SHORT COMMUNICATION

BJC

British Journal of Cancer (2014) 111, 976–980 | doi: 10.1038/bjc.2014.294

Keywords: vitamin D intake; vitamin D supplements; cancer incidence; cancer mortality; meta-analysis; randomised controlled trial

Vitamin D supplements and cancer incidence and mortality: a meta-analysis

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Background: Observational studies suggest that effects of vitamin D may be stronger for cancer mortality than for incidence. Yet, existing randomised controlled trials (RCTs) of vitamin D supplementation have limited power to examine the relationships as their primary end points are not cancer incidence or mortality.

Methods: Meta-analyses of RCTs of vitamin D supplementation and total cancer incidence and mortality were conducted.

Results: Over 2–7 years of duration, vitamin D supplementations had little effect on total cancer incidence (400–1100 IU per day, summary relative risk (RR) = 1.00, 95% confidence interval (CI) = 0.94–1.06, $I^2 = 0\%$; four RCTs with combined 4333 cases), but significantly reduced total cancer mortality (400–833 IU per day, summary RR = 0.88, 95% CI = 0.78–0.98, $I^2 = 0\%$, three RCTs with combined 1190 deaths).

Conclusions: Over 2–7 years of duration, the benefit of vitamin D supplementation may be limited to cancer mortality.

Based on an inverse association between region ultra-violet-B radiation and colorectal cancer mortality rates, Garland and Garland (1980) first proposed that vitamin D has anti-cancer properties. Subsequently, in numerous animal models, activation of the vitamin D pathway with calcitriol, the active component of vitamin D, or its analogues reduced tumour development and growth (Krishnan *et al*, 2010; Mehta *et al*, 2012; Pereira *et al*, 2012). To date, at least 15 types of cancers, especially colorectal and breast cancers, have been associated with low sun exposure (Grant and Garland, 2006). An inverse association has also been observed between pre-diagnostic circulating 25(OH)D and risk for colorectal cancer (Lee *et al*, 2011; Ma *et al*, 2011; Touvier *et al*, 2011). However, the association has been less consistent for other cancer types (Gallicchio *et al*, 2010; Gandini *et al*, 2011).

Several lines of evidence suggest that effects of vitamin D may be stronger for cancer mortality than for incidence. For example, higher ultra-violet-B exposure or other vitamin D surrogates such as predicted 25(OH)D score were more strongly associated with lower cancer mortality than with incidence (Boscoe and Schymura, 2006; Giovannucci *et al*, 2006; Chen *et al*, 2010). Also, cancer patients with higher pre-diagnostic 25(OH)D have lower risks of dying from prostate (Fang *et al*, 2011) and colorectal cancers (Ng *et al*, 2008; Fedirko *et al*, 2012). Finally, higher circulating 25(OH)D levels at the time of diagnosis or treatment were related to an improved survival from cancers of the breast (Goodwin *et al*, 2009), colorectum (Mezawa *et al*, 2010), prostate (Tretli *et al*, 2009), lung (Zhou *et al*, 2007), and melanoma (Newton-Bishop *et al*, 2009), though the association could be due to confounding by an unknown prognostic factor that predicts a poor prognosis and lowers circulating 25(OH)D levels.

Randomised controlled trials (RCTs) are considered the 'gold standard' for establishing causality. To date, RCTs have not been conducted to examine the effect of vitamin D on cancer incidence or mortality as primary end points. However, there have been a small number of RCTs of 2–7 years of duration, involving moderate doses of supplemental vitamin D (400–1100 IU per day), and for reasonable numbers for total cancer incidence and mortality. Thus, we conducted meta-analyses of the RCTs of vitamin D supplementation and total cancer incidence and mortality.

MATERIALS AND METHODS

Two authors (EG and NK) participated in the literature search, study selection, and data extraction independently. Inconsistency between researchers was resolved through discussion.

