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A hospital-based case–control study of non-Hodgkin lymphoid neoplasms in Shanghai: Analysis of environmental and occupational risk factors by subtypes of the WHO classification

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ABSTRACT

The objectives were (1) to investigate potential environmental and occupational risk factors of non-Hodgkin lymphoid neoplasms (NHLN), and (2) to explore the relationships between risk factors and NHLN subtypes according to the World Health Organization (WHO) classification. The investigation was a hospital-based case–control study consisting of 649 newly diagnosed NHLN cases (August 2003 through January 2008) and 1298 individually gender-age-matched patient controls at 25 hospitals in Shanghai. A 17-page questionnaire was used to obtain information on demographics, medical history, family history, lifestyle risk factors, employment history, residential history, and occupational and non-occupational exposures. Certain occupations of interest triggered a second questionnaire, which was occupation-specific and asked for more details about jobs, tasks, materials used and work environment. Exposure assessments were based on the questionnaires, on-site workplace investigations, data published in the Chinese literature, historical exposure measurements maintained by government health agencies, and expert opinions of a panel of local scientists who were familiar with workplaces in Shanghai. Risk estimates (odds ratios and 95% confidence intervals) of individual risk factors were calculated using conditional logistic regression models. A number of potential environmental and occupational risk factors were associated with an increased risk of NHLN (all subtypes combined) and/or individual subtypes; including home/workplace renovation, living on a farm, planting crops, raising livestock or animals, farm workers, fabric sewing and cutting workers, welders and sheet metal workers, masonry and plastering workers, product and chemical testing workers, toy manufacturing, agriculture industry, and beauty salon. Exposures associated with an increased risk of NHLN (all subtypes combined) and/or individual subtypes included benzene, solvents, petroleum fuels, metals, insecticides, herbicides, fertilizers, and glues and adhesives. Multivariate models were used to adjust for potential confounding exposures, and several potential risk factors were subsequently eliminated. The results of the investigation indicated that some risk factors applied to all or most subtypes (e.g., insecticides and overall NHLN and subtypes of B-cell lymphoid neoplasms), while others to specific subtypes only (e.g., benzene and follicular lymphoma). Thus, some risk factors were subtype-specific. The difference in risk by subtype underscores the importance of the etiologic commonality and heterogeneity of NHLN subtypes.

1. Introduction

Neoplasms of the lymphoid tissue consist of a diverse yet related group of malignancies: Hodgkin lymphoma, non-Hodgkin lymphoma, lymphocytic leukemias and multiple myeloma. Hodgkin lymphoma, with the characteristic Reed–Sternberg cells, is usually treated separately from the rest of lymphoid neoplasms. Other lymphoid neoplasms, for convenience, will be referred to as non-Hodgkin lymphoid neoplasms (NHLN) in this paper.

Non-Hodgkin lymphoma (NHL), the largest subgroup of NHLN, itself represents a heterogeneous group of malignancies whose common link is a characteristic monoclonal expansion of malignant B- or T-cells and is the single largest group of neoplasms of the immune system. The estimated number of newly diagnosed NHL in the US for 2008 was 66,120 [1]. Based on the US National

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Cancer Institute's (NCI) Surveillance Epidemiology and End Results (SEER) data for 2001–2005, the adjusted annual incidence rates for males and females were 23.5/100,000 and 16.3/100,000, respectively [2]. There are some variations in incidence by ethnicity and geographical location. For example, in the US the rates for males and females classified as "Asian/Pacific Islanders" are 16.0/100,000 and 11.1/100,000, respectively, which are lower than those for their white counterparts (24.3/100,000 and 17.1/100,000). Generally, the incidence of NHL is higher in developed countries than in less developed nations. Incidence rates of NHL in Asian countries such as China and India are generally lower than those in the US or other western nations [3].

Most early epidemiologic studies treated NHL as a single diagnostic category, partly because of the limited number of patients by subgroups of NHL in individual studies and partly because of the lack of detailed diagnostic information or the ever-changing diagnostic classification of NHL subtypes. Epidemiologic research of NHL has been hampered by the complexity and the confusion of historical changes in NHL subtype classification [3–5]. Some of the NHL classification systems used in the last few decades included the Rappaport classification, the Kiel classification, the Luke–Collins system, and the US National Cancer Institute's Working Formulation. In 1994, the International Lymphoma Group's Revised European-American Lymphoma (REAL) classification was introduced, which gained wide acceptance internationally. Since then an increasing number of epidemiologic studies have begun to focus on specific NHL subtypes, but some investigations still treat NHL as a single diagnostic entity.

Lymphocytic leukemias, part of the new World Health Organization (WHO) classification of NHLN, accounted for an estimated 20,540 cases in the US in 2008 [1]. The annual incidence rates of chronic lymphocytic leukemia (CLL) for 2001–2005 were 5.6/100,000 for men and 2.8/100,000 for women [2]. In the US the CLL incidence rates for white men and women were approximately five times those of American men and women classified as Asian/Pacific Islanders. Similarly, Asian countries such as China have much lower rates of CLL than the US or other western nations [6]. The annual incidence rates of acute lymphocytic leukemia for 2001–2005 in the US were 1.8/100,000 for men and 1.4/100,000 for women, with little difference between whites and Asians.

Several previous comprehensive reviews have listed a large number of potential risk factors of NHL (all subtypes combined) or individual subtypes reported in epidemiologic investigations; including personal and family medical histories (such as immunodeficiency-related disorders, family aggregation, organ transplantation, blood transfusion, and prior Hodgkin disease), lifestyle (such as tobacco and hair dyes), environmental exposures (such as living on a farm), occupations and industries (such as farmers, hairdressers, construction workers, shoe workers, printers, metal and foundry workers, welders, and masonry workers), and exposures to chemical, physical or biological agents (such as agricultural chemicals, petrochemicals, solvents, radiation, and viruses) [3,4,7–9]. Potential risk factors for lymphocytic leukemias reported in epidemiologic studies included a history of rheumatoid arthritis, allergy-related disorders, blood transfusion, farming, and carpet manufacturing [6]. In addition, some recent studies have reported a positive association between anthropometric measurements (e.g., body mass index) and lymphatic and hematopoietic malignancies including NHL and CLL [10–13].

The findings of NHL risk factors reported in epidemiologic studies, however, have not always been consistent. The apparent inconsistency can be attributed partially to the fact that the diagnostic category of NHL actually consists of several distinct subtypes and, hence, the need for epidemiologic studies of NHL to treat these subtypes as separate diagnostic entities [3]. A new classification of lymphoid neoplasms was introduced by WHO in 2001 [14,15]. At the present, only a few epidemiologic studies have investigated the effect of environmental and occupational risks of NHLN and individual subtypes based on the WHO classification. Epidemiologic studies to systematically investigate the etiologic commonality and heterogeneity of subtypes of lymphoid neoplasms using the new WHO classification are needed.

The objectives of the present study are twofold: (1) to investigate potential environmental and occupational risk factors of NHLN, and (2) to explore the relationships between risk factors and specific NHLN subtypes according to the new WHO classification of lymphoid neoplasms. A previous analysis of the data in the study has identified several potential risk factors associated with personal characteristics or lifestyle, including low-level education, home or workplace renovation, living on a farm, planting crops, and raising livestock or animals; whereas the use of traditional Chinese medicines and consumption of alcohol were associated with a reduced risk [16]. In the current paper we will report the results of an analysis based on occupational or industrial categories and specific exposures.

2. Materials and methods

We conducted a hospital-based case–control study of NHLN in Shanghai. Participants of and contributors to the study included health agencies, hospitals, universities and research organizations in China and US. A list of the participants and a detailed description of the materials and methods of the study can be found in a parallel study of acute myeloid leukemia published in the current issue of *Chemico-Biological Interactions* [17]. The study protocols were approved by Chinese and US Institutional Review Boards of respective organizations. Potential cases were defined as patients aged 18 or older and newly diagnosed with NHLN ("provisional diagnosis") at 25 participating hospitals between August 2003 and January 2008. The WHO 2001 classification of lymphoid neoplasms was used in the diagnosis [14,15]. A new laboratory "the Joint Sino-US Clinical and Molecular Laboratory (JCML)" at Fudan University in Shanghai, staffed with Chinese and US scientists, functioned as the centralized diagnostic laboratory. Each participant was asked to sign an informed consent. Peripheral blood, bone marrow aspirates, tissue and core biopsies were collected in conjunction with diagnostic procedures and were sent to JCML for analysis [18,19]. For each case, two individually age-gender-matched controls (within 5 years of the case) were randomly selected from patients at the same hospital, who must be free of any malignant or non-malignant diseases of the lymphatic and hematopoietic system. For some cases, suitable controls within 5 years of age were not available and the age requirement was relaxed slightly.

A 17-page general questionnaire and selected occupation-specific questionnaires were used to obtain relevant demographic, lifestyle, environmental and occupational information from the patients in face-to-face interviews. Neither the patients nor the interviewers were informed about the specific objectives of the study, and the interviewers were not informed of the case/control status. Occupations and industries reported by the patients were coded according to the official Chinese standard classification systems [20,21]. An exposure assessment for benzene was performed by a committee of local experts, who were blinded with regard to the case/control status [17,22,23]. Exposure to benzene was categorized into five exposure groups (EG): EG0 (non-exposure), EG1 (<1 mg/m^3), EG2 (1–10 mg/m^3), EG3 (10–100 mg/m^3), and EG4 (>100 mg/m^3); with corresponding exposure group scores (EGS) of 0–4. Data analysis was carried out with the SAS statistical software [24]. Conditional logistic regression models taking into account the matching between cases and controls (gender and age) were used to calculate odds ratios (ORs) and 95% confidence intervals (95% CIs). Multivariate models were used to adjust for potential confounding exposures, including lifestyle and non-occupational risk factors identified in a previous analysis [16].

3. Results

Twenty-five hospitals contributed NHLN patients to the case–control study. The majority of the hospitals were municipal or university-affiliated hospitals and most of the remaining ones were district hospitals. In total, these 25 hospitals covered a sizable percentage of the cancer patient population of the city. Between August 2003 and January 2008, of all the patients with a provisional diagnosis of NHLN referred to JCML, 855 were subsequently confirmed with a diagnosis of NHLN according to the WHO 2001 criteria. A total of 206 patients, who were without informed consent forms or with incomplete interviews, were excluded from the case–control study. Thus, the case–control study consisted of 649 confirmed NHLN patients with informed consents and completed questionnaires, representing a participation rate of 76%. For every NHLN case, two individually matched controls from the same hospital were subsequently recruited, resulting in a total of 1298 control patients with a variety of diagnoses (the most frequent categories being diseases of the circulatory system, endocrine, respiratory system, digestive system and cancer). The interviewees (i.e., persons answering the questions during the interviews) could be (1) the patients themselves, (2) the patients plus family members, or (3) family members only. However, a great majority of the patients (96.46% cases and 97.76% controls) participated in the interviews (for case, 75.04% patients only and 21.42% patients plus family members; for controls, 83.83% patients only and 13.94% patients plus family members). The reason for a higher percentage of "patients plus family members" among the cases was that more NHLN patients than control patients were too weak to complete the entire interview (average 45 min) and needed assistance from family members.

Table 1 presents demographic and other personal characteristics of the cases and controls. The similarities in gender and age between the cases and controls indicate that matching was successful (60.40% males in both cases and controls, and mean ages of 52.5 for cases and 52.7 for controls). The distribution of the 1298 controls by their age differences comparing with the cases was as follows: within 5 years (n = 1122 or 86%), 6–8 years (n = 148 or 11%), 9–10 years (n = 20 or 2%), and 11–13 years (n = 8 or 1%). The cases and controls were remarkably similar with respect to the most common marital status; close to 84% in both groups reported as "married." Based on a comparison in Table 1, more controls than cases attended high schools (24.96% vs. 20.65%) or university and postgraduate schools (21.65% vs. 15.87%). Several anthropometric measures were included in the questionnaire, including height and weight (before the current illness), from which BMI were calculated. The mean BMI of the controls (22.8) was almost identical to that of the cases (22.6).

The distribution of the 649 NHLN cases by WHO subtypes is given in Table 2. In the WHO classification, two major subgroups of NHLN are recognized: (1) B-cell neoplasms, and (2) T- and NK-cell neoplasms [14,15]. The two major subgroups are divided into precursor and mature (peripheral) B-cell and T-cell neoplasms. Cases of mature B-cell and T-cell neoplasms are further classified into subtypes according to their clinical presentations. The WHO classification considers lymphomas and lymphoid leukemias of the same cell type as one disease with different clinical presentations or stages. For example, B-cell chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) are considered one disease (CLL/SLL) at different stages. There were 521 (80.28%) cases of B-cell neoplasms, of which 134 (20.65%) were classified as precursor B lymphoblastic leukemia/lymphoma. Of the 387 (59.63%) cases of mature B-cell neoplasms, the three largest subtypes were: CLL/SLL (n = 67, 10.32%), follicular lymphoma (n = 45, 6.93%), and diffuse large B-cell lymphoma (n = 186, 28.66%). Among the T- and NK-cell neoplasms, 31 were precursor T lymphoblastic leukemia/lymphoma and the remaining 118 belonged to various subtypes of mature T- or NK-cell neoplasms.

