The role of vitamin D supplementation for primary prevention of cancer: meta-analysis of randomized controlled trials

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ABSTRACT

Background: In the USA cancer is the second leading cause of mortality, as such, primary prevention of cancer is a major public health concern. Vitamin D supplementation has been studied as a primary prevention method for multiple diseases including cardiovascular disease, osteoporosis, diabetes mellitus and cancer. The role of Vitamin D as primary prevention of cancer is still controversial. With fast emergence of large randomized controlled trials (RCTs) in that regards, we aimed to evaluate the efficacy of Vitamin D supplementation as primary prophylaxis for cancer.

Methods: A comprehensive electronic database search was conducted for all RCTs where comparison of Vitamin D supplementation versus placebo for the prevention of any type of disease with at least 3 years of Vitamin D supplementation was used and where cancer incidence or mortality was reported. The primary outcome was cancer-related mortality and cancer incidence. We calculated risk ratios (RRs) and 95% confidence intervals (CIs) using a random-effects model at the longest follow-up.

Results: We included 10 RCTs with 79,055 total patients, mean age of 68.07 years, a female percentage of 78.02% and a minimum follow-up of 4 years and more. Vitamin D was associated with significant reduction of cancer-related mortality compared with placebo (RR 0.87; 95% CI: 0.79–0.96; P = 0.05; I² = 0%). Compared with placebo, Vitamin D was not associated with significant reduction of cancer incidence (RR: 0.96; 95% CI: 0.86–1.07; P = 0.46; I² = 31%).

Conclusion: With inclusion of studies, which did not primarily examine vitamin D for the purpose of preventing cancer or reducing cancer mortality our meta-analysis highlights that the use of vitamin D supplementation for primary prevention of cancer is encouraged as it does possibly decrease cancer-related mortality once cancer is diagnosed; however, it has no role or effect on cancer incidence.

1. Introduction

Epidemiological studies showed that vitamin D deficiency is associated with increased mortality; however, there was not enough evidence that vitamin D status is inversely associated with cancer mortality [1]. The association between cancer risk and vitamin D has been studied in many epidemiologic studies, while data from interventional studies remain insufficient [2]. Almost all studies have proven that vitamin D has a strong and beneficial effect antagonizing and blocking multiple mitogenic processes related to tumorigenesis [2]. The association between solar ultraviolet-B exposure and cancer was proven, and it was stronger for mortality than for incidence for many cancers in the USA and China [3,4].

Vitamin D is highly important for bone health and mineral metabolism, and it is quite known that vitamin D deficiency can lead to rickets, osteomalacia and many other diseases [5]. In the recent past, however, vitamin D has been studied for the prevention of many highly prevalent cancer types. One of the most important studies was a randomized controlled trial (RCT) in 2003 that provided good evidence of the antineoplastic effect that vitamin D had in the colon, in addition to the role of vitamin D in reducing the recurrence of colorectal adenoma [6]. In a recent meta-analysis of observational studies, low 25-hydroxy vitamin D level was directly related to breast cancer, while total vitamin D and supplemental vitamin D intake had an inverse relationship with breast cancer [7].

Although The USA Preventive Services Task Force stated in 2014 that data were insufficient to confirm the effectiveness of vitamin D supplementation for...
cardiovascular disease or cancer prevention [8], yet, the role of vitamin D supplementation in primary prevention for cancer is promising [9]. With rapidly surface large randomized controlled trials (RCTs) studying this subject [10–13], we aimed to evaluate the efficacy and safety of vitamin D supplementation as a means of primary prevention of cancer.

### 2. Methods

#### 2.1. Data sources

The study was performed using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) Statement 2015 [14]. A comprehensive search of literature using PubMed,
Embase, and the Cochrane Collaboration Central Register of Controlled Trials from inception to December 2018 was performed by TH, IG and YZ. Any disagreements were resolved via consensus. The search terms and their substitutes used were as follows: vitamin D, primary prevention, mortality, cancer incidence, bleeding and cancer.

