Occupational Risk Factors of Lymphohematopoietic Cancer in Rayong Province, Thailand

Apinya Punjindasup MD*,
Suleeporn Sangrajrang PhD**, Chatchai Ekpanyaskul MD, MSc*

** Department of Preventive and Social Medicine, Faculty of Medicine, Srinakharinwirot University, Nakhon Nayok, Thailand*
*** Research Division, National Cancer Institute, Ministry of Public Health, Bangkok, Thailand*

Background: *The Lymphohematopoietic Cancer (LHC) incidence rate in Thailand has been rising over the past decade with unknown etiology, including Rayong province. One hypothesis of LHC risks is exposure to occupational carcinogens.*
Objective: *To determine the association of occupational exposure and LHC risks in Rayong province, Thailand.*
Material and Method: *This matched hospital-based case-control study was conducted in a Rayong provincial hospital from September 2009 to January 2013. One LHC case was matched with four controls in gender and age, ±5 years. Demographic data, residential factors, behavioral factors, and occupational exposure-including chemical exposure-were obtained by interviews and collected by occupational health care officers. The risk factor was analyzed by conditional logistic regression and reported in odds ratio with 95% confidence interval.*
Results: *This study found 105 LHC cases which met the inclusion criteria and were included in the study, yielding a 66% cover rate of cases reported in the database. The histology of LHC were 51 leukemia cases (47.7%), 43 lymphoma cases (42.0%), and 11 multiple myeloma cases (10.3%). The results revealed that occupational exposure to pesticide and smoke were statistically significantly associated with LHC with adjusted ORs 2.26 (95% CI 1.30-3.91) and 1.99 (95% CI = 1.13-3.51), respectively. When stratified to histological subtype of LHC by WHO 2000, leukemia was statistically significantly associated with occupational exposure to smoke, adjusted ORs 2.43 (95% CI 1.11-5.36), with occupational pesticide exposure a significant risk of lymphoma, adjusted ORs 4.69 (95% CI 2.01-10.96). However, neither fumes, wood dust, working outdoors, cleaners, contact with animals, petroleum products and chlorine; nor occupational exposure to volatile organic compounds (VOCs) such as benzene or organic solvents, were statistically significant risk factors of LHC. In addition, there were no significant risks in the demographic data, residential factors, and behavioral factors.*
Conclusion: *Occupational exposure to pesticides and smoke were important occupational risks in developing LHC in Rayong province. However, the ability or power to detect this problem due to the small sample size and recall bias from the study design could not be excluded.*

Keywords: *Lymphohematopoietic cancer, Occupational risk factor, Occupational exposure*

J Med Assoc Thai 2015; 98 (Suppl. 10): S13-S22
Full text. e-Journal: *http://www.jmatonline.com*

Lymphohematologic cancers (LHC) are initiated by myeloid stem cells in bone marrow. LHCs have been classified by the WHO 2000 as leukemia, multiple myeloma and lymphoma[1]. The age standardized incidence rate (ASR) of LHC worldwide out of every 100,000 people for leukemia was 5.1; multiple myeloma, 1.5; and non-Hodgkin lymphoma, 6.1[2]. High incidence rates occur among residents of Western Europe, Canada, the USA, Australia and New Zealand[3]. The Asian region has low incidence rates, including Thailand[4]. In the past, LHC was not a common cancer occurring in the Thai population. With changes in the Thai lifestyle, progressing from rural agriculture to city-based industry, there has been a slight increase in this cancer. According to the Thai national cancer registry for 2007-2009, leukemia had an ASR of 5.2 (males) and 4.3 (females) per 100,000; and lymphoma had an ASR of 6.5 (males) and 4.4 (females) per 100,000[4]. With the LHC incidence rate in Thailand rising over the past decade with unknown etiology, in industrial areas such as Rayong province, the ASR of leukemia has risen to 10.1 (male) and 9.5 (female) per 100,000, and lymphoma has an ASR 12.2 (male) and 9.9 (female) per 100,000[4] in the same period.

Correspondence to:
Ekpanyaskul C, Department of Preventive and Social Medicine, Faculty of Medicine, Srinakharinwirot University, 62 Moo 7 Ongkharak, Nakhon Nayok 26120, Thailand.
Phone: +66-37-395085 ext. 10727
E-mail: dr_chatchai@hotmail.com

The causes of LHC are complex and diverse, and only partially understood. Previous studies have reported the risks of cancer such as genetics, smoking, alcohol, infection, exposure to radiation, and environmental and occupational exposure[5]. All of the known factors are easy to prevent in occupational contexts by eliminating the source of exposure through occupational health concepts. The International Agency for Research on Cancer (IARC) classified some chemical and microbiological agents that had sufficient and limited carcinogenic evidence of LHC[6]. Occupational exposure to benzene increased the risk of leukemia[7] and multiple myeloma[8]. Occupational exposure to petroleum increased the risk of leukemia[9]. Occupational exposure to organic solvents increased the risk of leukemia[10], multiple myeloma[11] and non-Hodgkin's lymphoma[12]. Occupational exposure to pesticides increased the risk of leukemia[13], multiple myeloma[14] and non-Hodgkin's lymphoma[13]. However, knowledge of other potential occupational risk factors is still limited. In contrast, some studies have suggested occupational exposure to benzene and organic solvents do not increase risks of leukemia[14], and occupational exposure to pesticides have been reported as no leukemia, multiple myeloma and non-Hodgkin's lymphoma risk[15].

