

ASSOCIATION BETWEEN AGENT ORANGE EXPOSURE AND DISEASE PREVALENCE OF ENDOCRINE, IMMUNE, AND NERVOUS SYSTEM IN KOREAN VIETNAM WAR VETERANS : KOREAN VIETNAM WAR VETERANS COHORT STUDY

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Introduction

US military used a various herbicide for defoliation and crop destruction during 1962-1971 in Vietnam.¹ A total of 320 thousand Korean soldiers of three combat units and four supporting units participated in Vietnam War from September 1964 to March 1973. Some epidemiologic studies were conducted to find association between Agent Orange exposure and health problems among Vietnam war veterans in Korea. In this study, Agent Orange exposure was estimated using exposure opportunity index by Stellman team's model². The aim of this study was to investigate association between Agent Orange exposure and disease prevalence of endocrine, immune and nervous system in Korean Vietnam War veterans.

Subjects and Methods

Agent Orange Exposure

The army post locations, the tactical areas of operational responsibility and stationing dates of Korean military units was retrieved by reviewing military archives.³ The 6 digit Military Grid Reference System coordinate was used to identify the location. The Exposure Opportunity Index E4 scores of given coordinate and dates, were retrieved by Stellman team. E4 scores for dioxin contaminated herbicides were used. Given the date, the Agent Orange exposure of a unit was the average scores of all E4 scores of coordinates by 1km * 1km within its tactical areas. The E4 score of the Vietnam War veterans was calculated by summation of average E4 scores of the veterans' service unit during their service period in Vietnam. The final Agent Orange exposure (Le4) was calculated by common log transformation of the veterans E4 score. The average of Agent Orange exposure(Le4) of 156,657 veterans was 3.2(±2.1) and the median value was 4.1. The high exposure group(4.0 or greater) was 51.2% and low exposure group was(less than 4.0) 48.8%. 20.5% of veterans were rarely estimated to be exposed to Agent Orange (Figure).

Subjects

The data of the name, date of birth, military identification number, military service unit, period of service and military class at the end of Vietnam service of 297,349 veterans was obtained from the database of the military headquarters. Among 187,897 veterans who were personally identified by national resident registration system, the Agent Orange exposure assessed by Stellman's exposure opportunity index model could be applied to 156,657 veterans.³ Excluding those died, or emigrated before 30 June 2004, a total of 136,603 veterans was included for analysis of disease prevalence. The numbers of low and high exposure group were 67,238 and 69,365, respectively.

Examination of the Disease Prevalence and Statistical Analysis

Period prevalence was calculated from 1 January 2000 to 30 September 2005. Disease prevalence were

derived from health utilization data from the Health Insurance Review Agency Database. A veteran who used medical facility at least once for a specific disease during the period was considered as a prevalence case. Number of cases and prevalences were calculated. Logistic regression models were used to evaluate the relation between Agent Orange exposure and disease prevalence. Age and military class adjusted odds ratios(ORs) and 95% confidence Intervals(CIs) were expressed for the results and probability values were calculated by the 2-tailed test. All statistical analyses were done using SAS software, Version 9.1(SAS Institute, Cary, NC).

Results

Compared to low exposure group, disease prevalences of high exposure group was significantly higher on Neoplasm of uncertain on Thyroid gland(OR=1.55), diabetes mellitus(both insulin dependent, non dependent types), disorders of other endocrine glands, acromegaly(OR=1.76), hypofunction of pituitary gland, metabolic disorders such as lipidaemias and amyloidosis(OR=3.79), episodic and paroxysmal disorders, nerve disorders(G50-G59), polyneuropathies(G60-G64), other epidermal thickening, and xerosis cutis. Post traumatic stress disorder was higher among high exposure group(OR=1.32) with a borderline significance(Table).

Acknowledgments

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References

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2. Stellman SD, Stellman JM. Exposure opportunity models for Agent Orange, dioxin, and other military herbicides used in Vietnam, 1961-1971. *J Expo Anal Environ Epidemiol.* 2004 Jul;14(4):354-62.
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Figure. Distribution of Agent Orange Exposure among Korean Vietnam Veterans