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Received 5 January 2014; revised 13 April 2014; accepted 8 May 2014; published online 10 June 2014

PubMed and Embase were searched for studies published up to April 2014, using the following keywords and corresponding database thesaurus: vitamin D, cholecalciferol, ergocalciferol, cancer, tumour, carcinoma, neoplasm, carcinoma, and words beginning with 'random'. The search was limited to english articles about humans and no other restrictions were imposed. Abstracts and unpublished results were not included. The reference lists of selected systematic reviews and meta-analyses, and all the articles included in our analysis were reviewed for additional papers.

To be included, studies had to be a RCT providing information on the effect of vitamin D supplementation (with or without calcium supplementation) on total cancer incidence or mortality. When there were several publications from the same trial, the publication most fully covering the intervention period was selected. This study selection process is summarised in Figure 1.

The following information was extracted: definitions of interventions and control, most fully adjusted relative risk (RR) (risk ratio or hazard ratio) based on intention-to-treat analysis and 95% confidence interval (CI), level of serum 25(OH)D (at baseline, at follow-up), and relevant study characteristics (Table 1).

For statistical analyses, the summary RR and 95% CI were calculated using a random effects model. Heterogeneity across studies was assessed by Q test and I^2 (Higgins and Thompson, 2002). Potential for small-study effects, such as publication bias, was assessed using Egger's test (Egger *et al*, 1997) and Begg's test (Begg and Mazumdar, 1994). Sensitivity analysis was performed by excluding the Women's Health Initiative (WHI), as its comparison of combined vitamin D and calcium supplementation against placebo does not allow for testing an independent effect of vitamin D supplementation. For statistical significance, two-sided α was set at $P = 0.05$. All statistical analyses were conducted using STATA 12 (StataCorp, College Station, TX, USA).

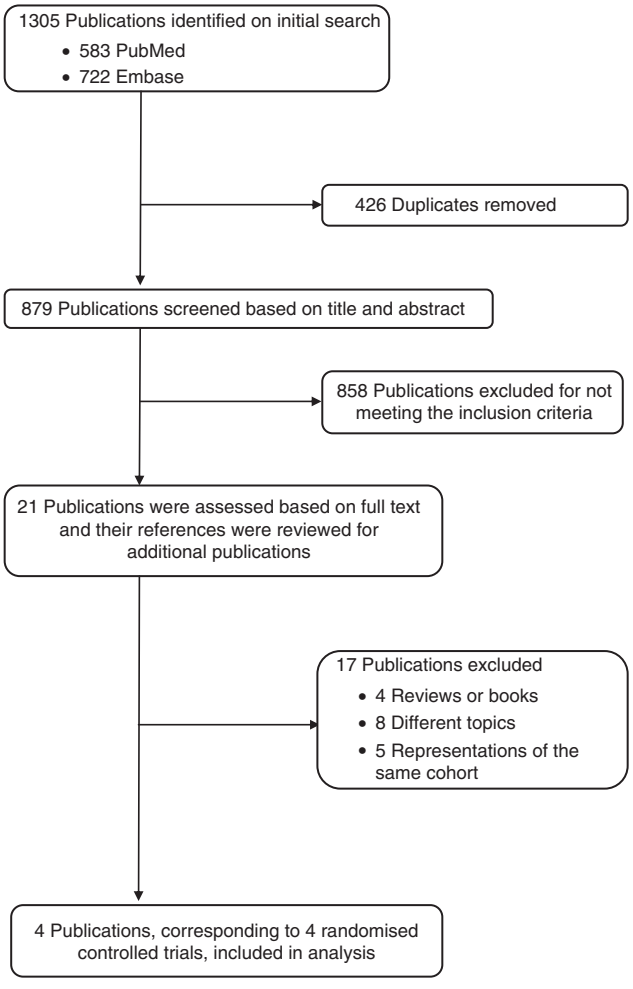

Figure 1. Flowchart of study selection.

