The Effects of Agent Orange on Biochemical Recurrence After Radical Prostatectomy in U.S. Vietnam War Veterans: A Correlational Study

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Writer's Comment: My father's fight with prostate cancer from 2005-2006 had always left me curious about the disease. I was able to intern with one of his former physicians, Dr. David Albala, and was finally able to learn the specifics of diagnosing and treating prostate cancer. When Dr. Melissa Bender assigned a literature review in which we could choose our own topic, I knew that I wanted to investigate some aspect of prostate cancer. My personal connection to the disease and my strong interest in veterans populations after work with PTSD treatment organizations motivated me to complete thorough research and construct this paper with the help of Dr. Bender. Many issues plague the veterans' community including prostate cancer, and while prostate cancer treatments are advancing, the post-surgical effects of treatments like radical prostatectomies especially in Agent Orange-exposed individuals must be studied in order for medical providers to provide the best treatments. I hope that readers find it both intriguing and use it to consider further issues within healthcare especially pertaining to military veterans.

Instructor's Comment: The literature review is a challenging genre to master at any stage in one's education. After gathering and reading the most recent studies conducted on a narrow area of scientific research, one must find a way to tell a research story about the materials that will be significant and useful for an audience of experts. In addition, the writer must take on the role of expert and take responsibility for evaluating the methods and results of the research. These can be daunting tasks for many undergraduates, but Jackson Anderson

meets these challenges with professional flare in this literature review. His decision to zero in on research related to a particular demographic group—Vietnam veterans—was both wise in terms of setting appropriate limitations for his review, and timely. As Jackson points out, many veterans are now entering into the age range when prostate cancer is common. All the more reason why Jackson's review and his call for more research in this area is worthy of readers' attention.

—Melissa Bender, University Writing Program

Introduction

Nearly 1 in 9 men will be diagnosed with prostate cancer (PC) in their lifetime. It is estimated that 164,690 new cases of prostate cancer will be diagnosed in 2018 in the U.S. alone [1]. PC is primarily observed in males 65 or older, with those of African American descent having a 56%-312% greater chance of developing PC. Additionally, males with blood relatives previously diagnosed with PC have higher risks to develop PC and typically develop it at younger ages than those without blood relatives previously diagnosed with PC [1,3,14]. Other risk factors to developing PC include rare genetic mutations of the BRCA1 and BRCA2 genes, exposure to ionizing radiation, exposure to the pesticide Agent Orange (AO), and smoking. However, these are not known to be the leading risk factors of PC, while age, race, and family history are [3]. In order to screen for PC, there are two methods in use in the U.S.: a digital rectal exam (DRE) in which physicians check for lumps on the prostates via massage, and a blood exam which tests prostate-specific antigen (PSA) levels. If concerned about lumps or high PSA levels, physicians will recommend a biopsy in which cells from several areas of the prostate are removed in order to check for cancerous cells [2,3,8,14]. If results are cancerous, the patient is given a Gleason Score, which is a number between 2 and 10 representing aggressiveness of the tumor and likeliness to spread based on the pathological characteristics of the cells [11]. There are several available treatment methods for PC: radical prostatectomy (RP), radiation therapy (RT), androgen deprivation therapy (ADT), and active surveillance (AS) [5,7,12]. After treatment, there is a risk of biochemical recurrence (BCR) of cancer in patients [3,5,7,12,13].

This review will focus on the current state of research of BCR in men who underwent a RP for PC and were exposed to AO (AOe) serving in the U.S. armed forces during the Vietnam War. From 1962-1971, the U.S. military used nearly 19 million gallons of the defoliant herbicide AO in Operation Ranch Hand in order to expose enemy insurgents hiding in Vietnamese forests. AO is a mixture of 2,4-dichloro-phenoxyacetic acid and 2,4,5-trichlorophenoxyacetic acid. However, due to the manufacturing process associated with AO, it was contaminated with .05-50 ppm of the known carcinogen 2,3,7,8-tetrachlorodibenzodioxin (TCDD) or dioxin [2,7,12-14]. AO exposure has been linked to several forms of cancer such as soft tissue sarcoma and Non-Hodgkin's Lymphoma [2]. The National Academy of Science has determined that there is limited or suggestive evidence of increased PC risk due to AOe [2,7,13]. As many Vietnam War veterans are coming into the age range where PC is most common, more research is being conducted into outcomes of AOe patients. This includes patient outcomes after RP where data has been collected in AOe military veterans to investigate BCR after RP. This data so far has been inconclusive and the effects of AOe on BCR after RP have been largely disputed in recent years. Many studies have found links between AOe and BCR after RP, and many have not. This leaves a considerable amount of room for prospective future studies to find more evidence regarding the effects of AOe in BCR after RP in order to draw more valid conclusions.

