The Effect of Vitamin D Supplementation on Prostate Cancer: A Systematic Review and Meta-Analysis of Clinical Trials

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ABSTRACT

Vitamin D has received attention for its potential to disrupt cancer processes. However, its effect in the treatment of prostate cancer is controversial. This study aimed to assess the effect of vitamin D supplementation on patients with prostate cancer. In the present study, PubMed, Scopus, ISI Web of Science, and Google Scholar were searched up to September 2017 for trials that evaluated the effect of vitamin D supplementation on prostate specific antigen (PSA) response, mortality, and its possible side effects in participants with prostate cancer. The DerSimonian and Laird inverse-weighted random-effects model was used to pool the effect estimates. Twenty-two studies (16 before-after and 6 randomized controlled trials) were found and included in the meta-analysis. The analysis of controlled clinical trials revealed that PSA change from baseline [weighted mean difference (WMD) = –1.66 ng/ml, 95 % CI: –0.69, 0.36, p = 0.543)], PSA response proportion (RP = 1.18, 95 % CI: 0.97, 1.45, p = 0.104) and mortality rate (risk ratio (RR) = 1.05, 95 % CI: 0.81–1.36; p = 0.713) were not significantly different between vitamin D supplementation and placebo groups. Single arm trials revealed that vitamin D supplementation had a modest effect on PSA response proportion: 19 % of those enrolled had at least a 50 % reduction in PSA by the end of treatment (95 % CI: 7 % to 31 %; p = 0.002). Although before-after studies showed that vitamin D increases the PSA response proportion, it does not seem that patients with prostate cancer benefit from high dose vitamin D supplementation and it should not be recommended for the treatment.

Introduction

Prostate cancer is the second most frequent cancer in men, worldwide [1]. In the United States of America and European countries, approximately 25 % of new cancer cases in men are due to prostate cancer [1, 2] . The pathogenesis of this disease is complex. It is suggested that the growth of prostate cancer is highly dependent on circulating androgens, especially testosterone. In many cases, cancer has extended beyond the prostate gland at the time of diagnosis and primary hormone therapy cannot stop or slow its progression [3]. Before 2004, chemotherapy was not considered a viable treatment for this cancer, but after 2 trials, chemotherapy, especially using docetaxel, has been found to be effective [4, 5].

Several studies have investigated the therapeutic effect of nutritional supplements like pomegranate juice or extract pills [6, 7] and green tea [8, 9] on prostate cancer. Beyond the classic role of vitamin D

in regulating bone health [10], cardiometabolic risk factors [11, 12] and proper hormonal function [13, 14], vitamin D supplementation has attracted attention for its possible therapeutic effect on prostate cancer [15, 16] because some trials have shown that vitamin D supplementation reduces circulating androgens (including testosterone and dihydrotestosterone) [17], reduces PSA secretion and inhibits cell growth [18] of hormone-sensitive prostate cancer cell line (LNCaP cells) [19], and improves apoptosis[20]. Several clinical trials tried to investigate the effect of high dose vitamin D administration on prostate cancer, in recent years [18, 21, 22], however, the results are inconsistent. For instance, Schwartz et al. [23] and Morris et al. [24] could not show a significant response to vitamin D in combination with chemotherapy whereas Shamsedine et al. [21] and Beer et al. [25] observed a significant effect of vitamin D supplementation on Prostate-Specific Antigen (PSA) levels when accompanied with chemotherapy. In contrast, a study done by Srinivas et al. [26] was halted due to the results of a trial, using DN101 in combination of docetaxel because of a higher death rate in vitamin D supplemented group compared to placebo group.

According to our knowledge there has been no systematic review published of the effect of vitamin D supplementation on prostate cancer progression. In the present study, we review the published clinical evidence, and carry out a meta-analysis to quantify the effect of vitamin D supplementation on: 1) serum PSA levels; and 2) prostate cancer survival. In addition, we report on the toxicity and adverse events reported in these trials as a result of vitamin D administration in patients with prostate cancer.

Materials and Methods

The present systematic review is conducted and reported based on PRISMA guidelines. The study protocol was registered in the international prospective register of systematic reviews (PROSPERO) database (http://www.crd.york.ac.uk/PROSPERO, registration no: CRD42015015770).

