Environmental Research 133 (2014) 56–65

Contents lists available at ScienceDirect

Environmental Research

journal homepage: www.elsevier.com/locate/envres

Agent Orange exposure and disease prevalence in Korean Vietnam veterans: The Korean veterans health study

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ARTICLE INFO

Article history:
Received 7 February 2014
Received in revised form
21 April 2014
Accepted 22 April 2014
Available online 4 June 2014

Keywords:
Agent Orange
Dioxins
Herbicides
Prevalence
Veterans

ABSTRACT

Between 1961 and 1971, military herbicides were used by the United States and allied forces for military purposes. Agent Orange, the most-used herbicide, was a mixture of 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid, and contained an impurity of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). Many Korean Vietnam veterans were exposed to Agent Orange during the Vietnam War. The aim of this study was to evaluate the association between Agent Orange exposure and the prevalence of diseases of the endocrine, nervous, circulatory, respiratory, and digestive systems. The Agent Orange exposure was assessed by a geographic information system-based model. A total of 111,726 Korean Vietnam veterans were analyzed for prevalence using the Korea National Health Insurance claims data from January 2000 to September 2005. After adjusting for covariates, the high exposure group had modestly elevated odds ratios (ORs) for endocrine diseases combined and neurologic diseases combined. The adjusted ORs were significantly higher in the high exposure group than in the low exposure group for hypothyroidism (OR=1.13), autoimmune thyroiditis (OR=1.93), diabetes mellitus (OR=1.04), other endocrine gland disorders including pituitary gland disorders (OR=1.43), amyloidosis (OR=3.02), systemic atrophies affecting the nervous system including spinal muscular atrophy (OR=1.27), Alzheimer disease (OR=1.64), peripheral polyneuropathies (OR=1.09), angina pectoris (OR=1.04), stroke (OR=1.09), chronic obstructive pulmonary diseases (COPD) including chronic bronchitis (OR=1.05) and bronchiectasis (OR=1.16), asthma (OR=1.04), peptic ulcer (OR=1.03), and liver cirrhosis (OR=1.08). In conclusion, Agent Orange exposure increased the prevalence of endocrine disorders, especially in the thyroid and pituitary gland; various neurologic diseases; COPD; and liver cirrhosis. Overall, this study suggests that Agent Orange/2,4-D/TCDD exposure several decades earlier may increase morbidity from various diseases, some of which have rarely been explored in previous epidemiologic studies.

1. Introduction

Between 1961 and 1971, around 77 million liters of military herbicides were used by the United States and allied forces in Vietnam to defoliate forests, to clear the perimeters of military installations, and to destroy the enemy's crops (Stellman et al., 2003). The best-known and the most-used herbicide was Agent Orange, which was a mixture of 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T). The phenoxy herbicides in Agent Orange, especially 2,4,5-T, were contaminated with varying levels of dioxin congeners including 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) (Stellman et al., 2003).

Agent Orange was sprayed at base perimeters, roadways, and communication lines, mainly by C-123, military transport aircraft,

Abbreviations: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; AD, Alzheimer disease; aOR, adjusted odds ratio; AhR, aryl hydrocarbon receptor; ALS, amyotrophic lateral sclerosis; BMI, body mass index; CI, confidence interval; CNS, central nervous system; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; EOI, Exposure Opportunity Index; GIS, geographic information system; ICD-10, International Classification of Diseases and Related Health Problems 10th Revision; $Log_{10}E4$, log-transformed E4; NA, not available; NS, nerve system; PD, Parkinson disease; ROK, Republic of Korea; SCC, squamous cell carcinoma; TCDD, 2,3,7,8-tetrachloro-dibenzo-p-dioxin

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http://dx.doi.org/10.1016/j.envres.2014.04.027
0013-9351/

as well as helicopters, riverboats, and trucks (Michalek et al., 1990). Some ground troops who were not on spraying missions were stationed at or saw action in defoliated areas, and they were exposed to Agent Orange by soil contact, drinking water, or bathing (Institute of Medicine, 2011). From the initial deployment of 1964 to complete withdrawal on March 1973, around 320,000 Republic of Korea (ROK) military personnel were deployed in Vietnam (Yi et al., 2001) and many of those veterans were exposed to Agent Orange.

