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Relationship between selenium and prostate cancer risk; systematic review and meta-analysis and meta-regression

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ABSTRACT

Prostate cancer is one of the five most common cancers in men. It is suspected that selenium protect or exacerbate the risk of prostate cancer. The aim of this study was to determine the association between prostate cancer risk and selenium in the serum, toenail and supplements. So it was tried to do a systematic review and meta-analysis and meta-regression of 22 studies (5 toenail studies, 14 serum studies and 3 supplements studies) in order to obtain detailed results of these studies' data. Meta-regression results showed that location of study (p value <0.001), type of study (p value = 0.04) and age (p value =0.008) have significant effects on heterogeneity. There was no publication bias in studies (Begger's test: z-value = 1.98; P value=0.067). In general, unlike selenium supplements [OR=0.86 (CI: 0.7-1.06, P value=0.15], selenium increase in serum [OR=0.76 (0.59-0.99, P value=0.04] and toenail [OR=0.58 (0.4-0.86, P value=0.01] significantly decreased the risk of prostate cancer by %24 and 42 %. In general, the odds ratio between prostate cancer caused by selenium in the random effect model OR: 0.71 (CI: 0.59-0.86%, P value <0.001) and heterogeneity was moderate (I^2 = 70.6%, P value <0.001). The results of this study supported the lowering effect of selenium in serum and toenail on the risk of prostate cancer.

Key words: Selenium, Prostate Cancer, Serum, Toenail, Supplements, Meta-analysis and Meta-regression

INTRODUCTION

In prostate cancer, like other cancers, cells grow and multiply in an uncontrollable manner. Then cancer cells spread in the surrounding tissues, such as lymph nodes and bones [1]. In 2008, 13.8% (900,000) of all cancers in men were prostate cancer [2]. Although death from prostate cancer in the United States declined from 2000 to 2008, it is still a common disease. Prostate cancer is the fifth most common cancer and the second most common cancer in men [3].

It is estimated that 29% of all diagnosed cancers in men and 9% of death is related to prostate cancer [4]. Ecological studies have shown that the incidence of prostate cancer is low in Asia and Africa and is high in North America, Australia, New Zealand and northern Europe [5-7]. Prostate cancer prevention is helpful in both aspects of health and economics because in the United States the cost of treatment for every person is $ 10,000 [8]. Studies have shown that genetic and racial differences are effective in control [9,10] and treatment of prostate cancer by supplements of trace elements such as selenium [11-13]. For example, the incidence of prostate cancer in blacks is more than whites [14].

Trace elements play an important role in different intracellular processes. Instability of these elements disrupts cell functions and eventually causes disease [1]. One of these trace elements is selenium. Non-metallic selenium forms are selenite and selenite and organic selenium includes methylselenic acid and selenomethionine [15]. Selenium is combined with amino acids and therefore is called selenoproteins [16,17]. According to EPA reference dosage of selenium for prevention of adverse effects on health is 0.005 mg/kg-day [18].

Because of differences in the content of agricultural soil [19] and water [20] uptake of trace elements in various countries is different. Selenium in body can be both useful and harmful to human health. Selenium uptake to a certain extent has anticancer effects but too much uptake of selenium causes chronic toxicity in humans and causes diseases such as loss of hair and toenail, gastrointestinal problems, skin rash, garlic breath odor, nervous system abnormalities [21] and Keshan disease and Kashin-Beck disease [22]. Several mechanisms have been proposed to explain the anticancer effects of selenium which include: rehabilitation of damaged DNA, induction of phase II enzymes, increase of immunity, inhibition of cell cycle, angiogenesis and induction of apoptosis [23,24]. It should be noted that role and mechanism of trace elements in inhibition and development of cancer is very complex. Especially in the case of prostate cancer that little information exists about the effects of trace metals on cancer processes [1,25]. The protective effects of selenium on prostate cancer are approved by Nutritional Prevention of Cancer [26]. A systematic review and meta-analysis of the association between serum selenium and prostate cancer risk in 2007 showed that 10 ng/mL increase, reduce prostate cancer risk by 10%[27]. Another systematic review and meta-analysis in 2012 showed that toenail selenium in the range of 0.85 and 0.94 μg/g reduce the risk of prostate cancer (estimated RR: 0.29; 95% CI: 0.14, 0.61) [28]. But recent studies are not in line with these results

[30,29,9] . Some studies have shown that high intake of selenium supplements cannot reduce the risk of prostate cancer [29,31]. Some studies also showed that the use of selenium supplement not only don't reduce the risk of prostate cancer but also increase this risk (blood selenium concentration 122 μg/L) [32,33]. In general, some of the studies have shown selenium and prostate cancer association and others have shown no association [28]. Therefore, this study attempted to update a systematic review and meta-analysis and meta-regression of studies until 2016, and do a detailed assessment of the association between selenium and risk of prostate cancer.

