The association between Selenium and Prostate Cancer: a Systematic Review and Meta-Analysis

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Abstract

Background: Evidence of relationship between selenium and prostate cancer has been inconsistent. The present meta-analysis was conducted to determine relationship between selenium and prostate cancer. Methods: A systematic review and meta-analysis was carried out using preferred reporting items for systematic reviews and meta-analysis (PRISMA). We searched PubMed, Scopus, Web of Science, ScienceDirect, Embase, CINAHL, Cochrane Library, EBSCO and Google scholar search engines and the reference lists of the retrieved papers for relevant data, without any limitation regarding language or time until 2016. Heterogeneity among studies was evaluated using Q test and $I^2$ Index. Finally, a random effects model was used for combining results using STATA software version 11.1. P<0.05 was considered significant. Results: Thirty-eight studies including 36,419 cases and 105,293 controls were included in the final analysis. The pooled relative risk (RR) of relation between selenium and prostate cancer was 0.86 (95% Confidence Interval [CI]:0.78-0.94). Sub-group analyses based on case-control, cohort, and RCT studies gave values of 0.89 (95% CI: 0.80-1.00), 0.77 (95% CI: 0.52-1.14) and 0.90 (95% CI: 0.74-1.09), respectively. RRs based on serum, plasma and nail samples were 0.69 (95% CI: 0.51-0.95), 0.85 (95% CI: 0.61-1.17), 0.66 (95% CI: 0.41-1.05), respectively. According to 10 studies, investigated the relation between advanced prostate cancer and selenium in which the RR was 0.67 (95% CI: 0.52-0.87). Conclusions: This meta-analysis indicated that selenium most probably has a protective role against development of prostate cancer and its progression to advanced stages. Therefore, selenium supplementation can be proposed for prevention of prostate cancer.

Keywords: Selenium- prostate cancer- meta-analysis

Introduction

Prostate cancer is the most common type of cancer worldwide. The estimates by World Health Organization (WHO) show the yearly incident cases and death cases of prostate cancer in worldwide are 1,100,000 and 307,000, respectively (Humphrey and Schuz, 2014). These estimations for the United States are 181,000 incident cases and 26,100 death cases (Siegel et al., 2016). The lifetime risk of this cancer for American men is 1 in 6 men (Siegel et al., 2011).

Given the importance of prostate cancer in terms of morbidity and mortality, many studies tried to identify risk factors for developing prostate cancer in order to prevent and control it. Several risk factors have been identified for prostate cancer such as age, race, nationality, family history of prostate cancer and insulin growth factor (Grönberg, 2003) and there is a significant difference in predisposition to prostate cancer in different countries (Miller, 2012). Intense changes in lifestyle may influence the progression of low grade and early prostate cancer (Ornish et al., 2005). One of the factors investigated by the studies is selenium. Although many studies investigated the relation between selenium and prostate cancer, there is no consensus on it, and results obtained by these studies show inconsistency. When there is the inconsistency, one of the best strategies to understand and find the conclusion is to conduct a systematic review and meta-analysis (Sayehmiri et al., 2015; Azami et al., 2017; Moher et al., 2009).

Virtamo (1987) study found no association between serum level of selenium and the prospective risk of cancer. A study by Lippman et al., (2009) show that selenium alone or in combination with vitamin E doesn’t prevent prostate cancer. A cohort study using toenail sample confirmed the protective role of selenium in prostate cancer (Van den Brandt et al., 2003). Study of Chan et al., (2009) showed a slight increase by presenting with...
aggressive disease in higher plasma level of selenium. In a cohort study on cancer mortality in northern Italy in an area with unusually high selenium content tap water, we did not find strong results to support the protective role of selenium supplements on cancer mortality (Vinceti et al., 1995). Meta-analysis is one of the best strategies to find the consensus between studies and is a statistical technique for combining the results of two or more different studies to find a single result (Sayehmiri et al., 2015; Azami et al., 2017; Moher et al., 2009).