Initial studies on 2,4-D revealed neurotoxic effects of the exposure (Brahmi et al., 2003), and 2,4,5-T exposure was associated with neurotoxicity (Singer et al., 1982) as well as reproductive and developmental toxicity (Lemaire et al., 2006), while TCDD was found to be an endocrine disruptor and a carcinogen to humans, among other toxicities (Baan et al., 2009). The possibility that Agent Orange may cause non-malignant diseases has not received adequate attention; the association between related chemicals and diseases has been explored mainly by mortality studies (Barrett et al., 2001; Consonni et al., 2008; Cypel and Kang, 2010; Pesatori et al., 2003), in which individuals suffering less severe diseases sometimes are underestimated, especially in cases with more severe co-morbidities (Pesatori et al., 2003; Sin et al., 2006). Meanwhile, many non-cancerous morbidity studies have focused on a small number of diseases or broad categories of several diseases combined (Barrett et al., 2001; Goldner et al., 2010; Michalek et al., 2001; Michalek and Pavuk, 2008), and they have generally failed to explore various specific morbidities in populations potentially exposed to Agent Orange/TCDD-related chemicals, partly because of the small number of subjects included in their investigations.

This large-scale study in Korean Vietnam veterans examined the prevalence of various disorders of the endocrine, nervous, circulatory, respiratory, and digestive systems, and evaluated the hazardous effects of Agent Orange exposure on human health by exploring associations between Agent Orange exposure and specific morbidities, after adjusting for major health-related covariates. Agent Orange exposure was assessed by a geographic information system (GIS)-based model.

2. Material and methods

2.1. Study subjects

This study is a part of the Korean Veterans Health Study (KVHS), which was primarily established to evaluate the association between experience in Vietnam and Agent Orange exposure, and the morbidities and mortality from various diseases. In the KVHS study, the authors identified 187,897 veterans in 1999–2000 and then their current address and residence status were obtained as of June 2004 (Yi et al., 2013). Since the original KVHS cohort had information based only on military records during the Vietnam era, it lacked health-related variables and details about the unit in which the veterans had served. After excluding 23,689 individuals who were deceased or had emigrated, 164,208 living veterans were selected for a postal survey. The survey was sent out July 27, 2004, and 114,562 veterans replied (response rate of 69.8%). Finally, 111,726 veterans, whose Agent Orange exposure index was constructed, were included in the analysis. This study was approved by Institutional review board of Kwandong University.

2.2. Case ascertainment

The Korea National Health Insurance (KNHI) claims data from the Health Insurance Review and Assessment Service of Korea from January 1, 2000 to September 30, 2005 were collected. For medical care covered directly by the government through the Veterans Health Service, Veterans Health Service claims data of the same period were collected. The disease diagnosis was identified by the primary diagnosis and first coexisting condition based on the 10th revision of the International Classification of Diseases (ICD-10) codes that were reported in the claims data. We considered a veteran to be a prevalent case when he visited a medical institution for the diagnosed diseases at least once between January 1, 2000 and September 30, 2005 (period prevalence). The research investigated the prevalence of endocrine diseases (E00-E90), neurologic diseases (G00-G99), circulatory diseases (I00-I99), respiratory diseases (J00-J99), and digestive diseases (K00-K93).