Data sources and search strategy

We used the following 2 groups of MeSH and non-MeSH keywords for searching PubMed, Scopus, ISI web of science and Google scholar up to 10 September 2017: 1) “Vitamin D”, “Ergocalciferols”, “Cholecalciferol”, “Calcitriol”, “Calcifediol”, “25-Hydroxyvitamin D 2”, “25-hydroxyvitamin D” ,“1-25-dihydroxy-23,23-difluorovitamin D3, “25(OH)D, “25-OH vitamin D”, “1,25(OH)(2)D, “1,25(OH)D, “1,25-(OH)(2) D(3)”, “25-hydroxyvitamin D”, “Vitamin D”, “25-(OH)D(3)”, “25-(OH)D(2)”, “Vitamin D 3”, “Vitamin D3”, “Cholecalciferols, “Ergocalciferol” , “Vitamin D 2”, “Vitamin D2”, “DN101” and 2) “Prostate“, “Prostatic Neoplasms”, “Prostatic Neoplasm”, “Prostatic Cancer”, “Cancer of Prostate”, “Prostate Neoplasm”, “prostate cancer”, “prostate carcinoma”, “gamma-Seminoprotein”, “gamma Seminoprotein”, “hK3 Kallikrein”, “Semenogelase”, “Kallikrein hK3”, “Seminin”, “Prostate Specific Antigen” and “PSA”. No language, date, or study design filters were applied to our search. The reference list of retrieved primary and review articles were reviewed to identify studies possibly missed by our search strategy. All titles and abstracts were reviewed separately by 2 authors (SS and ASA) and any disagreement was resolved through discussion.

Eligibility criteria

All clinical trials (single group, parallel or cross over RCTs), which examined the effect of vitamin D supplementation on adult men with prostate cancer were included in the present systematic review.

Data extraction

Data on surname of the first author, publication date, sample size, participants’ age, vitamin D dose used for supplementation, calcium restriction prescription, medications used for chemotherapy and their dose, number of participants with PSA response proportion (reduction of serum PSA level to lower than half of baseline level), mortality rate in treatment and control group, PSA change, and data on toxicity were extracted separately by 2 independent authors (SS and ASA).

Quality assessment

The Cochrane Collaboration’s tool for risk of Bias assessment was used by 2 authors (SS and ASA) independently for assessment of the quality of the controlled clinical trials [27]. We judged the quality of the studies on the basis of 5 domains (random sequence generation, allocation concealment, blinding of outcome assessment, incomplete outcome data, and selective reporting). Each study was rated by the reviewers as being at low, high, or unclear risk of bias for each of the 5 domains. Studies, which were low risk according to at least 3 domains were considered as low risk-of-bias and those with 2 and lower than 2 low risk domains were regarded to be at some or and high risk-of-bias, respectively, [27]. All of the single group studies were classified as high risk, because they do not have a control group.

Statistical analysis

The sample size and number of patients with a PSA response proportion (defined as a reduction of serum PSA level to lower than half of baseline level) in the intervention group was used to calculate the PSA response proportion (as event rate). Event rates were transformed, and the event rate and corresponding standard error (SE) was used as the effect size in meta-analysis for single arm studies. For the controlled clinical trials, the response rate in the intervention and control group was used to calculate the risk ratio (response rate ratio), and the natural logarithm of the risk ratio and its corresponding SE was used for meta-analysis. We also computed mortality rate in each arm of randomized clinical trials to calculate the mortality rate ratio to be used as the effect size for meta-analysis. A number of controlled clinical trials also reported the effect of vitamin D on serum PSA levels for baseline and after intervention period. We calculated the mean change in serum PSA levels. As none of included studies reported standard deviation (SD) for baseline, after intervention and change in serum PSA levels at the same time, the SD for PSA change was calculated, assuming a correlation of 0.5 between baseline and post- intervention values.

The DerSimonian and Laird random-effects model was used to pool the effect estimates in all meta-analyses [28]. Statistical heterogeneity between studies was evaluated using Cochran’s Q test and the I-squared statistic (I^2) [29]. Sensitivity analyses were performed by recalculating the pooled effects after: 1) removing the highest-weighted study from a given analysis (the “leave-one-out” analysis) [30]; and 2) testing alternatives to the 0.5 correlation between baseline and post-treatment values, which were set to 0.1 and 0.9.

The potential for publication bias was assessed by visual inspection of funnel plots and using statistical tests of asymmetry, including Egger's regression asymmetry test and Begg's adjusted rank correlation test [31]. Statistical analyses were conducted using STATA version 11.2 (Stata Corp, College Station, TX, USA). p-Values less than 0.05 were considered as statistically significant for treatment differences; and less than 0.10 for assessments of publication bias and statistical heterogeneity.