PRISMA checklist was completed (Table 1).

2.2. Selection criteria and data extraction
The study inclusion criteria were as follows: (1) All studies are RCTs; (2) Vitamin D is used for primary prevention; (3) Vitamin D is compared to placebo; (4) Cancer mortality or cancer incidence is reported; (5) The vitamin D supplementation is for at least a period of 3 years for all patients. From each eligible study, two authors, TH and IG, extracted the data and a third author, HD, resolved any discrepancies.

2.3. Outcomes
Our primary outcomes were cancer-related mortality and cancer incidence.

2.4. Quality assessment
The quality of the included studies was assessed independently by two authors, TH and VS, based on the Jadad scoring system (Table 2).

2.5. Statistical analysis
We calculated summary risk ratios (RRs) and 95% confidence intervals (CIs) using the Mantel–Haenszel method for dichotomous data. We used a random-effects model to account for the between-study heterogeneity. Heterogeneity was measured by the Cochran’s Q statistic and $I^2$ statistic test. Publication bias was
### Table 3. Details of the randomized clinical trials.

| Studies   | Country/Sites | Total number of patients/Subgroups | 25-hydroxy vitD level (standard deviation in nmol/liter) | Study design                          | Follow-up | Vit D form and dose                                      | Duration of therapy | Primary outcomes                                                                 | Secondary outcomes                                                                 |
|-----------|---------------|-----------------------------------|--------------------------------------------------------|---------------------------------------|-----------|--------------------------------------------------------|---------------------|---------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|
| Gallagher 2001 USA | Vit-D: 203 Placebo: 213 Total: 416 | Initial: Vit-D: 79 (25.5) Placebo: 78.9 (25.9) Randomized, double blinded, placebo controlled trial | 3 years                               | Calcitriol (0.25ug twice daily), | 3 years | Bone mineral density of: Femoral neck - Spine. | 5 years | -Fracture incidence -Total mortality by cause | Bone mineral density of: -Trochanter -Total hip -Total body -Radius NA |
| Trivedi 2003 UK | Vit-D: 1,345 Placebo: 1,341 Total: 2,686 | Post treatment levels: Vit D: 72.0 (22.5) Placebo: 45.37 (17.6) Randomized, double blinded, Placebo controlled trial | 5 years                               | 100,000 IU cholecalciferol every 4 months | 5 years | -Fracture incidence -Total mortality by cause | 7 years | Reduction in total mortality. | Reduction in total mortality. |
| Lappe 2007 USA | Vit-D: 446 Placebo: 733 Total: 1,179 | Initial: Vit-D: 71.8 (20) Placebo: 71.9 (20.6) 12 month change: Vit-D: 96.0 (21.4) Placebo: 71 (20.1) Randomized, double blinded, placebo-controlled trial. | 4 years                               | 1100 IU Cholecalciferol every 6 months | 7 years | Reduction in total mortality. | 7 years | Reduction in total mortality. | |
| Lacroix 2009 USA | Vit-D: 18,176 Placebo: 18,106 Total: 36,282 | Randomized, double blinded, placebo-controlled trial | 7 years                               | 400 IU Cholecalciferol daily | 4 years | Hip fracture prevention | 4 years | -Other fracture prevention -Colorectal cancer prevention | |
| Sanders 2010 Australia | Vit-D: 1,131 Placebo: 1,125 Total: 2,256 | Initial: Vit-D Median (IQR): 53 (40–65) Placebo Median (IQR): 45 (40–57) Randomized, double blinded, placebo controlled trial | 5 years                               | 500,000 IU Cholecalciferol per year | 3–5 years | Incidence of falls and fractures | 3 years | All cause mortality, vascular disease mortality, cancer mortality and cancer incidence. | Mortality from -Cardiovascular -Cerebrovascular |
| Avenell 2012 UK | Vit-D: 2,649 Placebo: 2,643 Total: 5,292 | Initial: accumulative 38 nmol/liter Randomized, double blinded, placebo-controlled trial | 3 years                               | 800 IU Cholecalciferol per day | 3 years | | | | |
| Baron 2015 USA | Vit-D: 1,130 Placebo: 1,129 Total: 2,259 | Initial: Vit-D: 59 (22.2) Placebo: 60.2 (21.9) Randomized, double-blinded, placebo controlled trial | 5 years                               | 1,000 IU Cholecalciferol per day | 3 or 5 years | Recurrent colorectal adenomas | NA | | |
| Jorde 2016 Norway | Vit-D: 256 Placebo: 255 Total: 511 | Initial: Vit-D: 59.9 (21.9) Placebo: 61.1 (21.2) 5-year visit: Vit D: 122.3 (25.3) Placebo: 66.7 (18.6) Randomized, double blinded, placebo controlled trial | 5 years                               | 20,000 IU Cholecalciferol per week | 5 years | Progression to Diabetes Mellitus Type II | Change in -Glucose levels, -Insulin resistance, -Serum lipids, -Blood pressure. | |

