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EDITED BY

Francesca Bravi,
University of Milan, Italy

REVIEWED BY

Jason Wong,
National Cancer Institute (NIH),
United States
Fabio Grizzi,
Humanitas Research Hospital, Italy
Georgios Mikellides,
University of Nicosia, Cyprus

*CORRESPONDENCE

Won-Jun Choi

✉ wjchoi@gachon.ac.kr

Jin-Ha Yoon

✉ flyinyou@gmail.com

†These authors share first authorship

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Cancer risk in Vietnam war veterans from the Korean Vietnam war veterans' health study cohort

Wanhyung Lee^{1†}, Soyoung Park^{2†}, Seong-Kyu Kang¹,
Seunghon Ham¹, Jin-Ha Yoon^{3,4*} and Won-Jun Choi^{1*}

¹Department of Occupational and Environmental Medicine, Gil Medical Center, Gachon University College of Medicine, Incheon, Republic of Korea, ²Department of Occupational and Environmental Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea, ³Department of Preventive Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea, ⁴The Institute for Occupational Health, Yonsei University College of Medicine, Seoul, Republic of Korea

Introduction: During the Vietnam War, several unknown chemicals, such as Agent Orange, were used in Vietnam by the military. Therefore, there have been continuous health concerns among the Vietnamese population and veterans exposed to these hazardous chemicals. This study aimed to investigate the risk of all cancers and also organ-specific cancers among Korean veterans of the Vietnam War.

Methods: This study used a national representative cohort that included all Korean Vietnam War veterans as the interest group, with 1:4 age-sex-region-matched general Korean citizens as the reference group, from 2002 to 2018. Age-standardized incidence ratios (SIRs) and 95% confidence intervals (CIs) were calculated for all cancers and for 31 organ-specific cancer categories based on the medical facility visit data.

Results: An increased SIR of 1.07 (95% CI, 1.06–1.08) was observed for all cancers among the veterans. There was a significantly increased risk of cancer among 22/31 organspecific cancers, with 18 cancer categories showing a significantly higher risk than all cancers. The highest risk was observed for "malignant neoplasms of other parts of the central nervous system" (SIR, 1.71; 95% CI, 1.51–1.92).

Discussion: This study evaluated the risk of cancer among Korean Vietnam War veterans. Further studies are warranted to investigate various health determinants in the veterans as well as the Vietnamese population.

KEYWORDS

KOVECO, agent orange, vietnam war, veterans, cancer

1 Introduction

The Republic of Korea dispatched over 300,000 troops during the Vietnam War (VW) (1). There is an ongoing tragedy affecting the health of Korean VW veterans because of the various unknown chemicals used in the war. For example, VW veterans may have been exposed to defoliants, or Agent Orange (AO), during the 1960s and the early 1970s (2). AO is a herbicide that mainly comprises the phenoxy herbicides 2,4-dichlorophenoxyacetic acid and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) (3). Although various kinds of herbicides were sprayed during the VW, AO represents all the phenoxy herbicides used then. As 2,4,5-T was contaminated with dioxin as a byproduct of the manufacturing process, exposure to AO resulted in exposure to dioxin or 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD).

There have been concerns regarding the adverse health effects from the various unknown chemicals used in the war, including cancer. The association between dioxin and some cancer types, such as soft tissue sarcoma, lymphomas, respiratory tract cancer, and prostate cancer, has been reported previously; however, there are limited or inconsistent results for some other cancer types. In Korea, Yi et al. reported cancer incidence among Korean VW veterans (4). From 1992 to 2003, 180,251 veterans were followed-up for cancer incidence. Compared to the low AO exposure group, the high AO exposure group showed significantly higher hazard ratios for cancers such as oral cancer, salivary gland cancer, stomach cancer, small intestine cancer, and lung cancer. There have been no further reports on cancer incidence in Korea since this study. Furthermore, previous studies on the cancer risk among the VW veterans focused only on veterans (5, 6).

This study aimed to investigate and compare the risk for, and status of, cancer incidence between Korean VW veterans and Korean citizens using the newly opened national representative cohort data of the Korean Vietnam War Veterans' Health Study Cohort (KOVECO) (7).