Results

The literature search retrieved 1290 potentially-relevant citations. After screening titles/abstracts and removal of irrelevant records, 40 potentially related articles were selected and their full-text was assessed for eligibility. Eighteen reports were excluded because they were conducted on the same study populations as other included studies (n = 6) [19, 25, 32–35], did not provide relevant outcome (n = 9) [36–44], were review article (n = 1) [45], authors' reply (n = 1) [46] and study protocol (n = 1) [47]. Consequently, twenty-two studies [3, 15, 16, 18, 21–24, 26, 32, 35, 48–58] were included in the systematic review (▶ **Fig. 1**). Sixteen studies were single arm trial in design [3, 18, 21–24, 26, 32, 48–54, 56] and 6 were randomized controlled trials [15, 16, 35, 55, 57, 58]. The study characteristics for single group and randomized clinical trials are included in ▶ **Tables 1** and ▶ **2** respectively. These papers have been published between 1995 and 2013; one of them was conducted in Middle East [21] and 3 studies in the European continent [18, 22, 55] and the rest were conducted in North America [3, 15, 16, 23–26, 32, 35, 48, 49, 51–54, 56–58]. The sample size ranged from 14 to 953 patients with prostate cancer. Some studies examined the effect of vitamin D alone and the others administered chemotherapy drugs including docetaxel, naproxen, zoledronic acid, dexamethasone, carboplatin, and mitoxantrone along with vitamin D supplementation (▶ **Table 1**, **2**).

Risk of bias across included studies

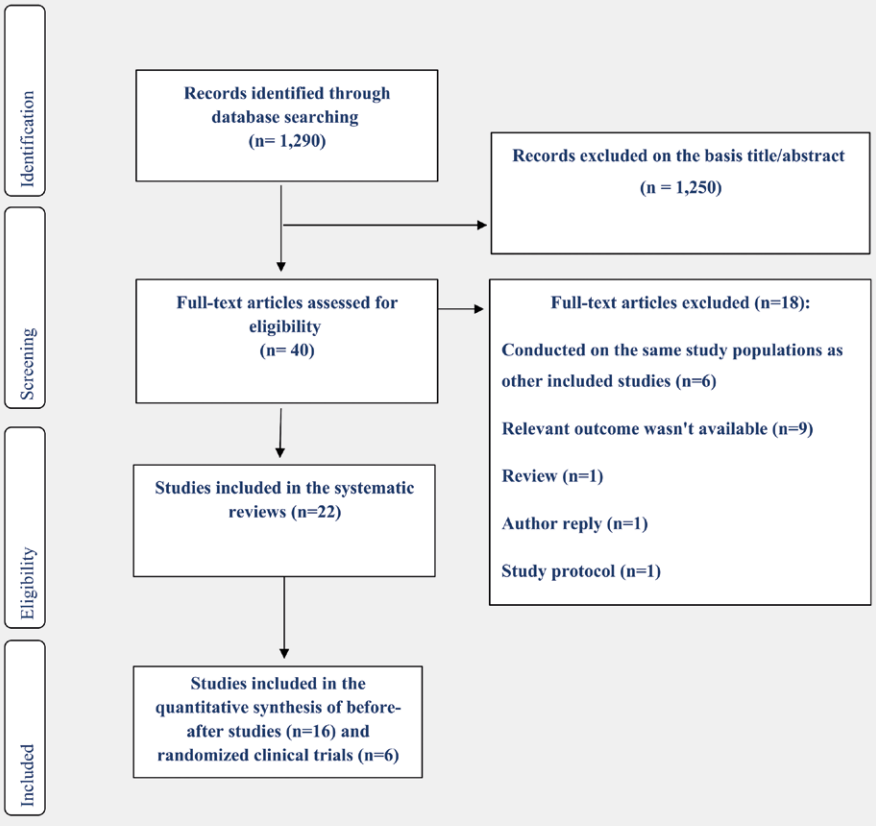
▶ **Table 3** provides information on the risk of bias for each of the randomized controlled trials included in the present study. Only 6 studies were placebo controlled trial; therefore, we assessed for methodological quality using Cochrane collaboration's tool for assessing risk of bias [15, 16, 35, 55, 57, 58]. All eligible studies were low risk regarding 4 or more domains and were ranked as good quality.

