Optimizing vitamin D status to reduce colorectal cancer risk: an evidentiary review

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CRD summary
This review concluded that given the overall safety profile and its wide range of health benefits, it was reasonable and practical to recommend a daily intake of 1,000 international units of vitamin D. The study results were inconsistent and the details of the review process were not reported, which means that these conclusions should be treated with caution.

Authors' objectives
To examine the effects of vitamin D on the prevention and risk reduction of colorectal cancer.

Searching
MEDLINE, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials (CENTRAL), and CINAHL databases were searched for articles from 2002 up to 2008. The reference lists of relevant articles were handsearched and the search terms were reported.

Study selection
Randomised controlled trials (RCTs) that assessed vitamin D as the intervention and cohort or case-control studies that measured the serum 25-hydroxyvitamin D levels or vitamin D intake from diet, supplements, or both were included if they assessed the association with colorectal neoplasm, colorectal adenomas, or polyps.

The patients, the doses, and the scheduling of interventions varied greatly across the studies. Some studies combined vitamin D with calcium supplementation. Study duration ranged from six months to 14 years.

The authors did not state how many reviewers selected the papers for the review.

Assessment of study quality
Validity was not fully assessed, but the studies were assigned one of seven levels of evidence, based on their design and conduct.

The authors did not state how many reviewers performed this assignment.

Data extraction
The authors appear to have extracted relative risks, odds ratios, and their associated 95% confidence intervals from each study.

They did not state how many reviewers extracted the data for the review.

Methods of synthesis
The results were combined in a narrative synthesis, grouped by the intervention assessed.

Results of the review
Twenty-five studies, comprising four RCTs, 11 cohort studies, and 10 case-control studies, were included in the review. Most of them were assigned an evidence level two (well-designed RCT) or four (well-designed cohort or case-control study). Sample size ranged from 19 to 36,282 in the RCTs and from 193 to 191,011 in the cohort and case-control studies.

The results from the four RCTs were inconsistent. One trial (n=1,179 participants) examined the incidence of all cancer in postmenopausal women taking calcium alone versus calcium (1.4 to 1.5g daily) plus vitamin D (1,100 international units, IU, daily). It showed a 60% risk reduction in the calcium plus vitamin D group (RR 0.4, 95% CI 0.2 to 0.82) over
four years. This trial also showed no difference in toxicity profile for a vitamin D intake of 1,100 IU per day compared with placebo. Two small RCTs demonstrated that a daily intake of 400 IU vitamin D plus 1.5g of calcium for six months reduced the epithelial cell proliferation of colorectal mucosa and colorectal polyp mucosa. In contrast, a very large RCT (n=36,282) in postmenopausal women found no effect of a daily intake of 1g of calcium plus 400 IU of vitamin D over seven years (RR 1.08, 95% CI 0.86 to 1.34).

Eleven cohort and case-control studies examined the dose-response relationship between the 25-hydroxyvitamin D level and colorectal cancer risk. Of these, seven demonstrated an inverse relationship between serum 25-hydroxyvitamin D levels and colorectal cancer and four showed an inverse relationship with adenoma risk. Seven of the 10 studies assessing the effect of vitamin D intake from diet and supplementation on colorectal cancer risk found that higher vitamin D intake was associated with reduced colorectal cancer risk.

**Cost information**
The cost-benefit ratio of vitamin D supplementation at 1,000 IU per day was 1:24 from cancer alone, based on a number-needed-to-treat of 20 (one RCT, n=1,179), at a cost for vitamin D supplements of $1,600 for 20 people, and a cost of $152,520 for a single cancer case, over four years.

**Authors' conclusions**
The authors concluded that given the overall safety profile and its wide range of health benefits, it was reasonable and practical to recommend a daily intake of 1,000 IU vitamin D.

**CRD commentary**
This review had a clear research question and the inclusion criteria were well defined for study design and intervention, but the patient population and outcomes of interest were less well defined. There were no specific attempts to identify unpublished studies, which may have introduced publication bias, and language restrictions were not reported. The authors did not report using methods designed to reduce reviewer bias and error at any stage of the review process. There was a high level of clinical heterogeneity between the studies and a narrative synthesis was appropriate.

While the summaries of each type of evidence were an accurate reflection of the results presented, the inconsistency of the randomised evidence means that, in the absence of a pooled estimate, there was little evidence to support the conclusion that a daily intake of 1,000 IU vitamin D was reasonable. This, together with the poor reporting of the review process, suggests that these conclusions should be treated with caution.

**Implications of the review for practice and research**
**Practice:** The authors stated that patients should be encouraged to take 1,000 IU per day of vitamin D with a calcium intake of 1.2g per day for men and premenopausal women and 1.5g per day for postmenopausal women and patients with osteoporosis or osteopenia. They recommended that vitamin D deficiency should be corrected by extra vitamin D intake to maintain a level of 25-hydroxyvitamin D in the range of 32 to 100 nanograms per mL, but the best levels for most patients were 50 to 100 nanograms per mL.

**Research:** The authors stated that large, population-based, longitudinal RCTs, using adequate doses of vitamin D (to keep the 25-hydroxyvitamin D level within 32 to 100 ng/mL) and running over 10 years were required to assess the long-term effects. They noted that the ongoing Vitamin D/Calcium Polyp Prevention Study was likely to produce important results in 2017.

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