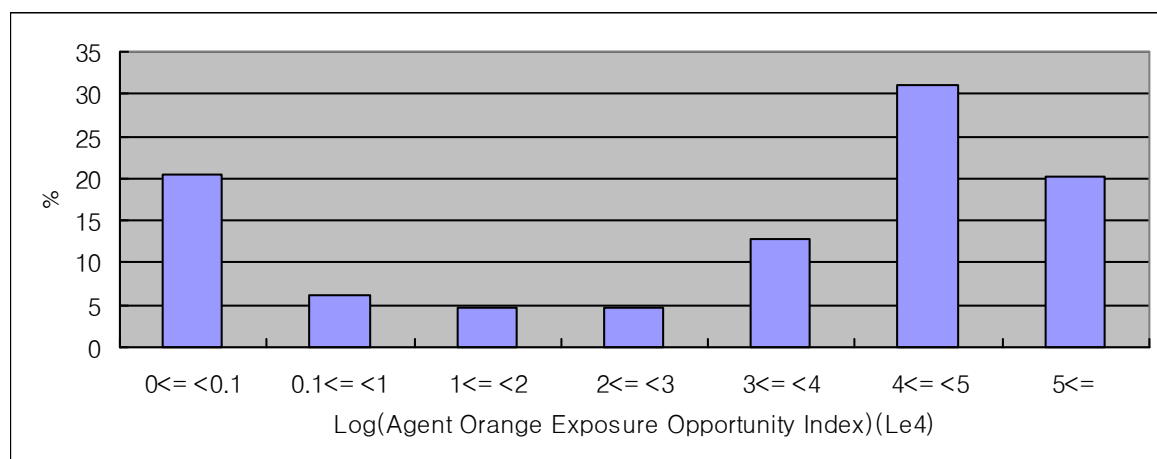


Table. Number of Cases, Prevalences, Odds ratios of Diseases by Agent Orange Exposures

Diseases	ICD10†	Low Exposure*		High Exposure*				
		No. Cases	Prevalence s‡	No. Cases	Prevalence s‡	p-value	Odds ratio§	95% CI
Benign neoplasm of thyroidgland	D34	183	27.2	221	31.9	0.094	1.20	0.97-1.47
Benign neoplasm: Adrenal gland	D35.0	28	4.2	39	5.6	0.130	1.50	0.89-2.52
Benign neoplasm: Pituitary gland	D35.2	39	5.8	59	8.5	0.099	1.43	0.94-2.19
Neoplasm of uncertain or unknown behaviour: Thyroid gland	D44.0	46	6.8	63	9.1	0.037	1.55	1.03-2.35
Neoplasm of uncertain or unknown behaviour: Adrenal gland	D441	9	1.3	15	2.2	0.232	1.73	0.71-4.22
Neoplasm of uncertain or unknown behaviour: Pituitary gland	D44.3	7	1.0	15	2.2	0.165	1.92	0.76-4.84
Idiopathic thrombocytopenic purpura	D69.3	31	4.6	33	4.8	0.823	0.94	0.57-1.57
Certain disorders involving the immune mechanism	D80-D89	16	2.4	25	3.6	0.171	1.59	0.82-3.11
Disorders of thyroid gland	E00-E07	2,947	438.3	3,156	455.0	0.218	1.03	0.98-1.09
Other hypothyroidism	E03	781	116.2	823	118.6	0.843	0.99	0.89-1.10
Other nontoxic goitre	E04	530	78.8	549	79.1	0.648	1.03	0.91-1.17
Thyrotoxicosis [hyperthyroidism]	E05	1,387	206.3	1,418	204.4	0.896	0.99	0.92-1.08
Thyroiditis	E06	262	39.0	253	36.5	0.431	0.93	0.77-1.12
Autoimmune thyroiditis	E06.3	62	9.2	64	9.2	0.780	1.05	0.72-1.54
Diabetes mellitus	E10-E14	17,782	2644.6	20,000	2883.3	<0.001	1.06	1.03-1.09
Insulin-dependent diabetes mellitus	E10	2,673	397.5	3,214	463.3	0.001	1.10	1.04-1.16
Non-insulin-dependent diabetes mellitus	E11	14,875	2212.3	16,821	2425.0	<0.001	1.06	1.03-1.09
Disorders of other endocrine glands	E20-E35	536	79.7	652	94.0	0.010	1.17	1.04-1.33
Acromegaly and pituitary gigantism	E22	35	5.2	54	7.8	0.016	1.76	1.11-2.77
Hyperprolactinaemia	E22.1	19	2.8	28	4.0	0.113	1.65	0.89-3.08
Hypofunction and other disorders of pituitary gland	E23	97	14.4	139	20.0	0.005	1.50	1.13-1.98
Hyperaldosteronism	E26	7	1.0	11	1.6	0.624	1.28	0.47-3.46
Primary hyperaldosteronism	E26.0	0	0.0	5	0.7	0.937	>999	0.00->999
Other endocrine disorders	E34	105	15.6	126	18.2	0.199	1.20	0.91-1.59
Metabolic disorders	E70-E90	15,078	2242.5	15,996	2306.1	0.006	1.04	1.01-1.07
Disorders of lipoprotein metabolism and other lipidaemias	E78	14,125	2100.7	14,978	2159.3	0.006	1.04	1.01-1.07
Amyloidosis	E85	5	0.7	15	2.2	0.016	3.79	1.28-11.25
Dementia in Alzheimer's disease	F00	174	25.9	215	31.0	0.859	0.98	0.80-1.21
Vascular dementia	F01	101	15.0	104	15.0	0.179	0.82	0.62-1.09
Schizophrenia	F20	479	71.2	478	68.9	0.280	0.93	0.81-1.06
Paranoid schizophrenia	F20.0	122	18.1	131	18.9	0.394	1.12	0.86-1.47
Depressive episodes	F32-F33	3,775	561.4	4,181	602.8	0.956	1.00	0.95-1.05
Post-traumatic stress disorder	F43.1	95	14.1	126	18.2	0.056	1.32	0.99-1.75
Systemic atrophies primarily affecting the central nervous system	G10-G13	168	25.0	198	28.5	0.599	1.06	0.85-1.32
Spinal muscular atrophy and related syndromes	G12	143	21.3	171	24.7	0.619	1.06	0.84-1.34
Motor neuron disease	G12.2	51	7.6	54	7.8	0.791	0.95	0.63-1.42

