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Letter to the Editor

Whether vitamin D supplementation protects against colorectal cancer risk remains an open question

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Dear Editor,

Observational studies implicate vitamin D deficiency in the aetiology of several common cancers. Despite much controversy, higher circulating 25-hydroxyvitamin D (25OHD) has been consistently associated with a lower risk of colorectal cancer (CRC) [1]. However, a definitive causal relationship remains unproven [2]. Three recent studies failed to demonstrate any effect of vitamin D supplementation on cancer risk. Two large population studies (Vitamin D and Omega-3 [*VITAL*] Trial [3] and the Vitamin D Assessment [*ViDA*] study [4]) showed that vitamin D supplementation did not provide any detectable difference in the incidence of any cancer type. Similarly, Baron *et al.* reported no reduction in risk of recurrent colorectal adenomas after 3–5 years of supplementation [5].

Several features of these studies may have limited the ability to identify an effect of supplementation on the observed clinical end-points. First, each of these studies recruited subjects who were predominantly already sufficient or replete for vitamin D thereby capping the health benefit that might be achieved. These studies had very limited recruitment of people in the low exposure group who are expected to benefit more from the

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supplementation. Observational data suggest that the 25OHD level threshold associated with lowest risk of CRC is ~30 ng/ml [6]. Treating a cohort with an already high baseline 25OHD level (i.e. high exposure control group) would limit benefit of supplementation as a threshold effect, or a sigmoid-shaped rather than a linear dose–response relationship likely exists [7]. In the VITAL study, mean baseline 25OHD was 30.8 ng/ml with 90% sufficient for vitamin D, whereas in the *ViDA* and adenoma studies, baseline 25OHD was ~25 ng/ml. High baseline 25OHD will limit power to identify a benefit from trial supplementation because small or absent effects in this group will dilute the impact supplementation might have in deficient individuals.

Each study reports a high prevalence of 'off protocol' vitamin D supplementation in control groups, which will also attenuate any beneficial effect in the active agent group. In the *VITAL* control group, 42.7% were taking ≤800IU/day at baseline and 10.8% > 800IU/day at 5 years. Similarly, in the Baron adenoma study, 57% participants were taking supplements at baseline. Meanwhile, the *VITAL* and adenoma studies were conducted across the United States including some regions with high UVB exposure (median daily UVB Houston—7.35 kJ/m^2). Personal vitamin D supplement use together with high UVB exposure will decrease the *relative* contribution of the trial intervention to vitamin D status; in the context of randomised control trial (RCTs), they will contribute to the heterogeneity of treatment effects making detection of the intervention effect difficult. Populations with lower 25OHD levels domiciled in areas of low UVB (i.e. high northern latitude) may be more suitable for vitamin D trials (e.g. median daily UVB Edinburgh—1.70 kJ/m^2).

Each study conducted a subgroup analysis in subjects with low 25OHD and reported no difference in invasive cancer/adenoma recurrence between vitamin D arms. However, these subjects were a small minority, and analyses were underpowered to detect even major effects on risk (see Table 1).

The *VITAL* and *ViDA* studies also do not consider other issues relevant to vitamin D intervention studies, such as co-nutrient optimisation (calcium supplementation) and population genetic heterogeneity (variable response or action of vitamin D because of participant genetics). Baron *et al.* subsequently addressed the issue of gene-environment interaction on adenoma recurrence, demonstrating a significant effect of vitamin D3 supplementation on advanced adenomas when stratified by genotype for functional Vitamin D receptor gene single nucleotide polymorphisms (*VDR* SNPs) (rs7968585 and rs731236) [8].

Finally, despite the large sample sizes in *VITAL* and *ViDA*, the number of specific events was low. Only 98 and 38 incident CRC cases were observed in the *VITAL* and *ViDA* studies respectively. We estimate that over 200,000 participants would be required in the VITAL study to identify a modest effect (e.g. hazards ratio [HR] = 0.80, see Table 1), accepting the high baseline 25OHD. Using plausible baseline 25OHD levels and CRC event rate, we have modelled the requirements for an adequately powered trial in a low exposure population such as Scotland [9]. We estimate that such a trial would require ~32,000 participants with 10-year follow-up (Table 1).

In a subanalysis, the *VITAL* study does report a lower rate of all cancer deaths when examining events after 2 years of follow-up (HR 0.75; 95% confidence interval = 0.59–0.96), strengthening the case for longer term follow-up. This and the statistically significant effect of vitamin D on high-risk adenoma recurrence in subgroups with defined functional genetic variants [10] provides evidence supporting calls for further well-powered trials studying the effect of vitamin D

Table 1
Vitamin D intervention studies and with post hoc estimated hazard ratios for deficient subpopulations and estimated required sample size to detect putative difference in CRC incidence.

Study	Dose	Follow-up	Deficient (<20 ng/ml)	All cancer risk		CRC/adenoma risk	
				Incidence	Post hoc HR calculation	Incidence	Post hoc sample size
VITAL N = 25,871	2000IU per day	5.3 years	12.7%[a]	6.25%	0.55	0.4%	N = 201,284
ViDA N = 5108	100000IU monthly	3.3 years	30%	6.4%	0.52	0.74%	N = 94,822
Baron N = 2259	1000IU per day	3.8 years	N/A	N/A	N/A	9.45%	N = 6838
SOCCS N = 2235	N/A	10 years	77%	N/A	N/A	2.17%[b]	N = 31,914

VITAL, Vitamin D and Omega-3 Trial; ViDA, the Vitamin D Assessment; IU, international units; CRC, colorectal cancer; HR, hazard ratio. The **'post hoc HR calculation (all cancer)'** is the reduction in risk of all cancer that would be required for the study to identify a treatment effect (assuming power = 0.80, α = 0.05) if the study only included those patients in the deficient group (i.e. <20 ng/ml). It assumes the baseline risk of all cancer as reported in the respective studies. The Baron paper and the Study of Colorectal Cancer in Scotland (SOCCS) study only assesses colorectal pathology i.e. not all cancer risk, and so this calculation is not applicable; The **'post hoc sample size (CRC) (HR 0.80)'** is the estimated sample size for a study investigating the effect of supplementation on colorectal cancer/adenoma risk. It assumes a modest overall effect (i.e. HR = 0.80) and standard trial criteria (power = 0.80, α = 0.05). It assumes the baseline risk of colorectal cancer/adenoma as reported in the respective studies. This calculation ignores the high baseline 25OHD reported in the respective trials. For the Baron study, this calculation considers advanced adenoma incidence, not CRC.

[a] Only 15,787 of the study sample had 25OHD measured at baseline.

[b] Scottish ISD data taken from https://www.isdscotland.org/10,859 new cases of CRC registered in 2011–2016 in age 60–79 years (5 year incidence 1.08). Extrapolating to 10-year incidence = 2.17%.

supplementation on colorectal cancer risk in populations with a high prevalence of deficiency because of diet and geographical location. We propose that the protective effect of vitamin D supplementation on CRC cancer risk in deficient populations remains an open question.

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Conflict of interest statement

None declared.

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