The inconclusive risk of LHC through occupational exposure in many studies include few studies in Thailand, and no study in Rayong province, where unknown causes of increasing ASR of leukemia and lymphoma are expected from exposure to risks at work. A significant gap in knowledge is the occupational risk factors of LHC in Thai people. Therefore, the objective of this epidemiological study was to identify the occupational risk factors of LHC among patients in Rayong province in order to support the hypothesis that exposed occupational carcinogens may be associated with LHC.

Material and Method

This is a matched hospital-based case-control study conducted at Rayong provincial hospital that enrolled subjects between September 2008 and January 2013. The study was approved by the ethical committee of Rayong provincial hospital. The entire study population was native to Rayong province. The included LHC cases were older than 15 years of age, diagnosed according to the International Classification of Disease; ICD 10 code C91-96, and receiving treatment in the hematologic medical clinic of the internal medicine department of Rayong provincial hospital during the study period. Cases were classified into subtype by WHO 2000 as leukemia, multiple myeloma or lymphoma. The accurate diagnosis of LHC stratified by those subtypes, were histologically confirmed by hematologists and pathologists. All LHC cases had been living in Rayong province more than 1 year, able to provide data for themselves. All cases were still continuing follow-up therapy with a hematologist and data collection evidence of date and details of diagnosis were abstracted from medical records in Rayong provincial hospital. The inclusion of 420 controls were also older than 15 years of age, were hospital-based controls without any cancer or haematological disease as clarified before data collection. The controls also had to live in Rayong province at least 1 year prior, and admission to other in-patient departments such as obstetrics and gynecology, orthopedic surgery, ophthalmology, otolaryngology, general surgery and general internal medicine departments were included in this study. All subjects were interviewed by trained occupational health care officers. After identifying each case, the 4 controls were found and matched with gender and age +5 years. The information was recorded in a pre-designed questionnaire of the Thai National Cancer Institute. This form contained socio-demographic information such as age, gender, race, residential area, family history of cancer; unhealthy behavior, such as smoking or alcohol consumption; and selected occupational exposure during their work or in their working environment.

The definition of each confounding variable was as follows: residential area was classified as living in or out of pollution control areas; smoking included ex-smokers, current smokers of any type at any time of tobacco smoked or not; alcohol consumption included ex-drinkers and current drinkers exposed to any type at any time of alcoholic beverages consumed or not; family history of cancer defined as history of any type cancer in a first relative; duration of work was described as the period since beginning work in Rayong province to being diagnosed with LHC, and controls were asked their longest work at one job until time interviewed. For occupational exposure information, they were asked about their previous or current occupation lasting at least one year. Then, the interviewer asked about their job description and whether they had ever been exposed to possible carcinogens in any routine exposure at work. The report showed the following hazards in their work or work environment: Volatile Organic Compounds (VOCs) included benzene and organic solvents; chlorine; petroleum products; contact

to animals; cleaners; pesticides included insecticides, fungicides and herbicides; working outdoors; wood dust; fumes and smoke including smoke from cigarettes, exhaust engines, burning industrial processes, grilled and baked foods, etc. This study quantified a minimum exposure of at least one year (non cumulative) per carcinogen type. These interview results were used to classify individuals as having been occupationally exposed to LHC carcinogens.

Statistical analysis

Each case and control variable was summarized using standard descriptive statistics, including frequency and percentage for qualitative data and mean and standard deviation for quantitative data. The normally distributed quantitative data was also checked by a Kolmogorov-Smirnov test. The longest occupation of cases and controls were classified by the first digit job title codes of International Standard Classification of Occupations (ISCO) 1968[16]. The test of difference in demographic data and occupation data were done by Chi-square or independent t-test. The differences were considered statistically significant when the *p*-value was <0.05. Conditional logistic regression analysis was applied for obtaining the risk estimates between LHC or each LHC subtype and each occupational exposure. The risk is presented with both crude and adjusted odds ratio (ORs) and its 95% confidence intervals. Adjusted risk was the control by family history of cancer, smoking and alcohol consumption. If there is no case in each occupational exposure category of LHC or each LHC subtype, that category will not be included in the analysis due to inability to estimate precision risk. All statistical analysis was performed using SPSS for Windows (version 19.5, SPSS Incorporated).