Table 3 shows the distribution of demographic and personal characteristics of all NHLN cases (NHLN-total) and by selected major WHO subtypes (B-cell neoplasms, precursor B-cell neoplasms, mature B-cell neoplasms, CLL and SLL [CLL/SLL], follicular lymphoma [FL], diffuse large B-cell lymphoma [DLBCL], and T-cell and NK-cell [T/NK-cell] neoplasms). Precursor B-cell neoplasms had the lowest male-to-female ratio, whereas CLL/SLL the highest. Similarly, patients diagnosed with precursor B-cell neoplasms were youngest on the average (mean age = 43.3 years), whereas CLL/SLL patients the oldest (mean age = 60.4 years).

Table 4 presents the risk analysis of NHLN-total and major subtypes for more than 30 occupational groups. These occupational groups were chosen based on a consideration of potential exposures, findings from previous studies reported in the literature and frequency in our study. It appeared that occupations related to sciences, engineering, health-care, finance, teaching, management, office, and retail sales were either not at any increased risk or at slightly reduced risk of NHLN-total and major subtypes.

A significantly increased risk of NHLN-total was associated with the category "general farm workers, grains" (OR = 1.39, 95% CI = 1.08–1.78) and similar risks were observed for subtypes of B-cell neoplasms as well. There was no increased risk of T/NK-cell neoplasms associated with "farm workers, grain" (OR = 0.97, 95% CI = 0.53–1.78). According to the description in the official Chinese Standard Classification of Occupations, farm workers in this category grow grains such as rice, wheat, corn, mullet, bean, potatoes, etc. [18]. A similar significant excess of risk for NHLN-total was also found for the broader group "general farm workers, grains and other products" (OR = 1.42, 95% CI = 1.13–1.78). This group includes "general farm workers, grains" and those who grow crops such as vegetables, fruits, tea, cotton, etc. "Farm workers (all types)," which include the service sector as well, experienced a similar elevated risk for NHLN-total (OR = 1.42, 95% CI = 1.14–1.78) and increased risks were noted across several subtypes of B-cell neoplasms, except CLL/SLL and FL. A significant risk for NHLN-total was found for "fabric sewing and cutting workers," which included workers engaged in the cutting and sewing of fabrics for apparel, shoes, hats, tents, cushions and decorations (OR = 3.89, 95% CI = 1.95–7.76). Furthermore, it appeared that the risks of most subtypes of both B-cell and T/NK-cell neoplasms were elevated; especially for precursor B-cell neoplasms (OR = 10.29, 95% CI = 2.27–46.66), DLBCL (OR = 5.62, 95% CI = 1.14–27.75), and T/NK-cell neoplasms (OR = 8.00, 95% CI = 0.89–71.56). On the other hand, no increased risk associated with "fabric sewing and cutting workers" was found for FL. Welder and sheet metal workers were at an increased risk of DLBCL (OR = 3.33, 95% CI = 1.21–9.17). An increased risk of B-cell neoplasms was associated with "masonry and plaster workers" (OR = 2.46, 95% CI = 1.15–5.24). "Product and chemical testing workers" (workers involved in inspecting and testing of manufactured products such as electronics, equipment, tea, tobacco, chemicals, shoes, ceramics, etc.) were at an elevated risk of B-cell neoplasms (OR = 1.89, 95% CI = 1.11–3.21), especially mature B-cell neoplasms (OR = 2.14, 95% CI = 1.17–3.93) and FL (OR = 10.00, 95% CI = 1.17–85.59); but neither CLL/SLL nor T/NK-cell neoplasms were affected.

Analysis by industrial categories is presented in Table 5. A significantly increased risk of approximately 50% associated with the industrial category "crop plantation" was found for NHLN-total (OR = 1.44, 95% CI = 1.15–1.80) and the increase risk seemed to come from B-cell neoplasms (OR = 1.53, 95% CI = 1.19–1.96). In particular,

Table 1
Distribution of demographic and personal variables of non-Hodgkin lymphoid neoplasm (NHLN) cases and controls.

Variable	Cases		Controls	
Number	649	100.00%	1298	100.00%
Male	392	60.40%	784	60.40%
Female	257	39.60%	514	39.60%
Mean age (standard deviation) in years	52.5	(16.53)	52.7	(15.86)
Marital status				
Married	546	84.13%	1088	83.82%
Divorced	2	0.31%	8	0.62%
Never married	60	9.24%	119	9.17%
Widowed	36	5.55%	77	5.93%
Missing data	5	0.77%	6	0.46%
Education				
None	50	7.70%	78	6.01%
Primary school	140	21.57%	211	16.26%
Middle school	218	33.59%	399	30.74%
High school	134	20.65%	324	24.96%
University or higher	103	15.87%	281	21.65%
Missing data	4	0.62%	**5**	0.39%
Smokers (ever)	272	41.91%	537	41.37%
Body mass index (BMI) (standard deviation)	22.6	(3.48)	22.8	(3.37)

Table 2
Distribution of non-Hodgkin lymphoid neoplasms (NHLN) by subtype according to the WHO 2001 classification.

Category	ICD-O[a] code	Number	Percent
B-cell neoplasms			
Precursor B-cell neoplasms			
Precursor B lymphoblastic leukemia/lymphoma	9835/3, 9728/3	134	20.65
Subtotal		134	20.65
Mature B-cell neoplasms			
Chronic lymphocytic leukemia	9823/3	30	4.62
Small lymphocytic lymphoma	9670/3	37	5.70
B-cell prolymphocytic leukemia	9833/3	4	0.62
Lymphoplasmacytic lymphoma	9671/3	6	0.92
Splenic marginal zone lymphoma	9689/3	5	0.77
Hairy cell leukemia	9940/3	2	0.31
Plasma cell myeloma	9732/3	21	3.24
Solitary plasmacytoma of bone	9731/3	1	0.15
Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue: (MALT-lymphoma)/nodal marginal zone B-cell lymphoma	9699/3	23	3.54
Follicular lymphoma	9690/3	45	6.93
Mantel cell lymphoma	9673/3	16	2.47
Diffuse large B-cell lymphoma; intravascular large B-cell lymphoma	9680/3	186	28.66
Burkitt lymphoma/leukemia	9687/3, 9826/3	11	1.69
Subtotal		387	59.63
Total B-cell neoplasms		521	80.28
T-cell and NK-cell neoplasms			
Precursor T-cell neoplasms			
Precursor T lymphoblastic leukemia/lymphoma	9837/3,9729/3	31	4.78
Subtotal		31	4.78
Mature T-cell and NK-cell neoplasms			
T-cell prolymphocytic leukemia	9834/3	3	0.46
T-cell large granular lymphocytic leukemia	9831/3	4	0.62
Aggressive NK-cell leukemia	9948/3	8	1.23
Extranodal NK/T-cell lymphoma, nasal type	9719/3	3	0.46
Hepatosplenic T-cell lymphoma	9716/3	3	0.46
Peripheral T-cell lymphoma, unspecified	9702/3	32	4.93
Angioimmunoblastic T-cell lymphoma	9705/3	24	3.70
Anaplastic large cell lymphoma	9714/3	10	1.54
Subtotal		87	13.41
Total T-cell and NK-cell neoplasms		118	18.18
Unknown cell type or not otherwise specified lymphoid neoplasms		10	1.54
Total non-Hodgkin lymphoid neoplasms		649	100.00

[a] International Classification of Diseases for Oncology.

Table 3
Distribution of demographic and personal variables of non-Hodgkin lymphoid neoplasms (NHLN) cases by selected major WHO subtypes.

Variable	NHLN-total		B-cell neoplasms (all)		Precursor B-cell neoplasms		Mature B-cell neoplasms (all)		CLL/SLL		Follicular lymphoma		Diffuse large B-cell lymphoma		T/NK-cell neoplasms	
Number	649	100.00%	521	100.00%	134	100.00%	387	100.00%	67	100.00%	45	100.00%	186	100.00%	118	100.00%
Male	392	60.40%	312	59.88%	64	47.76%	248	64.08%	51	76.12%	29	64.44%	106	56.99%	76	64.41%
Female	257	39.60%	209	40.12%	70	52.24%	139	35.92%	16	23.88%	16	35.56%	80	43.01%	42	35.59%
Mean age in years (standard deviation)	52.5	(16.53)	53.8	(15.95)	43.3	(17.28)	57.5	(13.7)	60.4	(12.87)	54.3	(12.95)	57.2	(13.45)	46.6	(17.97)
Education																
None	50	7.70%	40	7.68%	11	8.21%	29	7.49%	3	4.48%	2	4.44%	19	10.22%	7	5.93%
Primary school	140	21.57%	114	21.88%	24	17.91%	90	23.26%	13	19.40%	9	20.00%	51	27.42%	26	22.03%
Middle school	218	33.59%	168	32.25%	43	32.09%	125	32.30%	24	35.82%	16	35.56%	58	31.18%	45	38.14%
High school	134	20.65%	110	21.11%	33	24.63%	77	19.90%	12	17.91%	12	26.67%	33	17.74%	24	20.34%
University or higher	103	15.87%	86	16.51%	23	17.16%	63	16.28%	14	20.90%	6	13.33%	24	12.90%	15	12.71%
Missing data	4	0.62%	3	0.58%	0	0.00%	3	0.78%	1	1.49%	0	0.00%	1	0.54%	1	0.85%
Marital status																
Married	546	84.13%	445	85.41%	103	76.87%	342	88.37%	62	92.54%	43	95.56%	162	87.10%	91	77.12%
Divorced	2	0.31%	2	0.38%	1	0.75%	1	0.26%	0	0.00%	0	0.00%	1	0.54%	0	0.00%
Never married	36	5.55%	38	7.29%	27	20.15%	11	2.84%	1	1.49%	1	2.22%	4	2.15%	22	18.64%
Widowed	60	9.24%	32	6.14%	3	2.24%	29	7.49%	3	4.48%	1	2.22%	16	8.60%	4	3.39%
Missing data	5	0.77%	4	0.77%	0	0.00%	4	1.03%	1	1.49%	0	0.00%	3	1.61%	1	0.85%
Smokers (ever)	272	41.91%	219	42.03%	44	32.84%	175	45.22%	30	44.78%	23	51.11%	73	39.25%	50	42.37%
Mean BMI (standard deviation)	22.6	(3.48)	22.7	(3.50)	22.3	(3.34)	22.8	(3.55)	22.3	(2.86)	23.5	(2.76)	23.3	(3.56)	22	(3.41)

NHLN: non-Hodgkin lymphoid neoplasms; CLL: chronic lymphocytic leukemia; SLL: small lymphocytic lymphoma; BMI: body mass index.

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Table 4
Odds ratios and 95% confidence intervals for non-Hodgkin lymphoid neoplasms (NHLN) and selected major WHO subtypes by occupational categories.

