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## REFERENCE

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## Dairy products, calcium, and prostate cancer risk in the Physicians' Health Study

Dear Sir:

The recent paper in the Journal by Chan et al (1) may affect decisions a person may make to optimize nutrient intakes and to determine which clinical strategies to use to treat prostate cancer. They report that high intakes of dairy products or calcium increase the risk of prostate cancer and propose that anything that lowers circulating 1,25-dihydroxyvitamin D<sub>3</sub> [1,25(OH)<sub>2</sub>D<sub>3</sub>] concentrations—particularly the consumption of calcium or dairy products—could increase the risk of prostate cancer.

They state in the discussion section, "epidemiologic studies suggest that 1,25(OH)<sub>2</sub>D<sub>3</sub> may protect against prostate cancer" (1). However, most of the epidemiologic studies they cite (2-5) do not support this statement. No study, except that by Corder et al (6), shows a relation between circulating 1,25(OH)<sub>2</sub>D<sub>3</sub> concentrations and prostate cancer. Corder et al reported that the mean prediagnostic 1,25(OH)<sub>2</sub>D<sub>3</sub> concentration was significantly lower in patients with prostate cancer than in a control cohort by 4.6 pmol/L (1.83 pg/mL). This difference in 1,25(OH)<sub>2</sub>D<sub>3</sub> concentrations is poor evidence of a role for 1,25(OH)<sub>2</sub>D<sub>3</sub> in prostate cancer given that normal concentrations typically range from 40 to 140 pmol/L.

The epidemiologic evidence relating prostate cancer to vitamin D or 25-hydroxyvitamin D<sub>3</sub> concentrations [25(OH)D<sub>3</sub>] is based on ecologic studies that show an inverse correlation between ultraviolet light exposure and mortality rates from prostate cancer in the United States (5). Ultraviolet light has profound effects on circulating concentrations of 25(OH)D<sub>3</sub> but practically no effect on circulating 1,25(OH)<sub>2</sub>D<sub>3</sub>, the concentration of which is stimulated by low calcium intakes.

Chan et al report that the mean 1,25(OH)<sub>2</sub>D<sub>3</sub> concentration was significantly different only between the lowest and highest quartiles of calcium intake. However, the full increase in the relative risk of prostate cancer was already present, both in the third quartile of dairy calcium intake and in the third quintile of dairy product intake (Table 2 in reference 1). In other words, anything beyond just one glass of milk daily seems to increase the risk of prostate cancer, yet the risk is not correlated with 1,25(OH)<sub>2</sub>D<sub>3</sub> concentrations. We are left to wonder whether the beneficial effect of calcium in lowering blood pressure, preventing osteoporosis, and even preventing the progression of existing prostate cancer (7) needs to be balanced against the risk of developing prostate cancer.

The mechanism explaining why ultraviolet light might prevent prostate cancer was elucidated by Schwartz et al (8) and

others (9, 10), who showed that prostate cells synthesize their own 1,25(OH)<sub>2</sub>D<sub>3</sub> from 25(OH)D<sub>3</sub>. More importantly, the desirable in vitro effects of 1,25(OH)<sub>2</sub>D<sub>3</sub> on prostate cells are achievable with 25(OH)D<sub>3</sub> supplementation alone (9).

In groups of men likely to have higher circulating 25(OH)D<sub>3</sub> concentrations than the subjects in the study by Chen et al, dietary calcium and circulating 1,25(OH)<sub>2</sub>D<sub>3</sub> concentrations do not correlate with the prevalence of prostate cancer. Nomura et al (11) and Giovannucci (12) attributed the lack of a relation between 1,25(OH)<sub>2</sub>D<sub>3</sub> concentrations and prostate cancer in men in Hawaii to their higher 25(OH)D<sub>3</sub> concentrations. Likewise, high 25(OH)D<sub>3</sub> concentrations might also explain the lack of an effect of calcium on prostate cancer risk in men in Milan, Italy (13).

When circulating 25(OH)D<sub>3</sub> is high enough, the prostate can generate the amount of 1,25(OH)<sub>2</sub>D<sub>3</sub> needed to regulate proliferation and differentiation of its cells. In contrast, when circulating 25(OH)D<sub>3</sub> is so low that the prostate cannot produce enough of its own 1,25(OH)<sub>2</sub>D<sub>3</sub>, a higher circulating 1,25(OH)<sub>2</sub>D<sub>3</sub> concentration resulting from a severe calcium intake restriction, as shown by Chan et al (1), appears relevant to the biology of the prostate gland.

The health implication becomes clear when the epidemiologic studies comparable with those of Chan et al are considered as a group (1, 11, 13). If 1,25(OH)<sub>2</sub>D<sub>3</sub> is a locally manufactured paracrine hormone that regulates prostate cells (8-10), then we need to ensure that the 25(OH)D<sub>3</sub> concentration is optimal for this purpose. Unfortunately, the seasonal cycle of 25(OH)D<sub>3</sub> concentrations makes it difficult to test this implication in the Physicians' Health Study cohort, unless the concentrations are adjusted according to season.

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## Reply to R Vieth

Dear Sir:

In response to Vieth, we state in our article (1) that “in vitro, in vivo, and epidemiologic studies suggest that 1,25(OH)<sub>2</sub>D<sub>3</sub> may protect against prostate cancer” and list the references for both experimental and epidemiologic studies. We included references for all the epidemiologic studies (null and statistically significant); some of the nested case-control studies suggest trends in association that were not statistically significant. In 2 paragraphs we reviewed the strength of the experimental literature in contrast with the epidemiologic studies, acknowledging clearly that only 1 of the 4 epidemiologic studies observed a significant inverse association between serum 1,25-dihydroxyvitamin D<sub>3</sub> [1,25(OH)<sub>2</sub>D<sub>3</sub>] concentrations and the risk of prostate cancer. We concluded that the “results of studies in humans in which a single serum measure of 1,25(OH)<sub>2</sub>D<sub>3</sub> was used are conflicting.” The evidence for this hypothesis is not solely from ecologic studies, as Vieth indicates.

Vieth asserts that a statistically significant difference of 4.6 pmol/L (1.83 pg/mL) in the mean concentration of 1,25(OH)<sub>2</sub>D<sub>3</sub> between the experimental and control groups in the study by Corder et al (2) is physiologically and etiologically unimportant. To the contrary, small differences in population means can translate to large relative

risks when quantiles of the population distribution of any given exposure are compared. Indeed, in the study by Corder et al, men in the top 25th percentile of 1,25(OH)<sub>2</sub>D<sub>3</sub> concentrations had up to an 85% lower risk of developing prostate cancer than did men in the lowest 25th percentile; the results were statistically significant among men who were concurrently in the lowest 25th percentile of the 25-hydroxyvitamin D distribution. A comparison of mean concentrations between the experimental and control groups, especially in hormone or biomarker concentrations that are etiologically important within clinically normal ranges, can mask biologically meaningful associations. For example, high cholesterol concentrations increase the risk of coronary artery disease, but a comparison of population means between experimental and control groups generally indicates only a 4% difference in total cholesterol. In contrast, a comparison of the extreme quintiles showed an 86% elevated risk of coronary artery disease (3).

Vieth also comments that our article does not address the potential need to balance the benefits of calcium intake for the prevention of osteoporosis and other diseases against the possible increase in the risk of prostate cancer. Obviously, this was beyond the scope of our paper. We believe it is premature to recommend any change in diet for prostate cancer prevention on the basis of these results.

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