

RESEARCH COMMUNICATION

Liver Cancer in Viet Nam: Risk Estimates of Viral Infections and Dioxin Exposure in the South and North Populations

Le Tran Ngoan, Takesumi Yoshimura

Abstract

Risk factors for PLC due to viral infections and exposure to herbicides have not been available in south Viet Nam. The aim of this study was to clarify geographical differences in cancer incidence of PLC and its risk factors such as HBV and HCV infections and dioxin exposure between Ho Chi Minh (south) and Hanoi (north). Data for cancer incidence of PLC in Ho Chi Minh (1995-96) and Hanoi (1991-93) were used to calculate rate ratios for the two populations. Published reports on the association between HBV, HCV infections, dioxin (2,3,7,8-TCDD) exposed and HCC in Viet Nam were reviewed. Cancer incidence of PLC was found to be higher in HCM than in Hanoi for males (RR = 1.22, 95% CI = 1.09-1.36) and in females (RR = 1.21, 95% CI = 0.98-1.49). Risk factors for PLC due to viral infections were seen to be lower in HCM than in Hanoi for patients with HBV infection, (OR = 37.8, 95% CI = 11.6-121.4 VS. OR = 61.7, 95% CI = 30.0-128.0) and also for patients with HCV infection and HBsAg (-), (OR = 6.8, 95% CI = 2.1-22.1 VS. OR = 38.1, 95% CI = 2.8-1443.0). The risk of PLC due to exposure to herbicides was significantly increased for persons who suffered exposure for 10 years or more, OR = 8.8, 95% CI = 1.9-41 independent of HBV infection. Dioxin levels (2,3,7,8-TCDD) in blood samples from people living in the south were more than 2 times higher than in the north (32.6 VS. 15.7 ppt.). Based on the present findings, it is suggested that high incidence of liver cancer in HCM could partly be explained by herbicide exposure.

Key words: Viet Nam - liver cancer - viral infections - exposure to dioxin - risk factors

Asian Pacific J Cancer Prev, 2, 199-202

Background

Primary liver cancer (PLC) is an important public health problem in Viet Nam. That is, the incidence of PLC was estimated to be the second highest in males and the fifth in females in 1990 nationwide, (GLOBOCAN, 1999). PLC had the highest cancer incidence in males (ASR 25.3 per 100,000) and the fifth most common in females (ASR 5.9 per 100,000) in Ho Chi Minh City (HCM) in south Viet Nam from 1995-96, (Quoc et al., 1998). In addition, a striking increase of the proportion of liver cancer from 3.5% to 19.7% in males and from 0.6% to 5.9% in females between the 1970s and 1990s, respectively, in HCM was also observed, (Quoc et al., 1998; Truong, 1986).

Eighty per cent of liver cancer has been estimated to be due to chronic HBV infection throughout the world (World Health Organization, 1983). Viet Nam is a highly endemic

area of hepatitis viral infections, (Blumberg et al., 1970; Cordier et al., 1993; Corwin et al., 1996; Kakumu et al., 1998; Nakata et al., 1994; Song et al., 1994; Tran et al., 1993; Tuan, 1986). However, risk levels with HBV and HCV infections have not yet been documented, especially in south Viet Nam. During the Viet Nam War, herbicides were sprayed over 16.5% of the southern surface area, (Dai et al., 1986). Exposure to 2,3,7,8-TCDD followed the SEVESO accident in Italy in 1976, and hepatobiliary cancers (ICD-9: 155-6) were found to be significantly increased, (RR = 2.8, 95% CI = 1.2-6.3), (Bertazzi et al., 1993). However, the association between dioxin exposure and HCC among the southern population in Viet Nam has not yet been fully investigated. In the present study, our aim was to clarify geographical differences in liver cancer incidences and its risk factors such as HBV and HCV infections and dioxin exposure in Ho Chi Minh (south) and Hanoi (north).

