Original Article

Agent Orange Exposure and Cancer Incidence in Korean Vietnam Veterans: A Prospective Cohort Study

Sang-Wook Yi, MD, PhD[1]; and Heechoul Ohrr, MD, PhD[2]

BACKGROUND: During the Vietnam War, US and allied military sprayed approximately 77 million liters of tactical herbicides including Agent Orange, contaminated with 2,3,7,8-tetrachlorodibenzo-p-dioxin. To the authors' knowledge, few studies to date have examined the association between Agent Orange exposure and cancer incidence among Korean veterans who were exposed to Agent Orange during the Vietnam War. **METHODS:** An Agent Orange exposure index, based on the proximity of the veteran's military unit to the area that was sprayed with Agent Orange, was developed using a geographic information system-based model. Cancer incidence was followed for 180,251 Vietnam veterans from 1992 through 2003. **RESULTS:** After adjustment for age and military rank, high exposure to Agent Orange was found to significantly increase the risk of all cancers combined (adjusted hazards ratio [aHR], 1.08). Risks for cancers of the mouth (aHR, 2.54), salivary glands (aHR, 6.96), stomach (aHR, 1.14), and small intestine (aHR, 2.30) were found to be significantly higher in the high-exposure group compared with the low-exposure group. Risks for cancers of all sites combined (aHR, 1.02) and for cancers of the salivary glands (aHR, 1.47), stomach (aHR, 1.03), small intestine (aHR, 1.24), and liver (aHR, 1.02) were elevated with a 1-unit increase in the exposure index. **CONCLUSIONS:** Exposure to Agent Orange several decades earlier may increase the risk of cancers in all sites combined, as well as several specific cancers, among Korean veterans of the Vietnam War, including some cancers that were not found to be clearly associated with exposure to Agent Orange in previous cohort studies primarily based on Western populations. ***Cancer* 2014;120:3699-706.** *© 2014 American Cancer Society.*

KEYWORDS: Agent Orange, cancer, cohort studies, dioxins, herbicides, incidence, Korea, veterans.

INTRODUCTION

During the Vietnam War, the United States and allied military sprayed approximately 77 million liters of tactical herbicides for military purposes.[1] 2,4,5-trichlorophenoxyacetic acid in Agent Orange, the herbicide used most often in Vietnam, was being contaminated by 2,3,7,8-tetrachloro-dibenzo-p-dioxin (TCDD),[2] a known human carcinogen.[3] Agent Orange contained >1000 times the TCDD level of commercial 2,4,5-trichlorophenoxyacetic acid manufactured for domestic use.[2] From 1964 to 1973, the Republic of Korea (ROK) sent approximately 320,000 military personnel to Vietnam.[4] Many of these military personnel were presumed to be exposed to Agent Orange.

Several cohort studies have shown that those exposed had a lower mortality or incidence of cancer than the general population, largely because more healthy and fit individuals were selected to be workers or soldiers (the "healthy worker effect").[5-8] To investigate the association between exposure to TCDD/herbicides with cancer in populations in which a strong healthy worker effect was observed, the risk of cancer in the exposed individuals should be compared with more comparable controls rather than the general population.[6,9]

To the best of our knowledge, the association between Agent Orange exposure and cancer incidence by exposure level has rarely been examined in Korean veterans of the Vietnam War.[4] Corresponding American studies on Vietnam veterans have had limitations in exploring infrequent cancers due to a small number of subjects.[10,11] The purpose of the current large-scale cohort study was to investigate the association between exposure to Agent Orange and cancer incidence in Korean Vietnam veterans.

Corresponding author: Heechoul Ohrr, MD, PhD, Department of Preventive Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea. 50 Yonsei-ro, Seodaemun-gu, Seoul, 120-752, Republic of Korea; Fax (011) 82-2-392-8133; ohrr@yuhs.ac

[1]Department of Preventive Medicine and Public Health, Catholic Kwandong University College of Medicine, Gangneung, Gangwon-do, Republic of Korea; [2]Department of Preventive Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea.

See editorial on pages 3595-7, this issue.

We wish to express sincere appreciation to Dr. J.M. Stellman and Dr. S.D. Stellman for their permission to use their herbicide exposure data. We also thank the staff of the National Cancer Center of Korea for the National Cancer Incidence Database.

Additional Supporting Information may be found in the online version of this article.

