ASSOCIATION BETWEEN AGENT ORANGE EXPOSURE AND CANCER INCIDENCE AMONG KOREAN VIETNAM WAR VETERANS USING EXPOSURE OPPORTUNITY INDEX MODEL : KOREAN VIETNAM WAR VETERANS COHORT STUDY

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Abstract

A total of 320 thousand Korean soldiers of three combat units and four supporting units participated in Vietnam War. The aim of this study was to investigate association between Agent Orange exposure and cancer incidence in Korean Vietnam War veterans. Agent Orange exposure was estimated using exposure opportunity index model by Stellman. A total of 153,463 veterans was included for analysis. The numbers of low and high exposure group were 74,978 and 78,485, respectively. Indirectly standarized incidence ratio(ISIR), and ratio of indirectly standardized incidence ratio (RISIR) by exposure group and 95% confidence interval was calculated using exact method. Cancer incidence of all sites of cancer was not significantly associated with Agent Orange exposure. High exposure group had increased risks of lip and oral cavity cancer(RISIR=1.87, 95% CI: 1.13-3.18), and chronic myeloid leukemia(RISIR=2.56, 95% CI=0.88-8.99, p=0.092) with a borderline significance. Agent Orange exposure was not associated with the incidences of Hodgkin's disease, non-Hodgkin's lymphoma, lung cancer, laryngeal cancer and multiple myeloma.

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 model[2]. The aim of this study was to investigate association between Agent Orange exposure and cancer incidence 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 archieves.[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($\pm$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 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, emigrated, or developed cancer before 31 December 1992, a total of 153,463 veterans was included for analysis of cancer incidence. The numbers of low and high exposure group were 74,978 and 78,485, respectively.

Follow up on Death and Statistical Analysis

The study subjects were followed up from 1 January, 1993 to 31 December 2002. Data on cancer incidence were obtained from the National Cancer Incidence Database by the Central Cancer Registry. Age standardized incidence and indirectly standardized incidence ratio(ISIR) was calculated using 37-81 year-old male general population in Korea during 1993-2002 as standard population. Ratio of indirectly standardized incidence ratio (RISIR) and 95% confidence interval was calculated using exact method.[4]

Results

Total cancer cases of all sites of cancer among the low and high exposure group were 3055 and 3766 respectively. The ISIR of all sites of cancer among the low and hight exposure group were 0.93 and 0.97 respectively. Cancer incidence of all sites in high exposure group was slightly but insignificantly higher than that in low exposure group(The high exposure group to low exposure group ratio of ISIR(RISIR)=1.04, 95% confidence interval 0.99-1.09, p-value=0.104). RISIR showed that high agent orange exposure was significantly associated with increasing incidence of lip and oral cavity cancer(RISIR=1.87). The high agent orange exposure was bordeline significantly associated with increasing incidence of chronic myeloid leukemia(RISIR=2.56). Those cancers suggested by Institute of Medicine [5] as sufficient or suggestive evidence of association with Agent Orange, such as Hodgkin's disease, non-Hodgkin's lymphoma, lung cancer, laryngeal cancer and multiple myeloma was not significantly associated with Agent Orange in this study(Table 1).

Acknowledgments

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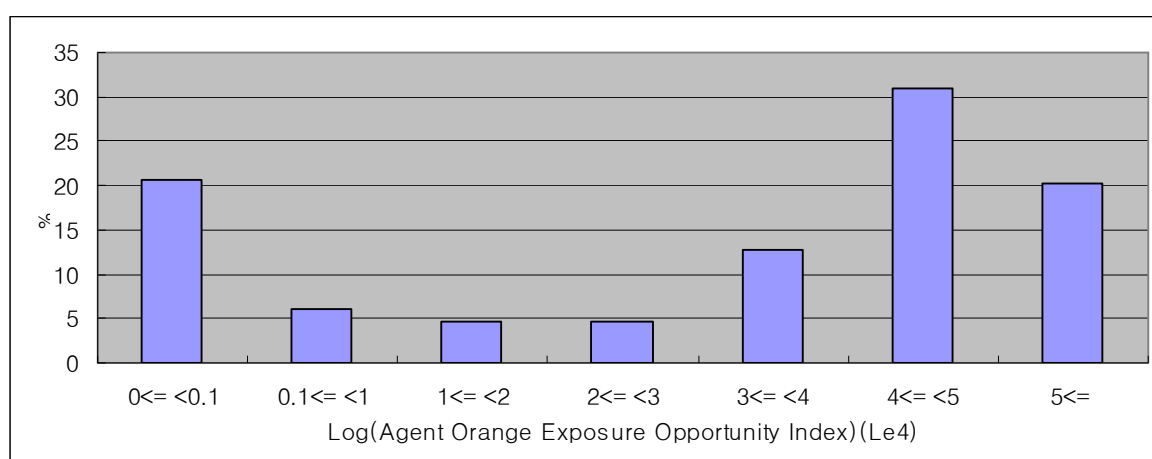

