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Review

Are men with low selenium levels at increased risk of prostate cancer?

Maree Brinkman[a,*], *Raoul C. Reulen*[b], *Eliane Kellen*[a], *Frank Buntinx*[a,c], *Maurice P. Zeegers*[a,b]

[a]*Department of General Practice, Katholieke Universiteit Leuven, Kapucijnenvoer 33, Blok J, 3000 Leuven, Belgium*
[b]*Department of Public Health and Epidemiology, University of Birmingham, Birmingham B15 2TT, United Kingdom*
[c]*Department of General Practice and Research Institute Caphri, Maastricht University, The Netherlands*

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ABSTRACT

A meta-analysis was undertaken to quantitatively determine if men with low selenium levels were at increased risk of prostate cancer.

PubMed, EMBASE and current contents were searched to identify relevant studies. The effect size was calculated by pooling the mean difference for serum, plasma and toenail selenium levels (95% confidence intervals) separately and combined using a random effects model. Meta-regression analysis explored possible sources of heterogeneity.

Twenty epidemiologic studies were selected. Mean differences were: –5.55 μg/l (–9.82; –1.27; $p = 0.01$), –0.01 μg/g (–0.03; 0.006; $p = 0.19$), –0.52 μg/l (–4.63; 3.58; $p = 0.80$) for serum, toenail and plasma studies, respectively. Overall, the pooled standardized mean difference between cases and controls was; –0.23 (–0.40; –0.05; $p = 0.01$) indicating a possible inverse association between selenium levels and risk of prostate cancer.

Differences in selenium levels between populations, a possible threshold effect and the relationship between selenium and the different stages of prostate cancer require further investigation.

1. Introduction

Prostate cancer is the second most common cancer in men worldwide.[1] Incidence varies greatly between populations and is highest in Western countries such as USA, Australia, and Western Europe and lowest in Asian countries.[1] Incidence rates range from 119.9 cases per 100,000 in USA to 1.6 cases per 100,000 in China.[1] Migratory studies reporting dramatic increases in prostate cancer within one generation in men who have moved from areas of low to high incidence, suggest that environmental factors such as diet may be involved in its aetiology.[2]

Selenium is an essential dietary trace element which is present in a wide range of foods such as grains, fish, meat and eggs and has been suggested to have a protective effect against prostate cancer.[3] Concentrations of selenium in the food supply like the incidence of prostate cancer vary greatly between different populations.

Early epidemiological studies[4,5] suggested an inverse association between selenium levels and the risk of cancer. However, results from the Nutritional Prevention of Cancer Trial (NPCT)[6] involving 1312 subjects who received 200 μg of selenized yeast or a placebo per day for 4.5 years (mean) reported a strong inverse association between selenium and prostate

* *Corresponding author:* Tel.: +32 16 332 696; fax: +32 16 337 480.
E-mail address: brinkman@skynet.be (M. Brinkman).
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cancer specifically. Although incidence of non-melanoma skin cancer was the primary outcome of this study, secondary analysis revealed a 63% reduced risk in prostate cancer among subjects taking selenium supplementation.[6]

Additional follow-up and analysis for the complete treatment period of this trial indicated that selenium supplementation continued to significantly reduce the overall incidence of prostate cancer.[7] This protective effect however, was restricted to participants in the lowest tertiles of plasma selenium (<123.2 ng/ml).[7]

Clinical trials investigating the relationship between selenium and the risk of prostate cancer are currently underway.[8,9] However, results from the SELECT trial[10] involving 32,400 men will not be available until 2013. Several epidemiological studies investigating selenium levels and the risk of prostate cancer have found both an inverse association[11–15] and no association.[16–18]

A recent meta-analysis[19] of observational studies investigated the effect of selenium intake on prevention of prostate cancer and reported that a higher selenium intake may reduce the risk of prostate cancer. This study used blood, toenail and plasma measures and dietary questionnaires to estimate selenium intake. There are however problems associated with pooling selenium data using different sources and scales. It is also difficult to estimate selenium intake using dietary questionnaires without validation from human biomarkers as large variations in food supplies and importation of food between countries can influence measurement. Analysis of risk association solely in terms of comparison between quantiles also does not seem appropriate as the reported highest levels from some regions do not reach the lowest levels from others.

This meta-analysis provided an update of the literature and an alternative approach to investigating the association between selenium and the risk of prostate cancer. Actual mean differences in serum, plasma and toenail levels between cases and controls/cohorts were analysed both separately and combined using a random effects' model to investigate the association between selenium levels and the risk of prostate cancer.

2. Methods

2.1. Search strategy

A computerised search of PubMed (1966-Jan 2006), EMBASE (1974-Jan 2006) and Current Contents (1998-Jan 2006) was conducted to identify epidemiologic studies relating to selenium and prostate cancer.

The combination of free text terms *prostat* cancer and selen** formed the basis of the search. These were combined with *chemoprevention, case–control studies, cohort studies, epidemiologic studies OR prospective studies.* Medical subject heading (*MeSH*) terms *prostatic neoplasms, urological neoplasms, or urogenital neoplasms* were also combined with selenium (MeSH). Selenium levels or antioxidants and risk were added to *prostat*cancer. Selen*, cancer and epidemiologic studies* were used to locate any further studies containing prostate cancer cases. There was no language restriction placed on the search.

All references from retrieved publications were thoroughly checked until no further studies could be identified.

2.2. Inclusion/exclusion criteria

Inclusion criteria for studies were: (1) articles from peer reviewed medical journals; (2) cohort, nested case–control studies and case–control studies; (3) studies containing selenium serum, plasma and toenail measures; (4) studies providing numbers, mean selenium measures and standard deviations (SDs) for both cases and controls; (5) if SDs were not available they could be calculated by alternative means; and (6) studies which reported prostate cancer incidence.

