

Editorial

Shedding New Light on the Etiology of Prostate Cancer?

Abraham Nomura¹ and Laurence N. Kolonel

Kuakini Medical Center [A. N.], and Cancer Research Center of Hawaii [A. N., L. N. K.], Honolulu, Hawaii 96817

Prostate cancer has the highest incidence rate of any cancer among men in the United States (1). It is estimated for 1993 that 165,000 new prostate cancer cases will be diagnosed in the country, representing 28% of all new cancer cases among men (2). Although its incidence is rising, little is known about the causes of this disease. Researchers suspect that genetic, hormonal, and dietary factors, among others, have a role in the development of prostate cancer (3).

Dietary studies of prostate cancer have focused attention mainly on fat (both saturated and unsaturated) and vitamin A. Most case-control studies of dietary fat have reported a positive association, whereas recent cohort studies have been unable to confirm these results (3). However, if dietary fat exerts its effect at a late stage in the development of prostate cancer, then case-control studies, in which diet histories are based on food consumption patterns relatively close to the time of diagnosis, could actually provide better measures of the relevant exposure than cohort studies, in which the diet information is more remote. The validity of this explanation for the discrepant results could be tested by comparing the findings for prostate cancer cases occurring at various time intervals in a prospective cohort.

Epidemiological investigations of dietary vitamin A or its precursors have also produced equivocal results (3). Dietary studies have reported both increases and decreases in risk of prostate cancer associated with this nutrient. Serum studies of vitamin A have produced inconsistent results (4–6) that may be related to the different sources of vitamin A or its precursors in the diet. Although a protective effect of vitamin D against prostate cancer has been hypothesized (7), no reports on this subject have appeared previously.

In this issue of *Cancer Epidemiology, Biomarkers and Prevention*, Corder *et al.* (8) describe the first such study. They found that low serum levels of the vitamin D metabolite, 1,25-D,² were associated with an increased risk of prostate cancer, but only in older men. The study participants were members of the Kaiser Permanente Medical Care Plan in Oakland and San Francisco, California. A nested case-control study design was used, in which stored prediagnostic serum from 181 prostate cancer cases and from 181 matched controls was tested. The authors concluded that, in men 57 years of age or older, 1,25-D was an important predictor of risk for palpable and anaplastic prostate tumors, but not for incidental tumors.

Based on these results, and the much higher incidence rate of prostate cancer among U.S. blacks than whites, one would expect blacks to have lower serum levels of 1,25-D than whites. However, in the study of Corder *et al.* (8), blacks have somewhat higher 1,25-D levels than whites. This observation merits further investigation if the overall findings of this study are confirmed.

Vitamin D is a major physiological regulator of bone and mineral metabolism (9). The biological activity of 1,25-D is 500–1000-fold higher than its precursor, 25-D. 1,25-D, together with parathyroid hormone and calcitonin, exerts action on the target tissues of calcium metabolism. They include bone, parathyroid glands, kidney, and intestine. In addition, receptor proteins of 1,25-D have been found in almost every tissue that has been examined. They include bone, parathyroid glands, small intestines, colon, skin, breast, uterus, ovary, testes, circulating lymphocytes, and monocytes. This raises the possibility that 1,25-D may be involved in the functioning of tissues not primarily associated with bone and mineral metabolism.

As pointed out by the authors, there are plausible reasons for suspecting that vitamin D may be protective against prostate cancer. They note that vitamin D receptors are present in normal prostate cells and that 1,25-D inhibits the proliferation of cells in established prostate cancer cell lines. On the other hand, they somewhat overstate the inverse correlation of prostate cancer mortality with exposure to UV light. For example, UV exposure levels in Hawaii are among the highest in the U.S. (10), yet prostate cancer incidence rates among whites in Hawaii are also among the highest in the U.S. (11). Further study of such outlier populations may help to refine (or refute) the vitamin D hypothesis of prostate cancer.

Inhibitory effects of 1,25-D have also been observed for human leukemia, colon cancer, breast cancer, malignant melanoma, and other solid tumor cell lines (9, 12). An earlier serum study found that subjects with a low 25-D level had an increased risk for colon cancer (13). A study of breast cancer found that patients with 1,25-D receptor tumors had a longer disease-free interval than patients with receptor-negative tumors (14). These reports indicate that other tumors besides prostate cancer may be affected by vitamin D metabolites.

