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How Agent Orange impacts prostate cancer risk, pathology, and treatment outcomes

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Abstract

Between 2.6 and 3.8 million veterans served in Vietnam while the US military dispersed Agent Orange (AO), although the exact number of exposed individuals is unknown. Agent Orange, an herbicide, is a known risk factor for various cancers, including sarcoma and leukemia, but less is known about its link with prostate cancer (PC). Prostate cancer is the most commonly diagnosed malignancy in men and the fifth most common cause of cancer-related death in men worldwide. In 2023, approximately 288,300 patients will be given a diagnosis of PC, and an estimated 34,700 fatalities will occur in the United States. However, whether the pathologic characteristics of PC among those exposed to AO differ from those in the general population remains unclear. Our review synthesizes the literature regarding the impact of AO exposure on PC incidence and disease course. A comprehensive PubMed literature search of articles published beginning in 1950 was performed using the primary search terms "Agent Orange," "TCDD," and "tetrachlorodibenzodioxin" and the secondary search terms "prostate cancer" or "prostate neoplasm." The search was limited to studies that focused on human participants and were published in English. Four authors thoroughly reviewed the retrieved articles for relevancy to the study aims: discussion of PC diagnosis, prognosis, or management among patients exposed to AO. Of 108 studies identified in our search, 13 were included in this systematic review. Findings within studies concerning AO exposure with relation to PC incidence, age at diagnosis or treatment initiation, and PC severity seemed to be mixed and generally conflicting. However, the literature seems to indicate that there are no significant differences in survivorship between exposed and unexposed veterans who are given a diagnosis of PC. Given these heterogeneous outcomes, the evidence does not encourage a significantly different approach to the diagnosis and management of PC for veterans exposed to AO. Clinicians should make case-by-case decisions regarding PC screening and potential treatment options for this patient group, weighing clinical suspicion against the harms of diagnostic workup and treatment.

Keywords: Agent Orange; 2,3,7,8-Tetrachlorodibenzo-p-dioxin; Prostate cancer; Veterans

1. Introduction

Nearly 3 million American servicemen were deployed to Vietnam in the 1960s and early 1970s, when the military used large quantities of herbicidal defoliant formulations. These included Agent Orange (AO), which was used with the intention of controlling and reducing tall grass and other vegetation to secure perimeters.[1,2] A considerable portion of the population was exposed to AO in this process. Although exact numbers are unknown, estimates indicate that up to 2.6–3.8 million people could have been potentially exposed to herbicides, mostly AO.[3] Agent Orange is a known risk factor for various cancers, including sarcomas, lung cancer, and leukemia, but its link with prostate cancer (PC) is unclear.[2] Prostate cancer is the most commonly diagnosed malignancy in men and the fifth leading cause of cancer-related death among men globally. In 2023, an estimated 288,300 men will be given a diagnosis of PC, with approximately 34,700 men dying from PC in the United States.[4] Although there is an abundance of research on AO and its connections with various malignancies, the association between AO exposure and PC diagnosis and the relationship between exposure and oncologic outcomes are not well established.

The purpose of this study was to examine whether there is a relationship between exposure to AO or 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), the key carcinogenic component in AO, and PC. In addition, we aimed to study the potential impact of AO exposure on PC treatment outcomes, including screening, medication response, radiation response, surgical outcomes, and survival. We intend to address this gap in the literature by performing a systematic review of PC patients with a history of AO or TCDD exposure and analyzing their treatment outcomes.

2. Materials and methods

2.1. Literature search

This systematic review was conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analyses Protocols guidelines[5] and was registered with the National Institute for Health and Care Research. This systematic review was also registered on PROSPERO (International Prospective Register of Systematic Reviews; registration no. CRD42022380814). On December 20, 2022,

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team members searched articles in the PubMed/MEDLINE database published beginning in 1950. The search was limited to studies in humans and those published in English. Search queries were structured to match primary and secondary search terms in sequence. Primary search terms were related to the various terminology associated with AO: Agent Orange, TCDD, or 2,3,7,8-tetrachlorodibenzo-p-dioxin. Secondary search terms referred to PC: prostate cancer, urogenital cancers, urologic cancers, or genitourinary cancers.

2.2. Study selection

Four reviewers (A.P., E.D., Z.S., and A.A.) independently assessed a list of eligible articles deemed relevant to ensure that the inclusion criteria were satisfied. Patients having a history of AO exposure or a laboratory-confirmed history of AO or TCDD exposure who were also given a diagnosis of PC were included. Articles describing PC diagnostic and treatment interventions, such as radiation (brachytherapy or external-beam radiation therapy), chemotherapy, and surgical interventions, were included. Studies examining duplicate cohorts or patients who did not present with both AO exposure and a PC diagnosis were excluded. Figure 1 presents a flow diagram depicting the systematic process for study selection.

