# RESEARCH ARTICLE

# Multicentre Hospital-based Case-control Study of Diffuse Large B-cell Lymphoma in Shanghai, China

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## Abstract

   **Background:** Several potential risk factors have been identified for diffuse large B-cell lymphoma (DLBCL); however, epidemiological studies investigating the association between these risk factors and DLBCL have yielded inconsistent results. **Objectives:** To investigate potential medical, lifestyle, and environmental risk factors of DLBCL in Shanghai, China through a hospital-based case-control study. **Method:** One-hundred-and-forty-seven newly diagnosed DLBCL patients and 294 sex- and age-matched controls were recruited from 11 hospitals in Shanghai between 2003 and 2007. A standardized structured questionnaire was used to obtain patient data on demographics, medical history, family history, lifestyle, and environmental exposures. Conditional logistic regression models were used to estimate odds ratios (ORs), with 95% confidence intervals (CIs), for risk associated with each data category. **Results:** History of tuberculosis (TB) infection and "living on a farm" were positively associated with DLBCL (TB: OR=3.05, 95% CI: 1.19-7.80; farm: OR=1.82, 95% CI: 1.21-2.73). In contrast, taking traditional Chinese medicine was negatively associated with DLBCL (OR=0.36, 95% CI: 0.14-0.89). No significant correlation with DLBCL risk was found for any of the other potential risk factors (p>0.05), including but not limited to hair dyes, alcohol drinking, smoking, and home/workplace renovation within one year. **Conclusions:** Consistent with results from previous studies in other DLBCL case populations, traditional Chinese medicine appeared to have a direct or indirect protective effect against DLBCL. However, this study also identified a possible predisposition for DLBCL in TB sufferers and farmers.

**Keywords:** Diffuse large B-cell lymphoma - epidemiology - case-control study - risk factors - environment - China

## Introduction

   Diffuse large B-cell lymphoma (DLBCL) is a type of aggressive lymphoma and the most common subtype of non-Hodgkin lymphomas (NHL) diagnosed in North America, Western Europe, and China. The US alone reported 70,130 newly-diagnosed NHL cases in 2011, and it is estimated that 30-40% are DLBCL (Siegel et al., 2012). Likewise, the continually increasing incidence rate of DLBCL in China is estimated to reach that of the US (Wang, 2006).

   DLBCL tumors originate in the lymphoid tissues of the immune system, but readily migrate to other organs, such as the liver, spleen, bone marrow, skin, bowels, and bone. This type of systemic distribution facilitated by the extensive and interconnected lymph system makes DLBCL a particularly threatening form of cancer. While the molecular pathogenic processes underlying DLBCL are the topic of extensively research, the precise causes of this disease remain to be fully elucidated. Several epidemiologic studies of NHLs have identified a

large number of potential risk factors (Keller-Byrne et al., 1997; Chang et al., 2005; Hoffmann et al., 2008; Khan et al., 2008; Geyer et al., 2010; Sangrajrang et al., 2011; Jiao et al., 2012), including personal and family medical histories (such as blood transfusion, alkylating drugs for cancer treatment, diagnostic X-rays, rheumatoid arthritis, retrovirus infection, and family history of blood disorders), lifestyle (such as use of tobacco, alcohol, and hair dye), and environmental exposures (such as living on a farm, living near electrical power transmission lines, benzene solvents, and radiation). Several of the NHL case-control studies have stratified their analyses and investigated the risk factors for DLBCL specifically (Smedby et al., 2006; Ekstrom Smedby et al., 2008; Frankenfeld et al., 2008; Monnereau et al., 2008). However, no unified risk profile has yet been established for DLBCL.

   Given the alarming rate of DLBCL in China, we aimed to perform a case-control study of DLBCL in the populous Shanghai metropolis, investigating all of the previously suggested potential risk factors, including those related to medical history, lifestyle, and environmental exposures.