Studies only assessing dietary intake were excluded due to large variability in the selenium content of food and limitations associated with food frequency questionnaires and other dietary measurements.[16] Due to the generally long time interval between prostate cancer diagnosis and death, mortality studies were excluded from this review.[20] Cross-sectional studies were considered ineligible because they report prevalence and not incidence.[21] As benign prostate hyperplasia (BPH) may be a precursor to prostate cancer, studies using only controls with this disease were also excluded.[22]

2.3. Data extraction

Two researchers (M.B. and E.K.) independently reviewed all studies and abstracted data using a standardised form. One researcher (E.K.) was blinded to the author, title of the journal, references, acknowledgements and associations of all papers. Year of publication was available to both researchers to enable analysis of prostate cancer pre and post prostate specific antigen (PSA) era. A study was considered to be in the PSA era if it was conducted after 1989 when PSA measurement became more routinely available to clinicians in most developed countries.[23] Results were available to both researchers for quantitative data extraction.

2.4. Qualitative data extraction

Study characteristics extracted from each paper were: country, year of publication, design (cohort, nested case-control study, case–control study), selenium measure (serum, plasma and toenail), ethnicity (defined as white, black, Asian or unknown when an ethnic group consisted of more than 50% of the total number of subjects), setting (population, cancer registry, hospital and specimen bank), number of patients and controls/cohort, stage of disease (local, advanced, both and unknown), method of diagnosis (histological, pathological, hospital record and unknown) mean age and SD of subjects. Authors of retrieved articles were contacted where necessary and asked to provide additional information. Any disagreement between researchers was resolved by continuing discussions until consensus was reached.

2.5. Quantitative data extraction

The mean difference in selenium levels between prostate cancer cases and their controls/cohorts was the major outcome of this study. Mean selenium levels and standard deviations for cases and controls/cohorts were extracted from all individual studies. When standard deviations were unavailable they were calculated from the range of selenium

measures,[12,15,24,25] standard error of the mean,[26] standard error of the mean difference,[27,28] confidence intervals (CIs)[29] or obtained directly from the author.[25] Where only the median and no other selenium values were available, then this was used in analysis.[15,25]

A third, independent researcher (RR) also extracted quantitative data, checked calculations and repeated the analysis in order to prevent mathematical errors.

2.6. *Statistical analysis*

The effect size[30] was calculated for each study using the mean difference divided by the pooled estimate of the standard deviation in order to express the effect size in a common metric; the standardized mean difference (SMD). SMDs and corresponding 95% CIs were pooled using a random effects model. A SMD of 0.2 was considered small, 0.5 medium and 0.8 large[31] and was considered statistically significant if zero was not included in the 95% CI. Following standardisation of selenium measures for each group, *e.g.* serum studies (μg/l); plasma studies (μg/l); toenail studies (μg/g), actual mean differences and corresponding standard error of mean difference for each individual study were pooled in each group also using a random effects model. The Q statistic which measures the homogeneity between studies was used to determine the presence of heterogeneity.[32] Sensitivity and subgroup analyses were conducted in preference to quality scoring as they were considered to be a more appropriate way of dealing with methodological differences between studies. Possible sources of heterogeneity were explored using meta-regression analysis to examine the influence of the following study characteristics: study design, different selenium measures, ethnicity and PSA era on the SMD. Mean age was similar both among the studies and between cases and controls/cohorts and was not included in meta-regression analysis. Stage of the disease was also not included in the meta-regression analysis due to lack of available information. In a sensitivity analysis, highly influential studies were excluded to increase homogeneity and analysis was repeated to compare results without these studies. Variance between studies was estimated iteratively using the empirical Bayes' method.[33] Publication bias was investigated visually by a funnel plot and statistically via Egger's unweighted regression test which measures the degree of funnel plot asymmetry.[34] The trim and fill method[35] which is based on the funnel plot was also used to investigate publication bias. This method provides an estimate of the number of possible missing studies and then repeats a meta-analysis which also includes these studies. The correlation between mean selenium levels of controls/cohorts and SMD was also examined. All statistical analyses were performed by Stata statistical software version 8.[36]

3. Results

3.1. *The literature search*

The search strategy (Fig. 1) identified 51 epidemiologic studies. Subsequent evaluation resulted in the exclusion of 32 studies from the analysis. These included: six dietary studies;[16,17,37–40] six mortality studies;[20,41–45] two cross-sectional studies;[21,46] two studies which measured only prostate tissue;[47,48] one study which used controls with BPH;[22] 14 studies which did not contain either the number of prostate cases or selenium measures[49–62] and one study which had only one case.[63] A total of 19 papers[11–15,18,24–29,64–70] met inclusion criteria of which one[26] contained two separate study populations (black and white), resulting in 20 studies which were included in the analysis.

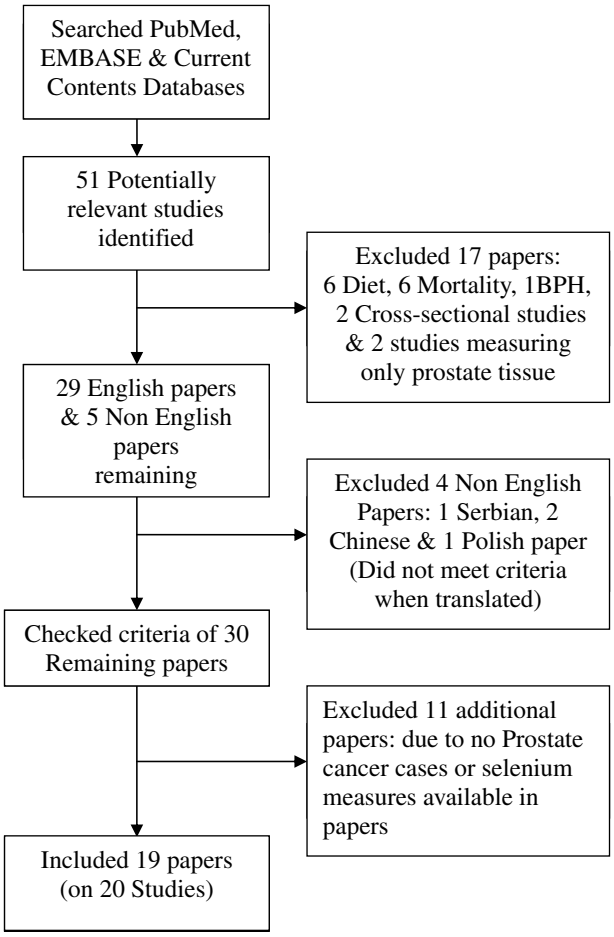

Fig. 1 – Flow chart of results of the literature search.