2.3. Data extraction

The following data were collected from each study: sample size, study duration, study design, year of publication, variables assessed, analysis techniques presented, and a synopsis of findings. There were no statistical analyses performed. This study was assessed only via a thematic lens, and a report on the frequencies of relevant items was produced. Agent Orange exposure and PC incidence, age of AO-exposed patients at PC diagnosis and treatment initiation, severity of PC course among AO-exposed veterans, and survival of AO-exposed veterans with PC were included in our thematic analysis.

3. Results

The 2 most comprehensive articles from our review were those by Etheridge et al. and Chang et al. Etheridge et al. performed a large observational study of 87,344 Vietnam War veterans being managed for PC, with 3475 veterans having documented AO exposure based on the Veterans Affairs (VA) criteria. Agent Orange exposure by VA criteria includes having a diagnosis associated with AO, service during a specified period in specific areas (Vietnam or Korea), and "evidence that the disease manifested to a degree of 10% or more" after service.[6] The VA considers PC, along with a variety of other cancers, as a presumptive diagnosis, assuming AO exposure based on service location and assuming a malignancy as having arisen as a result of presumptive exposure.[7] Chang et al. presented a narrative review of relevant literature, including some of the highest-quality cohorts. This review included studies

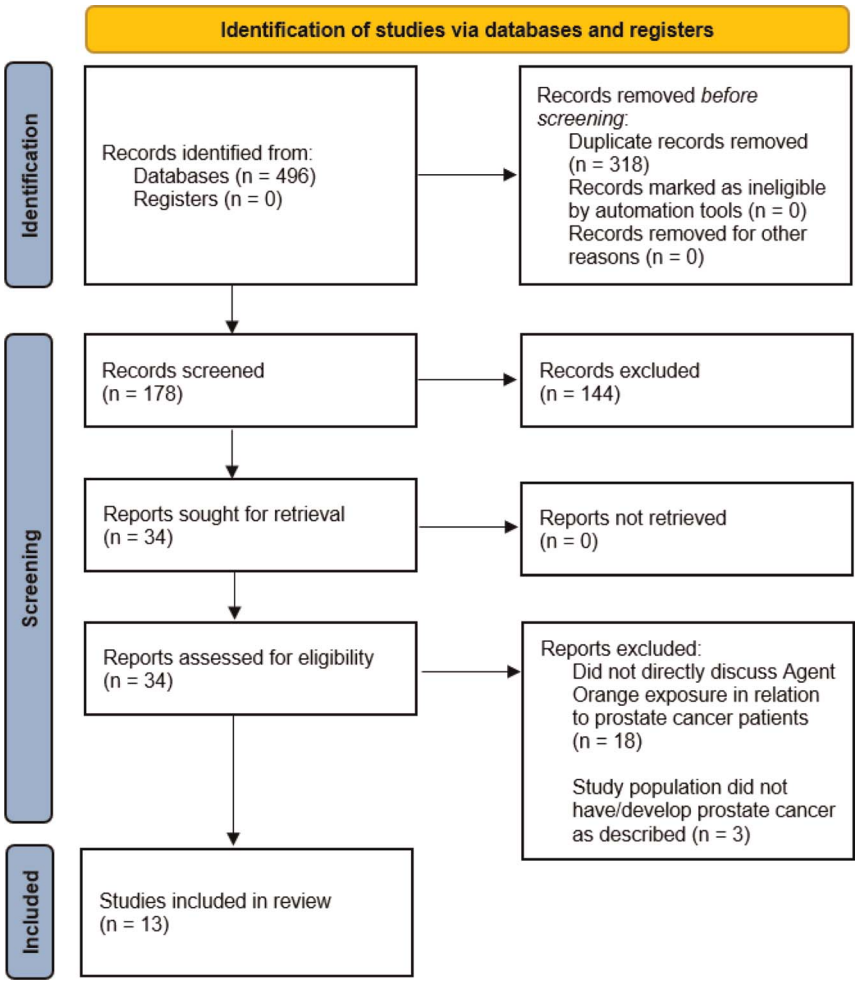

Figure 1. PRISMA flow diagram.

of veterans with measured serum TCDD levels, relevant nonveteran cohorts exposed to TCDD, and studies with reported AO exposure.

