Title
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Journal
Urologic Oncology: Seminars and Original Investigations, 33(7)

ISSN
1078-1439

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Publication Date
2015-07-01

DOI
10.1016/j.urolonc.2015.04.012

Peer reviewed

ELSEVIER

CrossMark

Urologic Oncology: Seminars and Original Investigations 33 (2015) 329.e1–329.e6

UROLOGIC ONCOLOGY

Original article

Agent Orange and long-term outcomes after radical prostatectomy

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Received 30 December 2014; received in revised form 14 April 2015; accepted 19 April 2015

Abstract

Purpose: To investigate the association between Agent Orange (AO) exposure and long-term prostate cancer (PC) outcomes.

Material and Methods: Data from 1,882 men undergoing radical prostatectomy for PC between 1988 and 2011 at Veterans Affairs Health Care Facilities were analyzed from the Shared Equal Access Regional Cancer Hospital database. Men were stratified by AO exposure (binary). Associations between AO exposure and biopsy and pathologic Gleason sum (GS) and pathologic stage were determined by logistic regression models adjusted for preoperative characteristics. Hazard ratios for biochemical recurrence (BCR), secondary treatment, metastases, and PC-specific mortality were determined by Cox models adjusted for preoperative characteristics.

Results: There were 333 (17.7%) men with AO exposure. AO-exposed men were younger (median 59 vs. 62 y), had lower preoperative prostate-specific antigen levels (5.8 vs. 6.7 ng/ml), lower clinical category (25% vs. 38% palpable), and higher body mass index (28.2 vs. 27.6 kg/m^2), all $P < 0.01$. Biopsy GS, pathologic GS, positive surgical margins, lymph node positivity, and extracapsular extension did not differ with AO exposure. At a median follow-up of 85 months, 702 (37.4%) patients had BCR, 603 (32.2%) patients received secondary treatment, 78 (4.1%) had metastases, and 39 (2.1%) died of PC. On multivariable analysis, AO exposure was not associated with BCR, secondary treatment, metastases, or PC mortality.

Conclusions: AO exposure was not associated with worse preoperative characteristics such as elevated prostate-specific antigen levels or biopsy GS nor with BCR, secondary treatment, metastases, or PC death. Thus, as data on AO-exposed men mature, possible differences in PC outcomes observed previously are no longer apparent.

Keywords: Agent Orange; Prostate cancer; Prostatectomy

1. Introduction

Operation Ranch Hand was the military code name for the spraying of herbicides in Southeast Asia from 1962 through 1971. Approximately 19 million gallons of herbicides were sprayed, of which 11 million gallons contained Agent Orange (AO). The spray was used in South Vietnam to destroy the vegetation used by Vietcong and North Vietnamese forces for concealment [1]. All of the herbicides, including AO, contained the compound 2,4,5-trichlorophenoxyacetic acid and were contaminated to some extent by the toxin 2,3,7,8-tetrachlorodibenzodioxin, commonly known as dioxin.

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http://dx.doi.org/10.1016/j.urolonc.2015.04.012
1078-1439/

Scientific evidence from animal, human, epidemiologic, mechanistic, and mode-of-action studies demonstrate the carcinogenic potential of dioxin. Dioxin binds to the aryl hydrocarbon receptor, located in virtually every tissue in the body, contributing to the wide array of adverse effects associated with dioxin exposure. Dioxin is an extremely powerful growth deregulator and has the ability to effect proliferation, differentiation, and apoptosis in cells grown in vitro [2–4].

The evidence linking AO exposure to an increased risk of prostate cancer (PC) was demonstrated by studies of farmers and forestry workers exposed to herbicides containing dioxin [5–7]. An initial study by Zafar and Terris [8] failed to establish an association between AO and prostate biopsy results in 400 consecutive patients. Conversely, a study by Chamie et al., which included more than 6,000 patients exposed to AO, demonstrated an association between exposure and the incidence of PC. Furthermore, the patients exposed to AO developed PC at a younger age and had more aggressive pathology when compared with their unexposed counterparts [9]. Similarly, Ansbaugh et al. [10] demonstrated an increased risk of high-grade PC on biopsy and suggested that AO exposure could be used to intelligently screen patients for PC.