Results

On checking the Rayong hospital database, there were 158 LHC cases in the study period. This study enrolled 105 LHC cases as participants, yielding a 66% coverage rate. The missing cases are due to referrals for treatment in other provinces, loss of follow-up, and death. The participating cases comprised 51 leukemia cases (47.7%) classified as 17 acute myeloid leukemia (33.3%), 26 chronic myeloid leukemia (51.0%), 5 acute lymphoid leukemia (9.8%) and 3 chronic lymphoid leukemia (5.9%); 11 multiple myeloma cases (10.3%); and 43 lymphoma cases (42.0%). The mean age of the cases and controls was 47.62 years (SD 16.20, range 15-82 years) and 47.03 years (SD 16.24, range 15-82 years), respectively. There were 56 males (53.33%) and 49 females (46.67%) and the 4-fold matching controls were therefore 224 males and 196 females. By occupation, most were in ISCO group 6-agricultural, animal husbandry and forestry workers, fishermen and hunters (38.10% in cases and 30.71% in controls). The descriptive data of cases and control group, and the statistical comparison between the two groups, are shown in Tables 1 and 2.

Table 1. Characteristics of cases and controls in this study

Factors	Characteristics	Cases (%); n = 105	Controls (%); n = 420	*p*-value
Gender	Male	56 (53.33)	224 (53.33)	1.00[a]
	Female	49 (46.67)	196 (46.67)	
Age	Mean ± SD (year)	47.62±16.20	47.03±16.24	0.74[b]
Family history of cancer	Yes	21 (20.00)	81 (19.29)	0.87[a]
	No	84 (80.00)	339 (80.71)	
Race	Thai	104 (99.05)	417 (99.29)	1.00[a]
	Others	1 (0.95)	3 (0.71)	
Residential area	In polluted control area	27 (25.71)	109 (25.95)	0.96[a]
	Out of polluted control area	78 (74.29)	311 (74.05)	
Duration of work	Mean ± SD (year)	22.45±17.03	18.17±16.01	0.02[b]
Alcohol drinking	Yes	50 (47.62)	186 (44.29)	0.54[a]
	No	55 (52.38)	234 (55.71)	
Smoking	Yes	67 (63.81)	237 (56.43)	0.17[a]
	No	38 (36.19)	183 (43.57)	

[a] Chi-square; [b] Independent t-test

The following factors from Table 1 were selected as confounders: genetic factors such as first degree relatives with any cancer and health behavior such as smoking and alcohol consumption. The most common three occupational exposures in cases were outdoor work, pesticides and smoke; while for controls they were outdoor work, wood dust and VOCs. Of these, the significant occupational carcinogenic exposures were pesticides and smoke. There were 25 cases (23.81%) and 52 controls (12.38%) of exposure to pesticides, and 21 cases (20%) and 45 controls (10.71%) exposed smoke. After adjusting for these confounders, workers who had been exposed to pesticides had 2.26 times (95% CI = 1.30-3.91) higher risk of LHC compared

Table 2. The longest occupation of cases and controls in this study classified by International Standard Classification of Occupation (ISCO) version 1968

Major group of occupation		Cases (%); n = 105	Controls (%); n = 420	*p*-value
0	Umemployed	3 (2.86)	32 (7.62)	0.28[a]
1	Professional, Technical and Related workers	7 (6.67)	12 (2.86)	
2	Administration and Managerial workers	0	5 (1.19)	
3	Clerical and Related workers	3 (2.86)	15 (3.57)	
4	Sales workers	4 (3.81)	26 (6.19)	
5	Service workers	10 (9.52)	51 (12.14)	
6	Agricultural, Animal Husbandry and Forestry workers, Fishermen and Hunters	40 (38.10)	129 (30.71)	
7	Foremen, Miners, Metal processors, Wood paper makers, Chemical processors, Spinners, Food beverage, Tobacco and Tailors	9 (8.57)	36 (8.57)	
8	Shoemakers, Cabinetmakers, Stone cutters, Blacksmiths, Machinery, Electrical fitters, Broadcasting, Plumber and Welders	12 (11.43)	39 (9.29)	
9	Rubber product makers, Plastic makers, Printers, Painters, Bricklayers, Riggers, Dockers, Transport operators and Laborers	17 (16.19)	75 (17.86)	
	Total	105 (100)	420 (100)	

[a] Chi-square

Table 3. Crude and Adjusted odds ratio and 95% confidence intervals for each occupational exposure and risk of LHC

Occupational exposure	Total lymphohematopoietic cancer			
	Cases (%); n = 105	Controls (%); n = 420	Crude ORs	Adjusted ORs*
VOCs	14 (13.33)	55 (13.10)	1.02 (0.55-1.89)	0.99 (0.53-1.84)
Benzene	4 (3.81)	20 (4.76)	0.79 (0.27-2.37)	0.78 (0.26-2.35)
Organic solvents	10 (9.52)	36 (8.57)	1.12 (0.54-2.32)	1.07 (0.52-2.23)
Chlorine	2 (1.90)	8 (1.90)	1.00 (0.21-4.71)	0.94 (0.20-4.50)
Petroleum product	10 (9.52)	28 (6.67)	1.51 (0.69-3.28)	1.54 (0.70-3.40)
Contact with animals	3 (2.86)	10 (2.38)	1.22 (0.32-4.71)	1.16 (0.30-4.47)
Cleaners	2 (1.90)	26 (6.19)	0.29 (0.07-1.25)	0.29 (0.07-1.24)
Pesticides	25 (23.81)	52 (12.38)	2.26 (1.31-3.91)	2.26 (1.30-3.91)
Working outdoors	51 (48.57)	177 (42.14)	1.31 (0.85-2.03)	1.31 (0.84-2.03)
Wood dust	17 (16.19)	76 (18.10)	0.87 (0.49-1.56)	0.87 (0.49-1.55)
Fumes	6 (5.71)	27 (6.43)	0.88 (0.35-2.20)	0.86 (0.34-2.15)
Smoke	21 (20.00)	45 (10.71)	2.04 (1.17-3.58)	1.99 (1.13-3.51)