Chang et al. suggested that there is a lack of convincing evidence connecting AO exposure to PC and that AO exposure does not confer a mortality difference among patients with PC based on their literature review. They cited a cohort study of 1261 Air Force veterans who directly participated in Operation Ranch Hand, a program that involved spraying herbicides during the Vietnam War. Exposure status was strengthened by the serum TCDD levels of these participants measured in 1987.[8] Follow-up was conducted through 2000.[8] They also referenced an Army Chemical Corps cohort study of 894 veterans with significantly higher serum TCDD levels than matched controls that was expanded in a later study to include 2872 veterans with an assignment to the Chemical Corps that was followed through 2005.[8] Chang et al. found no significant association between TCDD exposure and PC incidence among studies featuring cohorts with either a serum-confirmed or self-reported high likelihood of exposure. In the Ranch Hand cohort, there was no significant difference between the pathologic grade of PC in the exposed and control groups, and in the Chemical Corps cohort, there was no difference in mortality secondary to PC.[8] However, the mortality finding is based on a comparison of only 5 deaths (exposed, n = 2872) and 2 deaths (non-Vietnam veterans, n = 2737).[8] Several other studies discussing the mortality of AO-exposed veterans with PC are similarly limited by small sample sizes. Chang et al. went on to refute positive associations between reported AO exposure and PC from a multitude of smaller studies, some of which are included in this review, and report findings from studies of 2 surrogate cohorts. They reported a National Institute for Occupational Safety and Health study of approximately 21,000 factory workers exposed to herbicides (with heterogeneous follow-up) and a study of residents of Seveso, Italy, exposed to TCDD after an industrial accident in 1976 with follow-up through 1996.[8] Both of these studies revealed no effect of TCDD exposure on PC incidence.[8] Although Chang et al. provide a comprehensive review of the literature studying veterans with a confirmed or high likelihood of TCDD exposure and include relevant comparison patient groups, a potential conflict of interest could exist as the review was financially supported by Dow Chemical Company and Monsanto Company.

Etheridge et al. studied 87,344 VA patients being managed for PC, including 3475 patients with AO exposure recorded in the VA database. All of the patients were given a diagnosis of cancer between 2000 and 2008, and follow-up was conducted until 2016.[6] Surprisingly, there was increased overall survival among the exposed group (hazard ratio [HR], 0.84; 95% confidence interval [CI], 0.73–0.97; p = 0.02) after inverse propensity score weighted adjustment for confounding variables.[6] There was no difference in cancer-specific survival (HR, 0.79; 95% CI, 0.60–1.03; p = 0.08) or the risk of metastasis (HR, 1.04; 95% CI, 0.80–1.35; p = 0.77).[6] However, AO-exposed patients were younger (60 vs. 75 years old, $p < 0.001$) and more likely to receive both local treatment and chemotherapy.[6] There was no difference in Charlson Comorbidity Index scores or prostate-specific antigen (PSA) levels between the 2 groups.[6] Therefore, Etheridge et al. did not reveal reduced survival for those exposed to AO, and the aggressiveness of the disease was also not different.

Leng et al. performed a meta-analysis of cohort studies including 40,286 individuals exposed to TCDD and examined PC mortality, incidence, and relative risk ratios (RRs). They reported a meta-standardized mortality ratio (SMR) of 1.26 (95% CI, 1.00–1.57; p = 0.046) based on 13 studies (n = 16,621, 92 observed deaths) and suggested that TCDD exposure may increase the risk of PC.[9] Despite the high number of individuals studied, there were some methodological flaws and conflicting results that do not support this suggestion. First, none of the studies, when examined individually, included an SMR, RR, or standardized incidence ratio that was statistically significant. In addition, the CI for the meta-SMR was bound to the left by 1.00, but only 2 decimal places were shown.[9] Sensitivity analysis based on "leave-one-out" exclusion revealed several instances in which the meta-SMR was nonsignificant due to the CI including 1.00.[9] In addition, the meta-RR for PC after TCDD exposure was not significant (1.04; 95% CI, 0.85–1.28) after examining 4 studies with more participants (n = 23,625, 133 observed cases).[9] By using SMR (ratio of observed vs. expected deaths) instead of standardized incidence ratio to assess PC risk, we could not exclude the possibility that severe PC mortality, rather than PC incidence (which is associated with risk), was driving the difference. Therefore, it is difficult to support the claim that TCDD exposure increases PC risk using the study by Leng et al.

The rest of the studies in our review studied cohorts of individuals exposed to AO ranging from 32 to 6214 individuals and examined the association between AO exposure and PC incidence, the age of AO-exposed patients at PC diagnosis or treatment initiation, the aggressiveness of PC in AO-exposed PC patients, and the survival of AO-exposed PC patients compared with the general PC population.

Table 1 provides a systematic overview of the included studies.