DOI: 10.1002/cncr.28961, **Received:** March 1, 2014; **Revised:** May 1, 2014; **Accepted:** May 21, 2014, **Published online** August 7, 2014 in Wiley Online Library (wileyonlinelibrary.com)

MATERIALS AND METHODS

Study Subjects

The current study is a part of the Korean Veterans Health Study, which was established primarily to evaluate the association between military service in Vietnam and Agent Orange exposure, and the morbidities and mortality from various diseases. In the Korean Veterans Health Study, the authors identified 187,897 veterans between 1999 and 2000 and confirmed their official residential status as of June 2004 with the cooperation of the Ministry of National Defense and then the Ministry of Government Administration and Home Affairs.[4] Because the administrative database of resident registration deleted most information on the deceased before 1992, the study cohort was considered to be established as of January 1, 1992. After excluding 7646 individuals who were deceased (1390 individuals), emigrated to another country (444 individuals), had an unknown residency status (303 individuals), were reported to have cancer before 1992 (495 individuals), or whose exposure to Agent Orange could not be determined due to a lack of necessary information (5014 individuals), a final total of 180,251 veterans were selected to follow with regard to cancer incidence starting from January 1, 1992.

Follow-Up and Case Ascertainment

The Korea National Cancer Incidence Database (NCIDB) enabled us to confirm the veterans' cancer diagnosis during 1992 through 2003.[12] When a veteran was diagnosed with cancer or died of any cause before a cancer diagnosis was made by December 31, 2003, the reported date of cancer diagnosis or death was considered the end of follow-up. When veterans emigrated to another country or their residential status was cancelled (residency unknown) before December 31, 2003, the changed date of residential status was considered to be the date of their being lost to follow-up. A complete follow-up was made for 176,605 veterans (98%). No cancer detected by death certificate only was included. The current study was approved by Institutional Review Board of Kwandong University.

Cancer Classification

Codes from the *International Classification of Diseases, 10th Revision* (ICD-10) provided from the NCIDB were used to categorize cancer by site. The classification of cancer followed the grouping used by the International Agency for Research on Cancer (IARC).[12] Several subcategories of leukemia were also included in the analysis.

Assessment of Agent Orange Exposure

An Agent Orange exposure index was constructed for the study that adopted the geographic information system-based Exposure Opportunity Index model E4.[13] This index was based on the proximity of the military unit to the area that was sprayed with Agent Orange. Researchers identified the coordinates of the ROK military unit's post location and tactical area of responsibility during the Vietnam War. Information regarding the deployed unit of the veterans was obtained from the Ministry of National Defense for the division or brigade level. Each unit's post location was collected by point coordinates. Furthermore, polygons representing each unit's tactical area of responsibility were constructed. Each coordinate representing 1 kilometer by 1 kilometer within those polygons was then obtained.[4]

The coordinate information was sent to the team of Stellman et al in the United States and they constructed E4 scores based on the dates and coordinates using the Exposure Opportunity Index model.[13] For a given date, the average score of all coordinates of a tactical area of responsibility was used for the combat unit and construction support group, and the average score of all coordinates of the post locations was used for those support units without a tactical area of responsibility (37,547 [20.8%]) (Table 1). 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.

An individual E4 score was obtained from the unit in which the veteran served and his period of deployment; veterans with the same military unit and period of service would have the same exposure score. After adding 1 to each E4 score, the common log-transformed E4 score ($Log_{10}E4$; range, 0.0-5.8) was made and it was used as the individual's Agent Orange exposure index.[4]

The veterans were categorized into 2 groups of low ($Log_{10}E4 < 4.0$) and high ($Log_{10}E4 \geq 4$) exposure and 4 groups of 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 ($Log_{10}E4 \geq 5.0$) exposure.[4] The number of veterans in the no-exposure, low-exposure, moderate-exposure, and high-exposure groups were 45,341 (25.2%), 49,101 (27.2%), 51,062 (28.3%), and 34,747 (19.3%) veterans, respectively.

Statistical Analysis

The chi-square test was used to compare the proportion between Agent Orange exposure categories. Cox proportional hazards regression analysis, controlling for age at time of cohort entry (as of January 1, 1992) and military rank (enlisted, noncommissioned officer, or officer), was implemented. Military rank was included in the regression model because, especially during the 1960s and 1970s, it could be considered a reflection of veterans'

TABLE 1. Age and Vietnam Service Characteristics by Agent Orange Exposure Among Korean Vietnam Veterans (N=180,251)

Characteristics	Classification	Low Exposure N=94,442		High Exposure N=85,809		P^a
		No.	%	No.	%	
Age as of January 1, 1992, y	<45	59,639	84.1	11,281	15.9	<.001
	45-49	27,080	29.9	63,342	70.1	
	50-54	4434	35.6	8004	64.4	
	≥55	3289	50.8	3182	49.2	
Deployed unit	Capital Division (Combat)	29,855	45.6	35,561	54.4	<.001
	9th Division (Combat)	30,978	50.7	30,096	49.3	
	Marine 2nd Brigade (Combat)	2745	49.1	2850	50.9	
	ROK Army Headquarters	5106	100.0	0	0.0	
	Construction Support Group	6662	68.4	3075	31.6	
	Naval Transport Group	502	89.3	60	10.7	
	100th Logistic Command	18,114	56.8	13,765	43.2	
	Unknown	480	54.4	402	45.6	
Military rank	Enlisted	73,708	52.6	66,517	47.4	<.001
	Noncommissioned officer	12,426	49.4	12,705	50.6	
	Company officer	6676	54.8	5499	45.2	
	Field officer or general	1632	60.0	1088	40.0	
First y of deployment	Up to 1966	10,303	32.9	21,035	67.1	<.001
	1967-1968	6146	12.5	42,916	87.5	
	1969-1970	33,764	60.7	21,858	39.3	
	1971 and beyond	44,229	100.0	0	0.0	