More studies are needed. The finding of Corder *et al.* (8) of an inverse association of prostate cancer with 1,25-D and the suggestion of an interaction between 1,25-D and 25-D needs to be confirmed. In addition, the relation of vitamin D metabolites to other cancers, such as colon, breast, and possibly malignant melanoma should be explored.

In the meantime, Corder *et al.* (8) should be complimented on their provocative study. If their finding that vitamin D metabolites may affect prostate cancer risk is confirmed by others, an important advance in our understanding of the pathogenesis of prostate cancer will have been made.

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¹ To whom requests for reprints should be addressed.

² The abbreviations used are: 1,25-D, 1,25-dihydroxyvitamin D; 25-D, 25-hydroxyvitamin D.

References

1. Ries, L. A., Hankey, B. F., Edwards, B. K., eds. *Cancer Statistics Review 1973-1987*, Washington, D.C (NIH Publ. No. 90-2789). U.S. Government Printing Office, 1990.
2. American Cancer Society. *Cancer Facts and Figures: 1993*, p. 7. Atlanta, CA: ACS, 1993.
3. Nomura, A. M. Y., and Kolonel, L. N. Prostate cancer: a current perspective. *Epidemiol. Rev.*, 13: 200-227, 1991.
4. Reichman, M. E., Hayes, R. B., Ziegler, R. G., Schatzkin, A., Taylor, P. R., Kahle, L. L., and Fraumeni, J. F., Jr. Serum vitamin A and subsequent development of prostate cancer in the First National Health and Nutrition Examination Survey Epidemiologic Follow-up Study. *Cancer Res.*, 50: 2311-2315, 1990.
5. Coates, R. J., Weiss, N. S., Daling, J. R., Morris, J. S., and Labbe, R. F. Serum levels of selenium and retinol and the subsequent risk of cancer. *Am. J. Epidemiol.*, 128: 515-523, 1988.
6. Hsing, A. W., Comstock, G. W., Abbey, H., and Polk, F. Serologic precursors of cancer. Retinol, carotenoids, and tocopherol and risk of prostate cancer. *J. Natl. Cancer Inst.*, 82: 941-946, 1990.
7. Schwartz, G. G., and Hulka, B. S. Is vitamin D a risk factor for prostate cancer? (Hypothesis) *Anticancer Res.*, 10: 1307-1312, 1990.
8. Corder, E. H., Guess, H. A., Hulka, B. S., Friedman, G. D., Sadler, M., Vollmer, R. T., Lobaugh, B., Drezner, M. K., Vogelstein, J. H., and Orentreich, N. Vitamin D and prostate cancer: a prediagnostic study with stored sera. *Cancer Epidemiol., Biomarkers & Prev.*, 2: 467-472, 1993.
9. Reichel, H., Koeffler, H. P., and Norman, A. W. The role of vitamin D endocrine system in health and disease. *N. Engl. J. Med.*, 320: 980-991, 1989.
10. Scotto, J., Fears, T. R., and Gore, G. B. Measurements of Ultraviolet Radiation in the United States and Comparisons with Skin Cancer Data. DHEW Publ. No. (NIH) 76-1029, U.S. Dept. of Health, Education, and Welfare, Public Health Service, National Institutes of Health, November 1975.
11. Parke, D. M., Muir, C. S., Whelan, S. L., et al. *Cancer Incidence in Five Continents, Vol. VI*. IARC Scientific Pub. No. 120. Lyon, France: International Agency of Research on Cancer, 1992.
12. Frampton, R. J., Omond, S. A., and Eisman, J. A. Inhibition of human cancer cell growth by 1,25-dihydroxyvitamin D₃ metabolites. *Cancer Res.*, 43: 4443-4447, 1983.
13. Garland, C. F., Comstock, G. W., Garland, F. C., Helsing, K. J., Shaw, E. K., and Gorham, E. D. Serum 25-hydroxyvitamin D and colon cancer: eight-year prospective study. *Lancet*, 2: 1176-1178, 1989.
14. Colston, K. W., Berger, U., and Coombes, R. C. Possible role for vitamin D in controlling breast cancer cell proliferation. *Lancet*, 1: 188-191, 1989.