3.1. Agent Orange exposure and prostate cancer incidence

Five additional studies discussed the relationship between AO exposure and PC incidence.[15–19] Chamie et al. reported that AO exposure doubled the likelihood of PC (odds ratio [OR], 2.19; 95% CI, 1.75–2.75) when comparing 6214 AO-exposed veterans with 6930 unexposed veterans (239 and 124 veterans were given a diagnosis of PC, respectively). Mullins and Loeb included in their analysis the study by Chamie et al. and 2 additional studies (Akhtar et al. and Pavuk et al.) that examined the relationship between AO exposure and PC incidence. Akhtar et al. found an increased incidence of PC among 36 Operation Ranch Hand veterans with measured serum dioxin levels when compared with national data. Conversely, Pavuk et al. found increased rates of PC among veterans who served in Vietnam but no significant association with serum TCDD levels, casting doubt on a potential direct relationship between AO exposure and PC. A separate study conducted by Ansbaugh et al. found a 52% increased risk of being given a diagnosis of PC (adjusted OR, 1.52; 95% CI, 1.07–2.13) after prostate biopsy in 203 AO-exposed veterans (72 PC cases) compared with 2517 veterans who were not exposed to AO (822 PC cases). Chang et al. questioned the reliability of the findings of Chamie et al. and Ansbaugh et al. because of their reliance on the VA's presumptive AO exposure criteria. Furthermore, Chang et al. believed that PC frequency in veterans is likely to be higher than the national average due to increased access to health care, which may account for the findings of Akhtar et al. Therefore, 2 of the studies mentioned in Mullins and Loeb, in addition to that by Ansbaugh et al., reported an increased incidence of PC after AO exposure, but their findings may be diminished by the uncertainty behind exposure status or possibly confounded by increased healthcare utilization and access.[19–21] Regarding the remaining studies, Zafar and Terris reported no correlation between AO exposure and PC (r = 0.06) when comparing 32 AO-exposed patients and 96 matched control patients referred for prostate biopsy. Giri et al. reported that veterans with PC were 2 times more likely to report AO

Table 1

Summary of study sample characteristics, design, variable(s) studied, analysis technique(s), and synopsis of findings.

	Sample characteristics	Design	Variable(s) studied	Analysis technique(s)	Synopsis of findings
Outcomes/ detection					
Etheridge et al.[6]	**Sample size:** 87,344 total VA patients managed for PC, 3475 AO-exposed and 83,869 nonexposed **Study duration:** Cancer diagnosis, 2000–2008; study follow-up to May 2016	Retrospective chart study of VA databases of ADT-treated men with PC	Several PC-related clinical and pathological variables, demographic variables	Adjusted Cox proportional hazards model after propensity score adjustment	→ AO-exposed patients (n = 3475) were younger, had lower PSA levels, and received more local treatment and chemotherapy. → AO improved OS (HR, 0.84). No differences in development of bone metastases or cancer-specific survival were noted. → Local and systemic chemotherapy administration was more common among those who were younger at ADT initiation.
Tward and Tward[10]	**Sample size:** 631 total veterans with prostate adenocarcinoma diagnosis, 70 AO-exposed and 561 nonexposed (median follow-up, 10.0 yr) **Study duration:** All patients in the University of Utah database search since 2012	Single-institution, retrospective chart review of US military veterans born between 1930 and 1956	NCCN risk group, Charlson comorbidity score, smoking status, type of initial therapy	Cox proportional hazards regression analysis	→ AO-exposed veterans were younger and presented at more advanced stages. → No difference in OS, metastasis-free survival, or progression-free survival between the exposed and nonexposed groups. → The AO-exposed group had a younger age and higher stage at presentation, but oncologic outcomes were similar for both groups.
Everly et al.[11]	**Sample size:** 81 Vietnam veterans, 29 AO-exposed and 52 nonexposed; 433 nonveterans of comparable age who underwent prostate brachytherapy **Study duration:** May 1995 to Jan 2005	Single-institution, retrospective chart review of US military veterans born between 1937 and 1953	Several PC-related clinical and pathological variables, demographic variables	Multivariate analysis	→ With 9 yr of follow-up, AO-exposed men were more likely to experience biochemical recurrence (ie, rise in PSA levels). → No significant differences in cause-specific survival or OS → AO exposure did not predict any survival parameters.
Li et al.[12]	**Sample size**: 93 men who underwent RP for PC, 37 AO-exposed and 56 nonexposed **Study duration**: Patients who underwent RP between April 2005 and September 2009. Patients were followed for a median of 5.3 yr for biochemical recurrence.	Single-institution, prospective longitudinal cohort	Several PC-related clinical and pathological variables, health, demographic variables	Multivariate logistic regression	→ Adipose tissue dioxin-TEQ increases in AO-exposed RP patients. → AO exposure and high dioxin-TEQ were not linked to increased risk of biochemical recurrence after RP. → Without associations, AO's carcinogenicity in PC patients was, at best, limited. → AO-exposed men were more likely to be older and non-Black and present with higher dioxin-TEQ levels.
Ovadia et al.[13]	**Sample size:** 1882 men undergoing RP for PC, 333 AO-exposed and 1549 nonexposed **Study duration:** Patients undergoing RP between 1988 and 2011	Multi-institution prospective longitudinal cohort	Several PC-related clinical and pathological variables, health, demographic variables	Logistic regression model and Cox proportional hazards regression analysis	→ AO men were younger and had lower preoperative PSA and clinical staging. → Pathologic staging did not differ between the 2 groups. → AO exposure was not associated with recurrence, receiving secondary treatment, metastasis, or mortality. → No survival difference between the AO-exposed group and the rest of the sample. → AO-exposed men were younger.
Shah et al.[14]	**Sample size:** 1495 veterans with PC undergoing RP, 206 AO-exposed and 1289 nonexposed **Study duration:** Patients undergoing RP between 1988 and 2011	Multi-institution prospective longitudinal cohort	Several PC-related clinical and pathological variables, health, demographic variables	Logistic regression model, linear regression model, and Cox proportional hazards regression analysis	→ AO exposure in patients treated with RP was more common in Black men and younger men. → AO exposure was associated with lower clinical stage, lower preoperative PSA levels at presentation, and poor outcomes. → AO exposure was indicative of increased likelihood of faster biochemical progression and PSA doubling time. → AO exposure was not linked to adverse pathologic features.

