

Low vitamin D levels again linked to cancer risk – 2007 AACR meeting

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Low vitamin D levels again linked to cancer risk

4/17/2007 – Vitamin D deficiency is linked to an increased risk of cancer, researchers have told attendees at the annual meeting of the American Association for Cancer Research, with results from a clinical trial hoped to show benefits of high-dose vitamin D replacement in individuals with high risk of lung cancer.

The link between vitamin D intake and protection from cancer dates from the 1940s when Frank Apperly demonstrated a link between latitude and deaths from cancer, and suggested that sunlight gave "a relative cancer immunity."

Vitamin D refers to two biologically inactive precursors – D3, also known as cholecalciferol, and D2, also known as ergocalciferol. The former, produced in the skin on exposure to UVB radiation (290 to 320 nm), is said to be more bioactive. The latter is derived from plants and only enters the body via the diet.

Both D3 and D2 precursors are hydroxylated in the liver and kidneys to form 25-hydroxyvitamin D (25(OH)D), the non-active 'storage' form, and 1,25-dihydroxyvitamin D (1,25(OH)2D), the biologically active form that is tightly controlled by the body.

Donald L. Trump, president and CEO of Roswell Park Cancer Institute told attendees at the American Association for Cancer Research centennial meeting that substantial epidemiological data indicate a link between low vitamin D levels and an increased risk of a number of cancers.

Trump said that no large-scale prospective trials have been conducted to test the hypothesis that aggressive vitamin D supplementation may influence cancer risk, and Roswell Park Cancer Institute recently initiated a clinical trial of high-dose vitamin D3 in individuals with high risk of lung cancer.

"The goal of this study is to delineate the biologic effects of 1,25(OH)2D supplementation in high-risk patients," said Trump.

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Preclinical studies have demonstrated an anti-proliferative and pro-differentiative effects of high-dose 1,25(OH)₂D in vitro and in vivo, said Trump, with all tumour models sensitive to vitamin D.

"While preclinical data and limited clinical data strongly suggest that 1,25(OH)₂D has a role in the suppression of established cancer, there are numerous unanswered questions about optimal dose, schedule and formulation of 1,25(OH)₂D," said Trump.

Calls to increase vitamin D intake have been growing. Indeed, only recently fifteen experts from universities, research institutes, and university hospitals around the world called for international agencies to "reassess as a matter of high priority" dietary recommendations for vitamin D because current advice is outdated and puts the public at risk of deficiency (The American Journal of Clinical Nutrition, Vol. 85, pp. 860–868).

A recent review of the science reported that the tolerable upper intake level for oral vitamin D₃ should be increased five-fold, from the current tolerable upper intake level (UL) in Europe and the US of 2000 International Units (IU), equivalent to 50 micrograms per day, to 10,000 IU (250 micrograms per day).

Source: Annual meeting of the American Association for Cancer Research
16 April 2007, Abstract

"Vitamin D: Sunshine, Diet and Supplements – Cancer Prevention and Therapy"

Authors: D.L. Trump, M. Fakhri, I. Chung, C.S. Johnson

Excerpted from

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<http://www.nutraingredients-usa.com/news/ng.asp?n=75809-vitamin-d-cancer-supplements>

Below the above mentioned abstract:

<http://tinyurl.com/2ldoks>

"Substantial epidemiologic data indicate a link between low vitamin D level and an increased risk of a number of cancers. Perhaps the most persuasive study of many relating vitamin D and cancer risk is that of Giovannucci and colleagues [J Natl Cancer Inst 2006;98:451 – 9]. These investigators prospectively developed an algorithm to estimate serum 25(OH) vitamin D₃ concentration (the accepted measure of vitamin D stores) based on dietary, residence and physical characteristics. They then applied this algorithm to the 47,800 participants in the Health Professionals Study. In their analysis an increment of 25 nmol/L in 25(OH)D₃ level was associated with a 17% reduction in total cancer incidence (RR = 0.83, 95% confidence interval [CI]