2.3. Agent Orange exposure assessment

An Agent Orange exposure index was constructed for the study, adopting the GIS-based Exposure Opportunity Index (EOI) model E4 (Stellman et al., 2003; Yi et al., 2013). This index was based on the proximity of the veterans' military unit to an Agent Orange-sprayed area. A unit-level E4 score was calculated; then an individual E4 score was constructed from the unit served and period deployed. Thus, veterans with the same military unit and period would have the same exposure score. After adding 1 to each E4 score, the common log-transformed E4 score ($Log_{10}E4$) was used as the individual's index of exposure to Agent Orange (Yi et al., 2013). The average score $\pm$ standard deviation, minimum, and maximum of $Log_{10}E4$ were 2.6 ± 2.2, 0.0, and 6.3, respectively.

For the combat units, we used the average E4 score of the operational area when each unit participated in the operation, but when the unit was not part of the operation, we used the E4 score of the unit's post-location to determine the unit's E4 score. For the Construction Support Group, the average score of the tactical area of responsibility was used as the unit's E4 score, while the average score of the post locations was used as the unit's E4 score for the other 3 support units that did not have a tactical area of responsibility. For the veterans whose units served were not identified (0.5%, Table 1), the average score of all units was used as their E4 score.

The Veterans' deployed unit was obtained from the survey. The information on the combat unit in which a veteran served was obtained at the battalion or company level; meanwhile, for the support units, the veterans were asked in which unit they served among ROK Army Headquarters, the Construction Support Group, Naval Transport Group, and 100th Logistic Command. Information on each veteran's period of deployment was obtained from military records.

The veterans were categorized into 2 groups (low ($Log_{10}E4 < 4.0$) and high exposure ($Log_{10}E4 \geq 4$)) and 4 groups (no ($Log_{10}E4 < 0.1$), low ($0.1 \leq Log_{10}E4 < 4.0$), moderate ($4.0 \leq Log_{10}E4 < 5.0$), and high exposure ($Log_{10}E4 \geq 5.0$)). More details about the exposure index can be found elsewhere (Yi et al., 2013). In a total of 111,726 veterans, Agent Orange exposure at the battalion/brigade level was constructed. The distribution of no, low, moderate, and high exposure groups was 34,478 (30.9%), 34,827 (31.2%), 22,452 (20.1%), and 19,969 (17.9%) veterans, respectively.

2.4. Covariates

A veteran's age was calculated, as of January 1, 2000, using the birthdate in the resident registry, and the military rank was obtained from military records. Information on health-related variables, such as smoking, drinking, exercise, body mass index (BMI), domestic (non-military) use of herbicides, education, and household income, as well as the military unit at the battalion or company level in which veterans had served during the Vietnam War, was obtained from the survey. The BMI was calculated from self-reported weight (kg) divided by the squared value of the height (m).

2.5. Statistical analysis

A chi-squared test and ANOVA were performed to compare individual characteristics and prevalence by categories of Agent Orange exposure. Logistic regression analysis was performed to demonstrate the impacts of the exposure on disease prevalence while adjusting for age, military rank (enlisted soldier, noncommissioned officer, officer), smoking (current smoker, past smoker, never smoker), drinking frequency (times; 5 or more/week, 1–4/week, 1–3/month, 1–11/year, no drinking), physical activity (frequency, 10 min or more of moderate or vigorous physical activity; 4 or more times/week, 1–3/week, 1–2/month, no activity), experience of domestic herbicide use (never, ever), education (elementary school or no education, middle or high school, college or over), household income (Korean won, 1 USD=1170 Korean won as of August 1, 2004; < 1,000,000, 1,000,000–1,490,000, 1,500,000–2,490,000, ≥ 2,500,000) and BMI (< 20.5, 20.5–22.9, 23.0–24.9, 25.0–26.9, ≥ 27.0). The Agent Orange exposure was analyzed as a continuous variable ($Log_{10}E4$), and as categorical variables with 2 groups and 4 groups. Analysis for trend was done using an ordinal variable representing the 4 groups of Agent Orange exposure. The *p*-value was calculated with two-sided tests, and a statistical significance level of 0.05 was applied. All statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC, USA).

3. Results

The average age as of January 2000 in the low and high exposure groups was 53.9 ± 3.7 and 55.1 ± 3.1 years, respectively.