MATERIALS AND METHODS

This study was a systematic review and meta-analysis of studies about association between selenium concentration in serum, toenail and Supplements with risk of prostate cancer. To find studies in Iran and in the world, SID, Irandoc, Scopus, Pubmed and ISI Web of Science databases were used.

The criteria of selection and evaluating quality of studies

At first a list of titles and abstracts of all studies included in mentioned databases by three researchers (Ya.F, Ha.K, Ab.B) was developed to avoid biased researchers. Related titles were evaluated independently and then studies that were published between 1990 and 2016 were analyzed. Search was done for 2 weeks from 18.01.2016 to 02.02.2016 and then related studies to the method of blinding initial assessment were independently entered into the study process. Similar studies were excluded. The main criterion inclusion of different articles to this study was refers to the selenium concentration in serum and blood and the prevalence of prostate cancer. Studies that were not part of the initial research and studies about treatment, determination of the clinical characteristics, clinical decision making and investigations unrelated to prostate cancer were excluded from research. In the second phase abstracts of different selected studies were evaluated by researcher using STROBE[1] checklist which is a standard checklist. This checklist contains 43 different sections and evaluates varied aspects of methodology including sampling methods, measuring the variables, statistical analysis and objectives of the study [34]. In this checklist the minimum attainable score was considered 40 and the maximum attainable score was considered 45. Eventually, best articles which gained the least score (40) from checklist questions were used in study and their data were extracted to conduct a meta-analysis process. To determine the sensitivity of study or Publication bias, Funnel Plot and Begg-

[1]Strengthening the reporting of observational studies in epidemiology

Mazumdar and Eggers tests were used. Also to determine the effect of other variables on heterogeneity, Meta Regression was used[35].

Data extraction

In this study 22 articles were evaluated. In all of them nearly the same methodology was used and they had been completed between 1990 and 2013. Important information needed to analyze data contains information related to the title and methodological information which includes way of study, kind of study, time of study, the odds ratio, sex, selenium concentration in serum and blood, the sample size and confidence level.

Data synthesis and analysis

All statistical analyses were done by Comprehensive Meta-Analysis V. 2.2.064 software. In this analysis statistics I^2 and t^2 using method moment base was calculated to determine the heterogeneity. After determining the low heterogeneity of the studies (I^2<50%) based on the fixed effect model, the mean odds ratio was calculated. After the initial analysis forest plot in stochastic model was used to determine the association between selenium and prostate cancer. Using meta-regression method, effects of variables like sample size, time of study and selenium concentrations that were suspected of causing heterogeneity in study, were investigated. A significance level was considered for the covariance of studies (P value < 0.05).

RESULTS

Twenty-two studies with a total of 82,927 participants and 7,543 cases were meta-analyzed (Table 1).

