Setting the Stage: What Are the Critical Factors for Evaluating Sunlight and Dietary Vitamin D and Cancer Risk?

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Compelling evidence from epidemiologic, laboratory, and clinical trials indicates that vitamin D metabolites decrease the risk of several common cancers[1]. In order to set the stage for a discussion of future needs, we first need to *clear* the stage of encumbrances that have retarded progress. Key areas that have been the source of confusion include the difference between vitamins and hormones; the meaning of vitamin "deficiency"; differences between disease prevention and therapy with vitamin D metabolites; and the timing of vitamin D exposure with respect to disease risk.

For example, because cholecalciferol (vitamin D_3) is synthesized from the effects of sunlight on the skin, "vitamin" D_3 is not a vitamin. Moreover, the concept of "deficiency" is meaningful only with respect to some endpoint; the amount of vitamin D sufficient to maintain a normal skeleton may be insufficient to maintain the differentiated phenotype of breast or prostate cells.

We have shown that, like the kidney, normal prostate cells synthesize the vitamin D hormone, $1,25(OH)_2D$, from the prohormone, 25-Hydroxyvitamin D, whose serum levels are principally determined by casual exposure to sunlight. This is the presumed mechanism whereby sunlight exposure reduces prostate cancer risk. Cancerous prostatic cells have lost much of this ability. Thus vitamin D (e.g., cholecalciferol) may prevent prostate cancer; it is unlikely to treat advanced disease. Although cancerous prostate cells cannot synthesize $1,25(OH)_2D$, they possess receptors for it (VDR), and thus are candidates for therapy with $1,25(OH)_2D$ and/or its analogs[2]. Thus, prevention and therapy are different tasks and require different forms of vitamin D.

Although exposure to vitamin D may reduce the risk of cancer, precisely when during the life cycle vitamin D is important is unclear. The timing and the mechanism of this exposure may differ for different cancers. Thus, if vitamin D metabolites act to maintain the differentiated phenotype of target cells, a protective effect of vitamin D may occur relatively early in life. This prodifferentiating effect on normal tissue is different from the (more widely-studied) antiproliferative effects of vitamin D metabolites on cancerous cells. These different mechanisms require different types of exposure assessment in epidemiologic studies. For example, if sunlight/vitamin D metabolites exert prodifferentiating effects early in life, serologic studies of vitamin D metabolites among adults will be insensitive to detect these.

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[1] Schwartz GG, Skinner HG. Vitamin D and cancer: New insights. Current Opinion in Clinical Nutrition and Metabolic Care, 2007, 10: 6–11.

[2] Schwartz GG. Vitamin D and the epidemiology of prostate cancer. Seminars in Dialysis 2005, 18:276–289.