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Journal

Endocrine Practice, 22(6)

ISSN

1530-891X

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Publication Date

2016-06-01

DOI

10.4158/ep151108.or

Peer reviewed

Published in final edited form as:

Endocr Pract. 2016 June ; 22(6): 699–702. doi:10.4158/EP151108.OR.

HIGH PREVALENCE OF AGENT ORANGE EXPOSURE AMONG THYROID CANCER PATIENTS IN THE NATIONAL VA HEALTHCARE SYSTEM

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Abstract

Objective—Thyroid cancer is the most common endocrine malignancy and the most rapidly increasing cancer in the U.S. Little is known regarding the epidemiology and characteristics of patients with thyroid cancer within the national Veterans Health Administration (VHA) integrated healthcare system. The aim of this study was to further understand the characteristics of thyroid cancer patients in the VHA population, particularly in relation to Agent Orange exposure.

Methods—This is a descriptive analysis of the VA (Veterans Affairs) Corporate Data Warehouse database from all U.S. VHA healthcare sites from October1, 1999, to December 31, 2013. Information was extracted for all thyroid cancer patients based on International Classification of Diseases–ninth revision diagnosis codes; histologic subtypes of thyroid cancer were not available.

Results—There were 19,592 patients (86% men, 76% white, 58% married, 42% Vietnam-era Veteran) in the VHA system with a diagnosis of thyroid cancer within this 14-year study period. The gender-stratified prevalence rates of thyroid cancer among the Veteran population during the

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DISCLOSURE

The authors have no multiplicity of interest to disclose.

study period were 1:1,114 (women) and 1:1,023 (men), which were lower for women but similar for men, when compared to the U.S. general population in 2011 (1:350 for women and 1:1,219 for men). There was a significantly higher proportion of self-reported Agent Orange exposure among thyroid cancer patients (10.0%), compared to the general VHA population (6.2%) ($P<.0001$).

Conclusion—Thyroid cancer patients, in this sample, have a higher prevalence of self-reported Agent Orange exposure compared to the overall national VA patient population.

INTRODUCTION

The incidence of thyroid cancer, the most common endocrine malignancy, has been steadily increasing in recent decades worldwide. In the U.S., the incidence of thyroid cancer increased by 2.4 fold (from 3.6 to 8.7 per 100,000) from 1973 to 2002, in part due to increased use of diagnostic studies over the past few decades (1). There were approximately 62,980 new cases and 1,890 deaths from thyroid cancer in the U.S. during 2014 (2). Thyroid cancer is more prevalent in women and individuals with a family history of thyroid cancer and in individuals with a history of exposure to head and neck ionizing radiation (3). The Veterans Affairs (VA) patient population may have additional risk factors unique to this specific cohort, including exposure to Agent Orange.

The potential endocrine-disrupting effects of environmental toxicants, including pesticides, have recently been a topic of growing interest, and there are some limited animal literature supporting a possible relationship between pesticide exposure and thyroid cancer (4). The types, indications for use, and extent of exposure of each of these pesticides are likely quite heterogeneous. Agent Orange was the most widely used herbicide in the Vietnam War and was sprayed to remove foliage concealing North Vietnamese troops and to destroy their food crops. It was a mixture of two herbicides (2,4,5-trichlorophenoxyacetic acid and 2,4-dichlorophenoxyacetic acid) but contaminated in minute concentrations with the byproduct 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) during the manufacturing process. The mixture of herbicides was referred to as “Agent Orange” due to the orange stripe painted on the 55-gallon containers in which it was stored. Agent Orange was manufactured by the former Monsanto Company, one of the nine wartime government contractors, and was produced for and used by the U.S. government. Although U.S. planes sprayed approximately 19 million gallons of Agent Orange between 1962 and 1971 over 3.6 million acres in Vietnam (5), it was also applied by boat and ground forces by individuals using back-mounted equipment. The U.S. government has assumed responsibility among Americans for any medical conditions that might be related to Agent Orange exposure.

