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Abstract

Most studies on the relationship between Agent Orange and prostate cancer have focused on US veterans of the Vietnam War. There have been few studies focusing on the relationship between levels of prostate-specific antigen (PSA) and dioxins or steroid hormones in Vietnamese men. In 2009–2011, we collected blood samples from 97 men who had resided in a "dioxin hotspot" and 85 men from a non-sprayed region in Vietnam. Then, levels of PSA, dioxins, and steroid hormones were analyzed. Levels of most dioxins, furans, and non-*ortho* polychlorinated biphenyls were higher in the hotspot than in the non-sprayed region. Levels of testosterone, dehydroepiandrosterone and estradiol differed significantly between the hotspot and non-sprayed region, but there were no correlations between levels of PSA and steroid hormones and dioxins in either of the two regions. Our findings suggest that PSA levels in Vietnamese men are not associated with levels of dioxins or steroid hormones in these two regions.

Keywords Prostate-specific antigen, polychlorinated dibenzodioxins, polychlorinated dibenzofurans, polychlorinated biphenyls, steroid hormones, Vietnamese men

Abbreviations

PSA	prostate-specific antigen
DHT	dihydrotestosterone
DHEA	dehydroepiandrosterone
BMI	body mass index
PCBs	polychlorinated biphenyls
PCDDs	polychlorinated dibenzo-*p*-dioxins
PCDFs	polychlorinated dibenzofurans
TCDD	2,3,7,8-tetrachlorodibenzo-*p*-dioxin

INTRODUCTION

Between 1962 and 1971, the United States Air Force sprayed ≈107 million pounds of herbicides in South Vietnam for defoliation and crop destruction in a program code-named "Operation Ranch Hand" (CRS Report for Congress 2008). "Agent Orange" is a herbicide defoliant that was sprayed extensively in Vietnam from August 1965 to December 1971. This herbicide comprised a 1:1 mixture of 2,4-dichlorophenoxyacetic acid and 2,4,5-trichlorophenoxyacetic acid, with the latter being found subsequently to be contaminated with 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) (Stellman JM et al. 2003).

Our previous study suggested that people living close to former US airbases in Vietnam might have been exposed to Agent Orange and other sources of dioxin-like compounds (Manh HO et al. 2014). In 1998, the National Academy of Science concluded that "limited/suggestive evidence" existed of an association between Agent Orange and prostate cancer (Institute of Medicine, 1998).[4] In addition, Agent Orange is known to affect reproduction, and has been observed to alter levels of steroid hormones in laboratory rodents and other species (Peterson RE et al. 1993). A recent study found an inverse correlation between serum levels of TCDD and testosterone in US veterans (Gupta A et al. 2006). Several epidemiologic studies have prospectively assessed the association between circulating concentrations of sex steroid hormones and prostate cancer (Hsing AW 2001). The Physicians' Health Study confirmed the starting hypothesis, namely that testosterone and dihydrotestosterone (DHT) were positively associated with estradiol, and that sex hormone binding globulin was inversely associated with prostate cancer (Gann PH et al. 1996). In recent years, several clinical studies of hormone treatment for prostate cancer have been done (Cai C et al. 2011; Chang KH et al. 2011; Mostaghel EA et al. 2011; Richards J et al. 2012; Mostaghel EA 2013). Prostate-specific antigen (PSA) is a glycoprotein produced almost exclusively by the epithelial cells of the prostate gland, and is used as a marker for the diagnosis and monitoring of prostate cancer (Hudson MA et al. 1989; Oesterling JE 1991; Armbruster DA 1993).

Recent studies on the relationship between Agent Orange and prostate cancer have focused on US veterans of the Vietnam War (Ketchum NS et al. 1998; Zafar MB et al. 2001; Akhtar FZ et al. 2004; Giri VN et al. 2004; Justine L et al. 2006; Pavuk M et al. 2006; Chamie K et al. 2008). However, only one study has focused on the relationship between PSA and Agent Orange in Vietnamese men (Sun XL et al. 2013). Here, we wished to explore the association between PSA, dioxins, and steroid hormones in Vietnamese men.