3.2. *Study characteristics*

The characteristics of all studies are presented in Table 1. A total of 2889 cases and 5032 controls/cohort members (including one sub-sample from a cohort;[14]) were identified from the 20 studies. Study designs included nine nested case–control studies;[11–13,15,18,27,28,64,65] nine case–control studies[24–26,29,66,68–70] (Ref. [26] contains two studies in one paper); one cohort[67] and one case–cohort study.[14] Serum, toenail and plasma selenium measures were used in 11,[12,18,26–29,65,67–69] six[13–15,24,25,66] and three studies[11,64,70], respectively. Fifteen studies[11–15,24–26,29,64–66,68,70] were undertaken during the PSA era. The mean age for cases and controls/cohorts was calculated from 15 studies[11,12,14,15,18,24–27,29,65,66,69,70] and were 63.7 and 61.6

Table 1 – Summary of studies included in analysis

Country	Study design	No. of cases	No. of controls	Measure	Results
USA	Nested cc	52	96	Plasma	OR = 0.24 (0.08–0.77; p = 0.01) highest *versus* lowest quartile
USA	Nested cc	586	577	Plasma	OR = 0.52 (0.28–0.98; *p*-trend = 0.05) highest *versus* lowest quintile (advanced cases)
Poland	Case–control	32	39	Plasma	Se 70.9 ng/ml (SD; 13.9) cases; 73.9 ng/ml (SD; 13.0) controls
USA	Nested cc	11	22	Serum	Se 0.128 μg/ml cases; 0.139 μg/ml controls; (SEMD; 0.009; *p* = 0.12)
USA	Case–control	101	112	Serum	OR = 0.68 (0.28–1.61; *p*-trend = 0.14) highest *versus* lowest quartile
USA	Case–control	111	121	Serum	OR = 0.70 (0.30–1.64; *p*-trend = 0.51) highest *versus* lowest quartile
USA	Nested cc	249	249	Serum	OR = 0.5 (0.30–0.9; *p*-trend = 0.02) highest *versus* lowest quartile
USA	Nested cc	235	456	Serum	OR = 1.02 (0.65–1.60; *p*-trend = 0.69) highest *versus* lowest quartile
Finland	Nested cc	51	92	Serum	OR = 1.15; *p*-trend = 0.71 highest *versus* lowest fifths
Spain	Case–control	116	107	Serum	Se 69.90 μg/l (95% CI: 67.74–72.07) cases; 74.88 μg/l (95% CI: 72.0–77.76) controls; $p < 0.05$
USA	Nested cc	14	28	Serum	Se 0.120 μg/ml cases; 0.117 μg/ml controls; (SEMD; 0.007)
Finland	Cohort study	14	964	Serum	Se 58.9 μg/l (SEM; 4.3) cases; 55.3 μg/l (SEM; 0.5) controls
Turkey	Case–control	10	101	Serum	Se 68.3 μg/l (SD; 11.9) cases; 94.1 μg/l (SD; 12.5) controls
Bulgaria	Case–control	34	33	Serum	Se 41.66 μg/l (SD; 9.45) cases; 54.73 μg/l (SD; 10.80) controls; $p = < 0.001$
England	Case–control	300	300	Nail	OR = 1.24 (0.73–2.10) highest *versus* lowest quartile
Netherlands	Case-cohort	522	1211	Toenail	OR = 0.69 (0.48–0.99; *p*-trend = 0.008) highest *versus* lowest quintile
USA	Nested cc	181	181	Toenail	OR = 0.35 (0.16–0.78; *p*-trend = 0.03) highest *versus* lowest quintile
USA	Nested cc	117	233	Toenail	OR = 0.65 (0.32–1.32; *p*-trend = 0.28) highest *versus* lowest quintile;significant when gamma tocopherol levels high
Canada	Case–control	83	82	Toenail	OR = 1.14 (0.46–2.83; *p*-trend = 0.62) highest *versus* lowest quartile
Austria	Case–control	70	28	Toenail	Se 528 ng/g (range: 393–4274) cases; 502 ng/g (range: 201–831) controls (*P* value not significant)

Nested cc, nested case–control study; case–control, case–control study; case-cohort, case-cohort study; Se, selenium; OR, odds ratio; figures in parentheses following odds ratio = 95% Confidence Intervals; SD, standard deviation; SEMD, standard error of the mean difference; SEM, standard error of the mean.

years, respectively. White was either the sole or predominant ethnic group in 12 studies.[11,14,15,18,24–28,64–66]

Seven studies[18,24,25,28,65–67] reported no association between case status and selenium level; 13[11–15,26,27,29,64,68–70] indicated an inverse association of which eight[11–14,29,64,68,69] were statistically significant; four[26,27,70] were not statistically significant and one[15] was statistically significant when γ-tocopherol levels were high.