First Author	Year	Country	Type study	Subject	Case	Age	Measurements of selenium	Odds ratio	Low	High	Outcome	Ref
Geybels et al	2013	Netherlands	Prospective	2074	898	55–69	Toenail selenium	0.37	0.27	0.51	Toenail selenium was associated with a substantial decrease in risk of advanced PCa.	[36]
Grundmark et al	2011	Sweden	Prospective	2045	208	50	Serum selenium	0.83	0.6	1.16	S-Se levels and smoking habits influence long-term risk of prostate cancer. Smoking as a risk factor for PrCa in men with low s-Se is relevant to explore further. Exploratory analyses of variations in OGG1 and MnSOD genes indicate that hypotheses about patterns of exposure to selenium and smoking combined with data on genetic variation in genes involved in DNA repair can be valuable to pursue	[37]
Steinbrecher et al	2010	European	Cross-sectional	734	244	40–64	Serum selenium	0.78	0.49	1.22	support a role of selenium and polymorphisms in selenoenzymes in prostate cancer etiology, which warrants confirmation in future studies	[38]
Gill et al	2009	USA	Cross-sectional	1403	467	45–75	Serum selenium	0.82	0.59	1.14	No association of serum antioxidants or 15-isoprostaneF2t with the risk of prostate cancer. The observed inverse association of selenium with prostate cancerin African-Americans needs to be validated in other studies.	[39]
Allen et al	2008	Europe	Cross-sectional	2018	959	43–76	Serum selenium	0.96	0.7	1.31	Plasma selenium concentration was not associatedwith prostate cancer risk in this large cohort of Europeanmen	[40]
Pourmand et al	2008	Iran	Cross-sectional	130	62	40–90	Serum selenium	0.16	0.06	0.47	Serum selenium levels in prostate cancer cases were lower than in controls, which supportsthe hypothesis that selenium may protect against prostate cancerthe hypothesis that selenium may protect against prostate cancer	[41]
Peters et al	2008	Usa	Cross-sectional	35242	693	50–76	Selenium supplement	1	0.68	1.5	Genetic variation in seleno enzymes may modify the potential chemo preventive effect of selenium and need to be further investigated. Additional large observational studies using biomarkers of selenium intake and intervention trials, such as the Selenium and Vitamin E Cancer Prevention Trial, will be important to further evaluate the potential chemo preventive effect of selenium. Furthermore, characterization of functional effects of polymorphisms in seleno enzymes is needed.	[12]
Peters et al	2007	Usa	Cross-sectional	1603	724	55–74	Serum selenium	0.84	0.62	1.14	In this prospective cohort, long-term supplemental intake of vitamin E and selenium were notassociated with prostate cancer risk overall.	[42]
Li et al	2004	Usa	Prospective	1143	586	40–84	Serum selenium	0.78	0.54	1.13	The inverse association between baseline plasma selenium levels and risk of advanced prostate cancer, even among men diagnosed during the post-PSA era, suggests that higher levels of selenium may slow prostate cancer tumor progression. Ongoing randomized trials of selenium supplements may help to further evaluate this issue	[43]
Allen et al	2004	Britain	Case-control	600	300	44–77	Toenail selenium	1.24	0.73	2.1	Selenium is not strongly associated with prostate cancer risk in British men	[44]
Van den Brandt et al	1993	Netherlands	Prospective	1751	540	55–69	Toenail selenium	0.69	0.48	0.99	These data support a suggestive but inconsistent inverse association between selenium levels and risk of stomach and prostatecancers .	[45]
Goodman et al	2001	Usa	Cross-sectional	691	235	45–74	Serum selenium	1.02	0.65	1.6	In a subpopulation of 174 prostate cancer patients who had clinical and pathological staging material reviewed, there was no association between serum selenium and Gleason score or clinical or pathological stage. In the CARET population of current and former smokers consuming an ad libitum diet, the serum concentration of selenium was not a risk factor for either lung cancer or prostate cancer	[46]
Brooks et al	2001	Usa	Cross-sectional	148	52	68	Serum selenium	0.24	0.07	0.77	Low plasma selenium is associated with a 4 to 5-fold increased risk of prostate cancer. These results support the hypothesis that supplemental selenium may reduce the risk of prostate cancer. Because plasma selenium decreases with patient age, supplementation may be particularly beneficial to older men.	[47]
Ghadirian et al	2000	Canada	Cross-sectional	165	83	35–84	Toenail selenium	1.14	0.46	2.83	In a subpopulation of 174prostate cancer patients who had clinical and pathologicalstaging material reviewed, there was no associationbetween serum selenium and Gleason score or clinical orpathological stage. In the CARET population of currentand former smokers consuming an ad libitum diet, theserum concentration of selenium was not a risk factor foreither lung cancer or prostate cancer	[48]
Helzlsouer et al	2000	Usa	Cross-sectional	350	117	70	Serum selenium	0.38	0.17	0.85	When examined by fertile, the oddsratio associated with the lowest fertile of selenium compared to thehighest fertile was 2.06. Serum levels of retinol!, retinol-binding protein,and /9-carotene were similar among cases and controls. These resultssupport a role for selenium in the prevention of prostate cancer	[49]