* Adjusted by family history of cancer, smoking and alcohol consumption

with non-exposed workers; and those exposed to smoke had 1.99 times (95% CI = 1.13-3.51) higher risk of LHC than those non-exposed, as seen in Table 3.

When stratified by subtype of LHC by WHO 2000, leukemia was statistically significantly associated with occupational exposure to smoke at adjusted ORs 2.43 (95% CI = 1.11-5.36). Occupational pesticide exposure was a significant risk of lymphoma, adjusted ORs 4.69 (95% CI = 2.01-10.96). However, occupational exposure to VOCs, including benzene and organic solvents, chlorine, petroleum products, contact with animals, cleaners, working outdoors, wood dust, and fumes did not present statistically significant risk factors of LHC in any subtype, as presented in Table 4.

Discussion

Cancers are less attributed to occupational factors compared with other lifestyle factors. But occupational factors are easily preventable by elimination of or a decrease in exposure levels, or other preventive occupational health methods. Occupational exposure has long been linked to the risk of LHC through exposure to chemicals. Many chemicals are carcinogens and co-carcinogens in gene-environment interactions[17]. Some carcinogens attack hematopoietic stem cells, developing LHC. A previous study presented risk factors for only leukemia in Thailand by a case control study in which benzene, organic solvents and pesticides were significantly associated with leukemia[5]. This, however, is the first epidemiological study of occupational cancer in Rayong province, with its highest incidence of LHC[4]. LHC cases participating in this study are mainly male and older than 45 years old, which is no different from national statistics[3,4]. The dominant occupation according to ISCO coding in both case and control groups is Agricultural Occupations (Group 6). This picture is consistent with the geography of Rayong province which has more than half of its land under agriculture, mostly growing tropical fruit, with the other half being developed as industrial areas, the base of the petrochemical industry[18].

This study revealed that occupational exposure to pesticides and smoke was significantly associated with LHC. When stratified by subtype of LHC, lymphoma was statistically significantly associated with pesticide exposure and leukemia was statistically significantly associated with smoke exposure.

For pesticides, including insecticides, fungicides and herbicides, the biological mechanism underlying the linkage to the pathogenesis of LHC remains largely unknown. However, several mechanisms are conceivable. Developing cancer is a complex process, including multiple factors in the gene-environment interaction[17]. Chronic exposure factors merge in the body and turn to cancer depending on genetic susceptibility. With occupational exposure to carcinogenic pesticides, the body changes exogeneous chemical carcinogens to procarcinogens by over-expression of reactive oxygen species (ROS) with cytochrome P-450 and accumulates in the tissue of the whole body. Procarcinogens gradually are released into the blood stream, with bone marrow being one of the target organs affecting the hematopoietic system[19] leading to possibly extensive DNA damage, protein damage and hematopoietic irregularities[20]. This study reveals occupational exposure to pesticides is highly associated with LHC at adjusted ORs 2.26 (95% CI 1.30-3.91), corresponding with a previous study[17] that pesticide exposure is a risk factor of hematopoietic cancer. Agriculturists in Greece exposed to pesticides on farms had a significant risk factor to LHC ORs 3.29 (95% CI 1.81-5.98) and myelodysplastic syndrome ORs 3.67 (95% CI 1.18-12.11)[21]. When stratified by subtype, lymphoma was highly associated with pesticide exposure in work, with adjusted ORs 4.69 (95% CI 2.01-10.96), similar to agriculture and livestock work related to non-Hodgkin's lymphoma[22]. Thai agriculture methods, particularly the gardening of fruits and vegetables, use a mixture and variety of pesticides, sold under trade names, to control damage to plants from insects, mold, and weeds. Often they are used with unknown types of application, lack of awareness, and without body protection. Therefore, the specific pesticides relating to LHC risk are difficult to know and could not be differentiated in this study.

