REVIEW

**Editorial Process:** Submission:03/02/2025 Acceptance:09/26/2025 Published:10/17/2025

# The Association Between Selenium Levels and Risk of Prostate Cancer: A Systematic Review and Meta-analysis of 16,964 Participants (1980–2024)

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## Abstract

**Background:** Numerous studies worldwide have explored the link between selenium levels and prostate cancer, yet their findings remain inconsistent. This systematic review and meta-analysis aimed to clarify this association by synthesizing results from analytical observational studies, including cohort and case-control studies. The insights from this meta-analysis could significantly impact healthcare decisions, clinical management, and treatment guideline updates. **Method:** This study utilized a systematic review and meta-analysis approach, conducting a comprehensive literature search across international databases such as PubMed (Medline), Scopus, Web of Science, and Embase with relevant keywords. Articles were screened at the title, abstract, and full-text levels, followed by a quality assessment using the NOS checklist. Statistical analysis was performed using STATA version 17. **Results:** After pooling data from eleven studies investigating the relationship between plasma or serum selenium and prostate cancer risk, findings indicated that higher selenium levels were associated with an 11% reduced risk of prostate cancer (RR= 0.89; 95% CI: 0.83 - 0.95; P-value= 0.03; I square= 34.46%). When selenium dosage was considered, with doses below 70 µg as the reference, individuals exposed to 130-160 µg exhibited a reduced cancer risk of 0.85 (RR= 0.85; 95% CI: 0.76 - 0.96; P-value= 0.18; I square= 27.37%), while those exposed to doses of 160 µg or higher had an RR of 0.89 (95% CI: 0.69 - 1.15; P-value= 0.19; I square= 0.00%). Additionally, an inverse relationship was found between selenium levels in toenails and prostate cancer risk (RR= 0.61; 95% CI: 0.50 - 0.75; P-value= 0.63; I square= 0.00%) and advanced prostate cancer (RR= 0.73; 95% CI: 0.67 - 0.80; P-value= 0.00; I square= 69.79%). **Conclusion:** This meta-analysis suggests that selenium may have a protective effect against prostate cancer. Strategies to optimize selenium intake should be considered for prostate cancer prevention and management.

**Keywords:** Selenium Leve- Prostate Cancer- Evidence Synthesis- Meta-Analysis

*Asian Pac J Cancer Prev,* **26 (10)**, 3571-3580

## Introduction

Prostate cancer is one of the most prevalent malignancies in men, accounting for approximately 25% of all cancer cases globally and ranking as the second most common cancer among men worldwide [1]. According to the estimations of the World Health Organization (WHO) in 2020, the annual cases and deaths from prostate cancer worldwide were equal to 1,400,000 and 375,000, respectively. The continent of Europe had the highest number of cases with 473,000 cases, and the continent of Asia had the highest number of deaths with 108,000 deaths. This statistic for the United States was 239,000 cases and 37,000 deaths [2]. The lifetime risk of developing this cancer for American men is 1 in 6 men [3]. Based on 2018 GLOBOCAN data and the International Agency for Research on Cancer, by 2025, the number of prostate cancer cases is projected to rise significantly across Middle Eastern countries, including Jordan (24%), Saudi Arabia (59%), Bahrain (72%), Kuwait (79%), UAE (104%), and Qatar (114%) [4]. Given the growing burden of this malignancy, further research into its potential risk factors is crucial [5]. Additionally, prostate cancer imposes substantial healthcare costs and financial burdens on patients and their families. Thus, proactive efforts to refine prevention, treatment, and management strategies are essential [6].

The etiology of prostate cancer remains incompletely understood, though dietary factors have gained considerable attention in recent years. In particular, the

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potential influence of vitamin D and selenium on prostate cancer progression and recurrence has been extensively investigated [7]. Selenium, an essential trace element that the human body cannot synthesize, is naturally present in grains, fish, eggs, meat, and dairy products [8]. It has been hypothesized that selenium may offer protective benefits against cancer [9]. The cancer-preventive mechanisms of selenium likely stem from its incorporation into selenoproteins, which are involved in oxidative stress reduction, DNA damage repair, immune system enhancement, and apoptosis induction [10, 11].

A growing body of evidence highlights the role of various dietary components in cancer development [12, 13]. Notably, research suggests that dietary modifications could potentially prevent up to 40% of all cancer cases [14]. Selenium intake in the diet varies around the world and depends on the intensity of selenium in the soil [15]. Changes in human dietary intake are reflected in global variations in blood selenium levels [16], with relatively low levels in Europe and higher levels in the United States [17, 18]. These geographical differences in selenium levels have been considered in the discussion of selenium and its relationship with the risk of prostate cancer, and have led to various studies with different results in the world [19].

