

## ASSOCIATION BETWEEN DISEASES OF THE PROSTATE AND TCDD IN US AIR FORCE VETERANS OF THE VIETNAM WAR

Marian Pavuk<sup>1</sup>, Arnold Schecter<sup>1</sup>, Joel Michalek<sup>2</sup>

<sup>1</sup> University of Texas Health Science Center, School of Public Health, Dallas Regional Campus  
5323 Harry Hines Blvd., V8.112, Dallas, TX 75390, USA

<sup>2</sup> Air Force Research Laboratory, Brooks City-Base, 2655 Flight Nurse, San Antonio, TX 78235,  
USA

### Introduction

The Air Force Health Study (AFHS) is a 20-year prospective study examining health, mortality and reproductive outcomes of the operation Ranch Hand veterans responsible for handling and aerial spraying of herbicides, including Agent Orange contaminated with 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), in Vietnam from 1962 to 1971<sup>1-2</sup>. In this study we examine potential health effects related to diseases of the prostate including prostate cancer, benign prostatic hyperplasia and inflammatory diseases of the prostate.

Exposure to TCDD was positively associated with increased incidence or prevalence of prostate cancer in several studies of occupationally exposed workers<sup>2-5</sup> but some other studies have found no association<sup>6-7</sup>. Results of some animal studies suggest that TCDD may also be involved in hyperplasia of prostatic gland manifested primarily as increased volume and tenderness of the gland<sup>8-10</sup>.

### Materials and Methods

The Air Force Health Study (AFHS) compares the health status and the cumulative morbidity and mortality experience of Ranch Hand Vietnam veterans with a comparison group of other Air Force veterans who served in Southeast Asia during the same time period but were not involved in spraying herbicides. Comparison veterans are matched to Ranch Hand veterans on age, race, and military occupation. All Ranch Hand and Comparison veterans are male. Details of the study design and methods were published elsewhere<sup>1</sup>.

Comprehensive medical examinations of veterans were conducted in 1982, 1985, 1987, 1992, 1997, and 2002. Blood for TCDD measurements for most of the veterans was collected in 1987. Participation was voluntary and written informed consent was obtained at the examination site after a complete description of the study and a full explanation of all procedures. Diseases of the prostate were identified using International Classification of Diseases, ninth revision (ICD-9). Codes 600.1, 600.2, 600.3, and 600.9 for hyperplasia of the prostate, codes 601.0, 601.1, 601.2 and 601.9 for inflammatory diseases of the prostate, codes 602.0, 602.1, 602.2, 602.8 and 602.9 for other prostate disorders, and C619 for prostate cancer were identified in medical records of participating veterans and used in this analysis. Data was available for 2438 veterans (1009 Ranch Hand and 1429 Comparison) who participated in at least one of the first five physical examinations and had a measurement of serum TCDD.

We employed logistic regression models to contrast cohorts with regard to prostate cancer incidence, and the first diagnosed incidence of non-malignant diseases of the prostate. We assigned each veteran to one of four exposure categories: Comparison, Background, Low, and High, based on his cohort (Ranch Hand, Comparison), dioxin concentration, and half-life extrapolated initial dioxin concentration. Ranch Hand veterans with dioxin exceeding 10 ppt had their initial dioxin at the end of service in Vietnam estimated using a first-order kinetics model with a constant half-life of 7.6 years. Ranch Hand veterans with a dioxin level exceeding 10 ppt and an initial dioxin lower than or equal to 118.5 ppt (the median dioxin in veterans with dioxin level > 10 ppt), were assigned to the Low category and those with an initial dioxin higher than 118.5 ppt were assigned to the High category. We analyzed by category of time spent in Southeast Asia (SEA), with a cut point of 24 months, and category of the percentage of time spent in Vietnam (Ranch Hand 100% time in Vietnam, Comparisons 0% time in Vietnam). Statistical models were adjusted for age at tour of duty in SEA, primary military occupation, and race. Veterans with cancer or other diseases of the prostate during or prior to their service in SEA were excluded from all analyses.