(Continued)
assessed by visual inspection of the funnel plot. Furthermore, we explained any heterogeneity (≥20%) by performing sensitivity and meta-regression analyses. Sensitivity analyses were performed by removing trials sequentially and by removing small trials with a patient population less than 1000 patients, or based on follow-up period (< or > 5 years). We performed meta-regression analysis based on age, body mass index (BMI), therapy duration, follow-up duration, initial vitamin D level, and vitamin D dose. Analysis was performed using RevMan v5.3 Windows and Comprehensive Meta-Analysis software v3.

3. Results

3.1. Study selection and trial characteristics

Figure 1 illustrates the study selection process. We included 10 RCTs [10,11,12,13;15,16,17,18,19,20] with 79,055 total patients, mean age of 68.07 years, a female percentage of 78.02% and a minimum follow-up of 3 years. Tables 3 and 4 illustrate the characteristics of the included trials and patient demographics, respectively.

In the 10 included studies, 5 studies explored the role of vitamin D to decrease fracture risk and increase bone health, 3 assessed vitamin D for primary prevention of cancer, 1 study assessed vitamin D’s role in colorectal adenoma and 1 study assessed aspirin for use in prevention of diabetes mellitus progression. All studies were randomized controlled trials. Almost all studies were assessed to be of moderate to high quality (Table 2). Nine of the 10 studies used cholecalciferol as the mean for vitamin D replacement, whereas 1 study used calcitriol; the doses and frequency of supplementation varied from 400 international units (IU) daily to 2000 IU, with reported regimens either daily, weekly, monthly or yearly. Follow-up duration ranged from 3 years to 7 years, while duration of therapy varied from 3 to 6 years. All studies compared vitamin D to placebo.

3.2. Primary outcome

Vitamin D was associated with significant reduction of cancer-related mortality compared with placebo (RR 0.87; 95% CI: 0.79–0.96; P = 0.05; I² = 0%). Compared with placebo, vitamin D was not associated with significant reduction of cancer incidence (RR: 0.96; 95% CI: 0.86–1.07; P = 0.46; I² = 31%) (Figure 2). Examination of the funnel plot did not suggest any publication bias (Figure 3). Sensitivity analysis by removing each trial sequentially demonstrated consistent results.