Meta-analysis

Meta-analysis of controlled clinical trials

Prostate cancer progression

Out of 6 placebo controlled trials [15, 16, 35, 55, 57, 58], 3 studies with 1486 participants, examined the effect of vitamin D supplementation on serum PSA levels. Our analysis showed that the mean PSA change from baseline was not significantly different between vitamin D supplementation and placebo groups [weighted mean difference (WMD) = –1.66 ng/ml, 95 % CI: –0.69, 0.36, p = 0.543)



▶ **Fig. 1** Flow diagram for study selection process. .

▶ **Table 1** Main characteristics of single arm studies included in the systematic review.

Authors (year) [Ref]	Location	No. Partic-ipants	Age (median)	Vitamin D prescription	Calcium restric-tion diet	Chemotherapy or usage of other drugs	Results
Osborn et al. (1995) [48]	USA	14	77	1.5 µg of calcitriol daily, after 15 days 1 µg of calcitriol daily, after 28 days 1.5 µg of calcitriol daily	No	Type of chemotherapy not mentioned	No objective responses were observed
Liu et al. (2003) [49]	USA	26	70	12.5 µg 1a-OH-D2 (5 each of 2.5 µg capsules) continuous once a day before their AM meals	No	No chemotherapy regimens	No objective responses were observed
Beer et al. (2003) [50]	USA	39	73	Calcitriol 0.5 µg/kg was given orally in 4 divided doses over 4 h on day 1	Yes	Docetaxel + Dexamethasone	Thirty of 37 patients (81 %; 95 % CI = 68–94 %) achieved a PSA response
Beer et al. (2003) [51]	USA	22	69	Calcitriol 0.5 µg/kg was given orally once a week orally once a week. Each weekly dose was divided into 4 doses and taken orally during each hour of a 4-h	Yes	Type of chemotherapy not mentioned	No objective responses were observed
Beer et al. (2004) [52]	USA	18	76	Calcitriol 0.5 µg/kg was given orally over a 4-h period.	Yes	Dexamethasone + Carboplatin	One of 17 patients (6 %, 95 % CI = 0–28 %) achieved a confirmed PSA response
Morris et al. (2004) [24]	USA	32	70	Calcitriol dose administered: 4, 6, 8, 10, 14, 20, 24, or 30 µg taken orally before bedtime on days 1, 2, and 3 of each week	No	Dexamethasone + Zoledronate	No objective responses were observed
Tiffany et al. (2005) [53]	USA	24	67	Calcitriol (60 µg as 0.5 g tablets) was given orally in 4 divided doses for 4 h on day 1	No	Dexamethasone + Estramustine + Docetaxel + Aspirin + warfarin	Seven of the 22 patients (32 %, 95 % CI = 12–51 %) achieved a confirmed PSA response
Schwartz et al. (2006) [23]	USA	18	74	Paricalcitol i. v. 3 times per week on an escalating dose of 5 to 25 µg	No	Type of chemotherapy not mentioned	No objective responses were observed
Trump et al. (2006) [32]	USA	43	69	Calcitriol was administered weekly at a dose of 8 µg for 1 month, and at a dose of 12 µg, for 1 month, at a dose of 10 µg every 3 days of a week	No	Dexamethasone	Eight of 43 patients (18.6 %) (median decrease 64 %; range, 55–92 %) achieved a confirmed PSA response
Flaig et al. (2006) [54]	USA	40	72	0.5 µg of daily calcitriol added at the start of week 5	Yes	Dexamethasone + Carboplatin	13 of 34 treated patients (38.2 %; 95 % CI = 22.2–56.4 %) achieved a confirmed PSA response
Petrioli et al. (2007) [22]	Italy	26	68	Calcitriol (32 µg as 0.5 µg tablets) given orally in 3 divided doses on day 1	No	Docetaxel + Dexamethasone	Eight patients (31 %, 95 % CI = 16.5–50.1 %) achieved a confirmed PSA response
Chan et al. (2008) [56]	USA	19	70	180 µg of DN-101 on day 1	No	Mitoxantrone	Five of 19 patients (26 %, 95 % CI = 9–51 %) achieved a confirmed PSA response
Newsom et al. (2009) [18]	UK	26	68	Most patients received vitamin D 25 µg once daily, 7 treated earlier in the study were given 10 µg once daily	No	Dexamethasone	Two patients (8 %) (95 % CI = 25–50 %) achieved a confirmed PSA response
Srinivas et al. (2009)[26]	USA	21	64	high dose calcitriol (DN101) (45 µg once per week)	Yes	Naproxen	No objective responses were observed
Chadha et al. (2010) [3]	USA	18	68	Intravenous calcitriol on Day 2 of each week (74 µg) over 1 h, 4 to 8 h	No	Dexamethasone	No objective responses were observed
Shamseddine et al. (2013) [21]	Lebanon	30	75	Calcitriol 0.5 µg/kg orally in 4 divided doses over 4 h on day 1 of each treatment week	No	Docetaxel + Zoledronate	Eleven of 30 patients achieved a confirmed PSA response

