fingernail selenium and prostate cancer risk in British men (83) showed no significant association of fingernail selenium with total prostate cancer risk over quartile median ranges of 0.456 to 0.837 ppm, with an OR of 1.24 (95% CI: 0.73, 2.10) in the highest quartile (83). However, for the group of men in the highest quartile of toenail selenium (median: 0.837 ppm), the risk of advanced prostate cancer was slightly lower (RR:

0.78; 95% CI: 0.27, 2.25) when compared with the lowest quartile (median: 0.456 ppm) (83). Lipsky et al 2004 (79) found no association between toenail selenium and prostate cancer; however, all except one of the participants (n = 150) had relatively low toenail selenium (<0.85 μg/g), and all of the participants had values below the estimated protective range.

Toenail selenium is an accurate long-term marker of selenium status and intake (90–92) and tissue and organ selenium status (93, 94). Toenail selenium values >0.61 μg/g have also been linked with a reduced risk of other types of cancer, including esophageal squamous cell carcinoma and gastric cardia adenocarcinoma (95) and hepatocellular cancer mortality (96). Overall, consistent evidence supports the association between toenail selenium and prostate cancer risk over a narrow range of toenail selenium status, and further high-quality human studies are required in populations at risk, particularly in populations with low selenium intake and status.

Study limitations

One of the strengths of this review was that we were able to complete the dose-response analysis on subgroups, such as those with total prostate cancer and advanced prostate cancer, and also for the selenium biomarkers of status when there were sufficient studies (toenail selenium and plasma/serum selenium). We were able to complete the sensitivity analysis including only nested case-control studies for the relation between plasma/serum selenium and prostate cancer risk, but not for the nonlinear dose-response toenail selenium fractional polynomial plot because there were too few studies. We were also not able to investigate the effect of different genotype subgroups on the dose-response plots or meta-analysis results because of a lack of data. Recent studies investigating single nucleotide polymorphisms in relation to selenium and prostate cancer risk suggest that several single nucleotide

polymorphisms may be associated with prostate cancer risk and selenium status (73, 97, 98). Also, prostate specific antigen (PSA) may be linked to the effect of selenium. For example, in the NPC trial, the protective effect of selenium-enriched yeast and elevated serum selenium seemed more effective for men who had a baseline PSA ≤4 ng/mL (42); however, because of the lack of appropriate study data, we were unable to subgroup according to PSA status. We were also not able to investigate the effect of data from countries with PSA screening policies on the total prostate cancer estimated risk dose-response plots because of the limited number of studies. It was also not possible to investigate the cause and effect to determine whether plasma/serum selenium and toenail selenium are markers for other risk factors.

Finally, we were not able to further investigate the form or species of selenium associated with decreased prostate cancer risk using meta-analysis methods because of the lack of data on intake of different selenium species and effects on prostate cancer risk. Further research on the cancer-protective effects of different species of selenium in at-risk selenium-deficient populations is required.

Study implications and conclusions

Several data outputs from the large US SELECT Trial that have not been published yet, including the toenail selenium concentration data and analysis of outcome per quantile of selenium status at baseline will be very important and informative data sets in the near future. Further large trials are required in the United Kingdom and Europe to test the hypothesis that there is an optimal selenium status and range of selenium intakes associated with a reduced risk of prostate cancer. This is especially important because plasma/serum selenium concentrations in certain regions are low; a review of several studies from Europe showed that plasma/serum selenium concentrations ranged between 50.22 and 145.29 ng/mL, with

most <78.96 ng/mL (12)). The dose-response nonlinear meta-analysis data presented in this systematic review indicate that the relation between selenium status and prostate cancer risk may be over the relatively narrow ranges of toenail selenium and plasma/serum selenium investigated (eg, toenail selenium ~0.85 up to ~1.0 μg/g and plasma selenium concentrations >120 to <170 ng/mL). Further high-quality RCT data are required in populations with low selenium intake and status.

Contributors: The authors' responsibilities were as follows—RH, LH, TN, and SJF-T: conceived the study design and aims; RL, DA, TN, RV, JS, and RB: completed the literature search and data extraction; RH, LH, DCG, and SJF-T: performed the analysis, interpreted the results, and drafted the manuscript; JACS and DCG: were statistical advisors; and all authors: critically reviewed the manuscript for content and approved the final version. None of the authors had any conflicts of interest to disclose.

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Figure legends

Figure 1: Flow chart for the inclusion of studies

Abbreviations used in the Figure: Se, selenium; PC, prostate cancer.