The relationship between selenium and cancer has been one of the hot debates in human health in the past decades [20]. A 1969 study found that cancer mortality in the United States was inversely related to the geographic distribution of selenium in the soil. This was the first report that showed that selenium deficiency may be related to cancer [21, 22]. A systematic review and meta-analysis by Hurst et al., published as part of an updated report by the International Fund for Cancer Research, demonstrated an inverse relationship between plasma/serum selenium levels and advanced prostate cancer. Their findings also suggested a possible U-shaped association, where both selenium deficiency and excess might influence prostate cancer risk [19]. Numerous studies have been conducted around the world to evaluate the link between selenium and prostate cancer. However, the results are contradictory, and no clear relationship has been found [23]. In general, selenium as a chemical protective agent against prostate cancer needs more and more detailed studies [24]. This meta-analysis study was conducted to determine the association between selenium levels and prostate cancer by combining results of analytical observational studies such as cohort and case-control studies. The results of the present meta-analysis can be very effective in health decisions, clinical care, and updating treatment guidelines.

## Materials and Methods

*Search strategy*

This systematic review and meta-analysis aimed to investigate the relationship between selenium levels and the risk of prostate cancer, adhering to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The literature search was conducted in major international databases, including PubMed (Medline), Scopus, Web of Science, and Embase. A comprehensive search strategy was formulated using relevant keywords and their synonyms from Medical Subject Headings (MeSH). The primary keywords included "Selenium" and "Prostate Cancer", with synonyms such as "Selenium Supplement," "Serum Selenium", "Plasma Selenium", "Toenail Selenium", "Antioxidant", "Minerals", "Prostatic Neoplasm", and various other terms related to prostate malignancies. In addition to database searches, a manual review of reference lists from selected studies was performed to identify additional relevant articles. Two independent authors carried out the entire search process. The search covered a period from January 1980 to January 2024.

*Inclusion and exclusion criteria*

To ensure the selection of high-quality primary studies, specific inclusion criteria were applied. Eligible studies included case-control studies reporting odds ratios (OR) with 95% confidence intervals and cohort studies presenting risk ratios (RR) with 95% confidence intervals. Studies needed to assess selenium concentrations in biological samples (serum, plasma, or toenails) and their association with prostate cancer risk, including both localized and advanced stages. The classification of advanced or metastatic cancer had to follow globally recognized criteria, and selenium measurement methods had to be clearly described.

Studies that did not meet the inclusion criteria were excluded. Specifically, editorials, brief reports, conference abstracts, review articles, cross-sectional studies, and clinical trials were not considered. Additionally, case-control and cohort studies that lacked the necessary data or did not align with the research objectives were excluded. Articles for which full-text access was unavailable were also omitted. The selection process involved screening titles, abstracts, and full texts using Endnote version 8 to manage and organize references.

*Data Extraction Process*

A structured data extraction form was used to collect relevant information from each study, including the first author's name, year of publication, study location, sample size, study design, target population, participant age range, follow-up duration (for cohort studies), methods of exposure and outcome assessment, and reported effect estimates with confidence intervals.

*Risk of Bias or Quality Assessment*

The quality of included studies was assessed using the Newcastle-Ottawa Scale (NOS), a tool designed to evaluate potential bias in case-control and cohort studies. The NOS checklist consists of ten criteria covering study selection, comparability of groups, and outcome assessment. Each study was assigned a quality score ranging from 0 to 9, with higher scores indicating better methodological quality.

*Statistical analysis*

The desired indicators for analysis include OR and RR, along with confidence intervals reported in primary studies. Since these indices are skewed to the right, they should be converted to normal distribution for

analysis, which is why the logarithm of these indices was included in the analysis. The desired model for analysis was random effects or fixed effects (taking into account the conditions). The degree and percentage of heterogeneity in this study were expressed using $I_{square}$ and Cochrane's Q index. According to the criteria reported by Cochrane, 0 to 25% indicates no heterogeneity, 25 to 50% indicates low heterogeneity, 50 to 75% indicates high but acceptable heterogeneity, and 75 to 100% indicates high and unacceptable heterogeneity. The distribution bias was evaluated using the Funnel Plot and Eggers test. Subgroup analyses were performed based on the type of prostate cancer, sampling site, different doses of selenium, continent, and location of selenium (nails or serum/plasma).