A subgroup analysis including the three RCTs that included cancer as a primary outcome only was also conducted where vitamin D was associated with
| Studies       | Age (years) | Sex (female pts) | Race (no. of pts) | Hormonal use (no. of pts) | BMI       | Smoking Hx (no. of pts) | HTN (no. of pts) | DM (no. of pts) | Cardiac disease (no. of pts) | Cancer Hx (no of pts) | Alcohol use (no. of pts) |
|---------------|-------------|------------------|-------------------|---------------------------|-----------|------------------------|-----------------|--------------|-----------------------------|------------------------|------------------------|
| Gallagher    | 2001        | Vit-D: 71.5(3.5) | Placebo: 71.5(4.6)| Total: White 480 Black 6 Asian 2 | Vit-D: 102 Placebo: 101 | Vit-D: 27.1(4.1) Placebo: 27.2 | -               | -            | -                           | -                      | -                      |
| Trivedi      | 2003        | Vit-D: 73.7(4.5) | Placebo: 73.6     | Total: White 480 Black 6 Asian 2 | Vit-D: 21 Placebo: 21 | Vit-D: 24.4 (3.8) Placebo: 24.3 (3.8) | -               | -            | Vit-D: 65 Placebo: 55       | -                      | -                      |
| Lappe        | 2007        | Vit-D: 66.7(7.3) | Placebo: 67.3     | Total: White 480 Black 6 Asian 2 | Vit-D: 21 Placebo: 21 | Vit-D: 29.7(4.1) Placebo: 29.7(4.1) | -               | -            | Vit-D: 20 Placebo: 24       | -                      | -                      |
| Lacroix      | 2009        | Vit-D: 62.4(7.0) | Placebo: 62.4(6.9)| Total: White 480 Black 6 Asian 2 | Vit-D: 20 Placebo: 20 | Vit-D: 29.7(4.1) Placebo: 29.7(4.1) | -               | -            | Vit-D: 15 Placebo: 10       | -                      | -                      |
| Sanders      | 2010        | Vit-D: 76       | Placebo: 76.1     | Total: White 480 Black 6 Asian 2 | Vit-D: 21 Placebo: 21 | Vit-D: 29.7(4.1) Placebo: 29.7(4.1) | -               | -            | Vit-D: 26 Placebo: 260      | -                      | -                      |
| Avenell      | 2012        | Vit-D: 77.6(6)  | Placebo: 77.6(6)  | Total: White 480 Black 6 Asian 2 | Vit-D: 21 Placebo: 21 | Vit-D: 29.7(4.1) Placebo: 29.7(4.1) | -               | -            | Vit-D: 0 Placebo: 0         | -                      | -                      |
| Baron        | 2015        | Vit-D: 58.6(8)  | Placebo: 57.8(6.6)| Total: White 480 Black 6 Asian 2 | Vit-D: 21 Placebo: 21 | Vit-D: 29.7(4.1) Placebo: 29.7(4.1) | -               | -            | Vit-D: 0 Placebo: 0         | -                      | -                      |
| Jorde        | 2016        | Vit-D: 62.3(8.1)| Placebo: 61.3(9.2)| Total: White 480 Black 6 Asian 2 | Vit-D: 21 Placebo: 21 | Vit-D: 29.7(4.1) Placebo: 29.7(4.1) | -               | -            | Vit-D: 0 Placebo: 0         | -                      | -                      |
| Lappe        | 2017        | Vit-D: 65.2(6.9)| Placebo: 65.2(7.1)| Total: White 480 Black 6 Asian 2 | Vit-D: 21 Placebo: 21 | Vit-D: 29.7(4.1) Placebo: 29.7(4.1) | -               | -            | Vit-D: 0 Placebo: 0         | -                      | -                      |
| Manson       | 2018        | Vit-D: 67.1(7.1)| Placebo: 67.1(7.1)| Total: White 480 Black 6 Asian 2 | Vit-D: 21 Placebo: 21 | Vit-D: 29.7(4.1) Placebo: 29.7(4.1) | -               | -            | Vit-D: 0 Placebo: 0         | -                      | -                      |

Abbreviations: Vit-D: Vitamin D; pts: patients; no: number; BMI: body mass index; Hx: history; HTN: hypertension; DM: diabetes mellitus;
significant reduction of cancer-related mortality when compared to placebo (RR 0.84; 95% CI: 0.72–0.97; P = 0.02; I² = 0%). However, when compared with placebo, vitamin D in this subgroup of RCTs was not associated with significant reduction of cancer incidence (RR: 0.96; 95% CI: 0.84–1.09; P = 0.54; I² = 51%) (Figure 4).

