Association between Agent Orange Exposure and Nonmelanotic Invasive Skin Cancer: A Pilot Study

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Background: Agent Orange, or 2,3,7,8-tetrachlorodibenzodioxin, has been shown to cause indirect DNA damage, producing malignancies. However, its connection to nonmelanotic invasive skin cancer is unclear. This study investigated whether 2,3,7,8-tetrachlorodibenzodioxin exposure increases the incidence of this cancer.

Methods: The authors retrospectively reviewed the medical records of 100 consecutive male patients with Fitzpatrick skin types I through IV who enrolled in the Agent Orange registry at the Veterans Affairs Hospital of Washington, D.C., between August of 2009 and January of 2010.

Results: The study population's mean age was 65.7 years (range, 56 to 80 years). 2,3,7,8-Tetrachlorodibenzodioxin exposure included living or working in contaminated areas (56 percent), actively spraying it (30 percent), or traveling in contaminated areas (14 percent). Fifty-one percent of patients had nonmelanotic invasive skin cancer; 43 percent had chloracne; and 26 percent had other malignancies, such as prostate (14 percent), colon (3 percent), or bladder cancer (2 percent). The nonmelanotic invasive skin cancer incidence rate in the study population (51 percent) was significantly higher than the national age-matched incidence rate (23.8 percent; $p < 0.001$). High Fitzpatrick skin type score ($p = 0.010$) and dark eye color ($p = 0.036$) were associated with a decreased incidence of the cancer. Exposure by means of active spraying (73 percent versus 67 percent; $p = 0.003$) and presence of chloracne (81 percent versus 28 percent; $p < 0.001$) were associated with increased nonmelanotic invasive skin cancer incidence rates.

Conclusions: 2,3,7,8-Tetrachlorodibenzodioxin exposure appears to be associated with the development of nonmelanotic invasive skin cancer. Further studies are warranted to determine the relative risk within this patient population and to determine appropriate management strategies. (*Plast. Reconstr. Surg.* 133: 432, 2014.)

CLINICAL QUESTION/LEVEL OF EVIDENCE: Risk, II.

Agent Orange is the code name for an herbicide and jungle defoliant developed by the United States military during the Vietnam War. It was composed of a 1:1 mixture of 2,4,5-trichlorophenoxyacetic acid and 2,4-dichlorophenoxyacetic acid.[1] Agent Orange included the toxic compound 2,3,7,8-tetrachlorodibenzodioxin,[2] which, like other dioxins, is a biologically active chlorinated aromatic compound that persists for decades in the environment. 2,3,7,8-Tetrachlorodibenzodioxin has been shown to cause indirect DNA damage through induction or activation of certain compounds.[3] In 1979, Arthur Galston, a Yale biologist studying the compound, referred to it as "perhaps the most toxic molecule ever synthesized by man."[4]

Between 1962 and 1971, more than 20 million gallons of Agent Orange were sprayed over densely forested and rural areas in Vietnam,

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Laos, and Cambodia.[5] Reports showed that up to 13 times the U.S. Department of Agriculture–mandated maximum amount of Agent Orange was applied in some places. Soil and water concentrations in some areas were 100 times greater than the U.S. Environmental Protection Agency "safe" level. Postwar studies showed that levels of 2,3,7,8-tetrachlorodibenzodioxin in Vietnam veterans were also elevated. As early as 1952, the U.S. government knew that Agent Orange was contaminated with 2,3,7,8-tetrachlorodibenzodioxin, although this information was not revealed to the public until 1969. Today, the U.S. Department of Defense and the U.S. Department of Veterans Affairs recognize an association between 2,3,7,8-tetrachlorodibenzodioxin exposure and the following diseases: peripheral neuropathy, amyloidosis, B-cell leukemia, birth defects, chronic lymphocytic leukemia, type 2 diabetes mellitus, Hodgkin and non-Hodgkin lymphoma, ischemic heart disease, multiple myeloma, Parkinson disease, porphyria cutanea tarda, prostate cancer, respiratory cancers, soft-tissue sarcomas, and chloracne.[6,7] As of 2009, there were 485,760 Vietnam veterans with documented Agent Orange exposure registered with the U.S. Department of Veterans Affairs, and many of these veterans reported significant health problems.[8]

Skin cancer is the most common cancer in the United States. The American Cancer Society reports that more than 3.5 million cases of skin cancer were diagnosed in 2010.[9] Each year, there are more new diagnoses of skin cancer than new diagnoses of breast, prostate, lung, and colon cancer combined.[10] One in five Americans will develop skin cancer in their lifetime, and 26 percent of Americans older than 65 years will be diagnosed with skin cancer at least once.[11,12] Basal cell carcinoma, a type of nonmelanotic invasive skin cancer, is the most common form of skin cancer, affecting more than 2.8 million Americans annually. Squamous cell carcinoma, another nonmelanotic invasive skin cancer, is the second most common skin cancer, with more than 700,000 new cases reported annually.

