

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

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See related editorial on pages 000-000, this issue.

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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, pre-biopsy 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. *Cancer* 2008;113(6 suppl):000-000. © 2008 American Cancer Society.

KEYWORDS: neoplasms, prostate, dioxins, Vietnam veterans, Agent Orange.

Nearly 10% of former South Vietnam was sprayed with phenoxy-herbicides as part of the United States campaign in Vietnam. Approximately 19 million gallons of Agent Orange were sprayed beginning in 1962, spraying intensified in 1967, and it was continued until 1971. Phenoxy-herbicides commonly were contaminated by 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), one of the most toxic and oncogenic human-made chemicals.^{1,2}

The effect of Agent Orange on soft tissue sarcomas was reported initially in 1977.³ In 1991, The Agent Orange Act was enacted. This legislation directed the Secretary of Veteran Affairs (VA) to request the National Academy of Sciences to review and evaluate all information regarding the health effects of exposure to Agent Orange and other herbicides that were used in the Vietnam War. Although there is sufficient evidence linking soft tissue sarcomas, Hodgkin disease, and non-Hodgkin lymphoma with Agent Orange exposure,⁴ evidence of the risk of subsequent prostate cancer has been much less robust.⁵⁻¹⁰ Operation Ranch Hands, a longitudinal study that was conducted on Air Force veterans, identified no increased incidence of prostate cancer compared with a similar cohort of veterans. However, that study did observe an increased risk compared with the standard US population of white men.^{10,11} The primary limitations of the prior studies were related to small sample size and young cohort age. The convergence of an appropriately aged cohort of men and the evolution of the VA's clinically enriched electronic medical records now allow for an accurate reassessment of this potential exposure-risk association. With that in mind, we sought to determine the incidence of prostate cancer in the entire Northern California VA Health System.

MATERIALS AND METHODS

After we obtained Institutional Review Board approval, we identified all Vietnam era veterans registered within the Northern California VA Health System. Then, this cohort was stratified as either exposed ($n = 6214$) or unexposed ($n = 6930$) to Agent Orange. Veterans were excluded if they were stationed outside of the Vietnam theater during their period of active duty. If a veteran reported exposure to Agent Orange on the initial application for medical benefits and was stationed in known areas that were sprayed with Agent Orange during 1962 through 1971, then a veteran was classified as being exposed. Seven patients initially claimed no exposure to Agent Orange and, after they developed prostate cancer, changed their testimony and claimed that they were

exposed. Although this is not a VA requirement, these 7 patients were excluded from our analysis. Thirty-eight patients filed an initial application for medical benefits after a diagnosis of prostate cancer, and these patients were kept in the study.

In its 1994 report on Agent Orange, the National Academy of Sciences concluded that individual TCDD levels in Vietnam veterans are not meaningful because of background exposures to TCDD in all Americans, poorly understood variations in TCDD metabolism, relatively large measurement errors, and exposure to herbicides that did not contain TCDD. For screening purposes, the VA makes a presumption of Agent Orange exposure for Vietnam veterans. Those who report exposure are offered an opportunity to undergo an Agent Orange meeting at which a detailed exposure history is established. During the Agent Orange meeting, patients undergo a full history and physical examination and are screened for sterility, birth defects in their offspring (such as spina bifida), non-Hodgkin lymphoma, soft tissue sarcoma, peripheral neuropathy, Hodgkin disease, porphyrinuria cutanea tarda, multiple myeloma, respiratory cancers, prostate cancer, diabetes, and gum disease. Most patients who attend an Agent Orange meeting undergo prostate-specific antigen (PSA) screening and have a digital rectal examination.

Strata-specific annual incidence rates of prostate cancer (International Classification of Diseases, 9th Revision code 185.0) were calculated for the years 1998 through 2006. We chose the start date of 1998 because the VA introduced Computerized Patient Record System (CPRS), a comprehensive electronic medical record, in that year. Before that date, all records were kept in paper charts. Because data before 1988 are not searchable electronically, all patients with a diagnosis of prostate cancer before 1998 were excluded.