Occupational exposure to smoke in this study included any smoke occurrence during the working environment or work process, such as passive smoke in a pub or restaurant, working by the roadside or car park, working near burning industrial processes and smoke from cooking. Occupational smoke exposure associated with LHC in this study had adjusted ORs 1.99 (95% CI 1.13-3.51). However, it is only significantly associated with leukemia with adjusted ORs 2.43 (95% CI 1.11-5.36). The important carcinogen components from all smoke sources were PAHs, Benzo(a)pyrene, and dioxin[17,23]. Inhalation can cause carcinogen damage in the DNA[23], disturb DNA synthesis, and DNA methylation alterations mutate into LHCs such as leukemia[24]. Some mechanisms explain this as

Table 4. Crude and Adjusted odds ratio and 95% confidence intervals for occupational exposure and risk of subtype leukemia, multiple myeloma and lymphoma

Occupational exposure	Leukemia				Multiple myeloma				Lymphoma			
	Cases (%); n = 51	Controls (%); n = 204	Crude ORs	Adjusted ORs*	Cases (%); n = 11	Controls (%); n = 44	Crude ORs	Adjusted ORs*	Cases (%); n = 43	Controls (%); n = 172	Crude ORs	Adjusted ORs*
VOCs	8 (15.69)	33 (16.18)	0.97 (0.42-2.21)	0.86 (0.37-2.01)	1 (9.09)	2 (4.55)	2.00 (0.18-22.06)	2.19 (0.14-33.65)	5 (11.63)	20 (11.63)	1.00 (0.37-2.72)	0.98 (0.35-2.69)
Benzene	2 (3.92)	12 (5.88)	0.66 (0.14-3.00)	0.62 (0.13-2.84)	1 (9.09)	1 (2.27)	4.00 (0.25-63.95)	4.68 (0.19-116.44)	1 (2.33)	7 (4.07)	0.55 (0.07-4.71)	0.53 (0.06-4.54)
Organic solvents	6 (11.76)	21 (10.29)	1.16 (0.45-3.02)	1.03 (0.38-2.79)	0	1 (2.27)	-	-	4 (9.30)	14 (8.14)	1.15 (0.37-3.55)	1.13 (0.36-3.56)
Chlorine	1 (1.96)	3 (1.47)	1.33 (0.14-12.82)	1.45 (0.14-14.98)	0	1 (2.27)	-	-	1 (2.33)	4 (2.33)	1.00 (0.11-8.95)	0.97 (0.11-8.87)
Petroleum product	4 (7.84)	11 (5.39)	1.50 (0.45-4.96)	1.53 (0.45-5.17)	2 (18.18)	3 (6.82)	5.06 (0.40-64.00)	4.38 (0.18-62.47)	4 (9.30)	14 (8.14)	1.16 (0.36-3.79)	1.12 (0.34-3.69)
Contact to animals	2 (3.92)	3 (1.47)	3.15 (0.43-23.36)	2.52 (0.34-18.62)	0	1 (2.27)	-	-	1 (2.33)	6 (3.49)	0.65 (0.07-5.72)	0.66 (0.07-5.83)
Cleaners	1 (1.96)	13 (6.37)	0.29 (0.04-2.28)	0.28 (0.04-2.23)	0	4 (9.09)	-	-	1 (2.33)	9 (5.23)	0.42 (0.05-3.48)	0.43 (0.05-3.59)
Pesticides	7 (13.73)	21 (10.29)	1.45 (0.56-3.80)	1.43 (0.53-3.84)	3 (27.27)	11 (25)	1.11 (0.28-4.43)	1.11 (0.27-4.73)	15 (34.88)	20 (11.63)	4.04 (1.81-8.98)	4.69 (2.01-10.96)
Working outdoors	19 (37.25)	80 (39.22)	0.91 (0.48-1.75)	0.88 (0.45-1.70)	8 (72.73)	23 (52.27)	2.19 (2.56-8.62)	2.98 (0.64-13.91)	24 (55.81)	74 (43.02)	1.70 (0.86-3.36)	1.76 (0.89-3.51)
Wood dust	7 (13.73)	39 (19.12)	0.67 (0.28-1.61)	0.69 (0.29-1.68)	1 (9.09)	7 (15.91)	0.55 (0.07-4.71)	0.48 (0.05-4.27)	9 (20.93)	30 (17.44)	1.26 (0.54-2.95)	1.25 (0.53-2.93)
Fumes	5 (9.80)	14 (6.86)	1.50 (0.50-4.50)	1.49 (0.49-4.57)	0	2 (4.55)	-	-	1 (2.33)	11 (6.40)	0.35 (0.05-2.79)	0.35 (0.04-2.84)
Smoke	12 (23.53)	21 (10.29)	2.60 (1.19-5.66)	2.43 (1.11-5.36)	1 (90.9)	4 (90.09)	1.00 (0.11-8.95)	1.07 (0.11-10.80)	8 (18.60)	20 (11.63)	1.73 (0.71-4.24)	1.68 (0.68-4.18)

* Adjusted by family history of cancer, smoking and alcohol consumption

carcinogens interrupting Gap Junctional Intercellular Communication (GJIC), supporting the process of progression[23]. Occupational smoke causing chronic inflammation generate free radicals incur ROS to caused DNA adduct and block GJIC[25]. In a laboratory study, mice were fed with contaminated benzo(a)pyrene which suppressed bone marrow function, leading to leukemia[23]. When describing experiments in mice by mathematical methods, the carcinogen benzo(a)pyrene was found to be toxic to bone marrow, especially granulopoietic cells rather than erythropoietic cells[26].