= 0.74 to 0.92), a 29% reduction in total cancer mortality (RR = 0.71, 95% CI = 0.60 to 0.83) and a 45% reduction in digestive–system cancer mortality (RR = 0.55, 95% CI = 0.41 to 0.74). Estimates from this study as well as numerous studies in which 25(OH)D3 concentrations have been measured demonstrate that serum content of 25(OH)D3 is low in a large proportion of normal individuals as well as patients under medical care. Our own studies among more than 300 ambulatory cancer patients (colorectal, prostate) as well as 100 normal controls indicate that >70% have serum 25(OH)D3 concentrations less than the generally accepted lower limit of normal (80nmol/L). Vitamin D deficiency appears to be a common phenomenon. There is controversy about the optimal blood level of vitamin D and the optimal way to achieve that level. While exposure to sunlight is an effective way to increase systemic vitamin D levels, concern about the negative effects of UV light exposure (skin damage, carcinogenesis) make dietary supplementation a more attractive and dependable approach to optimizing D levels. Careful studies indicate that the level of 25(OH)D3 increases 1.75 nmol/L for every 100 IU/day increment in vitamin D3 (cholecalciferol). However, it is uncertain what blood level of 25(OH)D3 is optimal for health. While it is widely recognized that vitamin D deficiency predisposes to secondary hyperparathyroidism and osteomalacia/osteoporosis, there are intriguing data which link vitamin D status and other diseases: multiple sclerosis, falls and muscle strength among the elderly, infectious diseases (tuberculosis, influenza) and thrombosis and cardiovascular disease (JAMA. 2006 Dec 20;296(23):2832–8; Endocrinology 2003;144:5138–5144; Arch Intern Med 2006;166:424–430; J Am Geriatr Soc. 1999 Feb;47(2):220–6; Science. 2006 Mar 24;311(5768):1770–3; Blood 1998;92:160–167; Br J Haematol. 2006 Nov;135(3):392–4. Epub 2006 Sep 19). If one accepts that the vitamin D receptor (VDR) knock–out mouse may provide clues regarding the physiologic effects of ?absolute? vitamin D deficiency, the occurrence of hypertension, cardiomyopathy and abnormal microvascular structure may provide clues linking vitamin D deficiency and a number of important physiologic variables. These data suggest that vitamin D deficiency may predispose to the occurrence of a number of types of cancer AND increase the likelihood of numerous complications well–recognized to occur in cancer patients.

Clinical Trials – Cancer Prevention

No large scale prospective trials have been conducted which test the hypothesis that aggressive vitamin D supplementation influences cancer risk. A recent report from the Women’s Health Initiative (WHI) indicates that calcium (1000mg/d) and cholecalciferol (400IU/d) did not reduce the frequency of invasive colorectal cancer (CRC) and more than 36,000 women

randomized to supplementation or placebo. In this trial a nested control analysis did reveal a lower occurrence of CRC among women in the highest quartile of baseline 25(OH)D3 serum concentration. It is important to realize, however, that the dose of cholecalciferol employed in the WHI was low – admittedly it was the recommended daily allowance – but this amount of cholecalciferol has been shown to be insufficient to restore serum 25(OH)D3 levels to the normal range in the great majority of individuals. We have recently initiated a trial of high dose calcitriol replacement (45mcg/week) in individuals with high risk of lung cancer in whom serial LIFE bronchoscopy and bronchial biopsies will be done. The goal of this study is to delineate the biologic effects of calcitriol supplementation in high risk patients.

Clinical Trials – Cancer Treatment

Numerous preclinical studies demonstrate the antiproliferative and prodifferentiative effects of high dose calcitriol treatment in in vitro and in vivo models. In the laboratory there appears to be no tumor type that is uniquely sensitive to vitamin D treatment – leukemia, lymphoma, myeloma and solid tumor models are all sensitive. A large number of mechanisms have been associated with the antitumor effects of calcitriol: cell cycle inhibition, induction of apoptosis, reduction of invasion and motility are all associated with vitamin D treatment. Chung and colleagues have recently investigated the antiangiogenic effects of calcitriol and shown that high dose calcitriol preferentially suppresses the growth of endothelial cells isolated from tumor microenvironments and that this suppression is associated with epigenetic suppression of the activity of CYP24, the predominant calcitriol catabolizing enzyme. These data indicate the importance of vitamin D synthesis and breakdown – in the tumor microenvironment – in the anticancer and potentially chemopreventive effects of vitamin D. There are few preclinical or clinical studies of the mechanisms of resistance to vitamin D.

Clinical trials of vitamin D in cancer treatment have focused primarily on the use of calcitriol. Limited trials with calcitriol analogues fail to indicate advantages of any analogue in the clinic. Most studies of calcitriol in cancer therapy have focused on the use of calcitriol in prostate cancer. Calcitriol alone and cholecalciferol have each been shown to reduce the rate of doubling of the prostate specific antigen (PSA) in men with androgen dependent prostate cancer (Nutrition and Cancer, 51(1), 32–36 2005; J Urol. 1998;159:2035–2039). Calcitriol + glucocorticoids result in a 28% PSA response rate in men with castration resistant prostate cancer. (Cancer 2006). While preclinical data and limited clinical data strongly suggest that calcitriol and other

vitamin D analogues have a role in the suppression of established cancer, there are numerous unanswered questions about optimal dose, schedule and formulation of calcitriol. A new formulation (DN-101) developed specifically for use as a cancer therapy has undergone evaluation with docetaxel in a randomized trial in men with castration resistant prostate cancer. Among 250 men randomized either to docetaxel + placebo vs docetaxel + DN-101, survival was superior and thromboembolic events less among men receiving DN-101 (Proc ASCO 2005; Br J Haematol. 2006 Nov;135(3):392-4. Epub 2006 Sep 19)

While a number of questions remain to be addressed, available data indicate that vitamin D deficiency is common and that cancer risk is higher among those individuals with low vitamin D levels. Administration of vitamin D has anticancer activity and exploration of optimized agent, schedule and dose in both cancer prevention and therapy models is clearly indicated."

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Matti Narkia