In 1970, the first scientific report was published showing that 2,4,5-trichlorophenoxyacetic acid could cause birth defects in laboratory animals.[13,14] This finding prompted a series of studies in mice that examined the possible negative effects of 2,3,7,8-tetrachlorodibenzodioxin exposure. It was shown to promote the formation of skin papillomas and squamous cell carcinomas in mice and hamsters in multiple studies in subsequent years.[15] Subsequent studies have confirmed that it is a tumor promoter and could potentially act as a promoter for skin cancer initiators. Although 2,3,7,8-tetrachlorodibenzodioxin exposure has been linked to many diseases, its influence in the risk of developing skin cancer in humans remains unclear. Our clinical experience suggests that exposure could influence the risk of developing nonmelanotic invasive skin cancer, perhaps depending on the duration and type of exposure and certain patient characteristics. However, no data supporting this connection are currently available. The purpose of this study was to determine whether prior 2,3,7,8-tetrachlorodibenzodioxin exposure was associated with an increased incidence of nonmelanotic invasive skin cancer.

PATIENTS AND METHODS

After Veterans Affairs Institutional Review Board approval, a retrospective chart review was performed for 100 consecutive patients who enrolled in the Agent Orange Exposure Registry for the Veterans Affairs Hospital of Washington, D.C., between January of 2009 and May of 2010. Patients with Fitzpatrick skin type V or VI were excluded from the analysis. Fitzpatrick skin type, eye color, number of years exposed to 2,3,7,8-tetrachlorodibenzodioxin, type of exposure, time since exposure, number of cutaneous skin cancers (specifically, melanoma, basal cell carcinoma, and squamous cell carcinoma), time between exposure and first diagnosis of nonmelanotic invasive skin cancer (if present), other systemic cancers, and presence of chloracne were determined through chart review, questionnaire, and/or physician interview. Types of exposure included actively spraying 2,3,7,8-tetrachlorodibenzodioxin compounds, living or working in contaminated facilities, or traveling through contaminated areas. Eye color was classified as blue, green/hazel, or brown. Skin malignancies were diagnosed by a board-certified pathologist following excisional biopsy.

Obtaining control data from the Veterans Affairs database for this pilot study was not possible and therefore normative data were used for comparison of the Agent Orange–exposed cohort. Normative data on nonmelanotic invasive skin cancer incidence from the United States general population were used for comparison. In 2006, the estimated total number of new cases of nonmelanotic invasive skin cancer in the U.S. population was 3,507,693, for an overall incidence

of 1.175 percent.[16] However, the incidence of nonmelanotic invasive skin cancer is estimated to be 23.8 percent among those aged 60 to 69 years (annual incidence, 0.279 percent) and 28.3 percent among those aged 70 to 79 years (annual incidence, 0.332 percent).[17–19]

Statistical Analysis

Fitzpatrick skin type classification, eye color, exposure type, and demographic variables were summarized by frequencies. The chi-square test and/or Fisher's exact test (when sample sizes were small) were used to compare the incidence of nonmelanotic invasive skin cancer between subgroups. A binomial test was performed for comparison of study data to normative data in the general population. Values of $p < 0.05$ were considered statistically significant. All tests were two-sided. Statistical analyses were performed in SAS 9.2 (SAS Institute, Inc., Cary, N.C.).

RESULTS

A total of 100 patients were evaluated. The mean age of the study population was 65.7 years (range, 56 to 80 years) (Table 1). Mean time since 2,3,7,8-tetrachlorodibenzodioxin exposure was 41 years (range, 35 to 46 years). Average duration of exposure was 2 years (range, 1 to 4 years). Thirty percent of patients were exposed by actively spraying it, 56 percent were exposed by living or working in contaminated areas, and 14 percent were exposed by traveling in contaminated areas. Fifty-one percent of patients had nonmelanotic invasive skin cancer, 43 percent had chloracne, and 26 percent had other malignancies, including prostate cancer (14 percent), bladder cancer (2 percent), colon cancer (3 percent), laryngeal cancer (3 percent), leukemia (2 percent), lung cancer (1 percent), testicular cancer (1 percent), thyroid cancer (1 percent), and multiple myeloma (1 percent) (Table 1). The incidence of cutaneous melanoma among subjects was 9 percent. In comparison, the overall incidence of melanoma is 3.8 percent[20] in the U.S. general population and 8.8 percent[21] in men aged 65 years and older. The overall average number of nonmelanotic invasive skin cancer lesions per patient was 3.25 (range, 0 to 69).