Although several studies have examined AO and the incidence and grade of PC on biopsy, few studies have investigated associations between AO exposure and treatment outcomes. Prior analysis of the Shared Equal Access Regional Cancer Hospital (SEARCH) database has significantly linked AO exposure with biochemical recurrence (BCR) after radical prostatectomy (RP), despite the absence of worse pathologic features in AO-exposed men [11]. Additionally, Kane et al. [12] showed that AO-exposed men in the SEARCH database who were candidates for active surveillance had a hazard ratio (HR) of 2.08 (1.06–4.07, $P = 0.03$) for developing BCR in a univariate Cox proportional hazard analysis. Since the prior analyses, the SEARCH database has expanded to include a larger patient cohort and longer follow-up time. Therefore, our goal was to reinvestigate the association between AO exposure and PC-specific survival and metastasis rates among patients treated with RP.

2. Material and methods

2.1. Study cohort

After obtaining institutional review board approval from each institution and being granted a waiver of consent, SEARCH data were abstracted from patients who underwent RP between 1988 and 2011 at Veterans Affairs (VA) Health Care Facilities in West Los Angeles, Palo Alto, and San Diego, CA; Durham and Asheville, NC; and Augusta, GA. Of the 3,916 men enrolled in SEARCH, AO exposure status was known for 2,872 (73.34%). Of these, we excluded men with other incomplete data for analysis, resulting in a study population of 1,882 (48%).

2.2. Treatment

In the SEARCH database, the surgical approach (radical retropubic, perineal, or robotic) and extent of pelvic lymphadenectomy was determined by the surgeon. Postoperative androgen deprivation therapy (ADT) was administered at the discretion of the treating physician. ADT or radiotherapy (RT) initiated with an undetectable serum prostate-specific antigen (PSA) was considered adjuvant. The dosimetry of adjuvant or salvage radiation therapy was at the discretion of the treating radiation oncologist. It is noteworthy that SEARCH excludes patients treated with preoperative ADT or RT.

2.3. Follow-up

Follow-up protocols for this retrospective analysis were not predetermined and were left to the discretion of the treating physicians at each of the 6 centers. Surgery date was considered time zero for all outcomes. The RP specimens were sectioned according to each institution's protocol. BCR was defined as 1 PSA level >0.2 ng/ml, 2 levels of 0.2 ng/ml, or secondary treatment for a detectable PSA level after RP. Men receiving adjuvant therapy for ≤ 6 months after surgery for an undetectable PSA level were considered nonrecurrent at the time of adjuvant therapy, with follow-up censored at that point. Secondary treatment was defined as any hormonal or radiation therapy (adjuvant or salvage) after prostatectomy. The decision to perform radiographic imaging was at the discretion of the treating physician. Distant metastases were determined by review of radionuclide bone scans, magnetic resonance imaging, computed tomography, plain radiograph reports, and clinical progress notes. PC-specific death was defined as death in any patient with metastases showing PC progression following ADT.

2.4. Exposure

AO exposure was determined in 2 ways. First, a veteran self-reports suspected exposure and submits a claim to the VA. This report is verified by a VA committee that reviews service records to determine whether the veteran was stationed in an area that was sprayed with AO during the service period. Therefore, self-reported claims of AO exposure are not included if documentation of proximity to spray area cannot be confirmed.

2.5. Statistical analysis

The study cohort was stratified by the presence or absence of exposure to AO. To describe the differences in demographic, clinical, and pathologic factors between the exposed and unexposed groups, we used Pearson chi square

or Fisher tests as appropriate for categorical variables and Kruskal-Wallis rank sum tests for continuous variables. All continuous variables were expressed as median with interquartile ranges unless otherwise specified. Follow-up interval, year of RP, age at RP, body mass index (BMI), and preoperative PSA levels were examined as continuous variables. As PSA level was not normally distributed, values were analyzed after logarithmic transformation. Center, surgical margin status, biopsy Gleason sum (bGS), race, clinical stage, pathologic GS (pGS), extracapsular extension, seminal vesicle (SV) invasion, and lymph node status were examined as categorical variables.

In our primary analysis, we used Kaplan-Meier plots and Cox proportional hazards regression models adjusted for age, race, clinical stage, PSA level, BMI, center, and bGS to identify associations between BCR, secondary treatment (ADT or RT), metastases, PC-specific death, and AO exposure. The results were reported as HRs with 95% confidence intervals. In our secondary analysis, associations between bGS ≥ 8, pGS ≥ 8, and adverse pathology (defined by extracapsular extension, positive lymph node, SV invasion, or RP GS ≥ 8) and AO exposure were determined using logistic regression models. Results were expressed as odds ratios (OR) with 95% confidence intervals adjusting for several preoperative factors: age, race, center, year of RP, clinical stage, PSA level, and BMI.

All tests were 2 tailed, and P values <0.05 were considered significant. All statistical analyses were performed using R version 3.0.1 (R Foundation for Statistical Computing, Vienna, Austria) with the *survival*, *survplot, MASS,* and *epitools* packages installed.