## Results

*Qualitative results*

After searching in the desired international databases, a total of 2070 studies were retrieved, which left 992 studies after removing duplicates. The main point of conducting this study was to update the findings related to the study by Hurst Rachel et al., which was conducted in 2011, so the search for this study began when the search for Hurst-Rachel et al.'s research was completed. Therefore, after screening the studies retrieved in the present meta-analysis 12 selected studies in Hurst Rachel et al.'s study were also added to the final studies of the present meta-analysis [25-36]. After removing the duplicates and screening the abstract and title, 42 articles were evaluated for eligibility, and 26 articles were also eliminated at this stage. Details of the search and study selection process are provided in Figure 1. In general, 16 studies, including 15 case-control studies [25, 26, 32, 37], 1 cohort study [38] with a total of 16,964 participants, and 8,097 prostate cancer cases met the inclusion criteria for the present meta-analysis. Four studies in Europe [25, 35, 37, 11] and seven studies in America [28-30, 32-34, 36] with 13537 participants and 5539 cases of prostate cancer in meta-analysis of plasma/serum selenium data and three studies in Europe [33, 38, 39] and two studies in America [26, 27] with 6419 participants and 2558 cases of prostate cancer were included in the meta-analysis of toenail selenium data. Most studies adjusted for several major confounders such as education level, body mass index (BMI), alcohol consumption, and smoking. 11 cases [28-31, 33-38, 11, 39] of advanced prostate cancer, three cases [30, 35, 37] of low-grade prostate cancer (Gleason score six or less) and four cases [30, 35, 37, 11] reported high-grade prostate cancer (Gleason score eight or more). The general characteristics of these studies are listed in Supplementary Table 1.

*Quality assessment results*

Quality scores were assigned to each article using criteria specified by the NOS for case-control and cohort studies. The mean score for the case-control studies was 8.25 (standard deviation = 0.7), the nested control case was 8.36, and the included cohort study was 9. 6 was the lowest score, and 9 was the highest. Individual quality assessment scores are presented in Table 1.

*Plasma/serum selenium concentration and prostate cancer risk*

Eleven articles evaluated the relationship between plasma or serum selenium levels and the risk of prostate cancer [25, 28-30, 32-37, 11]. Ten articles reported the correlation of plasma or serum selenium level with the risk of total prostate cancer [25, 28-30, 32-36, 11], and the

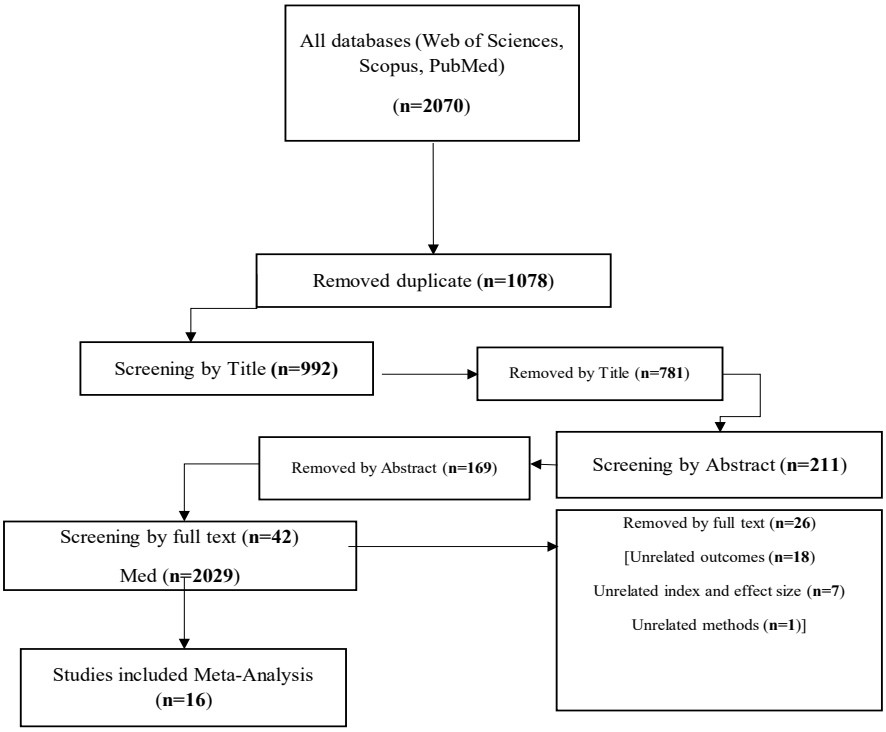


Figure 1. A Flow Diagram Demonstrating the Study Selection Process

Table 1. The Results of Quality Assessment based on the Newcastle Ottawa Quality Assessment Scale

