

ASSOCIATION BETWEEN AGENT ORANGE EXPOSURE AND MORTALITY AMONG KOREAN VIETNAM VETERANS USING EXPOSURE OPPORTUNITY INDEX BY STELLMAN TEAM'S MODEL : 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. Until recently, many of Korean Vietnam veterans have been complaining of various health problems which they attributed to exposure to Agent Orange. Some epidemiologic studies were conducted to find association between Agent Orange exposure and health problems among Vietnam war veterans in Korea. However, the Agent Orange exposure assessment model was one of the most important limitations of those studies. 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 mortality 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 1).

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 was 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 31 December 1992, a total of 153,899 veterans was included for analysis of mortality between low and high exposure group.

Follow up on Death and Statistical Analysis

The study subjects were followed up from 1 January, 1993 to 31 December 2004. Data on deaths and their causes were obtained from the Statistics on the Causes of Death by Korea National Statistical Office. Age standardized mortality and indirectly standardized mortality ratio (ISMR) was calculated using 37-82 year-old male general population in Korea during 1993-2004 as standard population. Ratio of indirectly standardized mortality ratio (RISMR) and 95% confidence interval was calculated using exact method.⁴

Results

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 1).

The indirectly standardized mortality ratio (ISMR) of all causes of death among the low and high exposure group to general male population aged 37-82 was 0.79 and 0.87 respectively. The all cause mortality in high exposure group was slightly but statistically higher than that in low exposure group (The high exposure group to low exposure group ratio of ISMR (RISMR)=1.09, 95% confidence interval 1.06-1.13, p-value<0.001). RISMR showed that high agent orange exposure was significantly associated with increasing mortality of neoplasms (RISMR=1.10), lung cancer (RISMR=1.22), thyroid cancer (RISMR=7.88), Chronic myeloid leukemia (RISMR=4.81), diseases of the respiratory system (RISMR=1.25), diseases of the digestive system (RISMR=1.12), liver diseases (RISMR=1.11), alcoholic liver diseases (RISMR=1.34), external causes of mortality (RISMR=1.16), transport accidents (RISMR=1.15) and falls (RISMR=1.35). The high agent orange exposure was borderline significantly associated with increasing mortality of angina pectoris (RISMR=1.83), chronic lower respiratory diseases (RISMR=1.36) and exposure to fire (RISMR=1.76) (Table 1).

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References

1. Institute of Medicine. Veterans and Agent Orange: Health Effects of Herbicides Used in Vietnam. Washington DC. National Academy Press. 1994
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.
3. Ohrr H, Yi SW, Hong JS, et al. An Epidemiologic study on adverse health effects of Agent Orange among Korean Vietnam war Veterans. Yonsei Medical Center, Ministry of Patriots & Veterans Affairs. Seoul, Korea. 2006 (Korean)
4. Breslow NE, Day NE. *Statistical Methods in Cancer Research : Volume II: The Design and Analysis of Cohort Studies.* IARC Scientific Publication, No 82. Lyon: International Agency for Research on Cancer (distributed by Oxford Univ. Press); 1987.

Figure 1: Distribution of Agent Orange Exposure[Log(Agent Orange Exposure Opportunity Index)] among Korean Vietnam Veterans