Figure 2 A and B: Dose response plots displaying the nonlinear relationships between plasma/serum selenium and the risk of total and advanced prostate cancer. Figure 2A represents dose-response analysis of data on plasma/serum selenium and total prostate cancer risk extracted from the publications, Vogt 2003 (33), Hardell 1995 (34), Nomura 2000 (3), Goodman 2001 (35), Li 2004 (2), Peters 2007 (36), Allen 2008 (11), Gill 2009 (37) and Brooks 2001 (38) according to methods and protocol. Figure 2B displays the best fitting fractional polynomial plot for data from publications Li 2004 (2), Nomura 2000 (3), Goodman 2001 (35), Peters 2007 (36), Allen 2008 (11), Gill 2009 (37) representing the association between plasma/serum selenium and advanced prostate cancer risk.

Figure 3: Dose response plot displaying the relationship between toenail selenium and prostate cancer risk represents meta-analysis of data from publications Ghadirian 2000 (39), Helzlsouer 2000 (40), van den Brandt 2003 (41). Figure 3A displays the relationship using restricted cubic splines combined using multivariate meta-analysis and Figure 3B displays the best-fitting fractional polynomial plot.

Figure 1. Flow chart for the inclusion of studies (22)

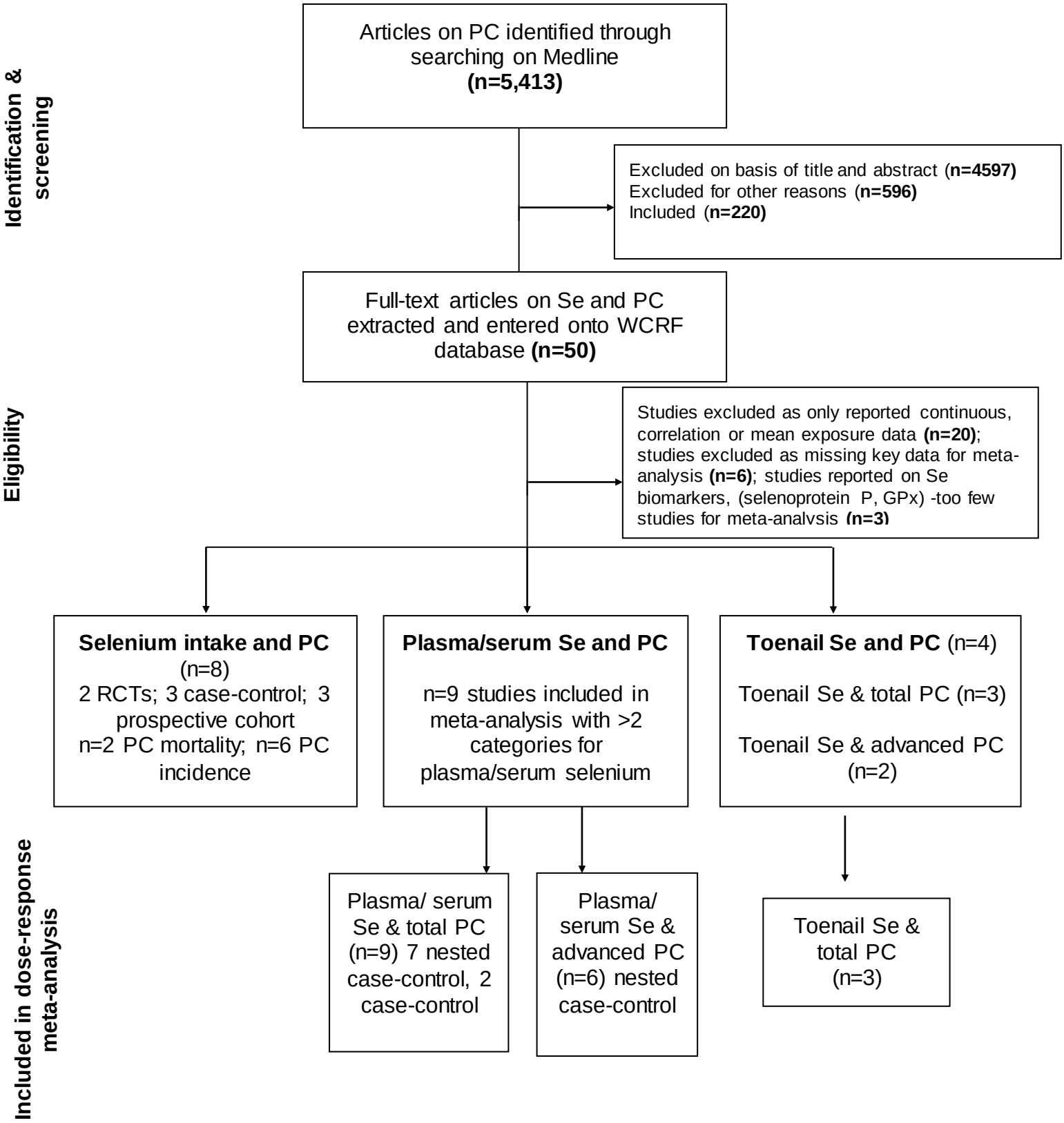

Figure 2A: the relationship between plasma/serum selenium and total prostate cancer