The nonmelanotic invasive skin cancer incidence rate in the study population was significantly higher than that of the general population of a similar age group [study population (mean age, 65.7 years), 51 percent; age-matched (60 to 69 years) general population, 23.8 percent ($p < 0.001$)]. The mean time between 2,3,7,8-tetrachlorodibenzodioxin exposure and first nonmelanotic invasive skin cancer diagnosis was 28 years (range, 2 to 43 years).

Table 1. Patient Characteristics

Variable	Total No.	No. with NMISC (%)	*p*
Total	100	51 (51)	
Age			0.100
≤65 yr	61	26 (43)	
>65 yr	39	25 (64)	
Fitzpatrick skin type			0.010*
I	14	10 (71)	
II	37	22 (59)	
III	42	19 (45)	
IV	7	0 (0)	
Eye color			0.036*
Blue	38	25 (66)	
Green/hazel	15	9 (60)	
Brown	47	17 (36)	
Exposure type			0.003*
Traveled	14	3 (21)	
Lived or worked	56	26 (46)	
Sprayed	30	22 (73)	
Years exposed			0.096
1	21	12 (57)	
2	61	26 (43)	
3	10	6 (60)	
4	8	7 (88)	
Time since exposure ± SD, yr	41 ± 2.0	41 ± 2.2	0.243
Systemic cancer			0.088
Yes	26	18 (69)	
No	74	33 (45)	
Chloracne			<0.001*
No	57	16 (28)	
Yes	43	35 (81)	

NMISC, nonmelanotic invasive skin cancer.
*Statistically significant.

Fitzpatrick skin type classification significantly affected the nonmelanotic invasive skin cancer incidence rate. The incidence rate was significantly lower among patients with high Fitzpatrick skin type scores (darker skin) than among patients with low Fitzpatrick skin type scores (type I, 71 percent; type II, 59 percent; type III, 45 percent; type IV, 0 percent; $p = 0.01$). Incidence rates were also significantly lower among patients with dark eyes than among those with light eyes (brown, 36 percent; green/hazel, 60 percent; blue, 66 percent; $p = 0.036$).

The incidence of nonmelanotic invasive skin cancer was significantly higher among patients who actively sprayed 2,3,7,8-tetrachlorodibenzodioxin than among patients who traveled to or lived or worked in a contaminated area (sprayed, 73 percent; lived or worked, 46 percent; traveled, 21 percent; $p = 0.003$). However, the length of exposure did not significantly affect nonmelanotic invasive skin cancer incidence ($p = 0.096$), nor did the mean time since exposure ($p = 0.243$).

The incidence of nonmelanotic invasive skin cancer was significantly higher among patients with chloracne than among those who did not have chloracne (chloracne, 81 percent; no chloracne, 28 percent; $p < 0.001$); however, the incidence of other systemic cancers did not significantly affect nonmelanotic invasive skin cancer incidence ($p = 0.088$). The following case reports describe patients who presented to the Veterans Affairs plastic and reconstructive surgery clinic during the period studied and are representative of the study population.

CASE REPORTS

Case 1

A 65-year-old Vietnam veteran who had actively sprayed 2,3,7,8-tetrachlorodibenzodioxin initially presented to the plastic surgery clinic at the Veterans Affairs Hospital of Washington, D.C., in 2009, after undergoing more than 10 excisions of multiple nasal basal cell carcinomas. He had lived his entire life in the Midwest (Wisconsin) and noted minimal lifetime sun exposure. He underwent extensive reconstructive operations, including multiple excisions of nasal basal cell carcinomas involving the dorsum and the right and left medial canthus. He presented again in 2011 with extensive recurrence (T4bN0Mx) involving his right maxillary sinus, nasal cavity, and right orbit extending into his ethmoid air cells and frontal sinus. The tumor board reached the consensus that surgery was not a viable option because of extensive disease. The patient finally underwent palliative chemotherapy and radiation therapy. This illustrates a case of aggressive basal cell carcinoma not commonly seen in populations with minimal sun exposure.