Correspondence to: Le Tran Ngoan, Department of Clinical Epidemiology, Institute of Industrial Ecological Sciences, University of Occupational and Environmental Health, 1-1 Iseigaoka, Yahatanishi-ku, Kitakyushu 807-8555, JAPAN Tel: (+)-81-93-691-7456, Fax: (+)-81-93-603-015 E-mail: letngoan@med.uoeh-u.ac.jp

Table 1. Liver Cancer Incidences (age standardized incidence rate) per 100,000 in Ho Chi Minh and Hanoi by Gender

Population	Ho Chi Minh* (1)	Hanoi** (2)	Rate ratio, 95% CI, (1) / (2)
Males	25.3	20.3	1.22, 1.09-1.36
Females	5.9	4.9	1.21, 0.98-1.49

Sources: * (Quoc et al., 1998), ** (Anh et al., 1997)

Materials and Methods

Data of cancer incidences of liver in Ho Chi Minh (1995-96), (Quoc et al., 1998) and Hanoi (1991-93), (Anh et al., 1997) were used to calculate stratified incidence rate ratios between the two populations. The method for comparison of cancer incidence in the two groups was used in the present analysis. We obtained the Mantel-Haenzel combined estimate using STATA Statistical Software, (STATA, 1997).

Published reports in English and Vietnamese on the association between HBV, HCV infections, and exposure to dioxin (2,3,7,8-TCDD) and HCC in Viet Nam were reviewed. A case-control study was designed to recalculate odds ratio and its 95% confident interval among persons exposed to HBV and HCV infections. The criteria of eligibility of the study subjects are that both cases and controls were examined in the same study. Dioxin level (2,3,7,8-TCDD) in blood and adipose tissue samples that was the weighted mean as lipid basis, parts per trillion (ppt.) was also reviewed in selected populations in the south and north, (Schechter et al., 1995).

Results

Cancer incidences of liver were found to be higher in HCM than in Hanoi for males (RR = 1.22, 95% CI = 1.09-1.36) and in females (RR = 1.21, 95% CI = 0.98-1.49), (Table 1).

For HBV infection in south Viet Nam, among 306 patients examined, sixty-one patients with PLC and forty-one patients as hospital controls without liver diseases were examined at the same time and recruited from the same three hospitals in HCM. All samples were airmailed to the University of Oklahoma Health Science Center. HBsAg was detected there

Table 2. Relative risks (RRs) of HBsAg (+) and anti-HCV (+) among HBsAg (-) in Ho Chi Minh (south) and Hanoi (north), Viet Nam

Virus infections	RRs, (95% CI)	
	Ho Chi Minh	Hanoi
HBsAg (+)	37.8, (12.0-121.4)*	61.7, (30.0-128.0)***
Anti-HCV (+)	6.8, (2.1-22.1)**	38.1 (2.8-1443.0)***

Sources: *(Welsh et al., 1976), **(Lien et al., 1995), *** (Cordier et al., 1993)

by immunoelectroosmophoresis (IEOP) and by solid phase radioimmunoassay (RIA). Forty-nine patients with PLC and four controls were positive HBsAg and the author concluded that HBsAg (+) was 8 times more frequent in the patients with PLC than in the hospital controls. After recalculating, the odds ratio was 37.8, 95% CI = 11.6-121.4.

For HCV infection in the south, among 403 individuals tested for HCV infection, 260 persons who were eligible blood donors and 35 patients with PLC were examined in the same hospital. Anti-HCV was detected by the ELISA test. Among 35 patients, the number with PLC, HBV infection alone, HBV and HCV infections combined, and HCV infection alone was 18, 6, and 6, respectively, and 5 patients had no HBV nor HCV viral infections. Among 260 blood donors, because thirty-nine were positive Anti-HCV, the author concluded that HCV infection was a big problem in HCM City. After recalculating, the odds ratio of PLC cases was 6.8, 95% CI = 2.1-22.1, (Table 2).

In the north, HBV infection increased the risk of PLC, (OR = 61.7, 95% CI = 30.0-128.0), and HCV infection increased the risk of PLC among patients with HBsAg (-), (OR = 38.1, 95% CI = 2.8-1443.0). That is, risk factors of PLC due to viral infections were seen to be lower in HCM than in Hanoi for patients with HBV infection, (OR = 37.8 VS. 61.7) and also for patients with HCV infection (OR = 6.8 VS. 38.1), (Table 2). In this study, no cases in both patients with PLC and hospital controls were positive for both HBV and HCV infections in Hanoi while it was 17.1% in series cases of PLC in HCM City.