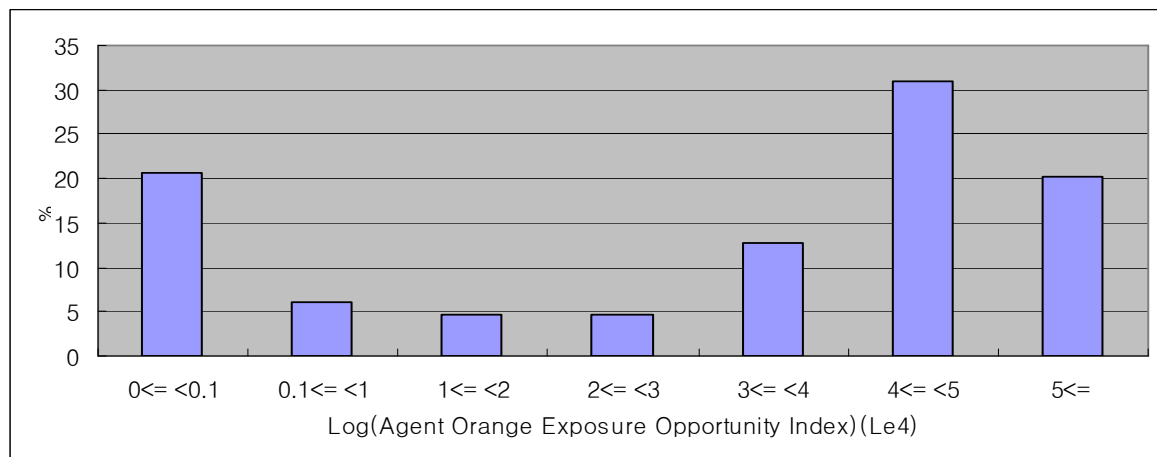


Table 1. Number of Death and Standardized Mortality Ratio by Causes of Death and Exposure Group

Causes of Death	ICD10	Low exposure group*		High exposure group*				
		No. of Death	ISMR†	No. of Death	ISMR †	p-value	RISMR ‡	95% CI
All causes of death	A00-R99, V01-Y89	6294	0.79	7808	0.87	<0.001	1.09	1.06-1.13
Certain infectious and parasitic diseases	A00-B99	150	0.62	154	0.59	0.693	0.95	0.75-1.20
Neoplasms	C00-D48	2135	0.83	2809	0.92	0.001	1.10	1.04-1.17
Oral cavity cancer	C00-C14	26	0.63	34	0.68	0.890	1.07	0.63-1.86
Esophagus cancer	C15	48	0.55	81	0.73	0.145	1.32	0.91-1.93
Stomach cancer	C16	374	0.78	495	0.85	0.218	1.09	0.95-1.25
Small intestine cancer	C17	4	0.68	11	1.43	0.304	2.09	0.62-8.98
Colo-rectal cancer	C18-C21	126	0.90	161	0.97	0.585	1.07	0.85-1.37
Liver cancer	C22	740	0.90	893	0.95	0.343	1.05	0.95-1.16
Gall bladder cancer	C23-C24	75	0.87	95	0.93	0.702	1.07	0.79-1.47
Pancreas cancer	C25	85	0.82	111	0.90	0.567	1.10	0.82-1.47
Larynx cancer	C32	25	0.69	39	0.84	0.528	1.21	0.72-2.09
Lung cancer	C33-C34	363	0.80	546	0.97	0.004	1.22	1.06-1.39
Bone cancer	C40-C41	5	0.68	5	0.65	>0.999	0.95	0.22-4.14
Prostate cancer	C61	12	1.02	15	1.02	>0.999	0.99	0.43-2.33
Renal cancer	C64-C66	26	1.05	27	0.87	0.597	0.83	0.47-1.49
Bladder cancer	C67	17	0.87	29	1.20	0.363	1.38	0.73-2.68
Central nerve system cancer	C70-C72	26	0.73	29	0.72	>0.999	0.99	0.56-1.74
Thyroid cancer	C73	1	0.24	9	1.86	0.036	7.88	1.09-345.
Non-Hodgkin's lymphoma	C82-C85	32	0.90	46	1.09	0.463	1.22	0.76-1.97
Multiple myeloma	C90	15	1.20	13	0.81	0.394	0.68	0.30-1.52
Leukemia	C91-C95	39	0.99	49	1.05	0.886	1.06	0.68-1.65
Acute myeloid leukemia	C92.0	16	1.24	20	1.42	0.804	1.15	0.57-2.37
Chronic myeloid leukaemia	C92.1	2	0.45	12	2.19	0.037	4.81	1.07-44.2