Case 2

A 71-year-old Vietnam veteran who had worked in a 2,3,7,8-tetrachlorodibenzodioxin–contaminated area continuously over a 3-year period (Fig. 1) had chloracne and had undergone 26 excisions for basal cell and squamous cell carcinomas throughout his body. He was initially referred to the Veterans Affairs Hospital of Washington, D.C., for wide excision of a recurrent basosquamous cell carcinoma of his nose in 2009. Subsequently, he underwent multiple additional excisions and a partial rhinectomy, neck dissections, and removal of the anterior table of his frontal sinus. He also received chemotherapy and radiation therapy for recurrent satellite lesions on the left side of his face and left submandibular area and metastasis to his lungs. In 2011, the patient was referred for hospice care. This is an example of aggressive disease that involved multiple regions of a patient's body following 2,3,7,8-tetrachlorodibenzodioxin exposure.

DISCUSSION

2,3,7,8-Tetrachlorodibenzodioxin is among the most carcinogenic compounds ever to undergo widespread use in the environment. To the best of our knowledge, the present study was the first to directly compare 2,3,7,8-tetrachlorodibenzodioxin exposure and the occurrence of nonmelanotic invasive skin cancer in Vietnam veterans. We found that the incidence of nonmelanotic invasive skin cancer was significantly higher among veterans who were exposed to 2,3,7,8-tetrachlorodibenzodioxin than in an age-matched subset of the general population. Furthermore, type of exposure, eye color, and Fitzpatrick skin type affected nonmelanotic invasive skin cancer incidence among the veterans.

The causal relationship between 2,3,7,8-tetrachlorodibenzodioxin and a number of malignancies is well established. In 2004, it was shown that it produces nonmelanotic invasive skin cancer in animal models.[15] Most recently, dioxins were found to cause inflammatory and chloracne-like skin

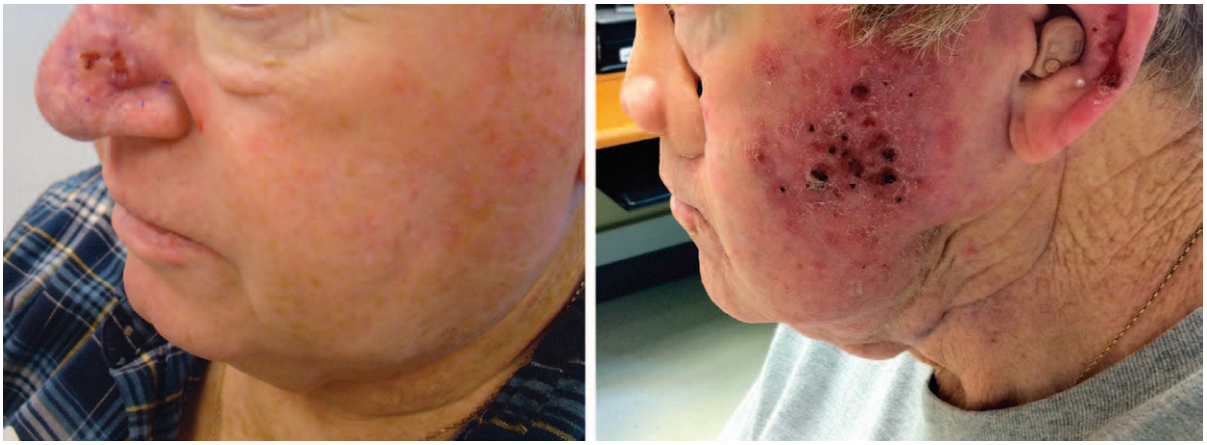

Fig. 1. Squamous cell carcinoma. The patient initially presented with chloracne and a recurrent basosquamous cell carcinoma of his nose in 2009 (*left*). Multiple recurrences required extensive excisions, progressing to a partial rhinectomy that required reconstruction with a paramedian forehead flap and ultimately a prosthesis in 2010. With recurrent satellite lesions on the left side of his face and left submandibular region (*right*) and distant metastasis to his lungs, the patient was referred for hospice care.

lesions in mice exposed to 3,3′,4,4′-tetrachloroazobenzene.[22,23] 2,3,7,8-Tetrachlorodibenzodioxin has been found to be associated with both chloracne and nonmelanotic invasive skin cancer in animal models.[24] The results of our study are consistent with the findings of the animal studies; we found that 2,3,7,8-tetrachlorodibenzodioxin exposure was associated with an increased incidence of both chloracne and nonmelanotic invasive skin cancer in our patient population.