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Table 1 *(Continued)*

	Sample characteristics	Design	Variable(s) studied	Analysis technique(s)	Synopsis of findings
Zafar and Terris[15]	**Sample size:** 400 veterans referred for prostate needle biopsy, 32 AO-exposed with 13 having PC and 96 nonexposed age-matched controls with 33 having PC **Study duration:** 1998–2000	Single-institution case-control study	Several clinical and pathological variables	Simple linear regression	→ No correlation between AO exposure and development of cancer. No differences in PSA or pathology between exposed and nonexposed individuals. → No differences in referral of AO-exposed patients and others for prostate biopsy. → AO did not seem to have a causal role in the development of PC.
Risks					
Chang et al.[8]	Studies explored: 37	Narrative review	N/A	N/A	→ No significant increase in PC incidence or mortality among AO-exposed individuals. → No consistent or convincing evidence of a causal relationship between AO and PC.
Chamie et al.[16]	**Sample size:** 6214 AO-exposed and 6930 nonexposed men in the Northern California VA system: 239 AO-exposed with PC and 124 nonexposed with PC **Study duration:** Veterans followed from 1998 to 2006	Multi-institution case-control study	Several PC-related clinical and pathological variables, health, demographic variables	Cox proportional hazards model and multivariate logistic regression	→ Twice as many patients exposed to AO developed PC. → The mean time from exposure to diagnosis was 407 mo. → AO exposure was associated with PC diagnosis at a younger age. These patients were more likely to have advanced disease at presentation. → AO was a predictor of developing PC, high-grade pathology, and metastatic disease at presentation.
Mullins and Loeb[17]	Studies explored: 37	Narrative review	N/A	N/A	→ Numerous studies show an increased incidence of PC among veterans exposed to AO, especially among patients involved in the herbicide distribution operation. → The National Academy of Science investigated AO and found a positive association between AO and various malignancies, including soft tissue sarcomas and several hematologic malignancies. However, there was only "limited or suggestive" evidence of an association between PC and AO exposure. → The VA considers PC as related to AO, providing eligibility for disability compensation.
Giri et al.[18]	**Sample size:** 47 military veterans with PC and 142 controls without PC; of those with PC, 11 AO-exposed and 29 nonexposed **Study duration:** June 2000 to July 2001	Case-control study; single institution	Several PC-related clinical and pathological variables, health, demographic variables	Logistic regression	→ Men with PC were 2 times more likely to report exposure to AO.
Ansbaugh et al.[19]	**Sample size:** 2720 veterans who underwent prostate biopsy, 203 AO-exposed and 2517 nonexposed **Study duration:** N/A	Retrospective cohort study	Several PC-related clinical and pathological variables, health, demographic variables	Logistic regression	→ AO exposure was associated with a 52% increased risk of PC and a 75% increased risk of high-grade PC.
Leng et al.[9]	Studies explored: 17 **Sample size:** 40,286 individuals exposed to TCDD	Meta-analysis	N/A	N/A	→ The risk of developing PC increased with TCDD exposure. TCDD's association with PC was likely due to a combination of factors.

ADT = androgen deprivation therapy; AO = Agent Orange; HR = hazard ratio; NCCN = National Comprehensive Cancer Network; N/A = not applicable; OS = overall survival; PC = prostate cancer; PSA = prostate-specific antigen; RP = radical prostatectomy; TCDD = 2,3,7,8-tetrachlorodibenzo-p-dioxin; TEQ = total equivalent quantity; VA = Veterans Affairs.

exposure compared with those without PC, but their results did not reach statistical significance (OR, 2.06; 95% CI, 0.85–5.23).