Abbreviation: ROK, Republic of Korea.
[a] Determined using the chi-square test.

socioeconomic status.[4,5] To identify linear dose-response relationships between Agent Orange exposure and cancer incidence, $Log_{10}E4$ was used in the analysis. In addition, subgroup analyses were performed among veterans who served in units with a defined tactical area (3 combat units and a construction support group) and among those who served for >6 months (>180 days) in Vietnam as sensitivity analyses.

The *P* value was calculated with 2-sided tests and a statistical significance level of .05 was applied. All statistical analysis was performed using SAS statistical software (version 9.2; SAS Institute Inc, Cary, NC).

RESULTS

The total number of follow-up person-years was 2,051,098. The average age of Korean veterans was 46.3 years (standard deviation, 3.5 years) as of January 1, 1992. The Capital Division and the Ninth Division, 2 major combat units, comprised the majority of the ROK Army. Enlisted personnel accounted for 77.8% of Vietnam veterans (Table 1).

The adjusted hazards ratio (aHR) for all cancer sites combined (hereafter referred to as "all cancer") in the high-exposure group was significantly higher than that in the low-exposure group (Fig. 1). The aHRs for cancers of the mouth, salivary gland, stomach, and small intestine in the high-exposure group were significantly higher and aHRs for cancers of the esophagus, liver, and lung as well as for chronic myeloid leukemia were found to be nonsignificantly higher in the high-exposure group compared with the low-exposure group. However, the excess risk for cancers of the stomach, liver, and lung was modest.

Although the aHR for all cancer significantly increased with an increasing $Log_{10}E4$, the risk of all cancer was found to be highest in the group with moderate Agent Orange exposure, and the aHRs for many cancers did not increase monotonically with increasing Agent Orange exposure (see online supporting information). aHRs for cancers of the salivary glands, stomach, small intestine, and liver were found to be significantly elevated with an increasing $Log_{10}E4$.

In the subgroup analyses among veterans who served in units with a defined tactical area (see online supporting information) and among those who served for >6 months (see online supporting information), the analyzed results were generally similar to those of the main analysis. In both subgroup analyses, the associations between Agent Orange exposure and all cancer were modestly stronger than in the main analysis and the aHRs for cancers of the esophagus, stomach, liver, and lung in the high-exposure group were significantly higher than in the low-exposure group (see online supporting information).