| Studies | Selection | Comparability | Exposure | Total |
|---|---|---|---|---|
| Outzen et al. [39] | *** | ** | ** | 7 |
| Steinbrecher et al. [37] | **** | ** | ** | 8 |
| Outzen et al. [11] | **** | ** | *** | 9 |
| Li et al. [33] | ** | ** | ** | 6 |
| Goodman et al. [30] | ** | ** | *** | 7 |
| Gill et al. [36] | **** | ** | ** | 8 |
| Brooks et al. [29] | **** | ** | *** | 9 |
| Allen et al. [35] | **** | ** | ** | 8 |
| Peters et al. [34] | **** | ** | ** | 8 |
| Nomura et al. [28] | *** | ** | *** | 8 |
| Vogt et al. [32] | **** | ** | *** | 9 |
| Hardell et al [25] | *** | ** | *** | 8 |
| Ghadirian et al. [26] | **** | * | *** | 8 |
| Helzlsour et al. [27] | **** | ** | ** | 8 |
| Van den brandt et al. [31] | **** | ** | ** | 8 |

total sample size was equal to 4363 people with prostate cancer and 5294 healthy people. The pooled effect size for this association was 0.89 (RR= 0.89; 95% CI: 0.83 – 0.95; P-value= 0.03; $I_{square}$ = 34.46%). There was a low heterogeneity ($I_{square}$ = 34.46%) between these studies, so it can be said that the merged studies had high homogeneity

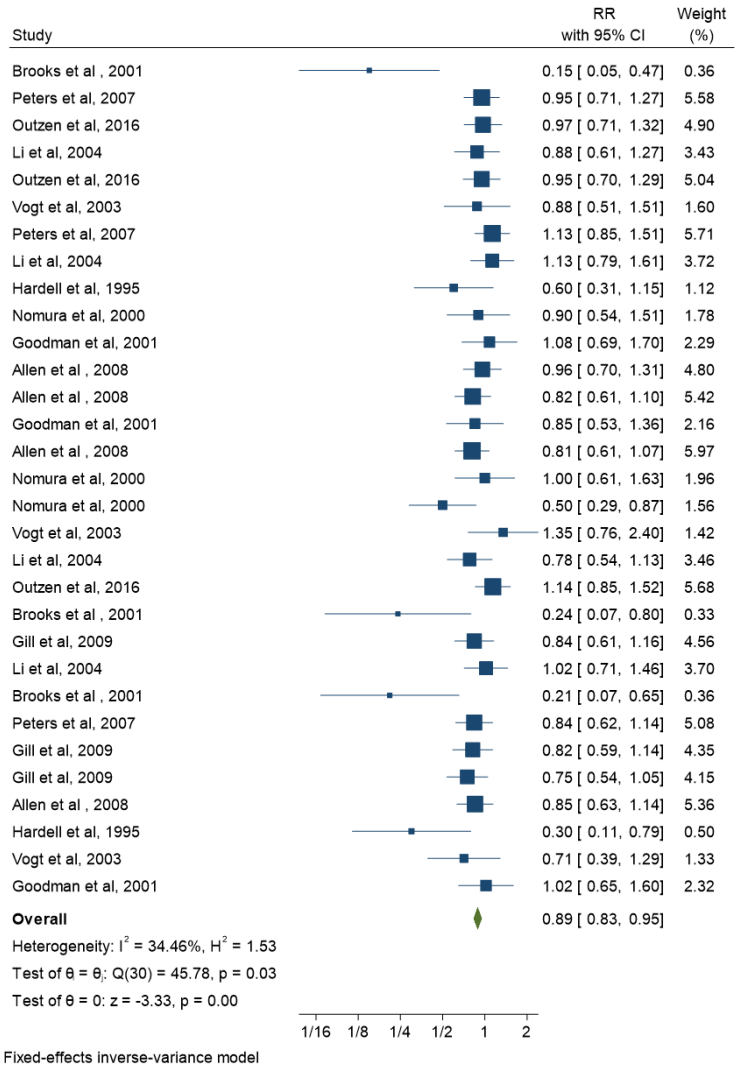


Figure 2. The Effect of Plasma Selenium Level on the Occurrence of Total Grade of Prostate Cancer