Considering the importance of prostate cancer and several studies investigating the relationship between prostate cancer and selenium and lack of consensus between their results, we conducted a study based on systematic review and meta-analysis to find this association by combing related studies and presenting a final result.

Materials and Methods

This systematic review and meta-analysis study was conducted using preferred reporting items for systematic reviews and meta-analysis (PRISMA) (Moher et al., 2009). All steps of study were conducted by two independent researchers, and the issue was resolved by a third author in cases of disagreement.

Inclusion and exclusion criteria

The Inclusion criteria were the studies about the relation between selenium and prostate cancer were published in English without time limitation. The exclusion criteria included animal studies, exposure/intervention except for selenium, results other than prostate cancer, non-related articles, review studies, case reports, and letters to the editor.

Search strategy

We searched databases such as PubMed, Scopus, Web of Science (ISI), Science Direct, Embase, CINAHL, Cochrane Library, EBSCO and Google scholar search engine using search strategies, developed for each database using MeSH keywords of “selenium”, “prostate cancer”, and “trace elements”. Moreover, we searched reference list of the retrieved papers for finding more papers. The systematic search has been conducted without any time limitation until 2016.

Study selection

Reading the title and abstract of papers, we conducted the primary screening for selecting relevant papers. Afterwards, we read the full text of the papers for study selection. The retrieved papers were collected and stored in Endnote software. The duplicated papers were excluded in this step.

Data extraction

Information on the final selected studies in the previous step, including author(s) name, country of study, year, name of journal, samples characteristics (e.g. gender, mean age and size), diagnostic criteria, relative (RR) or odds ratio (OR), confidence interval (CI), were extracted and stored in Excel program.

Statistical analysis

Pooled RRs or ORs and 95% CIs were estimated for the associations between selenium exposure and the risk of prostate cancer using a random effects model. To evaluate the heterogeneity of the studies, index were used (Deeks et al, 2011; Harbord et al., 2009). Cumulative meta-analysis was used to show the trend of effect size and effects of new studies of effect size. Subgroup analysis was done according to the country, samples (nail, blood and etc.), methods, and year. Egger’s test and funnel plot were used to check publication bias. Data were analyzed using the STATA software version 11.1. P<0.05 was considered significant.

Results

At first, 660 articles were retrieved. In the next step, 330 articles with the same title and author were excluded. Of 330 remaining articles, abstracts of all existing papers were studied and 140 irrelevant studies were excluded. Then the full text of the remaining articles has been studied to find related articles. Finally, thirty-eight articles including 36,419 cases and 105,293 controls entered the final analysis (Figure 1).

The Overall Association of Selenium and Prostate Cancer. Data analysis showed a RR of 0.86 (95% CI: 0.78-0.94) and showed the significant protective role of selenium in prostate cancer (Figure 2) Significant heterogeneity was observed (I$^2$ = 69.4, P<0.001). Cumulative analysis was showed in Figure 3.

Sub-group analysis of Selenium and Prostate Cancer

In subgroup analysis based on place of study, most of the studies were conducted in the USA (57.3%) and RR was 0.89 (95% CI: 0.78-1.02) (Table 2).
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Selenium and advanced prostate cancer

In the ten studies about the relation between selenium and advanced prostate cancer, RR was 0.67 (95% CI: 0.52-0.87), showing the significant protective role of selenium in advanced prostate cancer (Figure 4).