Occupational category	NHLN-total			B-cell neoplasms (all)			Precursor B-cell neoplasms			Mature B-cell neoplasms (all)			CLL/SLL			Follicular lymphoma			Diffuse large B-cell			T/NK-cell neoplasms (all)		
	OR (95% CI)	Ca	Co	OR (95% CI)	Ca	Co	OR (95% CI)	Ca	Co	OR (95% CI)	Ca	Co	OR (95% CI)	Ca	Co	OR (95% CI)	Ca	Co	OR (95% CI)	Ca	Co	OR (95% CI)	Ca	Co
Science and engineering researchers	1.07 (0.45–2.52)	8	15	1.17 (0.46–2.96)	7	12		0	4	1.75 (0.64–4.83)	7	8		2	0		0	2	2.00 (0.40–9.91)	3	3	0.67 (0.07–6.41)	1	3
Engineering technicians	0.44 (0.26–0.76)	17	75	0.45 (0.24–0.85)	12	52	0.11 (0.01–0.88)	1	15	0.59 (0.30–1.16)	11	37	0.40 (0.05–3.42)	1	5		0	1	0.57 (0.24–1.35)	7	24	0.38 (0.13–1.11)	4	21
Health-related workers	0.74 (0.40–1.40)	14	37	0.90 (0.47–1.72)	14	31	1.00 (0.29–3.50)	4	8	0.86 (0.40–1.85)	10	23	1.00 (0.23–4.35)	3	6	2.00 (0.50–8.00)	4	4	0.18 (0.02–1.46)	1	10	–	0	6
Physicians and nurses	0.77 (0.37–1.59)	11	28	0.87 (0.42–1.82)	11	25	0.84 (0.20–3.49)	3	7	0.88 (0.37–2.09)	8	18	0.77 (0.13–4.48)	2	5	4.00 (0.73–21.84)	4	2	0.20 (0.02–1.64)	1	9	–	0	3
Financial workers	0.73 (0.47–1.13)	31	82	0.77 (0.47–1.24)	26	66	0.25 (0.07–0.88)	3	21	1.03 (0.60–1.74)	23	45	1.62 (0.51–5.19)	6	8	0.54 (0.10–2.79)	2	7	0.90 (0.40–2.00)	10	22	0.64 (0.22–1.84)	5	15
Teachers	0.72 (0.48–1.08)	34	93	0.66 (0.42–1.03)	27	80	0.93 (0.37–2.33)	7	15	0.60 (0.36–1.00)	20	65	0.72 (0.23–2.27)	5	13	0.89 (0.27–2.89)	4	9	0.38 (0.16–0.94)	6	30	1.00 (0.38–2.66)	6	12
Managers	0.70 (0.53–0.91)	93	248	0.68 (0.51–0.91)	76	207	0.56 (0.29–1.08)	14	45	0.71 (0.51–0.99)	62	162	0.70 (0.34–1.46)	13	34	0.68 (0.26–1.80)	9	23	0.63 (0.38–1.05)	24	70	0.83 (0.43–1.61)	16	37
Clerks	0.53 (0.32–0.87)	21	77	0.48 (0.27–0.84)	16	64	0.10 (0.01–0.78)	1	18	0.64 (0.35–1.16)	15	46	0.65 (0.17–2.50)	3	9	0.50 (0.06–4.47)	1	4	0.70 (0.32–1.55)	9	25	0.67 (0.22–2.07)	4	12
Police officers, firefighter and soldiers	1.18 (0.82–1.70)	53	92	1.14 (0.76–1.73)	42	75	2.50 (0.88–7.11)	10	10	0.98 (0.62–1.55)	32	65	1.22 (0.43–3.47)	6	10	0.50 (0.11–2.36)	2	8	0.96 (0.49–1.88)	15	31	1.60 (0.71–3.61)	11	14
Retail sales persons	1.11 (0.77–1.60)	52	96	1.18 (0.80–1.75)	46	81	1.05 (0.51–2.15)	14	28	1.24 (0.78–1.98)	32	53	0.70 (0.21–2.35)	4	11	0.54 (0.10–2.79)	2	7	1.24 (0.62–2.49)	15	25	0.90 (0.29–2.77)	5	11
Building workers	0.92 (0.53–1.62)	18	39	0.90 (0.48–1.71)	14	31	1.00 (0.29–3.50)	4	8	0.87 (0.41–1.83)	10	23	0.67 (0.07–6.41)	1	3	0.50 (0.06–4.47)	1	4	1.17 (0.46–2.96)	7	12	1.14 (0.34–3.90)	4	7
Chefs and other food preparation workers	0.89 (0.49–1.61)	16	36	1.04 (0.54–2.00)	14	27	0.80 (0.16–4.12)	2	5	1.09 (0.54–2.23)	12	22	1.33 (0.22–7.98)	2	3	1.00 (0.09–11.03)	1	2	1.53 (0.63–3.73)	9	12	0.57 (0.12–2.75)	2	7
General farm workers, grains	1.39 (1.08–1.78)	146	233	1.44 (1.09–1.90)	118	183	1.28 (0.68–2.40)	20	33	1.48 (1.08–2.02)	98	150	1.13 (0.49–2.62)	13	24	1.20 (0.52–2.78)	11	19	1.62 (1.06–2.49)	54	78	0.97 (0.53–1.78)	24	49
General farm workers, grains and other products	1.42 (1.13–1.78)	188	298	1.51 (1.17–1.94)	155	236	1.58 (0.94–2.67)	32	45	1.49 (1.12–1.98)	123	191	0.78 (0.36–1.68)	15	35	1.00 (0.46–2.19)	12	24	1.87 (1.24–2.80)	70	96	0.88 (0.50–1.53)	27	59
Farmworkers (all types)	1.43 (1.14–1.78)	195	310	1.52 (1.19–1.96)	162	247	1.50 (0.89–2.52)	34	51	1.53 (1.15–2.04)	128	196	0.83 (0.40–1.74)	16	36	1.18 (0.54–2.60)	14	25	1.85 (1.24–2.76)	71	98	0.88 (0.50–1.53)	27	59
Metalworkers	0.75 (0.39–1.46)	12	32	0.64 (0.29–1.42)	8	25	0.75 (0.20–2.83)	3	8	0.59 (0.22–1.60)	5	17	0.40 (0.05–3.42)	1	5	–	0	1	0.80 (0.16–4.12)	2	5	1.14 (0.34–3.90)	4	7
Chemical workers	1.60 (0.63–4.05)	8	10	1.75 (0.64–4.83)	7	8	8.00 (0.89–71.56)	4	1	0.86 (0.22–3.32)	3	7	–	0	0		0	0	0.80 (0.16–4.12)	2	5	1.00 (0.09–11.03)	1	2
Rubber and plastic workers	1.43 (0.53–3.89)	7	10	1.36 (0.47–3.99)	6	9	1.33 (0.22–7.98)	2	3	1.38 (0.36–5.29)	4	6	1.44 (0.19–11.12)	2	3		0	0	4.00 (0.36–44.11)	2	1	2.00 (0.13–31.97)	1	1
Fabric workers	1.00 (0.48–2.09)	11	22	1.06 (0.47–2.42)	9	17	1.20 (0.29–5.02)	3	5	1.00 (0.37–2.74)	6	12	–	1	0	2.00 (0.13–31.97)	1	1	0.73 (0.18–2.91)	3	8	1.00 (0.18–5.46)	2	4
Leather workers	1.67 (0.51–5.46)	5	6	1.33 (0.38–4.73)	4	6	0.67 (0.07–6.41)	1	3	2.00 (0.40–9.91)	3	3	–	0	1	–	0	0	2.00 (0.28–14.20)	2	2	–	1	0
Fabric sewing and cutting workers	3.89 (1.95–7.76)	26	16	3.87 (1.81–8.25)	22	14	10.29 (2.27–46.66)	11	3	2.29 (0.90–5.81)	11	11	4.00 (0.36–44.11)	2	1	0.67 (0.07–6.41)	1	3	5.62 (1.14–27.75)	7	4	8.00 (0.89–71.56)	4	1
Wood and furniture workers	1.54 (0.87–2.70)	23	31	1.21 (0.63–2.34)	15	25	1.55 (0.43–5.58)	5	7	1.11 (0.51–2.41)	10	18	1.50 (0.34–6.70)	3	4		0	2	1.25 (0.41–3.82)	5	8	3.17 (0.92–10.99)	7	5
Printers and related workers	0.50 (0.06–4.48)	1	4	0.50 (0.06–4.48)	1	4	–	0	0	0.50 (0.06–4.47)	1	4	–	0	2		1	0	–	0	1	–	0	0
Locksmiths	0.70 (0.31–1.56)	8	23	0.60 (0.24–1.50)	6	20	–	0	4	0.75 (0.29–1.92)	6	16	0.50 (0.06–4.47)	1	4	0.67 (0.07–6.41)	1	3	1.00 (0.25–4.00)	3	6	1.33 (0.22–7.98)	2	3
Metal cutting and grinding workers	1.00 (0.60–1.68)	22	44	0.80 (0.44–1.48)	15	37	0.67 (0.18–2.46)	3	9	0.85 (0.43–1.70)	12	28	0.20 (0.02–1.64)	1	9	0.57 (0.12–2.75)	2	7	1.80 (0.57–5.69)	6	7	1.71 (0.58–5.10)	6	7
Machinery mechanics and repairers	1.03 (0.60–1.76)	21	41	0.97 (0.54–1.73)	18	37	0.39 (0.08–1.97)	2	9	1.15 (0.62–2.14)	16	28	1.71 (0.58–5.10)	6	7	3.00 (0.50–17.95)	3	2	0.18 (0.02–1.41)	1	11	1.50 (0.34–6.70)	3	4
Welders and sheet metal workers	1.34 (0.73–2.46)	18	27	1.38 (0.71–2.68)	15	22	0.67 (0.14–3.30)	2	6	1.66 (0.78–3.50)	13	16	1.00 (0.09–11.03)	1	2	1.00 (0.09–11.03)	1	2	3.33 (1.21–9.17)	10	6	1.20 (0.29–5.02)	3	5
Painters	0.60 (0.19–1.89)	4	13	0.88 (0.26–2.99)	4	9	4.00 (0.36–44.11)	2	1	0.47 (0.09–2.35)	2	8	4.00 (0.36–44.11)	2	1	–	0	1	–	0	3	–	0	4
Masonry and plastering workers	2.24 (1.12–4.47)	18	17	2.46 (1.15–5.24)	16	14	4.00 (0.73–21.84)	4	2	2.16 (0.92–5.05)	12	12	2.00 (0.28–14.20)	2	2	4.00 (0.36–44.11)	2	1	2.68 (0.74–9.68)	6	5	1.33 (0.22–7.98)	2	3
Loading and unloading workers	0.76 (0.38–1.51)	12	31	0.53 (0.23–1.18)	8	29	1.18 (0.30–4.63)	4	7	0.35 (0.12–1.04)	4	22	2.00 (0.13–31.97)	1	1		0	2	0.24 (0.05–1.05)	2	16	4.00 (0.73–21.84)	4	2
Automobile and other drivers	1.07 (0.65–1.74)	26	49	0.95 (0.54–1.65)	19	40	1.00 (0.29–3.50)	4	8	0.94 (0.50–1.74)	15	32	1.23 (0.27–5.75)	3	5	4.00 (0.73–21.84)	4	2	1.00 (0.40–2.48)	7	14	1.13 (0.35–3.70)	5	9
Product and chemical testing workers	1.54 (0.94–2.50)	29	38	1.89 (1.11–3.21)	27	29	1.25 (0.41–3.82)	5	8	2.14 (1.17–3.93)	22	21	0.80 (0.16–4.12)	2	5	10.00 (1.17–85.59)	5	1	1.75 (0.64–4.83)	7	8	0.57 (0.12–2.75)	2	7
Packaging and storage workers	1.16 (0.77–1.73)	40	71	0.98 (0.62–1.55)	30	62	1.36 (0.54–3.47)	9	15	0.89 (0.53–1.50)	21	47	2.00 (0.70–5.70)	7	7		0	6	0.85 (0.39–1.89)	9	21	2.10 (0.80–5.49)	9	9

NHLN: non-Hodgkin lymphoid neoplasms; CLL: chronic lymphocytic leukemia; SLL: small lymphocytic leukemia; OR: odds ratio; 95% CI: 95% confidence interval; Ca: exposed cases; Co: exposed controls.

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Table 5
Odds ratios and 95% confidence intervals for non-Hodgkin lymphoid neoplasms (NHLN) and selected major WHO subtype by industrial categories.