Nomura et al	2000	Usa	Cross-sectional	498	249	44–85	Serum selenium	0.5	0.3	0.9	the association was mainly present in current or past cigarette smokers rather than nonsmokers, which leads to caution in the interpretation of the results	[50]
Hartman et al	1998	Usa	Prospective	29460	317	61	Serum selenium	1.32	0.7	2.47	associations between prostate cancer and vitamin E and some of the baseline dietary tocopherols differedsignificantly by a-tocopherol intervention status, with the suggestion of a protective effect for total vitamin Eamong those who received the a-tocopherol intervention (relative risk was 1.00, 0.68, 0.80, and 0.52 for increasingquartiles; P = 0.07).	[51]
Yoshizawa et al	1998	Usa	Cross-sectional	362	181	40–75	Toenail selenium	0.35	0.16	0.78	Our results supportearlier findings that higher seleniumintakes may reduce the risk of prostatecancer. Further prospective studies andrandomized trials of this relationshipshould be conducted.	[52]
Hardell et al	1995	Sweden	Cross-sectional	245	124	44–87	Serum selenium	0.3	0.1	0.7	No significant differences in levels of glutathione peroxidase in erythrocytes were found between cases and controls	[53]
Knekt et al	1990	Finland	Prospective	N/A	46	15-99	Serum selenium	1	0.42	2.4	Low serum selenium levels were associated with an increased risk of developing cancer at several sites, especially cancers of the stomach and lung among men. The relative risk of lung cancer between the highest and lowest decline of serum selenium was 0.11, and it differed significantly from unity (P<.001). These findings are in agreement with the hypothesis that low selenium intake may increase the risk of some cancers among men	[54]
Lippman et al	2009	Canada	Cross-sectional	8696	416	>50	Selenium supplement	1.04	0.83	1.3	Selenium or vitamin E, alone or in combination at the doses and formulations used, did not prevent prostate cancer in this population of relatively healthy men.	[29]
Duffid-Lillico et al	2003	Usa	Cross-sectional	470	42	65	Selenium supplement	0.48	0.28	0.8	To the end of the blinded treatment the NPC trial continued to show a significant protective effect of SS on the overall incidence of prostate cancer, although the effect was restricted to those with lower baseline PSA and plasma selenium concentrations.	[33]

In the Isi, Pubmed, Scopus, Irandoc and Sid databases, 362 studies were observed. 318 studies were excluded due to the difference in the title or abstract and some other reasons. 22 studies were excluded from the meta-analysis due to the lack of data (4 studies) or correlation or risk ratio (15 studies) and biomarker report (3 studies). 22 studies were meta-analyzed which contained 5 toenail studies, 14 serum studies and 3 supplement studies and examined the association between selenium and prostate cancer (Figure 1).