On the other hand, occupational exposure to VOCs, benzene, organic solvents, chlorine, petroleum products, contact with animals, outdoor working, wood dust, cleaners and fumes were not significantly associated with LHCs. There are many possible explanations such as exposure to small amounts, unidentified specific type of chemical substances from occupational exposure, changes in working behavior; it could be difficult to identify the frequency or duration, and find the relationships. Moreover, the small sample size of each occupational exposure as well as the low participating number of LHC cases may not be considered representative of the population of patients, and may be of low statistical power to analyze the association of risk factors of LHC. However, the control up to four fold could help increase the power of the statistics for analysis in this study. Confounding factors influential with the development of LHC from individual genetics and unhealthy behavior (smoking and alcohol consumption) were controlled by multivariate analysis. The analysis of the interaction between these factors and occupational exposure was not done due to the small sample size.

Recall bias might be unavoidable in a case control study. This study did not ask subjects to recall and identify specific exposures, or specific periods of duration of those exposures. Recall bias may have therefore occurred. LHC cases may have made recollections of exposure more than control subjects, even though the interviewer did not tell the specific objective of this study to either group. Although controls selected from a hospital base are not representative of the residents in Rayong province, they should have paid attention to possible occupational exposure in the same way as the cases. If this bias really occurs, some hazard such as chlorine exposure, which is easily remembered by its odorous quality, must also be significant in the association in this study. Exposure assessment in this study was a quality assessment, but also its limitation. To avoid this bias, this study quantified a minimum exposure of at least one year (non cumulative). The interviewer training before doing the interviews made it easy to collect details of job descriptions that could easily be linked to each occupational exposure hazard as well as excluding environmental exposure sources. However, environmental exposure is still problematic in this study, as some areas in Rayong province have environmental pollution from industries. It is difficult to differentiate these from occupational exposure by interview only.

Nevertheless, the present result should be considered carefully and confirmed with further studies. Future research study designs should be more rigorous analytical studies such as cohort study or a study of a specific type of chemical that may make it easier to identify the associated risk of LHC, such as classified pesticides, organic solvents, petroleum products, fumes or smoke. Exposure to chemicals should be assessed in detail by each occupational exposure risk by other methods, such as quantitative exposure measurement or using a job exposure matrix to increase the validity of the assessment. It may also identify the dose response and reduce the confounding factors. In addition, selection of a control group from the general population in Rayong province would help to analyze the research results more accurately.

For prevention and control of the epidemic problem of occupational cancer in the future, the relevant parties should develop and implement occupational health protocols in all levels of the health services. Public health officers should be more proactive in preventing, controlling, and monitoring these occupational risk factors. They should not forget that other occupations such as agriculture or service settings, not only industrial ones, are associated with cancer. The first step that should be taken is to decrease carcinogen exposure as much possible by occupational health methods such as substituting by other pesticides, good ventilation to reduce smoke in the working environment, and use of personal protective equipment. The development of an exposure assessment database is another important surveillance system for future studies.

In conclusion, the present findings support the hypothesis that occupational pesticides exposure is associated with the increased risk of LHC, and this association varies widely across disease subtype lymphoma. Occupational smoke exposure is associated with the increased risk of LHC and leukemia subtype in Rayong province. However, the ability or power to detect this problem due to the small sample size

and recall bias from the study design could not be excluded.

What is already known on this topic ?

The causes of lymphohematopoietic cancer (LHC) are complex and diverse. Some risk factors are partially understood, such as genetics, smoking, alcohol, infection, exposure to radiation, and benzene. However, understanding of occupational exposure to other carcinogens from work is still limited and inconclusive.

What this study adds ?

This study found that pesticides and smoke exposure from work are risk factors of LHC among patients in Rayong province, where the rising incidence rate is higher than National statistics. It supports the hypothesis that exposure to occupational carcinogens are associated with LHC. This occupational risk factor is easy to prevent by eliminating the source of exposure through occupational health methods.

Acknowledgement

This work was supported by the Faculty of Medicine, Srinakharinwirot University and the Thai National Cancer Institute. The authors would like to thank to Mr. Ashley Backhouse for proofread the article.

Potential conflicts of interest

None.