Anatomical site (ICD-10)	Low[b] Cases n	High Exposure (n=85,809) Cases n	*P*-value	aHR[c]	95% CI
All sites (C00-C97, MPD,MDS)	4,009	4,583	<0.001	1.08	(1.03, 1.13)
Lip (C00)	2	1	0.84	1.36	(0.07, 26.2)
Tongue (C01-C02)	14	17	0.95	1.02	(0.49, 2.15)
Mouth (C03-C06)	9	23	0.02	2.54	(1.13, 5.70)
Salivary gland (C07-C08)	2	13	0.01	6.96	(1.50, 32.3)
Tonsil (C09)	12	10	0.79	0.88	(0.35, 2.20)
Other oropharynx (C10)	3	6	0.35	1.98	(0.48, 8.17)
Nasopharynx (C11)	29	21	0.21	0.69	(0.39, 1.23)
Hypopharynx (C12-C13)	12	18	0.93	1.04	(0.49, 2.20)
Esophagus (C15)	71	113	0.05	1.36	(1.00, 1.85)
Stomach (C16)	973	1,154	0.004	1.14	(1.04, 1.24)
Small intestine (C17)	11	19	0.04	2.30	(1.03, 5.15)
Colon (C18)	228	210	0.16	0.87	(0.72, 1.06)
Rectum (C19-C20)	231	265	0.16	1.14	(0.95, 1.38)
Anus (C21)	2	7	0.15	3.32	(0.64, 17.1)
Liver (C22)	933	1,023	0.07	1.09	(0.99, 1.20)
Gall bladder etc. (C23-C24)	93	125	0.13	1.24	(0.94, 1.63)
Pancreas (C25)	84	100	0.45	1.12	(0.83, 1.51)
Nose, sinuses, etc. (C30-C31)	8	11	0.24	1.79	(0.68, 4.72)
Larynx (C32)	67	87	0.26	1.21	(0.87, 1.69)
Lung (C33-C34)	505	649	0.06	1.12	(1.00, 1.27)
Other thoracic organs (C37-C38)	9	11	0.10	2.46	(0.84, 7.21)
Thymus (C37)	7	7	0.46	1.61	(0.45, 5.80)
Bone (C40-C41)	11	8	0.47	0.70	(0.27, 1.82)
Melanoma of the skin (C43)	10	9	0.83	0.90	(0.36, 2.30)
Other skin (C44)	38	40	0.98	0.99	(0.63, 1.57)
Mesothelioma (C45)	1	2	0.18	7.42	(0.39, 141)
Connective and soft tissue (C47+C49)	20	13	0.19	0.62	(0.30, 1.27)
Peritoneum (C48)	4	3	0.73	0.76	(0.16, 3.54)
Breast (C50)	5	3	0.39	0.53	(0.12, 2.26)
Penis (C60)	1	0		0.00	
Prostate (C61)	71	53	0.05	0.70	(0.49, 1.00)
Testis (C62)	3	2	0.48	0.51	(0.08, 3.27)
Other male genital organs (C63)	2	1	0.99	1.01	(0.07, 15.1)
Kidney (C64)	102	79	0.05	0.74	(0.55, 1.00)
Renal pelvis (C65)	12	11	0.91	1.05	(0.44, 2.50)
Ureter (C66)	8	11	0.63	1.26	(0.50, 3.18)
Bladder (C67)	122	133	0.96	0.99	(0.77, 1.28)
Other urinary organs (C68)	1	1	0.75	1.74	(0.06, 52.4)
Eye (C69)	2	1	0.69	0.60	(0.05, 7.79)
Brain, nervous system (C70-C72)	30	32	0.98	1.01	(0.60, 1.68)
Thyroid (C73)	43	41	0.84	1.05	(0.67, 1.65)
Adrenal gland (C74)	0	4		NA	
Hodgkin lymphoma (C81)	6	7	0.68	1.27	(0.41, 3.93)
Non-Hodgkin lymphoma (C82-C85)	89	96	0.58	1.09	(0.81, 1.47)
Multiple myeloma (C90)	23	28	0.65	1.14	(0.65, 2.01)
Lymphoid leukemia (C91)	9	5	0.16	0.45	(0.15, 1.37)
Acute lymphoblastic leukemia (C91.0)	5	3	0.38	0.52	(0.12, 2.23)
Myeloid leukemia (C92-C94)	38	45	0.58	1.13	(0.73, 1.77)
Acute myeloblastic leukemia (C92.0)	25	20	0.59	0.84	(0.46, 1.56)
Chronic myeloid leukemia (C92.1)	6	17	0.08	2.37	(0.91, 6.18)
Other leukemia (C95)	8	7	0.74	0.84	(0.29, 2.38)
Myeloproliferative disease (MPD)	4	5	0.71	1.30	(0.33, 5.04)
Myelodysplastic syndrome (MDS)	2	3	0.68	1.46	(0.24, 8.86)

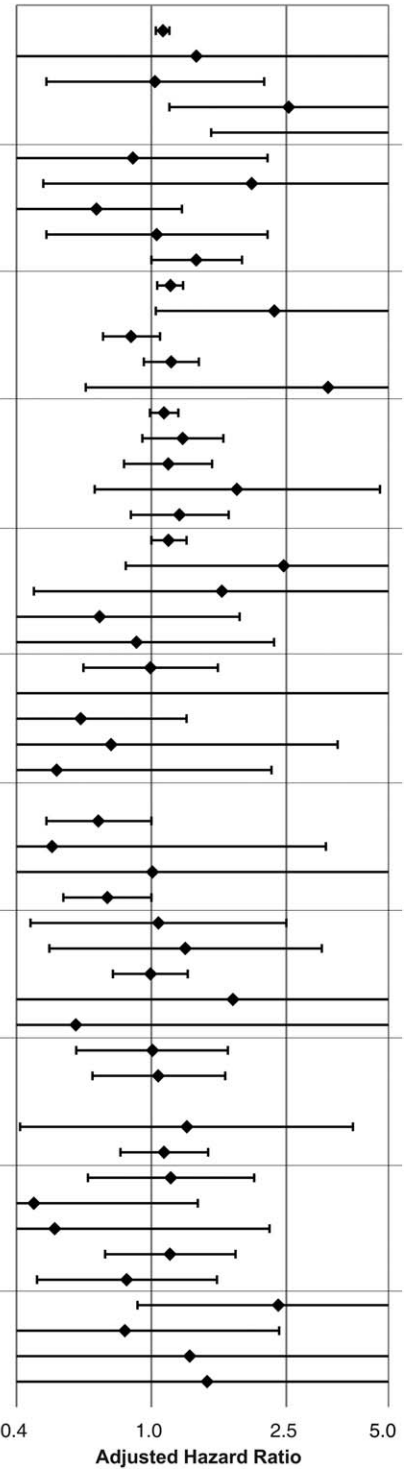

Figure 1. Number of cases and adjusted[a] are shown for cancers in Korean veterans of the Vietnam War with high exposure to Agent Orange compared with a group with low exposure obtained from 1992 through 2003. Abbreviations: ICD-10, *International Classification of Diseases, 10th Revision*; 95% CI, 95% confidence interval; MPD, myeloproliferative disease; MDS, myelodysplastic syndrome; NA, not available; [a]Cox proportional hazard model, adjusted for age at cohort entry (as of January 1, 1992) and military rank during service in Vietnam; [b]low-exposure group (n = 94,442); [c]high-exposure group compared with low-exposure group (the referent).