For cancer incidence, meta-regression analysis based on age (R² = 46%; b = 0.01; SE < 0.01; P = 0.09), BMI (R² = 28%; b = -0.06; SE = 0.04; P = 0.12), therapy duration (R² = 0%; b = 0.01; SE = 0.06; P = 0.81), follow-up duration (R² = 0%; b < -0.01; SE = 0.07; P = 0.91), initial vitamin D level (R² = 0%; b < -0.01; SE < 0.01; P = 0.47), and vitamin D dose (R² = 0%; b < -0.01; SE < 0.01; P = 0.51) did not significantly explain the heterogeneity.

4. Discussion

In this meta-analysis of 10 RCTs, vitamin D supplementation was compared to placebo. With the use of vitamin D supplementation for at least 3 years, it was found to have benefit in reducing cancer-related mortality, however, it had no effect on cancer incidence. And when conducting a subgroup
analysis including the three RCTs where cancer was reported as a primary outcome, the results were also consistent with the initial analysis results.

Several retrospective studies, large RCTs and meta-analyses have evaluated the role of vitamin D in cancer primary prevention. According to the last review that studied the role of vitamin D in primary prevention of cancer, it was proven that vitamin D supplementation alone as primary prevention had no effect on cancer mortality and incidence. And that was after including 30 RCTs that reported cancer in their outcomes and despite including those that had long-term follow-up [21].

Keum et al., in their 2014 review, which included four RCTs with a minimum of 5 years of vitamin D supplementation, proved that long-term vitamin D supplementation did have a benefit in cancer prevention, however, only limited to cancer-related mortality [22].

In 2014, a Cochrane review also concluded that there could be decreases in all-cause mortality and cancer-related mortality among vitamin D–treated people in comparison with those who never received it. However, these results could be due to random errors [23].

Keum et al. recently reanalyzed their initial meta-analysis by adding newer RCTs with longer follow-up, which proved that vitamin D supplementation significantly reduced total cancer mortality but did not reduce total cancer incidence [24].

The strengths of our meta-analysis include an extensive search of the available literature. Furthermore, we included only RCTs, which helps eliminate the likelihood of confounding bias from nonrandomized studies. However, there are several limitations in the included clinical trials. First, over half of the included trials were not primarily studying vitamin D with the intent of preventing cancer and rather all the results were obtained by examining other reported primary outcomes. Second, due to various trial designs and protocols, there were major differences in the vitamin D forms and dosing. Third, only a few clinical trials reported all the predetermined outcomes of our study, and some trials reported only one of the two outcomes either directly or indirectly. Fourth, the follow-up period was short in some of the trials. Fifth, not all trials reported the end of trial 25-hydroxy vitamin D level to examine if the blood vitamin D levels had any effect on cancer mortality or incidence.

5. Conclusion

With inclusion of studies, which did not primarily examine vitamin D for the purpose of preventing cancer or reducing cancer mortality our meta-analysis highlights that the use of vitamin D supplementation for primary prevention of cancer is encouraged as it does possibly decrease cancer-related mortality once cancer is diagnosed; however, it has no role or effect on cancer incidence. However, this also opens questions for the future with the need for clinical trials that can account for all the limitations of our study including vitamin D form and dosing, length of therapy and exact therapeutic vitamin D levels, to provide stronger evidence and recommendations for the future.

Disclosure statement

No potential conflict of interest was reported by the authors.

Financial disclosure

No financial disclosure to declare.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and

Figure 4. Forest plot for subgroup analysis (cancer-related mortality and cancer incidence).
with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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