RESULTS

Vitamin D supplementation and total cancer incidence. Four RCTs were included in the meta-analysis (4333 cases, 45 151 participants) (Table 1) (Trivedi *et al*, 2003; Wactawski-Wende *et al*, 2006; Lappe *et al*, 2007; Avenell *et al*, 2012). The summary RR for intervention *vs* control group was 1.00 ($P = 0.998$, 95% CI = 0.94–1.06) with no evidence of heterogeneity ($I^2 = 0\%$, $P_{\text{heterogeneity}} = 0.54$) (Figure 2A). In a sensitivity analysis excluding WHI (Wactawski-Wende *et al*, 2006), the summary RR was 1.06 ($P = 0.33$, 95% CI = 0.94–1.21, $I^2 = 0\%$, $P_{\text{heterogeneity}} = 0.63$). Small-study effects, such as publication bias, were not indicated in both primary ($P_{\text{Egger}} = 0.84$, $P_{\text{Begg}} > 0.999$) and sensitivity analyses ($P_{\text{Egger}} = 0.32$, $P_{\text{Begg}} = 0.60$).

Vitamin D supplementation and total cancer mortality. Three RCTs were included in the meta-analysis (1190 deaths, 44 260 participants) (Table 1) (Trivedi *et al*, 2003; Wactawski-Wende *et al*, 2006; Avenell *et al*, 2012). The summary RR for intervention vs control groups was 0.88 ($P = 0.02$, 95% CI = 0.78–0.98) with no evidence of heterogeneity ($I^2 = 0\%$, $P_{\text{heterogeneity}} = 0.94$) (Figure 2B). In a sensitivity analysis excluding WHI (Wactawski-Wende *et al*, 2006), the summary RR was 0.85 ($P = 0.09$, 95% CI = 0.71–1.03, $I^2 = 0\%$, $P_{\text{heterogeneity}} = 0.96$). Small-study effects, such as publication bias, were not indicated in both primary ($P_{\text{Egger}} = 0.45$, $P_{\text{Begg}} = 0.60$) and sensitivity analyses ($P_{\text{Egger}} =$ not available, $P_{\text{Begg}} = 0.32$).

DISCUSSION

Our results suggest that vitamin D supplementation at doses of up to 800 IU per day and attaining 25(OH)D levels of approximately 54–75 nmol l^{-1} is unlikely to have an appreciable effect on cancer incidence within 2–7 years. The RCT by Lappe *et al* (2007) which used 1100 IU per day did indicate a potential short-term effect on incidence, but was based on only 30 cases. Two larger UK studies (Trivedi *et al*, 2003; Avenell *et al*, 2012) (with 1104 combined cases) were of comparable duration, used slightly lower doses (800–833 IU per day) and achieved comparable increments of 25(OH)D within the intervention groups (24 nmol l^{-1}) (Avenell *et al*, 2012) or contrasts between intervention and control group (21 nmol l^{-1}) (Trivedi *et al*, 2003) as did the Lappe study (1100 IU per day; 24.2 nmol l^{-1} increment; 25 nmol l^{-1} contrast). Yet these studies indicated no comparable effect on total cancer incidence. Because the Lappe study population had higher baseline 25(OH)D levels and the dose was slightly higher, the attained 25(OH)D level of 96 nmol l^{-1} was higher than that in the two null studies (74.4 and 62 nmol l^{-1}) (Trivedi *et al*, 2003; Avenell *et al*, 2012). The WHI, the largest study, showed a negligible effect on incidence, but the increment was smaller (12 nmol l^{-1}) and the estimated attained median level of 25(OH)D was only 54 nmol l^{-1}. A recent article that reviewed 20 meta-analyses of observational studies on cancer outcomes also concluded that circulating 25(OH)D or 1,25$(OH)_2$D concentrations are unlikely to be related to cancer incidence (Theodoratou *et al*, 2014).

Unlike cancer incidence, vitamin D supplementation was related to a statistically significant 12% reduction in cancer mortality. Publication bias was unlikely as we did not identify comparably large studies that had data on cancer mortality. Furthermore, unlike for cancer incidence, an inverse relationship was