Industrial category	NHLN-total			B-cell neoplasms (all)			Precursor B-cell neoplasms			Mature B-cell neoplasms (all)			CLL/SLL			Follicular lymphoma			Diffuse large B-cell lymphoma			T/NK-cell neoplasms (all)		
	OR (95% CI)	Ca	Co	OR (95% CI)	Ca	Co	OR (95% CI)	Ca	Co	OR (95% CI)	Ca	Co	OR (95% CI)	Ca	Co	OR (95% CI)	Ca	Co	OR (95% CI)	Ca	Co	OR (95% CI)	Ca	Co
Crop plantation	1.44 (1.15–1.80)	208	332	1.53 (1.19–1.96)	173	267	1.49 (0.89–2.50)	36	55	1.54 (1.16–2.04)	137	212	0.88 (0.43–1.79)	18	39	1.26 (0.56–2.85)	15	26	1.93 (1.30–2.89)	76	104	0.93 (0.54–1.60)	29	61
Agriculture	1.48 (1.18–1.85)	211	332	1.54 (1.21–1.98)	174	267	1.49 (0.89–2.50)	36	55	1.56 (1.18–2.07)	138	212	0.88 (0.43–1.79)	18	39	1.26 (0.56–2.85)	15	26	1.99 (1.33–2.98)	77	104	1.03 (0.59–1.78)	31	61
Electricity production and supply	0.55 (0.22–1.35)	6	22	0.75 (0.29–1.92)	6	16	4.00 (0.73–21.84)	4	2	0.29 (0.07–1.26)	2	14	–	1	0	–	0	4	0.33 (0.04–2.77)	1	6	–	0	6
Cotton textile manufacturing	0.96 (0.59–1.56)	25	53	1.00 (0.58–1.73)	20	41	1.67 (0.57–4.89)	7	10	0.84 (0.44–1.60)	13	31	1.60 (0.43–5.96)	4	5	0.29 (0.04–2.32)	1	7	1.17 (0.46–2.96)	7	12	1.00 (0.33–3.04)	5	10
Textile and other fabric manufacturing	1.01 (0.71–1.45)	50	100	1.03 (0.69–1.53)	41	81	1.88 (0.87–4.06)	14	17	0.83 (0.52–1.33)	27	64	1.34 (0.47–3.84)	7	11	0.75 (0.20–2.83)	3	8	0.96 (0.48–1.93)	13	27	1.22 (0.51–2.90)	9	15
Garment manufacturing	1.73 (1.01–2.97)	26	31	1.66 (0.90–3.07)	20	25	1.55 (0.51–4.69)	6	8	1.71 (0.82–3.58)	14	17	1.00 (0.18–5.46)	2	4	0.77 (0.13–4.48)	2	5	2.55 (0.80–8.14)	7	6	3.00 (0.85–10.63)	6	4
Shoe manufacturing	–	0	1	–	0	1	–	0	0	–	0	1	–	0	0	–	0	0	–	0	1	–	0	0
Leather and leather products	1.20 (0.44–3.30)	6	10	1.33 (0.48–3.75)	6	9	1.33 (0.22–7.98)	2	3	1.33 (0.38–4.73)	4	6	–	0	0	–	0	1	1.50 (0.34–6.70)	3	4	–	0	1
Furniture manufacturing	1.46 (0.59–3.62)	8	11	1.00 (0.30–3.32)	4	8	0.67 (0.07–6.41)	1	3	1.20 (0.29–5.02)	3	5	2.00 (0.13–31.97)	1	1	–	0	1	2.00 (0.28–14.20)	2	2	2.67 (0.60–11.91)	4	3
Paper manufacturing	1.00 (0.34–2.93)	5	10	1.14 (0.34–3.90)	4	7	1.33 (0.22–7.98)	2	3	1.00 (0.18–5.46)	2	4	–	0	0	–	1	0	1.00 (0.09–11.03)	1	2	0.67 (0.07–6.41)	1	3
Printing industry	1.60 (0.63–4.05)	8	10	1.75 (0.64–4.83)	7	8	0.67 (0.07–6.41)	1	3	2.40 (0.73–7.86)	6	5	–	1	0	–	2	0	1.33 (0.22–7.98)	2	3	1.00 (0.09–11.03)	1	2
Toy manufacturing	4.67 (1.21–18.05)	7	3	4.67 (1.21–18.05)	7	3	8.00 (0.89–71.56)	4	1	3.00 (0.50–17.93)	3	2	–	0	0	–	0	0	6.00 (0.62–57.68)	3	1		0	0
Agricultural chemicals manufacturing	2.00 (0.65–6.20)	6	6	1.50 (0.34–6.70)	3	4	2.00 (0.13–31.97)	1	1	1.33 (0.22–7.98)	2	3	2.00 (0.13–31.97)	1	1	–	1	0	–	0	1	6.00 (0.62–57.68)	3	1
Organic chemicals, chemical fibers and other products	0.68 (0.35–1.32)	12	35	0.68 (0.31–1.48)	9	26	1.00 (0.09–11.03)	1	2	0.65 (0.29–1.48)	8	24	–	0	7	–	0	1	0.31 (0.07–1.44)	2	12	0.75 (0.20–2.83)	3	8
Paint manufacturing and paint factories	1.33 (0.22–7.98)	2	3	2.00 (0.28–14.20)	2	2	–	2	0	–	0	2	–	0	1	–	0	0	–	0	1	–	0	1
Drug manufacturing	1.00 (0.34–2.93)	5	10	1.14 (0.34–3.90)	4	7	4.00 (0.73–21.84)	4	2	–	0	5	–	0	0	–	0	0	–	0	2	0.67 (0.07–6.41)	1	3
Rubber and plastic manufacturing	1.71 (0.91–3.22)	18	21	1.41 (0.67–2.96)	12	17	1.00 (0.18–5.46)	2	4	1.54 (0.68–3.51)	10	13	4.00 (0.73–21.84)	4	2		0	0	1.14 (0.34–3.90)	4	7	3.00 (0.85–10.63)	6	4
Concrete manufacturing	0.57 (0.25–1.35)	7	24	0.54 (0.20–1.49)	5	18	0.33 (0.04–2.77)	1	6	0.65 (0.20–2.08)	4	12	0.67 (0.07–6.41)	1	3	–	0	0	0.47 (0.09–2.35)	2	8	0.33 (0.04–2.77)	1	6
Glass and related product manufacturing	1.00 (0.38–2.66)	6	12	1.00 (0.34–2.93)	5	10	1.00 (0.18–5.46)	2	4	1.00 (0.25–4.00)	3	6	–	1	0	2.00 (0.13–31.97)	1	1	0.67 (0.07–6.41)	1	3	1.00 (0.09–11.03)	1	2
Metal milling and processing	0.92 (0.55–1.52)	22	48	0.86 (0.49–1.49)	18	42	1.14 (0.34–3.90)	4	7	0.80 (0.43–1.49)	14	35	0.86 (0.22–3.32)	3	7	1.00 (0.18–5.46)	2	4	0.59 (0.22–1.59)	5	17	1.00 (0.25–4.00)	3	6
Boiler, steam engine and other equipment manufacturing	1.00 (0.72–1.39)	59	118	1.00 (0.69–1.45)	47	94	0.96 (0.48–1.91)	13	27	1.02 (0.65–1.58)	34	67	0.71 (0.26–1.98)	5	14	1.00 (0.35–2.83)	6	12	0.96 (0.47–1.96)	13	27	0.91 (0.43–1.93)	11	24
Electronics manufacturing	0.86 (0.54–1.38)	27	63	0.81 (0.46–1.42)	18	45	0.80 (0.25–2.55)	4	11	0.81 (0.42–1.55)	14	34	0.84 (0.20–3.49)	3	7	2.00 (0.28–14.20)	2	2	0.58 (0.20–1.70)	5	16	0.93 (0.38–2.28)	8	17
Automobile manufacturing	0.50 (0.22–1.15)	7	28	0.40 (0.14–1.17)	4	20	1.20 (0.29–5.02)	3	5	0.13 (0.02–1.01)	1	15	–	0	3	–	0	1	0.40 (0.05–3.42)	1	5	0.50 (0.11–2.36)	2	8
General construction	1.28 (0.87–1.90)	44	70	1.24 (0.79–1.95)	33	54	0.93 (0.37–2.33)	7	15	1.37 (0.81–2.30)	26	39	4.67 (1.21–18.05)	7	3	6.00 (0.62–57.68)	3	1	0.90 (0.40–1.99)	10	22	1.48 (0.63–3.48)	10	14
Transportation (railroad, highway, water, air)	1.05 (0.69–1.59)	35	67	0.97 (0.61–1.53)	28	58	1.28 (0.49–3.33)	8	13	0.89 (0.53–1.51)	20	45	0.55 (0.15–1.96)	3	11	0.67 (0.14–3.30)	2	6	1.26 (0.61–2.60)	12	19	1.33 (0.48–3.75)	6	9

Table 5 (*Continued*)

Industrial category	NHLN-total			B-cell neoplasms (all)			Precursor B-cell neoplasms			Mature B-cell neoplasms (all)			CLL/SLL			Follicular lymphoma			Diffuse large B-cell lymphoma			T/NK-cell neoplasms (all)		
	OR (95% CI)	Ca	Co	OR (95% CI)	Ca	Co	OR (95% CI)	Ca	Co	OR (95% CI)	Ca	Co	OR (95% CI)	Ca	Co	OR (95% CI)	Ca	Co	OR (95% CI)	Ca	Co	OR (95% CI)	Ca	Co
Railroad transportation	1.67 (0.51–5.46)	5	6	1.60 (0.43–5.96)	4	5	2.00 (0.13–31.97)	1	1	1.50 (0.34–6.70)	3	4	2.00 (0.13–31.97)	1	1	–	0	0	–	2	0	2.00 (0.13–31.97)	1	1
Highway transportation	0.82 (0.46–1.47)	16	39	0.76 (0.40–1.45)	13	34	1.16 (0.32–4.22)	4	7	0.67 (0.31–1.42)	9	27	0.57 (0.12–2.75)	2	7	0.67 (0.07–6.41)	1	3	0.83 (0.29–2.37)	5	12	0.80 (0.16–4.12)	2	5
Water transportation	1.24 (0.62–2.47)	13	21	1.11 (0.51–2.41)	10	18	1.50 (0.34–6.70)	3	4	1.00 (0.40–2.48)	7	14	–	0	3	1.00 (0.09–11.03)	1	2	1.00 (0.30–3.32)	4	8	2.00 (0.40–9.91)	3	3
Domestic commercial business	1.13 (0.84–1.52)	77	139	1.06 (0.76–1.47)	62	119	0.79 (0.41–1.49)	15	38	1.18 (0.81–1.73)	47	81	1.00 (0.39–2.60)	7	14	0.62 (0.15–2.53)	3	9	0.83 (0.46–1.52)	17	40	1.73 (0.79–3.79)	13	16
Food and beverage industry	0.69 (0.36–1.32)	12	35	0.71 (0.35–1.47)	10	28	0.86 (0.22–3.32)	3	7	0.67 (0.28–1.57)	7	21	–	0	2	2.00 (0.28–14.20)	2	2	0.73 (0.23–2.28)	4	11	0.80 (0.16–4.12)	2	5
Beauty salon	5.99 (1.21–29.65)	6	2	3.00 (0.50–17.93)	3	2	–	3	0	–	0	2	–	0	0	–	0	0	–	0	2	–	3	0
Health-care facilities	0.72 (0.40–1.29)	16	44	0.90 (0.48–1.70)	15	33	0.79 (0.24–2.61)	4	10	0.95 (0.46–2.00)	11	23	0.29 (0.03–2.65)	1	6	2.50 (0.67–9.31)	5	4	0.31 (0.07–1.44)	2	12	0.18 (0.02–1.41)	1	11
Hospitals	0.82 (0.44–1.53)	15	36	1.04 (0.53–2.04)	14	27	1.00 (0.29–3.50)	4	8	1.06 (0.48–2.34)	10	19	0.35 (0.04–3.36)	1	5	3.33 (0.80–13.95)	5	3	0.34 (0.07–1.59)	2	11	0.22 (0.03–1.75)	1	9
Education	0.80 (0.59–1.10)	62	151	0.76 (0.53–1.09)	47	121	0.77 (0.42–1.44)	16	41	0.76 (0.49–1.17)	31	80	0.42 (0.11–1.57)	3	13	1.11 (0.37–3.32)	5	9	0.76 (0.41–1.39)	16	41	1.00 (0.49–2.06)	14	28
Higher education	0.88 (0.55–1.40)	29	66	0.83 (0.49–1.41)	21	51	0.66 (0.28–1.55)	8	24	0.96 (0.49–1.90)	13	27	0.77 (0.13–4.48)	2	5	2.00 (0.50–8.00)	4	4	0.77 (0.27–2.16)	5	13	1.08 (0.42–2.78)	8	15
Middle education	0.82 (0.51–1.33)	24	58	0.69 (0.39–1.23)	16	46	1.00 (0.34–2.93)	5	10	0.61 (0.31–1.20)	11	36	–	0	6		0	4	0.84 (0.36–1.94)	8	19	1.43 (0.53–3.89)	7	10
Lower level education	0.75 (0.39–1.46)	12	32	0.64 (0.30–1.36)	9	28	1.33 (0.38–4.73)	4	6	0.46 (0.17–1.20)	5	22	0.50 (0.06–4.47)	1	4	1.00 (0.09–11.03)	1	2	0.31 (0.07–1.36)	2	13	1.00 (0.18–5.46)	2	4
Military	1.07 (0.72–1.58)	42	79	0.97 (0.63–1.50)	33	68	1.55 (0.51–4.69)	6	8	0.89 (0.55–1.43)	27	60	1.22 (0.43–3.47)	6	10	0.75 (0.20–2.83)	3	8	0.62 (0.27–1.41)	8	25	2.10 (0.80–5.49)	9	9
Government	0.82 (0.57–1.18)	45	108	0.79 (0.53–1.17)	38	94	0.84 (0.30–2.34)	6	14	0.78 (0.51–1.20)	32	80	1.22 (0.43–3.47)	6	10	0.25 (0.03–2.00)	1	8	0.59 (0.32–1.09)	15	48	1.29 (0.49–3.44)	7	11

NHLN: non-Hodgkin lymphoid neoplasms; CLL: chronic lymphocytic leukemia; SLL: small lymphocytic leukemia; OR: odds ratio; 95% CI: 95% confidence interval; Ca: exposed cases; Co: exposed controls.

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Table 6
Odds ratios and 95% confidence intervals for non-Hodgkin lymphoid neoplasms (NHLN) and selected major WHO subtypes by occupational exposures.