AOe and BCR

Prior to modern AO studies on Vietnam War veterans, studies such as those by Keller-Byrne et al. and Morrison et al. had investigated AOe as a risk factor for PC in farmers and forestry workers [6,10,12,13]. Claims of a link between AOe and PC in these studies brought about new studies aimed at determining if there is statistical significance linking AOe and PC in military veterans. More studies have been conducted in recent years as veterans are reaching the age range in which PC risk is increased [13]. A 2013 study by Ansbaugh et al. determined that AOe can affect the strength of the PC. Veterans with AOe showed a 75% increased risk for developing high grade prostate cancer (HGPC) and a 2.1-fold increase in Gleason Scores of 8 or higher [2]. We can affirm that there is some link between AOe and PC by demonstrating that there

is statistically significant data to support the claim that AOe can affect HGPC and Gleason Scores. Knowing there is a link and understanding the effects of this link on BCR is important in understanding post-treatment risks for AOe individuals.

The association between AOe and BCR after RP has been highly disputed. In 2013, a study by Li et al. found that while AOe increased toxic-dioxin levels in adipose tissue, this did not correlate with increased risk of BCR after RP. It found that better predictors of BCR are tumor stage and Gleason Scores. However, the study had a small, isolated sample size and failed to take into account many variables such as family history, history of smoking, and physical activity after RP [7]. To alleviate the issue of having a small, isolated sample population, and to gain more patient information, studies have begun utilizing the Shared Equal Access Regional Cancer Hospital (SEARCH) database. This database allows statistical analysis over less centralized populations and from varying time periods with an increase in available patient information [5,7,12,13].

In utilizing the SEARCH database, studies still found contradictory results. A study by Ovadia et al. in 2015 claimed that while 37.4% of their subjects developed BCR, there was no significant evidence to link AOe and increased chances of BCR after RP in military veterans [12]. However, a 2010 study by Kane et al. alleged that in veterans who were candidates for AS, meaning low Gleason Scores, low PSA levels, and low stage cancers, AOe was significantly associated with a higher risk of life-threatening PC with BCR after RP. This study used similar regressions models and multivariate analyses with information from the SEARCH database as in Ovadia et al. [5]. This was supplemented by further research by Shah et al. using the SEARCH database where it was found that in a small cohort of 206 AOe individuals there was an increased risk of BCR after RP when adjusting for clinical characteristics and race [13].The previously discussed studies and their claims show highly inconsistent results, suggesting a need for further study. Additional studies could benefit from larger, more representative patient cohorts to gain statistical significance. These studies should also use non-centralized sample sizes, as enabled by the SEARCH database. This would ensure that the patient population would not be a confound and would aid in credibility. Another potential avenue into research on BCR after PC in AOe individuals would be to investigate different populations. Race has been linked to PC risk and it has been shown that people of African

descent are at higher risk for PC than other races. African American troops represented 23% of all combat troops in Vietnam in 1967 [2-5,7,12-14]. In the above-mentioned studies, African Americans represented 42% of the study population in Kane et al., 40% in Ovadia et al., 45% in Shah et al., and 38% in Ansbaugh et al., and [2,5,12,13]. These percentages may reflect the increased PC risk for African Americans or may be a result of AOe. This could be a potential confound in the data which should be taken into account in future studies. Further studies could be more precise and eliminate confounds using the above-mentioned methods and could yield more conclusive results.

AOe and PSA levels after RP

As stated in the introduction, PSA levels can be a significant predictor of PC. However, in recent years, use of PSA testing has been controversial as it can lead to overdiagnosis. This has resulted in many men receiving unnecessary, aggressive treatments for early-stage, slow growing PC. Regardless, use of PSA screenings is still common in regular exams in order to maintain low PC death rates [3,14].