DISCUSSION

All Cancers Combined

The risk of all cancer in Korean veterans of the Vietnam War was found to be significantly elevated with exposure to Agent Orange. A few cohort studies have demonstrated a modest but significantly increased risk of all cancer with potential TCDD exposure.[14-16] An estimation of individual Agent Orange exposure and comparison of cancer incidence with internal controls by exposure level, rather than the general population, may have generated the positive association observed in the current study.[5,6] In animal experiments, TCDD is a proven multiorgan carcinogen that induces cancer in various species and strains.[17] Although TCDD has been recognized as a known human carcinogen by the IARC and the US National Toxicology Program, some researchers have questioned whether TCDD is a carcinogen to humans.[18] The current study supports the IARC classification of TCDD as being carcinogenic to humans.[3]

Cancers of Oral Cavity and Pharynx

The incidence of mouth and salivary cancer was found to be positively associated with Agent Orange exposure in the current study. The incidence of buccal cavity cancer among white US Air Force veterans was nonsignificantly higher than in the white control group.[10] In Australian Vietnam veterans, the incidences of oral cavity and pharynx cancer were substantially higher than would be expected in the general population.[16] In occupational cohorts, mortality rates from oral cavity and pharynx cancer in TCDD-exposed workers were found to be higher than in the general population, but the difference was not statistically significant.[14,19-21] In the current study, the aHR of oral cavity cancers combined (ICD-10 codes C00-C09) in the high-exposure group was also found to be significantly higher (aHR, 1.61; 95% confidence interval, 1.05-2.45) compared with the low-exposure group. A study from the US National Toxicology Program reported that the incidence of oral squamous cell carcinoma (SCC) was significantly higher in female rats treated with TCDD and dioxin-like compounds.[22] Recently, human papillomavirus (HPV) has been recognized as a cause of oropharyngeal SCC,[23] and a mechanistic hypothesis, namely that Agent Orange/TCDD exposure may contribute to susceptibility to HPV infection or action, has been emphasized.[24] In the current study, when the analysis was restricted to 27 microscopically verified cases of SCC of the mouth (ICD-10 codes C03-C06), the aHR in the high-exposure group was also significantly higher (aHR, 2.94; 95% confidence interval, 1.19-7.25) than in the low-exposure group. With regard to salivary gland cancer in the current study, all 3 verified SCC cases (20%) happened to be diagnosed in the high-exposure group, whereas among Korean patients with oral cancer, the presence of HPV DNA was found to be higher among those with nonsquamous salivary gland cancers than those with oral SCC, as reported in previous research.[25]

Cancers of Digestive Organs

In this study, Agent Orange exposure was found to significantly increase the risk of cancer of the stomach and small intestine, and nonsignificantly increase the risk of esophageal cancer ($P = .05$ in 2-group analysis), whereas the increase in HRs in cases of cancer of the esophagus and stomach was modest. Except for a case-control study in New Zealand in which cancer of the small intestine was found to be associated with forestry work,[26] to our knowledge there has been little evidence of an increased risk of cancer of the small intestine in human research. Some studies have reported a nonsignificant increase in the mortality or incidence of esophageal cancer with potential TCDD exposure.[14,16,19-21,26] A positive significant association between potential TCDD exposure and stomach cancer has been reported, mainly in case-control studies.[26,27] TCDD-aryl hydrocarbon receptor-induced carcinogenesis of the stomach and upper gastrointestinal tract has been noted in previous research.[28] Evidence from TCDD-related cohort studies of a positive significantly increased risk of upper gastrointestinal cancers is lacking.[14,15,17,19,29] The association, if it exists, may not have been demonstrated due in part to the small number of cases noted to occur among low-incidence populations in previous research.