To summarize, Etheridge et al. studied the most cases of PC among AO-exposed veterans (n = 3475) and found no increased risk based on exposure. Chang et al. reported a similar result from their narrative review of several studies. Leng et al. had conflicting results for 2 cohorts with approximately 100 cases each while having significant methodological limitations. Chamie et al. and Ansbaugh et al. reviewed a smaller yet substantial number of cases (n = 239 and n = 72, respectively) and reported an increased risk of PC, and the remaining studies (Mullins and Loeb, Zafar and Terris, and Giri et al.) lacked statistical power. Although Etheridge et al. studied a substantially larger cohort than Chamie et al. and Ansbaugh et al., they were all limited by their reliance on the VA's presumption of AO exposure based on service area, increasing the risk for misclassification bias. As a whole, the current literature does not convincingly support an increased risk of PC secondary to AO exposure and is hampered by assumptions regarding presumed AO exposure.

3.2. Age of Agent Orange–exposed patients at prostate cancer diagnosis/treatment initiation

Seven studies examined the age of AO-exposed veterans at PC diagnosis.[6,10,13–16,19] Etheridge et al., Ovadia et al., and Shah et al. reported an earlier age at PC treatment initiation for AO-exposed veterans (n = 3475, n = 333, and n = 206, respectively) treated with androgen deprivation therapy or radical prostatectomy as compared with nonexposed groups (60 vs. 75 years, $p < 0.001$; 59 vs. 62 years, $p < 0.01$; and 58.8 vs. 62.0 years, $p < 0.001$, respectively). Chamie et al. (n = 239) and Tward and Tward (n = 70) both reported a younger age at PC diagnosis for AO-exposed veterans (59.7 vs. 62.2 years, $p = 0.002$, and 64.0 vs. 65.7 years, $p = 0.013$, respectively). Ansbaugh et al. reported that 203 AO-exposed veterans underwent prostate biopsy an average of 4 years earlier than 2517 unexposed veterans (mean age, 60.6 vs. 65.0 years; $p < 0.0001$), and the 74 AO-exposed veterans with a positive biopsy were diagnosed approximately 5 years earlier than the 822 nonexposed veterans with a positive biopsy (mean age, 61.4 vs. 66.1 years; $p < 0.0001$). Zafar and Terris presented the only study designed to answer whether AO exposure is associated with earlier PC onset. Within a 400-veteran cohort referred for biopsy, cancer was detected in 5/17 AO-exposed veterans (29%) and 10/24 veterans without exposure (42%) in the 51- to 60-year age group.[15] By contrast, among patients 50 years or younger, PC was identified in 1/11 (9.1%) and 10/30 (33.3%) veterans with and without AO exposure, respectively.[15] In addressing the possibility of AO exposure lowering the threshold for PC suspicion by providers, the authors reported an average of 1.07% of patients with AO exposure (n = 1194) were referred for prostate biopsy (yearly, 1998–2000) compared with 1.33% of patients without exposure (n = 33,608).[15]

In aggregate, 6 studies including over 4000 patients reported a younger age at PC diagnosis or treatment initiation (approximately 60 years) for veterans exposed to AO when compared with nonexposed veterans, with varying degrees of age difference.[6,10,13,14,16,19] However, Zafar and Terris found decreased detection of PC among AO-exposed veterans versus nonexposed veterans in younger veterans, despite similar biopsy referral rates. Although age stratification is ideal, the small number of patients with a diagnosis of PC renders the study vulnerable to sampling bias, and it cannot reliably be compared with the other studies. Therefore, the evidence suggests that AO exposure is associated with earlier diagnosis and treatment of PC, but the heterogeneity of nonexposed group ages across the studies renders the magnitude of this difference unclear and its clinical significance indeterminate.