	NHLN-total			B-cell neoplasms (all)			Precursor B-cell neoplasms			Mature B-cell neoplasms (all)			CLL/SLL			Follicular lymphoma			Diffuse large B-cell lymphoma			T/NK-cell neoplasms (all)		
	OR (95% CI)	Ca	Co	OR (95% CI)	Ca	Co	OR (95% CI)	Ca	Co	OR (95% CI)	Ca	Co	OR (95% CI)	Ca	Co	OR (95% CI)	Ca	Co	OR (95% CI)	Ca	Co	OR (95% CI)	Ca	Co
Benzene	1.06 (0.74–1.51)	50	95	1.16 (0.77–1.73)	40	70	1.57 (0.63–3.94)	9	12	1.07 (0.68–1.69)	31	58	2.05 (0.79–5.32)	10	11	7.00 (1.45–33.70)	7	2	0.66 (0.31–1.42)	9	27	0.55 (0.0.23–1.33)	7	24
Solvents	1.15 (0.62–2.14)	16	28	1.22 (0.63–2.37)	14	23	12.00 (1.45–99.67)	6	1	0.73 (0.32–1.63)	8	22	1.20 (0.29–5.02)	3	5	4.00 (0.36–44.11)	2	1	0.36 (0.08–1.64)	2	11	0.77 (0.13–4.48)	2	5
Paint thinners	0.91 (0.32–2.62)	5	11	1.00 (0.34–2.93)	5	10	2.00 (0.13–31.97)	1	1	0.89 (0.27–2.89)	4	9	4.00 (0.36–44.11)	2	1	4.00 (0.36–44.11)	2	1	–	0	5	–	0	1
Toluene	1.00 (0.30–3.32)	4	8	1.33 (0.38–4.73)	4	6	–	3	0	0.33 (0.04–2.77)	1	6	2.00 (0.13–31.97)	1	1	–	0	0	–	0	3	–	0	2
Xylene	1.08 (0.43–3.32)	7	13	1.20 (0.44–3.30)	6	10	–	2	0	0.80 (0.25–2.55)	4	10	1.33 (0.22–7.98)	2	3	–	1	0	0.50 (0.06–4.47)	1	4	0.67 (0.07–6.41)	1	3
Petroleum fuels	1.15 (0.08–1.64)	53	94	1.06 (0.70–1.60)	40	76	1.32 (0.5–3.16)	9	14	1.00 (0.63–1.60)	31	62	1.71 (0.63–1.60)	9	12	6.61 (1.37–31.76)	8	4	0.67 (0.31–1.48)	9	26	1.23 (0.57–2.65)	11	18
Kerosene	0.57 (0.19–1.74)	4	14	0.62 (0.20–1.89)	4	13	–	1	0	0.46 (0.13–1.62)	3	13	1.00 (0.09–11.03)	1	2	–	1	0	–	0	3	–	0	1
Gasoline	1.28 (0.83–1.96)	37	59	1.25 (0.76–2.07)	27	44	1.12 (0.36–3.49)	5	9	1.29 (0.73–2.26)	22	35	1.34 (0.37–4.93)	5	8	–	6	0	0.76 (0.31–1.89)	7	18	1.07 (0.45–2.57)	8	15
Diesel fuel	1.11 (0.68–1.82)	26	47	1.09 (0.61–1.95)	19	35	1.00 (0.29–3.50)	4	8	1.12 (0.56–21.6)	15	27	1.77 (0.50–6.24)	5	6	1.62 (0.31–8.40)	3	4	0.50 (0.11–2.36)	2	8	1.17 (0.46–2.96)	7	12
Cutting and lubricating oils	0.91 (0.56–1.47)	27	59	0.79 (0.46–1.38)	20	49	0.17 (0.02–1.28)	1	12	1.03 (0.56–1.89)	19	37	0.73 (0.24–2.24)	5	13	1.50 (0.34–6.70)	3	4	1.00 (0.35–2.83)	6	12	1.20 (0.44–3.30)	6	10
Diesel or gasoline engine exhaust	0.57 (0.12–2.75)	2	7	0.33 (0.04–2.77)	1	6	1.00 (0.09–11.03)	1	2	–	0	4		0	1	–	0	1	–	0	1	2.00 (0.13–31.97)	1	1
Metals (general)	1.31 (0.82–2.10)	30	46	1.10 (0.66–1.84)	23	42	1.78 (0.69–4.61)	8	9	0.91 (0.49–1.69)	15	33	0.77 (0.13–4.48)	2	5	1.00 (0.18–5.46)	2	4	1.41 (0.59–3.37)	9	13	3.50 (1.03–11.96)	7	4
Metals at smelters or steel mills	1.09 (0.54–2.23)	12	22	0.95 (0.44–2.05)	10	21	0.80 (0.16–4.12)	2	5	1.00 (0.42–2.38)	8	16	1.44 (0.19–11.12)	2	3	–	0	1	1.14 (0.34–3.90)	4	7	4.00 (0.36–44.11)	2	1
Welding	1.29 (0.56–2.97)	9	14	1.46 (0.59–3.62)	8	11	2.00 (0.40–9.91)	3	3	1.25 (0.41–3.82)	5	8	2.00 (0.13–31.97)	1	1	–	1	0	2.00 (0.40–9.91)	3	3	0.67 (0.07–6.41)	1	3
Heavy metals	1.16 (0.32–4.22)	4	7	0.54 (0.10–2.79)	2	7	–	2	0	–	0	7		0	2	–	0	1	–	0	2	–	2	0
Insecticides	1.59 (1.22–2.07)	125	176	1.66 (1.39–2.49)	110	138	1.96 (1.04–3.68)	22	25	1.83 (1.32–2.55)	88	113	1.76 (0.76–4.08)	14	19	1.64 (0.62–4.34)	11	16	2.02 (1.28–3.19)	47	55	0.57 (0.27–1.19)	12	37
Herbicides	1.77 (1.02–3.05)	25	29	1.98 (1.05–3.73)	20	21	0.57 (0.12–2.75)	2	7	2.79 (1.33–5.82)	18	14		1	0	–	3	1	3.00 (1.07–8.43)	9	6	1,00 (0.30–3.32)	4	8
Fertilizers	1.53 (1.17–2.00)	119	172	1.68 (1.25–2.27)	101	135	1.62 (0.83–3.17)	19	26	1.70 (1.22–2.37)	82	109	1.51 (0.63–3.64)	11	16	0.84 (0.30–2.34)	7	16	1.97 (1.27–3.06)	48	56	0.74 (0.36–1.51)	14	35
Wood and/or wood dust	1.62 (0.76–3.42)	13	16	1.04 (0.41–2.61)	7	13	–	2	0	0.77 (0.27–2.16)	5	13	0.67 (0.07–6.41)	1	3	2.00 (0.13–31.97)	1	1	0.75 (0.20–2.83)	3	8	5.00 (0.97–25.77)	5	2
Paint and other coatings	0.79 (0.35–1.83)	8	20	0.93 (0.38–2.29)	7	15	2.67 (0.60–11–91)	4	3	0.50 (0.14–1.77)	3	12	1.00 (0.18–5.460	2	4	2.00 (0.13–31.97)	1	1	–	0	5	–	0	4
Glues and adhesives	2.21 (1.11–4.40)	19	19	2.47 (1.08–5.67)	13	11	6.61 (0.72–60.86)	4	2	2.00 (0.79–5.04)	9	9	2.00 (0.13–31.97)	1	1	2.00 (0.13–31.97)	1	1	3.50 (1.03–11.96)	7	4	1.55 (0.43–5.58)	5	7
Inks and pigments	2.00 (0.50–8.00)	4	4	2.00 (0.40–9.91)	3	3	–	1	0	1.33 (0.22–7.98)	2	3	2.00 (0.13–31.97)	1	1	–	1	0	–	0	1	2.00 (0.13–31.97)	1	1
Fumigants, sterilizers and preservatives	0.60 (0.17–2.18)	3	10	0.75 (0.20–2.83)	3	8	2.00 (0.28–14.20)	2	2	0.33 (0.04–2.77)	1	6	–	0	1		0	0	–	0	3	–	0	2
Radiation	0.29 (0.04–2.32)	1	7	0.33 (0.04–2.77)	1	6	–	1	0	–	0	6	–	0	1		0	0	–	0	3	–	0	1
Electromagnetic field	–	0	7	–	0	5	–	0	2	–	0	3	–	0	0		0	0	–	0	3	–	0	2

NHLN: non-Hodgkin lymphoid neoplasms; CLL: chronic lymphocytic leukemia; SLL: small lymphocytic lymphoma; OR: odds ratio; 95% CI: 95% confidence interval; Ca: exposed cases; Co: exposed controls.

Table 7
Odds ratios and 95% confidence intervals for selected combinations of NHLN subtypes and occupational or industrial categories and exposures.

Combinations of NHLN subtypes and occupational risk factors	OR (95% CI)	*p*-Value	Ca	Co
Extranodal marginal zone B-cell lymphoma (MALT-lymphoma)/nodal marginal zone B-cell lymphoma				
Police officers, firefighters and soldiers	10.00 (1.17–85.59)	0.04	5	1
Peripheral T-cell lymphoma, unspecified				
Police officers, firefighters and soldiers	3.18 (0.92–11.00)	0.07	7	5
Government	6.00 (1.21–29.73)	0.03	6	2
Small lymphocytic leukemia				
Domestic commercial business	4.64 (0.91–23.81)	0.07	6	4
Mature T-cell and NK-cell neoplasms (all)				
Rubber and plastic manufacturing	3.33 (0.80–13.95)	0.10	5	3
Peripheral T-cell lymphoma (unspecified)				
Insecticides	0.25 (0.05–1.16)	0.08	3	16
Angioimmunoblastic T-cell lymphoma				
Cutting and lubricating oils	5.00 (0.97–25.77)	0.05	5	2

OR: odds ratio; 95% CI: 95% confidence interval; Ca: exposed cases; Co: exposed controls.

the increased risk for DLBCL was almost twofold (OR = 1.93, 95% CI = 1.30–2.89). Neither CLL/SLL nor T/NK-cell neoplasms seemed to be affected by employment in the industry “crop plantation.” The broader category “agriculture,” which included the service sector as well, showed almost identical results by subtype. A borderline significant increase of NHLN-total was reported for the garment manufacturing industry (OR = 1.73, 95% CI = 1.01–1.45). The increase was seen in most subtypes, albeit not statistically significant, except for CLL/SLL and FL. For toy manufacturing, a significantly increased risk of more than fourfold was observed for NHLN-total (OR = 4.67, 95% CI = 1.21–18.05), based on seven cases and three controls employed in the industry. Four of the cases were diagnosed with precursor B-cell neoplasms (OR = 8.00, 95% CI = 0.89–71.56) and the remaining three with DLBCL (OR = 6.00, 95% CI = 0.62–57.68). There was a significant risk increase of CLL/SLL associated with general construction (OR = 1.21–18.05) and a non-significant increase of FL (OR = 6.00, 95% CI = 0.62–57.68) for the same industry. A significantly elevated risk for NHLN-total was found for beauty saloon (OR = 5.99, 95% CI = 1.21–29.65), based on six cases and two controls in the industry. Three of the cases were diagnosed with precursor B-cell neoplasms, and the remaining three with T/NK-cell neoplasms.

Analysis by specific exposures (ever vs. never) is presented in Table 6. Exposure to benzene was not associated with NHLN-total (OR = 1.06, 95% CI = 0.74–1.51). Similarly, no significant increase associated with benzene exposure was found for specific subtypes, with the exception of FL. The OR for FL associated with benzene exposure was 7.00 (95% CI = 1.45–33.70), based on seven exposed cases and two exposed controls. Exposure to solvents was not associated with any increased risk of NHLN-total or specific subtypes, except precursor B-cell neoplasms (OR = 12.00, 95% CI = 1.45–99.67, six exposed cases and one exposed control). No association was found between NHLN-total or specific subtypes and exposure to paint thinners, toluene or xylene. A significant OR of 6.61 (95% CI = 1.37–31.76) for FL was associated with petroleum fuels, based on eight exposed cases and four exposed controls. More specifically, there were six FL cases and no control exposed to gasoline. No increased risk of NHLN was associated with kerosene, diesel fuel, cutting and lubricating oils, or diesel or gasoline engine exhaust. Exposure to insecticides increased the risks of NHLN-total (OR = 1.59, 95% CI = 1.22–2.07) and all subtypes of B-cell neoplasms (e.g., for diffuse large B-cell lymphoma, OR = 2.02, 95% CI = 1.28–11.96), but T/NK-cell neoplasms were not affected (OR = 0.57, 95% CI = 0.27–1.19). Similarly, exposure to herbicides or fertilizers was associated with an increased risk of NHLN-total and several subtypes. Exposure to glues and adhesives increased the risk of NHLN-total (OR = 2.21, 95% CI = 1.11–4.40) and B-cell neoplasms (OR = 2.47, 95% CI = 1.08–5.67). No increased risks for NHLN-total or major subtypes were found for exposures to welding, heavy metals, paint and other coatings, inks and pigments, fumigants, sterilizers and preservatives, radiation, or electromagnetic field.

Similar analysis by occupational or industrial categories and exposures was carried out for other rarer NHLN subtypes. We will not present all the numerical results in their entirety, as most ORs were based on small numbers (hence, unstable) and a presentation of all the ORs, 95% CIs and numbers of exposed cases and controls will take up too much space. Only ORs and 95% CIs for combinations of selected NHLN subtypes and risk factors with a *p*-value less than or equal to 0.10 (to include all significant as well as “suggestive” associations) are presented in Table 7. The occupational category “police officers, firefighter and soldiers” was found to be at an increased risk of extranodal marginal zone B-cell lymphoma (OR = 10.00, 95% CI = 1.17–85.59, based on five exposed cases and one exposed control) and “peripheral T-cell lymphoma, unspecified” (OR = 3.18, 95% CI = 0.92–11.00). With respect to industries, the only significant increase was for the subtype “peripheral T-cell lymphoma, unspecified” (OR = 6.00, 95% CI = 1.21–29.73) associated with the category “government.” A non-significant risk increase for mature T/NK-cell neoplasms was associated with rubber and plastic manufacturing (OR = 3.33, 95% CI = 0.80–13.95). Cutting and lubricating oils were associated with an elevated risk of angioimmunoblastic T-cell lymphoma (OR = 5.00, 95% CI = 0.97–25.77).

Because many study subjects were exposed to multiple risk factors, multivariate models were employed to adjust for confounding factors (personal characteristics, lifestyle, residential, employment, and occupational and non-occupational exposures). The choice of variables in the multivariate models was based on a consideration of results of individual effects of risk factors identified among the subjects in the current study, the frequencies of the variables in the current study, and findings in literature [3,4,7–9,16]. The variables included in the multivariate models are listed in Table 8, which shows the results of the multivariate analysis. Variables with a *p*-value greater that 0.20 were eliminated from the models, and only ORs of variables remaining in the models are presented. Because of the interest in the association between NHLN and benzene exposure, the latter was always in the models regardless of the *p*-value. The multivariate analysis indicated that the use of traditional Chinese medicines was associated with a significant reduction in risk of NHLN-total (OR = 0.55, 95% CI = 0.35–0.85), but a non-significant increase in risk was observed for CLL/SLL (OR = 2.75, 95% CI = 0.82–9.24). Residential exposure to home (or workplace) reno-

Table 8
Odds ratios (95% confidence intervals) of risk factors of non-Hodgkin lymphoid neoplasms (NHLN) by subtypes based on conditional multivariate logistic regression models.