Differences in patient and disease characteristics (age, race, family history, smoking history, body mass index [BMI], finasteride use, prebiopsy PSA level, clinical and pathologic stage, and Gleason score) were assessed. Smoking history was graded on a scale of from 0 to 5 (0 = lifetime nonsmoker, 1 = quit >14 years ago, 2 = quit >7 years ago, 3 = quit >4 years ago, 4 = quit in the last year, and 5 = current smoker). Age, race and family history of prostate cancer were used because they are associated with increasing risk of incidence of prostate cancer,¹²⁻¹⁴ whereas the use of finasteride is associated with higher grade but decreased incidence of disease.¹⁵ The use of smoking history and BMI, although controversial,¹⁶⁻¹⁸ does serve as a good indicator for the cohort.

TABLE 1
Demographics of the Entire Cohort

Characteristic	% and Mean (95% CI)		P
	Agent Orange Exposure, n = 6214	No Exposure, n = 6930	
Age, y	60.8 (60.6-60.9)	61.4 (61.2-61.5)	<.001
Race, % AA	22.3 (21-23.7)	19 (18-20.1)	<.001
Smoking history, 0-5*	2.7 (2.6-2.7)	2.9 (2.8-3)	<.001
BMI, kg/m ²	29.8 (29.6-30)	29.2 (29.1-29.4)	<.001
Finasteride use, %	3.1 (2.7-3.5)	3.8 (3.4-4.2)	.027
Screening PSA, %	71.5 (70.4-72.6)	71.7 (70.6-72.7)	.85
PSA, ng/mL	3.1 (1.6-4.6)	1.8 (1.3-2.3)	.11
Abnormal PSA (>4 ng/mL), %	9.1 (8.3-9.9)	6.1 (5.4-6.7)	<.001
Urologic evaluation, %	84.3 (80.8-87.8)	83.1 (78.9-87.3)	.67
Biopsy, %	81.8 (77.8-85.8)	77.7 (72.5-82.9)	.22

CI indicates confidence interval; AA, African American; BMI, body mass index; PSA, prostate-specific antigen.

*Smoking history was graded on a scale from 0 to 5 as follows: 0, lifetime nonsmoker; 1, quit >14 years ago; 2, quit >7 years ago; 3, quit >4 years ago; 4, quit in the last year; and 5, current smoker.

Statistical analyses were performed with STATA statistical software, version 10.0 (StataCorp, College Station, Tex). Statistical methods included chi-square tests, 2-sample Kolmogorov-Smirnov tests (nonparametric statistical analysis for PSA), Student 2-tailed tests, Cox proportional hazards model, and multivariate logistic regression. To identify the subsequent influence of Agent Orange exposure on the incidence and grade of prostate cancer and the propensity to metastasize on presentation, potential confounding variables (age, race, BMI, smoking history, finasteride use, and preoperative PSA) were included in the first steps of the regression, and Agent Orange exposure was the last step. Odds ratios (ORs) were calculated with 95% confidence intervals (95% CIs).

RESULTS

The records of 13,144 men in the Northern California VA Health System were included in the final cohort. Table 1 lists patient demographics of the 6214 men who were exposed to Agent Orange and the 6930 men who were not exposed to Agent Orange. The cohort of exposed men was slightly younger (60.8 years vs 61.4 years; $P < .001$), heavier (mean BMI, 29.8 kg/m² vs 29.2 kg/m²; $P < .001$), had a higher proportion of African Americans (22.3% vs 19%; $P < .001$), were less likely to smoke (2.7 vs 2.9; $P < .001$), and were less likely to have been exposed to finasteride (3.1% vs 3.8%; $P = .027$). Both groups had similar baseline PSA values (3.1 ng/mL vs 1.8 ng/mL for the exposed and unexposed cohorts, respectively; $P = .11$), and PSA screening rates were