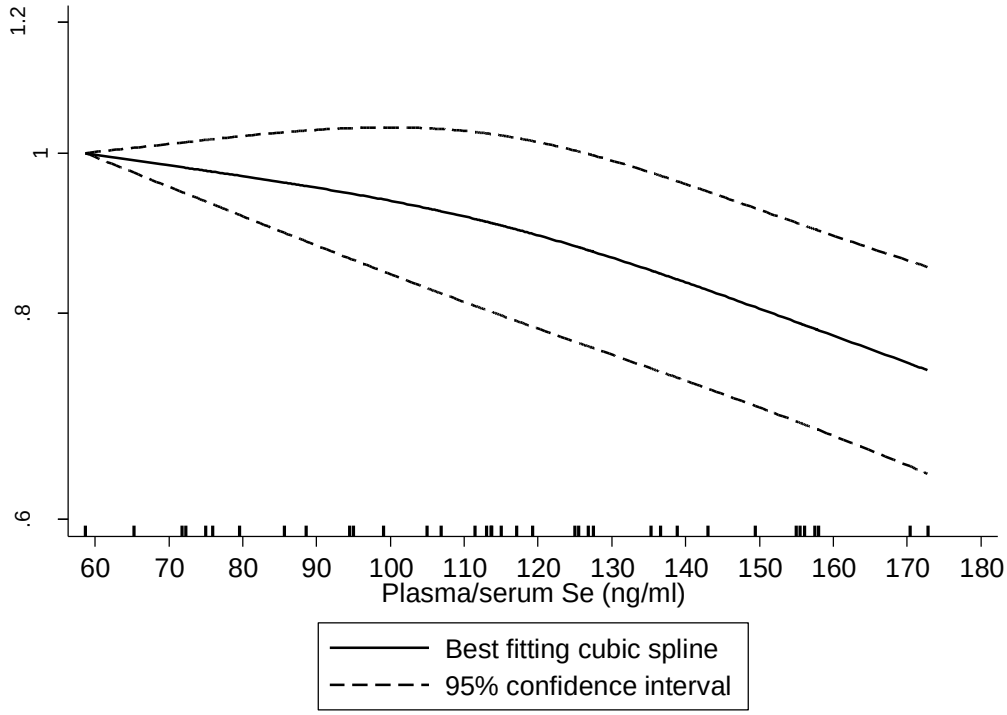

Figure 2B: the relationship between plasma/serum selenium and advanced prostate cancer risk

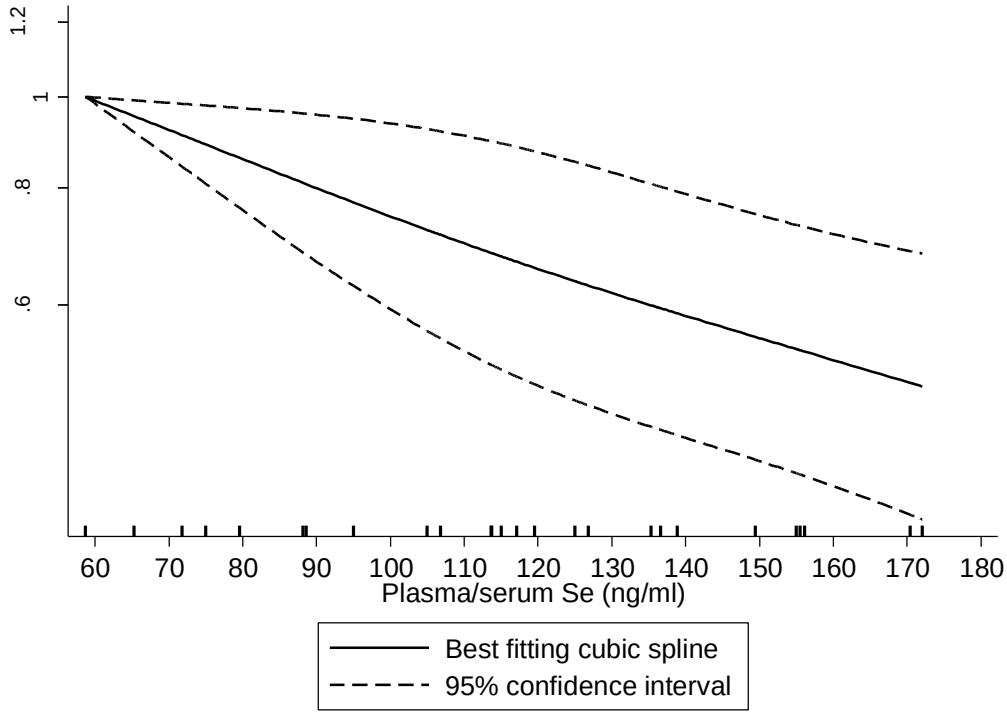

Figure 3A and B: the relationship between toenail selenium and prostate cancer risk