References

1. McKenna RW. Multifaceted approach to the diagnosis and classification of acute leukemias. Clin Chem 2000; 46: 1252-9.
2. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer 2010; 127: 2893-917.
3. Ekpanyaskul C. Descriptive epidemiology of hematologic cancer in adult. Thai Cancer J 2010; 30: 77-83.
4. Khuhaprema T, Sangrajrang S, Sriplung H, Wiangnon S, Sumitsawan Y, Attasara P. Cancer incidence in Thailand. Bangkok: National Cancer Institute, Thailand; 2009.
5. Kaufman DW, Anderson TE, Issaragrisil S. Risk factors for leukemia in Thailand. Ann Hematol 2009; 88: 1079-88.
6. International Agency for Research on Cancer (IARC). IARC Monographs on the evaluation of carcinogenic risks to humans [Internet] 2015 [cited 2015 Jan 5]. Available from: http://www.iarc.fr/en/publications/list/monographs/index.php
7. Glass DC, Gray CN, Jolley DJ, Gibbons C, Sim MR, Fritschi L, et al. Leukemia risk associated with low-level benzene exposure. Epidemiology 2003; 14: 569-77.
8. Infante PF. Benzene exposure and multiple myeloma: a detailed meta-analysis of benzene cohort studies. Ann N Y Acad Sci 2006; 1076: 90-109.
9. Kirkeleit J, Riise T, Bratveit M, Moen BE. Increased risk of acute myelogenous leukemia and multiple myeloma in a historical cohort of upstream petroleum workers exposed to crude oil. Cancer Causes Control 2008; 19: 13-23.
10. Schwilk E, Zhang L, Smith MT, Smith AH, Steinmaus C. Formaldehyde and leukemia: an updated meta-analysis and evaluation of bias. J Occup Environ Med 2010; 52: 878-86.
11. Bond GG, Bodner KM, Olsen GW, Cook RR. Mortality among workers engaged in the development or manufacture of styrene-based products—an update. Scand J Work Environ Health 1992; 18: 145-54.
12. Cocco P, t'Mannetje A, Fadda D, Melis M, Becker N, de Sanjose S, et al. Occupational exposure to solvents and risk of lymphoma subtypes: results from the Epilymph case-control study. Occup Environ Med 2010; 67: 341-7.
13. Svec MA, Ward MH, Dosemeci M, Checkoway H, De Roos AJ. Risk of lymphatic or haematopoietic cancer mortality with occupational exposure to animals or the public. Occup Environ Med 2005; 62: 726-35.
14. Rushton L, Romaniuk H. A case-control study to investigate the risk of leukaemia associated with exposure to benzene in petroleum marketing and distribution workers in the United Kingdom. Occup Environ Med 1997; 54: 152-66.
15. Merhi M, Raynal H, Cahuzac E, Vinson F, Cravedi JP, Gamet-Payrastre L. Occupational exposure to pesticides and risk of hematopoietic cancers: meta-analysis of case-control studies. Cancer Causes Control 2007; 18: 1209-26.
16. International Standard Classification of Occupations (ISCO-1968). Geneva: International Labor Organization (ILO); 1968.
17. Irigaray P, Belpomme D. Basic properties and molecular mechanisms of exogenous chemical

carcinogens. Carcinogenesis 2010; 31: 135-48.
18. Rayong Statistical reports 2007. The provincial database. Rayong, Thailand: Rayong Government Complex; 2008.
19. Niesink JM, de Vries J, Hollinger AM. Toxicology: principle and applications. Boca Raton, NY: CRC Press; 1996.
20. Jin J, Yu M, Hu C, Ye L, Xie L, Jin J, et al. Pesticide exposure as a risk factor for myelodysplastic syndromes: a meta-analysis based on 1,942 cases and 5,359 controls. PLoS One 2014; 9: e110850.
21. Kokouva M, Bitsolas N, Hadjigeorgiou GM, Rachiotis G, Papadoulis N, Hadjichristodoulou C. Pesticide exposure and lymphohaematopoietic cancers: a case-control study in an agricultural region (Larissa, Thessaly, Greece). BMC Public Health 2011; 11: 5.
22. Richardson DB, Terschuren C, Hoffmann W. Occupational risk factors for non-Hodgkin's lymphoma: a population-based case-control study in Northern Germany. Am J Ind Med 2008; 51: 258-68.
23. Anselstetter V, Heimpel H. Acute hematotoxicity of oral benzo(a)pyrene: the role of the Ah locus. Acta Haematol 1986; 76: 217-23.
24. Wiliams PL, James RC, Roberts SM. The principles of toxicology: environmental and industrial applications. 2nd ed. New York: Wiley-Interscience; 2000.
25. Melendez-Colon VJ, Luch A, Seidel A, Baird WM. Cancer initiation by polycyclic aromatic hydrocarbons results from formation of stable DNA adducts rather than apurinic sites. Carcinogenesis 1999; 20: 1885-91.
26. Scheding S, Loeffler M, Anselstetter V, Wichmann HE. A mathematical approach to benzo[a]pyrene-induced hematotoxicity. Arch Toxicol 1992; 66: 546-50.

ปัจจัยเสี่ยงจากการประกอบอาชีพของมะเร็งระบบเลือดในจังหวัดระยอง ประเทศไทย

อภิญญา พันธจ์นิดาทรัพย์, ศุลีพร แสงกระจ่าง, ฉัตรชัย เอกปัญญาสกุล

ภูมิหลัง: *อัตราอุบัติการณ์ของมะเร็งระบบเลือดในประเทศไทยเพิ่มมากขึ้นจากอดีตโดยไม่ทราบสาเหตุรวมถึงจังหวัดระยอง สมมติฐานหนึ่งของความเสี่ยงต่อการเกิดมะเร็งระบบเลือดคือ การสัมผัสสารก่อมะเร็งจากการประกอบอาชีพ*

วัตถุประสงค์: *เพื่อศึกษาหาความสัมพันธ์ของการสัมผัสเหตุอาชีพกับความเสี่ยงต่อการเกิดมะเร็งระบบเลือดในจังหวัดระยอง ประเทศไทย*