3. Results

In the study cohort, 1,549 (82.3%) men were without AO exposure and 333 (17.7%) had AO exposure. Men in the AO-exposed group were younger at the time of RP (median 59 vs. 62 years, $P < 0.01$), were treated in more recent years (2005 vs. 2002, $P < 0.01$), had a higher BMI (median 28.24 vs. 27.56, $P = 0.01$), had a lower preoperative PSA level (median 5.8 vs. 6.74 ng/ml, $P < 0.01$), and had lower clinical stage (24.62% vs. 38.41% cT2, $P < 0.01$). There were no significant differences between bGS margin status, race, pGS, extracapsular extension, and nodal involvement by AO exposure. However, men with AO exposure had a lower rate of SV invasion (6.99% vs. 10.87%, $P = 0.04$) (Tables 1 and 2).

At a median follow-up of 85 months, 702 (37.4%) patients had BCR, 603 (32.2%) patients had secondary treatment, 78 (4.1%) had metastases, and 39 (2.1%) died of PC. In our primary analysis BCR, secondary treatment, PC-specific death, and metastases were not associated with AO exposure in univariate or multivariate analyses (Table 3). The results of the univariate analyses are demonstrated on Kaplan-Meier plots in Fig., and the results of the multivariate analyses are in Table 3.

Similarly, our secondary analyses showed that AO exposure was not a significant predictor of bGS ≥ 8 when adjusting for

Table 1
Preoperative clinical and pathologic features of men who underwent RP, grouped by their history of AO exposure

Variable	AO exposure		
	Not exposed	Exposed	P value
No. of patients	1549 (82.3%)	333 (17.7%)	
Median age	62 (58–67)	59 (57–63)	**<0.01**
Median follow-up (months)	87.91 (48.87–123.5)	77.42 (50.21–101.5)	**0.01**
Median year of RP	2002 (1998–2005)	2005 (2002–2007)	**<0.01**
Race			0.24
Black	608 (39.25%)	128 (38.44%)	
White	858 (55.39%)	192 (57.66%)	
Asian	22 (1.42%)	2 (0.60%)	
Hispanic	50 (3.23%)	6 (1.80%)	
Other	11 (0.71%)	5 (1.50%)	
Median BMI	27.56 (24.95–30.56)	28.24 (25.54–31.75)	**0.01**
Median preoperative PSA level	6.74 (4.8–10.5)	5.8 (4.4–8.1)	**<0.01**
Clinical stage			**<0.01**
T1	948 (61.20%)	251 (75.38%)	
T2	595 (38.41%)	82 (24.62%)	
T3	6 (0.39%)	0 (0%)	
Biopsy Gleason sum			0.59
2–6	904 (58.36%)	203 (60.96%)	
7	492 (31.76%)	102 (30.63%)	
8–10	153 (9.88%)	28 (8.41%)	

Bold values indicates $P < 0.05$.

Table 2
Postoperative pathologic and treatment characteristics of men who underwent RP, grouped by their history of AO exposure

Variable	AO exposure		
	Not exposed	Exposed	*P* value
RP Gleason sum			0.25
2–6	591 (38.15%)	129 (38.74%)	
7	754 (48.68%)	171 (51.35%)	
8–10	204 (13.17%)	33 (9.91%)	
Positive margins	696 (45.52%)	148 (44.85%)	0.87
Extracapsular extension	303 (19.91%)	58 (17.63%)	0.38
SV invasion	166 (10.87%)	23 (6.99%)	0.04
Nodal involvement			0.78
No	977 (63.52%)	181 (54.68%)	
Yes	35 (2.28%)	9 (2.72%)	
Unknown	526 (34.20%)	141 (42.60%)	
Any ADT	264 (17.05%)	42 (12.61%)	0.06
Adjuvant ADT	27 (1.74%)	3 (0.90%)	0.38
Any RT	375 (24.2%)	90 (27.03%)	0.31
Adjuvant RT	60 (3.87%)	10 (3.00%)	0.55
Any ADT or RT	495 (32.00%)	108 (32.43%)	0.92
Adjuvant ADT or RT	66 (4.26%)	10 (3.00%)	0.37

preoperative factors. On multivariate analysis, AO exposure was found to be associated with a lower rate of pGS $\geq$ 8 (OR = 0.6, P = 0.02) and adverse RP pathology (as defined by extracapsular extension, positive lymph node, SV invasion or pGS $\geq$ 8) (OR = 0.74, P = 0.04) (Table 4).