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## Materials and Methods

*Study design*

This study was designed as a multicentre hospital-based case-control study of DLBCL in Shanghai, China. The study population was recruited from 11 participating hospitals between August 2006 and July 2010: Huashan Hospital, Zhongshan Hosptial, Huadong Hospital, Cancer Center, No. 5 People's Hospital of Fudang University, Tongji Hospital of Tongji University, Ruijin Hospital of Jiaotong University, Shuguang Hospital, Huangpu District Central Hospital, Zhabei District Central Hospital, and Jiading District Central Hospital.

All patients over 18 years of age diagnosed with DLBCL were eligible for study enrollment. Peripheral blood, bone marrow aspirates and core biopsies, and/or tissue biopsies were collected and forwarded to the Pathology Department of the Tumor Hospital at Fudan University for pathological review. DLBCL diagnosis was confirmed according to the pathological findings, and cases were further defined by the World Health Organization's 2001 classification system for lymphoid neoplasm (Harris et al., 2000).

The clinical coordinators of the study at each participating hospital were also responsible for recruiting controls. Upon each new case being enrolled in the study, two individual controls were immediately selected from the same hospital and matched by sex and age (±5 years). Patients with any malignant or non-malignant diseases of the lymphatic and hematopoietic system were excluded from the control population.

The study was approved by the Ethical Committee of Huashan Hospital. All study participants, including cases and controls, provided signed informed consent.

*Patient data gathering by questionnaire survey*

Cases and controls were contacted immediately after they had been identified in the admission records. Professional interviewers, who had been trained at Fudan University by a clinical epidemiologist, were retained to conduct the data collection. To minimize recall bias, neither the patients nor the interviewers were informed about the specific objectives or hypotheses of the study. A standardized structured questionnaire, which was completed by face-to-face interviewing, was used to obtain information on: personal medical history, familial history of cancer, lifestyle, and occupational and residential histories. The lifelong history of smoking included duration (in years) and number of cigarettes smoked per day. An ever-smoker was defined as an individual who had smoked at least one cigarette per day for one year at any time in the past. Lifelong alcohol consumption was recorded for duration (in years) and the number of alcoholic drinks consumed per week, with one unit of drink equating to 10 grams of alcohol, a can of beer, or 25 mL of white wine. An ever-drinker was defined as an individual who regularly drank at least one unit per month at any time in the past. The status of living on a farm was defined by residing/working on a farm for at least five years. The farm-related exposures that were recorded included participation in planting crops and animal husbandry, and/or use of agrochemicals on the farm site. All of the exposures collected predated the diagnosis of lymphoma.

*Statistical analysis*

Data from completed questionnaires were entered (double entry) into an Oracle database housed at Fudan University. Conditional logistic regression models were selected for analysis to facilitate matching between cases and controls (sex and age), and were used to calculate the odds ratios (ORs) and 95% confidence intervals (95% CIs) for risk associated with each data category. Since many study subjects were exposed to multiple risk factors, multivariate models were used to adjust for confounding factors (medical history, lifestyle, residential, and environmental exposure). Variables for the multivariate models were selected based upon consideration of the results for individual effects of risk factors identified among the study's cases and controls. Variables with a P-value greater than 0.10 were eliminated from the multivariate models. All statistical analyses were carried out with SPSS 13.0 software (Chicago, IL, USA). All tests were two-sided, and a 5% significance level was used.

## Results

*Quality analysis of study population*

A total of 149 patients were confirmed with a diagnosis of DLBCL. Two of these had incomplete interviews and were excluded from further analysis. Thus, 147 cases (final participation rate: 98.66%) and 294 controls (representing a variety of diagnoses) were analyzed. The diagnostic categories among the controls included: fracture (24.8%), dislocation (7.8%), heart failure (5.8%), hypertension (6.5%), breast cancer (1.0%), colon cancer (6.1%), peptic ulcer (6.5%), gastrointestinal hemorrhage (2.7%), brain injury (5.8%), wounds or injuries (18.0%), peripheral nervous disorders (1.7%), pneumonia (10.2%), and urinary tract infections (3.1%).