3.3. Severity of prostate cancer course among Agent Orange–exposed veterans

Seven studies examined the aggressiveness of PC in AO-exposed patients.[10,12–14,16,19] Chamie et al. compared 239 AO-exposed veterans with diagnosis of PC with 124 nonexposed veterans with a diagnosis of PC. They found higher mean Gleason scores and an increased proportion of high-grade (Gleason score, 8–10) disease in the AO-exposed group (21.8% vs. 10.5%, $p = 0.009$). Patients with AO exposure were also more likely to present with metastasis (13.4% vs. 4.0%, $p = 0.005$).[16] There were no significant differences in PSA levels between the groups.[16] Multivariate logistic regression controlling for race, smoking history, age, and preoperative PSA, among other variables, revealed that AO exposure increased the risk for high-grade disease more than twice (OR, 2.59; 95% CI, 1.30–5.13; $p = .007$) and increased the risk of metastatic disease 4-fold (OR, 4.32; 95% CI, 1.34–13.96; $p = .015$).[16] Similarly, Ansbaugh et al. reported a 2-fold increased risk of high-grade PC in 203 AO-exposed veterans with a Gleason score of 8 or higher, with no significant difference in the incidence of low-grade PC (Gleason score ≤ 6). Shah et al. found an increased risk of biochemical progression, referring to PSA elevation or need for additional treatment, and shorter PSA doubling times for 206 AO-exposed veterans who underwent radical prostatectomy when compared with 1289 unexposed veterans undergoing the procedure. However, there were no significant differences in pathologic grade, and AO-exposed veterans were more likely to have clinical T1 stage.[14] Tward and Tward reported that 70 AO-exposed veterans with a diagnosis of PC were in higher National Comprehensive Cancer Network risk groups, whereas there were no significant differences between metastasis and progression-free survival between these veterans and 561 unexposed veterans. Everly et al. reported no significant difference in grade or stage among 29 AO-exposed and 52 nonexposed veterans who underwent prostate brachytherapy but reported that AO exposure was associated with significantly higher pretreatment PSA and a reduced likelihood of biochemical control. Ovadia et al. examined the courses of 1882 men undergoing prostatectomy in VA records and found that AO exposure was not associated with biochemical recurrence, secondary treatment, or metastasis among 333 veterans exposed to AO, but they had lower preoperative PSA levels and pathologic grade compared with nonexposed veterans. Li et al. found that 37 AO-exposed veterans referred for prostatectomy had significantly higher serum dioxin levels than 56 unexposed veterans undergoing the procedure, but neither AO exposure nor serum dioxin levels were significantly associated with biochemical recurrence. The 7 studies described, in conjunction with the findings of Etheridge et al., are mixed regarding the aggressiveness of PC in veterans with a history of AO exposure.

3.4. Survival of Agent Orange–exposed veterans with prostate cancer

Three studies compared the survival of PC patients exposed to AO and those not exposed to AO.[10,11,13] Tward and Tward followed 70 AO-exposed veterans with PC (median age, 64.0 years) for a median of 10.0 years and found no overall survival difference when compared with 561 unexposed veterans. The authors included smoking status as a variable and found that it negatively impacted overall, metastasis-free, and progression-free survivals.[10] Most studies in our review did not account for smoking status. Ovadia et al. found no difference in overall survival between 333 AO-exposed veterans with PC and 1549 nonexposed veterans (median age, 59 years) with an 85-month follow-up. Everly et al. found similar findings, but the study was limited by a small sample size (29 AO-exposed patients vs. 52 nonexposed patients; median age, 56.5 years) and short follow-up period (median follow-up, 4.5 years). Furthermore, only 2 deaths occurred, both in the exposed group.

In summary, the studies by Etheridge et al. and Ovadia et al., both of which had relatively large cohorts of AO-exposed veterans with PC, found no increased mortality among AO-exposed veterans, whereas the studies cited by Chang et al. and the work by Everly et al. were limited by a small sample size. Ideally, all studies should control for the effect of smoking on mortality.

4. Discussion

Our review revealed strong evidence for an earlier onset of PC among veterans exposed to AO, mixed evidence tending toward increased aggressiveness of malignancy among exposed cohorts (with some studies citing higher grade cancers and shorter PSA doubling times), mixed evidence for increased PC risk (Leng et al. had several analytical issues, including a lack of statistical

significance as highlighted in the review by Chang et al.), and strong evidence for no overall survival differences in exposed veterans.

The heterogeneity of the literature included in this study can be attributed to several factors. The studies greatly varied in the number of participants, ranging from as few as 32 participants with AO exposure to as many as 6214 participants with AO exposure, and the number of centers involved, from single center to multicenter to national databases.[15,16] All studies except those from Operation Ranch Hand in the study by Chang et al. assigned exposure status based on self-reported data and therefore may suffer from response and recall biases. Many studies use the VA's definition of exposure, which determines exposure as service in Vietnam for any length of time between January 9, 1962, and May 7, 1975. Therefore, it is likely that a considerable portion of the exposure groups did not have AO exposure. Furthermore, among studies in which AO exposure was self-reported, it is possible that recall bias may have skewed the results. It has previously been shown that self-reported AO exposure estimates are not closely correlated with serum TCDD levels.[22] In addition, many studies did not control for confounders such as smoking status, which could have adverse effects on survival. Therefore, exposure misclassification, combined with potential surveillance bias, may lead to confounding and biased results, particularly in studies with limited sample sizes and those using single-center data.