METHODS AND MATERIALS

Study population

Blood samples (10 mL) were collected from 97 men in Phu Cat and 85 men from Kim Bang in August 2009, 2010, and 2011. All subjects were aged between 54 years and 81 years. Levels of PSA and dioxins were determined for all subjects, whereas levels of steroid hormones were determined for 50 men from Phu Cat and 48 men from Kim Bang. The Phu Cat Airbase is one of three "dioxin hotspots" in South Vietnam. All subjects, except for six, were known to have been living in and around the Phu Cat Airbase for more than 50 years. Hence, most subjects had resided in and around the Phu Cat Airbase during and after the Vietnam War. Kim Bang district is located in North Vietnam and was not exposed to herbicide operations during the war, which is why it was selected as the non-sprayed region.

All consenting subjects were asked to complete a health-status questionnaire to acquire information about age, residence history, smoking habits, alcohol consumption, and occupation. Before starting the study, we obtained permission from the Medical Ethics Committee of Kanazawa University [approval numbers 89 (2007) and 326 (2011); Kanazawa, Japan]. Written informed consent was obtained from all participants.

Measurement of levels of steroid hormones and dioxins in serum

Blood samples were obtained at the corresponding community health center. Blood was separated by centrifuged, and sera stored at –70°C.

Serum samples were spiked with a mixture of $^{13}C_{12}$-labeled polychlorinated dibenzo-*p*-dioxins (PCDDs)/polychlorinated dibenzofurans (PCDFs) plus polychlorinated biphenyls (PCBs) to serve as internal standards. The lipid fraction was obtained by liquid extraction and assayed using a gravimetric method. Then, this fraction was subjected to a series of purification operations using alkali digestion and multi-layer silica gel column chromatography. Finally, an active carbon-dispersed silica gel column was used to separate and collect PCDDs/PCDFs and non-*ortho* PCBs. The obtained fraction was quantified using gas chromatography–high-resolution mass spectrometry.

Human serum (200 μL) was mixed with purified water (1.0 mL) and mixed with cortisol-$^{2}H_4$ (1 ng), dehydroepiandrosterone (DHEA)-$^{2}H_4$ (100 pg), progesterone-$^{13}C_3$ (100 pg), estrone-$^{13}C_4$ (100 pg), and estradiol-$^{13}C_4$ (100 pg/100 μL) as internal standards. Hormone levels in the extracted fraction were estimated using liquid chromatography–tandem mass spectrometry.

The following ions were detected: cortisol and cortisol-$^{2}H_4$ = 468.2/309.2 and 472.2/454.3; cortisone and cortisol-$^{2}H_4$ = 468.2/309.2 and 472.2/454.3; DHEA and DHEA-$^{2}H_4$ = 394.3/175.1 and 398.1/179.4; A-dione and progesterone-$^{13}C_3$ = 287.4/109.0 and 318.3/100.1; estrone and estrone-$^{13}C_4$ = 376.1/156.9 and 380/160.8; estradiol and estradiol-$^{13}C_4$ = 483.3/264.0 and 487.2/268.2. The limits of detection for cortisol, cortisone, DHEA, A-dione, estrone, and estradiol were 50, 50, 5, 10, 1.0, and 0.5 pg/assay, respectively.

A detailed description of the analytical methods for steroid hormones and dioxin can be found elsewhere (Sun XL et al. 2014).

Measurement of PSA levels in serum

Total levels of PSA in serum were quantified for all samples using an enzyme immunoassay system.

Statistical analyses

Levels of PSA, dioxins, DHT, DHEA, testosterone, and androstenedione obtained were log-transformed to improve the normal distribution. The chi-squared test, Welch's *t*-test, Student's *t*-test, linear regression analyses, and multiple regression analyses were applied. Statistical analyses were done using JMP v9.0 (SAS Institute Japan, Tokyo, Japan). $p < 0.05$ was considered significant.

RESULTS

Personal and demographic characteristics of participants are shown in Table 1. Residency of subjects in the hotspot was significantly longer than for the non-sprayed region. Height and weight were significantly higher in the non-sprayed region, but the body mass index (BMI) did not differ significantly. There were no significant differences between the hotspot and non-sprayed region in terms of age, alcohol use, or tobacco use. The percentage of subjects in employment in the hotspot was significantly higher than in the non-sprayed region. Of these, the percentage of farmers in the hotspot was 79.1% and 62.8% in the non-sprayed region.