Table 2. Meta-Analysis Results of the association Selenium Level in Serum/Plasma and Risk of Prostate Cancer based on Sample Places, Dose of Selenium, Continents, and Type of Prostate Cancer

| Outcomes | Categories | RR (% 95 CI) | Heterogeneity Assessment | | | Publication bias | | |
|---|---|---|---|---|---|---|---|---|
| | | | I square | Q | P value | B | SE | P value |
| Prostate Cancer (High Grades) | Overall | 0.62 (0.51 – 0.75) | 0.00% | 8.46 | 0.75 | 2.13 | 1.21 | 0.12 |
| | Sample Places | | | | | | | |
| | Plasma | 0.58 (0.43 – 0.73) | 0.00% | 1.57 | 0.95 | | | |
| | Serum | 0.52 (0.32 – 0.71) | 0.00% | 4.43 | 0.49 | | | |
| | Dose of Selenium (Ref: <70) | | | | | | | |
| | 70 – 100 | 0..53 (0.40 – 0.66) | 0.00% | 3.27 | 0.92 | | | |
| | 100 – 130 | 0.55 (0.39 – 1.20) | 0.00% | 0.28 | 0.6 | | | |
| | >130 | 0.76 (0.07 – 1.45) | - | - | - | | | |
| | Continents | | | | | | | |
| | Europe | 0.53 (0.41 – 0.66) | 0.00% | 3.37 | 0.95 | | | |
| | USA | 0.90 (0.44 – 1.37) | 0.00% | 0.59 | 0.75 | | | |
| Prostate Cancer (Low Grades) | Overall | 0.95 (0.77 – 1.13) | 0.00% | 3.5 | 0.94 | 1.17 | 1.01 | 0.27 |
| | Sample Places | | | | | | | |
| | Plasma | 0.97 (0.75 – 1.20) | 0.00% | 0.77 | 0.86 | | | |
| | Serum | 0.92 (0.64 – 1.20) | 0.00% | 2.64 | 0.76 | | | |
| | Dose of Selenium (Ref: <70) | | | | | | | |
| | 70 – 100 | 0.93 (0.72 – 1.15) | 0.00% | 1.55 | 0.91 | | | |
| | 100 – 130 | 0.89 (0.31 – 2.56) | 17.58% | 1.22 | 0.27 | | | |
| | >130 | - | - | - | - | | | |
| | Continents | | | | | | | |
| | Europe | 0.94 (0.75 – 1.13) | 0.00% | 1.57 | 0.95 | | | |
| | USA | 1.00 (0.52 – 1.49) | 0.00% | 1.87 | 0.39 | | | |
| Prostate Cancer (Advanced Grades) | Overall | 0.86 (0.78 – 0.95) | 0.00% | 27.33 | 0.5 | 0.96 | 0.11 | 0.1 |
| | Sample Places | | | | | | | |
| | Plasma | 0.82 (0.71 – 0.96) | 0.00% | 9.96 | 0.44 | | | |
| | Serum | 0.89 (0.78 – 1.03) | 0.00% | 16.78 | 0.47 | | | |
| | Dose of Selenium (Ref: <70) | | | | | | | |
| | 70 – 100 | 0.81 (0.70 – 0.94) | 0.00% | 8.26 | 0.51 | | | |
| | 100 – 130 | 0.94 (0.68 – 1.31) | 0.00% | 1.15 | 0.89 | | | |
| | 130 - 160 | 0.96 (0.79 – 1.15) | 36.69% | 14.22 | 0.11 | | | |
| | >160 | 0.80 (0.70 – 0.94) | 0.00% | 0.81 | 0.51 | | | |
| | Continents | | | | | | | |
| | Europe | 0.78 (0.67 – 0.90) | 0.00% | 6.41 | 0.7 | | | |
| | USA | 0.94 (0.82 – 1.09) | 0.00% | 17.64 | 0.48 | | | |
| Prostate Cancer (Total Grades) | Overall | 0.89 (0.83 – 0.95) | 34.46% | 45.78 | 0.09 | 0.96 | 0.11 | 0.1 |
| | Sample Places | | | | | | | |
| | Plasma | 0.88 (0.80 – 0.97) | 54.96% | 33.3 | 0.01 | | | |
| | Serum | 0.90 (0.81 – 0.99) | 0.00% | 12.42 | 0.57 | | | |
| | Dose of Selenium (Ref: <70) | | | | | | | |
| | 70 – 100 | 0.93 (0.83 – 1.05) | 28.52% | 11.19 | 0.19 | | | |
| | 100 – 130 | 0.91 (0.75 – 1.08) | 62.50% | 18.67 | 0.01 | | | |
| | 130 - 160 | 0.85 (0.76 – 0.96) | 27.37% | 13.77 | 0.18 | | | |
| | >160 | 0.89 (0.69 – 1.15) | 0.00% | 0.49 | 0.19 | | | |
| | Continents | | | | | | | |
| | Europe | 0.90 (0.80 – 1.00) | 24.17% | 10.55 | 0.23 | | | |
| | USA | 0.89 (0.81 – 0.97) | 40.33% | 35.2 | 0.05 | | | |