TABLE 2
Demographics of the Cohort Diagnosed With Prostate Cancer*

Characteristic	% and Mean (95% CI)		P
	Agent Orange Exposure, n = 239	No Exposure, n = 124	
Age, y	59.7 (58.9-60.5)	62.2 [60.8-63.6]	.002
Race, % AA	33.9 (27.8-40)	29 (20.9-37.1)	.46
Family history, % positive	8.8 (5.2-12.4)	16.1 (9.6-22.7)	.05
Smoking history, 0-5*	1.7 (1.4-1.9)	1.6 (1.3-1.9)	.51
Finasteride use, %	2.6 (0.8-5)	3.4 (0.1-6.4)	.73
BMI, kg/m ²	29.6 (28.9-30.4)	28.8 (27.9-29.6)	.13
PSA, ng/mL	34.8 (5.7-63.6)	19.2 (0.1-38.3)	.38
Clinical T1c, %	69.9 (64-75.7)	64.5 (56-73.1)	.46

CI indicates confidence interval; AA, African American; BMI, body mass index; PSA, prostate-specific antigen.

*Smoking history was graded on a scale from 0 to 5 as follows: 0, lifetime nonsmoker; 1, quit >14 years ago; 2, quit >7 years ago; 3, quit >4 years ago; 4, quit in the last year; and 5, current smoker.

similar between the exposed and unexposed cohorts (71.5% vs 71.7%, respectively; $P = .85$). Of the men who received a screening PSA, 9.1% of those who were exposed and 6.1% of those who were not exposed had a PSA level >4 ng/mL ($P < .001$). The percentage of patients who were evaluated by a urologist for elevated PSA was similar (84.3% exposed vs 83.1% unexposed; $P = .65$). Of the men who were evaluated, 81.8% of the exposed group and 77.7% of the unexposed group underwent a transrectal ultrasound guided biopsy of the prostate ($P = .22$). Patients who were exposed to Agent Orange were twice as likely to develop prostate cancer as those who were unexposed (239 men vs 124 men; OR, 2.19; 95% CI, 1.75-2.75; $P < .001$). This increased risk was also observed in a Cox proportional hazards model from the time of exposure to the time of diagnosis (hazards ratio [HR], 2.87; 95% CI, 2.31-3.57). The mean time from exposure to Agent Orange was 407 months.

Among the patients who were diagnosed with prostate cancer, those who had been exposed to Agent Orange were younger (59.7 years vs 62.2 years; $P = .002$), had higher mean Gleason scores (6.8 vs 6.5; $P = .007$), had a 2-fold increase in the proportion of high-grade disease (21.8% vs 10.5%; $P = .009$), and were more likely to present with metastasis (13.4% vs 4%; $P = .005$). The proportion of African Americans (33.9% vs 29%; $P = .46$), mean BMI (29.6 kg/m² vs 28.8 kg/m²; $P = .13$), smoking history (score, 1.7 vs 1.6; $P = .51$), finasteride exposure (2.6% vs 3.4%; $P = .73$), and clinical stage (T1c 69.9% vs 64.5%; $P = .46$) were similar for both groups. Among those with prostate cancer, the mean PSA was not statistically higher in the Agent Orange cohort (34.8 ng/mL vs

TABLE 3
Disease Parameters of the Cohort Diagnosed With Prostate Cancer

Variable	No. of Patients (%)		P
	Agent Orange Exposure, N = 239	No Exposure, N = 124	
Gleason score			
≤6	103 (43.3)	64 (54.8)	.15
7	74 (31.1)	47 (37.9)	.20
8-10	52 (21.8)	13 (10.5)	.009
Metastasis on presentation	32 (13.4)	5 (4)	.005

TABLE 4
Multivariate Analysis for Developing Prostate Cancer

Variable	OR	95% CI	P
Agent Orange exposure	4.83	3.42-6.81	<.001
Preoperative PSA	1.93	1.82-2.06	<.001
Age at diagnosis	1.06	1.03-1.09	<.001
BMI	1.02	0.99-1.05	.21
Race (AA vs other)	1.55	1.06-2.26	.02
Finasteride	0.43	0.20-0.89	.02
Smoking history (0-5)*	0.78	0.72-0.85	<.001

OR indicates odds ratio; CI, confidence interval; PSA, prostate-specific antigen; BMI, body mass index; AA, African American.