Publication bias

In this study, p-value for publication bias of the relation between selenium and prostate cancer and its advanced

Table 1. Data Obtained from Studies to Evaluate the Relationship between Selenium and Prostate Cancer

| Method               | Authors name | Year | Place     | Sample | RR\[^a\] | 95% CI\[^b\] |
|----------------------|--------------|------|-----------|--------|---------|-------------|
| Case-control         | Lipsky (19)  | 2003 | Austria   | Nail   | 0.74    | 0.22-2.71  |
|                      | Helzlsouer (20) | 2000 | USA       | Nail   | 0.38    | 0.17-0.85  |
|                      | Goodmann(21) | 2001 | USA       | Serum  | 1.02    | 0.65-1.60  |
|                      | Nomura (22)  | 2000 | USA       | Serum  | 0.5     | 0.3-0.9    |
|                      | Yoshizawa (23) | 1998 | USA       | Nail   | 0.35    | 0.16-0.78  |
|                      | Brooks (24)  | 2001 | USA       | Plasma | 0.24    | 0.07-0.77  |
|                      | Allen (25)   | 2004 | United k  | Nail   | 1.24    | 0.73-2.10  |
|                      | Gill (26)    | 2009 | Hawaii    | Serum  | 0.82    | 0.59-1.14  |
|                      | Allen (27)   | 2008 | Europe    | Plasma | 0.96    | 0.07-1.31  |
|                      | Lee (28)     | 1998 | China     | Diet   | 1       | 0.99-1.04  |
|                      | Zhang (29)   | 2009 | USA       | Diet   | 1.3     | 0.30-5.70  |
|                      | Kristal (30) | 2010 | USA       | Diet   | 1       | 0.58-1.73  |
|                      | Li (31)      | 2004 | USA       | Plasma | 0.78    | 0.54-1.13  |
|                      | Ghadirian (32)| 2000| USA       | Nail   | 1.14    | 0.46-2.83  |
|                      | Pourmand (33)| 2008| Iran      | Serum  | 0.16    | 0.06-0.47  |
|                      | Knekt (34)   | 1990 | Finland   | Serum  | 1.15    |             |
|                      | Coates (35)  | 1988 | USA       | Serum/Plasma | 0.3 |             |
|                      | Vogt (17)    | 2003 | USA       | Serum  | 0.71    | 0.39-1.28  |
|                      | West (36)    | 1991 | USA       | Diet   | 1.6     | 1.2-8.0    |
|                      | Hardell (37) | 1995 | Sweden    | Plasma | 0.3     | 0.10-0.70  |
|                      | Qutzen (38)  | 2016 | Danish    | Plasma | 1.01    | 0.94-1.08  |
|                      | Jain (18)    | 1999 | USA       | Diet   | 0.93    | 0.68-1.28  |
| Cohort               | Van den brant (9) | 2003| Netherlands | Nail | 0.69    | 0.48-0.99  |
|                      | Hartman (39) | 1998 | Finland   | Diet   | 0.84    | 0.43-1.67  |
|                      | Peters (40)  | 2008 | USA       | Diet   | 0.9     | 0.62-1.30  |
|                      | Peters (41)  | 2007 | USA       | Serum  | 0.84    | 0.62-1.14  |
|                      | Chan (10)    | 2009 | USA       | Plasma | 1.35    | 0.99-1.84  |
|                      | Geybels (42) | 2013 | Netherlands | Nail | 0.37    | 0.27-0.51  |
| Randomized controlled trial | ippman (8) | 2009 | USA | Sel supplementation | 1.04  | 0.90-1.18 |
|                      | Duffield Lillico-(43) | 2002 | USA | Sel supplementation | 0.48  | 0.28-0.80 |
|                      | Kristal (44) | 2014 | USA | Sel supplementation | 1.25  | 0.79-1.98 |
|                      | Klein (45)   | 2011 | USA       | Sel supplementation | 1.09  | 0.93-1.27 |
|                      | Clark (46)   | 1998 | USA       | Sel supplementation | 0.37  | 0.18-0.71 |
|                      | Duffield Lillico-(47) | 2003 | USA | Sel supplementation | 1.14  | 0.51-2.59 |
|                      | Algator (48) | 2013 | USA | Sel supplementation | 0.9   | 0.48-1.70 |
|                      | Algator (48) | 2013 | USA | Sel supplementation | 0.94  | 0.52-1.70 |
|                      | Dunn (49)    | 2010 | USA       | Sel supplementation | 1.04  | 0.87-1.24 |
|                      | Marshal (50) | 2011 | USA       | Sel supplementation | 0.82  | 0.40-1.69 |

\[^a\] Relative risk; \[^b\] Confidence interval

In subgroup analysis based on type of study in case-control, cohort and RCT (Randomized controlled trial), the RR was estimated to be 0.89 (95% CI: 0.80-1.00), 0.77 (95% CI: 0.52-1.14), 0.90 (95% CI: 0.74-1.09), respectively (Table 2).