Table 1. Number of Cases and Standardized Incidence Ratio by Types of Cancers and Exposure Group

Types of Cancer	ICD10	Low exposure group*		High exposure group*				
		No. of Cases	ISIR✝	No. of Cases	ISIR✝	p-value	RISIR ‡	95% CI
All cancers	C00-C97	3055	0.93	3766	0.97	0.104	1.04	0.99-1.09
Lip and oral cavity	C00-C09	24	0.51	51	0.95	0.013	1.87	1.13-3.18
Tongue	C01-C02	9	0.64	13	0.83	0.713	1.29	0.51-3.41
Mouth	C03-C06	6	0.36	17	0.90	0.070	2.50	0.94-7.74
Tonsil	C09	7	0.82	8	0.84	1.000	1.03	0.33-3.35
Pharynx	C10-C14	36	0.97	38	0.84	0.608	0.86	0.53-1.40
Oorpharynx	C10	3	0.82	5	0.99	1.000	1.21	0.23-7.76
Nasopharynx	C11	21	1.27	18	0.98	0.511	0.77	0.39-1.52
Pirigorm sinus and hypopharynx	C12-C13	11	0.71	13	0.65	0.984	0.92	0.38-2.26
hypopharynx	C13	8	0.80	9	0.67	0.898	0.84	0.29-2.50
Other oral cavity	C14	1	0.70	2	1.08	1.000	1.54	0.08-91.12
Esophagus	C15	61	0.69	93	0.80	0.396	1.17	0.83-1.64