### Results and Discussion

Personal and demographic characteristics of participants are presented in Table 1. TCDD levels in the Background Ranch Hand category veterans were comparable to the Comparison veterans [5.7 vs. 4.0 parts per trillion (ppt)], but the median values were three [15.1 vs. 4.0 (ppt)] and ten times [47.6 vs. 4.0 (ppt)] higher in the Low and High Ranch Hand categories.

We found a significantly increased risk of prostate cancer in white veterans who spent at most 2 years in SEA in the High exposure category (OR=6.74, 95% CI 1.76-25.8) (Table 2). The odds ratio was also increased for the Ranch Hand veterans in the High category who spent 100% of their SEA service in Vietnam relative to Comparison veterans who spent 0% of their SEA service in Vietnam and served elsewhere in SEA (OR=5.37, 95% CI 1.05-27.5). No increase in odds ratios for Ranch Hand veterans was observed if the veterans spent less than 100% of their time in Vietnam.

At this point, only the results of a preliminary analysis are available for non-malignant diseases of the prostate. These results suggest that the Ranch Hand veterans do not seem to have increased risk of first diagnosed non-malignant diseases of prostate. In general, inverse, statistically non-significant associations were observed in the High Ranch Hand category. For benign prostatic hyperplasia, the odds ratio was 1.02 (95% CI 0.74-1.42), for inflammatory diseases of the prostate it was 0.70 (95% CI 0.31-1.58), and for other diseases of the prostate it was 0.46 (0.10-2.04). Limiting analyses to veterans who spent at most 2 years in SEA or 100% of their duty in Vietnam (Ranch Hand) did not materially changed the observed associations. However, further analyses are needed before more definitive conclusions can be drawn.

The strengths of this study include a very detailed 20-year follow-up of veterans who participated in study, repeated verifications of their health status and medical records, and measured blood TCDD as a surrogate of individual exposure. Inferences that could be made from these data are limited by relatively small number of prostate cancer cases and low levels of serum TCDD in about half of Ranch Hand veterans. Elevated TCDD levels in the High category of Ranch Hand veterans were on average about 4 times lower than in some occupationally exposed workers<sup>3</sup>.

Alterations in incidence of prostate cancer in this still relatively young cohort of veterans is an important finding deserving further evaluation. These results are in support of previous finding in a study of Australian veterans that found an increase in risk in relation to national rates<sup>11</sup>. To date, it appears that no adverse associations with other diseases of the prostate were identified in this cohort.

#### **Acknowledgements**

This study was funded by the US Air Force. We thank all the veterans for their participation in this study.

#### **References**

1. Michalek JE, Wolfe WH, Miner JC. (1990) Health status of Air Force veterans occupationally exposed to herbicides in Vietnam, II. Mortality. *JAMA* 264(14):1832-1836.
2. Michalek JE, Ketchum NS, Akhtar FZ. (1998) Postservice mortality of US Air Force veterans occupationally exposed to herbicides in Vietnam: 15-Year follow-up. *Am J Epidemiol.* 148(8):786-792.
3. Steenland K, Piacitelli L, Deddens J, Fingerhut M, Chang LI. (1999) Cancer, heart disease, and diabetes in workers exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin. *J Natl Cancer Inst.* 91(9):779-786.
4. Bertazzi PA, Consonni D, Bachetti S, Rubagotti M, Baccarelli A, Zocchetti C, Pesatori AC. (2001) Health effects of dioxin exposure: a 20-year mortality study. *Am J Epidemiol.* 153(11):1031-44.
5. Fleming LE, Bean JA, Rudolph M, Hamilton K. (1999) Mortality in a cohort of licensed pesticide applicators in Florida. *Occup Environ Med.* 56(1):14-21.
6. Sharma-Wagner S, Chokkalingam AP, Malker HS, Stone BJ, McLaughlin JK, Hsing AW. (2000). Occupation and prostate cancer risk in Sweden. *J Occup Environ Med.* 42(5):517-525
7. Hertzman C, Teschke K, Ostry A, Hershler R, Dimich-Ward H, Kelly S, Spinelli JJ, Gallagher RP, McBride M, Marion SA. (1997) Mortality and cancer incidence among sawmill workers exposed to chlorophenolate wood preservatives. *Am J Public Health.* 87(1):71-79.
8. Ko K, Theobald HM, Peterson RE. (2002) In Utero and Lactational Exposure to 2,3,7,8-Tetrachlorodibenzo-p-dioxin in the C57BL/6J Mouse Prostate: Lobe-Specific Effects on Branching Morphogenesis. *Toxicol Sci.* 70(2):227-237.
9. Timms BG, Peterson RE, vom Saal FS. (2002) 2,3,7,8-tetrachlorodibenzo-p-dioxin interacts with endogenous estradiol to disrupt prostate gland morphogenesis in male rat fetuses. *Toxicol Sci.* 67(2):264-274.
10. Theobald HM, Roman BL, Lin TM, Ohtani S, Chen SW, Peterson RE. (2000) 2,3,7,8-tetrachlorodibenzo-p-dioxin inhibits luminal cell differentiation and androgen responsiveness of the ventral prostate without inhibiting prostatic 5 $\alpha$ -dihydrotestosterone formation or testicular androgen production in rat offspring. *Toxicol Sci.* 58(2):324-238.
11. Institute of Medicine. (2001) Veterans and Agent Orange. Update 2000. Washington DC, National Academy Press.