In subgroup analysis based on samples the RR was estimated 0.69 (95% CI: 0.51-0.95) for serum, 0.85 (95% CI: 0.61-1.17) for plasma, 0.66 (95% CI: 0.41-1.05) for nail. In selenium supplementation and placebo group and in group which dietary selenium examined, RR was 0.90 (95% CI: 0.74-1.09) and 1.00 (95% CI: 0.98-1.02), respectively (Table 2).
Table 2. Meta-Analysis of Studies Regarding the Relationship between Selenium and Prostate Cancer Based on Country, Type of study and sample of selenium. random effects model

| Variable                              | Study(N) | Case    | Control | I² (%) | 95% CI | RR
|---------------------------------------|----------|---------|---------|--------|--------|-----
| Country                               | USA      | 23      | 31,691  | 70,385 | 51.6   | 0.78,1.02 | 0.89 |
|                                       | Austria  | 1       | 70      | 80     | 0.21,2.60 | 0.74 |
|                                       | United Kingdom | 1 | 300    | 300    | 0.73,2.10 | 1.24 |
|                                       | Hawaii   | 1       | 450     | 936    | 0.59,1.14 | 0.82 |
|                                       | Europe   | 1       | 959     | 1,059  | 0.22,4.15 | 0.96 |
|                                       | China    | 1       | 133     | 265    | 0.98,1.02 | 1    |
|                                       | Iran     | 1       | 62      | 68     | 0.06,0.45 | 0.16 |
|                                       | Finland  | 1       | 317     | 28,816 | 0.43,1.66 | 0.84 |
|                                       | Sweden   | 1       | 164     | 121    | 0.11,0.79 | 0.3  |
|                                       | Denmark  | 1       | 784     | 784    | 0.94,1.08 | 1.01 |
|                                       | Netherlands | 2 | 540    | 1,211  | 84.4   | 0.27,0.92 | 0.5  |
| Type of study                         | Case-control | 19 | 8,639  | 16,967 | 59.1   | 0.80,1.00 | 0.89 |
|                                       | Cohort   | 6       | 3,786   | 66,682 | 85.5   | 0.52,1.14 | 0.77 |
|                                       | Randomized controlled trial | 9 | 23,994 | 21,644 | 54.3   | 0.74,1.09 | 0.9  |
| Sample of selenium                    | Serum    | 6       | 1,983   | 2,913  | 62.5   | 0.51,0.95 | 0.69 |
|                                       | Plasma   | 6       | 2,982   | 2,637  | 70.1   | 0.61,1.17 | 0.85 |
|                                       | Nail     | 6       | 2,189   | 3263   | 74.8   | 0.41,1.05 | 0.66 |
|                                       | Diet     | 7       | 5,206   | 74,814 | 0      | 0.98,1.02 | 1    |
|                                       | Selenium supplement and placebo | 9 | 23,994 | 21,644 | 54.3   | 0.74,1.09 | 0.9  |

*a*, Number ; b, Confidence interval ; c, Relative risk

Figure 2. Data Analysis of studies about the Relation between Selenium and Prostate Cancer. Mean point of each segment shows the estimation of Relative Risk (RR) and the length of each segment showed the 95% confidential interval in each study. The diamond mark shows the RR of each study.

Figure 3. Cumulative Forest Plot in the Meta-Analysis of Studies about the Relation between Selenium and Prostate Cancer.
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Discussion

Several studies have been done conducted worldwide to evaluate the relationship between selenium and prostate cancer. However, the results are inconsistent and the clear association have not been found. So our meta-analysis and systematic review study, which is a quantitative assessment of published data on the role of selenium in prostate cancer, was conducted to find the clear relation between prostate cancer and selenium without time limitation up to 2016.