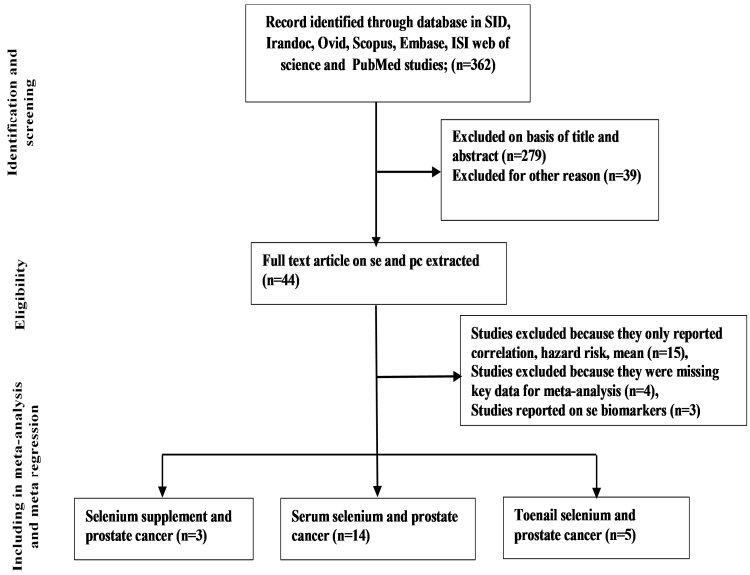


Fig. 1:Studies selection process for meta-analysis

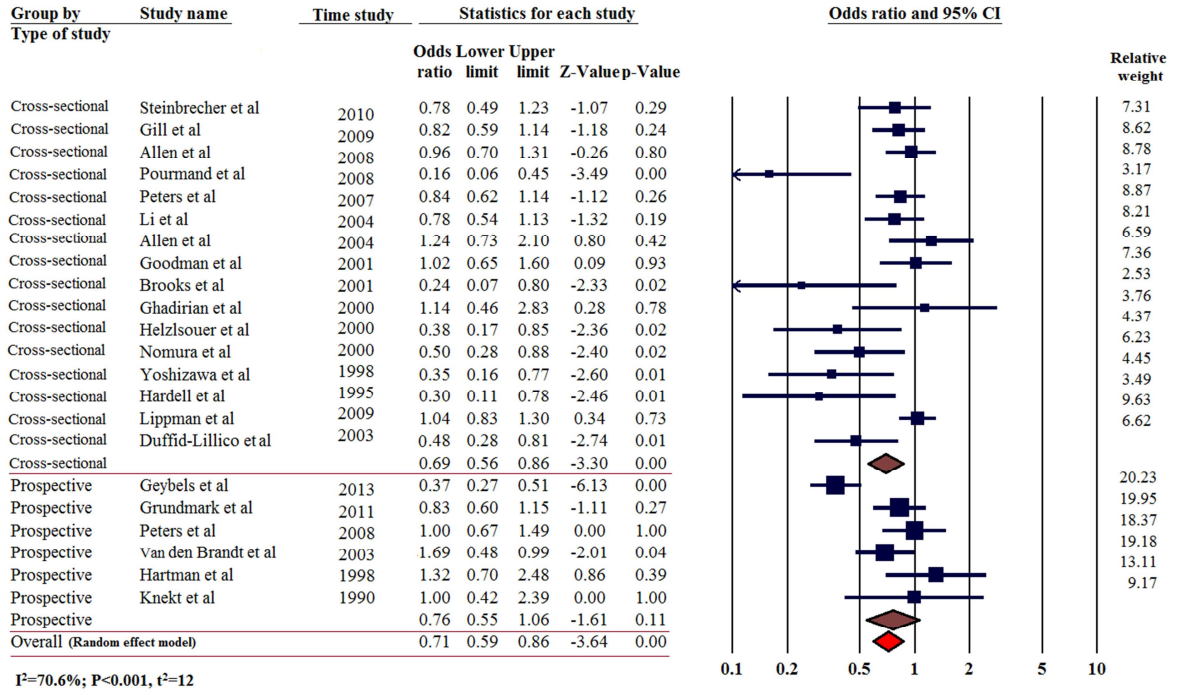
Effective variable in heterogeneity of studies was identified by meta-regression model. Therefore, covariances of location of study, time of study, type of study and sample size were used in meta-regression analysis in moment base method. Meta-regression results showed that location of study, kind of study and age have significant effects on heterogeneity. T^2 value after taking into account the covariances effect of age, date of study, location, sample number and type of study was respectively 0.11, 0.13, 0.08, 0.13 and 0.12 (Table 2).

The highest and lowest percentages of weight in cross-sectional studies were respectively related to the study of Hardell et al., (9.63%) and Brooks et al., (2.53%). In prospective studies the highest and lowest percentages of weight in cross-sectional studies were related to Geybls et al., (20.23%) and Knekt et al., (9.17%), respectively. The odds ratio mean in cross-sectional and prospective studies were respectively 0.69 (CI: 0.56-0.86) and 0.76 (CI: 0.55-1.06). In general, unlike selenium supplement (OR = 0.86 (0.7-1.06, P value = 0.15), increase of selenium in serum (OR= 0.76 (0.59-0.99, P value = 0.04) and toenail (OR = 0.58 (0.4-0.86, P value = 0.01) significantly decreases the risk of prostate cancer 24% and 42%, respectively (Figure 3).

The odds ratio of prostate cancer caused by selenium OR: 0.71 (0.59-0.86%, P value <0.001) to heterogeneity was moderate (I^2% = 70.6, P value<0.001) (Figure 2). Reverse Funnel plot showed the absence of publication bias (Figure 4). Statistical tests also confirmed this (Begger's test; z-value = 1.98; P = 0.067; Egger's test; t-value = -2.2, P = 0.086).