วัสดุและวิธีการ: *การศึกษา case-control แบบจับคู่ชนิดเลือกกลุ่มควบคุมจากในโรงพยาบาล ได้ทำการเก็บข้อมูลในโรงพยาบาลจังหวัดระยองระหว่างเดือนกันยายน พ.ศ. 2552 ถึงมกราคม พ.ศ. 2556 โดยผู้ป่วยมะเร็งระบบเลือด 1 รายจะถูกจับคู่กับกลุ่มควบคุม 4 รายด้วยเพศและอายุ ±5 ปี ข้อมูลพื้นฐาน ปัจจัยด้านที่อยู่อาศัย ปัจจัยด้านพฤติกรรมและการสัมผัสเหตุอาชีพซึ่งรวมการสัมผัสสารเคมี ได้ถูกเก็บข้อมูลด้วยวิธีการสัมภาษณ์โดยบุคลากรด้านอาชีวอนามัย ปัจจัยเสี่ยงเหล่านั้นจะนำมาวิเคราะห์ด้วยสถิติความถดถอยลอจิสติกแบบมีเงื่อนไขและรายงานค่าสถิติด้วยค่า odds ratio และค่าความเชื่อมั่นที่ร้อยละ 95*

ผลการศึกษา: *การศึกษานี้พบผู้ป่วยมะเร็งระบบเลือดจำนวน 105 รายที่เข้าเกณฑ์และนำมาศึกษาในครั้งนี้ คิดเป็นอัตราครอบคลุมร้อยละ 66 ของผู้ป่วยที่มีการรายงานในฐานข้อมูล ผลทางพยาธิวิทยาพบว่าเป็นมะเร็งเม็ดเลือดขาวชนิดลิวคีเมีย 51 ราย (ร้อยละ 47.7) มะเร็งต่อมน้ำเหลืองหรือลิมโฟมา 43 ราย (ร้อยละ 42.0) และมะเร็งเม็ดเลือดขาวชนิดมัลติเพิล มัยอีโลมา 11 ราย (ร้อยละ 10.3) ผลการศึกษาพบว่าการสัมผัสสารกำจัดศัตรูพืชและควันจากการประกอบอาชีพมีความสัมพันธ์กับการเกิดมะเร็งระบบเลือดอย่างมีนัยสำคัญทางสถิติด้วยค่า odds ratio ที่ปรับปัจจัยรบกวนเท่ากับ 2.26 เท่า (ความเชื่อมั่นที่ร้อยละ 95 1.30-3.91 เท่า) และ 1.99 เท่า (ความเชื่อมั่นที่ร้อยละ 95 1.13-3.51 เท่า) ตามลำดับ เมื่อทำการวิเคราะห์แยกชนิดของมะเร็งระบบเลือดตามองค์การอนามัยโลก พ.ศ. 2543 พบว่าการสัมผัสควันจากการประกอบอาชีพมีความเสี่ยงอย่างมีนัยสำคัญทางสถิติต่อมะเร็งเม็ดเลือดขาวชนิดลิวคีเมียด้วยค่า odds ratio ที่ปรับปัจจัยรบกวนเท่ากับ 2.43 เท่า (ความเชื่อมั่นที่ร้อยละ 95 1.11-5.36 เท่า) และสารกำจัดศัตรูพืชจากการประกอบอาชีพมีความเสี่ยงอย่างมีนัยสำคัญทางสถิติต่อมะเร็งต่อมน้ำเหลืองด้วยค่า odds ratio ที่ปรับปัจจัยรบกวนเท่ากับ 4.69 เท่า (ความเชื่อมั่นที่ร้อยละ 2.01-10.96 เท่า) อย่างไรก็ตามการศึกษานี้ไม่พบว่าควัน ฝุ่นไม้ การทำงานกลางแจ้ง น้ำยาทำความสะอาด การสัมผัสสัตว์ ผลิตภัณฑ์ปิโตรเลียม คลอรีน และสารประกอบระเหยอินทรีย์ เช่น เบนซีน ตัวทำละลายอินทรีย์ มีความเสี่ยงที่มีนัยสำคัญทางสถิติต่อมะเร็งระบบเลือด นอกจากนี้ยังไม่พบความเสี่ยงในข้อมูลพื้นฐาน ปัจจัยด้านที่อยู่อาศัย และปัจจัยด้านพฤติกรรม*

สรุป: *การสัมผัสสารกำจัดศัตรูพืชและควันจากการประกอบอาชีพเป็นปัจจัยเสี่ยงด้านอาชีพที่สำคัญต่อการเกิดมะเร็งระบบเลือดในจังหวัดระยอง ทั้งนี้ปัญหาเรื่องขนาดตัวอย่างผู้ป่วยจำนวนที่น้อยอาจส่งผลต่ออำนาจการทดสอบและอคติเรื่องการจดจำเหตุการณ์ในอดีตจากรูปแบบการศึกษา เป็นสิ่งที่ต้องคำนึงถึง*