*Smoking history was graded on a scale from 0 to 5 as follows: 0, lifetime nonsmoker; 1, quit >14 years ago; 2, quit >7 years ago; 3, quit >4 years ago; 4, quit in the last year; and 5, current smoker.

19.2 ng/mL in the unexposed cohort; $P = .38$). This was confirmed by using nonparametric statistical analysis ($P = .49$). Excluding outlier patients with PSA levels >100 ng/mL, the difference becomes quite small (PSA, 10.3 ng/mL vs 9.6 ng/mL; $P = .51$). Unexpectedly, a family history of prostate cancer was more prevalent in the unexposed cohort (16.1% vs 8.8%; $P = .05$). For patient and disease parameters, see Tables 2 and 3.

Multivariate logistic regression was performed with control in a stepwise manner for Agent Orange exposure, race, smoking history, finasteride use, BMI, age at diagnosis, and preoperative PSA level (Table 4). Agent Orange exposure (OR, 4.83; 95% CI, 3.42-6.81), Preoperative PSA (OR, 1.93; 95% CI, 1.82-2.06), African-American race (OR, 1.55; 95% CI, 1.06-2.26), and age (OR, 1.06; 95% CI, 1.03-1.09) were associated independently with an increased risk of developing prostate cancer. Surprisingly, in addition to finasteride (OR, 0.42; 95% CI, 0.20-0.89), smoking (OR, 0.78; 95% CI, 0.72-0.85) was associated with a reduced risk of developing prostate cancer. With regard to grade of cancer, Agent Orange exposure was identified as a stable and significant, independent risk factor for developing high-grade prostate cancer (OR, 2.59; 95%

TABLE 5
Multivariate Analysis for Developing High-grade Prostate Cancer

Variable	OR	95% CI	P
Agent Orange exposure	2.59	1.30-5.13	.007
Preoperative PSA	1.57	1.18-2.08	.002
Age at diagnosis	1.02	0.97-1.06	.46
BMI	0.97	0.92-1.03	.34
Race (AA vs other)	1.09	0.60-1.97	.79
Family history	1.51	0.63-3.59	.36
Finasteride use	0.96	0.20-4.73	.96
Smoking history (0-5)*	0.98	0.83-1.15	.81

OR indicates odds ratio; CI, confidence interval; PSA, prostate-specific antigen; BMI, body mass index; AA, African American.

*Smoking history was graded on a scale from 0 to 5 as follows: 0, lifetime nonsmoker; 1, quit >14 years ago; 2, quit >7 years ago; 3, quit >4 years ago; 4, quit in the last year; and 5, current smoker.

TABLE 6
Multivariate Analysis for Metastatic Prostate Cancer at Presentation

Variable	OR	95% CI	P
Agent Orange exposure	4.32	1.34-13.96	.015
Preoperative PSA	1.06	1.03-1.10	<.001
Age at diagnosis	1.00	0.93-1.07	.96
BMI	0.89	0.80-0.98	.016
Race (AA vs other)	0.41	0.14-1.14	.09
Family history	1.81	0.53-6.20	.34
Finasteride use	1.10	0.13-9.62	.93
Smoking history (0-5)*	0.76	0.57-1.01	.06

OR indicates odds ratio; CI, confidence interval; PSA, prostate-specific antigen; BMI, body mass index; AA, African American.

*Smoking history was graded on a scale from 0 to 5 as follows: 0, lifetime nonsmoker; 1, quit >14 years ago; 2, quit >7 years ago; 3, quit >4 years ago; 4, quit in the last year; and 5, current smoker.

CI, 1.30-5.13; $P = .007$) (Table 5). Similarly, Agent Orange exposure conferred a substantial increased risk of metastatic disease (OR, 4.32; 95% CI, 1.34-13.96; $P = .015$), Race, family and smoking history, finasteride use, and age at diagnosis were not associated with metastasis at presentation (Table 6). PSA predictably contributed to risk. We observed that a higher BMI conferred a small reduction in the risk of developing metastatic disease.