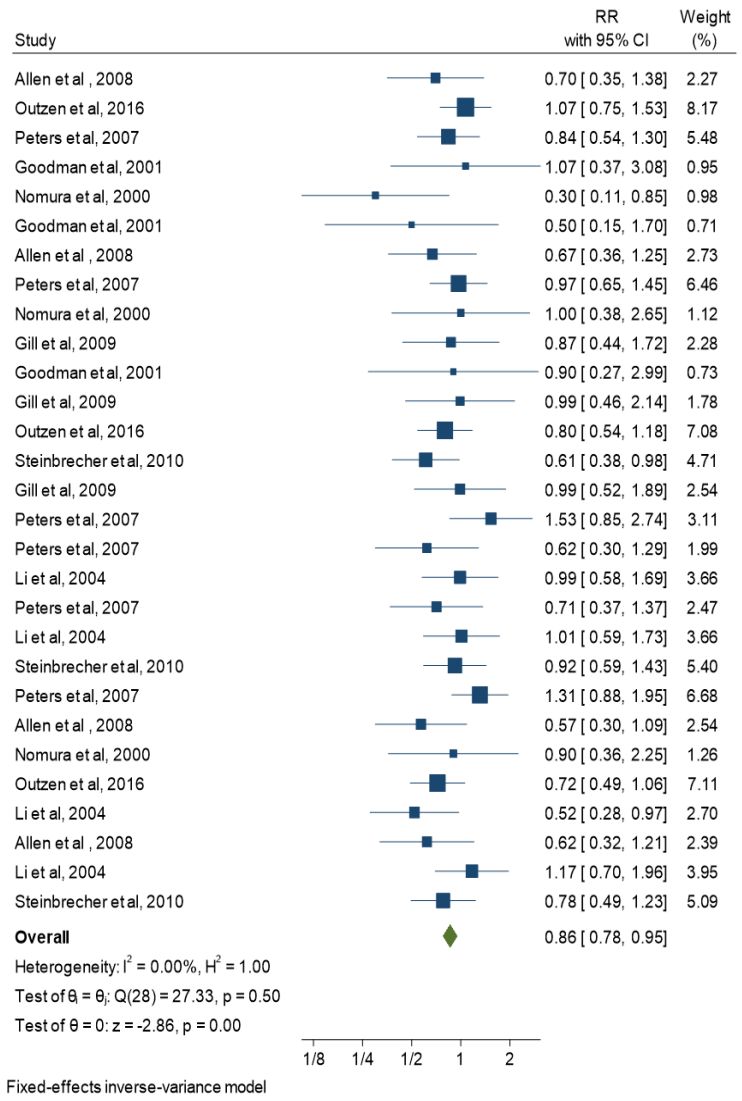


Figure 3. The Effect of Plasma Selenium Level on the Occurrence of Advanced Grade of Prostate Cancer

(Figure 2 and 3). The results of subgroup analyses are shown in Table 2. Based on the selenium dose, if a dose of less than 70 µg is considered as the reference dose, the risk of cancer in people exposed to a dose of 160-130 is equal to 0.85 (RR= 0.85; 95% CI: 0.76 – 0.96; P-value= 0.18; $I_{square}$ = 27.37%), exposure to a dose of 160 and above was equal to 0.89 (RR= 0.89; 95% CI: 0.69 – 1.15; P-value= 0.19; $I_{square}$ = 0.00%). Based on the continent, the results showed that the risk of prostate cancer in case of exposure to selenium in Europe and America is equal to 0.90 (RR= 0.90; 95% CI: 0.80 - 1.00; P-value= 0.23; $I_{square}$ = 24.17%) and 0.89 (RR= 0.89; 95% CI: 0.81 - 0.97; P-value= 0.05; $I_{square}$ = 40.33%). Based on whether the sample was from serum or plasma, the risk of prostate cancer due to contact with selenium did not differ much (Table 2).

In 8 studies [28-30, 33-37, 11] with 1124 cases of advanced cancer and 2608 healthy subjects, the correlation of plasma/serum selenium level with the risk of advanced prostate cancer was reported. After combining these studies, the size of the pooled effect was equal to 0.86 (RR= 0.86; 95% CI: 0.78 - 0.95; P-value= 0.50; $I_{square}$ = 0%). The degree of heterogeneity in these studies was equal to 0%, which indicated the absence of significant differences and contradictions in the working methods of these studies. At a dose greater than 160 micrograms, if the reference dose is less than 70 micrograms, the highest risk of prostate cancer was 0.80 (RR= 0.80; 95% CI: 0.70 - 0.94; P-value= 0.51; $I_{square}$ = 0%). In addition, depending on the place of sampling, the risk of prostate cancer in the case of selenium sampling from serum is lower than sampling in Baudrillard's plasma. Also, the findings showed that the relationship between selenium and the occurrence of advanced prostate cancer in the American population is higher than in the European population (Table 2). Four articles with 2226 cases of high-grade prostate cancer and 2791 healthy subjects reported the association of plasma/serum selenium levels with high-grade prostate cancer, and after combining the results of these studies, the combined effect size was 0.62 (RR= 0.62; %95 CI: 0.51 – 0.75; p-value= 0.75; $I_{square}$ = 0% ) [30, 35, 37, 11]. Three studies [30, 35, 37] also reported the association of plasma/serum selenium level with low-grade prostate cancer with a sample size of 1442 subjects with low-grade prostate cancer and 2007 healthy subjects, and after combining the results of these studies, the combined effect size was equal to 0.95 (RR= 0.95; 95% CI: 0.77 - 1.13;

Table 3. Meta-Analysis Results of the Association Selenium Level in Toenail and Risk of Prostate Cancer based on Sample Places, Dose of Selenium, Continents, and Type of Prostate Cancer

| Outcomes | Categories | RR (% 95 CI) | Heterogeneity Assessment | | | Publication bias | | |
|---|---|---|---|---|---|---|---|---|
| | | | $I_{square}$ | Q | P value | B | SE | P value |
| Prostate Cancer | Overall | 0.69 (0.64 – 0.74) | 56.88% | 16.44 | 0 | 0.51 | 0.05 | 0.28 |
| | Type of Cancer | | | | | | | |
| | High Grades | 0.93 (0.75 – 1.15) | 0.00% | 2.18 | 0.54 | | | |
| | Advanced | 0.73 (0.67 – 0.80) | 69.79% | 49.66 | 0 | | | |
| | Stage IV | 0.50 (0.42 – 0.60) | 81.75% | 16.44 | 0 | | | |
| | Total | 0.61 (0.50 – 0.75) | 0.00% | 8.04 | 0.63 | | | |
| | Dose of Selenium (Ref: ≤0.470) | | | | | | | |
| | 0.470 – 0.617 | 0.75 (0.70 – 0.81) | 57.40% | 53.99 | 0 | | | |
| | >0.617 | 0.39 (0.32 – 0.48) | 43.65% | 5.32 | 0.15 | | | |
| | Dose of Selenium (Ref: ≤0.750) | | | | | | | |
| | >0.750 | 0.58 (0.43 – 0.79) | 0.00% | 4.12 | 0.66 | | | |
| | Continents | | | | | | | |
| | Europe | 0.69 (0.65 – 0.75) | 71.39% | 94.36 | 0 | | | |
| | USA | 0.58 (0.43 – 0.79) | 0.00% | 4.12 | 0.66 | | | |

P-value: 0.94; I-square= 0%). The results of subgroup analyses are reported in Table 2.

*Toenail selenium concentration and prostate cancer risk*

Five articles investigated and reported the relationship between toenail selenium level and prostate cancer risk[26, 27, 31, 38, 39]. Three of these studies [26, 27, 31] with a sample size of 500 prostate cancer cases and 1525 healthy subjects reported the relationship between toenail selenium and total prostate cancer. After combining the results of these studies, the combined effect size was equal to 0.61 (RR= 0.61; 95% CI: 0.50 – 0.75; P-value= 0.63; $I_{square}$= 0.00%). In three studies [31, 38, 39] of toenail selenium and its relationship with the risk of advanced prostate cancer (with a sample size of 2358 cases and 3546 healthy subjects), it was reported that after combining the results of these studies, the combined effect size was equal to 0.73 (RR= 0.73; 95% CI: 0.67 – 0.80; P-value= 0.00; I square= 69.79%) (Table 3). Subgroup analyses based on selenium dose and continent to determine the relationship between toenail selenium and prostate cancer showed that this relationship has a higher risk in the European population than in the American population. Also, a dose of 0.470 to 0.617 reduces the risk of prostate cancer by 25% compared to a dose less than or equal to 0.470, while for a dose greater than 0.617, this risk decreases to about 61% (Table 3).