The results of the current study demonstrate that the risk of liver cancer modestly increased with an incremental exposure. In both humans and animal models, TCDD may promote hepatocarcinogenesis through cytotoxicity, chronic inflammation, and liver regeneration mediated by the sustained activation of the aryl hydrocarbon receptor,[30] whereas the evidence of TCDD as a human hepatocarcinogen has been less than convincing.[14,17,19] The hepatocarcinogenic effect of Agent Orange/TCDD may be more apparent in areas with high endemicity of the hepatitis virus, such as Korea, compared with Western countries.[31] Mechanisms such as the interaction among the hepatitis B virus X protein, the hepatitis B virus X-associated protein 2, aryl hydrocarbon receptor, and estrogen receptors might play a role in hepatocarcinogenesis.[32]

Other Sites of Cancer

In the current study, the modestly higher risk of lung cancer, noted especially in subgroup analyses, was concordant

with previous research.[3,24] Soft tissue sarcomas and non-Hodgkin lymphoma have been associated with TCDD exposure.[3,24] The current study results do not support an association between potential TCDD exposure and the development of soft tissue sarcoma (connective and soft tissue cancer in this study)[17,29] or non-Hodgkin lymphoma. Although prostate cancer and malignant melanoma have been associated with potential TCDD exposure among Vietnam veterans,[10,16] to the best of our knowledge evidence from the current study and other studies has been less than sufficient to verify the association.[15,17,19,20] The risk of chronic myeloid leukemia in the high-exposure group was found to be nonsignificantly higher in the current study. To our knowledge, few studies to date have examined the association between chronic myeloid leukemia and potential TCDD exposure, and those have demonstrated a nonsignificantly higher risk of chronic myeloid leukemia among individuals with potential TCDD exposure.[16,33]

Nonmonotonic Dose Response Between TCDD Exposure and Cancer

In the current study, the risk of all cancer was found to be highest among the group with moderate TCDD exposure. To our knowledge, many previous studies in which potentially TCDD-exposed populations were classified into several groups by exposure levels have not demonstrated monotonically increased mortality or incidence of all cancer with increasing exposure.[15,17,19-21,29] Meanwhile, the low-exposure group has been reported to have the highest cancer mortality among exposure groups compared with the reference group in studies of populations with a higher rate of TCDD exposure than Vietnam veterans.[15,19-21] These results suggest that the relationship between cancer and exposure to Agent Orange/TCDD may be nonmonotonic.[34] Further research will be needed to confirm the nature of the dose-response trend.

Limitations and Strengths of the Current Study

The Agent Orange exposure index used in the current study may have some limitations with regard to accuracy and precision.[4,35] For example, the estimated exposure may be more valid among veterans who served in units with a defined tactical area compared with those who served in units without such an area. Soldiers with a very short service period (and therefore considered herein to have low exposure) might actually have been those who returned home earlier than their peers due to illness after heavy exposure. The subgroup analyses, among veterans who served in the units with a defined tactical area and among those who served for >6 months, demonstrated the possibility that the association between exposure and cancers in the main analysis may be slightly underestimated. In the case of ground troops, who in general had low rates of exposure to Agent Orange/TCDD compared with well-known occupational and environmental cohorts,[36] most research has assessed Agent Orange exposure by veterans' participation in the war[4,9,10,16] or by subjective self-reported assessment.[4,37] Comparison of mortality between Vietnam veterans and the general population has shown a strong "healthy soldier effect," in which overall mortality in Korean Vietnam veterans was approximately 20% lower than expected from the general population.[6] A subjective exposure index to Agent Orange based on self-reported information demonstrated evidence of information bias, in that ill Vietnam veterans tended to report that they experienced greater exposure to Agent Orange than they actually did in accordance with research on US veterans.[4,37] We believe that this geographic information system-based exposure index, which is not generally influenced by the healthy soldier effect and information bias, is a more reliable and valid tool with which to assess exposure to Agent Orange than assessments based on subjective self-report or Vietnam War experience. In addition, the TCDD concentration in human tissue may not be a valid tool with which to assess Agent Orange exposure several decades after the exposure in populations with a low TCDD exposure, such as Korean Vietnam veterans.[36] It is also worth noting that the exposure index in the current study could most likely expose itself to nondifferential misclassification and thus may bias the relationships between exposure to Agent Orange and cancer toward the null.

To the best of our knowledge, the current study is the first published in a scientific journal to investigate the association between Agent Orange exposure and cancer incidence in Korean veterans of the Vietnam War. One of the strengths of the current study is the ability to examine rare cancers through a large-scale cohort study; to our knowledge such cancers have not been evaluated frequently due to a small number of cases in Western populations. As a cancer incidence study, the current study also has the advantages of using more accurate cancer diagnoses and detecting more of the less-fatal cancers than a mortality study would. However, there are some other limitations. First, the current study cohort was constructed as of January 1, 1992, when at least 19 years had passed after the veterans had returned from Vietnam. Although to our knowledge no clear patterns of risk of cancer have been observed by the latency period or years

since exposure in previous research,[17,19] the association between Agent Orange and cancers with short latency, such as lymphohematopoietic malignancies, may be underestimated.[38] The lack of an association between Agent Orange and lymphohematopoietic malignancies such as non-Hodgkin lymphoma noted in the current study might be explained by the exclusion of cancers diagnosed in earlier periods. Second, there may be a challenge concerning the completeness and quality of case ascertainment through the Korea NCIDB in the early and mid-1990s.[39] Because this influences all veterans with low or high rates of exposure to Agent Orange, authors do not consider that it serves as a substantial bias in HR estimation.[5] A third limitation is that only age at cohort entry and military rank but not other important variables such as smoking history, level of alcohol consumption, body mass index, and socioeconomic status were adjusted for. However, military rank, a surrogate of veterans' socioeconomic status,[5] was adjusted for, and smoking history, level of alcohol consumption, and body mass index did not appear to differ significantly according to Agent Orange exposure.[4]