Risk factors[a]	NHLN-total	B-cell neoplasms (all)	Precursor B-cell neoplasms	Mature B-cell neoplasms	CLL/SLL	Follicular lymphoma	Diffuse large B-cell lymphoma	T/N/K-cell neoplasms (all)
Low-level education	1.26 (0.96–1.66)	–	–	–	–	–	1.58 (1.00–2.51)	1.99 (0.92–4.32)
Traditional Chinese medicines	0.55 (0.35–0.85)	0.59 (0.36–0.97)	–	0.66 (0.38–1.14)	2.75 (0.82–9.24)	–	0.24 (0.08–0.70)	0.38 (0.11–1.27)
Alcohol	0.83 (0.63–1.09)	0.81 (0.60–1.10)	0.49 (0.22–1.11)			–	0.54 (0.32–0.92)	–
Home/workplace renovation	1.46 (1.05–2.05)	1.16 (1.08–2.30)	–	1.86 (1.23–2.80)	1.96 (0.74–5.17)	–	1.91 (1.06–3.44)	–
Living on a farm	1.29 (1.01–1.65)	1.26 (0.96–1.65)	–	–	–	–	–	1.47 (0.84–2.60)
Planting crops	–	–	–	–	–	–	0.28 (0.06–1.23)	–
Raising livestock or animals	–	–	2.92 (1.18–7.23)	–	–	–	–	–
Farm workers	–	–	–	–	–	–	–	–
Fabric sewing and cutting workers	2.33 (1.19–4.56)	3.98 (1.78–8.92)	24.59 (2.97–204.02)	2.19 (0.84–5.71)	6.41 (0.55–75.22)	–	5.48 (1.05–28.44)	6.40 (0.69–59.25)
Benzene	0.62 (0.35–1.10)	0.77 (0.42–1.42)	0.88 (0.28–2.75)	0.60 (0.29–1.26)	1.64 (0.58–4.67)	7.00 (1.45–33.70)	0.56 (0.23–1.34)	0.33 (0.09–1.22)
Solvents	–	–	19.47 (1.78–212.90)	–	–	–	–	–
Toluene	–	–	–	–	–	–	–	–
Xylene	–	–	–	–	–	–	–	–
Petroleum fuels	–	–	–	–	–	–	–	4.37 (1.26–15.19)
Kerosene	–	–	–	–	–	–	–	–
Gasoline	–	–	–	2.40 (0.97–5.92)	–	–	–	–
Agricultural industry	–	–	–		0.41 (0.12–1.36)	–	5.95 (1.36–25.98)	–
Insecticides	1.39 (0.94–1.79)	1.69 (1.19–2.40)	2.13 (0.97–4.70)	1.66 (1.15–2.39)	2.97 (0.73–12.09)	–	–	0.34 (0.13–0.86)
Herbicides	–	–	0.12 (0.02–0.82)	2.01 (0.88–4.55)	–	–	–	–
Fertilizers	–	–	–	–	–	–	–	–
Glues and adhesives	2.16 (1.02–4.55)	2.13 (0.88–5.15)	–	1.95 (0.73–5.22)	–	–	3.50 (0.93–13.11)	2.72 (0.62–11.97)
Inks and pigments	3.22 (0.66–15.75)	–	–	–	–	–	–	–

NHLN: non-Hodgkin lymphoid neoplasms; CLL: chronic lymphocytic leukemia; SLL: small lymphocytic lymphoma.
[a] All risk factors (variables) listed in the column were included in the multivariate model. Variables with p-value greater than 0.20 (except benzene) were eliminated from the model. Only the ORs (95% CIs) of variables remaining in the models are presented.

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Table 9
Odds ratios and 95% confidence intervals for non-Hodgkin lymphoid neoplasms (NHLN) and selected major WHO subtypes by benzene exposure variables.

	NHLN-total			B-cell neoplasms (all)			Precursor B-cell neoplasms			Mature B-cell neoplasms (all)			CLL/SLL			Follicular lymphoma			Diffuse large B-cell lymphoma			T/NK-cell neoplasms (all)		
	OR (95% CI)	Ca	Co	OR (95% CI)	Ca	Co	OR (95% CI)	Ca	Co	OR (95% CI)	Ca	Co	OR (95% CI)	Ca	Co	OR (95% CI)	Ca	Co	OR (95% CI)	Ca	Co	OR (95% CI)	Ca	Co
Benzene (ever vs. never)	1.06 (0.74–1.51)	50	95	1.16 (0.77–1.73)	40	70	1.57 (0.63–3.94)	9	12	1.07 (0.68–1.69)	31	58	2.05 (0.79–5.32)	10	11	7.00 (1.45–33.70)	7	2	0.66 (0.31–1.42)	9	27	0.55 (0.23–1.33)	7	24
Length of exposed jobs (years)	1.00 (0.98–1.02)	50	95	1.00 (0.98–1.03)	40	70	1.00 (0.94–1.07)	9	12	1.00 (0.98–1.03)	31	58	1.03 (0.97–1.09)	10	11	1.42 (0.76–2.67)	7	2	0.98 (0.94–1.02)	9	27	0.95 (0.89–1.02)	7	24
Non-exposed	1.00 reference	599	1203	1.00 reference	481	972	1.00 reference	125	256	1.00 reference	356	716	1.00 reference	57	123	1.00 reference	38	88	1.00 reference	177	345	1.00 reference	111	212
<10 years	1.12 (0.67–1.85)	24	43	1.29 (0.73–2.26)	20	31	1.92 (0.61–6.01)	6	6	1.12 (0.58–2.16)	19	31	2.42 (0.73–7.98)	6	6	1.00 (0.09–11.03)	1	2	0.98 (0.34–2.87)	5	10	0.62 (0.19–1.98)	4	12
>10 to <20 years	0.88 (0.43–1.83)	11	25	0.90 (0.38–2.14)	8	18	0.58 (0.06–5.26)	1	4	1.01 (0.39–2.61)	5	18	5.78 (0.48–69.70)	2	1	–	1	0	0.40 (0.05–3.42)	1	5	0.98 (0.24–3.91)	3	6
>20 years	1.12 ((0.59–2.11)	15	27	1.15 (0.56–2.37)	12	21	2.00 (0.28–14.20)	2	2	1.06 (0.49–2.31)	7	9	1.00 (0.16–6.42)	2	4	–	5	0	0.50 (0.14–1.77)	3	12	–	0	6
	p-Trend = 0.80			*p*-Trend = 0.78			*p*-Trend = 0.93			*p*-Trend = 0.79			*p*-Trend = 0.34			*p*-Trend = 0.27			*p*-Trend = 0.31			*p*-Trend = 0.15		
Maximum exposure (EGS)	1.03 (0.85–1.26)	50	95	1.10 (0.89–1.37)	40	70	1.38 (0.85–2.23)	9	12	1.04 (0.82–1.33)	31	58	1.23 (0.78–1.98)	10	11	2.01 (0.90–4.52)	7	2	0.87 (0.58–1.32)	9	27	0.59 (0.31–1.14)	7	24
Non-exposed	1.00 reference	599	1203	1.00 reference	481	972	1.00 reference	125	256	1.00 reference	356	716	1.00 reference	57	123	1.00 reference	38	88	1.00 reference	177	345	1.00 reference	111	212
EGS1	1.14 (0.73–1.78)	32	56	1.18 (0.70–2.00)	23	39	1.00 (0.29–3.50)	4	8	1.21 (0.68–2.16)	19	31	3.68 (0.89–15.29)	6	4	–	5	0	0.59 (0.22–1.60)	5	17	0.67 (0.26–1.72)	6	17
EGS2	0.75 (0.35–1.64)	9	24	0.80 (0.35–1.85)	8	20	4.64 (0.46–46.86)	3	2	0.57 (0.21–1.52)	5	18	1.29 (0.22–7.41)	2	4	2.00 (0.13–31.98)	1	1	0.40 (0.05–3.42)	1	5	0.64 (0.07–6.14)	1	3
EGS3 and 4	1.21 (0.53–2.76)	9	15	1.64 (0.68–3.97)	9	11	2.00 (0.28–14.20)	2	2	1.57 (0.49–2.31)	7	9	1.33 (0.22–7.98)	2	3	2.00 (0.13–31.98)	1	1	1.17 (0.28–4.89)	3	5	–	0	4
	p-Trend = 0.76			*p*-Trend = 0.37			*p*-Trend = 0.19			*p*-Trend = 0.74			*p*-Trend = 0.37			*p*-Trend = 0.09			*p*-Trend = 0.51			*p*-Trend = 0.12		
First exposure (decades)																								
Non-exposed	1.00 reference	599	1203	1.00 reference	481	972	1.00 reference	125	256	1.00 reference	356	716	1.00 reference	57	123	1.00 reference	38	88	1.00 reference	177	345	1.00 reference	111	212
1940–1959	0.69 (0.24–2.01)	5	14	0.88 (0.26–2.98)	4	9	–	0	1	1.00 (0.29–3.50)	4	8	2.38 (0.38–14.97)	3	3	–	0	0	–	0	3	0.35 (0.04–3.36)	1	5
1960–1979	1.37 (0.83–2.26)	27	40	1.51 (0.83–2.73)	20	27	1.04 (0.19–5.68)	2	4	1.59 (0.84–3.01)	18	23	2.67 ((0.70–10.23	5	4	–	6	0	1.00 (0.29–3.50)	4	8	0.66 (0.21–2.05)	4	12
1980–1999	0.95 (0.51–1.77)	15	32	0.98 (0.50–1.93)	13	27	1.48 (0.44–4.97)	5	7	0.82 (0.36–1.87)	8	20	1.68 (0.27–10.63)	2	3	2.00 (0.13–31.98)	1	1	0.73 (0.23–2.28)	4	11	0.70 (0.13–3.64)	2	5
2000–	0.67 (0.18–2.46)	3	9	0.86 (0.22–3.32)	3	7	–	2	0	0.29 (0.04–2.32)	1	7	–	0	1	–	0	1	0.40 (0.05–3.42)	1	5	–	0	2

NHLN: non-Hodgkin lymphoid neoplasms; CLL: chronic lymphocytic leukemia; SLL: small lymphocytic lymphoma; OR: odds ratio; 95% CI: 95% confidence interval; Ca: exposed cases; Co: exposed controls; EGS: exposure group score (see text).

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vation was associated with increased risks of NHLN-total (OR = 1.46, 95% CI = 1.05–2.05) as well as most subtypes. After taking confounding exposures into account, the OR for NHLN-total associated with "living on a farm" was reduced but remained significantly elevated (OR = 1.29, 95% CI = 1.01–1.65), but neither "planting crops" nor "being employed as farm workers" was a risk factor for NHLN-total or subtypes. Fabric sewing and cutting workers experienced increased risks for NHLN-total (OR = 2.33, 95% CI = 1.19–0.56) and all subtypes (e.g., for precursor B-cell neoplasms, OR = 24.59, 95% CI = 2.97–204.02), but not FL ($p > 0.20$). Exposure to benzene was associated with FL only (OR = 7.00, 95% CI = 1.45–33.70), but not any other subtype. Toluene or xylene was not associated with increased risks of NHNL-total or any subtype. Exposure to petroleum fuels significantly increased the risk of T/NK-cell neoplasms (OR = 4.37, 95% CI = 1.26–15.19) but not B-cell neoplasms. No significant risk for NHLN-total or any subtype was associated with kerosene or gasoline. Exposure to insecticides was associated with an increased risk of B-cell neoplasms (OR = 1.69, 95% CI = 1.19–2.40), but a reduced risk of T/NK-cell (OR = 0.34, 95% CI = 0.13–0.86). After controlling for confounding, exposure to herbicides or fertilizers was no longer related to any increased risk of NHLN-total or subtypes. Exposure to glues and adhesives significantly increased the risks of NHLN-total (OR = 2.16, 95% CI = 1.02–4.55). Furthermore, non-significant increases for B-cell neoplasms (all), mature B-cell neoplasms, DLBCL, and T/NK-cell neoplasms were associated with glues and adhesives.

Table 9 shows the analysis by benzene exposure variables: ever/never exposed, length of exposed jobs, maximum EG category, and decade of first exposure. For NHLN-total, there was no pattern with respect to any of the exposure variables, and no significant OR was detected for any individual category of any exposure variables. For FL, an overall increase was observed based on an "ever/never" comparison (OR = 7.00, 95% CI = 1.45–33.70, seven exposed cases and two exposed controls). When the FL data were examined with respect to benzene exposure variables in detail, no significant trend by length of exposed jobs was found, although it was noted that five of the seven exposed cases were exposed for more than 20 years. In terms of maximum exposure, the FL data suggested a non-significant trend (p-trend = 0.09). Five of the seven exposed FL cases were in the lowest category (EGS1), but no significant increase of FL was found for higher benzene exposure groups (EGS2, or EGS3 and 4). For all other subtypes, no increase was found for the "ever/never" comparison or by any benzene exposure variable.

Finally, to investigate the potential confounding between "farming" and "education level," we performed a logistic regression analysis of NHLN-total by education level stratified by the occupation "farm workers" (Table 10). In non-farm workers, a clear inverse relationship between education level and NHLN risk was observed (p-trend < 0.01). Although the data in farm workers seemed to suggest an inverse relationship between education level and NHLN risk as well, the trend was less clear and the gradient less steep (p-trend = 0.27).

Table 10
Odds ratios and 95% confidence intervals for non-Hodgkin lymphoid neoplasms (all subtypes) by education level in farm workers and non-farm workers.

	OR (95% CI)	Ca	Co
Farm workers			
Education level			
None	1.04 (0.57–1.91)	31	48
Primary school	1.30 (0.84–2.02)	74	97
Middle school (reference)	1.00 reference	67	118
High school	0.82 (0.42–1.61)	16	34
University or higher	0.80 (0.27–2.39)	5	11
Missing		2	2
	p-Trend = 0.27		
Non-farm workers			
Education level			
None	1.41 (0.75–2.64)	19	30
Primary school	1.18 (0.81–1.71)	66	114
Middle school (reference)	1.00 reference	151	281
High school	0.74 (0.55–1.00)	118	290
University or higher	0.65 (0.48–0.88)	98	270
Missing		2	3
	p-Trend < 0.01		

OR: odds ratio; 95% CI: 95% confidence interval; Ca: cases; Co: controls.