3.3. *Standardized mean difference*

The results of a meta-analysis for all 20 studies combined are presented in Fig. 2. A small negative but statistically significant SMD was obtained for the combined studies; –0.23 (95% CI: –0.40; –0.05; $p = 0.01$) indicating that selenium levels were lower in the prostate cancer cases compared to controls/cohorts. Heterogeneity was statistically significant between these studies; Q = 195.32 ($p = 0.00$). Meta-regression analysis examining the influence of four covariates; design, measure, PSA era and ethnicity on the SMD indicated that only study design had a significant effect on the results; $p = 0.046$. Results for ethnicity ($p = 0.06$), measure ($p = 0.71$) and PSA era ($p = 0.93$) were not significant. Three potentially influential studies are identified in Fig. 2. A statistically significant but very small negative SMD was also obtained after these studies were excluded from an additional meta-analysis of the remaining 17 studies; –0.06 (95% CI: –0.11; –0.01; $p = 0.02$). Heterogeneity was also no longer significant following removal of the influential studies (Q = 15.69; $p = 0.48$).

Although the funnel plot (Fig. 3) was slightly asymmetrical, this was not statistically significant according to Egger's unweighted regression test (–0.31) or from the trim and fill method which indicated no change in the SMD (data not shown). Subgroup analysis of retrospective and prospective study designs resulted in a SMD of –0.56 (95% CI: –1.06; –0.07; –0.03) and –0.07 (95% CI: –0.13; –0.002; –0.047), respectively. Heterogeneity remained significant for the retrospective design (Q = 175.40; –0.00) but was not significant for the prospective design (Q = 11.89; $p = 0.30$). No correlation was observed between mean selenium levels (controls/cohorts) and SMD (data not shown).

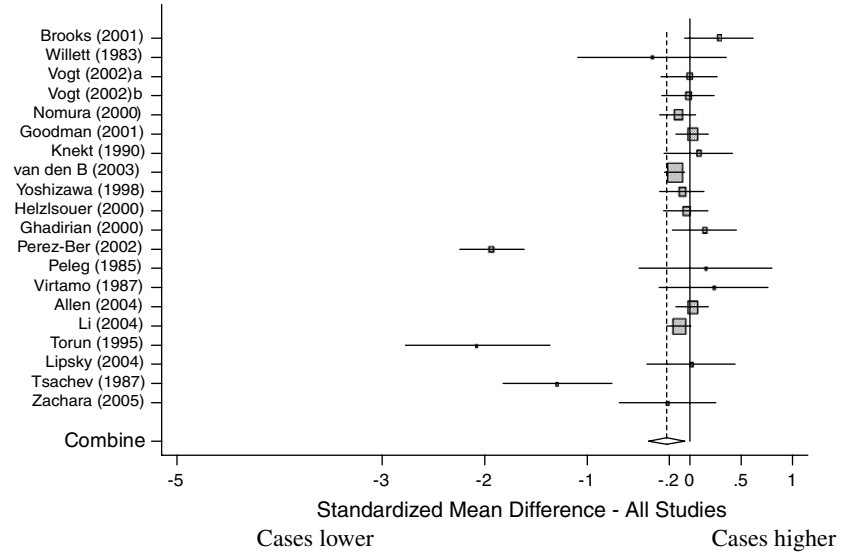

Fig. 2 – Forest plot of standardized mean differences (boxes) and 95% confidence intervals (horizontal lines) between prostate cancer cases and their controls/cohorts for all studies combined.

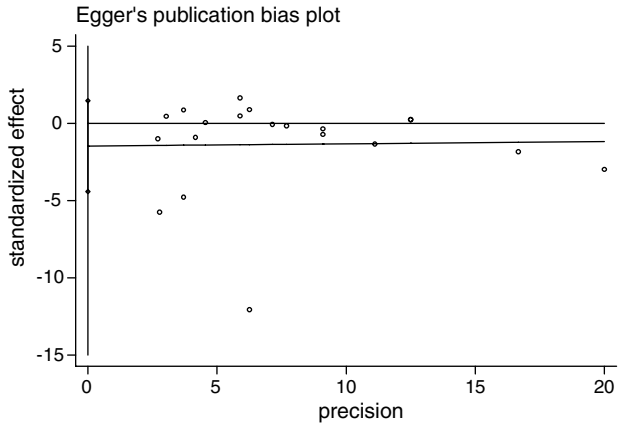

Fig. 3 – Publication bias funnel plot indicating effect estimates against estimated precision for each study.

3.4. *Mean differences*

A meta-analysis of the 11 serum studies (Fig. 4a) resulted in a large, negative and statistically significant mean difference between cases and controls; –5.55 μg/l (95% CI: –9.82; –1.27; $p = 0.01$). There was however, significant heterogeneity between these studies ($Q = 59.90$; $p = 0.00$). Meta-regression analysis of the covariates indicates that both design ($p = 0.003$) and ethnicity ($p = 0.03$) but not PSA era ($p = 0.43$) had an effect on the mean differences.

Pooling of the toenail studies (Fig. 4b) resulted in a very small, negative and not statistically significant mean difference between the cases and controls/cohorts; –0.01 μg/g (95% CI: –0.03; 0.006; $p = 0.19$). Heterogeneity was not significant between the six toenail studies ($Q = 4.07$; $p = 0.54$).

The combined mean difference for the three plasma studies (Fig. 4c) indicated that selenium levels were lower in cases but not statistically significant; –0.52 μg/l (–4.63; 3.58; $p = 0.80$). Heterogeneity was also not statistically significant between these studies ($Q = 4.59$; $p = 0.10$).

4. Discussion

This meta-analysis consisted of 20 epidemiological studies from diverse populations and found that selenium levels were lower in cases compared to controls/cohorts. Results from this meta-analysis agree with previous studies[7,19] which suggest that there is a possible inverse association between selenium and prostate cancer. Several studies reported that the inverse association between selenium levels and risk of prostate cancer was strongest in cases with advanced disease.[11–14] These findings suggest that selenium may not only be involved in incidence but may also have a role in progression of prostate cancer. The PSA era appeared to have no influence on the effect estimate. Vitamin E was reported to have both an effect[15,26,27] and no effect[14,24] on the association between selenium and prostate cancer.