Table 1. Main characteristics of the RCTs included in meta-analyses

Authors, year, country	Trial name, population (% M), age at baseline	Trial duration	Contrast for RR	Incidence: RR (95% CI), (*n* case/*n* total)	Mortality: RR (95% CI), (*n* case/*n* total)	25(OH)D level (nmol l^{-1}): baseline→ follow-up	Inclusion/ exclusion criteria regarding supplement use
Trivedi *et al*, 2003, UK	Pilot community trial, general population (76%) w or w/o history of cancer, 65–85 years	5 years	Vit D3 *vs* placebo Vit D3: 100 000 IU per 4 m (~833 IU per day)	1.09 (0.86, 1.36) (188/1345) *vs* (173/1341)	0.86 (0.61, 1.20) (63/1345) *vs* (72/1341)	Intervention: NA→ 74.4 at 4 years Control: NA→ 53.4 at 4 years	Excluded Vit D supplement users
Wactawski-Wende *et al*, 2006, USA	WHI, postmenopausal women (0%) w or w/o history of cancer, 50–79 years	7 years	Vit D3 + Ca *vs* placebo Vit D3: 400 IU per day Ca (carbonate): 1000 mg per day	0.98 (0.91, 1.05) (1634/18 176) *vs* (1655/18 106)	0.89 (0.77, 1.03) (344/18 176) *vs* (382/18 106)	Intervention: 42 (median)→ [a]54 at 2 years Control: 42 (median)→ NA	Allowed for non-protocol supplement of Vit D up to 600 IU per day; of Ca up to 1000 mg per day
Lappe *et al*, 2007, USA	Population-based trial, postmenopausal women (0%) w/o cancer at baseline, 66.7 years (7.3)	4 years	Vit D3 + Ca *vs* Ca Vit D3: 1100 IU per day Ca: carbonate 1500 mg per day or citrate 1400 mg per day	0.76 (0.38, 1.55) (13/446) *vs* (17/445)	NA	Intervention: 71.8→ 96 at 1 year Control: 71.6→ 71 at 1 year	Not specified
Avenell *et al*, 2011, UK	RECORD general population (15%) w/o cancer likely to metastasise to bone within 10 years prior to baseline, 77.2 years (6)	2–5.2 years	Vit D3 (w, w/o Ca) *vs* no Vit D3 (w, w/o Ca) Vit D3: 800 IU per day Ca (carbonate): 1000 mg per day	1.07 (0.92, 1.25) (338/2649) *vs* (315/2643)	0.85 (0.68, 1.06) (151/2649) *vs* (178/2643)	Intervention: 38→ 62 at 1 year Control: 38→ 43.6 at 1 year	Excluded supplement users of >200 IU per day of Vit D; >500 mg per day of Ca

Abbreviations: Ca = calcium; CI = confidence interval; M = male; m = month; n = number; NA = not available; RR = relative risk; Vit = vitamin; w = with; w/o = without.
[a]Estimated based on the statement that serum 25(OH)D level was 28% higher in the intervention group at 2 years after randomisation.

consistently observed in all the studies included in the meta-analysis on cancer mortality. A recent meta-analysis also found a statistically significant inverse association between circulating 25(OH)D levels and cancer mortality, based on 12 primary prevention cohort studies in which reverse causation is less likely than secondary prevention cohort studies (Chowdhury *et al*, 2014). Animal models support mechanisms whereby vitamin D status may influence processes such as metastasis (Krishnan *et al*, 2010; Mehta *et al*, 2012; Pereira *et al*, 2012), which could affect mortality.

Our analyses inherit the limitations of the available RCTs to examine many facets of the vitamin D-cancer hypothesis, in terms of doses, attained 25(OH)D levels, duration, and effects on specific cancer types. Further, only one of the four RCTs included in the meta-analysis examined vitamin D-only supplementation. The remaining three RCTs added calcium in their intervention regimes; while WHI could not distinguish an independent effect of vitamin D, calcium was balanced between the vitamin D and non-vitamin D groups in the two other trials. Yet, since the effect of vitamin D was tested in calcium-replete populations, our findings might not be generalisable to populations with a low calcium intake as calcium may be a modifier. Lastly, despite that meta-analysis generally enhances statistical power, considering that total cancer incidence and mortality were not the primary end points in the RCTs included, our meta-analysis might have had inadequate power to detect a meaningful association. Nevertheless combining RCTs allowed us to examine an interesting range of attained 25(OH)D levels for total cancer incidence and mortality over a period ranging from 2–7 years. The results should not be generalised beyond these limits.