DISCUSSION

In this study of 13,144 veterans, exposure to Agent Orange conferred a 2-fold increased risk of developing prostate cancer. In addition, exposed individuals developed more aggressive disease at a younger age and had higher rates of metastasis than unexposed individuals. This finding is particularly noteworthy given the failure of expected confounding variables, such as clinical stage and preoperative PSA, race,

BMI, or smoking history, to contribute to the observation. This observation was confirmed in a multivariate logistic regression analysis, because Agent Orange exposure was the most important variable in predicting high-risk prostate cancer in our cohort. Unexpectedly, after multivariate regression analysis, smoking history was associated with a lower incidence of developing prostate cancer, whereas a higher BMI was associated with decreased likelihood of metastatic disease on presentation. In the prostate cancer literature, the association of BMI and smoking with cancer is controversial.¹⁶⁻¹⁸ Because cardiovascular disease is more prevalent among smokers and among individuals with higher BMI, these patients may have been prescribed cholesterol-lowering medication and daily aspirin independently. And because aspirin and lipid-lowering medications have been reported to decrease the incidence and the stage of prostate cancer,^{19,20} it is likely that the aforementioned variation may have been confounded by these variables (statins and aspirin), which may have led to the unexpected findings. Despite the reduction in incidence and stage of cancer among the obese and those with a smoking history, this difference was small compared with the effect of Agent Orange exposure. Nevertheless, in the future, analyses should correct for these variables.

A small pilot study by Giri et al revealed a similar 2-fold increased incidence of prostate cancer among men with exposure to Agent Orange compared with a similar cohort without the exposure.⁷ However, their study was limited by small numbers of men and, thus, the results did not reach statistical significance. Those authors also observed no difference between groups in disease characteristics like Gleason score, metastasis, and age at diagnosis. Zafar and Terris evaluated patients who were referred for prostate biopsy.⁸ Of 400 patients who were referred for biopsy in that study, 32 patients reported exposure to Agent Orange. Although Zafar and Terris observed a slightly increased rate of prostate cancer in the group with Agent Orange exposure (41% vs 34%), the increase was not statistically significant.

By far the largest and most thorough assessment of Agent Orange exposure and incidence of prostate cancer comes from a 20-year longitudinal study of Air Force veterans who were involved in Operation Ranch Hand. The \$140 million research effort was very detailed and quantified TCDD exposure. Operation Ranch Hand pilots sprayed 95% of the Agent Orange and other herbicides during the Vietnam War. The investigators compared serum TCDD levels and observed no increased incidence of prostate cancer among Operation Ranch Hand pilots compared with

a similar cohort of Air Force veterans who served in Southeast Asia who did not spray Agent Orange.⁹ That study, although it was very complete, was limited by the young age of the cohort and the institution of PSA screening in 1997. The influence of introducing PSA screening led to a large increase in incidence of prostate cancer in the final years of observation (1999-2003), as expected. In addition, the same investigators previously reported that service in Southeast Asia for >2 years and background levels in a comparison group were associated with a 2-fold increase in the incidence of prostate cancer.¹⁰ They hypothesized that other unknown agents in addition to low levels of TCDD together may have placed veterans in Southeast Asia at twice the risk of the general population. Finally, Gupta et al, evaluating the same cohort, observed an inverse relation between serum TCDD levels and serum testosterone or the incidence of benign prostatic hyperplasia.²¹ Is it possible that patients with Agent Orange exposure have lower testosterone levels, smaller prostate glands, and quite possibly lower PSA levels? Because PSA is the most commonly used test to diagnose prostate cancer, some patients with Agent Orange exposure may have 'normal' PSA levels and may harbor prostate cancer without undergoing biopsy. Our data seem to suggest otherwise, because we observed a higher incidence of abnormal PSA levels in the Agent Orange exposed cohort compared with the unexposed cohort (9.1% vs 6.1%).