Understanding the effects of AOe on PSA levels after RP can be important in determining whether or not AOe is a significant predictor of BCR. In SEARCH database cohort studies by Ovadia et al. and Shah et al., it was found that PSA levels were lower preoperatively in AOe individuals than in non-AOe individuals (5.8ng/ml vs. 6.74ng/ml) [12,13]. Further, cohort studies by Kane et al., Milecki et al., and Shah et al. found that the mean PSA doubling time (PSADT) was shorter in AOe individuals after RP, especially when adjusted for clinical and pathological variables (8.4 months vs. 18.6 months). This shortened PSADT could suggest development of more aggressive tumors in AOe individuals after RP [5,9,13]. Studies which excluded the SEARCH database, also found that preoperative PSA levels were lower in AOe individuals than non-exposed individuals [2,7]. In a 2013 study by Li et al., the mean maximum PSA was found to be 8.8ng/ml vs. 23.0ng/ml preoperatively. This study also stated that there was no significant association between toxic-dioxin levels in Adipose tissues and PSA levels—in other words AOe did not significantly affect PSA [7]. PSA data could be helpful in finding links between BCR after RP in AOe individuals as significantly increased PSADT shows there are interacting factor between PSA, tumor growth,

and AOe, especially when preoperative PSA levels were so low.

The claim that there is an increase in PSADT in AOe individuals after RP needs to be subjected to further studies. This is an important avenue into understanding tumorigenesis and establishing definitive links between AOe and BCR in RP patients. These studies could address changes in PSA in AOe patients preoperatively and postoperatively and determine the doubling times in both situations. This could also be supported by in-depth studies of Gleason Scores to determine if associations exist between increased PSADT and tumor aggressiveness and growth. In future studies PSA can be an important means of linking AOe with BCR and can be an essential tool in understanding and mitigating BCR in AOe-exposed individuals post RP.

Conclusion

In this review, we examined findings from notable modern studies concerning the role of AOe in BCR after RP in Vietnam War veterans. The review detailed information on AOe and its effects on BCR as well as AOe's effects on PSA as a predictor for BCR. This elucidated the current state of research on the topic, and while it has been extensive and is continuing to shed light on the long-term impacts of AOe, it is obvious from the data described that there is not a consensus in the scientific community as to the effects of AOe on BCR after RP. Studies found very conflicting results which leads us to the conclusion that further research is necessary before any claims can be made.

Past claims concerning links between AOe on PC risk have prompted further studies to accept or rebut these links [2,7,13]. It is important to study BCR after RP in order to understand the effects of AOe and help to educate the medical community on post-treatment outcomes. PSA can be an important predictor of PC and for that reason it is important to study the effects of AOe on PSA after RP as this can correlate with increased BCR. Preoperative PSA levels in AOe individuals were found to be lower in multiple studies [2,7,12,13]. However, after RP, PSADT was found to be higher in AOe individuals, indicating that tumor growth could be occurring post RP [5,9,13]. This could be a significant means of backing claims that AOe increases BCR after RP. Studies which directly investigated post-RP BCR in AOe individuals found very scattered results. Some found evidence that BCR increased

with AOe [5,13]. However, others concluded that BCR and AOe did not correlate [7,12]. An interesting factor to address is that in the 2013 study by Li et al., it was found that AOe was not a good predictor of BCR, but PSA and Gleason Scores were [7]. After investigating the effects of AOe on PSA and seeing a potential increase in PSADT which could lead to BCR, this could confound the study as the AOe may not have predicted BCR but may have predicted PSA increases which correlated to increased BCR.

These studies have left significant room for improvement. In many cases we see small sample sizes or patient populations centralized around one hospital or area [2,5,7,13]. Further, in many studies, adjustments were not made to account for racial status. This is important especially in the case of African Americans who have been shown to have a significantly higher risk for PC, which should be accounted for in the data when African Americans are present [3,7,13,14]. Another factor which has not been addressed is mental health. Rates of depressive and trauma symptoms are significantly higher in veterans and this can affect their perception of the healthcare system as well as decrease the likelihood that they will undergo PC screenings. A 2014 cross-sectional study by Silberbogen et al. showed that in veterans with depressive symptoms there was a decrease in PC screenings and in veterans with depressive and trauma symptoms there was an increase in perceived barriers to screenings such as cost, lack of insurance, and fear of examination [14]. As mental health issues such as PTSD have become a well-known problem amongst veteran populations, especially in Vietnam War veterans, this information could significantly impact studies. The lack of screenings can affect diagnosis rates in veterans and can affect potential AOe data. This shows that there could potentially be a large pool of individuals who are potential candidates for future AOe studies who have yet to come forward, which could greatly affect study results.

While studies have made many attempts to identify links between AOe and BCR after RP, the results have been inconclusive. In addressing the issues mentioned above as well as taking into account more variables such as effects of AOe on PSA scores, future studies could lead towards more promising results. This could help medical professionals to establish new treatment parameters and aid other research into effects of pesticide exposure on post-treatment outcomes in PC patients.

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