## Discussion

This meta-analysis aimed to assess the relationship between selenium levels in plasma, serum, and toenails and the risk of different grades of prostate cancer. The findings indicate that maintaining appropriate selenium levels significantly reduces the risk of prostate cancer across various grades. The results demonstrate that adequate selenium levels are associated with a decreased risk of total prostate cancer across all three measurement methods (plasma, serum, and toenail). This protective effect was observed in both Europe and the Americas, though the magnitude of risk reduction varied between these regions. These differences may stem from variations in selenium intake due to global disparities in soil selenium content and cultural dietary practices [16, 9].

Over time, urbanization and lifestyle changes have also influenced food consumption patterns, contributing to regional differences in selenium levels [40]. In the United States, selenium intake is generally higher, often supplemented through diet [9], whereas in Europe, selenium consumption tends to be lower [16, 9]. As a result, the impact of adequate selenium levels on reducing prostate cancer risk appears to be more pronounced in Europe than in the United States.

In a previous systematic review conducted by Horst et al. in 2012, a meta-analysis of toenail selenium levels was performed only for total prostate cancer due to the lack of articles[19]. The present meta-analysis expands on this by including five studies that examined the association between toenail selenium levels and both total and advanced prostate cancer. The findings indicate that optimal selenium levels correspond to a 29% reduction in total prostate cancer risk, aligning with Horst et al.'s reported 30% reduction. Moreover, cohort studies from 2007 suggested that higher selenium levels could lead to a 20% decrease in advanced and aggressive prostate cancer risk [41, 27, 31, 42]. In this meta-analysis, adequate toenail selenium levels were linked to a 27% reduction in advanced prostate cancer risk. Furthermore, selenium's protective effect differed by continent, with reductions of 31% in Europe and 42% in the Americas. This study is the first to examine toenail selenium levels across different subgroups, reinforcing the link between selenium status and prostate cancer risk within a specific selenium range [19].

This analysis also explored the impact of different selenium doses on prostate cancer risk. A dose of 130-

160 micrograms was associated with a 15% reduction in total prostate cancer risk, whereas 70-100 micrograms was linked to a 47% reduction in high-grade prostate cancer and a 19% reduction in advanced prostate cancer risk. Since the human body requires only small amounts of selenium daily (recommended intake: 50 micrograms per day), excessive intake beyond 400 micrograms per day can be toxic [28]. The findings align with data from the third National Health and Nutrition Examination Survey (NHANES III) in the United States, which also supports selenium's dose-dependent effect on prostate cancer risk [43].

Waters DJ et al. reported a U-shaped dose–response relationship between toenail selenium levels and prostatic DNA damage, indicating that maintaining an optimal level of selenium is likely more advantageous in risk reduction than having either very low or very high concentrations [44]. Therefore, in the future, more detailed investigations can be done with a larger sample size to investigate the effect of selenium in different doses on different subgroups of prostate cancer classification.

Heterogeneity analyses revealed that variations in selenium intake levels, geographic differences, and sample types were key contributors to inconsistencies among studies. Subgroup analyses based on these factors significantly reduced heterogeneity, enhancing the robustness of the findings. Additionally, these results may help inform updated guidelines for prostate cancer prevention and management. A limitation of Hurst's meta-analysis was the small number of studies evaluating the link between nail selenium levels and prostate cancer. Future research should consider including more studies on this subject to strengthen the evidence base.

In conclusion, the current meta-analysis showed that selenium has a protective role in prostate cancer, so it is necessary to take measures to manage selenium levels to prevent the occurrence and progression of prostate cancer. However, more studies are needed in high-risk populations, especially in low-selenium-level populations.

## Author Contribution Statement

YM and MG conceptualized the idea for this review, formulated the study question, and objectives, assisted with the development of the final methods, contributed to the data analysis/ interpretation, and writing the manuscript. FM, HM, SF, YM, HD, and MG contributed to the writing of the manuscript. All authors read and approved the final manuscript.

## Acknowledgements

The authors would like to thank the deputy research and technology of Kurdistan University of Medical Sciences, Sanandaj, Iran. This manuscript is not part of any student thesis and hence is not submitted for any scientific body for approval.

*Ethics approval and Consent to Participate*

Since it is a meta-analysis and systematic review, no ethical permission was required for the study.

*Registering Authority*

This study was registered by PROSPERO (CRD42023444118).

*Consent for Publication*

All authors agree to publish.

*Data Availability*

The data supporting this study is available upon request from the corresponding author.

*Availability of Data and Material*

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding authors (Dr. Yousef Moradi).

*Competing of interest*

The authors declare that they have no competing interests.

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