4. Discussion

The present study is one of few investigations that determine the effect of AO exposure on PC-specific survival. In a previous cohort of patients who underwent brachytherapy, Everly et al. [13] demonstrated that AO exposure did not statistically affect survival in a multivariable analysis. Similarly, the study by Akhtar et al. [14] showed that AO exposure was not associated with increased all-cancer mortality in Operation Ranch Hand veterans when compared with age-matched controls and veterans serving in the same region. We found a similar lack of association between long-term oncologic outcomes and AO exposure in the current study of veterans treated with RP.

The lack of a statistically significant effect of AO exposure on BCR in our study differs from a prior study from our group that linked AO exposure with BCR. The article by Shah et al. demonstrated that AO exposure was associated with BCR (HR = 1.55, P = 0.004) after adjusting for clinical and pathologic characteristics. However, the mechanism is unclear, as there were no differences in RP pathologic features in the AO-exposed men [11]. The current study did not show an association between AO exposure and BCR, which is perhaps owing to longer follow-up and more AO-exposed patients. Conversely, this finding could reflect more vigilant screening of AO-exposed men at the VA in recent years. Patients who claim AO exposure through the VA are invited to undergo a registry examination, which includes PC screening. This screening approach may have contributed to why AO-exposed men were younger at the time of RP, had a lower preoperative PSA level, and were less likely to have clinical stage cT2 disease when compared with those with no history of AO exposure. To adjust for more intensive screening, we control for age and other clinical factors, including year of RP, given that detailed screening information is not available in SEARCH.

A limitation of the current study is that patients categorized as AO exposed were confirmed by the VA to have been exposed only after they placed a claim. Therefore, there may be individuals classified as non–AO exposed who were actually exposed but have not placed a claim with the VA. Although some patients have a financial incentive to claim AO exposure, raising the concern of overreporting, underreporting owing to recall bias or lack of information regarding claim options or processes could also contribute to the lack of difference in the 2 groups seen in our study. In the current study, there is a lack of quantification of levels of AO or dioxin. Consequently, the AO-exposed group includes men with a spectrum of exposure. The gold-standard assessment of dioxin exposure is measurement of its concentration in blood, milk, or adipose tissue. Li et al. [15] measured dioxin toxic equivalency levels in adipose tissue of veterans classified as AO exposed and demonstrated no association with BCR after RP. Importantly, their study validated AO exposure claimed by veterans, as the exposed group had significantly higher dioxin toxic equivalency than the unexposed group did. This validation reduces the concern for lack of quantification in our study.

Table 3
Hazard ratios of oncologic outcomes after RP with AO exposure

	Univariable			Multivariable[a]		
	HR	95% CI	*P*	HR	95% CI	*P*
Biochemical recurrence[b]	1.03	(0.84–1.25)	0.80	1.21	(0.99–1.49)	0.07
Secondary treatment[c]	1.08	(0.88–1.33)	0.48	1.21	(0.97–1.51)	0.09
Metastases	0.87	(0.45–1.69)	0.68	0.93	(0.30–2.66)	0.84
Prostate cancer–specific death	0.75	(0.27–2.14)	0.60	0.89	(0.46–1.85)	0.83

[a] Adjusted for age, biopsy GS, race, clinical stage, BMI, center, and preoperative PSA level (log transformed).
[b] Patients receiving adjuvant ADT were excluded.
[c] Any ADT or RT.