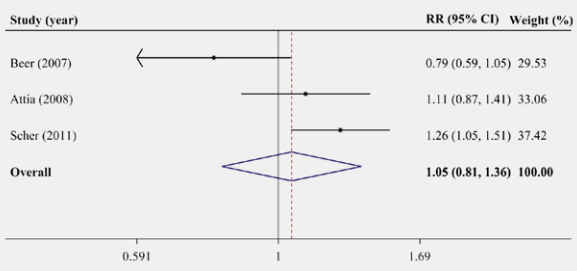
▶ **Table 2** Main characteristics of randomized controlled rials (RCTs) included in the meta-analysis.

Authors (year) [Ref]	Location	No. Partici-pants	Age	Vitamin D (interven-tion group)	Control group	Duration	Chemotherapy or usage of other drugs	Results
Colli et al. (2006) [55]	Italy	116	≥ 50	150 µg a vitamin D3 analogue (BXL628)	Placebo capsules, daily	12 weeks	Not mentioned	PSA change were not significant between intervention and control groups.
Beer et al. (2007) [15]	USA	250	≥ 18	45 µg vitamin D3 (DN-101) orally on day 1	45 µg placebo, orally on day 1	3 weeks of a 4-week cycle	Dexametha-sone + Docetaxel	Vitamin D treatment was associated with improved survival and PSA response
Attia et al. (2008) [16]	USA	70	≥ 18	10 µg doxercalciferol, day 1–28	10 µg placebo, day 1–28	A 4-week cycle	Docetaxel	Daily doxercalciferol with weekly docetaxel did not enhance PSA response rate or survival
Scher et al. (2011) [35]	USA	953	≥ 50	45 µg a high-dose vitamin D3 (DN-101) orally on day 1, 8, and 15	5 mg prednisone twice daily with 75 mg/m^2 docetaxel and 24 mg dexamethasone every 3 weeks	3 of every 4 weeks	Dexametha-sone + Docetaxel	Vitamin D treatment was associated with shorter survival than the control
Wagner et al. (2013) [57]	USA	66	≥ 50	Eligible patients were randomly allocated vitamin D3 doses: 1) 400 IU , 2) 10 000 IU and 3) 40 000 IU	Patients in the control (nonrandomized) arm did not receive any supplemental vitamin D	4 weeks	Not mentioned	PSA change were observed in 61%, 70%, and 81% of patients treated with 400, 10 000, and 40 000 IU/d of vitamin D3, respectively
Gee et al. (2013) [58]	Canada	31	≥ 50	10 µg 1α-hydroxyvitamin D2, daily	Just observation	A 3- to 8-week cycle	Not mentioned	PSA change was not significant between intervention and control groups

▶ **Table 3** Study quality and risk of bias assessment.[a]

First author (year) [Ref]	Sequence generation	Allocation concealment	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Score	Overall quality
Colli (2006) [55]	+	+	?	+	+	4	Good
Beer (2007) [15]	+	+	+	+	+	5	Good
Attia (2008)[16]	+	+	?	+	+	4	Good
Scher (2011) [35]	+	+	+	+	+	5	Good
Wagner (2013) [57]	–	+	?	+	+	3	Good
Gee (2013) [58]	+	+	?	+	+	4	Good

[a] +: Low risk; –: High risk; ?: Unclear.



▶ **Fig. 2** Meta-analyses of randomized controlled clinical trials investigating the effect of vitamin D supplementation on mortality rate. Analysis was conducted using random effects model.

[55, 57, 58], with no evidence of heterogeneity between studies (Cochrane Q test, Q statistic = 1.97, p = 0.373, I^2 = 0.0 %, τ^2 = 0.0). This result was not sensitive to the correlation coefficient selected to calculate the SD for change values.

Two trials investigated the effect of vitamin D supplementation on PSA response proportion [57, 58]. In these trials, vitamin D supplementation does not significantly affect PSA response proportion (RP = 1.18, 95 % CI: 0.97, 1.45, p = 0.104) and the heterogeneity was not significant (Cochrane Q test, Q statistic = 0.55, p = 0.46, I^2 = 0.0 %, τ^2 = 0.0).