The Air Force Health study and the Army Chemical Corps study both relied on confirmed elevated serum TCDD in veterans directly involved in Operation Ranch Hand, who were then matched with nonexposed veterans.[23,24] Both studies found no significant increase in PC incidence among participants with elevated serum TCDD. However, these studies were limited by sample size and were likely underpowered ($n = 19$ and $n = 59$, respectively). Further data were gathered during the Seveso disaster, a major industrial disaster in 1976 that resulted in the highest known civilian exposure to TCDD.[25] Subsequent large epidemiological studies performed with the Seveso community cohort showed increased rates of rectal, lung, and lymphohematopoietic neoplasms, in addition to others, among those exposed.[26] However, in this large sample prospective study ($n = 6745$), PC was not one of the cancers found to have a statistically significant elevated risk in exposed individuals.

Furthermore, there is limited experimental association of TCDD with PC. Toxicological data from animal experiments have shown TCDD to be linked to various benign and malignant tumors in laboratory animals, but no specific link has been found between TCDD and PC. Recently, TCDD was found to have both procarcinogenic and anticarcinogenic effects in a specialized breed of laboratory rat that was designed to model neuroendocrine PC, an aggressive form of PC.[27] In rats exposed in utero to TCDD, PC incidence was increased. However, TCDD was protective against the development of PC in rats exposed during adulthood.[27] Furthermore, 2,4-D and 2,4,5-T, the 2 main ingredients in the mixture of AO, demonstrated no apparent oncogenic effect in experimental animals.[28,29]

Several studies reported an earlier age of onset for PC among AO-exposed patients.[6,13,14] However, there was no change in overall survival among patients exposed to AO. Knowledge of AO exposure status prompts screening and lowers the threshold for PC biopsy. Therefore, the younger age at diagnosis found in studies such as that by Etheridge et al. may be lead time bias due to increased screening, which lowers the threshold for biopsy. Furthermore, although Zafar and Terris cited no statistically significant differences in biopsy rates between AO exposure groups as a whole, the proportion of AO-exposed patients going for biopsy was higher in younger age groups, which supports this theory.

Despite several studies exploring the link between PC and AO exposure, the evidence does not encourage a significantly different approach to the diagnosis and management of PC for veterans exposed to AO. Clinical management of PC, once discovered, should be in accordance with the National Comprehensive Cancer Network treatment guidelines.[30] Although the current US Preventive Services Task Force guidelines do not recommend routine PSA screening for PC regardless of patient risk group, clinicians may make case-by-case decisions regarding PC screening for this patient group based on patient preference and weighing clinical suspicion against the harms of extensive diagnostic workup and treatment.[31]

Despite an abundance of studies on veterans exposed to AO, there are very limited data on Vietnamese soldiers and civilians exposed to AO. Over the course of the Vietnam War, 42 million liters of AO were dispersed over an estimated 3.6 million hectares in Vietnam.[32] Given the increased risk of exposure and large number of individuals exposed, further exploration of the impact of AO on exposed Vietnamese residents is warranted.

This study was limited by the heterogeneity of the included articles, which hampered our ability to conduct a meta-analysis. Furthermore, this study was limited to articles available online. Given that the scientific literature on TCDD was expected to be at its peak in the period after the Vietnam War, many articles available only offline may have been missed. In addition, it is expected that there were many studies conducted in Vietnam and other countries, such as South Korea, that were involved in the Vietnam War. These studies may have been missed if they were not published in English in a PubMed-indexed journal. In addition, although this review was not funded by outside interests, it does include studies that were funded by manufacturers of AO, specifically the study by Chang et al. Because class-action lawsuits have been filed against the manufacturers of AO, it may be advantageous for manufacturers if studies showing null results between AO exposure and PC were published. Therefore, there may be concerns with conflicts of interest, particularly with Chang et al. whose study was funded by Monsanto. However, we broadly analyzed the collective literature and found these findings to be reported by other studies in which no conflicts of interest were present.

Future studies should use a prospective study design that enrolls individuals with a known exposure history. The exposure history can be further corroborated by serologic testing, and PC risk and disease course can be monitored over time to better understand how exposure may alter PC risk and treatment outcomes. Ideally, this would be conducted through the US VA Hospital System, as that is a population of interest. In addition, given the widespread use of next-generation sequencing in most patients, future research should also investigate the link between AO exposure and specific mutations that may increase the individual's susceptibility toward developing PC relative to other types of cancer.

5. Conclusions

Agent Orange may have an association with PC diagnosis, but its relationship to disease progression and survival is less clear. Future research is needed to clarify the effect of exposure on these secondary outcomes. This review is, to the best of our knowledge, the first and only study to examine not only the association between AO and PC but also how exposure impacts oncologic outcomes.

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Statement of ethics

Not applicable.

Conflict of interest statement

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Author contributions

AP, ZS: Conceptualization, methodology, writing–original draft, writing–review and editing;
AA: Methodology, writing–original draft, writing–review and editing;
ED, FW: Writing–original draft, writing–review and editing;
ZH: Conceptualization, supervision, writing–review and editing.

Data availablility

The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

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