Agent Orange Exposure, Vietnam War Veterans, and the Risk of Prostate Cancer

K. Chamie, R. W. Devere White, B. Volpp, D. Lee, J. Ok and L. M. Ellison

Department of Urology, University of California, Davis, Sacramento, California

Cancer 2008; ***113:*** *2464–2470.*

Background: It has been demonstrated that Agent Orange exposure increases the risk of developing several soft tissue malignancies. Federally funded studies, now nearly a decade old, indicated that there was only a weak association between exposure and the subsequent development of prostate cancer. Because Vietnam War veterans are now entering their 60s, the authors reexamined this association by measuring the relative risk of prostate cancer among a cohort of men who were stratified as either exposed or unexposed to Agent Orange between the years 1962 and 1971 and who were followed during the interval between 1998 and 2006. Methods: All Vietnam War era veterans who receive their care in the Northern California Veteran Affairs Health System were stratified as either exposed (n = 6214) or unexposed (n = 6930) to Agent Orange. Strata-specific incidence rates of prostate cancer (International Classification of Diseases, 9th Revision code 185.0) were calculated. Differences in patient and disease characteristics (age, race, smoking history, family history, body mass index, finasteride exposure, prebiopsy prostate-specific antigen (PSA) level, clinical and pathologic stage, and Gleason score) were assessed with chi-square tests, t tests, a Cox proportional hazards model, and multivariate logistic regression. Results: Twice as many exposed men were identified with prostate cancer (239 vs 124 unexposed men, respectively; odds ratio [OR], 2.19; 95% confidence interval [95% CI], 1.75–2.75). This increased risk also was observed in a Cox proportional hazards model from the time of exposure to diagnosis (hazards ratio [HR], 2.87; 95% CI, 2.31–3.57). The mean time from exposure to diagnosis was 407 months. Agent Orange-exposed men were diagnosed at a younger age (59.7 years; 95% CI, 58.9–60.5 years) compared with unexposed men (62.2 years; 95% CI, 60.8–63.6 years), had a 2-fold increase in the proportion of Gleason scores 8 through 10 (21.8%; 95% CI, 16.5%–27%) compared with unexposed men (10.5%; 95% CI, 5%–15.9%), and were more likely to have metastatic disease at presentation than men who were not exposed (13.4%; 95% CI, 9%–17.7%) than unexposed men (4%; 95% CI, 0.5%–7.5%). In univariate analysis, distribution by race, smoking history, body mass index, finasteride exposure, clinical stage, and mean prebiopsy PSA were not statistically different. In a multivariate logistic regression model, Agent Orange was the most important predictor not only of developing prostate cancer but also of high-grade and metastatic disease on presentation. Conclusions: Individuals who were exposed to Agent Orange had an increased incidence of prostate cancer; developed the disease at a younger age, and had a more aggressive variant than their unexposed counterparts. Consideration should be made to classify this group of individuals as 'high risk,' just like men of African-American heritage and men with a family history of prostate cancer.

Editorial Comment: This is the most mature study thus far that examines the relationship between exposure of Vietnam War veterans to Agent Orange and the risk of prostate cancer. The authors found that these men have a 2-fold increased risk of being diagnosed with prostate cancer, were younger at the time of diagnosis, had a 2-fold increased risk of Gleason 8 to 10 disease and were more likely to have metastatic disease at presentation

0022-5347/09/1811-0119/0
THE JOURNAL OF UROLOGY®

Vol. 181, 119-127, January 2009
Printed in U.S.A.
DOI:10.1016/j.juro.2008.09.084

than men who were not exposed. It is accompanied by an excellent editorial that examines a number of potential biases in this study which suggest that the differences between the exposed and unexposed patients reported in the current study may not be as great as reported.[1] However, despite these biases, they feel that the relationship between prostate cancer and Agent Orange in this study is quite impressive. They go on to say, "at a time when many Vietnam veterans with possible exposure to Agent Orange are reaching the age at which they are at increased risk for prostate cancer, primary care physicians and urologists should recognize this interaction and consider more aggressive screening."

Patrick C. Walsh, M.D.

1. Shah SR and Terris MK: Editorial comment on: Agent Orange exposure, Vietnam War veterans, and the risk of prostate cancer. Cancer 2008; **113:** 2382–2384.

Serum Vitamin D Concentration and Prostate Cancer Risk: A Nested Case-Control Study

J. Ahn, U. Peters, D. Albanes, M. P. Purdue, C. C. Abnet, N. Chatterjee, R. L. Horst, B. W. Hollis, W. Y. Huang, J. M. Shikany and R. B. Hayes; Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial Project Team

Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Bethesda, Maryland

J Natl Cancer Inst 2008; ***100:*** *796–804.*

Background: Epidemiological studies have yielded inconsistent associations between vitamin D status and prostate cancer risk, and few studies have evaluated whether the associations vary by disease aggressiveness. We investigated the association between vitamin D status, as determined by serum 25-hydroxyvitamin D [25(OH)D] level, and risk of prostate cancer in a case-control study nested within the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial. Methods: The study included 749 case patients with incident prostate cancer who were diagnosed 1–8 years after blood draw and 781 control subjects who were frequency matched by age at cohort entry, time since initial screening, and calendar year of cohort entry. All study participants were selected from the trial screening arm (which includes annual standardized prostate cancer screening). Conditional logistic regression was used to estimate adjusted odds ratios (ORs) with 95% confidence intervals (CIs) by quintile of season-standardized serum 25(OH)D concentration. Statistical tests were two-sided. Results: No statistically significant trend in overall prostate cancer risk was observed with increasing season-standardized serum 25(OH)D level. However, serum 25(OH)D concentrations greater than the lowest quintile (Q1) were associated with increased risk of aggressive (Gleason sum > or = 7 or clinical stage III or IV) disease (in a model adjusting for matching factors, study center, and history of diabetes, ORs for Q2 vs Q1 = 1.20, 95% CI = 0.80 to 1.81, for Q3 vs Q1 =1.96, 95% CI = 1.34 to 2.87, for Q4 vs Q1 = 1.61, 95% CI = 1.09 to 2.38, and for Q5 vs Q1 = 1.37, 95% CI = 0.92 to 2.05; P(trend) = .05). The rates of aggressive prostate cancer for increasing quintiles of serum 25(OH)D were 406, 479, 780, 633, and 544 per 100 000 person-years. In exploratory analyses, these associations with aggressive disease were consistent across subgroups defined by age, family history of prostate cancer, diabetes, body mass index, vigorous physical activity, calcium intake, study center, season of blood collection, and assay batch. Conclusion: The findings of this large prospective study do not support the hypothesis that vitamin D is associated with decreased risk of prostate cancer; indeed, higher circulating 25(OH)D concentrations may be associated with increased risk of aggressive disease.

Editorial Comment: I have been impressed by the accumulating evidence for a relationship between ultraviolet light exposure, vitamin D and prostate cancer risk. When I read this conclusion I was surprised at the strength of it. However, after reading the article I think it would have been more accurate to say that there was no relationship between prostate cancer risk and vitamin D levels measured 1 to 8 years prior to the diagnosis. To check on this, I contacted Gary Schwartz, associate professor of cancer biology and