Table 2. Meta-regression analysis of co-variances in the studies

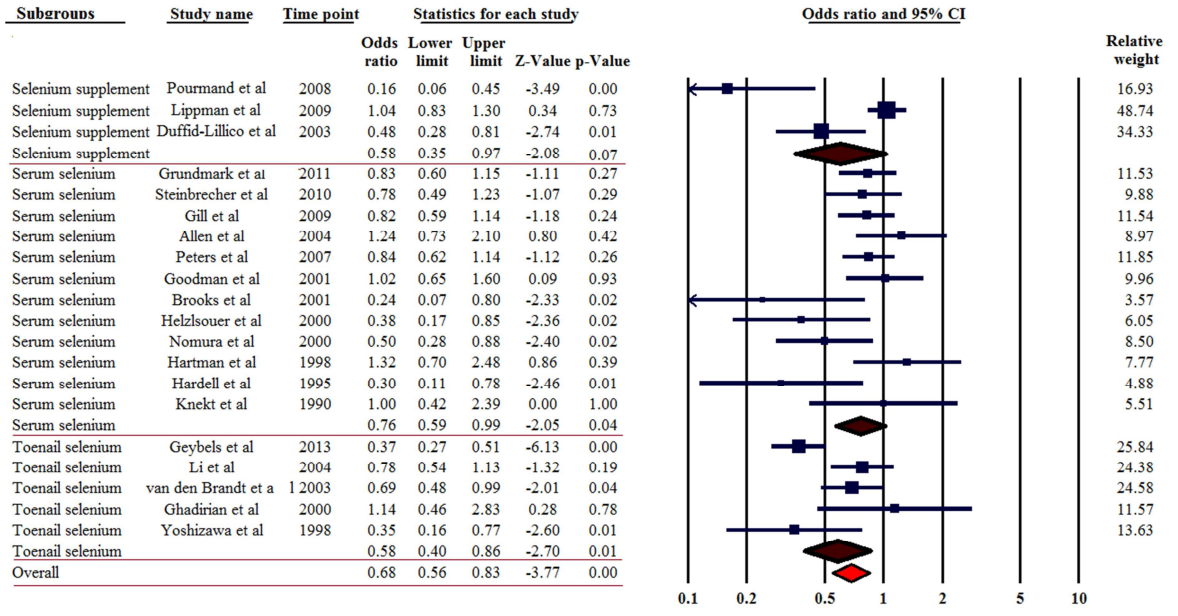
	Adjusted		t^2
Covariances	Coefficient	p-value	
Age	-0.03	0.008	0.11
Date	-0.004	0.69	0.13
Location	0.11	<0.001	0.08
Number sample	-0.0002	0. 27	0.13
Type of Study	0.21	0.04	0.12



Group by Type of study	Study name	Time study	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	Relative weight
Cross-sectional	Steinbrecher et al	2010	0.78	0.49	1.23	-1.07	0.29	7.31
Cross-sectional	Gill et al	2009	0.82	0.59	1.14	-1.18	0.24	8.62
Cross-sectional	Allen et al	2008	0.96	0.70	1.31	-0.26	0.80	8.78
Cross-sectional	Pourmand et al	2008	0.16	0.06	0.45	-3.49	0.00	3.17
Cross-sectional	Peters et al	2007	0.84	0.62	1.14	-1.12	0.26	8.87
Cross-sectional	Li et al	2004	0.78	0.54	1.13	-1.32	0.19	8.21
Cross-sectional	Allen et al	2004	1.24	0.73	2.10	0.80	0.42	6.59
Cross-sectional	Goodman et al	2001	1.02	0.65	1.60	0.09	0.93	7.36
Cross-sectional	Brooks et al	2001	0.24	0.07	0.80	-2.33	0.02	2.53
Cross-sectional	Ghadirian et al	2000	1.14	0.46	2.83	0.28	0.78	3.76
Cross-sectional	Helzlsouer et al	2000	0.38	0.17	0.85	-2.36	0.02	4.37
Cross-sectional	Nomura et al	2000	0.50	0.28	0.88	-2.40	0.02	6.23
Cross-sectional	Yoshizawa et al	1998	0.35	0.16	0.77	-2.60	0.01	4.45
Cross-sectional	Hardell et al	1995	0.30	0.11	0.78	-2.46	0.01	3.49
Cross-sectional	Lippman et al	2009	1.04	0.83	1.30	0.34	0.73	9.63
Cross-sectional	Duffid-Lillico et al	2003	0.48	0.28	0.81	-2.74	0.01	6.62
Cross-sectional			0.69	0.56	0.86	-3.30	0.00	
Prospective	Geybels et al	2013	0.37	0.27	0.51	-6.13	0.00	20.23
Prospective	Grundmark et al	2011	0.83	0.60	1.15	-1.11	0.27	19.95
Prospective	Peters et al	2008	1.00	0.67	1.49	0.00	1.00	18.37
Prospective	Van den Brandt et al	2003	1.69	0.48	0.99	-2.01	0.04	19.18
Prospective	Hartman et al	1998	1.32	0.70	2.48	0.86	0.39	13.11
Prospective	Knekt et al	1990	1.00	0.42	2.39	0.00	1.00	9.17
Prospective			0.76	0.55	1.06	-1.61	0.11	
Overall (Random effect model)			0.71	0.59	0.86	-3.64	0.00	

