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, I² = 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, I² = 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 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.
Vitamin D supplementation and total cancer incidence. Four RCTs were included in the meta-analysis (4333 cases, 45151 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_{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_{heterogeneity} = 0.63). Small-study effects, such as publication bias, were not indicated in both primary (P_{Egger} = 0.84, P_{Begg} > 0.999) and sensitivity analyses (P_{Egger} = 0.32, P_{Begg} = 0.60).

Vitamin D supplementation and total cancer mortality. Three RCTs were included in the meta-analysis (1190 deaths, 44260 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_{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_{heterogeneity} = 0.96). Small-study effects, such as publication bias, were not indicated in both primary (P_{Egger} = 0.45, P_{Begg} = 0.60) and sensitivity analyses (P_{Egger} = not available, P_{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 population (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}) when compared with the increments observed in the other studies.

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
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., 2010; Pereira et al., 2014), 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.

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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 | 1.09 (0.86, 1.36) (188/1345) vs (173/1341) | 0.86 (0.61, 1.20) (63/1345) vs (72/1341) | Interventions: 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 (8%) w/o w/o history of cancer, 50–79 years | 7 years | Vit D3 + Ca vs placebo | 0.98 (0.91, 1.05) (1634/18 176) vs (1655/18 106) | 0.89 (0.77, 1.03) (344/18 106) vs (382/18 106) | Intervention: 42 (median) → *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 60% w/o cancer at baseline, 66.7 years (7.3) | 4 years | Vit D3 + Ca vs Ca | 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) | 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.

*Estimated based on the statement that serum 25(OH)D level was 28% higher in the intervention group at 2 years after randomisation.
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.

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