Subgroup analyses of serum, toenail and plasma studies also found that selenium levels were lower in cases than controls/cohorts.

Even though publication bias was not evident, the epidemiological studies included in this review were heterogeneous. Advantages of this diversity and meta-analysis are that it highlights the contribution of each study to the available literature and areas which require further investigation.

4.1. *Selenium levels*

Selenium levels varied considerably between populations in this review. Generally, studies conducted in the United States had higher selenium levels in both cases and controls/cohorts than those in Europe. Some European studies[18,29] had values approximately a half or lower[69] than those reported from studies from the United States making comparison of the highest selenium levels to the lowest to determine relative

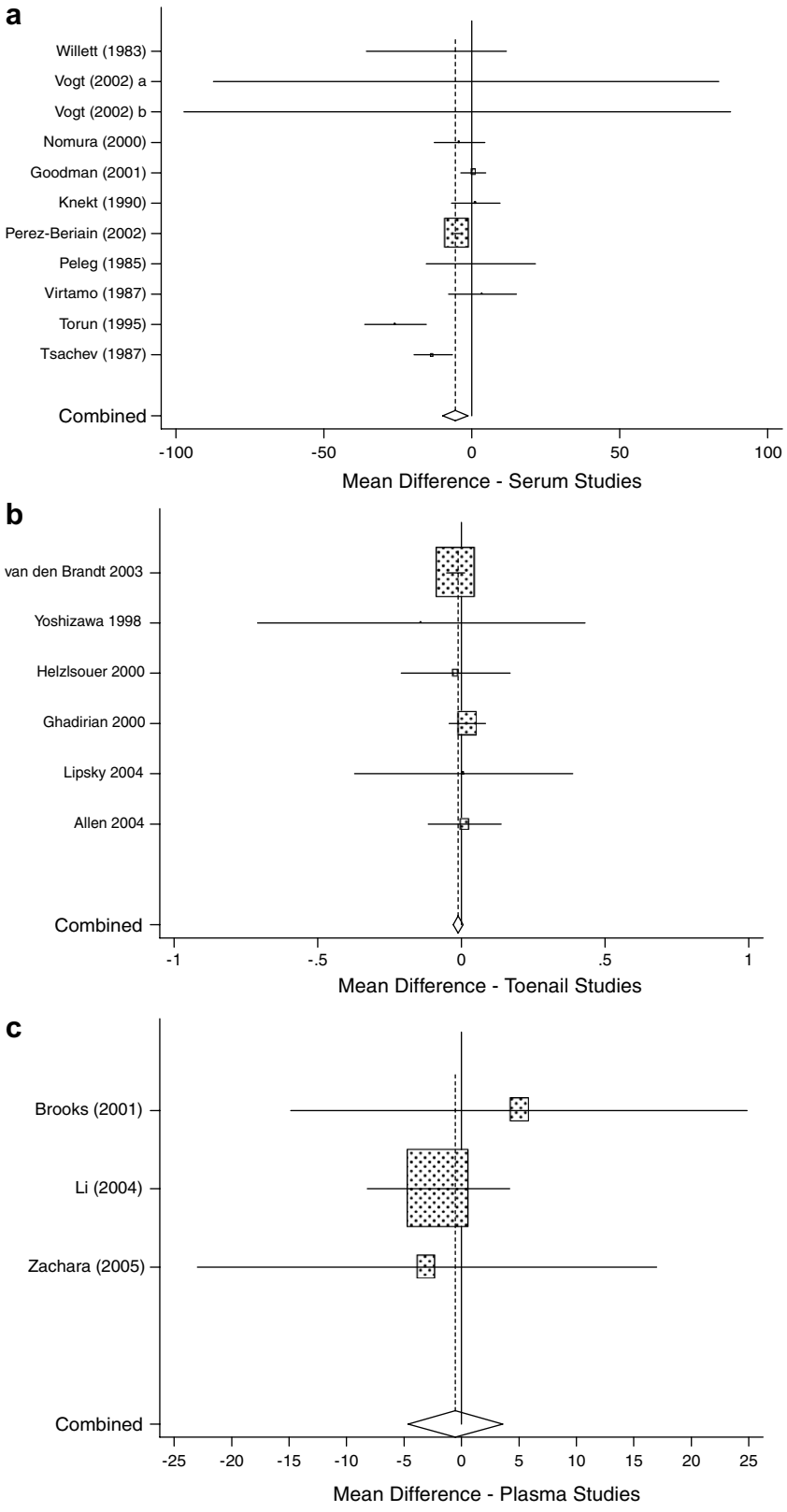

Fig. 4 – Forest plots of actual mean differences between cases and controls/cohorts for (a) serum studies (μg/l), (b) toenail studies (μg/g) and (c) Plasma studies (μg/l).

risks or odds ratios difficult. The influential studies [29,68,69] where the SMDs were greatest originated from Spain, Turkey and Bulgaria. These studies had the largest differences between cases and controls with very small variances resulting in larger SMDs. One US study[26] analysed serum selenium from black and white males separately and found that the

risk of prostate cancer was similar for both ethnic groups. This suggests that not only genetics is involved in these population differences but other factors must also be considered.