Figure 3A:

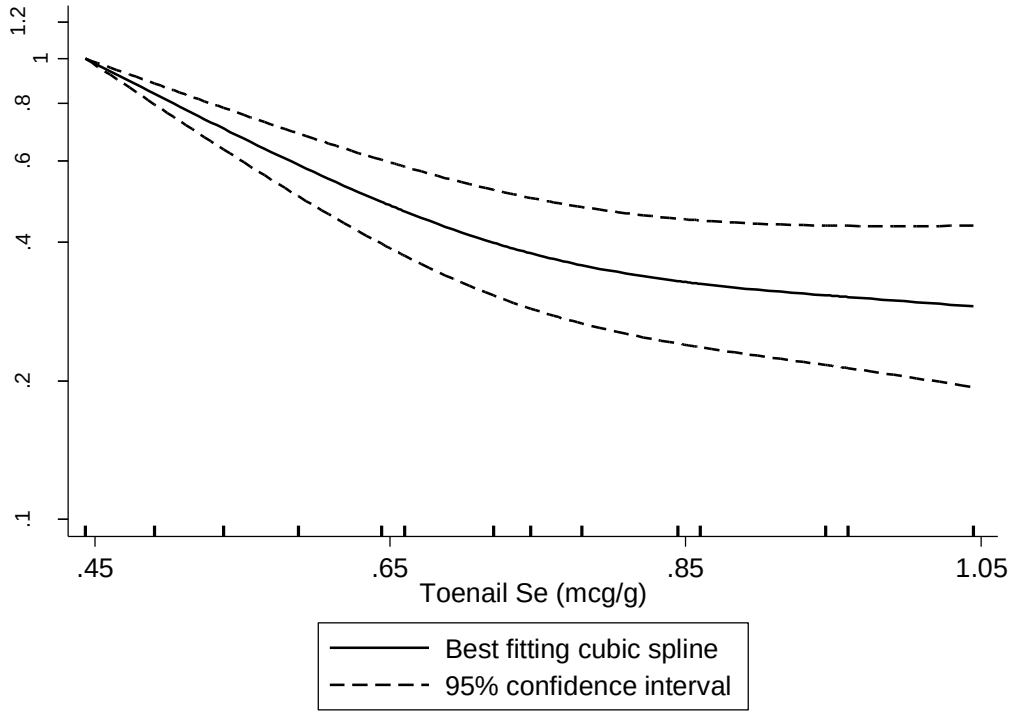

Figure 3B:

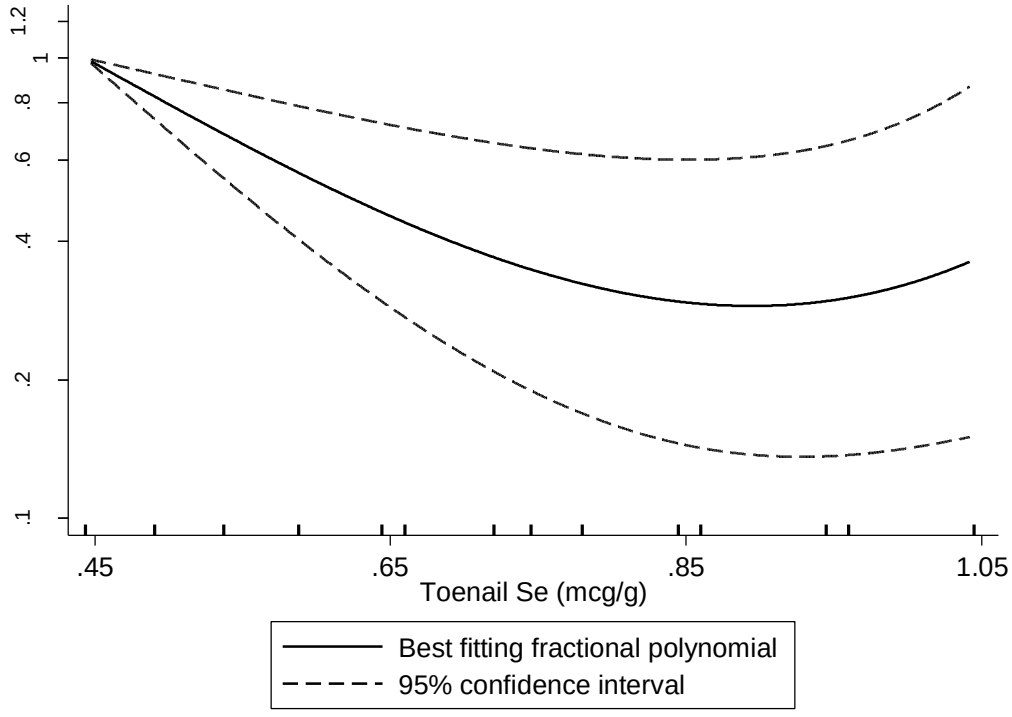

Table 1: Characteristics of the identified studies included in the meta-analyses on selenium status and prostate cancer

Study	Country	Study population	Study design	Age	Follow-up	No. of participants	Outcome(s)	Outcome assessment	Study description; size cohort
Plasma/serum selenium studies									
Allen et al 2008 (11)	Europe		Nested case-control	43-76		959 cases; 1059 controls	Prostate cancer incidence (total)	Cancer registry, medical records, pathology	European Prospective Investigation into Cancer and nutrition (EPIC); 127,811
						203 cases; 216 controls	Advanced prostate cancer incidence	Cancer registry, medical records, pathology	
Brooks et al 2001 (38)	USA	White	Nested case-control			52 cases; 96 controls	Prostate cancer incidence	Tissue analysis	Baltimore Longitudinal Study of Aging; 1,555
Gill et al 2009 (37)	USA	Multi-ethnic	Nested case-control	45-75		450 cases; 936 controls	Prostate cancer incidence	Cancer registry	Hawaii-Los Angeles Multiethnic Cohort (MEC) Study; 215,251
						123 cases; 344 controls	Advanced prostate cancer incidence	Cancer registry	

Goodman et al 2001 (35)	USA	Multi-ethnic (smoker or asbestos-exposed worker	Nested case-control	45-74		235 cases; 456 controls	Prostate cancer incidence	Tissue analysis	Carotene and Retinol Efficacy Trial (CARET); 18,314
						37 cases; 36 controls	Advanced prostate cancer incidence	Tissue analysis	
Hardell et al 1995 (34)	Sweden	Not stated	Case-control	44-87		164 cases; 121 controls	Prostate cancer incidence	Histology	Sweden 1987-1990
Li et al 2004 (2)	USA	Multi-ethnic	Nested case-control	40-84		586 cases; 577 controls	Prostate cancer incidence	Tissue analysis	Physicians' Health Study; 22,071
						171cases; 577 controls	Advanced prostate cancer incidence	Tissue analysis	
Nomura et al 2000 (3)	USA	Japanese	Nested case-control	44-85	12.4	249 cases; 249 controls	Prostate cancer incidence	Tissue analysis	Honolulu Heart Program; 9,345
						64 cases; 64 controls	Advanced prostate cancer incidence	Tissue analysis	
Peters et al 2007 (36)	USA	Black and white	Nested case-control	55-74	8	724 cases; 879 controls	Prostate cancer incidence (total)	Self reports, hospital records, death certificates	PLCO Cancer Screening Trial; 26,975
						278 cases; 879 controls	Advanced prostate cancer incidence	Self reports, hospital records, death certificates	
Vogt et al 2003 (33)	USA	Multi-ethnic	Case-control			212 cases; 233 controls	Prostate cancer incidence (total)	Histology	USA Georgia

								Michigan New Jersey 1986-1989
Toenail selenium studies								
Ghadirian et al 2000 (39)	Canada	Not stated	Case control study	35-84		83 cases; 82 controls	Prostate cancer incidence	Histology	Canada 1989-1993
Helzlsouer et al 2000 (40)	USA	White	Nested case-control			117 cases; 233 controls	Prostate cancer incidence	Tissue analysis	Campaign against Cancer and Heart Disease (CLUE II) study; 10,456
Van den Brandt et al 2003 (41)	Netherlands	Not stated	Nested case-control	55-69	6.3	300 cases; 1210 controls	Prostate cancer incidence	Tissue analysis	The Netherlands cohort study; 58,279

Table 2: Detailed outcome on selenium status and relative risks of prostate cancer

