INPLASY PROTOCOL

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None declared.

Vitamin D supplementation and cancer incidence, mortality: a meta-analysis of randomized controlled trials

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Review question / Objective: **1. To examine whether vitamin D supplementation with/without calcium, is associated with a reduction in total cancer incidence and total cancer related mortality in the population. 2. To examine whether vitamin D supplementation with/without calcium, is associated with site-specific cancer incidence and site-specific cancer related mortality. 3. To to explore whether cumulative data were adequately powered to evaluate outcomes by trial sequential analysis.**
Condition being studied: **1. Previous meta-analyses of randomized controlled trials (RCTs) of vitamin D supplementation and total cancer incidence and mortality found inconsistent results, and most included trials administered generally low doses of vitamin D. 2. Recently, several RCTs have been pubilished, we updated the meta-analysis by incorporating these to test higher doses of vitamin D supplements.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 29 June 2021 and was last updated on 29 June 2021 (registration number INPLASY202160109).

INTRODUCTION

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METHODS

Search strategy: 1. PubMed:("Vitamin D"[Mesh] OR vitamin D[tiab] OR vitamin D[ot]) OR Cholecalciferol*[tw] OR ergocalciferol*[tw] AND ("Neoplasms"[Mesh] OR cancer[tw] OR cancers[tw] OR tumor[tw] OR tumors[tw] OR tumour[tw] OR tumours[tw] OR neoplasm[tw] OR neoplasms[tw] OR neoplasia[tw] OR carcinoma[tw] OR carcinomas[tw]) AND random*[tw] NOT ("Animals"[Mesh] NOT "Humans"[Mesh]) 2. Scoups: (TITLE-ABS-KEY (neoplasms) OR TITLE-ABS-KEY (cancer) OR TITLE-ABS-KEY (cancers) OR TITLE-ABS-KEY (tumor) OR TITLE-ABS-KEY (neoplasia) OR TITLE-ABS-KEY (carcinoma) OR TITLE-ABS-KEY (carcinomas) AND (TITLE-ABS-KEY ("vitamin D") OR TITLE-ABS-KEY (cholecalciferol) OR TITLE-ABS-KEY (ergocalciferol))) AND ("randomized controlled trial") AND (LIMIT-TO (DOCTYPE , "ar")) AND (LIMIT-TO (LANGUAGE , "English")) 3. Embase: ('vitamin D'/exp OR 'vitamin D' OR cholecalciferol OR ergocalciferol) AND ('neoplasms'/exp OR neoplasms OR 'cancer'/exp OR cancer OR 'cancers'/exp OR cancers OR 'tumor'/exp OR tumor OR tumors OR 'tumour'/exp OR tumour OR tumours OR 'neoplasia'/exp OR neoplasia OR 'carcinoma'/exp OR carcinoma OR carcinomas) AND 'article'/it AND ('randomized controlled trial'/exp OR 'randomized controlled trial') 4. Reference of all relative articles were also manually checked to identify any potential additional studies.

Participant or population: Individuals over the age of 18 years (with/without diagnosis of cancer).

Intervention: Vitamin D supplementation (provided as cholecalciferol or ergocalciferol).

Comparator: A placebo of vitamin D.

Study designs to be included: Randomized controlled trials only.

Eligibility criteria: The trial "PICOS" inclusion criteria were as follows: (1) participants: individuals over the age of 18 years (with/without diagnosis of cancer); (2) intervention: vitamin D supplementation (provided as cholecalciferol or ergocalciferol); (3) comparators: a placebo of vitamin D; (4) outcome: cancer incidence or mortality, with the results as relative risk (RR) (Risk ratio or hazard ratio) and 95% confidence interval; or as the number of incident cases of cancer and/or cancer death in each arm; (5) study design: randomized controlled trials. Only English publications were included. The exclusion criteria included: (1) studies if they were case reports, case series, or observational studies; (2) if all the participants received vitamin D; (3) if they included pregnant or lactating women, or critically ill patients; (4) if the sample size less than 150; (5) if the follow-up time less than 1 year.

Information sources: Electronic databases, trial registers.

Main outcome(s): Total cancer incidence and total cancer related mortality.

Additional outcome(s): Site-specific cancer incidence and cancer related mortality.

Quality assessment / Risk of bias analysis: Two researchers independently assessed the quality of all included trials by using the Cochrane Collaboration risk of bias tool and the evaluation includes sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other bias of all included studies.

Strategy of data synthesis: We used risk ratios and their associated 95% confidence intervals to assess outcomes, and considered a P value less than 0.05 to be statistically significant. We assessed heterogeneity using the I2 test. If significant heterogeneity was not present (I2<50%), we used fixed effects models to pool outcomes; we used random effects models when significant heterogeneity was present (I2≥50%). The possibility of small study effects was assessed qualitatively by visual estimate of the funnel plot and quantitatively by calculation of the Egger test, the Begg test, and the Harbord test.

Subgroup analysis: We performed several subgroup analyses to test interactions according to Age (< 65 and ≥ 65 years), Gender (Female only and both), Body mass index (< 25, ≥ 25 kg/m2, and unknown), Publication date (Before 2016 and in or after 2016), Location (USA, Europe, New Zealand, and Asia), Follow-up period(< 5 and ≥ 5 years), Baseline mean 25-hydroxyvitamin D (< 20 and ≥ 20 ng/mL, and unknown), Type of Vitamin D (Vitamin D3and Vitamin D2), Daily dose equivalent (< 1000 and ≥ 1000 IU), Intervention (Vitamin D and Vitamin D plus calcium), No. of participants (< 2000 and ≥ 2000), and Population (with cancer and general population).

Sensitivity analysis: We conducted sensitivity analyses by excluding trials with high risk or unknown risk of bias of the different domains; excluding the largest trial; excluding trials with a follow-up of less than three year; using random effect models; and using trial duration rather than long term follow-up.

Language: English.

Country(ies) involved: China.

Other relevant information: None.

Keywords: Vitamin D, Cancer, Incidence and mortality, Meta-analysis, Randomized controlled trial.

Contributions of each author:

Author 1 - Zhangyou Guo - The author drafted the manuscript, conducted the research and analyzed data.
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Author 2 - Dandan Fan - The author conducted the research and provided statistical expertise.
Author 3 - Yuan Hong - The author contributed to the development of the selection criteria, and the risk of bias assessment strategy.
Author 4 - Ming Huang - The author read, provided feedback and approved the final manuscript.