| Types of Cancer | ICD10 | Low exposure group* | | High exposure group* | | | | |
		No. of Cases	ISIR✝	No. of Cases	ISIR✝	p-value	RISIR ‡	95% CI
Stomach	C16	738	0.87	942	0.94	0.124	1.08	0.98-1.19
Small intestine	C17	9	0.80	17	1.27	0.362	1.57	0.66-4.01
Colorectum	C18-C21	325	0.96	389	0.98	0.835	1.02	0.88-1.18
Colon	C18	164	1.07	168	0.94	0.254	0.88	0.70-1.09
Rectum	C19-C20	159	0.88	216	1.01	0.193	1.15	0.93-1.42
Anus	C21	2	0.57	5	1.14	0.646	2.02	0.33-21.18
Liver	C22	742	0.97	850	0.97	0.998	1.00	0.91-1.11
Biliary tract	C23-C24	71	0.92	108	1.16	0.141	1.27	0.93-1.73
Pancreas	C25	68	0.88	87	0.95	0.724	1.07	0.77-1.50
Nasal cavity and accessory sinuses	C30-C31	2	0.21	7	0.65	0.239	3.14	0.60-30.98
Acessory sinuses	C31	1	0.16	3	0.44	0.680	2.79	0.22-146.50
Larynx	C32	53	0.89	70	0.94	0.869	1.05	0.72-1.53
Lung	C33-C34	390	0.90	537	0.99	0.150	1.10	0.97-1.26
Other chest	C37-C38	10	1.16	10	1.04	0.977	0.89	0.33-2.39
Thymus	C37	7	1.34	6	1.02	0.828	0.76	0.21-2.65
heart and mediastinum	C38	3	0.89	4	1.07	1.000	1.21	0.20-8.23
Bone	C40-C41	6	0.91	8	1.09	0.963	1.19	0.36-4.15
Melanoma	C43	6	0.88	7	0.96	1.000	1.09	0.31-3.92
Other skin	C44	28	1.13	30	1.07	0.953	0.95	0.55-1.65
Mesothelioma	C45	1	0.54	1	0.42	1.000	0.77	0.01-60.58
Nerves, peritoneum, and other soft tissue	C47-C49	12	0.98	11	0.75	0.672	0.77	0.31-1.91
Peritoneum	C48	3	0.78	4	0.92	1.000	1.18	0.20-8.07
Breast	C50	5	2.41	3	1.39	0.679	0.57	0.09-2.95
Penis	C60	1	0.38	0	0.00	.	0.00	
Prostate	C61	49	1.60	39	0.98	**0.029**	**0.61**	**0.39-0.95**
Male genital organs	C60,C62,C63	5	0.87	1	0.15	0.156	0.17	0.00-1.54
Testis	C62	3	1.80	0	0.00	.	0.00	
Other male genital organs	C63	1	0.69	1	0.46	1.000	0.67	0.01-52.27
Kidney	C64	74	1.23	62	0.90	**0.084**	**0.73**	**0.51-1.04**
Renal pelvis	C65	11	1.66	10	1.28	0.696	0.77	0.29-1.99
Ureter	C66	6	1.23	9	1.37	1.000	1.11	0.35-3.78
Bladder	C67	92	1.06	104	1.01	0.775	0.95	0.71-1.27
Eye	C69	0	0.00	1	0.65	.	0.00	
Central nerve system	C70-C72	22	0.79	26	0.86	0.877	1.09	0.59-2.02
Brain	C71	19	0.75	24	0.88	0.730	1.17	0.61-2.25
Thyroid	C73	32	1.18	38	1.26	0.899	1.06	0.65-1.76
Adrenal gland	C74	0	0.00	3	1.23	.	0.00	
Hodgkin's disease	C81	6	1.21	4	0.77	0.706	0.64	0.13-2.70
Non-Hodgkin's lymphoma	C82-C85	61	0.95	75	1.04	0.672	1.09	0.77-1.56
Follicular Hodgkin's lymphoma	C82	5	1.13	3	0.62	0.641	0.55	0.09-2.85
Diffuse Hodgkin's lymphoma	C83	32	1.04	35	1.00	0.962	0.96	0.58-1.60
Diffuse Large cell lymphoma	C83.3	26	1.06	32	1.15	0.841	1.09	0.63-1.91

Types of Cancer	ICD10	Low exposure group*		High exposure group*				
		No. of Cases	ISIR✝	No. of Cases	ISIR✝	p-value	RISIR ‡	95% CI
T-cell lymphomas	C84	7	1.13	13	1.80	0.433	1.60	0.59-4.74
Peripheral T-cell lymphoma	C84.4	3	0.91	8	2.06	0.348	2.27	0.54-13.27
Multiple myeloma	C90	18	1.18	22	1.16	1.000	0.98	0.50-1.94
Multiple myeloma	C90.0	17	1.27	17	1.00	0.591	0.79	0.38-1.64
Lymphoid leukemia	C91	8	1.34	5	0.74	0.439	0.55	0.14-1.92
Acute lymphoblastic leukemia	C91.0	5	1.33	3	0.68	0.555	0.51	0.08-2.61
Myeloid leukemia	C92-C94	32	1.12	40	1.19	0.868	1.07	0.66-1.76
Acute myeloid leukemia	C92.0	22	1.34	18	0.95	0.351	0.71	0.36-1.38
Myeloid leukemia	C92	30	1.09	40	1.25	0.661	1.15	0.70-1.90
Chronic myeloid leukemia	C92.1	5	0.63	15	1.60	**0.092**	**2.56**	**0.88-8.99**
Other leukemia	C95	3	1.75	1	0.53	0.549	0.30	0.01-3.74

* Low exposure group(n=74,978), High exposure group(n=78,485)

✝ ISIR : Indirectly standardized incidence ratio, standardized to the total male population of 37-81 years-old in Korea by death-year, 1 year-old interval.

‡ ratio of ISIR, ISIR in high exposure group/ISIR in low exposure group