A number of the studies found that men in the lowest selenium level had the greatest risk of prostate cancer.[7,12,15,26,27,64] Serum levels above which there is reported to be a reduced risk of prostate cancer range from 115 to 147 ug/L.[12,27,64] While no threshold effect could be determined from this meta-analysis, it has been postulated that there is a possible threshold effect where selenium levels must reach certain concentrations to influence carcinogenesis.[26,64] This could explain inconsistencies present in the literature. Some previous studies have contained controls with selenium levels below the threshold to prevent carcinogenesis. Alternatively, one study noted that once selenium reached a certain level, there was no additional benefit from having higher values.[64] Age, smoking and manganese superoxide dismutase (*MnSOD*), glutathione *S*-transferase M1 (*GSTM1*) and 15-kDa selenoprotein (*SEP15*) polymorphisms are thought to reduce selenium levels.[11,14,26,64,71,72] It has been suggested that selenium supplementation may protect men who are in these categories. Potential toxicity is a serious issue when considering supplementation, however, doses of selenium between 200 μg and 3200 μg as selenised yeast have been administered in clinical trials without reports of serious adverse effects.[7,73]

4.2. *Study design*

Meta-regression analysis identified study design as a potential source of heterogeneity. Although inclusion of retrospective studies is not ideal when trying to establish aetiology, they make a large contribution to the literature investigating the association between selenium and prostate cancer, consisting of approximately 50% of the papers. A general concern associated with retrospective studies is the potential for recall bias; however as exposure was measured using biological markers this was avoided. Results from clinical trials have indicated that these biomarkers are useful indicators of selenium exposure.[6,74] Subgroup analysis of study design also found that results were in the same direction for both prospective and retrospective studies. As the nine case-control studies[24–26,29,66,68–70] were conducted in eight different countries these studies also highlighted the differences in selenium levels between populations.

5. Conclusion

This meta-analysis of all currently available epidemiological studies suggests that men with low selenium levels are at increased risk of prostate cancer.

Further exploration of genetic and environmental factors may help to explain population differences in selenium levels and prostate cancer incidence.

Future research should try to determine if there is a threshold level for selenium to protect against prostate cancer with particular reference to the stage of the disease and how it relates to current intake and recommended daily allowances. Results from ongoing clinical trials may help to address some of the issues raised in this paper.

Conflict of interest statement

The authors have no conflict of interest to declare.

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REFERENCES

1. Ferlay J, Bray F, Pisani P, Parkin DM. GLOBOCAN 2002. In: *Cancer incidence, mortality and prevalence worldwide. IARC Cancer Base No. 5 Version 2.0*. Lyon, France: IARC Press; 2004.
2. Shimizu H, Ross RK, Bernstein L, Yatani R, Henderson BE, Mack TM. Cancers of the prostate and breast among Japanese and white immigrants in Los Angeles County. *Br J Cancer* 1991;**63**(6):963–6.
3. Platz EA, Helzlsouer KJ. Selenium, zinc, and prostate cancer. *Epidemiol Rev* 2001;**23**(1):93–101.
4. Shamberger RJ, Tytko SA, Willis CE. Antioxidants and cancer Part VI. Selenium and age-adjusted human cancer mortality. *Arch Environ Health* 1976;**31**(5):231–5.
5. Schrauzer GN, White DA, Schneider CJ. Cancer mortality correlation studies–III: statistical associations with dietary selenium intakes. *Bioinorg Chem* 1977;**7**(1):23–31.
6. Clark LC, Combs Jr GF, Turnbull BW, et al. Effects of selenium supplementation for cancer prevention in patients with carcinoma of the skin. A randomized controlled trial. Nutritional Prevention of Cancer Study Group. *JAMA* 1996;**276**(24):1957–63.
7. Duffield-Lillico AJ, Dalkin BL, Reid ME, et al. Selenium supplementation, baseline plasma selenium status and incidence of prostate cancer: an analysis of the complete treatment period of the Nutritional Prevention of Cancer Trial. *BJU Int* 2003;**91**(7):608–12.
8. Stratton MS, Reid ME, Schwartzberg G, et al. Selenium and inhibition of disease progression in men diagnosed with prostate carcinoma: study design and baseline characteristics of the 'Watchful Waiting' Study. *Anticancer Drugs* 2003;**14**(8):595–600.
9. Stratton MS, Reid ME, Schwartzberg G, et al. Selenium and prevention of prostate cancer in high-risk men: the Negative Biopsy Study. *Anticancer Drugs* 2003;**14**(8):589–94.
10. Klein EA. Selenium and vitamin E cancer prevention trial. *Ann NY Acad Sci* 2004;**1031**:234–41.
11. Li H, Stampfer MJ, Giovannucci EL, et al. A prospective study of plasma selenium levels and prostate cancer risk. *J Natl Cancer Inst* 2004;**96**(9):696–703.
12. Nomura AM, Lee J, Stemmermann GN, Combs Jr GF. Serum selenium and subsequent risk of prostate cancer. *Cancer Epidemiol Biomarkers Prev* 2000;**9**(9):883–7.
13. Yoshizawa K, Willett WC, Morris SJ, et al. Study of prediagnostic selenium level in toenails and the risk of advanced prostate cancer. *J Natl Cancer Inst* 1998;**90**(16):1219–24.
14. Van den Brandt PA, Zeegers MP, Bode P, Goldbohm RA. Toenail selenium levels and the subsequent risk of prostate cancer: a prospective cohort study. *Cancer Epidemiol Biomarkers Prev* 2003;**12**(9):866–71.
15. Helzlsouer KJ, Huang HY, Alberg AJ, et al. Association between alpha-tocopherol, gamma-tocopherol, selenium, and subsequent prostate cancer. *J Natl Cancer Inst* 2000;**92**(24):2018–23.

