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The 'Cocaine Blues' and Other Problems in Epidemiologic Studies of Vitamin D and Cancer

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Compelling evidence from epidemiologic and laboratory studies and from clinical trials indicates that vitamin D metabolites decrease the risk of several common cancers.[1] To set the stage for future progress in the area of vitamin D and cancer risk, it is imperative to clear the stage of encumbrances that have retarded progress. This introduction highlights six key areas that have been sources of confusion: 1) the difference between vitamins and hormones, 2) the meaning of the term vitamin "deficiency", 3) the need for an explicit understanding of which form of vitamin D pertains to what hypothesis, 4) the timing of vitamin D exposure with respect to cancer risk, 5) the mechanism(s) of action of vitamin D metabolites, and 6) the difference between disease prevention and therapy with vitamin D metabolites. Many of these topics have been the subjects of recent reviews.[2-5]

Vitamins are essential substances required for normal functioning that the body cannot manufacture and therefore must consume; an example is vitamin C, a deficiency of which causes the disease scurvy. Conversely, hormones are essential substances that are synthesized in one part of the body, transferred via the blood, and exert effects at distant sites. $1,25(OH)_2D$ is the result of synthesis in the skin that begins when ultraviolet radiation converts 7-dehydrocholesterol to vitamin D3 (cholecalciferol). Vitamin D3 subsequently undergoes two hydroxylations, the first in the liver, forming 25-(OH)vitamin D, which has little biologic activity, and the second in the kidney and in extra-renal sites, forming $1,25(OH)_2D$, the active vitamin D metabolite. $1,25(OH)_2D$ exerts numerous effects in the body, classically on bone and mineral homeostasis, and therefore it is a hormone. Conversely, because cholecalciferol is synthesized in the skin following ultraviolet radiation, it is not a vitamin. Arguably, "vitamin D" could be considered a vitamin among African Americans. This is because persons with darkly pigmented skin make much less vitamin D from the same amount of solar exposure as persons with lightly pigmented skin since melanin, the major pigment in human skin, absorbs ultraviolet light and inhibits vitamin D synthesis. Consequently, the prevalence of hypovitaminosis D in the United States is much higher among African Americans than among Caucasian Americans.[6]

Profound vitamin D deficiency during childhood causes the bone-deforming disease rickets. Consequently, vitamin D deficiency historically was defined in terms of bone; the absence of rickets in childhood or the absence of osteomalacia in adulthood was considered to represent vitamin D sufficiency. However, the recognition that many "non-classical" organs, such as the prostate gland, respond to and even synthesize the vitamin D hormone, mandates that the concept of vitamin D deficiency be revised. In short, vitamin D "deficiency" is most meaningful with respect to a specific end point: the amount of vitamin D sufficient to maintain a normal skeleton is likely insufficient to maintain the differentiated phenotype of prostate and other cells.

Scientific acceptance of the hypothesis that vitamin D metabolites inhibit the development of cancer faced several obstacles. Chief among these was the difficulty in understanding how differences in serum levels of vitamin D metabolites could influence the behavior of "non-classical" cells, even though such cells possessed receptors for $1,25(OH)_2D$ (vitamin D receptors, or VDR). This is because, unlike serum levels of 25(OH)D, which are known to decrease with distance from the equator and are lower among persons with dark pigmentation, serum levels of $1,25(OH)_2D$ are tightly regulated and do not vary with geographic latitude or race.[7] This difficulty was effectively removed by the demonstration that normal prostate cells (and, by inference, other "non-classical" cells) possess the enzyme 25-(OH)vitamin D-1-α-hydroxylase and, like the kidney, synthesize $1,25(OH)_2D$ from circulating levels of 25(OH)D.[8] The autocrine synthesis of $1,25(OH)_2D$ was subsequently shown for many other organs, such as the colon, breast, and pancreas, and is

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the presumed mechanism whereby vitamin D/sunlight inhibits the development of cancer at these sites.[9]

In light of the above, the serum metabolite of interest with respect to epidemiologic studies of vitamin D and cancer risk appears to be 25(OH)D, the accepted marker of an individual's vitamin D status, not $1,25(OH)_2D$. A role for serum $1,25(OH)_2D$ and cancer risk has been posited by some authors. However, it is important to recognize that epidemiologic hypotheses about serum $1,25(OH)_2D$ are very different from epidemiologic hypotheses regarding sunlight and/or dietary vitamin D.

In the song "Cocaine Blues," the Reverend Gary Davis (1896–1972) penned the memorable lines, "Cocaine's for horses and it's not for men. They say it'll kill me but they won't say when." The "Cocaine Blues" is a useful metaphor for hypotheses that are plausible but imprecise. For example, many hypotheses claiming that "vitamin D prevents cancer" suffer from the "Cocaine Blues" because they don't say when exposure to vitamin D prevents cancer or when exposure to vitamin D is most important. Consequently, it is possible to miss a true effect of vitamin D by mistiming the measurement of the exposure. This is especially true if the function of vitamin D metabolites is to promote the differentiation of normal cells rather than to inhibit the proliferation of transformed ones.[10] For example, if sunlight/vitamin D exposure that occurs during early life exerts protective effects on cancer diagnosed in adulthood, as some recent evidence suggests,[11] serologic studies of vitamin D metabolites measured in adulthood will fail to detect these. These different mechanisms, the promotion of differentiation of normal cells versus the inhibition of proliferation/invasion among transformed cells, require different types of exposure assessment in epidemiologic studies.