I^2=70.6%; P<0.001, t^2=12

Fig. 2: Forest plot of meta-analysis on selenium and prostate cancer in the cross sectional and prospective subgroups



Subgroups	Study name	Time point	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	Relative weight
Selenium supplement	Pourmand et al	2008	0.16	0.06	0.45	-3.49	0.00	16.93
Selenium supplement	Lippman et al	2009	1.04	0.83	1.30	0.34	0.73	48.74
Selenium supplement	Duffid-Lillico et al	2003	0.48	0.28	0.81	-2.74	0.01	34.33
Selenium supplement			0.58	0.35	0.97	-2.08	0.07	
Serum selenium	Grundmark et al	2011	0.83	0.60	1.15	-1.11	0.27	11.53
Serum selenium	Steinbrecher et al	2010	0.78	0.49	1.23	-1.07	0.29	9.88
Serum selenium	Gill et al	2009	0.82	0.59	1.14	-1.18	0.24	11.54
Serum selenium	Allen et al	2004	1.24	0.73	2.10	0.80	0.42	8.97
Serum selenium	Peters et al	2007	0.84	0.62	1.14	-1.12	0.26	11.85
Serum selenium	Goodman et al	2001	1.02	0.65	1.60	0.09	0.93	9.96
Serum selenium	Brooks et al	2001	0.24	0.07	0.80	-2.33	0.02	3.57
Serum selenium	Helzlsouer et al	2000	0.38	0.17	0.85	-2.36	0.02	6.05
Serum selenium	Nomura et al	2000	0.50	0.28	0.88	-2.40	0.02	8.50
Serum selenium	Hartman et al	1998	1.32	0.70	2.48	0.86	0.39	7.77
Serum selenium	Hardell et al	1995	0.30	0.11	0.78	-2.46	0.01	4.88
Serum selenium	Knekt et al	1990	1.00	0.42	2.39	0.00	1.00	5.51
Serum selenium			0.76	0.59	0.99	-2.05	0.04	
Toenail selenium	Geybels et al	2013	0.37	0.27	0.51	-6.13	0.00	25.84
Toenail selenium	Li et al	2004	0.78	0.54	1.13	-1.32	0.19	24.38
Toenail selenium	van den Brandt et a	1 2003	0.69	0.48	0.99	-2.01	0.04	24.58
Toenail selenium	Ghadirian et al	2000	1.14	0.46	2.83	0.28	0.78	11.57
Toenail selenium	Yoshizawa et al	1998	0.35	0.16	0.77	-2.60	0.01	13.63
Toenail selenium			0.58	0.40	0.86	-2.70	0.01	
Overall			0.68	0.56	0.83	-3.77	0.00	

Fig. 3: Forest plot of meta-analysis on selenium and prostate cancer in the selenium supplements, serum selenium and toenail selenium subgroups

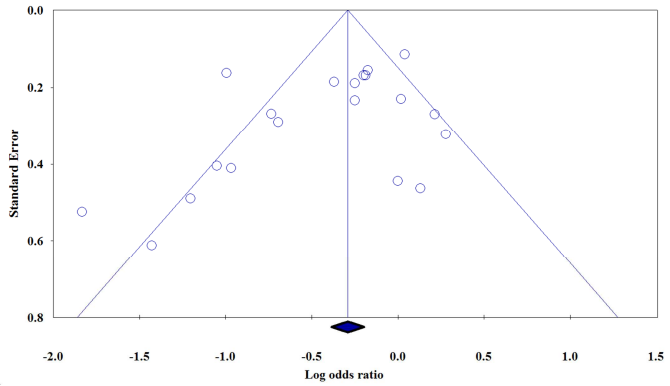


Fig. 4: Funnel plot of standard error by log adds ratio

DISCUSSION

The risk of prostate cancer was significantly less in people who had more selenium in their serum and toenail.

Comparison of studies

Unlike this study, Dennert et al., and Duffield-Lillico et al., (63% reduction) and Clark et al., studies showed that selenium supplement use significantly reduces the risk of prostate cancer [33,55,56].

Lippman et al., and Peters et al., studies showed that selenium supplement use will not decrease prostate cancer significantly

[29,42]. A criticism to Lipman et al., study is that among several types of selenium supplements, just one type of supplement was used. While studies have shown that selenium supplements have two organic forms of L-selenomethionine and selenium-methyl L-selenocysteine and one non-organic form of sodium selenite, that have shown different mechanisms and different anti-cancer effects [57-59].