16. West DW, Slattery ML, Robison LM, French TK, Mahoney AW. Adult dietary intake and prostate cancer risk in Utah: a case-control study with special emphasis on aggressive tumors. *Cancer Causes Control* 1991;**2**(2):85–94.
17. Hartman TJ, Albanes D, Pietinen P, et al. The association between baseline vitamin E, selenium, and prostate cancer in the alpha-tocopherol, beta-carotene cancer prevention study. *Cancer Epidemiol Biomarkers Prev* 1998;**7**(4):335–40.
18. Knekt P, Aromaa A, Maatela J, et al. Serum selenium and subsequent risk of cancer among Finnish men and women. *J Natl Cancer Inst* 1990;**82**(10):864–8.
19. Etminan M, FitzGerald JM, Gleave M, Chambers K. Intake of selenium in the prevention of prostate cancer: a systematic review and meta-analysis. *Cancer Causes Control* 2005;**16**(9):1125–31.
20. Kornitzer M, Valente F, De Bacquer D, Neve J, De Backer G. Serum selenium and cancer mortality: a nested case-control study within an age- and sex-stratified sample of the Belgian adult population. *Eur J Clin Nutr* 2004;**58**(1):98–104.
21. Navarro-Alarcon M, de la Serrana HL, Perez-Valero V, Lopez-Martinez C. Serum selenium levels as indicators of body status in cancer patients and their relationship with other nutritional and biochemical markers. *Sci Total Environ* 1998;**212**(2-3):195–202.
22. Hardell L, Degerman A, Tomic R, Marklund SL, Bergfors M. Levels of selenium in plasma and glutathione peroxidase in erythrocytes in patients with prostate cancer or benign hyperplasia. *Eur J Cancer Prev* 1995;**4**(1):91–5.
23. Moul JW. Population screening for prostate cancer and emerging concepts for young men. *Clin Prostate Cancer* 2003;**2**(2):87–97.
24. Allen NE, Morris JS, Ngwenyama RA, Key TJ. A case–control study of selenium in nails and prostate cancer risk in British men. *Br J Cancer* 2004;**90**(7):1392–6.
25. Lipsky K, Zigeuner R, Zischka M, et al. Selenium levels of patients with newly diagnosed prostate cancer compared with control group. *Urology* 2004;**63**(5):912–6.
26. Vogt TM, Ziegler RG, Graubard BI, et al. Serum selenium and risk of prostate cancer in U.S. blacks and whites. *Int J Cancer* 2003;**103**(5):664–70.
27. Willett WC, Polk BF, Morris JS, et al. Prediagnostic serum selenium and risk of cancer. *Lancet* 1983;**2**(8342):130–4.
28. Peleg I, Morris S, Hames CG. Is serum selenium a risk factor for cancer? *Med Oncol Tumor Pharmacother* 1985;**2**(3):157–63.
29. Perez-Beriain R, Comet A, Castrillo J, et al. Selenium and prostate. *Met Ion Biol* 2002;**7**:586–8.
30. Hedges L, Olkin I. *Statistical methods for meta-analysis*. Orlando (FL): Academic Press; 1985.
31. Cohen J. *Statistical power analysis for the behavioural sciences*. 2nd ed. Hillside (NJ): Erlbaum; 1988.
32. Egger M, Davey Smith G, Altman DG. *Systematic reviews in health care*. London: BMJ Publishing Group; 2001.
33. Berkey CS, Hoaglin DC, Antczak-Bouckoms A, Mosteller F, Colditz GA. Meta-analysis of multiple outcomes by regression with random effects. *Stat Med* 1998;**17**(22):2537–50.
34. Egger M, Davey SG, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;**315**(7109):629–34.
35. Duval S, Tweedie R. Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics* 2000;**56**(2):455–63.
36. Stata Statistical Software, Release 8.0 Intercooled, TX [computer program]; 2003.
37. Lee MM, Wang RT, Weal Hsing A. Case–control study of diet and prostate cancer in China. *Cancer Causes Control* 1998;**9**(6):545–52.
38. Norrish AE, Jackson RT, Sharpe SJ, Skeaff CM. Men who consume vegetable oils rich in monounsaturated fat: their dietary patterns and risk of prostate cancer (New Zealand). *Cancer Causes Control* 2000;**11**(7):609–15.
39. Key TJ, Silcocks PB, Davey GK, Appleby PN, Bishop DT. A case–control study of diet and prostate cancer. *Br J Cancer* 1997;**76**(5):678–87.
40. Jain MG, Hislop GT, Howe GR, Ghadirian P. Plant foods, antioxidants, and prostate cancer risk: findings from case–control studies in Canada. *Nutr Cancer* 1999;**34**(2):173–84.
41. Salonen JT, Salonen R, Lappetelainen R, Maenpaa PH, Alfthan P, Puska P. Risk of cancer in relation to serum concentrations of selenium and vitamins A and E: matched case–control analysis of prospective data. *Br Med J (Clin Res Ed)* 1985;**290**(6466):417–20.
42. Criqui MH, Bangdiwala S, Goodman DS, et al. Selenium, retinol, retinol-binding protein, and uric acid. Associations with cancer mortality in a population-based prospective case-control study. *Ann Epidemiol* 1991;**1**(5):385–93.
43. Fex G, Pettersson B, Akesson B. Low plasma selenium as a risk factor for cancer death in middle-aged men. *Nutr Cancer* 1987;**10**(4):221–9.
44. Kok FJ, De Bruijn AM, Hofman A, Valkenburg HA. Selenium status and chronic disease mortality: Dutch epidemiological findings. *Int J Epidemiol* 1987;**16**(2):329–32.
45. Drasch G, Schopfer J, Schrauzer GN. Selenium/cadmium ratios in human prostates: indicators of prostate cancer risk of smokers and nonsmokers, and relevance to the cancer protective effects of selenium. *Biol Trace Elem Res* 2005;**103**(2):103–7.
46. Nyman DW, Suzanne SM, Kopplin MJ, Dalkin BL, Nagle RB, Jay GA. Selenium and selenomethionine levels in prostate cancer patients. *Cancer Detect Prev* 2004;**28**(1):8–16.
47. Zachara BA, Szewczyk-Golec K, Wolski Z, et al. Selenium level in benign and cancerous prostate. *Biol Trace Elem Res* 2005;**103**(3):199–206.
48. Darago A, Sapota A, Duda-Szymanska J. Levels of cadmium, zinc, copper and selenium in subjects with diagnosed prostate cancer. *Rocz Panstw Zakl Hig* 2003;**54 Suppl.**:39–40.
49. Ujiie S, Kikuchi H. The relation between serum selenium value and cancer in Miyagi, Japan: 5-year follow up study. *Tohoku J Exp Med* 2002;**196**(3):99–109.
50. Jia ZG. Analysis of serum levels of selenium, zinc, and copper in 132 patients with malignant tumors. *Zhonghua Yu Fang Yi Xue Za Zhi* 1991;**25**(4):205–7.
51. Turan B. The serum selenium and immunoglobulins levels and healthy and cancer cases. *Biyokimya Dergisi* 1992;**17**:29–36.
52. Rohrmann S, Smit E, Giovannucci E, Platz EA. Association between serum concentrations of micronutrients and lower urinary tract symptoms in older men in the Third National Health and Nutrition Examination Survey. *Urology* 2004;**64**(3):504–9.
53. Ringstad J, Jacobsen BK, Tretli S, Thomassen Y. Serum selenium concentration associated with risk of cancer. *J Clin Pathol* 1988;**41**(4):454–7.
54. Coates RJ, Weiss NS, Daling JR, Morris JS, Labbe RF. Serum levels of selenium and retinol and the subsequent risk of cancer. *Am J Epidemiol* 1988;**128**(3):515–23.
55. Gupta S, Narang R, Krishnaswami K, Yadav S. Plasma selenium level in cancer patients. *Indian J Cancer* 1994;**31**(3):192–7.
56. Backovic D, Stamenic V, Marmut Z, Jorga J. Blood selenium in healthy persons and individuals with malignant diseases. *Srp Arh Celok Lek* 1998;**126**(1–2):18–22.
57. Salonen JT, Alfthan G, Huttunen JK, Puska P. Association between serum selenium and the risk of cancer. *Am J Epidemiol* 1984;**120**(3):342–9.
58. Bratakos MS, Vouterakos TP, Ioannou PV. Selenium status of cancer patients in Greece. *Sci Total Environ* 1990;**92**:207–22.