Conclusions

The results of the current large-scale cohort study indicate that exposure to Agent Orange/TCDD-related chemicals several decades earlier may increase the risk of all cancer combined as well as various specific cancers among Korean veterans of the Vietnam War. An elevated risk of mouth cancer; salivary gland cancer; and digestive cancers such as cancers of the stomach, small intestine, and liver, which were not found to be clearly associated with exposure to Agent Orange/TCDD in previous cohort studies primarily based on Western populations, is worth noting and requires further research.

FUNDING SUPPORT

Supported by a research grant from the Ministry of Patriots and Veterans Affairs (MPVA) in Korea (1999, 2003, and 2009). Except for a research grant and administrative support with the data collection, the MPVA had no role in the study design, analysis and interpretation of data, writing of the report, and decision to submit the article for publication.

CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

REFERENCES

1. Stellman JM, Stellman SD, Christian R, Weber T, Tomasallo C. The extent and patterns of usage of Agent Orange and other herbicides in Vietnam. *Nature*. 2003;422:681-687.
2. Institute of Medicine (US). Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides. Veterans and Agent Orange: Health Effects of Herbicides Used in Vietnam. Washington, DC: National Academy Press; 1994.
3. Baan R, Grosse Y, Straif K, et al; WHO International Agency for Research on Cancer Monograph Working Group. A review of human carcinogens–Part F: chemical agents and related occupations. *Lancet Oncol*. 2009;10:1143-1144.
4. Yi SW, Ohrr H, Hong JS, Yi JJ. Agent Orange exposure and prevalence of self-reported diseases in Korean Vietnam veterans. *J Prev Med Public Health*. 2013;46:213-225.
5. Yi SW. Cancer incidence in Korean Vietnam veterans during 1992-2003: the Korean veterans health study. *J Prev Med Public Health*. 2013;46:309-318.
6. Yi SW, Ohrr HC. Mortality patterns among Korean Vietnam veterans. *Korean J Occup Environ Med*. 2011;23:279-286.
7. Burns C, Bodner K, Swaen G, Collins J, Beard K, Lee M. Cancer incidence of 2,4-D production workers. *Int J Environ Res Public Health*. 2011;8:3579-3590.
8. McBride D, Cox B, Broughton J, Tong D. The mortality and cancer experience of New Zealand Vietnam war veterans: a cohort study. *BMJ Open*. 2013;3:e003379.
9. Cypel Y, Kang H. Mortality patterns of Army Chemical Corps veterans who were occupationally exposed to herbicides in Vietnam. *Ann Epidemiol*. 2010;20:339-346.
10. Akhtar FZ, Garabrant DH, Ketchum NS, Michalek JE. Cancer in US Air Force veterans of the Vietnam War. *J Occup Environ Med*. 2004;46:123-136.
11. Ketchum NS, Michalek JE, Burton JE. Serum dioxin and cancer in veterans of Operation Ranch Hand. *Am J Epidemiol*. 1999;149:630-639.
12. Curado MP, Edwards B, Shin HR, et al. Cancer Incidence in Five Continents. Vol IX. IARC Scientific Pub. No. 160. Lyon, France: International Agency for Research on Cancer; 2007.
13. Stellman JM, Stellman SD, Weber T, Tomasallo C, Stellman AB, Christian R Jr. A geographic information system for characterizing exposure to Agent Orange and other herbicides in Vietnam. *Environ Health Perspect*. 2003;111:321-328.
14. Flesch-Janys D, Steindorf K, Gurn P, Becher H. Estimation of the cumulated exposure to polychlorinated dibenzo-p-dioxins/furans and standardized mortality ratio analysis of cancer mortality by dose in an occupationally exposed cohort. *Environ Health Perspect*. 1998; 106(suppl 2):655-662.
15. Ruder AM, Yiin JH. Mortality of US pentachlorophenol production workers through 2005. *Chemosphere*. 2011;83:851-861.
16. Wilson EJ, Horsley KW, van der Hoek R. Cancer Incidence in Australian Vietnam Veterans Study 2005. Canberra, Australian Capital Territory: Department of Veterans' Affairs; 2005.
17. Pesatori AC, Consonni D, Rubagotti M, Grillo P, Bertazzi PA. Cancer incidence in the population exposed to dioxin after the "Seveso accident": twenty years of follow-up. *Environ Health*. 2009;8:39.
18. Boffetta P, Mundt KA, Adami HO, Cole P, Mandel JS. TCDD and cancer: a critical review of epidemiologic studies. *Crit Rev Toxicol*. 2011;41:622-636.
19. Kogevinas M, Becher H, Benn T, et al. Cancer mortality in workers exposed to phenoxy herbicides, chlorophenols, and dioxins. An expanded and updated international cohort study. *Am J Epidemiol*. 1997;145:1061-1075.
20. McBride DI, Collins JJ, Humphry NF, et al. Mortality in workers exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin at a trichlorophenol plant in New Zealand. *J Occup Environ Med*. 2009;51:1049-1056.
21. 't Mannetje A, McLean D, Cheng S, Boffetta P, Colin D, Pearce N. Mortality in New Zealand workers exposed to phenoxy herbicides and dioxins. *Occup Environ Med*. 2005;62:34-40.
22. Yoshizawa K, Walker NJ, Jokinen MP, et al. Gingival carcinogenicity in female Harlan Sprague-Dawley rats following two-year oral treatment with 2,3,7,8-tetrachlorodibenzo-p-dioxin and dioxin-like compounds. *Toxicol Sci*. 2005;83:64-77.
23. Marur S, D'Souza G, Westra WH, Forastiere AA. HPV-associated head and neck cancer: a virus-related cancer epidemic. *Lancet Oncol*. 2010;11:781-789.