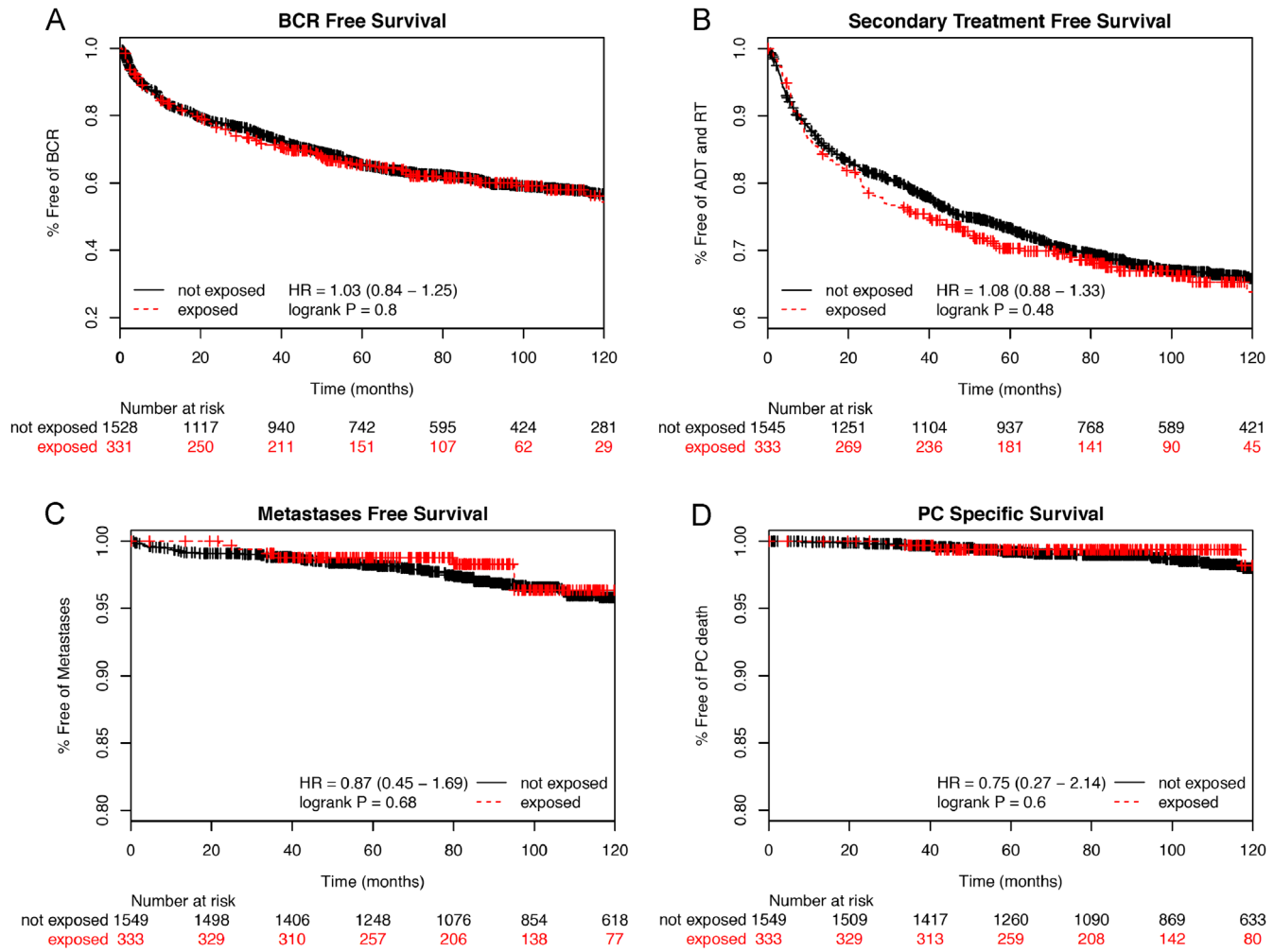

Fig. Kaplan-Meier plots from univariate analyses of AO exposure and (A) BCR, (B) secondary treatment (any ADT or RT), (C) metastases, and (D) PC-specific death.

Owing in part to the excellent long-term oncologic outcomes seen in this cohort, the number of PC deaths was modest. However, the effect sizes (HR for PC-specific death (0.89) and metastasis-free survival (0.83) both less than 1) do not suggest a lack of statistical power. As our cohort was restricted to men who underwent RP, the results may not be generalizable to the overall population of AO-exposed men with PC. Furthermore, this cohort does not provide information on the incidence of PC or overall mortality of men exposed to AO. Despite its limitations, this is largest study to date evaluating long-term oncologic outcomes in a cohort of veterans who were treated with RP.

Table 4
Odds ratios for RP pathologic features with AO exposure

	Univariable			Multivariable[a]		
	OR	95% CI	*P*	OR	95% CI	*P*
Biopsy GS ≥ 8	0.84	(0.54–1.26)	0.41	0.73	(0.46–1.14)	0.18
RP GS ≥ 8	0.73	(0.48–1.06)	0.11	0.60	(0.39–0.90)	0.02
Any adverse pathology[b]	0.73	(0.55–0.95)	**0.02**	0.74	(0.55–0.98)	0.04

[a]Adjusted for age, race, clinical stage, BMI, center, year of RP, and preoperative PSA level (log transformed).

[b]Defined by extracapsular extension, positive lymph node, seminal vesicle invasion, or RP GS ≥ 8.

5. Conclusions

In this cohort of veterans who underwent RP, exposure to AO was not associated with an increased risk of BCR, secondary treatment, metastases, or PC death. The data support that men with AO exposure treated with RP have excellent oncologic outcomes that are similar to those of unexposed men.

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