4. Discussion

This study represents an attempt to investigate the relationships between environmental and occupational risk factors and NHLN-total and NHLN subtypes according to the WHO 2001 classification of lymphoid neoplasms. The case–control study design allowed us to systematically examine a wide variety of risk factors in relation to specific NHLN subtypes. Had we chosen a cohort study design, exposures would have been limited to one specific group only (such as a single industry). Furthermore, unless the cohort size is very large, the numbers of cases in most subtypes would not have been sufficient for analysis. On the other hand, a general concern with this type of case–control study is the so-called "mass significance" (or multiple comparison) problem [25]. Because of the large number of ORs calculated (for the large number of combinations of risk factors and NHLN subtypes), some ORs could have been "statistically significant" by chance alone. Therefore, in interpreting the results, we must take consistency into consideration and isolated findings must be viewed with caution. Certain findings need to be confirmed in future studies.

In discussing our findings below, we will compare our results with those reported by other investigators in the literature. It should be noted that our study differed from previous studies of NHLN in a number of areas. We used the new WHO 2001 classification of NHLN, whereas most previous studies relied on REAL or the outdated rubrics for lymphomas used in the International Classification of Diseases (i.e., "lymphosarcoma and reticulosarcoma" and "other neoplasms of lymphoid tissue"). Since the WHO classification relies heavily on REAL, the two systems are quite similar in many aspects. In the WHO classification, acute lymphoblastic leukemia and lymphoblastic lymphoma are considered a single disease with different clinical presentations. Similarly, chronic lymphocytic leukemia and small lymphocytic lymphoma are considered biologically the same disease. The term NHL is used rather loosely by some investigators to include both lymphoid leukemias as well as lymphomas, whereas some researchers restrict the term NHL to lymphomas only. To avoid confusion we use the term non-Hodgkin lymphoid neoplasms (NHLN), which include lymphomas and lymphocytic leukemias. Second, occupations with the same titles may be quite different in terms of exposure between China and western countries. Many aspects of the same job (such as work practice, work environment and materials used) may be very different in China. In the past, exposures at workplaces in China have not always been closely monitored and exposure standards not been strictly enforced. For example, the national occupational exposure limits for benzene were 40 mg/m^3 for 1979–2002 and 10 mg/m^3 since 2002. Yet the Chinese medical journals are replete with reports of benzene overexposure (many in excess of 1000 mg/m^3) as well as reports of overt benzene poisoning cases in recent years [26,27,28]. According to a publication prepared by scientists at the Shanghai Municipal Institute of Public Health Supervision, the Shanghai Municipal Center for Disease Control and Prevention and the Fudan University School of Public Health, based on exposure measurements at workplaces in Shanghai, the average benzene levels were 138.6 mg/m^3 in 1965–1979, 120.1 mg/m^3 in 1980–1984, and 112.9 mg/m^3 in 1985–1989, and some 250 measurements were above 3000 mg/m^3 [29]. Obviously, the exposures of, for example, painters in China and those in western countries could be markedly different. In comparing our results and those from other studies, these differences must be noted.

We will first discuss our findings of "farm workers" and "education." One of the most consistent results in a previous analysis in the study was the inverse relationship between "education" and NHLN [16]. Based on a comparison to the category "middle school," the OR for the category "education, none" for NHLN-total was 1.37, whereas significantly reduced ORs were found for high school education (OR = 0.76) and university or higher education (OR = 0.64). In our study, farm workers were found to have an increased risk of NHLN-total (OR = 1.43, 95% CI = 1.14–1.78) as well as several subtypes. Thus, the observed increased risk of NHLN associated with low-level education could be an indirect association through farm workers. However, Table 10 shows that low-level education seemed to be an independent risk factor of NHLN-total in our study, although it appeared to be a stronger risk factor among non-farm workers than among farm workers.

In our study, regardless of the types of product (e.g., grains, vegetables, fruits or tea) or the type of work (production vs. service), farm workers experienced a significantly increased risk of approximately 40% for NHLN-total (OR = 1.43, 95% CI = 1.14–1.78) and similar risks for several subtypes, especially DLBCL (OR = 1.85, 95% CI = 1.24–2.80), but CLL/SLL or T/NK-cell neoplasms were not affected. Similar results were observed for the agriculture industry. The increased risk for farm workers (occupation) or agriculture (industry) in our study was in agreement with several previous studies reporting an increased risk of NHLN in the farming or agricultural industry, including the investigations in France and in Kansas and Nebraska [30,31]. Compared to some previous studies, the advantage of our study was the large number of farm workers (195 NHLN cases and 310 controls classified as farm workers) and the 95% CIs were quite narrow. Another advantage of our study is the detailed analysis by WHO subtypes. Currently there are only a few studies that examined NHLN subtype risks by WHO classification, although some previous studies were based on similar classifications such as REAL [4,9].

As stated above, a significantly increased risk of NHLN was also detected for "living on a farm" (OR = 1.47, 95% CI = 1.20–1.80) in our study in Shanghai. Many of the "farm workers" in our study were actually village farmers who worked and lived on small family-owned farms in the rural areas in the large Shanghai metropolitan area or former farmers who migrated from inland farming regions of China to the coastal city. Of the 876 patients (cases and controls) with a history of farm residence in our study, 501 (57.19%) were also farm workers, and were thus exposed to "farm environment" through both work and residence. We were interested in separating occupational exposures from environmental exposures in farms in our study. In other words, did persons who lived on a farm but who were not farmers by occupation experience an increased risk of NHLN? To do so, we took out study subjects who were farm workers by profession, and re-analyzed the remaining data using a conditional logistic regression model. The new analysis yielded a borderline significant risk of NHLN for "living on a farm" (OR = 1.33, 95% CI = 0.99–1.77), which was slightly smaller than the original OR = 1.47. In the conditional logistic regression analysis, the removal of farm workers from the data created some matched triplets with either no case or no controls, and these matched triplets were excluded from the conditional logistic regression model (matched analysis). To investigate whether the exclusion of these matched triplets had an impact on the result, we also performed an unconditional logistic regression analysis with age and gender as covariates in a dataset that excluded only individual farmers (but not matched triplets). The unconditional logistic regression model showed a similar result (OR = 1.32, 95% CI = 1.02–1.69). This analysis demonstrated that persons living on a farm, even if they did not work as farmers, were at an increased risk of NHLN, although the magnitude of the risk was somewhat modified. In other words, "living on a farm" was an independent risk factor for NHLN, apart from direct occupational exposures.

A significantly increased risk of NHLN and major subtypes was observed for the occupational category "fabric sewing and cutting workers" (workers engaged in the cutting and sewing of fabrics for apparel, shoes, hats, tents, cushions and decorations). The ORs was 3.89 for NHLN-total, 10.29 for precursor B-cell neoplasms, 2.29 for mature B-cell neoplasms, 5.62 for DLBCL, and 8.00 for N/TK-cell neoplasms. An Italian population-based case–control study did not find any increased risk of NHL and CLL (combined) for "tailors, dressmakers, sewers, upholsterers, and related workers (OR = 0.9) [32]. In a population-based case–controls study in Germany, a small non-significant increase of NHL for "tailors, dressmakers, sewers and upholsterers" was reported (OR = 1.3) [33]. In a population-based case–control study in Iowa and Minnesota, a non-significant increase of NHL was reported for the industry "apparel" (OR = 2.4) [34]. Finally, in a cohort study of workers potentially exposed to trichloroethylene, perchloroethylene, carbon tetrachloride, and other solvents at Hill Air Force Base in Utah, a significant increase in mortality from NHL was observed among women (mortality ratio = 2.12, 95% CI = 1.02–3.90) [35]. For women exposed to perchloroethylene, the mortality risk was increased by ninefold (mortality ratio = 9.68, 95% CI = 1.17–34.96). According to the authors, "an unusual proportion of women developing these diseases may have worked in either or both of two fabric-handling departments where 'dope' (a substance used in fabric treatment) and solvents were used." The finding of an increased risk of NHLN associated with the handling of fabrics warrants further investigations.

Our study did not detect any increased risk of NHLN-total or any subtypes associated with the occupational category "teachers." A German case–control study reported an OR of 1.0 for the category "education" and an OR of 0.8 for "teachers."[33] In contrast, a number of studies reported a significantly elevated risk of NHL in teachers [7,32,36]. There was an increased risk of DLBCL in welders and sheet metal workers in our study (OR = 3.33, 95% CI = 1.21–9.17). This finding was consistent with a reported increased OR of 3.4 for "welders and solderers" for diffuse NHL in the case–controls study in Kansas and Nebraska cited above [31]. We also found an increased risk of NHLN in masonry and plastering workers (OR = 2.24, 95% CI = 1.12–4.47). An increased risk for NHL was found associated with "bricklayers, carpenters, and other construction workers" in the Germany study cited above (OR = 1.7, 95% CI = 1.0–2.8) [33]. Similarly, a more than twofold increased risk of NHL was associated with "masonry, tile setting" (OR = 2.6, 95% CI = 0.9–3.8) in a study in Iowa and Minnesota [34]. One of the interesting findings in our study is the elevated NHLN risk for the occupational category "product and chemical testing workers" (OR = 2.14 and 95% CI = 1.17–3.93 for mature B-cell neoplasms, and OR = 10.00 and 95% CI = 1.17–85.59 for FL). Unfortunately, the potential exposures in this occupational category range from tea and tobacco to shoes and ceramics, and the finding based on this occupational category is difficult to interpret.

With respect to the analysis of industries, a few high-risk categories were identified. The finding of an increased risk associated with "agriculture" was consistent with other previous studies [7,30,31,34]. However, our study indicated that most B-cell subtypes are affected but not the subtypes CLL/SLL and T/NK-cell neoplasms. The specificity of the effect will require confirmation by additional investigations in the future. An interesting finding in our study was the significantly elevated risk of NHLN-total for "beauty salon" (OR = 5.99, 95% CI = 1.21–29.65). Similar excess risks of NHL were reported for "hairdressers, barbers, beauticians, and related workers in Italy (OR = 1.9, 95% CI = 0.7–5.8), and for "barbering, cosmetology" in Iowa and Minnesota (OR = 2.1, 95% CI = 0.7–5.9) [32,34]. However, no increased risk associated with "hairdresser, barbers, beauticians" was reported in the Germany study cited earlier (OR = 0.7) [33]. Further investigations of hairdressers need to take specific exposure into consideration, particularly hair coloring chemicals.

To assess the risk of specific chemicals, we developed both a structured primary questionnaire to prompt recall of jobs, tasks and hazards and more than 60 occupation-specific second questionnaires to solicit detailed exposure information from individual study participants having certain occupations of interest. These occupation-specific questionnaires were derived from a system of questionnaires developed by researchers at NCI for collecting detailed occupational information in community-based case–control studies [37]. Detailed information obtained from study subjects included the specific tasks that he or she performed in a job, the frequencies and durations of tasks, the chemicals used, and a general description of the work environment. Thus, specific exposure assignment in our study was based on a consideration of the specific tasks in individual jobs of the patient and not based on generic occupational titles.

A number of previous studies examined the relationship between benzene and NHL. In a cohort study of Chinese workers exposed to benzene, a non-significant risk ratio (RR) for NHL was reported (RR = 3.0, 95% CI = 0.9–10.5, based on 16 observed NHL deaths) [38]. In a cohort study of Pilofilm workers exposed to high concentrations of benzene in Ohio, no increased risk was detected (mortality ratio = 1.00, 95% CI = 0.32–2.33, based on five observed NHL deaths) [39]. Case–control studies of NHL conducted in the US, UK, Canada and Italy also reported no increased risk of NHL for benzene exposure; with ORs ranging from 0.49 to 1.2 [40–47]. Unfortunately, no separate analysis by NHL subtype was performed in these studies. A study in Iowa and Minnesota reported non-significant risk increases associated with "high intensity" benzene exposure for FL (OR = 1.9, 95% CI = 0.7–5.3) and diffuse lymphoma (OR = 1.8, 95% CI = 0.6–5.4) but no increase for all other lymphomas [34]. In an Italian study, exposure to medium or high levels of benzene was associated with a borderline significant risk of NHL (OR = 1.6, 95% CI = 1.0–2.4), whereas exposure at lower levels was associated with a significant reduction in risk (OR = 0.6, 95% CI = 0.4–0.9); and a trend analysis indicated no gradient (p = 0.44) [48]. The only subtype associated with a significantly increased risk from benzene exposure was "diffuse NHL" (OR = 2.4, 95% CI = 1.3–4.5). The authors did not calculate a risk estimate for FL because there were only two exposed cases. However, based on the numbers presented, it did not appear that there was an increased risk of FL (two exposed cases out of 100 [2%] compared with 35 exposed controls out of 1125 [3%]). In our study, exposure to benzene was not associated with an increased risk of NHLN-total (OR = 1.06, 95% CI = 0.74–1.51, based on 50 exposed cases and 95 exposed controls, Table 6), which was consistent with the literature. Furthermore, no increased risk was found for most subtypes of B-cell neoplasms, or T/NK-cell neoplasms (Table 6). However, seven cases of FL cases and two corresponding controls were exposed to benzene, resulting in a significant OR of 7.00. The 95% CI (1.45–33.70) was rather wide, primarily because the OR was based on only two exposed controls. A review of the exposed subjects' employment histories revealed a variety of occupations and industries, and no clusters of occupations or industries could be identified. Analysis based on benzene exposure variables (length, maximum EG, and first exposure) did not reveal any pattern for NHLN-total or specific subtypes, except for a non-significant trend for FL in terms of maximum exposure (Table 9). We also experimented with other benzene exposure variables in an effort to best characterize the pattern of exposure. The challenge was to maintain an appropriate balance between maximizing exposure information in the data on one hand and not over-quantifying the historical estimates on the other. For example, we constructed an exposure variable "cumulative EGS-years" = $\sum\{\text{EGS} \times \text{years of exposure}\}$ (summed over jobs and adjusted for frequency of exposure). No trend was detected for any subtype by cumulative EGS-years (for example, p-trend = 0.36 for NHLN-total, and p-trend = 0.47 for FL). Because of the wide range of the EGS categories (especially EG3 and EG4) and the inherent limitations of such historical estimates, exposure variables based on EGS must be viewed with caution.