Table 2 shows levels of PSA and dioxins for the two regions studied. PSA levels did not differ significantly between the hotspot and non-spayed region. However, levels of most dioxins, furans, and non-*ortho* PCBs were significantly higher in the hotspot than in the non-sprayed region.

Table 3 shows the correlation between PSA levels and age, residency, and dioxin levels for the hotspot and non-sprayed region. A significant correlation was found between PSA levels and age, but there were no correlations between PSA levels and residency or

dioxin levels for either of the two regions. Similarly, there was no significant correlation between PSA levels and dioxin levels after adjustment for age, BMI, or residency (data not shown).

Table 4 details a comparison of serum levels of steroid hormones in males from the hotspot and non-sprayed region. Levels of testosterone, DHEA, and estradiol differed significantly between the hotspot and non-sprayed region, but there was no significant difference with regard to levels of cortisol, cortisone, progesterone, DHT, androstenedione, or estrone.

Table 5 shows the correlation between levels of PSA and steroid hormones for the two regions studied. No significant correlation was found between these two parameters for either of the two regions studied. No significant correlation was found between levels of PSA and steroid hormones after adjustment for age, BMI, and residency (data not shown).

DISCUSSION

Prostate cancer is a common disease that affects many men in the sixth and seventh decade of life. PSA has been studied since the late 1980s and is used to detect, stage, and monitor prostate cancer. Indeed, it is the most commonly used test to diagnose prostate cancer (Brosman SA 2009). As such, PSA screening was used to detect prostate cancer in US veterans of the Vietnam War in 1999–2003 (Chamie K et al. 2008). Previous phases of the Vietnam Veterans Study suggested that exposure to Agent Orange is associated with an increased risk of prostate cancer (Zafar MB et al. 2001; Justine L et al. 2006; Chamie K et al. 2008). A positive family history is also an important risk factor for prostate cancer and, therefore, increases PSA levels (Keetch DW et al. 1994). However, none of the subjects in our study reported that a family member had suffered from prostate cancer.

This is the first study to explore the association between levels of PSA and dioxins and steroid hormones in Vietnamese men. We found no significant differences between the PSA levels of subjects in the hotspot and non-sprayed region. Likewise, there was no significant correlation between levels of PSA and dioxins in the two regions. However, we found levels of most dioxins, furans, and non-*ortho* PCB to be higher in the hotspot than in the non-sprayed region. Other studies have also found a lack of significant differences between veterans of the Vietnam War exposed or not exposed to Agent Orange in terms of PSA levels (Zafar MB et al. 2001; Chamie K et al. 2008). A prospective cohort study of air-force veterans of the Vietnam War found that exposure to Agent Orange reduces growth of the prostate gland. As such, older men heavily exposed to Agent Orange may have smaller prostate glands and, therefore, a lower tendency to develop benign prostatic hyperplasia (Gupta A et al. 2006). Therefore, subjects exposed to Agent Orange may have smaller prostate glands and, therefore, lower PSA levels. This phenomenon may explain why we found PSA levels not to differ significantly between the hotspot and non-sprayed region, in addition to the lack of a significant correlation between levels of PSA and dioxins.

In a clinical case study, the patient showed good progress after receiving transdermal estradiol as primary hormonal therapy for prostate cancer, which caused PSA levels to decrease and estradiol levels to increase (Bland LB et al. 2005). Furthermore, DHEA (which is synthesized by the adrenal glands through the sequential actions of the cytochrome P450 enzymes CYP11A1 and CYP17A1) makes CYP17A1 inhibitors such as abiraterone effective therapy for castration-resistant prostate cancer (Cai C et al. 2011). A recent study found an inverse correlation between serum levels of TCDD and testosterone in US veterans of the Vietnam War (Gupta A et al. 2006). Moreover, several epidemiologic studies have reported that low levels of testosterone have an adverse effect on men with newly diagnosed prostate cancer (Messengill JC et al. 2003; Schatzl G et al. 2003). It is known that prostate cancer can elevate PSA levels (Keetch DW et al. 1994). In addition, one study demonstrated that PSA production is associated with steroid hormone receptors (Yu H et al. 1994). We found that levels of testosterone, DHEA, and estradiol differed significantly between the hotspot and non-sprayed region, but no correlations were found between levels of PSA and testosterone, estradiol, or DHEA in either of the two regions. This phenomenon could be because the studies referred to above selected subjects from a population of prostate-cancer patients, whereas we selected subjects from the general population. Hence, finding

correlations between levels of PSA and steroid hormones in the hotspot and non-sprayed region would be difficult, and could explain why we did not find a correlation between levels of PSA and steroid hormones in these two regions.