The questionnaires had been completed by patients alone (cases: 80.5%; controls: 95.9%) or in the presence of family members (cases: 18.1%; controls: 4.1%). When interviewees were too weak to independently complete the

**Table 1. Odds Ratios and 95% Confidence Intervals for DLBCL According to Medical History Risk Factors**

| Variables | OR (95% CI) | P-value | Exposed cases, n | Exposed controls, n |
|---|---|---|---|---|
| History of blood transfusion | 0.97 (0.51-1.83) | 0.914 | 15 | 31 |
| Diabetes | 0.57 (0.19-1.74) | 0.324 | 5 | 16 |
| Tuberculosis | 2.56 (1.04-6.33) | 0.042 | 11 | 9 |
| Infectious mononucleosis | - | - | 0 | 0 |
| Rheumatic fever | - | - | 0 | 0 |
| HIV infection | - | - | 0 | 0 |
| Anti-allergy drugs | 0.86 (0.22-3.31) | 0.823 | 3 | 7 |
| Western medicines* | 1.46 (0.44-4.81) | 0.489 | 11 | 17 |
| Traditional Chinese medicines** | 0.29 (0.11-0.78) | 0.014 | 6 | 32 |

DLBCL, diffuse large B-cell lymphoma; OR, odds ratio; 95% CI, 95% confidence interval. *Western medicines included chloramphenicol, sulfonamides, anti-psychotics, sodium phenytoin, colchicine, cyclophosphamide, propylthiouracil, sulfonylurea, and primaquine. ** Only those traditional Chinese medicines that had been used continuously for at least one year were recorded

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**Table 2. Odds Ratios and 95% Confidence Intervals for DLBCL According to Lifestyle and Environmental Exposures**

| Variables | OR (95% CI) | P-value | Exposed cases, n | Exposed controls, n |
|---|---|---|---|---|
| Petrochemicals | 0.84 (0.45-1.59) | 0.914 | 15 | 35 |
| Metals, general* | 0.89 (0.27-2.89) | 0.845 | 4 | 9 |
| Diesel fuel and petroleum fuel | 0.51 (0.19-1.40) | 0.192 | 5 | 19 |
| Smoking status, ever | 1.03 (0.69-1.53) | 0.892 | 67 | 132 |
| Tobacco consumption, cig/day | | | | |
| 0 | 1.00 (reference) | - | 80 | 162 |
| ≤20 | 1.17 (0.55-2.48) | 0.688 | 56 | 106 |
| >20 | 1.25 (0.58-2.71) | 0.575 | 11 | 26 |
| Smoking duration, years | | | | |
| 0 | 1.00 (reference) | - | 80 | 162 |
| ≤30 | 0.65 (0.55-1.45) | 0.645 | 31 | 67 |
| >30 | 0.84 (0.46-1.51) | 0.55 | 36 | 65 |
| Alcohol drinking, ever/never ratio | 0.68 (0.39-1.18) | 0.173 | 28 | 71 |
| Alcohol consumption, unit/week** | | | | |
| 0 | 1.00 (reference) | - | 119 | 223 |
| ≤40 | 0.68 (0.36-1.29) | 0.24 | 17 | 44 |
| >40 | 0.69 (0.30-1.58) | 0.373 | 11 | 27 |
| Drinking duration, years | | | | |
| 0 | 1.00 (reference) | - | 119 | 223 |
| ≤30 | 0.58 (0.29-1.16) | 0.128 | 14 | 42 |
| >30 | 1.19 (0.40-1.77) | 0.648 | 14 | 29 |
| Hair dyes, ever/never ratio | 0.91 (0.60-1.39) | 0.517 | 54 | 115 |
| Hair dyes, total frequency | | | | |
| 0 | 1.00 (reference) | - | 93 | 179 |
| ≤20 | 0.95 (0.59-1.52) | 0.829 | 41 | 83 |
| >20 | 0.79 (0.40-1.56) | 0.494 | 13 | 32 |
| Home/workplace renovation | 1.63 (0.87-3.05) | 0.125 | 20 | 26 |
| Living within 100 m of high voltage electrical power transmission lines | 0.93 (0.58-1.48) | 0.75 | 35 | 74 |
| Living on a farm for >5 years | 2.00 (1.29-3.09) | 0.002 | 82 | 120 |
| Planting crops | 1.81 (1.15-2.84) | 0.01 | 57 | 80 |
| Animal husbandry*** | 1.82 (1.21-2.73) | 0.004 | 66 | 91 |
| Agrochemicals | 2.23 (1.34-3.70) | 0.002 | 41 | 46 |