Study	Plasma/ serum selenium or toenail selenium	Comparison: Plasma selenium quantile category midpoints (ranges) compared (units of serum/plasma, ng/ml; toenail selenium, µg/g)	Model, comparison	PC events (all PC)	RR (95% CI)	PC events (advanced PC)	RR (95% CI)	Adjustments for covariates/factors controlled for in multivariate analysis (maximally adjusted for both total and advanced PC)
Allen et al 2008 (11)	Plasma	58.65 (55.4-61.9)	Q1	229	1	59	1	BMI, smoking status, alcohol intake, physical activity, marital status, educational level
		65.25 (62-68.5)	Q2 vs Q1	179	0.81 (0.61-1.07)	42	0.67 (0.36-1.25)	
		71.8 (68.6-75)	Q3 vs Q1	192	0.85 (0.63-1.14)	33	0.57 (0.3-1.09)	
		79.55 (75.1-84)	Q4 vs Q1	172	0.82 (0.61-1.10)	33	0.7 (0.35-1.37)	
		88.55 (84.1-93)	Q5 vs Q1	187	0.96 (0.7-1.31)	36	0.62 (0.32-1.21)	
Brooks et al 2001 (38)	Plasma	94.5 (82-107)	Q1	20	1	n.a.	n.a.	Year before diagnosis, age, BMI, smoking habits, alcohol consumption
		113 (108-118)	Q2 vs Q1	9	0.15 (0.05-0.5)	n.a.	n.a.	
		125.5 (119-132)	Q3 vs Q1	10	0.21 (0.07-0.68)	n.a.	n.a.	
		157.5 (133-182)	Q4 vs Q1	13	0.24 (0.07-0.77)	n.a.	n.a.	
Gill et al 2009 (37)	Serum	117.07 (n.s.)	Q1	123	1	32	1	Geographical area, race, age at interview, date of blood collection, fasting condition, BMI, family history of cancer, educational level
		126.83 (n.s.)	Q2 vs Q1	111	0.84 (0.61-1.16)	33	0.99 (0.52-1.89)	
		136.59 (n.s.)	Q3 vs Q1	105	0.75 (0.53-1.04)	32	0.87 (0.44-1.72)	
		156.1 (n.s.)	Q4 vs Q1	111	0.82 (0.59-1.14)	26	0.99 (0.46-2.15)	
Goodman et al 2001 (35)	Serum	75.95 (50.7-101.2)	Q1	60	1	11	1	Year of randomisation, age, smoking habits, intervention arm, exposure population,
		106.9 (101.3-112.5)	Q2 vs Q1	51	0.85 (0.53-1.35)	10	0.9 (0.27-2.98)	
		119.25 (112.6-125.9)	Q3 vs Q1	65	1.08 (0.69-1.71)	5	0.5 (0.15-1.73)	

