

Abstract

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Effect of vitamin D and calcium supplementation on markers of apoptosis in normal colon mucosa: Results from a randomized clinical trial

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BACKGROUND: Calcium supplementation reduces colorectal adenoma recurrence, and higher serum vitamin D levels are associated with reduced risk for colorectal cancer, the second leading cause of cancer deaths in the US.

OBJECTIVE: In vitro and animal studies found anti-proliferative, pro-apoptosis, and pro-differentiation effects of vitamin D and calcium, but the independent and combined anti-neoplastic effects of calcium and vitamin D on normal human colon mucosa are unclear.

DESIGN: We conducted a pilot, randomized, double-blind, placebo-controlled, 2x2 factorial chemoprevention trial (n = 92) to test the effect of daily supplemental calcium 2.0 g and/or vitamin D3 800 IU vs. placebo over six months on apoptotic markers in the normal colorectal epithelium of 40-75 year old patients with resected sporadic colorectal adenoma. Dietary, lifestyle, demographic, and medical data were collected, and expression of Bcl-2 (an apoptosis inhibitor) and Bax (an apoptosis promoter) was detected and quantified in "non-prep" biopsies of normal-appearing rectal mucosa by automated immunohistochemistry and image analysis.

RESULTS: At baseline, there were no significant differences between the four study groups. After six months of treatment serum 25(OH)-vitamin D3 levels increased significantly in the vitamin D and calcium plus vitamin D groups. After six months treatment, Bax expression along the full lengths of crypts increased proportionately by 56% (p=0.02) in the vitamin D group and 33% in the calcium (p=0.31) and calcium plus vitamin D (p=0.36) groups relative to the placebo group. The vitamin D treatment effect was more pronounced in the upper 40% of crypts (76%; p=0.03). There were no statistically significant treatment effects on Bcl-2 expression. The estimated relative treatment effects on the ratio of Bax to Bcl-2 in the calcium, vitamin D, and calcium plus vitamin D groups were increases of 62% (p=0.52), 47% (p=0.37), and 71% (p=0.08), respectively. For the vitamin D group the proportional increase in the Bax to Bcl-2 ratio in the upper 20% relative to the lower 20% of crypts was 352% (p=0.04) relative to the placebo group.

CONCLUSION: Overall, these preliminary results suggest that 1) calcium and vitamin D, individually or together, may enhance apoptosis in the human colorectal epithelium; 2) that they do so via upregulating Bax expression alone or relative to Bcl-2 expression; and 3) the strongest treatment effects may be vitamin D related and in the upper sections of the colorectal crypts. We are currently investigating these findings within a large calcium/vitamin D and adenoma recurrence trial.