DLBCL, diffuse large B-cell lymphoma; OR, odds ratio; 95% CI, 95% confidence interval. *Metals included exposure to lead, nickel, mercury, copper, cadmium, chrome, beryllium, zinc, and arsenic; **1 unit=10 grams of alcohol or a can of beer or 25 mL of white wine; ***Animals included chickens, ducks, pigs, cows, sheep, dogs, cats

interview, the present family member would participate, but each answer was finally confirmed by the patient.

General analysis indicated that the cases and controls were appropriately matched in sex and age. The mean age of both the case and control groups was 58.3 years. Distribution of the 294 controls by their age differences from the cases showed that 93.2% were within 5 years (n=274), 6.5% were within 6-8 years (n=19), and 0.3% were within 9-10 years (n=1). For both groups, the male-to-female ratio was 1.4:1.0. The male bias is consistent with other previously published studies of DLBCL (Moller et al., 2004; Ameen et al., 2010).

*Univariate logistic regression analysis of medical, lifestyle, and environmental risk factors for DLBCL*

The results of the medical risk factors analysis are summarized in Table 1. History of suffering from tuberculosis (TB) showed a positive correlation with increasing risk of DLBCL (OR=2.56, 95% CI: 1.04-6.33). However, the use of traditional Chinese medicine (such as ox bezoars, chiretta, and angelica root) showed a protective effect against DLBCL (OR=0.29, 95% CI: 0.11-0.78). Other medical risk factors, including the history of other diseases (such as osteoarthritis,

**Table 3. Odds Ratios (95% Confidence Intervals) of Risk of DLBCL Based on Conditional Multivariate Logistic Regression Models**

| Risk factors | OR (95% CI) | P-value |
|---|---|---|
| Tuberculosis | 3.05 (1.19-7.80) | 0.02 |
| Traditional Chinese medicine | 0.36 (0.14-0.89) | 0.026 |
| Living on a farm | 1.82 (1.21-2.73) | 0.004 |

DLBCL, diffuse large B-cell lymphoma; OR, odds ratio; 95% CI = 95% confidence interval

infectious mononucleosis, rheumatic fever, human immunodeficiency virus (HIV) infection, and diabetes), anti-allergy drug use, Western medicine use (including chloramphenicol, sulfonamides, anti-psychotics, sodium phenytoin, colchicine, cyclophosphamide, propylthiouracil, sulfonylurea, and primaquine), did not show any significant associations with DLBCL (P>0.10).

Table 2 summarizes the results for DLBCL risks associated with lifestyle and environmental exposures. There was no association detected between smoking or alcohol consumption and risk of DLBCL. However, stratification analyses for current/former smoker status or type of cigarette were not carried out. Significant risk for DLBCL was detected for several of the farm-related exposures, including living on a farm for five years or more (OR=2.00, 95% CI: 1.29-3.09), planting crops (OR=1.81, 95% CI: 1.15-2.84), and animal husbandry (OR=1.82, 95% CI: 1.21-2.73). The most commonly reported crops and grains that were planted by the farmers in this study were rice, wheat, corn, mullet, bean, potatoes, vegetable, fruit, tea, and cotton. The most commonly reported animals from the farms were chickens, ducks, pigs, cows, sheep, dogs, and cats. However, stratification analyses by crop or animal type were not performed. A significantly increased risk of DLBCL was also found for agrochemical exposures (OR=2.23, 95% CI: 1.34-3.70), which included pesticides, herbicides, and fertilizers. Eighty-seven patients reported exposure to agrochemicals (cases, n=41; controls, n=46), all of whom lived on a farm and did not work in an agrochemicals factory. Environmental exposures to petrochemicals, metals (including lead, nickel, mercury, copper, cadmium, chrome, beryllium, zinc, and arsenic), use of hair dye, and living within 100 m of high voltage electrical power transmission lines were not associated with DLBCL (P>0.10).