Although the current dataset used was enriched clinically and the sample size was large, our study had several limitations. First, like in any retrospective study, selection bias is a concern. We identified all patients who had established care at the Northern California VA Health System. We do not have data on those veterans who were not eligible or who chose to receive healthcare outside of the VA Health System. However, with the advent of 'Remote View' and 'Deliverex' record management services, outside records and diagnoses are made available electronically by the VA system. Second, it is possible that patients who were exposed to Agent Orange were more likely to be followed closely. However, the intensity of screening, referral, and evaluation appears to be similar between the 2 groups (based on screening PSA, referral, urologic consultation, and biopsy). Also, if those with Agent Orange exposure had received better screening, then we would have observed both stage and grade migration toward low-risk, organ-confined prostate cancer. Instead, our data suggest otherwise, with a 2-fold increased risk of having a Gleason score from 8 to 10 and a 3-fold increased risk of having metastasis at presentation.

Third, is it possible that patients who received a diagnosis of prostate cancer changed their testimony regarding exposure to Agent Orange? We excluded 7 patients who initially reported no exposure to Agent Orange on their initial application but later changed their application to indicate that they had been exposed after a diagnosis of prostate cancer, as mentioned above (see Materials and Methods). Although this was not a requirement by the VA, it was a criterion in our current study. Therefore, all of the patients who were classified as being exposed must have reported it on their initial application for medical benefits. However, 38 patients did report exposure to Agent Orange on their initial application after they were diagnosed with prostate cancer. These patients did not change their testimony but simply came to the VA with an existing diagnosis of prostate cancer. However, even if we exclude these patients, the OR remains statistically significant at 1.85 (95% CI, 1.47-2.31; $P < .001$). In addition, the rates of metastasis (4%) and Gleason scores between 8 and 10 (10%) in the unexposed group are in line with what has been reported in the literature.^{22,23} It is also possible that Agent Orange may be associated with a higher PSA level. The net result of this effect would lead to a higher rate of biopsy among exposed veterans. To evaluate this effect, biopsy at a lower PSA threshold would be required. Although some may view the exclusion of patients before 1998 as a limitation, the risk profile for both groups was very low, as demonstrated by the Operation Ranch Hand study. It is only with passing age that the true risk has come into focus. Also, while the clinical information system is robust, there are no data regarding the quantification of serum levels of TCDD. Although the half-life of Agent Orange is long (≈ 7 years), the quantification of serum and lipid TCDD levels 5 or 6 half-lives later may not be justified in this current state of budgetary constraints on the VA system. The reliability of the data, even if attained, also has been questioned seriously, because there is a prolonged period between exposure and screening.²⁴ It is also noteworthy that 40% of the serum and lipid levels of TCDD among the veterans in Operation Ranch Hand (responsible for spraying 95% of Agent Orange) were not elevated, thus underscoring its imprecision.²⁵⁻²⁷ Finally, the lack of information on the service branch of Vietnam War era veterans and its association with incidence, grade, and metastatic potential of prostate cancer is a limitation. It would have been interesting to determine whether men 'on the ground' (infantrymen) who were exposed to Agent Orange have higher rates, grade, and metastatic potential of prostate cancer compared with airmen who also were exposed.

However, although some information on the branch of service may be available within the electronic record, it was not easily accessible. Nevertheless, this issue obviously warrants further research.

Unfortunately, the US Department of Defense no longer is funding the Operation Ranch Hand study; therefore, the long-term effects of Agent Orange may never be known. The findings of the current study suggest that Vietnam War era veterans who were exposed to Agent Orange warrant either more intense prostate cancer screening than those who were unexposed or a reopening of the Operation Ranch Hand study.

Exposure to Agent Orange is associated with an increased incidence of prostate cancer. Exposed individuals present at a younger age, have higher Gleason scores, and have a greater likelihood of developing metastasis. These observations are particularly important given the maturing of the Vietnam era veterans and their changing healthcare needs. **The current findings support aggressively screening these veterans for prostate cancer in the hopes of detecting high-risk cancers before metastases develop.** The expansion of benefits and screening programs will place further pressures on the VA healthcare system given the current level of budgetary appropriations.

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