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PROSTATE CANCER

Calcium promotes cancer; vitamin D decelerates

Data from a large interventional animal study have shown that a high-Ca^{2+} diet can accelerate progression of prostate cancer, but that this effect can be inhibited by vitamin D.

Previous studies have suggested that Ca^{2+} might promote prostate cancer, with a small — though significant — association with prostate cancer risk. Mechanisms for such an effect are currently unknown, but might include a reduction in circulating vitamin D, caused by the high Ca^{2+} levels. However, these studies focussed on the occurrence of new tumours and not on the evolution of existing tumours, which is likely to be far more clinically relevant when increasing numbers of men with the disease are managed using active surveillance protocols. "The human context that is targeted relates to patients harbouring early, slowly progressing prostate cancer, who are, therefore, on active surveillance," lead author Vincent Goffin told *Nature Reviews Urology*. "These patients have no treatment but regular follow-up, so it is important to identify environmental factors that might promote cancer progression to prevent it as far as possible, and to avoid reaching a disease status requiring surgical treatment."

Goffin and a multi-institutional team from Paris used cell lines and mouse models to investigate the effect of a high-Ca^{2+} diet on prostate intraepithelial neoplasia (PIN). Two mouse models, KIMAP and Pb-Prl, were used, both of which develop slowly progressing prostate cancer via different mechanisms. Mice were fed high-Ca^{2+} diets and sacrificed before the occurrence of overt prostate cancer. At dissection, the prostates of KIMAP mice showed no difference in gross morphology. However, at the histopathological level, mice fed a high-Ca^{2+} diet exhibited dose-dependent high-grade PIN, with cribriform patterns, cellular atypias, reversed nuclear:cytoplasmic ratio, and hyperchromatosis. An increase in inflammatory cell content was also noted. Similar effects were noted in the Pb-Prl mice. "We have shown that dietary Ca^{2+} promotes progression of early-stage prostate cancer in two unrelated genetically modified mouse models (PRL/Stat5 activation versus SV40 T antigen-driven)," explains Goffin. "This effect is supported by analysis of various cancer hallmarks such as histology, cell proliferation index, microinvasion, expression of cancer markers, and inflammation."

Interestingly, dietary vitamin D supplementation had little effect on PIN *per se*; however, it was able to inhibit the effects of the high-Ca^{2+} diet observed in both mouse models.

In order to investigate potential mechanisms for these effects, the team determined mRNA levels of known Ca^{2+} effectors, including transient receptor potential canonical 6 (TRPC6) and the G-protein receptor Ca^{2+}-sensing receptor (CaSR), both of which were strongly and dose-dependently upregulated by a high-Ca^{2+} diet, an effect blocked by addition of vitamin D.

They went on to study these effects *in vitro* using the PC3 prostate cancer cell line. Addition of Ca^{2+} to the culture medium not only increased cellular proliferation, but also dose-dependently increased TRPC6 and CaSR mRNA levels. Silencing of TRPC6 and CaSR reduced proliferation, even in high-Ca^{2+} medium, whereas overexpression increased proliferation in low-Ca^{2+} medium.

Overall, the data suggest a startling effect of high-Ca^{2+} diet on prostate cancer progression, and the inhibition of the effect by vitamin D raises the possibility of a role of vitamin D supplementation for men on active surveillance protocols. However, Goffin recommends care when interpreting the results: "Direct extrapolation of these preclinical results to the human context should be made with caution as many confounding factors might exist in humans. That said, one can note that the doses of dietary Ca^{2+} and vitamin D used in our preclinical study are in the range of what could be observed in humans regarding recommended Ca^{2+} and vitamin D daily intake."

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ORIGINAL ARTICLE Bernichtein, S. *et al.* Vitamin D3 prevents calcium-induced progression of early-stage prostate tumors by counteracting TRPC6 and calcium sensing receptor upregulation. *Cancer Res.* http://dx.doi.org/10.1158/0008-5472.CAN-16-0687 (2016)