Similar to benzene, our results indicated that exposure to petroleum fuels was associated with a significantly elevated risk for FL only (OR = 6.61, 95% CI = 1.37–31.48, eight exposed case and four exposed controls), but not with NHLN-total or other subtypes. The lack of an association between petroleum fuels and NHLN-total in our study was consistent with the result (mortality ratio = 0.90, 95% CI = 0.82–0.98, based on 506 observed NHL deaths) of a multinational cohort of more than 308,000 petroleum workers [5]. When specific petroleum fuels were examined in the current study, there was no significant increase of NHLN-total associated with gasoline exposure (OR = 1.28, 95% CI = 0.83–1.96). However, six FL cases and no control were exposed to gasoline; whereas neither kerosene nor diesel fuel seemed to have a significant impact on NHLN. Because of the potential confounding between benzene and petroleum fuels (individually or collectively), the data were analyzed using multivariate models. When exposures were analyzed simultaneously, the only significant risk factor for FL was benzene exposure (Table 8). Thus, our study indicates that exposure to benzene did not increase the risks of NHLN-total or most subtypes, with the exception of FL. The finding of an association between benzene and FL, however, should to be interpreted with caution as the OR was based on only two exposed controls and there was no clear pattern of increasing risk of FL associated with any benzene exposure variable. Further investigations of benzene exposure and FL are needed.

Several previous case–control studies investigated the relationship between solvents in general and NHL [30,34]. In the Italian study cited above, small non-significant increases of NHL risk were reported for medium or high exposures to solvents containing aromatic hydrocarbons (OR = 1.2, 95% CI = 0.9–1.7) and solvents containing chlorinated hydrocarbons (OR = 1.3, 95% CI = 0.9–1.8) [48]. A borderline significant OR of 1.6 (95% CI = 1.0–2.4) was reported for medium or high exposures to benzene. Significant increases for diffuse NHL were reported for exposures to xylene (OR = 2.3, 95% CI = 1.2–4.4) and toluene (OR = 2.4, 95% CI = 1.3–4.6). The authors commented that there was a high correlation among benzene, xylene, and toluene exposures and that 70% of the individuals exposed to benzene were also exposed either xylene or toluene or both. When the analysis was restricted to individuals with exposure to benzene only, the NHL OR for medium or high exposure was reduced to 1.2 (95% CI = 0.7–2.2). This Italian study clearly indicated that analysis of benzene exposure in epidemiologic studies is often confounded by exposures to other solvents.

In our study, "solvents" included mineral spirits, Stoddard solvent, VM and P naphtha, paint thinner, chlorinated solvents, perchloroethylene, trichloroethylene, toluene, xylene and other unspecific solvents. Exposure to "solvents" was not related to NHLN-total (OR = 1.15, 95% CI = 0.62–2.14) or specific subtypes, except for precursor B-cell neoplasms (OR = 12.00, 95% CI = 1.45–99.67, based on six exposed cases and one exposed control). We are not aware of any previous studies reporting an increased risk of precursor B-cell lymphoma and exposure to solvents. Furthermore, the finding in our study was based on only one exposed control, and, therefore, should be interpreted with caution and confirmed in future studies. With respect to specific solvents, neither toluene nor xylene was associated with an increased risk of NHLN-total or any subtype in our study.

In our study exposure to insecticides (including organic phosphate, carbamates and other unspecific insecticides) increased the risk of not only NHLN-total (OR = 1.59, 95% CI = 1.22–2.07) but also most subtypes of B-cell neoplasms. Similar associations between insecticides and NHL have been reported by others previously [30,49,50,51]. In a recent meta-analysis of 13 case–control studies, a significant increase of NHL was found (OR = 1.35, 95% CI = 1.2–1.5) [49]. However, significant heterogeneity (i.e., conflicting results) among studies was also detected. A pooled analysis of three case–control studies conducted in four midwestern states in the US reported a significant increase in risk of NHL associated with exposure to carbamate pesticides [50]. Similarly, a population-based case–control study in Canada reported increased risks of NHL for exposure to carbamate (OR = 1.92, 95% CI = 1.22–3.04) and to organophosphorus insecticides (OR = 1.73, 95% CI = 1.27–2.36) [51]. On the other hand, our study indicates that there was no association between insecticides and T/NK-cell neoplasms (OR = 0.57, 95% CI = 0.27–1.19). We are not aware of any reports of insecticides and T/NK-cell neoplasms in the literature. Although both herbicides and fertilizers were associated with increased risks of NHLN-total and subtypes when exposures were examined individually (Table 6), the associations disappeared when exposures were analyzed simultaneously in multivariate models (Table 8). It should be noted that, when exposures to specific agricultural chemicals were examined in multivariate models, the increased risks of NHLN-total and several subtypes associated with the agricultural industry (Table 5) disappeared, with the only exception of DLBCL (Table 8). Interestingly, the elevated risk of DLBCL associated with pesticides (OR = 2.02, Table 6) disappeared in multivariate models when confounding factors were taken into consideration (Table 8).

Based on the multivariate analysis, exposure to glues and adhesives increased the risk of NHLN-total (OR = 2.16, 95% CI = 1.02–4.55) as well as some subtypes of B-cell neoplasms and T/NK-cell neoplasms. Similarly, residential exposure to "home renovation" was related to increased risk of NHLN-total (OR = 1.46, 95% CI = 1.05–2.05) and most subtypes of mature B-cell neoplasms, except FL. We are not aware of any investigation linking home/workplace renovation and NHLN in adults. In a case–control study of 51 pediatric cases of lymphohematopoietic disorders (leukemia [including 6 cases of acute non-lymphocytic leukemia], NHL [8 cases], and aplastic anemia) in Ningxia, China, a significantly increased risk was associated with moving in less than 60 days after home renovation (OR = 16.19) [52]. Unfortunately, no separate analysis for NHL in the Ningxia study was possible because of the small number. Potential exposures from new or newly renovated homes or workplaces included a variety of chemicals; such as paints, adhesives, glues, solvents, preservatives, dust, treated fabrics and other building materials that might contain potentially hazardous chemicals. Activities associated with building renovations have not always been under strict regulation or monitoring in China. For example, in China benzene levels in the range of several hundred mg/m^3 associated with commercial painting have been reported [22,26–28]. With no mandatory regulations, the renovation of private homes could likely be even worse. Elevated levels of formaldehyde, benzene, toluene, xylene and other volatile organic chemicals (VOC) in newly renovated homes have been reported in China [53,54]. Given the elevated risk found in our investigation, exposure to new or newly renovated homes or workplaces can be a serious public health issue in China. Approximately 10% (n = 133) of the controls in our study were exposed to the risk factor "home/workplace environment," indicating a sizable number in the general population potentially at risk. As many cities in China, especially large metropolitan areas such as Shanghai, have recently undergone both economic and construction booms (both commercial buildings and residential homes), this public health problem will continue to grow unless regulations are more strictly enforced and public awareness more widely promoted.

In the WHO classification, CLL and SLL are considered the same disease at different stages. Therefore, CLL and SLL were combined into a single category (CLL/SLL) in our analysis. Our findings indicated that CLL/SLL was not associated with any occupational or industrial category or any specific exposure, with the only exception of the broad industrial category "general construction." In particular, exposures to benzene, solvents, or diesel engine exhaust were not associated with an increased risk of CLL/SLL. Our findings were in agreement with the literature. For example, in a case–control study in Baltimore, no increased risk of CLL was found for exposures to benzene [55]. Similarly, in a population-based case–control study in the US (Detroit, Atlanta, and selected countries in Washington and Utah), no increased risk of CLL was reported for the broad category of aromatic hydrocarbons (including benzene, toluene, xylene and creosote) (OR = 1.2, 95% CI = 0.8–2.0) or benzene in particular (OR = 1.1, 95% CI = 0.6–2.0) [56]. In a case–control study of lymphatic leukemia in the rubber industry in the US, exposures to several solvents resulted in significantly elevated ORs; including acetone, carbon disulfide, carbon tetrachloride, ethyl acetate, hexane and methanol [57]. No other solvents (including benzene, toluene and xylene) were associated with a significantly increased risk, although the numbers of cases exposed to individual solvents in the study were small. In a combined cohort of 208,000 workers with potential exposure to benzene in the petroleum industry in the US and UK, the mortality ratio for CLL was 0.84 (95% CI = 0.67–1.04, based on 83 deaths) [58].

An interesting finding in our study was the use of traditional Chinese medicines and reduced risks for NHLN-total (OR = 0.55, 95% CI = 0.35–0.85) and most subtypes of B-cell neoplasms (except CLL and SLL) and T/NK-cell neoplasms (Table 8). Traditional Chinese medicines used by subjects in our study (longer than one month) included several common varieties such as bezoar of ox, chiretta and angelica root. We searched the Chinese literature but were unable to find any investigation on NHLN and traditional Chinese medicines. One possible explanation is that indeed some traditional Chinese medicines have a beneficial effect on certain NHLN subtypes. Another explanation is that individuals in our patient population who regularly relied on traditional Chinese medicines might have avoided or minimized the use of some western medicines (such as penicillin and other antibiotics, and aspirin and other pain relievers), which have been linked to an increased risk of NHL [59–61]. One of the problems in evaluating the effects of medications is the potential confounding effect of the underlying diseases that prompt the use of medications. Obviously, the inverse relationship between traditional Chinese medicines and NHLN, regardless whether it is a direct or indirect one, requires additional investigations.

Several limitations of the study should be noted. First, the participation rate in our study was 76%, which was within the range commonly reported in most interview-based case–control studies. Many NHLN patients at the participating hospitals were outpatients and the opportunity (window of time) to interview them was limited. Although there is no reason or evidence to suggest that any bias was introduced by the non-participation of some patients, the representativeness of our sample could not be verified. Second, in an interview-based case–control study such as ours, recall or reporting bias is always a potential concern. To minimize such bias, we used structured questionnaires. Further, in our study neither the patients nor the interviewers were informed about the specific objectives or hypotheses of the study. The interviewers were not informed of the case/control status of the patients and the exposure assessment team was also blinded. Third, in some matched sets the age requirement for the controls (within 5 years of the case) was relaxed, because of the lack of eligible controls. Fourteen percent (14%) of controls had an age difference of more than 5 years when compared to their corresponding cases. Nevertheless, the mean ages of all the cases (52.5 years) and controls (52.7 years) were almost identical. In an analysis restricted to matched sets satisfying the original matching criterion (age difference <5 years), the results were similar to the results based on the entire dataset, except for some situations in which the ORs were no longer significant because of reduced sample sizes. Fourth, our study was hospital-based and consisted of patients from 25 hospitals in Shanghai. Thus, the patients in our study might not be a representative sample of the entire patient population in Shanghai. Moreover, potentially eligible cases (patients with a provisional diagnosis of NHLN) at these 25 participating hospitals were referred by the clinical coordinators at the hospitals to our clinical laboratory JCML for diagnostic confirmation. Although we believe that most eligible patients were referred to JCML, there was no practical way to validate the number. Fifth, because of the large number of combinations of risk factors by NHLN subtypes, a large number of risk estimates were calculated and some might be statistically significant simply by chance alone. Sixth, some of the risk estimates were based on small numbers and the results need to be interpreted with caution. Finally, even though the exposure assessment was based on several sources of historical exposure data unique to the study setting, the historical benzene exposure estimates must be viewed in the context of a community case–control study. In particular, given the retrospective nature of the assessment procedure and the uncertainties in the underlying data sources, the assignments of jobs to specific exposure groups (EG) necessarily involved subjective judgment, and analysis based on EG might have been affected by misclassification.

On the other hand, our study has a few strengths as well. The number of NHLN patients in our study was relatively large not only in the overall disease category (all NHLN subtypes combined) but also in some major subtypes of NHLN. The large sample allowed us to focus on specific subtypes, in addition to the overall broad category of NHLN. Another strength of the study is the detailed diagnosis based on the new WHO classification of lymphoid neoplasms, which classified patients by individual NHLN subtypes based on a consideration of not only morphologic findings but also genetic, immunophenotypic, biologic, and clinical features of the patients. With the large study size and the detailed diagnostic information, we were able to examine a wide spectrum of potential risk factors including personal characteristics, lifestyle, and environmental and occupational factors by subtype according to the new WHO classification. We believe our study is the first large-scale epidemiologic investigation of NHLN using the WHO classification.

5. Conclusion

In summary, we found several potential risk factors of NHLN (all subtypes combined) and/or individual subtypes associated with environmental or occupational exposures. Some risk factors applied to all or most subtypes (e.g., insecticides and NHLN-total and subtypes of B-cell lymphoid neoplasms), while others were limited to one or two subtypes (e.g., benzene and FL). The difference in risk by subtype underscores the importance of the etiologic commonality and heterogeneity of NHLN subtypes.

Conflict of interest

Funding of the study was provided by the Benzene Health Effects Consortium. In the past O. Wong has acted as a consultant/expert to some of the member companies of the Consortium.

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