Mortality

The effect of vitamin D supplementation on mortality rate in patients with prostate cancer was assessed in 3 trials [15, 16, 35] with 1273 participants and 477 events including 224 deaths in the control groups and 253 deaths in the vitamin D supplemented group occurred for any cause during the follow-up. There were no significant differences in total mortality between participants receiving vitamin D supplementation and those receiving placebo [risk ratio (RR) = 1.05, 95 % CI: 0.81–1.36; p = 0.713; ▶ **Fig. 2**, however, the heterogeneity between studies was high (Cochrane Q test, Q statistic = 7.34, p = 0.025, I^2 = 72.8 %%, τ^2 = 0.037). When a study done by Beer et al. [15] was excluded in the sensitive analysis, the overall result was changes and the analysis on the two remaining clinical trials [16, 35] showed that vitamin D supplementation increases the risk of mortality by 19 % (RR = 1.19, 95 % CI: 1.03–1.38; p = 0.014) with no evidence of heterogeneity (Cochrane Q test, Q statistic = 0.70, p = 0.402, I^2 = 0.0 %, τ^2 = 0.0).

Toxicity

The possible side-effects related to vitamin D supplementation was reported in a number of included studies were also investigated [15, 16, 35]. Results of the meta-analyses on the risk ratio of side-effects are reported in ▶ **Table 4.** In total, side-effects were generally similar in vitamin D supplemented and control group; however, our analysis revealed that nausea and loss of taste were experienced more in in the vitamin D supplemented group compared to placebo group.

Publication bias

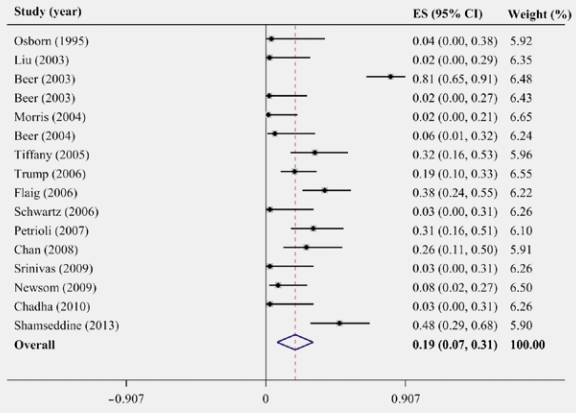
The funnel plot depicting the effect sizes against their corresponding error were symmetrical and the statistical asymmetry tests including Egger's and Begg's tests showed no evidence of publication bias for studies investigating the effect of vitamin D supplementation on serum PSA change from baseline (p-value for Egger's test = 0.441; p-value for Begg's test = 0.296) and mortality rate (p-value for Egger's test = 0.201; p-value for Begg's test = 0.296).

Meta-analysis of single arm clinical trials

The meta-analysis of 16 relevant trials with no control group [3, 18, 21–24, 26, 32, 48–54, 56] revealed a statically significant effect of vitamin D supplementation with or without chemotherapy medication on the improvement of prostate cancer in terms of PSA response proportion (the reduction in serum PSA levels) by 19 % (Event rate = 0.19, 95 % CI: 0.07–0.30, p = 0.002) (▶ **Fig. 3**). Heterogeneity was high across the selected studies (Cochrane Q test, Q statistic = 153.51, degrees of freedom = 15, p < 0.001, I^2 = 90.2 %%, τ^2 = 0.0517). The subgroup analysis by co-therapies calcium restriction in the treatment period and the type of vitamin D supplemented for study attendants is illustrated in ▶ **Table 5**. dexamethasone (response proportion = 0.48, 95 % CI: 0.12–0.84, p = 0.008) Moreover, vitamin D supplements increased the PSA response proportion on a calcium-unrestricted diet (response proportion = 0.15, 95 % CI: 0.0.64–0.285, p = 0.001) [25, 26, 51, 52, 54]. In the subgroup meta-analysis categorized based on type of vitamin D, only calcitriol treatment significantly affected PSA response

▶ **Table 4** The meta-analysis of the specific side-effects of vitamin D versus placebo extracted from randomized controlled clinical trials.