There were several limitations in our study including lack of access to all articles or their full text. Other limitations were the different design for papers and using different samples for detecting selenium. One of the advantages of this meta-analysis study was the ability to do a complete analysis on subgroups, such as type of studies (RCT, Cohort, Case-control), subgroup of total prostate cancer and advanced prostate cancer as well as the samples used (toenail and plasma, serum, diet, supplementation selenium). Analysis of data showed the RR of 0.86 (95% CI: 0.78-0.94) and since confidence interval doesn’t cross significant protective role of selenium in prostate cancer was found. The heterogeneity rate in the current study was 69.4% (p=0.000), accounted in the range of studies with moderate heterogeneity. Thus, random effects model in the meta-analysis was used.

Our study confirms the result of Etminan’s (2005) systematic review showing that selenium may have a protective role against prostate cancer. However, our study is not in line with another study which indicates the increase in the risk of prostate cancer in the state of low selenium (Brinkman et al., 2006). Hurst et al., (2012) in a systematic review and meta-analysis showed that the relationship between selenium status and decreased prostate cancer risk was examined over a relatively narrow range of selenium status and they suggested more studies in low-selenium population. In Brinkman’s (2006) review study, selenium levels were inversely associated with prostate cancer risk and the need to further investigations was recommended. In another systematic review and meta-analysis, no evidence of the effect of vitamins and multivitamins was found on the occurrence and severity of the prostate cancer (Brinkman et al., 2006). According

| Variable          | Study (N) | Case  | Control | F (%) | 95% CI         | RR   |
|-------------------|-----------|-------|---------|-------|----------------|------|
| Country           | USA       | 7     | 960     | 37,175| 10.8           | 0.45,0.81   | 0.6  |
|                   | United Kingdom | 1 | 89     | 300   |               | 0.27,2.25  | 0.78 |
|                   | Denmark   | 1     | 525     | 784   |               | 0.87,1.05  | 0.96 |
|                   | Netherlands | 1  | 183    | 1,211 |               | 0.37,1.04  | 0.62 |
| Type of study     | Case-control | 7 | 1,173  | 2,780 | 57.7           | 0.43,0.93  | 0.64 |
|                   | Cohort    | 3     | 584     | 36,690| 0              | 0.51,0.97  | 0.71 |
| Sample of selenium| Serum    | 4     | 485     | 1,817 | 6.7            | 0.51,1.03  | 0.72 |
|                   | Plasma    | 2     | 696     | 1,361 | 67.1           | 0.44,1.38  | 0.78 |
|                   | Nail      | 3     | 453     | 1,692 | 0              | 0.37,0.83  | 0.55 |
|                   | Diet      | 1     | 123     | 34,600| 0              | 0.17,1.27  | 0.46 |

* Number; † Confidence interval; ‡ Relative risk
to a review study published in 2015 based on SELECT (Selenium and Vitamin E Cancer Prevention Trial) studies, there was no significant decline in the risk of prostate cancer by selenium and vitamin E supplementations and it recommended further studies to find the probable mechanisms of prostate cancer and searching newer preventive agents (Ramanamurthy et al., 2015). In a systematic review and meta-analysis, no evidence of the effect of vitamins and multivitamins on the occurrence and severity of the prostate cancer was found (Stratton et al., 2011).

In conclusion, our study shows that selenium plays a protective role in prostate cancer. However, it is suggested that more studies be conducted with less limitation, considering other environmental factors such as other trace elements, economic situation and social situation such as level of education in future.

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Authorship contribution

Study concepts/study design: all authors; Collection demographic data: all authors; Meta-analysis: Koroush Sayehmiri; manuscript drafting: Zeinab Tarcheh; manuscript final version approval and manuscript editing: all authors.

Conflicts of interest

None.

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