		172.8 (126-219.6)	Q4 vs Q1	61	1.02 (0.65-1.6)	11	1.07 (0.37-3.06)	blood draw visit
Hardell et al 1995 (34)	Plasma	72.25 (65.54-78.96)	Q1	68	1	n.a.	n.a.	Age
		85.67 (78.96-92.38)	Q2 vs Q1	38	0.6 (0.3-1.1)	n.a.	n.a.	
		99.09 (92.38-105.8)	Q3 vs Q1	18	0.3 (0.1-0.7)	n.a.	n.a.	
Li et al 2004 (2)	Plasma	75 (60-90)	Q1	121	1	36	1	Age, smoking habits, duration follow-up
		95 (90-100)	Q2 vs Q1	137	1.13 (0.79-1.61)	45	1.17 (0.7-1.97)	
		105 (100-110)	Q3 vs Q1	105	0.88 (0.61-1.28)	37	1.01 (0.59-1.73)	
		115 (110-120)	Q4 vs Q1	127	1.02 (0.71-1.45)	35	0.99 (0.58-1.7)	
		155 (120-190)	Q5 vs Q1	96	0.78 (0.54-1.13)	18	0.52 (0.28-0.98)	
Nomura et al 2000 (3)	Serum	113.65 (108-119.3)	Q1	75	1	20	1	Smoking habits, age
		124.95 (119.3-130.6)	Q2 vs Q1	64	0.9 (0.5-1.4)	20	1 (0.4-2.8)	
		138.9 (130.6-147.2)	Q3 vs Q1	72	1 (0.6-1.6)	18	0.9 (0.4-2.5)	
		155.5 (147.2-163.8)	Q4 vs Q1	38	0.5 (0.3-0.9)	6	0.3 (0.1-0.8)	
Peters et al 2007 (36)	Serum	113.7 (50.5-126.79)	Q1	195	1	72	1	Age, time, year of interview, study centre
		135.3 (126.8-141.89)	Q2 vs Q1	189	0.95 (0.71-1.27)	71	0.97 (0.65-1.46)	
		149.4 (141.9-157.99)	Q3 vs Q1	198	1.13 (0.85-1.51)	84	1.31 (0.88-1.95)	
		170.4 (158-253)	Q4 vs Q1	142	0.84 (0.62-1.14)	51	0.84 (0.54-1.3)	
Vogt et al 2003 (33)	Serum	111.5 (104-119)	Q1	55	1	n.a.	n.a.	Age, geographic area, ethnicity/race
		127.5 (120-135)	Q2 vs Q1	73	1.35 (0.81-2.56)	n.a.	n.a.	
		143 (136-150)	Q3 vs Q1	47	0.88 (0.51-1.51)	n.a.	n.a.	
		158 (151-165)	Q4 vs Q1	37	0.71 (0.39-1.28)	n.a.	n.a.	
Ghadirian et al 2000 (39)	Toenail	0.745 (0.7-0.79)	Q1	20	1	n.a.	n.a.	Age, smoking habits
		0.845 (0.8-0.89)	Q2 vs Q1	21	0.61 (0.25-1.53)	n.a.	n.a.	
		0.945 (0.9-0.99)	Q3 vs Q1	15	0.67 (0.25-1.77)	n.a.	n.a.	
		1.045 (1-1.09)	Q4 vs Q1	27	1.14 (0.46-2.83)	n.a.	n.a.	
Helzlsouer et al 2000 (40)	Toenail	0.66 (0.63-0.69)	Q1	32	1	n.a.	n.a.	BMI, educational level, hours since last meal
		0.72 (0.69-0.75)	Q2 vs Q1	20	0.41 (0.18-0.93)	n.a.	n.a.	
		0.78 (0.75-0.81)	Q3 vs Q1	21	0.55 (0.26-1.17)	n.a.	n.a.	
		0.86 (0.81-0.91)	Q4 vs Q1	24	0.66 (0.33-1.33)	n.a.	n.a.	
		0.96 (0.91-1.01)	Q5 vs Q1	20	0.38 (0.17-0.85)	n.a.	n.a.	
van den Brandt et al 2003 (41)	Toenail	0.4435 (0.42-0.467)	Q1	82	1	n.a.	n.a.	Age, family history of specific cancer, smoking habits, educational level
		0.4905 (0.467-0.514)	Q2 vs Q1	72	0.87 (0.51-1.49)	n.a.	n.a.	
		0.537 (0.514-0.56)	Q3 vs Q1	44	0.53 (0.31-0.92)	n.a.	n.a.	
		0.588 (0.56-0.616)	Q4 vs Q1	65	0.79 (0.45-1.37)	n.a.	n.a.	

	0.644 (0.616-0.672)	Q5 vs Q1	38	0.46 (0.27-0.79)	n.a.	n.a.

BMI = body mass index

n.s. = not stated

n.a. = not applicable, data for advanced prostate cancer not investigated/presented in publication

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Figure legends for Supplemental figures

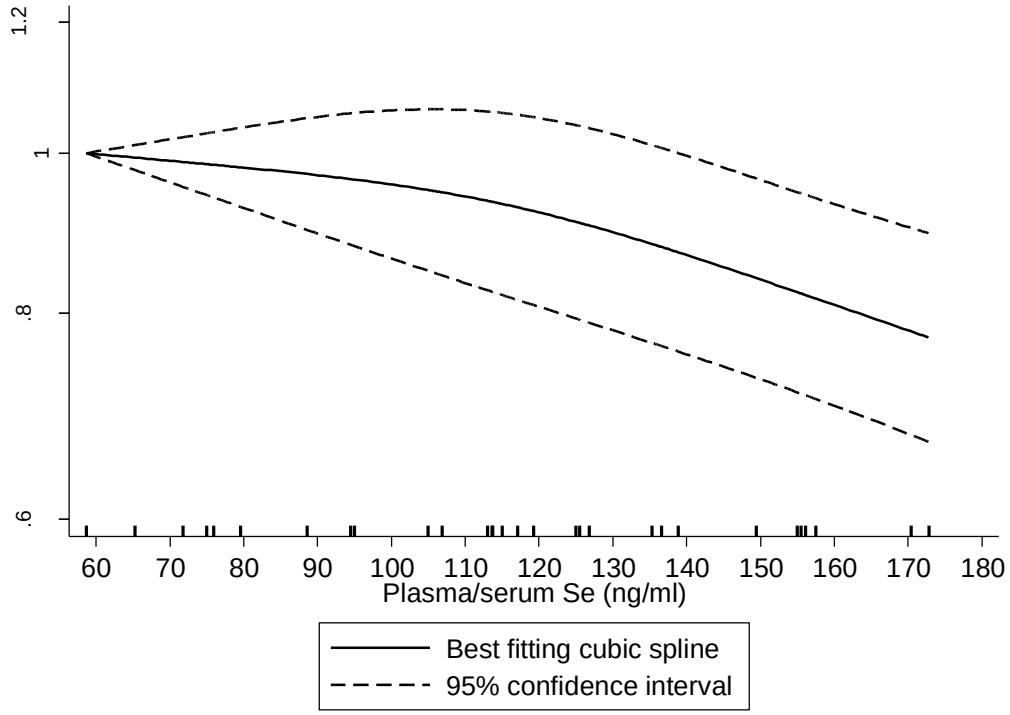
Supplementary Figure S1: Best fitting cubic spline plot representing data from nested case-control studies only (n=7)