Diseases	ICD10†	Low Exposure*		High Exposure*				
		No. Cases	Prevalence s‡	No. Cases	Prevalence s‡	p-value	Odds ratio§	95% CI
Extrapyramidal and movement disorders	G20-G26	811	120.6	952	137.2	0.627	1.02	0.93-1.13
Parkinson's disease	G20	275	40.9	324	46.7	0.900	0.99	0.84-1.17
Secondary parkinsonism	G21	100	14.9	133	19.2	0.600	1.07	0.82-1.40
Other degenerative diseases of the nervous system	G30-G32	337	50.1	453	65.3	0.079	1.14	0.98-1.32
Alzheimer's disease	G30	61	9.1	92	13.3	0.159	1.27	0.91-1.77
Demyelinating diseases of the central nervous system	G35-G37	275	40.9	368	53.1	0.121	1.14	0.97-1.34
Multiple sclerosis	G35	243	36.1	320	46.1	0.165	1.13	0.95-1.35
Episodic and paroxysmal disorders	G40-G47	12,927	1922.6	14,555	2098.3	0.002	1.04	1.02-1.07
Epilepsy	G40	1,636	243.3	1,951	281.3	0.065	1.07	1.00-1.15
Nerve, nerve root and plexus disorders	G50-G59	6,911	1027.8	7,951	1146.3	0.003	1.06	1.02-1.10
Polyneuropathies and other disorders of the peripheral nervous system	G60-G64	5,729	852.0	6,999	1009.0	<0.001	1.12	1.08-1.16
Cerebral palsy and other paralytic syndromes	G80-G83	1,330	197.8	1,638	236.1	0.148	1.06	0.98-1.14
Crohn's disease [regional enteritis]	K50	647	96.2	677	97.6	0.641	0.97	0.87-1.09
Ulcerative colitis	K51	478	71.1	547	78.9	0.150	1.10	0.97-1.25
Alcoholic liver disease	K70	6,545	973.4	7,031	1013.6	0.005	1.06	1.02-1.10
Toxic liver disease	K71	1,185	176.2	1,289	185.8	0.509	1.03	0.95-1.12
Chronic hepatitis, not elsewhere classified	K73	7,553	1123.3	8,055	1161.2	0.042	1.04	1.00-1.08
Fibrosis and cirrhosis of liver	K74	1,859	276.5	2,098	302.5	0.010	1.09	1.02-1.17
Tropical sprue	K90.1	0	0.0	1	0.1	0.947	>999	0.00->999
Erythema nodosum	L52	22	3.3	25	3.6	0.403	1.31	0.70-2.46
Hidradenitis suppurativa	L73.2	20	3.0	23	3.3	0.158	1.65	0.82-3.30
Vitiligo	L80	210	31.2	267	38.5	0.069	1.19	0.99-1.45
Other epidermal thickening	L85	2,697	401.1	3,238	466.8	<0.001	1.12	1.06-1.19
Xerosis cutis	L85.3	2,447	363.9	2,953	425.7	<0.001	1.13	1.06-1.19
Systemic connective tissue disorders	M30-M36	622	92.5	698	100.6	0.232	1.07	0.96-1.20
Wegener's granulomatosis	M31.3	1	0.1	6	0.9	0.197	4.15	0.48-36.02
Systemic lupus erythematosus	M32	45	6.7	50	7.2	0.469	1.18	0.76-1.82
Behçet's disease	M35.2	74	11.0	85	12.3	0.182	1.26	0.90-1.77

* Low exposure group(n=67,238), High exposure group(n=69,365)

† ICD10 : International Classification of Disease 10th Edition.

‡ Period prevalence, per 10,000

§ logistic regression analysis, adjusted for age as of January 2000, and military class at the end of Vietnam service.