Our study had limitations. First, we quantified dioxin levels in 2011, more than 40 years since the herbicide was sprayed in South Vietnam. As such, serum levels of dioxins in Vietnamese men exposed at any time during the Vietnam War would have decreased significantly. Furthermore, our study was based on a relatively small number of Vietnamese men: further studies will be needed with a larger sample size to confirm our findings.

CONCLUSION

PSA levels in Vietnamese men were not correlated with serum levels of dioxins or steroid hormones in the hotspot or the non-sprayed region.

Competing interests

The authors declare that they have no competing interests.

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Table 1 Demographic characteristics of participants from the hotspot and non-sprayed regions

	Hotspot (n=97)		Non-sprayed region(n=85)		
Continuous variable	Mean	SD	Mean	SD	*p* Value
Age (years)	67.8	6.1	66.5	5.2	0.109[1]
Residency (years)	63.4	12.4	55.2	9.1	0.000[2]
Height (cm)	156.9	5.3	159.4	4.9	0.001[2]
Weight (kg)	49.1	7.3	52.2	7.4	0.006[2]
BMI (kg/m^2)	19.9	2.5	20.5	2.6	0.107[2]
Categorical variables	N	%	N	%	
Alcohol use (yes)	46	47.4	42	49.4	0.531[3]
Tobacco use (yes)	60	61.9	62	72.9	0.113[3]
Currently employed (yes)	67	69.1	43	50.6	0.011[3]
Farmer	53	79.1	27	62.8	0.002[3]
Worker	0	0	2	4.7	
Fisherman	0	0	1	2.3	
Teacher	0	0	1	2.3	
Other job	14	20.9	12	27.9	

[1]Welch's *t* test [2]Student's *t* test [3]Chi squared test

SD: standard deviation, BMI: body mass index

Table 2 PSA and dioxin levels in the hotspot and non-sprayed regions

	Hotspot (n=97)	Non-sprayed area (n=85)	
Characteristics	GM GSD	GM GSD	*p* Value
PSA(ng/mL)	0.90 2.4	0.98 2.2	0.475
PCDD congeners (pg-TEQ/g lipid)			
2378-TeCDD	2.63 1.9	1.45 1.5	0.000
12378-PeCDD	8.32 1.9	2.40 1.9	0.000
123478-HxCDD	0.50 1.7	0.27 1.6	0.000
123678-HxCDD	1.91 1.9	0.45 1.7	0.000
123789-HxCDD	0.65 1.9	0.28 1.7	0.000
1234678-HpCDD	0.28 2.0	0.07 1.7	0.000
OCDD	0.10 1.9	0.02 1.8	0.000
PCDF congeners (pg-TEQ/g lipid)			
2378-TeCDF	0.16 1.6	0.15 1.6	0.119
12378-PeCDF	0.06 1.8	0.04 1.6	0.000
23478-PeCDF	3.98 1.7	2.14 1.6	0.000
123478-HxCDF	2.75 1.8	0.44 1.7	0.000
123678-HxCDF	2.09 1.8	0.49 1.7	0.000
123789-HxCDF	0.31 1.6	0.26 1.6	0.009
234678-HxCDF	0.38 1.6	0.26 1.6	0.000
1234678-HpCDF	0.41 2.0	0.04 1.9	0.000
1234789-HpCDF	0.04 1.7	0.03 1.6	0.000
OCDF	0.0023 1.6	0.0020 1.6	0.007
Non-ortho PCB congeners (pg-TEQ/g lipid)			
TeCB#81	0.005 1.5	0.004 1.6	0.000
TeCB#77	0.002 1.6	0.001 1.7	0.000
PeCB#126	3.55 2.1	3.02 2.1	0.000
HxCB#169	3.39 1.8	0.71 2.0	0.000
TEQ (pg/g lipid)			
Total PCDDs	14.8 1.8	5.1 1.6	0.000
Total PCDFs	10.5 1.7	4.0 1.5	0.000
Total PCDDs+PCDFs	25.7 1.7	9.1 1.5	0.000
Non-ortho PCBs	7.2 1.9	3.9 1.9	0.000
Total PCDD/DFs+PCBs	33.9 1.7	13.5 1.6	0.000