Figure S1 represents dose-response analysis of data on plasma/serum selenium and total prostate cancer risk from 7 nested case-control studies: Nomura 2000 (3), Goodman 2001 (35), Li 2004 (2), Peters 2007 (36), Allen 2008 (11), Gill 2009 (37), including a small nested case-control study Brooks 2001 (38). At 135 ng/ml, RR: 0.88, 95 % CI: 0.77-1.01 and at 170 ng/ml, RR: 0.78, 95 % CI: 0.68-0.90. The data points from the included studies are indicated by the tick marks on the inside of the x-axis.

Supplementary Figures S2A and B: Contour enhanced funnel plots for assessment of small study bias in the studies included in the meta-analysis of plasma/serum selenium and total prostate cancer risk

Studies included (n=9) in Figure 2A (2, 3, 11, 33-38) are represented in contour enhanced funnel plot Figure S2A. Nested case-control studies (n=7) included in Figure S1 (2, 3, 11, 35-38) are represented in contour enhanced funnel plot Figure S2B.

Figure S1: Best fitting cubic spline plot representing data from nested case-control studies only (n=7)



Supplementary Figures S2A and B: Contour enhanced funnel plots for assessment of small study bias in the studies included in the meta-analysis of plasma/serum selenium and total prostate cancer risk

Figure 2A: all included studies:

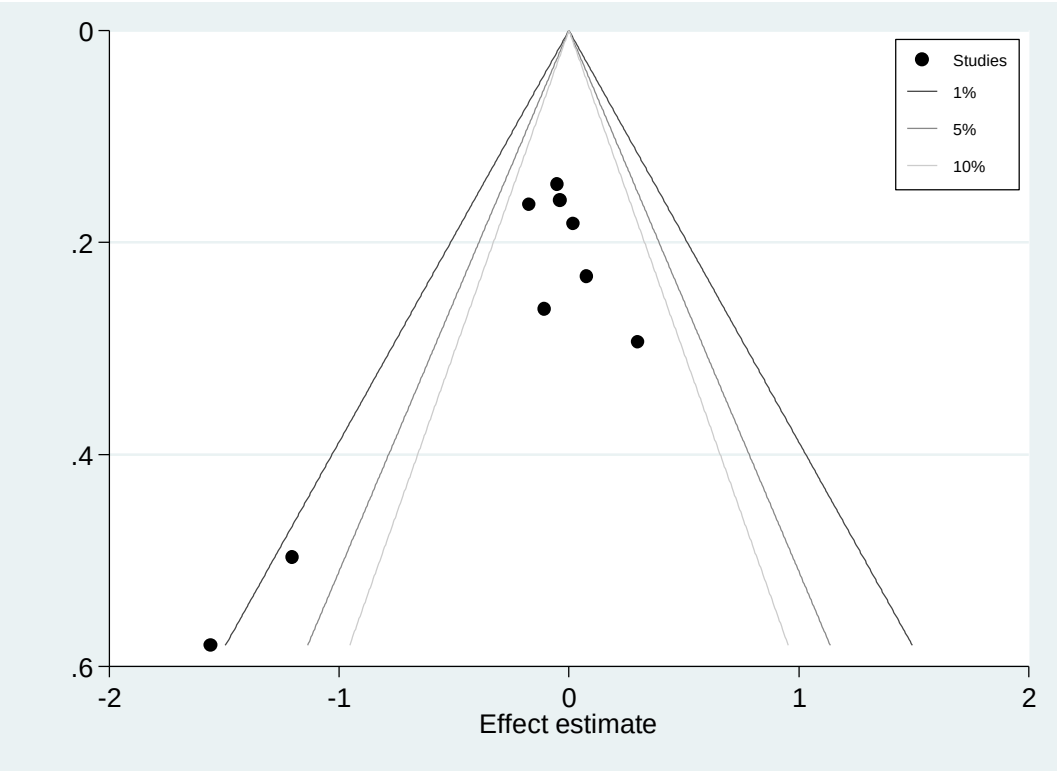


Figure 2B: nested case-control studies only: