

Circulating vitamin D concentration and risk of prostate cancer: a dose–response meta-analysis of prospective studies

Jialin Gao
Wei Wei
Gang Wang
Honglan Zhou
Yaowen Fu
Nian Liu

Department of Urology, The First Hospital of Jilin University, Changchun, People's Republic of China

Background: Though many studies have been performed to elucidate the association between circulating vitamin D and prostate cancer, no conclusive result is available. We carried out a dose–response meta-analysis to quantitatively examine the association of circulating 25-hydroxyvitamin D (25[OH]D) concentration with prostate cancer.

Methods: Only prospective studies examining the associations of circulating 25[OH]D concentration with prostate cancer were eligible for the meta-analysis. A random-effect meta-analysis was done first, to calculate the summary relative risk (RR) and 95% confidence intervals (CIs) comparing the higher concentration with the lower concentration of 25[OH]D. A dose–response meta-analysis using random-effects model was then carried out to evaluate the nonlinearity and calculate the summary RR caused per 10 ng/mL increment.

Results: Nineteen prospective cohort or nested case–control studies were included. Higher 25[OH]D concentration was significantly correlated with elevated risk of prostate cancer (RR = 1.15, 95% CI 1.06–1.24). No nonlinear relationship was found between 25[OH]D concentration and risk of prostate cancer ($P=0.654$). Dose–response meta-analysis showed that the summary RR caused per 10 ng/mL increment in circulating 25[OH]D concentration was 1.04 (95% CI 1.02–1.06). Subgroup analysis also found a modest dose–response relationship. Funnel plot and Egger's test did not detect publication bias.

Conclusion: The findings suggest that highest 25[OH]D concentration is correlated with elevated risk of prostate cancer and a modest dose–response effect exists in this association; however, more studies are needed.

Keywords: vitamin D, prostate cancer, dose–response meta-analysis

Introduction

Prostate cancer is the most common malignancy among men worldwide.¹ In addition, the incidence of prostate cancer has increased significantly in most Asian populations.² There has been a lot of progress in the therapeutic options including novel molecularly targeted therapeutics for prostate cancer patients in the past decade.^{3,4} Over the past decade, many clinical or experimental studies have provided many fundamental insights into the pathogenesis of prostate cancer.^{5–7} There are a number of risk factors for prostate cancer reported in published literatures, such as vasectomy and alcohol intake.^{8–10} However, there is still limited number of modifiable risk factors identified for prostate cancer and more studies are needed to identify some modifiable risk factors associated with prostate cancer.

The roles of vitamin D in human diseases have received increased attention, and it has been regarded as a vital hormone to maintain the normal functions of various

Correspondence: Nian Liu
Department of Urology, The First Hospital of Jilin University, Number 71 Xinmin Street, Changchun 130021, People's Republic of China
Tel +86 431 8878 2222
Email liunian1609@163.com

organs or systems in the bodies.^{11–14} Vitamin D has some extraskeletal biological functions including inhibiting the progression of cancer cells.^{15,16} A previous study has found that vitamin D can exert a key role in decreasing cancer risk.¹⁷ Meta-analyses of epidemiological studies have suggested that higher circulating 25-hydroxyvitamin D (25[OH]D) concentration is correlated with decreased risks of several common cancers, such as colorectal cancer and bladder cancer.^{18,19} Considering the preventive effect of vitamin D against cancer, many researchers also studied the association of circulating 25[OH]D concentration with prostate cancer.^{20–28} Some studies reported that higher serum 25[OH]D concentration modestly increased the risk of prostate cancer.^{26,29,30} However, other studies did not find any correlation of vitamin D with prostate cancer.^{25,27–29} These studies have obtained controversial results on the impact of circulating 25[OH]D on prostate cancer risk, and no conclusive result is available. Thus, we carried out a comprehensive literature search and performed a meta-analysis to examine the association of circulating 25[OH]D concentration with prostate cancer.

Methods

Search strategy and inclusion criteria

PubMed and Web of Science were searched for prospective studies, examining the correlation of circulating 25[OH]D concentration with prostate cancer, which were eligible for the meta-analysis. We carried out the literature search on December 20, 2016. We used combinations of the following keywords: (“vitamin D” or “25-hydroxyvitamin D” or “25[OH]D”) AND (“prostate cancer” or “prostate carcinoma”). The references from included articles were also checked to identify any additional studies.

Only prospective cohort studies or nested case–control studies examining the associations of circulating 25[OH]D concentration with prostate cancer and reporting relative risks (RRs) of prostate cancer across at least three categories of circulating 25[OH]D levels were eligible for the meta-analysis. Case–control studies, cross-sectional studies, and retrospective cohort studies were excluded. Studies without RRs of prostate cancer across at least three categories of 25[OH]D concentrations were also excluded. Studies containing overlapping data were also excluded.

Data extraction and quality assessment

Two investigators extracted data independently, and any disagreement was resolved by consensus among all investigators. For each study, we extracted RRs of prostate cancer comparing the upper categories of circulating 25[OH]D concentration with the lowest category of circulating 25[OH]D level.

For the dose–response meta-analysis, the number of cases and noncases, concentration level, and adjusted RR for each category and its 95% confidence interval (CI) were extracted. For the studies that did not provide the median or mean levels of serum 25[OH]D, we used the midpoint of each category as the alternative. For the open-ended category, the midpoint of this category was calculated by assuming that the interval was the same as that of the adjacent category. When the numbers of cases/noncases in each category were not available, the numbers were estimated by the methods proposed by Aune et al.³¹ For studies that did not set the lowest category as reference, we used the method described by Hamling et al.³² to make a transformation. Furthermore, we gathered information on study design, country, sample size, matching factors, and time of follow-up or from blood collection to diagnosis. Studies with >300 prostate cancer cases were defined as studies with large sample size, while those with <300 prostate cancer cases were defined as studies with small sample size. The quality assessment was done by the recommendation from Newcastle–Ottawa Scale (NOS), which encompassed three perspectives including selection of participants, comparability, and outcome assessment, and studies scoring at least 6 stars were classified as high-quality studies.³³

Statistical analysis

The homogeneity among those included studies was estimated by the I^2 statistic, and $I^2 > 50\%$ represented high concentration of heterogeneity.³⁴ A random-effect meta-analysis was first done to calculate the summary RR and 95% CI comparing the higher concentration with the lower concentration of 25[OH]D.³⁵ The dose–response meta-analysis was performed using the method proposed by Greenland and Longnecker³⁶ and Orsini et al.³⁷ In order to explore the nonlinear dose–response curve, serum 25[OH]D concentrations were modeled using restricted cubic splines with three knots at fixed percentiles (0.10, 0.50, and 0.90) of the distribution. The P -value of nonlinearity was calculated by testing against the null hypothesis that the coefficient of the second spline was equal to 0. If the nonlinearity was not statistically significant, the linear dose–response outcomes were presented per 10 ng/mL (25 nmol/L) increment in serum 25[OH]D by random-effects model.^{35–37}

Subgroup analysis was performed by sample size, publication year, study designs, and adjustment for calcium intake. Sensitivity analysis was carried out by excluding any single study by turns. Publication bias was evaluated by funnel plot and the Egger test.³⁸ The traditional meta-analysis was carried out using STATA (Version 12.0),

and the dose–response meta-analysis was performed by R and its *dosresmeta* package.³⁹

Results

Characteristics of included studies

The study selection process is shown in Figure 1. Though >1,530 articles were found, only 42 studies were possibly eligible and evaluated by checking the full texts.^{16,20–30,40–69} Twenty-three studies were then excluded,^{16,40–61} and the remaining 19 studies were considered eligible.^{20–30,62–69} There were three prospective cohort studies and 16 nested case–control studies (Table 1). Most studies were carried out in Europe and USA except one study from Japan (Table 1). The number of prostate cancer cases in those 19 studies varied obviously and ranged from 61 to 2,106 (Table 1). A total of 12,786 prostate cancer cases and 35,583 participants were included in those 19 studies. There were seven studies with <300 prostate cancer cases and 12 studies with >300 prostate cancer cases (Table 1). All 19 studies reported the adjusted RRs of prostate cancer across at least three categories of circulating 25[OH]D levels. According to the NOS criteria, all included studies scored >6 stars and thus had high quality.

Meta-analysis

When performing meta-analysis of RRs comparing the higher concentration with the lower concentration of 25[OH]D, there was good homogeneity among those included studies

($I^2=0\%$). Higher 25[OH]D concentration was significantly correlated with elevated risk of prostate cancer (RR =1.15, 95% CI 1.06–1.24, $P=0.001$) (Figure 2). The summary RR was not significantly changed in the sensitivity analysis. As shown in Table 2, in the subgroup analysis of studies with small sample size, with cohort study design, there was no significant correlation of circulating 25[OH]D concentration with prostate cancer. The adjustment for calcium supplementation did not change the positive association between the serum 25[OH]D and risk of prostate cancer.

For the dose–response meta-analysis, as shown in Figure 3, there was no nonlinear relationship between circulating 25[OH]D concentration and the risk of prostate cancer ($P=0.654$). When performing meta-analysis of RRs of prostate cancer risk caused by per 10 ng/mL increment in circulating 25[OH]D level, there was also good homogeneity among those included studies ($I^2=0\%$). Linear dose–response meta-analysis showed the summary RR caused by per 10 ng/mL increment in circulating 25[OH]D concentration was 1.04 (95% CI 1.02–1.06, $P<0.001$) (Figure 4). The summary RR was not significantly changed in the sensitivity analysis. As shown in Table 2, subgroup analysis using data from studies of large sample size also found a modest dose–response relationship (RR =1.04, 95% CI 1.02–1.06, $P<0.001$). However, subgroup analysis using data from studies of small sample size or cohort study design did not find an obvious dose–response relationship (Table 2).

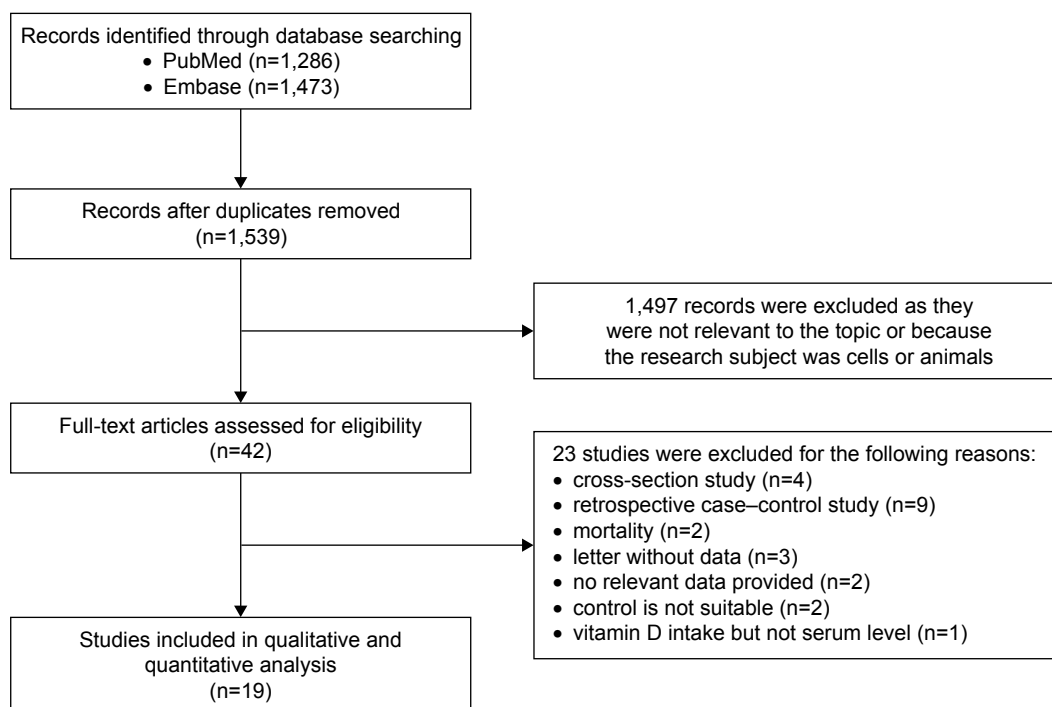


Figure 1 Selection of studies for inclusion in meta-analysis.

Table 1 Characteristics of included studies on the association between circulating vitamin D concentrations and prostate cancer

References	Design	Country	Participants	Time of follow-up or from blood collection to diagnosis	Quality (NOS score)
Braun et al (1995) ²⁰	Nested case-control	USA	61 prostate cancer cases and 122 matched controls	14 years	High (6)
Nomura et al (1998) ²¹	Nested case-control	USA	136 cases of prostate cancer and 136 matched controls	23 years	High (7)
Tuohimaa et al (2004) ⁶⁹	Nested case-control	Norway, Finland, and Sweden	622 prostate cancer cases and 1,451 matched controls	10 years	High (7)
Platz et al (2004) ⁶⁶	Nested case-control	USA	460 prostate cancer cases and 460 matched controls	2.2 years	High (9)
Jacobs et al (2004) ⁶⁴	Nested case-control	USA	83 prostate cancer cases and 166 matched controls	5.2 years	High (8)
Baron et al (2005) ²²	Prospective cohort	USA	672 men and 70 incident prostate cancer cases	10.3 years	High (8)
Faupel-Badger et al (2007) ⁶³	Nested case-control	Finland	296 prostate cancer cases and 297 matched controls	9.26 years	High (8)
Ahn et al (2008) ⁶²	Nested case-control	USA	749 case patients with incident prostate cancer and 781 matched control subjects	8 years	High (9)
Travis et al (2009) ⁶⁸	Nested case-control	Europe	652 prostate cancer cases matched to 752 controls	4.1 years	High (8)
Park et al (2010) ⁶⁵	Nested case-control	USA	329 prostate cancer cases and 656 matched controls	Not reported	High (7)
Barnett et al (2010) ²³	Prospective cohort	USA	5,995 men and 297 incident prostate cancer cases	5.3 years	High (7)
Albanes et al (2011) ³⁰	Nested case-control	Finland	1,000 prostate cancer cases matched to 1,000 controls	20 years	High (9)
Brandstedt et al (2012) ²⁴	Nested case-control	Sweden	943 prostate cancer cases and 943 matched controls	7.6 years	High (7)
Shui et al (2012) ⁶⁷	Nested case-control	USA	1,260 prostate cancer cases matched to 1,331 matched controls	5.2 years	High (9)
Meyer et al (2013) ²⁵	Nested case-control	Norway	2,106 prostate cancer cases matched to 2,106 matched controls	16.1 years	High (9)
Kristal et al (2014) ²⁶	Nested case-control	USA	1,731 prostate cancer cases and 3,203 cohort participants	Not reported	High (8)
Skaaby et al (2014) ²⁷	Prospective cohort	Denmark	12,204 individuals and 133 cases	11.3 years	High (8)
Schenk et al (2014) ²⁹	Nested case-control	USA	1,695 cases and 1,682 matched controls	7 years	High (9)
Sawada et al (2017) ²⁸	Nested case-control	Japan	201 cases and 402 matched controls	12.8 years	High (7)

Note: The quality was rated by NOS and studies scoring at least 6 stars were classified as high-quality studies.

Abbreviation: NOS, Newcastle–Ottawa Scale.

The funnel plot did not detect publication bias (Figure 5). Besides, the *P*-value of Egger test was 0.48 and provided another evidence for the lack of publication bias.

Discussion

Though the preventive roles of vitamin D have been found in several cancers, its role in the development of prostate cancer is still unclear. Those published studies did not report consistent findings. We therefore carried out a dose–response meta-analysis to quantitatively elucidate the impact of circulating 25[OH]D concentration on prostate cancer. A total of 19 prospective studies were finally eligible for the

meta-analysis. We found that higher 25[OH]D concentration was significantly correlated with elevated risk of prostate cancer (RR=1.15, *P*=0.001; Figure 1). Dose–response meta-analysis showed the summary RR of prostate cancer caused by per 10 ng/mL increment was 1.04 (*P*<0.001; Figure 2). Therefore, the findings from the meta-analysis suggested that higher 25[OH]D concentration was correlated with elevated risk of prostate cancer and a modest dose–response effect existed in this association.

In human bodies, vitamin D is mainly synthesized in the skin after exposure to solar UV radiation and vitamin D can also be ingested from some foods.^{70,71} 25[OH]D is the

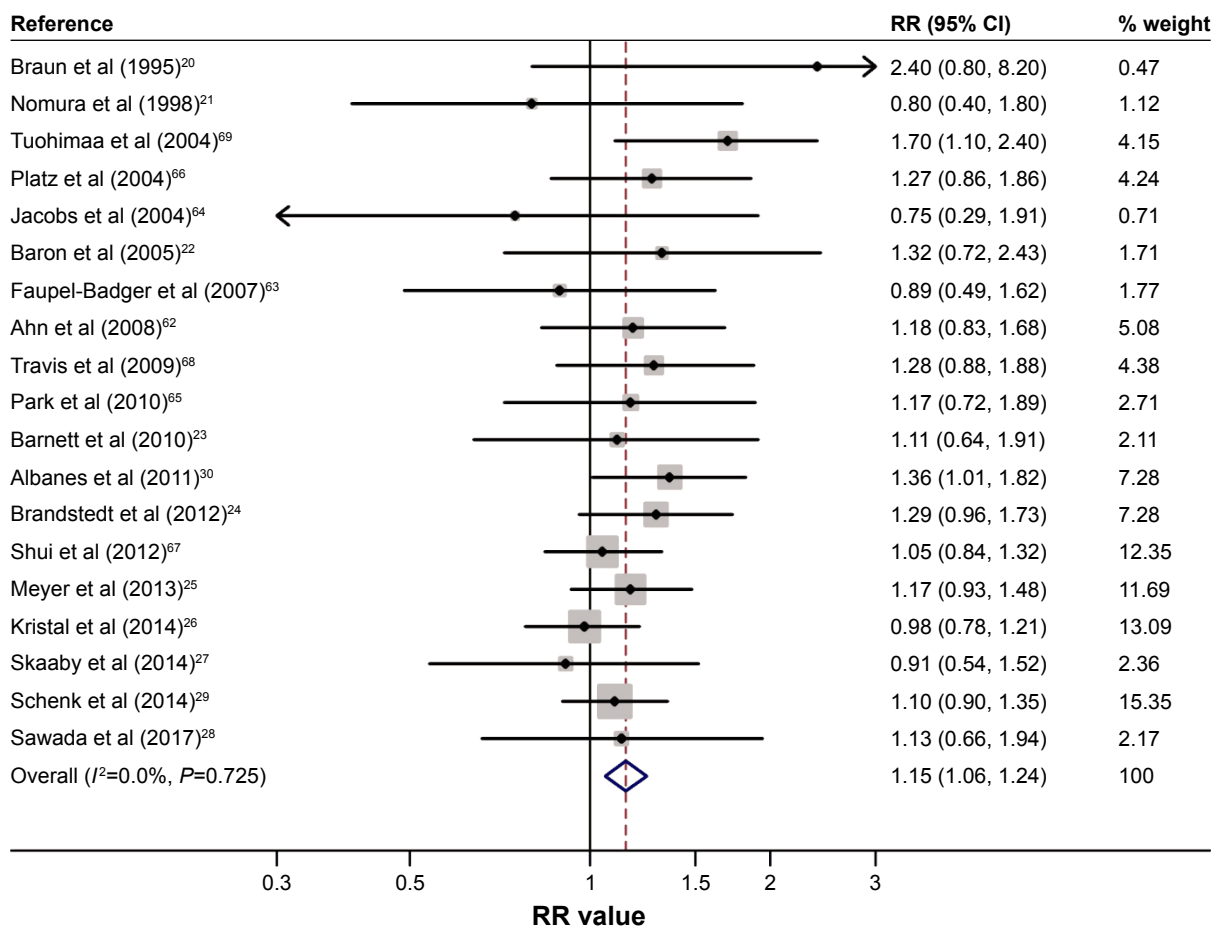


Figure 2 Higher 25[OH]D concentration was significantly correlated with elevated risk of prostate cancer.

Note: Weights are from random effects analysis.

Abbreviations: 25[OH]D, 25-hydroxyvitamin D; CI, confidence interval; RR, relative risk.

hydroxylated form of vitamin D, which is the mostly used biomarker of circulating vitamin D and widely used in clinical practice.⁷² A large number of published studies have found that vitamin D can exert a key role in decreasing cancer risk.^{17–19,73–75} The antitumor effects of vitamin D have been

well established in several cancers, such as colorectal cancer and bladder cancer.^{18,19} On the contrary, some studies found that vitamin D did not exert an antitumor effect in prostate cancer but even caused elevated risk of prostate cancer.^{26,29,30} This present meta-analysis of 19 prospective studies provided

Table 2 The results of subgroup analysis between 25[OH]D concentration and risk of prostate cancer

Subgroups	Number of studies	Number of cases/ participants	RR and 95% CI (higher vs lower)	RR and 95% CI (per 10 ng/mL increment)	Heterogeneity (I^2 , P -value)
All studies	19	12,824/35,583	1.15 (1.06–1.24)	1.04 (1.02–1.06)	0%, 0.725
Study size					
Small	7	1,207/8,999	1.00 (0.79–1.28)	0.99 (0.93–1.05)	0%, 0.746
Large	12	11,617/26,584	1.17 (1.07–1.27)	1.04 (1.02–1.06)	0%, 0.601
Publication year					
Before 2010	9	3,129/7,896	1.25 (1.07–1.48)	1.03 (0.99–1.10)	0%, 0.487
After 2010	10	9,695/27,687	1.12 (1.02–1.22)	1.06 (1.02–1.10)	0%, 0.825
Study designs					
Cohort	3	500/7,771	1.08 (0.78–1.49)	0.99 (0.89–1.12)	0%, 0.597
Nested case–control	16	12,324/27,812	1.15 (1.06–1.25)	1.05 (1.02–1.09)	0%, 0.654
Adjusted for calcium intake					
Adjusted	5	2,963/6,691	1.27 (1.08–1.50)	1.10 (1.02–1.18)	0%, 0.965
Not adjusted	14	9,861/28,892	1.11 (1.02–1.22)	1.03 (1.00–1.08)	0%, 0.570

Abbreviations: 25[OH]D, 25-hydroxyvitamin D; CI, confidence interval; RR, relative risk.

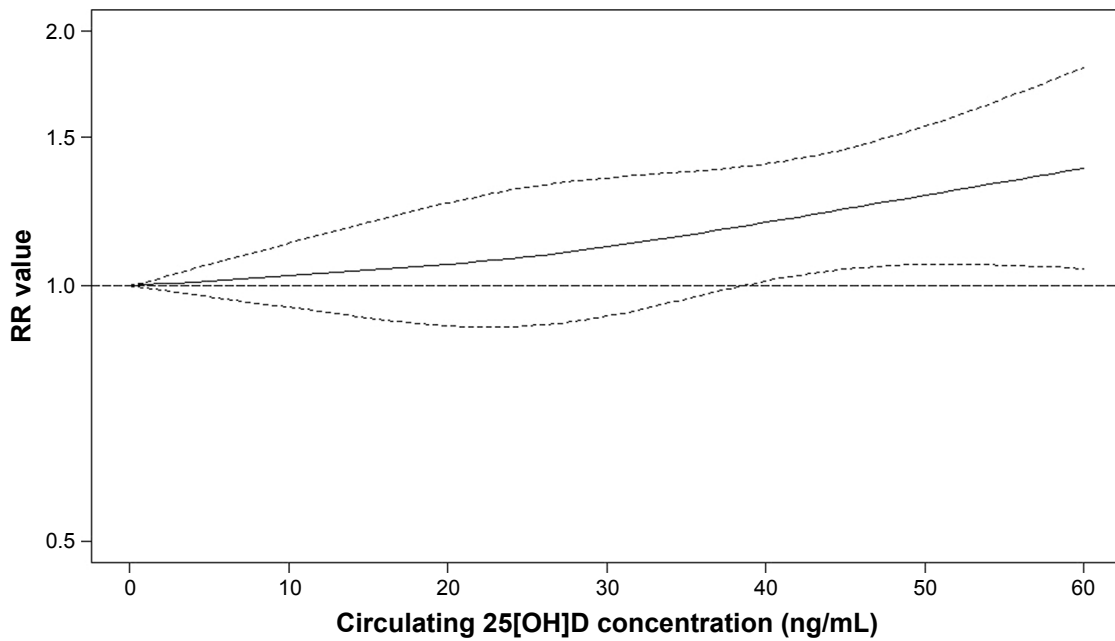


Figure 3 Nonlinear dose–response relationship between 25[OH]D concentration and risk of prostate cancer.
Abbreviations: 25[OH]D, 25-hydroxyvitamin D; RR, relative risk.

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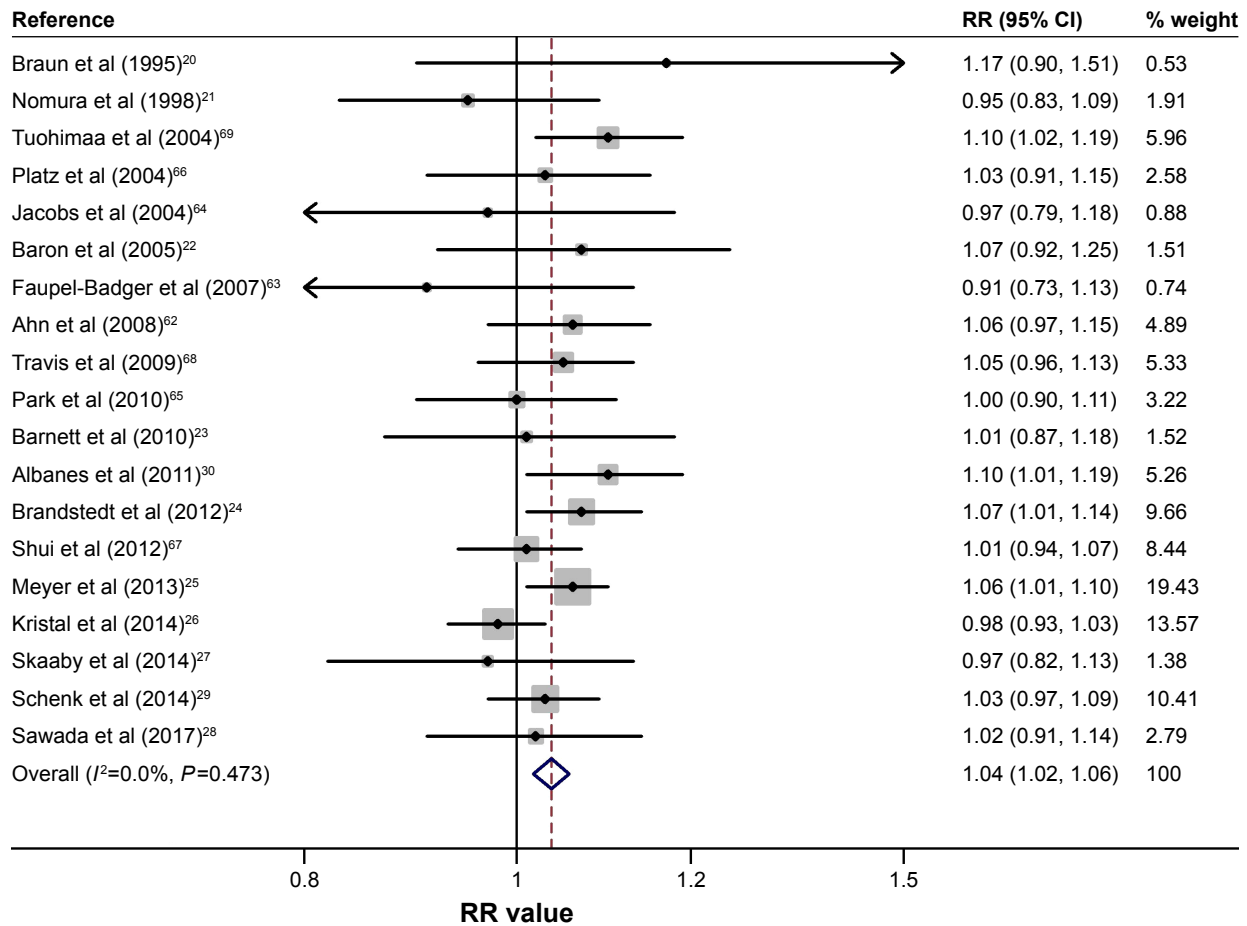


Figure 4 Linear dose–response relationship between circulating 25[OH]D concentration and prostate cancer.
Note: Weights are from random effects analysis.
Abbreviations: 25[OH]D, 25-hydroxyvitamin D; CI, confidence interval; RR, relative risk.

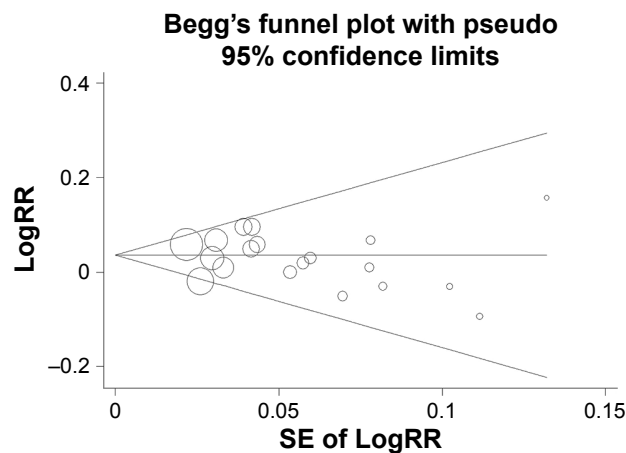


Figure 5 The funnel plot in the dose–response meta-analysis did not detect publication bias.

Abbreviations: RR, relative risk; SE, standard error.

epidemiological evidence for the tumor-promoting effect of vitamin D in prostate cancer though the effect was modest. However, no clear biological relationship has been found between high levels of vitamin D and an increased risk of prostate cancer. We can only speculate on the cause for the tumor-promoting effect of vitamin D in prostate cancer.²⁵ One reason might be that 25[OH]D may be a marker of other factors that related to the risk of prostate cancer. For example, insulin-like growth factor-I (IGF-I) has been related to prostate cancer^{76–78} and a relationship between 25[OH]D and insulin-like growth factor-I has been reported.⁷⁹ Moreover, higher 25[OH]D might be associated with an increased detection rate of prostate cancer.²⁵ However, we cannot rule out this detection bias using the summary outcome from the included studies in our research. The findings in the meta-analysis may have important indications from the supplementation of vitamin D in men. The use of vitamin D in men with high risk of prostate cancer may be cautious considering the tumor-promoting effect of vitamin D in prostate cancer.

A major strength of this meta-analysis was the inclusion of a total of 19 prospective cohort studies or nested case–control studies. The large number of participants in the meta-analysis could help us quantitatively examine the association of circulating 25[OH]D concentration with prostate cancer and get a more credible finding. As shown in Table 1, all included studies used a prospective design and reported adjusted RRs of prostate cancer, which ensured the appropriate selection of participants, the correct assessment of outcomes. In addition, there were 12 studies with >300 prostate cancer cases, which could increase the statistical power and decrease the risk of possible bias caused by small sample size (Table 1). Another strength of this meta-analysis was the good homogeneity among those

included studies ($I^2=0\%$), which suggested the lack of obvious heterogeneity in the meta-analysis. There was good homogeneity in both the meta-analysis of RRs comparing the higher concentration with the lower concentration of 25[OH]D and the meta-analysis of RRs of prostate cancer risk caused by per 10 ng/mL increment. There is no doubt that the homogeneity could strengthen the evidence for the tumor-promoting effect of vitamin D in prostate cancer found in the meta-analysis.

There were several limitations and the outcomes should be interpreted cautiously. First, some included studies did not consider the influence of other factors, such as vitamin D intake and sun exposure, on the association between circulating 25[OH]D concentration and prostate cancer, which might cause possible risk of bias. Therefore, more studies taking into account those factors are needed to provide a more definite assessment of the influence of circulating 25[OH]D concentration on prostate cancer risk. Second, the reagents used to detect circulating 25[OH]D concentration were various across those included studies, which could cause possible heterogeneity in the meta-analysis. However, there was good homogeneity among those included studies ($I^2=0\%$), which proved the little influence of different reagents used to detect circulating 25[OH]D concentration in the meta-analysis. Third, because all the included studies were done in developed countries and most studies were done in the Western countries (northern Europe and USA), the findings could not be generalized to other countries from different ethnicities. There was only one study with small sample size from Asian countries.²⁸ Participants in the studies that conducted in the USA were mostly white, and only one study with moderate sample size had multiple ethnics.⁶⁵ Therefore, more studies assessing the correlation of vitamin D with prostate cancer risk from other ethnicities and developing countries are needed. Finally, results of subgroups were based on a limited number of studies and we cannot rule out the possibility that insufficient statistical power may be present.

Conclusion

The findings from the meta-analysis suggest that higher 25[OH]D concentration is correlated with elevated risk of prostate cancer and a modest dose–response effect exists. Besides, these results need to be validated in further studies. The biological explanation for the positive correlation of vitamin D with prostate cancer risk is unclear, and further research is needed to address this issue.

Disclosure

The authors report no conflicts of interest in this work.

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