GM: geometric mean, GSD: geometric standard deviation

Table 3 Correlation between PSA and age, residency, and dioxin levels in the two regions studied

Characteristics	r	95%CI	*p* Value
Age	0.1760	-0.1619 - 0.4769	0.017
Residency	0.0580	-0.2758 - 0.3793	0.452
2378-TeCDD	-0.0253	-0.3509 - 0.3058	0.735
12378-PeCDD	-0.0491	-0.3716 - 0.2841	0.511
123478-HxCDD	-0.0229	-0.3488 - 0.3080	0.760
123678-HxCDD	0.0085	-0.3209 - 0.3361	0.909
123789-HxCDD	-0.0124	-0.3396 - 0.3174	0.868
1234678-HpCDD	0.0230	-0.3079 - 0.3489	0.758
OCDD	0.0022	-0.3266 - 0.3305	0.977
2378-TeCDF	0.0213	-0.3094 - 0.3474	0.775
12378-PeCDF	0.0067	-0.3226 - 0.3345	0.929
23478-PeCDF	-0.0550	-0.3767 - 0.2785	0.461
123478-HxCDF	-0.0033	-0.3315 - 0.3256	0.965
123678-HxCDF	0.0083	-0.3211 - 0.3359	0.912
123789-HxCDF	0.0066	-0.3226 - 0.3344	0.929
234678-HxCDF	-0.0338	-0.3584 - 0.2981	0.651
1234678-HpCDF	0.0186	-0.3119 - 0.3450	0.803
1234789-HpCDF	0.0299	-0.3016 - 0.3550	0.688
OCDF	-0.0156	-0.3424 - 0.3146	0.834
TeCB#81	0.0174	-0.3129 - 0.3440	0.815
TeCB#77	0.0167	-0.3136 - 0.3434	0.823
PeCB#126	0.0087	-0.3208 - 0.3363	0.907
HxCB#169	0.0090	-0.3205 - 0.3366	0.904
Total PCDDs	-0.0332	-0.3578 - 0.2986	0.656
Total PCDFs	-0.0162	-0.3429 - 0.3140	0.828
Total PCDDs+PCDFs	-0.0299	-0.3550 - 0.3016	0.689
Non-ortho PCBs	0.0133	-0.3166 - 0.3404	0.859
Total PCDD/DFs+PCBs	-0.0145	-0.3414 - 0.3156	0.846

CI: confidence interval

Table 4 Comparison of serum steroid hormone levels in males from the hotspot and non-sprayed regions

Characteristics		Hotspot (n=50)	Non-sprayed area (n=48)	*p* Value
Cortisol (Mean±SD)	(ng/mL)	81 ± 33	82 ± 30	0.772
Cortisone (Mean±SD)	(ng/mL)	15 ± 5	16 ± 3	0.568
Progesterone (Mean±SD)	(pg/mL)	47 ± 37	47 ± 35	0.972
Dihydrotestosterone (GM GSD)	(pg/mL)	620 1.5	537 1.4	0.075
Testosterone (GM GSD)	(pg/mL)	6310 1.4	5395.1 1.4	0.003
Dehydroepiandrosterone (GM GSD)	(pg/mL)	1260 1.6	1513 1.7	0.047
Androstenedione (GM GSD)	(pg/mL)	1510 1.5	1584 1.4	0.505
Estradiol (Mean±SD)	(Pg/mL)	13 ± 4	11 ± 3	0.024
Estrone (Mean±SD)	(Pg/mL)	28 ± 8	30 ± 9	0.571

SD: standard deviation, GM: geometric mean, GSD: geometric standard deviation

Table 5 Correlation between PSA and steroid hormone levels in the two regions studied

Characteristics	r	*p* Value
Cortisol	0.1728	0.351
Cortisone	0.1832	0.662
Progesterone	0.0980	0.322
Dihydrotestosterone	0.1067	0.560
Testosterone	0.1532	0.200
Dehydroepiandrosterone	-0.0559	0.400
Androstenedione	0.0462	0.872
Estradiol	0.1410	0.342
Estrone	-0.0091	0.794