The association between Agent Orange exposure and a medical condition was first reported in 1977 in a study demonstrating an increased prevalence of soft tissue sarcomas among exposed individuals (6). A class action lawsuit was filed in 1979 by hundreds of Veterans, resulting in the Agent Orange Act in 1991. This legislation by Congress requested that the National Academy of Sciences (NAS) review and evaluate all information regarding the potential adverse health effects related to exposure to Agent Orange and other herbicides used in the Vietnam War. A comprehensive summary published in 1994 reported that there was sufficient evidence of associations between Agent Orange exposure and soft tissue

sarcomas, Hodgkin disease, non-Hodgkin lymphoma, and two dermatologic conditions, chloracne and porphyria cutanea tarda (7). Subsequent reports by the NAS published every 2 years since have continued to evaluate the sufficiency of evidence supporting an association between Agent Orange exposure and multiple health outcomes. Limited evidence from the most recent update suggests additional possible relationships of Agent Orange exposure with certain respiratory cancers (lung, larynx, bronchus, and trachea), prostate cancer, multiple myeloma, type 2 diabetes mellitus, hypertension, stroke, ischemic heart disease, and other conditions (8,9). Following these and other reports, the U.S. has deemed that Agent Orange exposure is a potential adverse result of wartime service, and exposed Veterans and their families have become eligible for certain medical benefits (5). Most recently, a series of reports based on data from the Korean Veterans Health Study demonstrate associations between Agent Orange exposure and several diseases among Korean Vietnam Veterans, including cancers of the stomach, small intestine, liver, larynx, lung, bladder, and thyroid gland, as well as chronic myeloid leukemia (10–14).

The TCDD contaminant in Agent Orange is a known human carcinogen (15), but studies assessing its potential relationship with adverse human health outcomes have been challenging due to difficulties in quantifying the amount and duration of exposure and the long follow-up required. Moreover, the rising incidence of thyroid cancer in the U.S. has not been well-studied among men, who may have additional unique risk factors. The objective of this study was to further understand the epidemiologic characteristics of thyroid cancer in the veteran population on the national level, particularly in relation to Agent Orange exposure.

METHODS

We conducted a retrospective, descriptive epidemiologic study using the VA Corporate Data Warehouse database from all U.S. Veterans Health Administration (VHA) sites from October 1, 1999, to December 31, 2013. The epidemiologic data were extracted based on the International Classification of Diseases–ninth revision diagnosis code for thyroid cancer (i.e., 193.0). Histologic subtypes of thyroid cancer and surgical treatment data were not available.

Agent Orange exposure is self-reported at the initial enrollment of a Veteran into the VA healthcare system. Veterans who served anywhere in Vietnam during the time period from January 9, 1962, to May 7, 1975, and individuals in Korean demilitarized zones, in Thailand, and at U.S. military storage bases during specific timeframes are generally presumed to have been exposed to Agent Orange (16).

Statistical analyses were performed using SAS 9.4. Data were compared against Surveillance, Epidemiology, and End Results and U.S. Census 2011 estimates to calculate gender-stratified prevalence rates (2). A chi-square test was used to analyze differences between Agent Orange exposure among thyroid cancer patients and the general VA population.

RESULTS

All patients with a diagnosis of thyroid cancer in the national VA healthcare system from 1999–2013 (N = 19,592) were included. Patients were 76% white, 86% men, and 42% self-reported Vietnam-era Veterans. The U.S. states with the highest number of thyroid cancer cases were Florida (n = 1,694), California (n = 1,684), and Texas (n = 1,512).

The gender-stratified prevalence rates of thyroid cancer among the Veteran population during the study period were 0.090% (women) and 0.098% (men), which were lower for women but similar for men, when compared to the U.S. general population in 2011 (0.286% for women and 0.082% for men) (2).

The proportion of self-reported Agent Orange exposure was significantly higher among thyroid cancer patients compared to the nonexposed VHA population (10.0% versus 6.2%; $P<.0001$). Only 0.54% of thyroid cancer patients reported a history of ionizing radiation.

DISCUSSION

The incidence of thyroid cancer has been increasing over the past few decades. Tumorigenesis of thyroid cancer is multifaceted and involves both genetic and environmental factors, which include female gender, age, a history of external beam or ionizing radiation during childhood or adolescence, and family history of thyroid cancer. The present study is the first epidemiologic assessment of thyroid cancer among U.S. Veterans at the national level and suggests that Agent Orange exposure may be an additional risk factor in this sample. We confirmed that the gender-stratified prevalence rate of thyroid cancer for males is similar to that of the U.S. general population. The prevalence rate of thyroid cancer is lower in the female Veteran population, possibly due to the relatively younger mean age of this subgroup.