Causes of Death	Low exposure group*			High exposure group*				
	ICD10	No. of Death	ISMR†	No. of Death	ISMR †	p-value	RISMR ‡	95% CI
Diseases of the blood and blood-forming organs	D50-D89	8	0.99	13	1.35	0.643	1.36	0.52-3.79
Endocrine diseases	E00-E88	257	0.76	308	0.77	0.892	1.02	0.86-1.20
Diabetes mellitus	E10-E14	244	0.77	290	0.77	>0.999	1.00	0.84-1.19
Mental disorders	F01-F99	87	0.60	104	0.70	0.287	1.18	0.88-1.59
Mental disorders due to psychoactive substance use	F10-F19	74	0.62	90	0.74	0.273	1.20	0.87-1.66
Diseases of the nervous system	G00-G98	53	0.80	58	0.79	>0.999	0.99	0.67-1.46
Spinal muscular atrophy	G12	7	0.79	7	0.80	>0.999	1.02	0.31-3.41
Parkinson's diseases	G20-G21	11	1.42	8	0.80	0.300	0.56	0.20-1.53
Epilepsy	G40-G41	8	0.58	10	0.74	0.791	1.27	0.45-3.70
Diseases of the circulatory system	I00-I99	1171	0.79	1402	0.81	0.560	1.02	0.95-1.11
Hypertension	I10-I13	63	0.64	87	0.74	0.414	1.16	0.83-1.63
Ischaemic heart diseases	I20-I25	311	0.93	346	0.90	0.683	0.97	0.83-1.13
Angina pectoris	I20	16	0.76	37	1.40	0.054	1.83	0.99-3.52
Acute myocardial infarction	I21	263	0.92	277	0.84	0.336	0.92	0.77-1.09
Chronic ischaemic heart disease	I25	31	1.13	31	1.03	0.804	0.91	0.53-1.55
Subarachnoid haemorrhage	I60	51	1.00	50	0.94	0.864	0.95	0.63-1.43
Intracerebral haemorrhage	I61-I62	293	0.85	347	0.87	0.787	1.02	0.87-1.20
Cerebral infarction	I63	107	0.83	141	0.87	0.752	1.05	0.81-1.36
Diseases of the respiratory system	J00-J98	149	0.60	221	0.76	0.039	1.25	1.01-1.55
Pneumonia	J12-J18	44	0.81	51	0.83	0.964	1.03	0.68-1.58
Chronic lower respiratory diseases	J40-J47	56	0.52	92	0.71	0.077	1.36	0.97-1.94
Diseases of the digestive system	K00-K93	840	0.77	1009	0.86	0.021	1.12	1.02-1.22
Peptic ulcer	K25-K27	14	0.74	17	0.75	>0.999	1.01	0.47-2.21
Liver diseases	K70-K76	761	0.77	911	0.85	0.029	1.11	1.01-1.23
Alcoholic liver disease	K70	136	0.75	184	1.00	0.011	1.34	1.07-1.68
Liver cirrhosis	K74	559	0.76	670	0.84	0.102	1.10	0.98-1.23
Diseases of the musculoskeletal system and connective tissue	M00-M99	18	0.93	13	0.57	0.232	0.61	0.27-1.31
Diseases of the genitourinary system	N00-N98	72	0.87	81	0.84	0.876	0.96	0.69-1.34
Acute renal failure	N17	7	1.00	7	0.86	0.988	0.86	0.26-2.88
Chronic renal failure	N18	50	0.93	53	0.84	0.691	0.91	0.60-1.36
External causes of morbidity	V01-Y89	1188	0.87	1442	1.01	<0.001	1.16	1.08-1.26
Transport accidents	V01-V99	415	0.77	501	0.89	0.039	1.15	1.01-1.31
Falls	W00-W19	102	0.81	148	1.09	0.023	1.35	1.04-1.75
Accidental drowning	W65-W74	48	0.91	37	0.72	0.338	0.79	0.50-1.24
Exposure to fire	X00-X09	19	0.74	32	1.30	0.066	1.76	0.97-3.28
Accidental poisoning	X40-X49	29	0.76	47	1.14	0.110	1.49	0.92-2.46
Intentional self-harm	X60-X84	297	0.92	339	1.01	0.236	1.10	0.94-1.29
Assault	X85-Y09	31	1.14	37	1.47	0.357	1.29	0.78-2.15

* Low exposure group(n=75,170), High exposure group(n=78,737)

† ISMR : Indirectly standardized mortality ratio, standardized to the total male population of 37-82 years-old in Korea by death-year, 1 year-old interval.

‡ Ratio of ISMR, ISMR in high exposure group/ISMR in low exposure group