J Renal Inj Prev. 2024; x(x): e34296.

https://journalrip.com doi: 10.34172/jrip.2024.34296

Journal of Renal Injury Prevention

Association between serum vitamin D levels and prostate tumor: a systematic review and meta-analysis

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ARTICLE INFO

Article Type:
Meta-analysis

Article History:
Received: 12 Dec. 2023
Accepted: 13 Mar. 2024
Published online: 25 May 2024

Keywords:
Vitamin D
Prostate cancers
Prostate neoplasm

ABSTRACT

Introduction: Prostate cancer is among the most frequent neoplasms of the male reproductive system, and its relationship with serum vitamin D level is a controversial subject. The present study intended to investigate the relationship between serum vitamin D levels and the risk of prostate carcinoma.

Materials and Methods: This study is a systematic review and meta-analysis based on the PRISMA tool. The search was conducted in databases Web of Science, Cochrane, ProQuest, PubMed, and Google Scholar Search Engine until December 1, 2023. Data was analyzed using STATA 14 software.

Results: There was no significant relationship between serum vitamin D levels lower than 50 nmol/L (vitamin D level <50 nmol/L) and prostate cancer. In Finland, the risk of prostate carcinoma in male individuals with serum vitamin D levels lower than 50 nmol/L was 34% higher (OR: 1.34, 95% CI: 1.14, 1.54). In South Korea, on the other hand, serum vitamin D levels lower than 50 nmol/L prevented prostate cancer (OR: 0.94, 95% CI: 0.90, 0.99). There was no significant relationship between the serum vitamin D levels lower than 50 nmol/L and prostate neoplasm in men aged 60 to 69 years old (OR: 0.95, 95% CI: 0.83, 1.07), in men 50 to 59 years old. On the other hand, serum vitamin D levels lower than 50 nmol/L increased the risk of prostate tumor by 32% (OR: 1.32, 95% CI: 1.13, 1.55). Furthermore, no significant relationship was observed between serum vitamin D levels higher than 50 nmol/L (vitamin D level ≥ 50 nmol/L) and the risk of prostate cancer (OR: 1.06, 95% CI: 0.99, 1.14).

Conclusion: Generally, there was no significant relationship between serum vitamin D levels and the risk of prostate carcinoma; however, the relationship in some subgroups was statistically significant. We therefore recommend conducting additional studies on this subject.

Registration: This study has been compiled based on the PRISMA checklist, and its protocol was registered on the PROSPERO (ID: CRD42023491012) and Research Registry (UIN: reviewregistry1773) website.

Implication for health policy/practice/research/medical education:
In a meta-analysis study, we found that the relationship between serum vitamin D levels and prostate carcinoma risk is insignificant when considering the entire population. However, some subgroups within the study showed a statistically significant association, suggesting that further research is needed to explore this relationship in more detail.

Please cite this paper as: Ghaderi R, Abdollahi Z, Hamidi Madani M, Ghorbani Doshantapeh A, Moghimi B, Jarang M, Rezaei J, Ghaffariyan S, Jafari Arismani R. Association between serum vitamin D levels and prostate tumor: a systematic review and meta-analysis. J Renal Inj Prev. 2024; x(x): e34296. doi: 10.34172/jrip.2024.34296.

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Meta-analysis

Introduction

Uncontrolled cell proliferation in the prostate gland characterizes prostate cancer (1), which is among the most frequent malignant tumors of the male reproductive system, with 1.4 million cases of reported prostate carcinoma around the world in 2020 (1). Age, race, family history, and genetic factors are among the risk factors for prostate neoplasm (2). Normal and malignant prostate cells have vitamin D receptors and enzymes responsible for vitamin D metabolism (3). Vitamin D deficiency leads to various diseases, including cancer, which increases the burden on the health care system (4-6).

Vitamin D is a multifunctional prohormone with critical effects on calcium/phosphorus homeostasis, modulating the immune system, and anti-inflammatory, antioxidant, and anti-tumor roles (7,8). Vitamin D deficiency is common in all nations and more common in cancer patients during the treatment than in the general population (9). Vitamin D affects the body's immune system and causes anti-inflammatory effects and tumor-progression suppressive reactions (10,11). Previous studies reported that increased exposure to sunlight effectively reduced the risk of advanced prostate cancer (12). Other studies during the recent 20-30 years presented evidence indicating the relationship between vitamin D deficiency and increased risk of prostate carcinoma and rate of mortality (13,14). Hence, in this systematic review and meta-analysis, we aimed to investigate the relationship between serum vitamin D levels and the risk of prostate cancer.

Material and Methods

The current study was a systematic review and meta-analysis method based on the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) research tool (15). The study protocol was registered at the International Prospective Register of Systematic Reviews (PROSPERO) website.

Search strategy

The published articles from 2013 to December 1, 2023, were searched in databases including Web of Science, Cochrane, ProQuest, PubMed, and Google Scholar Search Engine. Medical Subject Headings (MeSH) keywords 'Vitamin D, Prostatic Neoplasms, Prostate Cancer, and Prostate Neoplasm' and their equivalents were used to search the sources. In the advanced search, the keywords were combined using the operators 'AND' and 'OR.' In manual search, on the other hand, we reviewed the list of eligible studies. The search strategy in the ProQuest database was as follows: abstract (Vitamin D) AND abstract (Prostatic Neoplasms OR Prostate Cancers OR Prostate Neoplasm).

PICO component:

- Population: studies that examined the relationship between the serum vitamin D level and prostate carcinoma.
- Intervention: serum vitamin D level.
- Comparison: individuals without prostate cancer.
- Outcomes: The relationship between serum vitamin D level and prostate cancer.

Inclusion criteria

Observational studies and randomized clinical trials (RCTs) investigated the relationship between serum vitamin D levels and prostate carcinoma.

Exclusion criteria

Duplicate studies, studies conducted on animal models, studies that examined the effect of vitamin D intake through diet or supplements on the risk of prostate neoplasms, case-report studies, posters, review articles, descriptive studies, low-quality studies, studies without accessible full-texts, and those that lacked the required data for analysis were excluded.

Quality assessment

The Newcastle-Ottawa Scale (NOS) was used to assess the quality of observational studies (16). The scale included three views: participant selection, comparability, and outcome assessment. Studies that achieved a minimum of six stars entered the present research as high-quality articles. RCTs were assessed using the checklist provided by Cochrane Institute (17). The checklist comprises seven questions with three answers. The answer to each question is one of the following items: high risk of bias, low risk of bias, and uncertain. Eventually, studies with four answers (out of the seven) indicating a low risk of bias were considered high-quality and entered this study. Then, the two researchers evaluated the cases of disagreements in answering the questions and finally reached an identical answer by consulting with each other.

Data extraction

Two researchers extracted the data independently. Extracted data included the author's name, study design, sample size, age group, study duration, serum vitamin D level, location and time of the study, odds ratio of serum vitamin D level to prostate cancer, and their 95% confidence intervals. The third researcher examined the data extracted by the previous researchers and addressed the inconsistencies.

Statistical analysis

The logarithm of the odds ratio (OR) and I^2 index were used to combine the studies and to examine the inter-study heterogeneity, respectively. The I^2 index includes three classes (lower than 25%: low, between 25% and 75%: moderate, and higher than 75% severe heterogeneity). Inter-study heterogeneity of studies on the relationship between serum vitamin D levels greater than or equal to

50 nmol/L and the risk of prostate carcinoma was low; hence, the fixed effects model was used. However, the interstudy heterogeneity in studies on the relationship between serum vitamin D levels lower than 50 nmol/L and the risk of prostate carcinoma was moderate; hence, a random effects model was used. Data analysis was conducted using the STATA 14 software, and test *P* values lower than 0.05 were considered significant ($P<0.05$).

Results

A total of 810 articles were found by searching the mentioned databases, 314 of which were duplicates and were removed from the study. Then, abstracts were reviewed, and 63 articles without accessible full-texts were removed. In the next step, 71 studies that lacked the required data for analysis exited the study. Another 346 studies were removed due to other exclusion criteria, and 16 high-quality studies remained (Figure 1).

This meta-analysis examined 16 studies (one cross-sectional, one randomized controlled trial, six cohort, and eight case-control studies). Table 1 presents the considerable data extracted from the studies.

There was no significant relationship between serum vitamin D levels lower than 50 nmol/L and the risk of prostate carcinoma (OR: 1.06, 95% CI: 0.98, 1.14) (Figure 2). Geographical location was among the factors affecting serum vitamin D levels. In Finland, men with serum vitamin D levels lower than 50 nmol/L (vitamin D level <50 nmol/L) indicated higher risks of prostate neoplasm (OR: 1.34, 95% CI: 1.14, 1.54). In South Korea, on the other hand, serum vitamin D levels lower than 50 nmol/L prevented prostate cancer (OR: 0.94, 95% CI: 0.90, 0.99). The relationship between serum vitamin D levels lower than 50 nmol/L and risk of prostate carcinoma in countries Denmark (OR: 1.15, 95% CI: 0.88, 1.51), Turkey (OR: 0.73, 95% CI: 0.33, 1.61), USA (OR: 1.02, 95% CI: 0.87, 1.20), and Australia (OR: 0.89, 95% CI: 0.65, 1.22) were not statistically significant.

The relationship between serum vitamin D levels lower than 50 nmol/L and the incidence of prostate carcinoma in male patients 60 to 69 years was statistically insignificant (OR: 0.95, 95% CI: 0.83, 1.07). However, serum vitamin D levels lower than 50 nmol/L increased the risk of prostate neoplasm in men aged 50 to 59 (OR: 1.32, 95% CI: 1.13, 1.55).

Study-type-based subgroup analysis showed that there

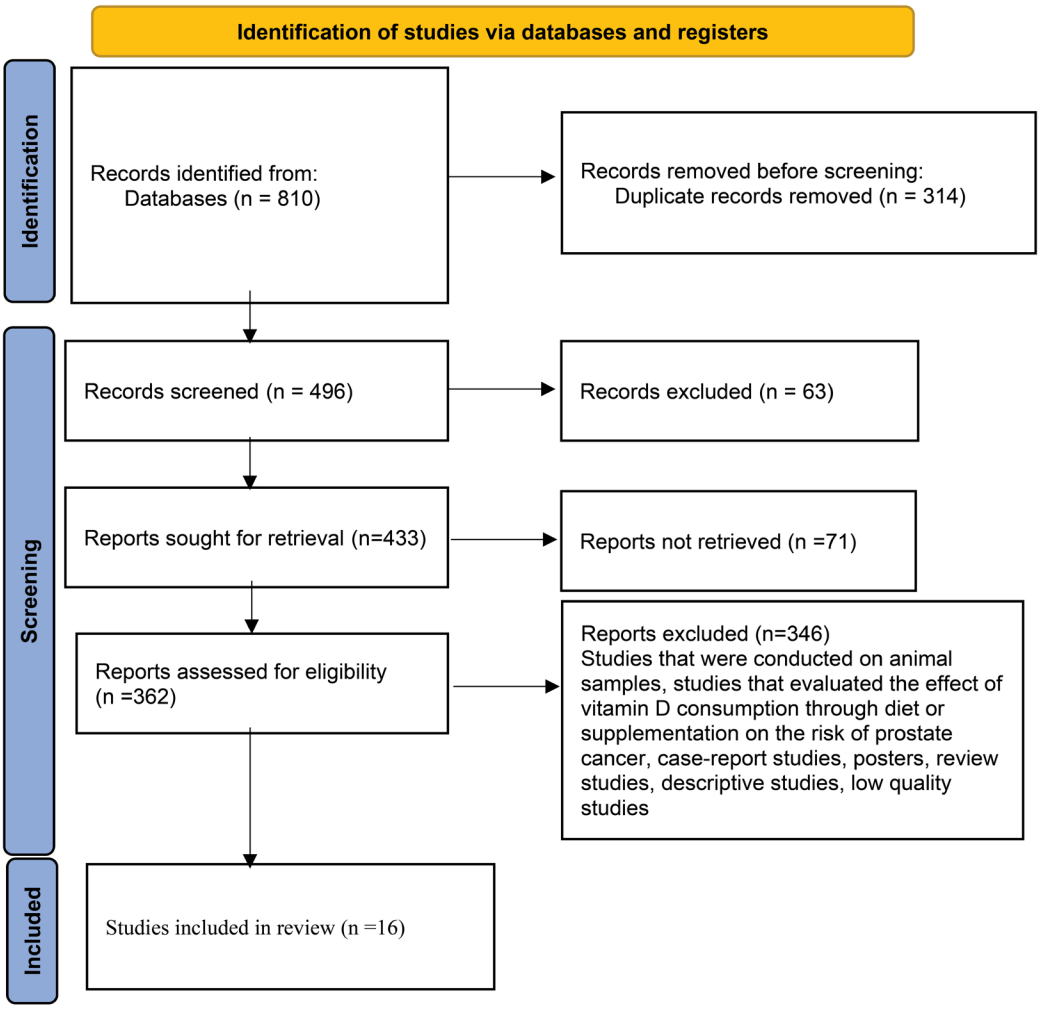

Figure 1. The flow chart of study selection (PRISMA).

Table 1. Data extracted from reviewed studies

Author, year	Country	Type of study	Total number	Mean age (y)	Period of study	Vitamin D Serum levels
Voutilainen A, 2023 (18)	Finland	Cohort	NR	NR	Baseline and December 31, 2019	<30 nmol/L
Voutilainen A, 2023 (18)	Finland	Cohort	NR	NR	Baseline and December 31, 2019	>50 nmol/L
Kim MH, 2022 (19)	South Korea	Cohort	224	67.5	NR	18.1 ng/mL
Stroomberg HV, 2021 (20)	Denmark	Cohort	4065	NR	2004 to 2010	<25 nmol/L
Stroomberg HV, 2021 (20)	Denmark	Cohort	NR	NR	2004 to 2010	25–50 nmol/L
Stroomberg HV, 2021 (20)	Denmark	Cohort	NR	NR	2004 to 2010	>75 nmol/L
Acikgoz A, 2020 (21)	Turkey	Case–Control	606	60.5	2008-2013	≤ 8.61 ng/mL
Acikgoz A, 2020 (21)	Turkey	Case–Control	NR	NR	2008-2013	8.62–13.67 ng/mL
Acikgoz A, 2020 (21)	Turkey	Case–Control	NR	NR	2008-2013	13.68–19.14 ng/mL
Park JS, 2020 (22)	USA	Cross-sectional	758	62.8	2007–2008	78.2 nmol/L
Park JS, 2020 (22)	USA	Cross-sectional	NR	NR	2007–2008	10.6 nmol/L
Heath AK, 2019 (23)	Australia	Cohort	NR	NR	NR	50.5-59.5 nmol/L
Heath AK, 2019 (23)	Australia	Cohort	NR	NR	NR	59.6-72.9 nmol/L
Heath AK, 2019 (23)	Australia	Cohort	NR	NR	NR	72.9-181.1 nmol/L
Yuan C, 2019 (24)	USA	Case–Control	NR	NR	Between 1993 and 1995	24.31-30.47 ng/mL
Yuan C, 2019 (24)	USA	Case–Control	NR	NR	Between 1993 and 1995	≥30.78 ng/mL
Layne TM, 2017 (25)	USA	Case–Control	678	55-74	Between 1993 and 2001	>28.5-40.3 nmol/L
Layne TM, 2017(25)	USA	Case–Control	NR	NR	Between 1993 and 2001	>55.8 nmol/L
Nelson SM, 2017(26)	USA	Cohort	155	40-85	Between the years 2001 and 2004	<20 ng/mL
Sawada N, 2017 (27)	Japan	Case–Control	603	40-69	1990–1994	32 ng/ml
Sawada N, 2017 (27)	Japan	Case–Control			1990–1994	49 ng/ml
Jackson MD, 2015 (28)	Jamaica	Case–Control	472	40–80	NR	27.07–34.26 ng/mL
Jackson MD, 2015 (28)	Jamaica	Case–Control	NR	NR	NR	34.27–93.20 ng/mL
Paller CJ, 2015 (29)	USA	Case–Control	51	64.14	Between 2005 and 2008	>30 ng/ml
Wong YYE, 2014 (30)	Australia	Cohort	295	76.8	1996-1999	<50 nmol/L
Wong YYE, 2014 (30)	Australia	Cohort			1996-1999	>75 nmol/L
Kristal AR, 2014 (31)	USA, Canada, Puerto Rico	Randomized, placebo-controlled trial	470	69.2	Between July 2001 and May 2004	37.5 to <50 nmol/L
Kristal AR, 2014 (31)	USA, Canada, Puerto Rico	Randomized, placebo-controlled trial	1070	69.2	Between July 2001 and May 2004	50 to <75 nmol/L
Kristal AR, 2014 (31)	USA, Canada, Puerto Rico	Randomized, placebo-controlled trial	1199	69.2	Between July 2001 and May 2004	≥75 nmol/L
Schenk JM, 2014 (32)	USA	Case–Control	NR	NR	NR	44.7 nmol/L
Schenk JM, 2014 (32)	USA	Case–Control	NR	NR	NR	56.8 nmol/L
Schenk JM, 2014 (32)	USA	Case–Control	NR	NR	NR	71.2 nmol/L
Weinstein SJ, 2013 (33)	Finland	Case–Control	NR	NR	Between 1985 and 1988	29.8 nmol/L
Weinstein SJ, 2013 (33)	Finland	Case–Control	NR	NR	Between 1985 and 1988	35.5 nmol/L
Weinstein SJ, 2013 (33)	Finland	Case–Control	NR	NR	Between 1985 and 1988	32.2 nmol/L
Weinstein SJ, 2013 (33)	Finland	Case–Control	NR	NR	Between 1985 and 1988	33.7 nmol/L

NR: Not reported.

was no statistically significant relationship between serum vitamin D levels lower than 50 nmol/L and risk of prostate cancer in the cohort (OR: 1.03, 95% CI: 0.88, 1.21), case-control (OR: 1.15, 95% CI: 0.97, 1.36), and RCT studies (OR: 1.08, 95% CI: 0.83, 1.41). Nevertheless, serum vitamin D level lower than 50 nmol/L was a prostate carcinoma risk factor in cross-sectional studies (OR: 1.03, 95% CI: 1, 1.05; Figure 3).

Figure 4 showed no significant relationship between serum vitamin D levels greater than or equal to 50 nmol/L and prostate neoplasm (OR: 1.06, 95% CI: 0.99, 1.14). Furthermore, the relationships between serum vitamin D levels greater than or equal to 50 nmol/L and prostate cancer in male individuals aged 50 to 59 (OR: 1.01, 95% CI: 0.72, 1.41) and 60 to 69 (OR: 0.98, 95% CI: 0.81, 1.19), were not significant.

Serum vitamin D levels greater than or equal to 50 nmol/L in countries Denmark (OR: 1.06, 95% CI: 0.99, 1.14), USA (OR: 1.06, 95% CI: 0.90, 1.23), Australia (OR: 1.12, 95% CI: 0.97, 1.29), Japan (OR: 1.01, 95% CI: 0.72, 1.41), and Jamaica (OR: 1.47, 95% CI: 0.99, 2.20) did not affect the risk of prostate cancer. On the other hand,

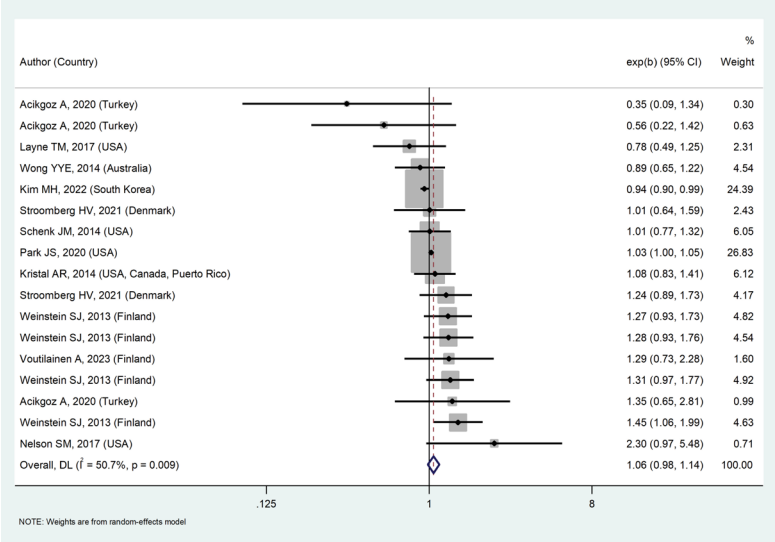

Figure 2. Forest plot showing the relationship between serum vitamin D levels <50 nmol/L and prostate tumor and its 95% confidence interval.

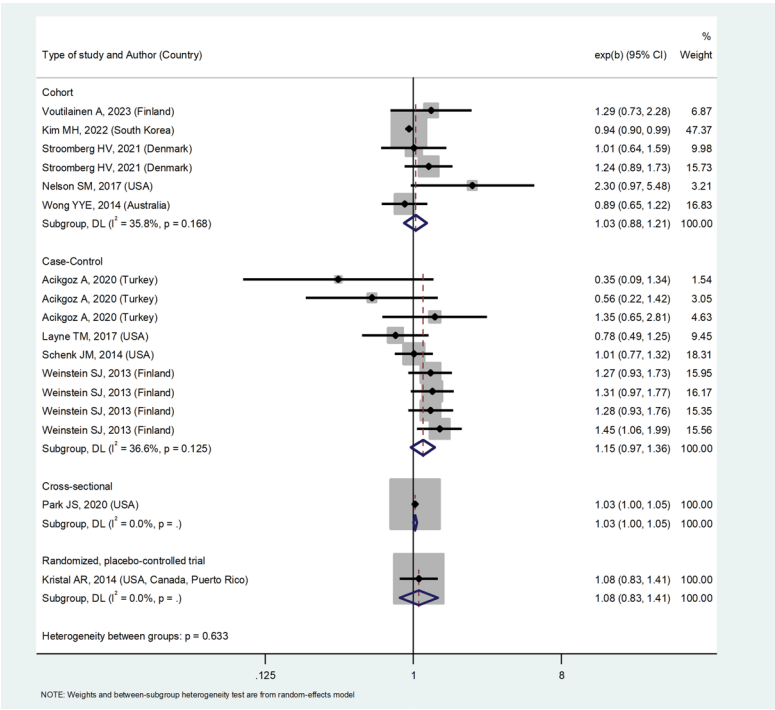

Figure 3. Forest plot showing the relationship between serum vitamin D levels <50 nmol/L and prostate tumor by design studies.

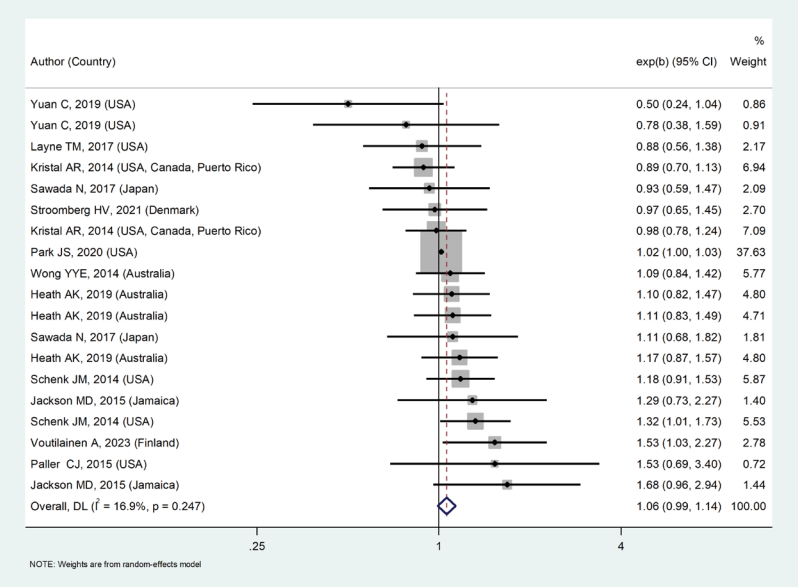

Figure 4. Forest plot showing the relationship between serum vitamin D levels ≥50 nmol/L and prostate tumor and its 95% confidence interval.

serum vitamin D levels greater than or equal to 50 nmol/L increased the risk of prostate carcinoma in Finland (OR: 1.53, 95% CI: 1.03, 2.27).

As shown by Figure 5, subgroup analysis indicated that the relationship between serum vitamin D levels greater than or equal to 50 nmol/L and prostate cancer in RCTs (OR: 0.93, 95% CI: 0.79, 1.10) and case-control studies (OR: 1.12, 95% CI: 0.95, 1.32) were not statistically significant. However, serum vitamin D levels greater than or equal to 50 nmol/L in the cohort (OR: 1.14, 95% CI: 1, 1.29) and cross-sectional (OR: 1.02, 95% CI: 1, 1.03) studies increased the risk of prostate carcinoma.

Discussion

A meta-analysis of a combination of 48 studies by Liu et al investigating the relationship between serum 25(OH) D levels and the risk of several neoplasms indicated that high serum 25(OH)D levels increased the risk of prostate

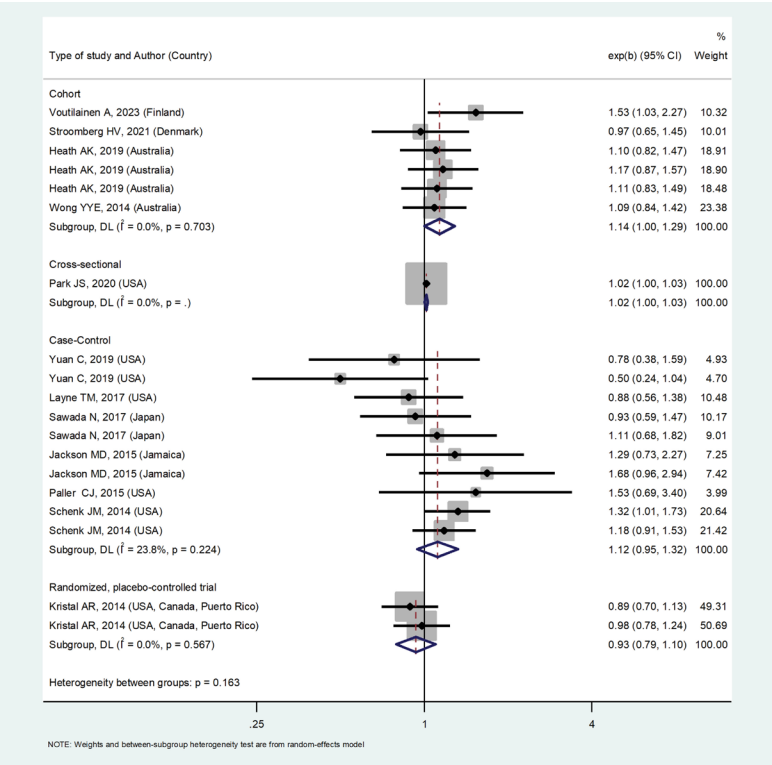

Figure 5. Forest plot showing the relationship between serum vitamin D levels ≥50 nmol/L and prostate tumor by design studies.

carcinoma (RR: 1.11; 95% CI: 1.03-1.20) (34). Another study by Travis et al concluded that high 25(OH)D concentrations increased the risk of prostate cancer (OR: 1.22; 95% CI: 1.13-1.31) (35). In a previous meta-analysis of 19 articles, Gao et al showed that higher 25(OH)D concentrations are directly associated with an increased risk of prostate carcinoma (RR: 1.15; 95% CI: 1.06–1.24) (36). Using the meta-analysis method, Xu et al reported that higher 25(OH)D levels in circulation increased the risk of prostate cancer by 17% (OR: 1.17; 95% CI: 1.05–1.30) (37). The mentioned studies indicated that high serum vitamin D levels can be a risk factor for prostate neoplasm and may increase the risk of prostate cancer. On the other hand, in the present meta-analysis, we concluded that there was no significant relationship between the serum vitamin D level and prostate cancer. However, there were many differences between the reviewed research in this meta-analysis and the previous meta-analyses. Most importantly, the previous meta-analyses reported the cutoff point of serum vitamin D levels using qualitative methods and did not define the highest and lowest vitamin D levels.

A recent meta-analysis by Yin et al on 11 studies reported that the relationship between the serum vitamin D level and prostate cancer was statistically insignificant (OR:1.03; 95% CI: 0.96–1.11) (38), which was consistent with our study.

The following studies reported that higher serum vitamin D levels prevented several neoplasms, including lung, liver, breast, and colorectal cancer, which was inconsistent with the present study. However, the disease and sex of the participants in our meta-analysis varied from the following studies, which may justify the inconsistencies. Arayici et al conducted a meta-analysis to examine the relationship between vitamin D and cancer risk. They reported that higher vitamin D intake (OR: 0.93; 95% CI: 0.90–0.96) and elevated serum 25(OH)D levels (OR: 0.80; 95% CI: 0.72–0.89) can prevent cancer (39). Similarly, Zhang et al showed that individuals with the lowest 25-OH-vitamin-D levels face lower risks of liver cancer (HR: 0.53; 95% CI: 0.41–0.68) (40). A previous meta-analysis by Zhang et al revealed that high serum vitamin D levels decreased the risk of lung cancer and prevented lung cancer (RR: 0.84; 95% CI: 0.78-0.90) (41). The results of another meta-analysis by Song et al showed that increasing the blood vitamin D level by five nmol/L reduced the risk of breast cancer by 6% (OR: 0.94; 95% CI: 0.93–0.96) (42). Hernandez-Alonso et al conducted a meta-analysis and found that compared with the lowest levels, the highest circulating vitamin D levels reduced the risk of colorectal cancer by up to 39% (OR: 0.61; 95% CI: 0.52–0.71) (43).

We were not able to divide the studies into subgroups and compare the serum vitamin D levels <25, 25-50, 50-75, and >75 nmol/L, which was the primary limitation of the current meta-analysis. Conducting this comparison may indicate a significant relationship between the serum vitamin D level and the risk of prostate cancer. The limitation of the number of conducted RCTs and cross-sectional studies was another limitation of the current study.

Conclusion

Generally, our meta-analysis indicated no significant relationship between high or low serum vitamin D levels and the risk of prostate carcinoma, and further studies on this subject are necessary. On the other hand, subgroup analysis showed that serum vitamin D levels lower than 50 nmol/L increased the risk of prostate cancer in Finland by 34%, in men aged 50 to 59 by 32%, and in cross-sectional studies by 3%. However, serum vitamin D levels lower than 50 nmol/L prevented prostate neoplasm in South Korea. Serum vitamin D levels greater than or equal to 50 nmol/L increased the risk of prostate carcinoma in Finland by 53%, in cohort studies by 14%, and in cross-sectional studies by 2%. We can conclude that serum vitamin D levels higher or lower than the normal range may increase the risk of prostate cancer in male patients. Accordingly, we recommend maintaining serum vitamin D levels of men within the normal range.

Acknowledgments

The authors would like to thanks Hamid Nasri and Hosein Mardanparvar for guidance and editing of manuscript registration on the PROSPERO website and Guissu Research Corporation for guidance and editing of manuscript registration on the Research Registry website.

Authors' contribution

Conceptualization: Reza Ghaderi and Zahra Abdollahi.
Data curation: Shahrzad Ghaffariyan and Rasoul Jafari Arismani.
Formal analysis: Jalal Rezaei.
Investigation: Mohamad Jarang and Reza Ghaderi.
Methodology: Mohammad Hamidi Madani.
Project management: Rasoul Jafari Arismani.
Resources: All authors.
Supervision: Reza Ghaderi.
Validation: Anna Ghorbani Doshantapeh and Boshra Moghimi.
Visualization: Zahra Abdollahi.
Writing-original draft: All authors.
Writing-reviewing & editing: All authors.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

This study has been compiled based on the PRISMA checklist, and its protocol was registered on the PROSPERO website (ID: CRD42023491012) and Research Registry website with (Unique Identifying Number (UIN)

reviewregistry1773) . Besides, ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the author.

Funding/Support

None.

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