The mechanism supporting a biologic relationship between Agent Orange exposure and tumorigenesis has been studied but remains incompletely understood. The primary concern related to Agent Orange exposure is its content of the dioxin, TCDD, produced as a byproduct contaminant during Agent Orange manufacture. TCDD is a known human carcinogen and endocrine disruptor (17) and is long-lasting in the soil; its half-life in humans is approximately 10 years due to its lipophilic properties. TCDD binds to the aryl hydrocarbon receptor nuclear translocator and activates transcription of several cytochrome P450 enzymes involved in the metabolism and bioactivation of carcinogens, especially polycyclic aromatic hydrocarbons (18). In addition, TCDD has been shown to alter immune balance by affecting dendritic cells, regulatory T cells, and $T_{helper}17$ and $T_{helper}22$ cells (19). Chronic TCDD exposure can disrupt the immune balance and increase susceptibilities to autoimmune disorders. One small observational study has suggested an increased risk of Graves disease, an autoimmune condition of the thyroid gland, among Agent Orange–exposed Veterans (19).

Furthermore, there is some evidence that suggests TCDD can alter thyroid function and metabolism by modulating thyroid transport proteins and/or inducing thyroid hormone catalytic enzymes (20). Experimental animal data in rodents show that TCDD causes a

decrease in serum total and free thyroxine (T4) levels (21). TCDD has been shown to competitively displace T4 from transthyretin, a thyroid hormone transport protein, thus possibly increasing T4 elimination. There are only four human studies that have investigated the effect of TCDD on adult serum human thyroid hormone levels, and the findings have been inconsistent, likely due to their smaller sample sizes and subject demographic patterns. Two studies of 409 individuals by Calvert et al (22) and Ott et al (23) demonstrated a positive association between serum TCDD concentrations and T4 levels in plant workers who had a history of occupational exposure to TCDD; no association was observed with serum thyroid-stimulating hormone (TSH) levels. An Australian study of 37 herbicide-spray workers showed that serum TCDD concentrations were inversely related to triiodothyronine and TSH (24). The largest study was the cross-sectional analysis by Pavuk et al (25), who analyzed serum thyroid hormone concentrations against serum TCDD levels in 1,009 U.S. Air Force Veterans with Agent Orange exposure and 1,429 controls. The investigators reported that there was a positive correlation between serum TCDD and TSH levels but not free T4 index.

In a cross-sectional observational study, Varanasi et al (26) assessed the prevalence of various thyroid conditions including thyroid cancers, thyroid nodules, hypothyroidism, and Graves disease among 225,000 Veterans in upstate New York. The investigators found that Graves disease was 3 times more prevalent among those with a history of Agent Orange exposure, compared to nonexposed Veterans. In contrast, hypothyroidism was less common in the exposed group; there were no differences in the prevalences of thyroid nodules or cancer between the two groups.

Limitations of this observational study include its retrospective design, the unavailability of data regarding thyroid cancer subtypes, linkage to cancer-associated morbidities and mortality, and self-report of Agent Orange exposure. As with any type of research question which requires the use of an electronic health record, the availability of complete, comprehensive, and easily extractable data fields are needed to provide the data required for a rigorous analysis. A particularly unique strength of this study is its large sample size, especially of male patients with thyroid cancer.

CONCLUSION

The study, as the first epidemiologic assessment of thyroid cancer among Veterans at the national level, utilizes the VHA’s single integrated medical record system and suggests that Agent Orange should be further studied in relationship to thyroid cancer. Additional research regarding the strength and consistency of this association may lead to a better understanding of the potential relationship between Agent Orange exposure and thyroid cancer within this population.

ACKNOWLEDGMENT

This work was supported in part by National Institutes of Health grant K23HD068552 (to A.M.L.).

Abbreviations

T4	thyroxine
TCDD	2,3,7,8-tetrachlorodibenzo-*p*-dioxin
TSH	thyroid-stimulating hormone
VA	Veterans Affairs
VHA	Veterans Health Administration

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