Adverse event	Number of studies	Number of participants	Risk ratio (95 % CI)	p	Heterogeneity				
					p	Q statistic	Degrees of freedom	Tau-squared	I^2 (%)
Anemia	2	1203	0.920 (0.527–1.606)	0.769	0.569	0.32	1	0.0000	0.0
Diarrhea	3	1273	1.220 (0.689–2.159)	0.495	0.271	2.61	2	0.1009	23.4
Dyspnea	3	1203	1.247 (0.530–2.932)	0.613	0.192	3.30	2	0.2670	39.3
Fatigue	3	1273	0.852 (0.308–2.359)	0.758	0.033	6.82	2	0.4891	70.7
Leukopenia	3	1273	0.905 (0.677–1.210)	0.500	0.417	1.75	2	0.0000	0.0
Hyperglycemia	3	1273	0.904 (0.685–1.193)	0.475	0.409	1.79	2	0.0000	0.0
Hypercalcemia	2	1023	3.511 (0.580–21.242)	0.171	0.840	0.04	1	0.0000	0.0
Loss of taste	2	1203	1.365 (1.088–1.712)	0.007	0.385	0.75	1	0.0000	0.0
Nausea	3	1273	1.180 (1.021–1.364)	0.025	0.866	0.29	2	0.0000	0.0
Neutropenia	3	1273	0.615 (0.267–1.418)	0.254	0.075	5.19	2	0.3175	61.4



▶ **Fig. 3** Forest plot describing the effect of vitamin D supplementation on PSA response proportion in single arm trials. Analysis was conducted using random effects model.

(response proportion = 0.23, 95 % CI: 0.07–0.40, p = 0.004) [3, 21, 22, 24, 25, 32, 48, 51–54].

Discussion

In this study, we found no convincing evidence of benefit of vitamin D supplements on serum PSA levels, PSA response proportion, or mortality. No effect on mortality was seen in studies of either design. We found that vitamin D modestly improves the PSA response proportion in single arm before-after studies, but not in randomized controlled trials. Further, the effect in the single arm studies was lower when limited to those trials, which administered vitamin D with calcium restriction prescription.

The protective effect vitamin D against developing prostate cancer was proposed by Schwartz and Hulka for the first time when they found that the risk of prostate cancer was elevated in the elderly with lower serum vitamin D levels [59]. Moreover, the inverse association between sun exposure as a main source of vitamin D synthesis and risk of prostate cancer supported the hypothesis of protective effect of vitamin D against the development of prostate cancer [60–62]. In contrast, A meta-analysis of 21 observational studies found an elevated risk of prostate cancer in subjects with increased 25-hydroxyvitamin D levels and announced that vitamin D supplementation should be administered with caution [63]. Furthermore, a recent meta-analysis of 19 prospective cohort or nested case–control studies suggested per 10 ng/ml increment in circulating 25[OH]D concentration, the risk of prostate cancer was approximately 4 % elevated [64]. Moreover, recent meta-analyses found the association between some race-related vitamin D receptors (VDR) polymorphisms (TaqI, FokI, Cdx2, ApaI, BsmI) and an increased risk of prostate cancer [65–67]. It should be noted that the seasonal variation might also affect the association found between the vitamin D and prostate cancer [68], since the sun exposure is the most important source regulator of serum vitamin D [69].

Posadzki et al. [70] reviewed double-blind, placebo-controlled randomized clinical trials of non-herbal dietary supplements and vitamins for evidence of reducing PSA levels in prostate cancer patients. Only one double-blind, placebo-controlled trial [52] was identified, which concluded that dietary supplements including vitamin D are not effective treatments for patients with prostate cancer. A narrative review by Giammanco et al. [71] of vitamin D and cancer concluded that vitamin D and its analogues might be effective in preventing the progression of some type of cancer including breast cancer and prostate cancer but they also concluded that vitamin D therapy in patients with prostate cancer had no beneficial effect. In the present systematic review, we have included before-after studies and demonstrated that these studies might be misleading and their result are different from parallel double blind studies. Furthermore, we included 6 randomized clinical trials.

The present meta-analysis revealed that vitamin D supplementation not only is not beneficial for patients with prostate cancer but although it was not statistically significant, might increase the risk of overall mortality. A justifiable mechanism is that vitamin D supplementation increase IGF-1 concentrations, consistent with the hypothesis that IGF-1 may increase the risk of prostate cancer.

▶ **Table 5** Subgroup analysis as well as overall analysis of the effects of vitamin D supplementation on PSA response in single arm trials included in the meta–analysis.