Meta-analysis study of Li et al., showed that among 152 538 participants, selenium supplements use decreased 24% of all cancers and 36% of prostate cancers. Since Li et al., had analyzed 9 studies and we analyzed 3 studies, the results of Li et al., study are more reliable [60].

It is noteworthy that the results of a recent study by Kenfield et al., among 4459 male participants showed that selenium supplement use increase death from prostate cancer [61]. Hartman et al., study also showed that with increase of selenium in supplement, prostate cancer increased too (OR = 1.36, 95% CI, 0.98,1.9) [51]. Of course, one of the flaws in Kenfield et al., study is that the progression of the disease was not considered. With increase of progression level of disease, the effectiveness of medicines and supplements will also decrease.

These differences in results may be due to the differences in the form of selenium in supplements, eating habits, dosage, population health, and prostate cancer progression [32].

As well as our study, in systematic study of Etminan et al., there was no significant association between reduction in risk of early prostate cancer (RR: 0.87; 95% CI: 0.68, 1.12) and progression of prostate cancer (RR: 0.69; 95 % CI: 0.48,1.01) [62].

In contrast to our study, results of Allen et al., (2004) study showed that increase of selenium in toenail had a weak association with reduction in risk of prostate cancer in the high quartiles in comparison to the low quartiles of Great Britain's men (OR 0.78, 95% CI, 0.27-2.25) [44].

Moreover, The results of the study by Allen et al., (2008) showed that there is no significant association between selenium in serum and prostate cancer risk in men in Europe (OR = 0.96; 95% CI: 0.7,1.31; P value: 0.25). Also there was no significant difference in risk of prostate cancer among smokers and non-smokers and plasma or

tocopherol concentration people [40]. Unlike the study of Allen et al., (2008), the results of Grundmark et al., and Nomura et al., studies showed that prostate cancer risk in smokers with low serum selenium concentration is more than non-smokers [37,50]. Generally more studies are needed to have an accurate conclusion about the effects of other variables such as smoking.

In addition to smoking, the disease level also affects the effectiveness of selenium. In Outzen et al., study it was found that serum selenium increase can significantly reduce the risk of prostate cancer in high-grade disease.

(HR 0.77; 95% CI 0.64, 0.94; P = 0.009) but in advanced prostate cancer, increase of selenium had no significant effect on reducing the risk of prostate cancer [63].

As our study, the results of Grundmark et al., study showed that increase of selenium concentration in serum reduces the risk of prostate cancer (OR = 0.83; 95% CI: 0.6,1.16).

Unlike our study, Van den Brandt et al., study showed that there is no significant inverse association between selenium concentration in toenail and risk of prostate cancer (OR = 0.69, 95% CI, 0.48,0.99). But Geybels et al., study showed that increase of selenium concentration in toenail, significantly reduces the risk of prostate cancer [36].

In contrast to our study, Hartman et al., study showed that increase of selenium concentration in serum not only does not reduce the risk of prostate cancer (OR = 1.32, 95% CI, 0.7,2.47) but also increases it. Gill et al., study also showed that selenium has no significant effect on the reduction of prostate cancer risk [39].

As our study, Pourmand et al., and Li et al., studies showed that increase of serum level in selenium can significantly reduce the risk of prostate cancer [40,43].

In general meta-analysis of studies showed that increase of selenium in toenail and serum significantly decreases risk of prostate cancer. One of the mechanisms of selenium that reduces risk is ant proliferative effect of selenium through its impact on cell-cycle regulators [64].

Although selenium supplements use had no significant effect on reducing prostate cancer, because of significant lowering effect of selenium in serum and toenail, also selenium supplements use can be effective in reducing prostate cancer. It should be noted that lowering effect is dependent on absorption rate and type of selenium supplement [65].

Limitations of the Study

Limitations of this study include incomplete subgroups, time domain of studies, disease level (primary, high grade and advanced), language of studies (except Persian and English), difference of some confounding factors such as age, income, race, smoking status, body mass index, physical activity and lack of studies about selenium supplements. To obtain the association between age and risk of prostate cancer in some studies, exact age of patients was not specified. Also, measurement errors including differences in the equipment, measurement methods, and employees in various studies were limitations of this study.

CONCLUSION

The results of a systematic review and meta-analysis of 22 studies showed that increase of selenium in serum and toenail will significantly reduce the risk of prostate cancer (P value<0.05). To get more accurate results about the effect of selenium supplements use on prostate cancer, further and more detailed studies are needed. Results of this study supported lowering effect selenium in serum and toenail on the risk of prostate cancer.

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