2 Methods

2.1 Data and participants

KOVECO is a merged dataset of data from the National Health Insurance Sharing Service (NHIS, <https://nhiss.nhis.or.kr/bd/ab/bdaba000eng.do>) and the Ministry of Patriots and Veterans Affairs (MPVA, <https://www.mpva.go.kr/english/index.do>) of Korea. NHIS collects, stores, and manages data obtained from mandatory public health insurance services for all Korean citizens, which has been available to researchers for policy and academic research purposes since 2002. The NHIS database comprises data regarding hospital facility visits based on the standardized protocol of the Korea Classification of Diseases and Causes of Death, 4th edition, which corresponds to the International Classification of Diseases (ICD), 10th revision. All diagnoses were described based on ICD codes, with individual codes, dates, and regions (8). Since 1995, the MPVA of Korea has been rewarding veterans by providing them with medical services and welfare. The MPVA data include a list of veterans,

identification information, and war participation information (rank, affiliation, class, date of entry into the war, and date of retirement). Thus, the KOVECO is an age-sex-region matched cohort that comprises tailored data from the MPVA, which includes information about Korean VW veterans, and the NHIS, which includes medical facility visit histories from 2002 to 2018.

All data merging and establishing processes were conducted by an independent data specialist from the NHIS, with individual information being anonymized. A total of 1,301,331 Koreans were enrolled in KOVECO in 2002, with 250,842 VW veterans as the interest group and 1,050,489 non-veterans as the reference group. In addition, 24,396,578 person-years were observed during the follow-up period. Figure 1 shows the detailed flow diagram of the study participants.

This study was performed in accordance with the ethical standards of the Declaration of Helsinki (1964) and its subsequent amendments. Data from the NHIS were collected after obtaining written informed consent from all the participants, and the information was anonymized. This study was approved by the Institutional Review Board of the Gachon University Gil Medical Center (IRB No. GCIRB2019-076).

2.2 Measurement and variables

The VW veteran group was defined based on VW-related information from the MPVA. The reference group was matched with the VW veterans group based on the 5-year-interval age groups, sex, and residence in 16 metropolitan cities in Korea in a 1:4 ratio.

Cancers were defined based on ICD diagnosis codes for malignant neoplasms for all cancers (C00–C97) and organ-specific categories according to the human organ system (9). During the follow-up period, only the first cancer diagnosis for each individual was included. The 31 organ-specific categories and their ICD codes are as follows: malignant neoplasms of lip, oral cavity, and pharynx (C00–C14); malignant neoplasms of esophagus (C15); malignant neoplasms of stomach (C16); malignant neoplasms of colon (C18); malignant neoplasms of rectosigmoid junction, rectum, anus, and anal canal (C19–C21); malignant neoplasms of liver and intrahepatic bile ducts

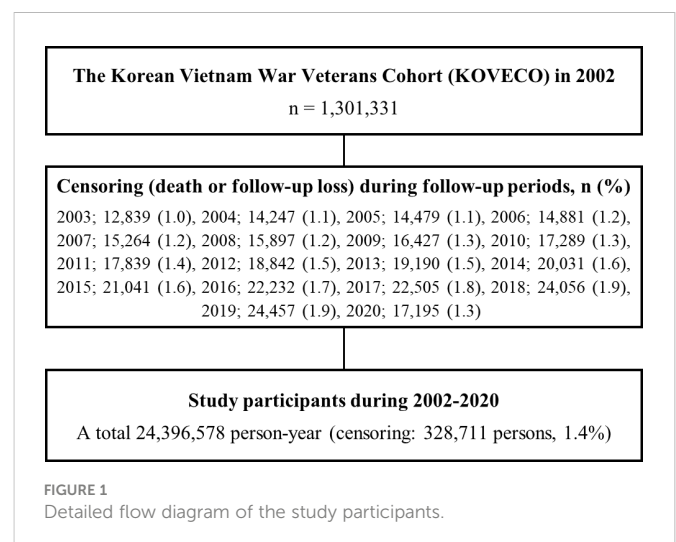


FIGURE 1
Detailed flow diagram of the study participants.