Subgroup (Ref)	Number of studies	Number of participants	Meta-analysis Event rate (95 % CI)	Heterogeneity						p between group
				p Effect	Q statistic	Degree of freedom	p within group	I^2 (%)	Tau-squared	
Chemotherapy drugs										
None	5	123	0.040 (0.017–0.105)	0.223	0.55	4	0.969	0.00	0.000	<0.001
Docetaxel and Dexamethasone	3	72	0.484 (0.126–0.841)	0.008	29.71	2	0.00	93.3	0.092	
Zoledronate	1	32	0.016 (0.001–0.118)	0.765	0.00	0	–	–	0.000	
Dexamethasone and Carboplatin	2	58	0.220 (0.001–0.537)	0.173	8.15	1	0.004	87.7	0.045	
Dexamethasone	2	61	0.114 0.001–0.270)	0.150	2.62	1	0.106	61.8	0.007	
Mitoxantrone	1	19	0.263 (0.071–0.455)	0.007	0.00	0	–	–	0.000	
Naproxen	1	21	0.026 (0.001–0.180)	0.738	0.00	0	–	–	0.000	
Docetaxel and Zoledronate	1	30	0.478 (0.285–0.672)	0.000	0.00	0	–	–	0.000	
Calcium restriction diet										
Yes	5	140	0.172 (0.1–0.281)	0.116	101.17	4	0.00	96.0	0.1321	0.001
No	11	276	0.150 (0.064–0.235)	0.001	35.08	10	0.00	71.5	0.0144	
Type of vitamin D treatment										
Calcitriol	11	306	0.239 (0.078–0.401)	0.004	133.90	10	0.000	92.5	0.068	0.004
Alfacalcidol	1	26	0.024 (0.001–0.167)	0.744	0.00	0	–	–	0.000	
Paricalcitol	1	18	0.026 (0.001–0.180)	0.738	0.00	0	–	–	0.000	
DN-101 (high-dose calcitriol)	2	40	0.138 (0.094–0.369)	0.245	3.56	1	0.059	71.9	0.020	
Ergocalciferol	1	26	0.080 (0.045–0.205)	0.209	0.00	0	–	–	0.000	
Overall	16	416	0.190 (0.072–0.308)	0.002	153.51	15	0.000	90.2	0.0517	

In a large clinical trial it was assumed that adding calcitriol to docetaxel might improve antitumor activity [15]. Vitamin D might be beneficial by offsetting the gastrointestinal toxicity of docetaxel, but this hypothesis needs conclusive evidence. Additional proposed mechanisms by which vitamin D may reduce toxicity include: effects on cell proliferation, gene expression, singling pathways, cell differentiation, apoptosis, autophagy, antioxidant defense and DNA repair, prostaglandin synthesis and metabolism, angiogenesis and an improved immune response [71]. The finding from microarray data analysis recently suggested that calcitriol via up-regulation expression of prostaglandin catabolizing enzyme 15-prostaglandin dehydrogenase (PGDH) and down-regulation expression of the prostaglandin synthesizing enzyme cyclooxygenase-2 (COX-2) inhibits prostaglandin actions in prostate cancer cells growth [72–74]. But our results cannot prove these effects in prostatic cancer patients.

Our finding suggests that vitamin D supplements has beneficial effect on PSA response proportion following diets without calcium restriction. Gao et al. by meta-analysis of twelve 12 prospective studies concluded that dairy product and calcium intakes were directly associated with the risk of prostate cancer [75]. A high calcium consumption lead to increased risk of prostate cancer by inhibiting the bioactive metabolite of vitamin D [76, 77].

There are a number of limitations that should be considered while interpreting the results. One of the limitations is that the included studies did not report the baseline and the after intervention vitamin D status of the participants. The effect of vitamin D supplementation might be different in patients deficient in vitamin D. The other noticeable issue in the present meta-analysis is that before-after studies are highly misleading compared to randomized controlled clinical trials. For example, vitamin D modestly increases the PSA response proportion in single arm studies, however, the similar effect was not observed in randomized controlled trials. Also we should consider that most of studies were single arm and the only 6 double blind randomized clinical trials were included in our meta-analysis however these studies were powerful ones.

Conclusion

In this systematic review and meta-analysis, we found that vitamin D supplementation does not benefit patients with prostate cancer. High dose vitamin D supplementation for improving the disease state should not be recommended based on our results. The possible beneficial effects of vitamin D supplementation in deficient subjects with prostate cancer should be examined in the future investigations.

Authors' Contribution

SSh, SSo, and ASA contributed in conception, search, screening, and data extraction and revised the manuscript; ASA, SSh and SSo provided the first draft of the manuscript. ASA also contributed in statistical analysis. RJD and MA contributed in the data interpretation and critically revised the manuscript. All authors contributed to the study design and drafting of the manuscript.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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