Dioxin level (2,3,7,8-TCDD) in blood samples from people living in the south was more than 2 times higher than in the north (32.6 VS. 15.7 ppt.). And among the north

Table 3. Dioxin (2,3,7,8-TCDD) Level in Blood by Areas in Viet Nam, Samples Collected from 1991-92

Areas	Number of tested samples	Mean of TEq* for each areas	Range of TEq* for each areas
North	133	15.7	12-18
Central Viet Nam	490	49.3	23-118.2
North-Veterans (Served in south Viet Nam)	35	40.3	40.3
South Viet Nam	2062	32.6	8.7-104.6

Source: (Schechter et al., 1995), *TEq: Dioxin toxic equivalents (lipid basis, parts per trillion)

population, dioxin level in blood samples from the north veterans was also higher than in non-veterans (40.3 VS. 15.7 ppt.), (Table 3). For results from epidemiological observation, the risk of PLC due to exposure to herbicides was significantly increased during 10 years or more of exposure, OR = 8.8, 95% CI = 1.9-41 independently of HBV infection. Risk of PLC due to exposure to herbicides was also significantly increased in patients exposed to them for 20 to 76 months, (OR = 4.4, 95% CI = 1.7-11.5). In addition, all subjects of the case-control study were recruited from only veterans in one military hospital. Veterans who served and were exposed to herbicide in the south for more than 5 years had an increased risk of PLC when compared with those who served in the north and were not exposed, (OR = 2.5, 95% CI = 1.2-5.0), (Table 4).

Discussion

Several reports have confirmed that cancer incidences of PLC were higher in HCM than in Hanoi. Incidences of PLC were stable in the 1990s, from 25.3 to 25.2 per 100,000 (ASR) in males, and from 5.9 to 6.4 per 100,000 (ASR) in females between 1995-96 and 1997 in HCM City. Incidences of PLC were the most common cancers in males and the fifth most common in females, (Hung et al., 1998; Quoc et al., 1998). Incidences of liver cancers were also higher in HCM compared to that in urban Hanoi City in 1988-90 for males (ASR 25.3 VS. 14.0 per 100,000) and for females (ASR 5.9 VS. 3.7 per 100,000), (Anh et al., 1993; Quoc et al., 1998).

Since the 1960s in the south, prevalence of HBV infection among healthy residents was reported to be very high prevalence as much as 6.3%, (Blumberg et al., 1970). Later in the 1970s, prevalence of HBV infection was found in 24% of 94 blood donors, 17% of 12 medical students, and 10% of 41 hospital controls without liver diseases, (Welsh et al., 1976). In the 1990s, the prevalence of HBV infection among children from 2-12 years of age was strikingly high

prevalence as much as 19.5% of 87 tested blood samples in one town near HCM City, (Katelaris et al., 1995). Recent results have shown that the prevalence of HBV infection among patients with PLC was 62.7% of 225 patients in HCM City, (Tran et al., 1993). Our results regarding risks of PLC due to viral infections were reasonable and represented a real problem in south Viet Nam, (Table 2). In addition, HBV and HCV infections combined were commonly observed among patients with PLC and also healthy residents in the south. That is, 17% of 35 patients with PLC and 0.2% of 890 healthy residents were found to have both HBV and HCV infections, (Kakumu et al., 1998; Lien et al., 1995). However, no cases of PLC with dual infections were found in Hanoi City, (Cordier et al., 1993).

For HBV and HCV infections in the north, prevalence of HBV infection in the general population based on stratified random samplings in Hanoi City was 12.5% in males and 10.1% in females, (Tuan, 1986). A very high prevalence of HBV infection among patients with PLC was found, as much as 77% of 57 subjects when compared to those of hospital controls without liver diseases, 20% of 160 subjects, (Luc & Nga, 1985).

Viral infections were the cause of PLC in most patients in both south and north, (Table 2). However, this may not explain the higher incidence of PLC in HCM than in Hanoi, (Table 1). In addition, a striking increase in the proportion of liver cancers from 3.5% to 19.7% in males and from 0.6% to 5.9% in females between the 1970s and 1990s, respectively in HCM was observed, (Quoc et al., 1998; Truong, 1986). These facts have suggested that risk factors of PLC were much prevalent in south Viet Nam. The lifetime cancer risk assessment using blood dioxin level was higher in the south than in the north, (6,000 VS. 2,900 per million), (Schechter & Olson, 1997). Based on results of epidemiological observations, persons exposed to herbicides for long time had an independent increased risk of PLC, (Cordier et al., 1993). Also dioxin level in blood was higher in the south, therefore, it is suggested that the high incidence

Table 4. Exposures to Herbicides in South Viet Nam during the Viet Nam War and Cancer Risk of HCC.