The effects of 2,3,7,8-tetrachlorodibenzodioxin may continue to manifest decades after initial exposure to the compound. Within this study, the mean time since exposure was 41 years (range, 35 to 46 years), and the mean time between exposure and the first nonmelanotic invasive skin cancer diagnosis was 28 years (range, 2 to 43 years). On return home from Vietnam in the 1970s, veterans began to report skin rashes, cancers, congenital anomalies, and psychological symptoms to health care specialists.[25] The veterans' concerns helped start health care programs, compensation programs, and studies centered on the long-term effects of 2,3,7,8-tetrachlorodibenzodioxin; fortunately, some of these programs continue to this day.

In 1994, the Institute of Medicine published a report entitled *Veterans and Agent Orange*.[26] The Institute of Medicine examines the most recent literature on Agent Orange exposure in biological, environmental, and occupational settings among Vietnam veterans and updates the report every 2 years. The most recent report stated that "although [the evidence is] intriguing [there is] inadequate and insufficient information to determine whether there is an association between exposure to [2,3,7,8-tetrachlorodibenzodioxin] and basal cell or squamous cell cancer." A literature search of PubMed yielded a total of four published articles that addressed the human health effects of Agent Orange.[27–29] To the best of our knowledge, the only article addressing a possible link between 2,3,7,8-tetrachlorodibenzodioxin and nonmelanotic invasive skin cancer was a Letter to the Editor in *Plastic and Reconstructive Surgery* in 1984.[30] Plastic surgeons in the California Veterans Affairs system asked readers whether other readers had noted an increased incidence of aggressive and diffuse nonmelanotic cancers in patients exposed to the agent. Similar individuals presenting to our clinic prompted the initiation of this study (see case studies).

The results of our study suggest that service personnel presenting with previous 2,3,7,8-tetrachlorodibenzodioxin exposure should be counseled on cutaneous sequelae in addition to the other malignancies associated with exposure to the agent. In addition, the degree of exposure appears to be related to the risk of developing nonmelanotic invasive skin cancer. Within our clinic, patients are subjected to frequent screenings for skin cancer (at 6-month intervals), which are essential for surveillance of these rapidly growing and invasive cancers. Lesions are treated with aggressive intense pulsed light laser therapy, topical fluorouracils, cryotherapy, and early surgical excision, although recurrence remains high.

This study has several limitations. As a retrospective pilot review, it is inherently subject to recall bias from events occurring decades earlier, specifically, the duration and type of exposure. Although detectable levels of 2,3,7,8-tetrachlorodibenzodioxin were initially measurable within exposed servicemen, its half-life unfortunately makes this information impossible to obtain today. Ideally, a study measuring the effects of 2,3,7,8-tetrachlorodibenzodioxin would compare data from the exposed veterans with data from an age-matched nonexposed population of veterans instead of a normative population. Consequently, the current study is unable to control for sun exposure in a tropical environment.[31] However, obtaining a control group for the current study was not feasible because of current restrictions on the sensitivity of veterans' health information, and thus comparison with a control group is warranted for future studies based on the initial findings of this pilot study. In addition, the results presented in this study are from a small population of patients presenting to the Veterans Affairs Hospital of Washington, D.C., and they may not reflect the general population of veterans. Possible causal relationships and mechanisms of disease etiology explaining the development of chloracne and nonmelanotic invasive skin cancer after 2,3,7,8-tetrachlorodibenzodioxin exposure would be necessarily speculative and require further investigation that extends beyond the scope of this pilot study.

CONCLUSIONS

Our results suggest that 2,3,7,8-tetrachlorodibenzodioxin exposure is associated with the development of chloracne and may be associated with an increased incidence of nonmelanotic invasive skin cancer. Patients involved directly with spraying the agent and those with light eye and skin colors may be most susceptible to the development of nonmelanotic invasive skin cancer. Currently, understanding of the

development of nonmelanotic invasive skin cancer following exposure is incomplete, and this pilot study emphasizes the need for high-quality comparative published data. Further studies that evaluate long-term outcomes in patients who were exposed to 2,3,7,8-tetrachlorodibenzodioxin will be useful in elucidating true incidence rates, outcomes, and ideal surveillance and treatment strategies.

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PATIENT CONSENT

The patient provided written informed consent for the use of his images.

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