Lastly, it is important to emphasize that prevention and therapy are different processes and likely require different forms of vitamin D.[12] For example, although normal prostate cells synthesize $1,25(OH)_2D$ from 25(OH)D, cancerous prostatic cells have lost much of this ability.[13] Thus, although vitamin D (e.g., cholecalciferol) may help to prevent prostate cancer, it is unlikely to treat advanced disease. Although cancerous prostate cells cannot synthesize $1,25(OH)_2D$, they still possess receptors for it and thus are candidates for therapy with $1,25(OH)_2D$ and/or its analogs.[14] The results of the ASCENT trial, which recently showed a large survival advantage in metastatic androgen-insensitive prostate cancer for men receiving high dose $1,25(OH)_2D$, is clear evidence of the success of $1,25(OH)_2D$ in prostate cancer therapy.[15]

REFERENCES

1. Schwartz GG, Skinner HG. Vitamin D and cancer: new insights. Curr Opin Clin Nutr Metab Care 2007; 10:6-11.
2. Schwartz GG. Vitamin D and the natural history of prostate cancer: from theory to therapy. Ann Epidemiol. 2007, in press.
3. Hansen CM, Binderup L, Hamberg KJ, Carlberg C. Vitamin D and cancer: effects of 1,25(OH)2D3 and its analogs on growth control and tumorigenesis. Front Biosci 2001;6:D820-D848.
4. Heaney RP. Functional indices of vitamin D status and ramifications of vitamin D deficiency. Am J Clin Nutr 2004;80:1706s-1709s.
5. Hollis BW. Circulating 25-hydroxyvitamin D levels indicative of vitamin D sufficiency: implications for establishing new effective dietary intake recommendations for vitamin D. J Nutr 2005;135:317-322.
6. Nesby-O'Dell S, Scanlon KS, Cogswell ME, Gillespie C, Hollis BW, Looker AC, et al. Hypovitaminosis D prevalence and determinants among African American and white women of reproductive age: Third National Health and Nutrition Examination Survey, 1988-1994. Am J Clin Nutr 2002;76: 187-192.
7. Chesney RW, Rosen JF, Hanstra AJ, Smith C, Mahaffey K, DeLuca HF. Absence of seasonal variation in serum concentrations of 1,25-dihydroxyvitamin D despite a rise in 25-hydroxyvitamin D in summer. J Clin Endocrin Metab 1981;53:139-143.
8. Schwartz GG, Whitlatch LW, Chen C, Lokeshwar BL, Holick MF. Human prostate cells synthesize 1,25 dihydroxyvitamin D3 from 25-hydroxyvitamin D3. Cancer Epidemiol Biomark Prev 1998;7:391-395.
9. Schwartz GG, Eads D, Rao A, Cramer SD, Willingham MC, Chen TC, et al. Pancreatic cancer cells express 25-hydroxyvitamin D-1-α-hydroxylase and their proliferation is inhibited by the prohormone, 25-hydroxyvitamin D3. Carcinogenesis 2004;25: 1015-1020.
10. Konety BR, Schwartz GG, Acierno JS, Becich MJ, Getzenberg RH. The role of vitamin D in normal prostatic growth and development. Cell Growth Differentiation 1996;7:1563-1570.
11. John E, Koo J, Schwartz GG. Sun exposure and prostate cancer risk: evidence for a protective effect of early life exposure. Cancer Epidemiol. Biomark Prev, 2007;16:1283-1286.
12. Schwartz GG. Vitamin D and the epidemiology of prostate cancer. Seminars in Dialysis 2005;18:276-289.
13. Whitlatch LW, Young MV, Schwartz GG, Flanagan JN, Burnstein KL, Lokeshwar BL, et al. 25-Hydroxyvitamin D-1-alpha-hydroxylase is diminished in human prostate cancer cells and is enhanced by gene transfer. J Steroid Biochem Mol Biol 2002;81: 135-140.
14. Schwartz GG, Hall MC, Stindt D, Patton S, Lovato J, Torti TM. A phase I/II trial of 19-nor-1-α -dihydroxyvitamin D2 (Paricalcitol) in advanced androgen-insentive prostate cancer. Clin Cancer Res 2005;11:8680-8685.
15. Beer TM, Ryan CW, Venner PM, Petrylak DP, Chatta GX, Ruetter JD, et al. Double-blinded randomized study of high-dose calcitriol plus docetaxel in androgen-independent prostate cancer: a report from the ASCENT investigators. J Clin Oncol 2007;25: 669-674.