Vitamin D3 prevents calcium-induced progression of early-stage prostate tumors by counteracting TRPC6 and calcium sensing receptor upregulation.


Abstract
Active surveillance has emerged as an alternative to immediate treatment for men with low-risk prostate cancer. Accordingly, identification of environmental factors that facilitate progression to more aggressive stages is critical for disease prevention. Although calcium-enriched diets have been speculated to increase prostate cancer risk, their impact on early-stage tumors remains unexplored. In this study, we addressed this issue with a large interventional animal study. Mouse models of fully penetrant and slowly-evolving prostate tumorigenesis showed that a high calcium diet dramatically accelerated the progression of prostate intraepithelial neoplasia, by promoting cell proliferation, micro-invasion, tissue inflammation and expression of acknowledged prostate cancer markers. Strikingly, dietary vitamin D prevented these calcium-triggered tumorigenic effects. Expression profiling and in vitro mechanistic studies showed that stimulation of PC3 cells with extracellular Ca2+ resulted in an increase in cell proliferation rate, store-operated calcium entry (SOCE) amplitude, cationic channel TRPC6 and calcium sensing receptor (CaSR) expression. Notably, administration of the active vitamin D metabolite calcitriol reversed all these effects. Silencing CaSR or TRPC6 expression in calcium-stimulated PC3 cells decreased cell proliferation and SOCE. Overall, our results demonstrate the protective effects of vitamin D supplementation in blocking the progression of early-stage prostate lesions induced by a calcium-rich diet.

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PMID: 27879271 DOI: 10.1158/0008-5472.CAN-16-0687

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