24. Institute of Medicine (U.S.) Veterans and Agent Orange: Update 2010. Washington, DC: National Academies Press; 2012.
25. Shin KH, Park KH, Hong HJ, et al. Prevalence of microsatellite instability, inactivation of mismatch repair genes, p53 mutation, and human papillomavirus infection in Korean oral cancer patients. *Int J Oncol*. 2002;21:297-302.
26. Reif J, Pearce N, Kawachi I, Fraser J. Soft-tissue sarcoma, non-Hodgkin's lymphoma and other cancers in New Zealand forestry workers. *Int J Cancer*. 1989;43:49-54.
27. Mills PK, Yang RC. Agricultural exposures and gastric cancer risk in Hispanic farm workers in California. *Environ Res*. 2007;104: 282-289.
28. Roth MJ, Wei WQ, Baer J, et al. Aryl hydrocarbon receptor expression is associated with a family history of upper gastrointestinal tract cancer in a high-risk population exposed to aromatic hydrocarbons. *Cancer Epidemiol Biomarkers Prev*. 2009;18:2391-2396.
29. Consonni D, Pesatori AC, Zocchetti C, et al. Mortality in a population exposed to dioxin after the Seveso, Italy, accident in 1976: 25 years of follow-up. *Am J Epidemiol*. 2008;167:847-858.
30. Kohle C, Schwarz M, Bock KW. Promotion of hepatocarcinogenesis in humans and animal models. *Arch Toxicol*. 2008;82:623-631.
31. Park KW, Park JW, Choi JI, et al. Survival analysis of 904 patients with hepatocellular carcinoma in a hepatitis B virus-endemic area. *J Gastroenterol Hepatol*. 2008;23:467-473.
32. Cai W, Kramarova TV, Berg P, Korbonits M, Pongratz I. The immunophilin-like protein XAP2 is a negative regulator of estrogen signaling through interaction with estrogen receptor alpha. *PLoS One*. 2011;6:e25201.
33. Brown LM, Blair A, Gibson R, et al. Pesticide exposures and other agricultural risk factors for leukemia among men in Iowa and Minnesota. *Cancer Res*. 1990;50:6585-6591.
34. Vandenberg LN, Colborn T, Hayes TB, et al. Hormones and endocrine-disrupting chemicals: low-dose effects and nonmonotonic dose responses. *Endocr Rev*. 2012;33:378-455.
35. Institute of Medicine (U.S.). Committee on Making Best Use of the Agent Orange Exposure Reconstruction Model. The Utility of Proximity-Based Herbicide Exposure Assessment in Epidemiologic Studies of Vietnam Veterans. Washington, DC: National Academies Press; 2008.
36. Yi SW, Ohrr H, Won JU, Song JS, Hong JS. Serum 2,3,7,8-tetrachlorodibenzo-p-dioxin levels and their association with age, body mass index, smoking, military record-based variables, and estimated exposure to Agent Orange in Korean Vietnam veterans. *J Prev Med Public Health*. 2013;46:226-236.
37. Decoufle P, Holmgreen P, Boyle CA, Stroup NE. Self-reported health status of Vietnam veterans in relation to perceived exposure to herbicides and combat. *Am J Epidemiol*. 1992;135:312-323.
38. Beane Freeman LE, Blair A, Lubin JH, et al. Mortality from lymphohematopoietic malignancies among workers in formaldehyde industries: the National Cancer Institute Cohort. *J Natl Cancer Inst*. 2009;101:751-761.
39. Jung KW, Won YJ, Park S, et al. Cancer statistics in Korea: incidence, mortality and survival in 2005. *J Korean Med Sci*. 2009;24: 995-1003.