(C22); malignant neoplasms of pancreas (C25); other malignant neoplasms of digestive organs (C17, C23, C24, C26); malignant neoplasms of larynx (C32); malignant neoplasms of trachea, bronchus, and lung (C33, C34); other malignant neoplasms of respiratory and intrathoracic organs (C30, C31, C37–C39); malignant neoplasms of bone and articular cartilage (C40, C41); malignant melanomas of skin (C43); other malignant neoplasms of skin (C44); malignant neoplasms of mesothelial and soft tissue (C45–C49); malignant neoplasms of breast (C50); malignant neoplasms of cervix uteri (C53); malignant neoplasms of other and unspecified parts of uterus (C54, C55); other malignant neoplasms of female genital organs (C51, C52, C56–C58); malignant neoplasms of prostate (C61); other malignant neoplasms of male genital organs (C60, C62, C63); malignant neoplasms of bladder (C67); other malignant neoplasms of urinary tract (C64–C66, C68); malignant neoplasms of eye and adnexa (C69); malignant neoplasms of brain (C71); malignant neoplasms of other parts of central nervous system (C70, C72); malignant neoplasms of other, ill-defined, secondary, unspecified, and multiple sites (C73–C80, C97); Hodgkin disease (C81); non-Hodgkin lymphoma (C82–C86); leukemia (C91–C95); and other malignant neoplasms of lymphoid, hematopoietic, and related tissue (C88–C90, C96).

2.3 Statistical analysis

We estimated the number of cases of each type of cancer during the follow-up period, based on the history of the first visit. Age-standardized incidence ratios (SIRs) and 95% confidence intervals (CIs) were calculated based on the 5-year-interval age groups. SIR was estimated using age-specific cancer incidence rates and the number of person-years in each age group of the reference group (non-VW veterans), indicating the age-specific expected incidence among VW veterans. The sum of the expected cases was compared with the total observed cases of the VW veterans, and the ratio was calculated. If the SIR and the lower limit of the 95% CI were both >1, the cancer risk was considered significantly higher in the VW veterans' group than in the reference group. The 95% CIs were estimated using Poisson distribution. All analyses were performed using SAS, version 9.4 (SAS Institute, Cary, NC, USA).

3 Results

KOVECO comprised 250,842 (19.2%) VW veterans (Table 1). Most participants were male (99.8%), and approximately 28% had one or more neoplasms. Veterans had a significantly higher cumulative incidence of cancer than non-veterans (29.4% vs. 27.3%; $p < 0.0001$).

The SIRs and 95% CIs according to neoplasm sites are shown in Table 2 and Figure 2. The SIR (95% CI) for all cancer types combined, that is, all neoplasms, was 1.07 (1.06–1.08), and it was statistically significant. The SIRs (95% CIs) of the malignant neoplasms of the following organ categories were statistically significantly elevated: lip, oral cavity, and pharynx (1.04; 1.01–1.08); stomach (1.04; 1.02–1.05); colon (1.09; 1.07–1.11); pancreas (1.06; 1.02–1.10); larynx (1.09; 1.03–1.15); trachea, bronchus, and lungs (1.10; 1.08–1.11); other respiratory and intrathoracic organs (1.22; 1.12–1.31); bone and articular cartilage (1.27; 1.16–1.39); malignant melanomas of skin (1.14; 1.01–1.28); other malignant neoplasms of skin (1.18; 1.12–1.25); mesothelial and soft tissue (1.27; 1.18–1.36); prostate (1.36; 1.33–1.39); urinary bladder (1.16; 1.12–1.20); other malignant neoplasms of urinary tract (1.23; 1.18–1.27); eye and adnexa (1.59; 1.31–1.92); brain (1.11; 1.03–1.18); other parts of central nervous system (1.71; 1.51–1.92); other, ill-defined, secondary, unspecified, and multiple sites (1.10; 1.08–1.13); non-Hodgkin lymphoma (1.25; 1.20–1.30); leukemia (1.14; 1.07–1.21); and other lymphoid, hematopoietic, and related tissue (1.15; 1.07–1.23). However, the SIRs (95% CIs) of the neoplasms of the following categories were not significantly elevated: esophagus, rectum and anus, breast, other female genital organs, other male genital organs, and Hodgkin's disease. The age-specific hospital admission status for neoplasms during the study period can be found in the Supplementary table.

4 Discussion

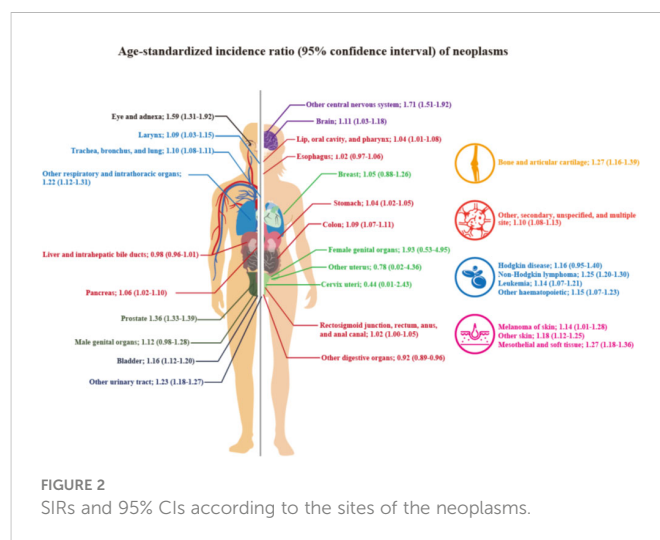
This study found an increased risk of all cancers among Korean VW veterans as compared to the general population. There was a significantly increased risk of cancer in 22/31 organ-specific categories, of which 18 categories showed a significantly higher risk

TABLE 1 Descriptive characteristics of the study participants of the Vietnam War veterans from the Korean Vietnam War Veterans' Health Study Cohort at baseline in 2002.

	Total participants		Vietnam War veterans n (%)				p-value
	n (%)		Yes		No		
Total participants	1,301,331	(100.0)	250,842	(19.2)	1,050,489	(80.6)	
Sex							<0.0001
Male	1,299,283	(99.8)	250,489	(19.3)	1,048,794	(80.7)	
Female	2,048	(0.2)	353	(17.2)	1,695	(82.8)	
All neoplasms							<0.0001
No	940,019	(72.2)	176,928	(18.8)	763,091	(81.2)	
Yes	361,312	(27.8)	73,914	(20.5)	287,398	(79.5)	

than that of all cancers. Although the highest risk was observed for “other malignant neoplasms of the female genital organs” among VW veterans, the difference was not statistically significant. VW veterans showed a significantly increased risk for “malignant neoplasms of other parts of central nervous system.”

TCDD is a known human carcinogen (10, 11). Many experimental animal studies have provided sufficient evidence regarding its carcinogenicity. In human epidemiological studies, exposure to TCDD showed an increased risk of overall cancer related mortality, but the cancer incidence was not significantly high (12). Although the exact mechanism of carcinogenicity is not fully understood, activation of the aryl hydrocarbon (Ah) receptor is considered to be one of the most critical steps (13, 14). When TCDD binds to the Ah receptor, various biological responses occur, including gene expression, transcription, and modulation of biochemical and cellular responses (15–17). However, the carcinogenicity of TCDD in humans is debated. One of the main issues is the long biological half-life of TCDD (7–10 years) (18). The slow rate of its metabolism, and formation of epoxides, may not lead to significant damage to intracellular organelles. Moreover, Ah receptor signaling pathways are complicated, and many genes are involved in the



modulation of TCDD (19, 20). These complex mechanisms may explain, at least in part, why several types of cancers, but not all, are

TABLE 2 Cases and incidence rate of neoplasms among Vietnam War veterans according to cancer site.

Type of neoplasms	ICD-10a	Cases	Incidence rate per 100,000 person-year	Minimum	Maximum
All cancers	C00–C97	73,914	2,976.8	2,957.1	2,983.2
Malignant neoplasms of lip, oral cavity and pharynx	C00–C14	3,314	135.6	131.0	1,402.7
Malignant neoplasms of esophagus	C15	1,879	77.7	74.3	81.3
Malignant neoplasms of stomach	C16	16,725	684.5	674.2	695.0
Malignant neoplasms of colon	C18	8,529	352.7	345.3	360.3
Malignant neoplasms of rectosigmoid junction, rectum, anus, and anal canal	C19–C21	6,049	250.0	243.7	256.4
Malignant neoplasms of liver and intrahepatic bile ducts	C22	8,372	348.1	340.7	355.6
Malignant neoplasms of pancreas	C25	2,716	112.3	108.1	116.6
Other malignant neoplasms of digestive organs	C17, C23–C24, C26	2,856	117.8	113.4	122.1
Malignant neoplasms of larynx	C32	1,386	57.4	54.4	60.5
Malignant neoplasms of trachea, bronchus and lung	C33–C34	13,733	559.7	550.4	569.1
Other malignant neoplasms of respiratory and intrathoracic organs	C30–C31, C37–C39	646	26.9	24.9	29.1
Malignant neoplasms of bone and articular cartilage	C40–C41	458	18.9	17.2	20.7
Malignant melanomas of skin	C43	302	12.5	11.1	13.9
Other malignant neoplasms of skin	C44	1,447	59.4	56.3	62.5
Malignant neoplasms of mesothelial and soft tissue	C45–C49	788	32.7	30.4	35.0
Malignant neoplasms of breast	C50	123	5.1	4.2	6.0
Malignant neoplasms of prostate	C61	9,668	400.4	392.5	408.5
Other malignant neoplasms of male genital organs	C60, C62–C63	212	8.7	7.6	9.9
Malignant neoplasms of bladder	C67	3,364	137.9	133.2	142.6
Other malignant neoplasms of urinary tract	C64–C66, C68	2,792	115.7	111.5	120.1

Malignant neoplasms of cervix uteri (C53), Malignant neoplasms of other and unspecified parts of uterus (C54–C55), and Other malignant neoplasms of female genital organs (C51–C52, C56–C58) were excluded from the table because these cancers had less than five cases during follow-up periods.

associated with TCDD exposure. Furthermore, the peak cancer risk related to AO manifests approximately 20 years after exposure; however, the toxic effects do not disappear after that time (3).

In this study, the incidence of several cancers was significantly higher in the VW veterans than in the non-veterans. According to reviews conducted by the National Academies of Sciences, Engineering, and Medicine (3), there is sufficient evidence of an association between exposure to herbicides and soft-tissue sarcoma, non-Hodgkin lymphoma, and Hodgkin disease. However, there is limited evidence of an association between herbicide exposure and certain other cancers, such as laryngeal cancer, cancer of the lungs, bronchi, or trachea, prostate cancer, and urinary bladder cancer. Although a previous Korean veterans study also indicated an increased risk of specific cancers, only prostate cancer showed a significantly increased risk due to limited observational periods and small number of cases of cancers (21). The current study demonstrated an elevated number of significantly increased risks of specific cancers, and most results of this study seem to corroborate previous reports (3). There were some notable results in our study.

We found a significantly higher incidence of malignant neoplasms of the central nervous system (SIR, 1.71; 95% CI, 1.51–1.92). An association between agricultural exposure to herbicides or pesticides and tumors of the central nervous system has been reported (22). Pesatori et al. reported a tendency towards an increased risk of pituitary tumors in areas where the concentration of dioxin was higher (23). Although the exact mechanism is unclear, germline mutations in Ah receptor-interacting proteins may be associated with the incidence of these tumors, including familial pituitary adenomas (24).

Cancers of the head and neck, including malignant neoplasms of the eye, adnexa, lip, oral cavity, and pharynx also showed significantly elevated SIRs. Several studies have reported the possible mechanisms of carcinogenicity with regard to Ah receptor actions (25–27) as well as epidemiologic research results, such as the increased risk of head and neck cancers in Vietnam Era veterans (4, 28). The findings of this study were consistent with those of previous studies. One possible reason for the failure to find a significant association between exposure to TCDD or AO and cancers of the head and neck or central nervous system may be the small number of cases due to low incidence of cancers (4).

This study has several strengths. First, we used nationally representative data from the NHISS, which includes all Korean VW veterans and is the largest, most reliable, and objective data currently found in the world. The follow-up period was sufficiently long to observe the incidence of cancer, which may have been higher in older patients. Second, this was the first study to include female VW veterans. Although the number of female participants was much lower than that of male participants, investigating health risks in female veterans should be encouraged. Third, we found a significantly increased incidence of malignant neoplasms of the central nervous system, malignant neoplasms of the eye and adnexa, and other head and neck cancers. The risk of these cancers has not been conclusive, owing to the small number of cases. We believe that the elevated risk of these cancers observed in this study is actual, rather than coincidental.

However, this study has some limitations. It only demonstrated the risk of cancer in VW veterans who were alive during the baseline data collection of KOVECO in 2002. The VW ended in the mid-1970s, and early onset or high-mortality cancers occurring before the start year of the cohort study may not have been included because of

lack of information from those periods in Korea. This is a type of left censoring cohort bias. However, the standards for the VW troop's conscriptions were reasonably high at that time, and only the healthy population may have been dispatched to the VW. Thus, the current results may have clinical implications for chronic non-severe cancer epidemiology in VW veterans. Some Korean VW veterans may also have served in the Korean Civil War from 1950 to 1953 or in dioxin-contaminated areas in Korea from the late 1960s to the early 1970s. However, the number of those veterans is believed to be small. Most importantly, Korean veterans who served in the VW were exposed to AO, although the exposure levels may differ. Therefore, whether the veterans had served in both wars did not seem to affect the exposure profile and their cancer incidence rates significantly. Furthermore, our study relied on hospital visit information to assess cancer diagnoses, and did not obtain pathological confirmation. If patients had ICD codes for neoplasms for diagnosis before confirmation, they might not have been actual cancer cases. However, this error has no direction with regard to the VW veteran group or the non-VW veteran group in the age-sex-region matched cohort; hence, non-differential misclassification may have occurred. Consequently, the risk of cancer may instead have a forward-to-null relationship. We could not demonstrate cancer-related factors, such as screening results, familial history, or other medical conditions, due to the nature of the dataset. Further studies on cancer-related factors are warranted. Finally, other conditions, such as the areas where the veterans served, and environmental conditions, may have affected exposure and health outcomes. Unfortunately, we could not obtain information about other environmental conditions besides the variables of veterans dispatched to the VW included in the manuscript owing to security reasons and lack of data. However, herbicides were sprayed in almost all areas of Vietnam during the war, even outside the official operations field. Therefore, all Korean veterans who serve in the VW should be considered exposed to AO, although the exposure levels may differ. A comparison between different situations or times requires a cautious approach.

The risk of certain cancer types in Korean VW veterans was higher than expected. Although the toxicological effect of various chemicals used in the VW such as AO or dioxin could explain the large body of biological mechanisms, not all the oncologic effects on the VW veterans can be explained by current analysis. Further studies are warranted to investigate the various health determinants in veterans.

Data availability statement

The datasets presented in this article are not readily available because they belong to the National Health Insurance System of Korea, and access requires certification. Requests to access the datasets should be directed to the corresponding author/s.

Ethics statement

The studies involving human participants were reviewed and approved by the Institutional Review Board of Gachon University Gil

Medical Center (IRB No. GCIRB2019-076). The patients/participants provided their written informed consent to participate in this study.

Author contributions

S-KK and W-JC conceived and supervised the project. WL, SP, J-HY and W-JC conducted data curation, analysis, and prepared the data visualization. WL, J-HY and W-JC contributed to the validation of results and data. WL, SP, S-KK, SH, J-HY and W-JC conducted the study and drafted the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fonc.2023.1048820/full#supplementary-material>

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