Our findings may have implications for future research. Increasing 25(OH)D levels to a range of 75 nmol l^{-1} is unlikely to influence total cancer incidence within 5 years. Whether attaining higher levels in the range of 90–100 nmol l^{-1} would reduce incidence remains unclear. Ongoing RCTs of relatively high doses will be able to test this hypothesis. Additionally, some interventions may require more than 5 years to elicit a substantial reduction in cancer incidence, as demonstrated for aspirin and colorectal cancer (Rothwell *et al*, 2010). Because very long-term RCTs may be unfeasible, further observational studies addressing long-term effects may provide useful information on the required duration.

It is unclear whether the potential benefit for vitamin D status on cancer mortality operates in the pre-diagnostic stages by influencing tumour aggressive behaviour and metastatic seeding, during treatment through interactions with therapies, in post-diagnostic stages by improving survival, or during multiple stages.

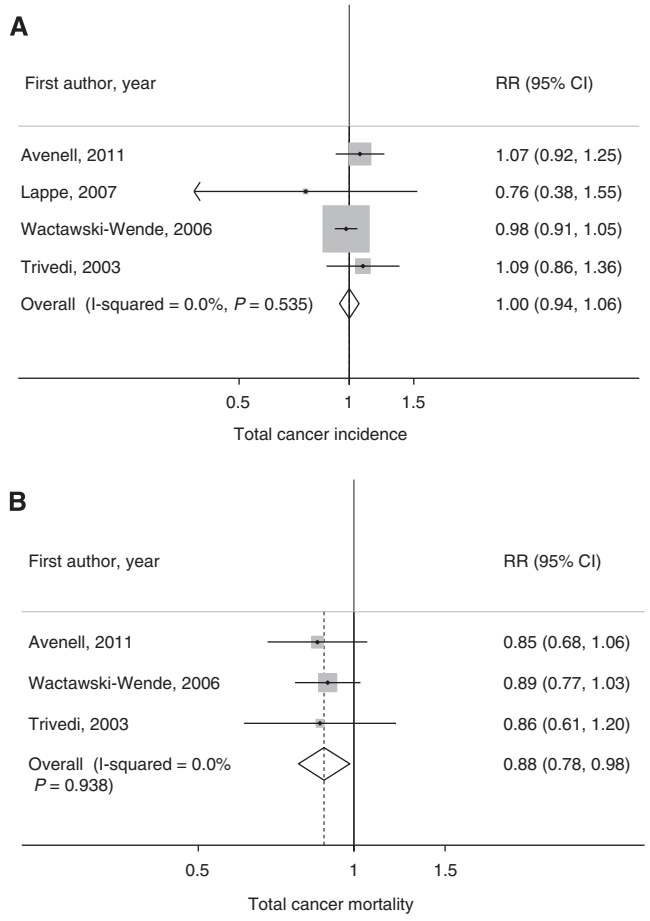

Figure 2. Meta-analyses of RCTs of vitamin D supplementation and total cancer incidence and mortality. (**A**) Total cancer incidence, (**B**) total cancer mortality. Abbreviations: CI = confidence interval; RR = relative risk.

Indeed, the RCTs did not exclude people with a prior history of cancer and the benefit was observed in such mixed populations. Given the high prevalence of vitamin D deficiency at the time of diagnosis, RCTs could feasibly be conducted in which high doses of vitamin D are provided to rapidly increase vitamin D stores at the time shortly before treatment to test the hypothesis that vitamin D status may favourably interact with treatment or be protective for survival. RCTs over a period of 5 years or so, such as VITAL, will be able to test whether vitamin D intervention begun in the pre-diagnostic period can reduce cancer mortality.

In the UK, approximately 159 000 people die of cancer annually, so a 15% reduction would result in a substantial number of potentially preventable deaths from cancer. Although not definitive, these data offer some support of attaining 25(OH)D levels of at least 75 nmol l^{-1}, as has been recommended by the Endocrine Society (Holick *et al*, 2011). There is no credible evidence of harmful effects of vitamin D in this range of exposure (Bischoff-Ferrari *et al*, 2010). Whether attaining considerably higher levels would provide further benefits on cancer currently cannot be addressed adequately based on the available RCT data.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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