59. McConnell KP, Broghamer Jr WL, Blotcky AJ, Hurt OJ. Selenium levels in human blood and tissues in health and in disease. *J Nutr* 1975;**105**(8):1026–31.
60. Broghamer WL, McConnell KP, Blotcky AL. Relationship between serum selenium levels and patients with carcinoma. *Cancer* 1976;**37**(3):1384–8.
61. Robinson MF, Godfrey PJ, Thomson CD, Rea HM, van Rij AM. Blood selenium and glutathione peroxidase activity in normal subjects and in surgical patients with and without cancer in New Zealand. *Am J Clin Nutr* 1979;**32**(7):1477–85.
62. Ke-Jun N, Feng-Jie X, Shi-Yong Y. Serum selenium and blood glutathione peroxidase in cancer patients. *Chin J Clin Oncol* 1998;**25**:51–3.
63. Shamberger RJ, Rukovena E, Longfield AK, Tytko SA, Deodhar CE, Willis CE. Antioxidants and cancer. I. Selenium in the blood of normals and cancer patients. *J Natl Cancer Inst* 1973;**50**(4):863–70.
64. Brooks JD, Metter EJ, Chan DW, et al. Plasma selenium level before diagnosis and the risk of prostate cancer development. *J Urol* 2001;**166**(6):2034–8.
65. Goodman GE, Schaffer S, Bankson DD, Hughes MP, Omenn GS. Predictors of serum selenium in cigarette smokers and the lack of association with lung and prostate cancer risk. *Cancer Epidemiol Biomarkers Prev* 2001;**10**(10):1069–76.
66. Ghadirian P, Maisonneuve P, Perret C, et al. A case–control study of toenail selenium and cancer of the breast, colon, and prostate. *Cancer Detect Prev* 2000;**24**(4):305–13.
67. Virtamo J, Valkeila E, Alfthan G, Punsar S, Huttunen JK, Karvonen MJ. Serum selenium and risk of cancer. A prospective follow-up of nine years. *Cancer* 1987;**60**(2):145–8.
68. Torun M, Aldemir H, Yardim S. Serum selenium levels in various cancer types. *Trace Elements Electroly* 1995;**12**(4):186–90.
69. Tsachev K, Tsvetkov M, Kumanov K, Mladenov D, Filev A. Serum selenium levels of patients with adenoma and carcinoma of the prostate gland. *Khirurgiia (Sofiia)* 1987;**40**(2):33–5.
70. Zachara BA, Szewczyk-Golec K, Tyloch J, et al. Blood and tissue selenium concentrations and glutathione peroxidase activities in patients with prostate cancer and benign prostate hyperplasia. *Neoplasma* 2005;**52**(3):248–54.
71. Hoque A, Albanes D, Lippman SM, et al. Molecular epidemiologic studies within the Selenium and Vitamin E Cancer Prevention Trial (SELECT). *Cancer Causes Control* 2001;**12**(7):627–33.
72. Kumaraswamy E, Malykh A, Korotkov KV, et al. Structure-expression relationships of the 15-kDa selenoprotein gene Possible role of the protein in cancer etiology. *J Biol Chem* 2000;**275**(45):35540–7.
73. Reid ME, Stratton MS, Lillico AJ, et al. A report of high-dose selenium supplementation: response and toxicities. *J Trace Elem Med Biol* 2004;**18**(1):69–74.
74. El Bayoumy K, Richie Jr JP, Boyiri T, et al. Influence of selenium-enriched yeast supplementation on biomarkers of oxidative damage and hormone status in healthy adult males: a clinical pilot study. *Cancer Epidemiol Biomarkers Prev* 2002;**11**(11):1459–65.