**Table 1.** Demographic characteristics of US Air Force veterans by TCDD category

|                                     | Comparison | Ranch Hand |             |               |
|-------------------------------------|------------|------------|-------------|---------------|
|                                     |            | Background | Low         | High          |
| Number                              | 1429       | 442        | 284         | 283           |
| Mean TCDD (SD) ppt                  | 4.4 (2.8)  | 5.8 (2.3)  | 16.1 (4.5)  | 70.2 (67.1)   |
| Median TCDD                         | 4.0        | 5.7        | 15.1        | 47.6          |
| Range                               | 0.4-54.8   | 0.6-10.0   | 10.0-29.2   | 18.0-617.8    |
| Extrapolated Mean TCDD <sup>a</sup> |            |            | 55.0 (18.0) | 302.5 (327.3) |
| Extrapolated Median TCDD            |            |            | 51.7        | 194.7         |
| Range                               |            |            | 27.2-93.8   | 94-3290.2     |
| Age at tour (SD)                    | 29.9 (7.3) | 30.6 (7.0) | 31.2 (7.3)  | 26.8 (6.8)    |
| BMI at tour (SD) kg/m <sup>2</sup>  | 24.9 (3.0) | 24.0 (2.7) | 25.3 (3.1)  | 25.2 (3.1)    |
| Black Number (%)                    | 92 (6.4)   | 23 (5.2)   | 23 (8.1)    | 14 (4.9)      |
| Military occupation                 |            |            |             |               |
| Officer                             | 542 (38)   | 266 (60)   | 106 (37)    | 8 (3)         |
| Enlisted flyer                      | 225 (16)   | 55 (12)    | 59 (21)     | 59 (21)       |
| Enlisted ground crew                | 662 (46)   | 121 (27)   | 119 (42)    | 216 (76)      |

<sup>a</sup> Half-life extrapolated at the end of the tour of duty in Vietnam.

**Table 2.** Odds ratios for prostate cancer by dioxin category and time spent in South East Asia in white US Air Force veterans.

|                                      | Comparison | Background | Low       | High             |
|--------------------------------------|------------|------------|-----------|------------------|
| At most 2 years in SEA               | N=580      | N=287      | N=151     | N=174            |
| Number (%)                           | 7 (1.21)   | 10 (3.48)  | 6 (3.97)  | 5 (2.87)         |
| Odds Ratio <sup>a</sup>              | 1.00       | 2.28       | 2.54      | <b>6.74</b>      |
| 95% CI                               | Ref.       | 0.83-6.23  | 0.82-7.87 | <b>1.76-25.8</b> |
| RH 100% in Vietnam,<br>Comparison 0% | N=291      | N=252      | N=132     | N=165            |
| Number (%)                           | 3 (1.03)   | 9 (3.57)   | 4 (3.03)  | 4 (2.42)         |
| Odds Ratio <sup>a</sup>              | 1.00       | 2.66       | 2.56      | <b>5.37</b>      |
| 95% CI                               | Ref.       | 0.56-12.6  | 0.48-13.7 | <b>1.05-27.5</b> |

<sup>a</sup> All analyses adjusted for age at tour of duty in SEA and military occupation.