Number of cases and controls	Time period	Results
152 male HCC cases 241 hospital controls	1989-1992 (1)	HCC risk by length of military service in the south after 1960: Never : OR* = 1, (reference) 1-4 years: OR* = 0.9, 95% CI: 0.4-2.3 5-9 years: OR* = 1.4, 95% CI: 0.5-4.0 ≥10 years: OR*: 8.8, 95% CI: 1.9-41
76 male HCC cases 152 hospital controls (Veterans only)	1985-1989 (2)	HCC risk by length of military service in the south after 1960: Never: OR = 1, (reference) 1-5 years: OR = 0.9, 95% CI: 0.4-1.9 5 years: OR = 2.5, 95% CI: 1.2-5.0
62 male HCC cases 124 hospital controls	1982-1985 (3)	HCC risk after exposure to herbicides at least for 20 months: OR = 4.4, 95% CI: 1.7-11.5

*Cases and controls were matched by hospital, age, and place of residence, HBsAg positive and drinking habits were adjusted. Sources: (1): (Cordier et al., 1993). (2): (Long et al., 1993), (3): (Van et al., 1986)

of liver cancer in HCM would partly be explained by herbicide exposure.

Acknowledgements

We especially appreciate Dr. Nguyen Ba Duc, the director of Hanoi Cancer Hospital and Prof. Nguyen Chan Hung, the director of Ho Chi Minh City Oncology Center for their kind assistance. We are grateful to Dr. D. M. Parkin for his encouragement to study on cancer in Viet Nam. We thank Dr. Pham Hoang Anh and Dr. Nguyen Manh Quoc for their kindly assistance to visit the cancer registries in the city of Hanoi and Ho Chi Minh. We also especially thank the staff members of the Dept. of Clinical Epidemiology, IIES, UOEH, for their assistance. This work was partly supported by the Japanese Ministry of Health and Welfare, (Marui study group) and by the Japanese Government (Monbusho) Scholarship for Research Student.

References

- Anh P T H, Duc N B, Khang H X, Truong T H, Nga N H (1997). Viet Nam, Hanoi 1991-1993. In *Cancer Incidence in Five Continents Vol. VII*, Parkin D M, Whelan S L, Ferlay J, Raymond L, Young J (eds) pp. 442-445. IARC, WHO, IACR: IARC Scientific Publications No. 143, Lyon, 1997.
- Anh P T H, Parkin D M, Hanh N T, Duc N B (1993). Cancer in the population of Hanoi, Viet Nam, 1988-1990. *Br J Cancer*, **68**, 1236-42.
- Bertazzi A, Pesatori A C, Consonni D, et al (1993). Cancer incidence in a population accidentally exposed to 2,3,7,8-tetrachlorodibenzo-para-dioxin. *Epidemiology*, **4**, 398-406.
- Blumberg B S, Sutnick A I, London W T (1970). Australia antigen as a hepatitis virus. Variation in host response. *Am J Med*, **48**, 1-8.
- Cordier S, Le T B, Verger P, et al (1993). Viral infections and chemical exposures as risk factors for hepatocellular carcinoma in Vietnam. *Int J Cancer*, **55**, 196-201.
- Corwin A L, Dai T C, Duc DD, et al (1996). Acute viral hepatitis in Hanoi, Viet Nam. *Trans R Soc Trop Med Hyg*, **90**, 647-8.
- Dai L C, Quynh H T, Thanh L, et al (1986). Xay dung ban do nhung vung bi rai chat doc hoa hoc trong chien tranh Dong Duong lan thu II. (Map of Dioxin sprayed in the Second Indochina War). In *Second National Symposium on Herbicides and Defoliants in War: the long -Term Effects on Human Health*, 10-80, U.B. (ed) pp. 19-23. Uy Ban 10-80: Hanoi, Viet Nam.
- GLOBOCAN (1999). GLOBOCAN. <http://www-dep.iarc.fr/globocan/globocan.htm>.
- Hung N C, Quoc N M, Man P D, Truc N Q (1998). The population-based cancer registry in Ho Chi Minh City, 1997. *Journal of Medical Science of the City of Ho Chi Minh, (Special issue of oncology in Vietnamese)*, **2**, 11-9.
- Kakumu S, Sato K, Morishita T, et al (1998). Prevalence of hepatitis B, hepatitis C, and GB virus C/hepatitis G virus infections in liver disease patients and inhabitants in Ho Chi Minh, Viet Nam. *J Med Virol*, **54**, 243-8.
- Katellaris P H, Robertson G, Bradbury R, et al (1995). Seroprevalence of hepatitis viruses in children in rural Viet Nam. *Trans R Soc Trop Med Hyg*, **89**, 487.
- Lien P B, Bao T V, Phiet P H (1995). The problem of HCV infection at Cho Ray Hospital. *Scientific reports of National Institute of Hematology and Blood Transfusion (in Vietnamese with English abstract)*, **196**, 27-30.
- Long T, Mao H V, Cau N B, et al (1993). Association between primary liver cancer with dioxin exposed in Viet Nam, a case-control study. In *Second international conference on effect of dioxin to human health and environment* pp. 320-326. 10-80 committee (in Vietnamese): Hanoi, Viet Nam, 1993 November 15-18.
- Luc N Q, Nga N T (1985). HBV infection among certain groups of persons in Viet Duc Hospital. In *Viet Duc Hospital workshop* pp. 6-11: Hanoi, Viet Nam.
- Nakata S, Song P, Duc DD, et al (1994). Hepatitis C and B virus infections in populations at low or high risk in Ho Chi Minh and Hanoi, Viet Nam. *J Gastroenterol Hepatol*, **9**, 416-9.
- Nguyen H D (1986). Thong bao mot trung hop ung thu gan da duoc phan tich dinh luong Dioxin trong mo mo. (Dioxin analyzed results from adipose tissue sample from one patient with liver cancer). In *Second National Symposium on Herbicides and Defoliants in War: the long -Term Effects on Human Health*, 10-80, U.B. (ed) pp. 134. Uy Ban 10-80: Hanoi, Viet Nam.
- Phiet P H, Phuong N T N, Tan N V, Schecter A (1993). Dinh luong Dioxin trong mo mo cua 93 benh nhan song o mien Nam Viet Nam. (Dioxin level in adipose tissue samples from 93 patients in the south Viet Nam). In *Second International conference on effect of dioxin to human health and environment*, 10-80, U.B. (ed) pp. 21-25. Uy Ban 10-80: Hanoi, Viet Nam.
- Quoc N M, Hung N C, Parkin D M (1998). Cancer incidence in Ho Chi Minh City, Viet Nam, 1995-1996. *Int J Cancer*, **76**, 472-9.
- Schecter A, Olson J R (1997). Cancer risk assessment using blood dioxin levels and daily dietary TEQ intake in general populations of industrial and non-industrial countries. *Chemosphere*, **34**, 1569-77.
- Schecter A, Dai L C, Thuy L T, et al (1995). Agent Orange and the Vietnamese: the persistence of elevated dioxin levels in human tissues. *Am J Public Health*, **85**, 516-22.
- Song P, Duc DD, Hien B, et al (1994). Markers of hepatitis C and B virus infections among blood donors in Ho Chi Minh City and Hanoi, Viet Nam. *Clin Diagn Lab Immunol*, **1**, 413-8.
- Tran V B, Buu M, Nguyen thi M, Morris G E (1993). Hepatitis B in Ho Chi Minh City, Viet Nam. *Trans R Soc Trop Med Hyg*, **87**, 262.
- Truong L T (1986). Viet Nam, Ho Chi Minh City, 1976-81. In *Cancer occurrence in developing countries*, Parkin, D.M. (ed) pp. 309-311. IARC Scientific Publications No. 75: Lyon, France.
- Tuan T (1986). Epidemiological surveillance for carriers of HBV infection in the Population of Hanoi City. In *Department of Epidemiology*. Hanoi Medical School: Hanoi, Viet Nam.
- Van D D, Bach T T, Cuong N P (1986). Primary liver cancer and dioxin exposed. In *Second National Symposium on Herbicides and Defoliants in War: the long -Term Effects on Human Health* pp. 123-127. 10-80 committee (in Vietnamese): Hanoi Viet Nam.
- Welsh J D, Brown J D, Arnold K, Mathews H M, Prince A M (1976). Hepatitis B_s antigen, malaria titers, and primary liver cancer in south Viet Nam. *Gastroenterology*, **70**, 392-6.
- World Health Organization. (1983). Prevention of liver cancer, report of a WHO Meeting. In *World Health Organization Technical Report Series 691*: Geneva.