*Multivariate logistic regression analysis revealed positive and negative risk factors of DLBCL*

Nearly all of the study participants who reported having planted crops, raised animals, and being exposed to agrochemicals lived on a farm. Therefore, these three variables were removed from the multivariate models. The variables that were included in the multivariate models are listed in Table 3.

TB and living on a farm retained their significant positive correlation with DLBCL in the multivariate analysis model (OR=3.05, 95% CI: 1.19-7.80 and OR=1.82, 95% CI: 1.21-2.73, respectively). Similarly, the significant negative correlation between use of traditional Chinese medicine and DLBCL was retained in the multivariate analysis model (OR=0.36, 95% CI:

0.14-0.89). Thus, the multivariate analysis indicated that TB and living on a farm increased the risk for developing DLBCL, while traditional Chinese medicine decreased the risk of DLBCL.

## Discussion

This study represents an attempt to investigate the relationship between medical, lifestyle, and environmental risk factors and DLBCL in the Shanghai region of China. The case-control study design facilitated a systematic examination of a wide variety of risk factors with a relatively small study population, as opposed to the cohort study design, which would have required a large cohort size and long time to survey.

Analysis of the factors associated with a patient's medical history indicated that TB was positively related to DLBCL. This finding is similar to that reported by two Italian studies (Tavani et al., 2000; Vineis et al., 2000). In addition, a 40 year follow-up cohort study of a Swedish population found that the risk of NHL is increased in individuals with a history of TB, particularly in individuals with severe TB and a long history of diagnosis (Askling and Ekbom, 2001). Finally, another study reported that NHL and TB infection coexisted in the same organ (Fanourgiakis et al., 2008). Infection and tissue inflammation are recognized as risk factors for cancer. Indeed, evidence of increased lung cancer among individuals with TB has been reported (Wu et al., 2011; Yu et al., 2011). Several mechanisms have been proposed for such correlative pathogeneses. Nitric oxide (NO) and oxygen radicals produced by and around infected and inflamed tissues can damage DNA and contribute to the process of carcinogenesis (Ohshima and Bartsch, 1994; Sonveaux et al., 2009). TB is known to move to the lymph nodes, wherein it produces a chronic inflammatory state. The cytokines that accompany chronic inflammation may further promote carcinogenesis, particularly that of DLBCL. Thus, DLBCL may be a result of increased susceptibility, rather than a consequence of TB itself.

Tobacco smoking and alcohol consumption, especially at high rates of intake, are well-recognized risk factors of many diseases, including diabetes, peptic ulcer, cardiovascular disease, chronic obstructive pulmonary diseases, and cancer. However, a previous study in France reported an inverse relationship between smoking and NHL (Monnereau et al., 2008). The results were different in an Italian study, in which tobacco intake was shown to be positively correlated to NHL (Talamini et al., 2005). Other studies of NHLs comparing never-smokers and never-alcohol drinkers with ever-smokers and ever-alcohol drinkers demonstrated that tobacco and alcohol use was correlated with a poorer survival rate (Talamini et al., 2008; Geyer et al., 2010). In our study population, neither smoking nor alcohol drinking was found to be associated with DLBCL. Further research is necessary to confirm our findings and determine the precise role of smoking and alcohol in DLBCL pathogenesis.

An interesting finding of the current study was the reduced risk for DLBCL correlated with use of traditional Chinese medicine. The mechanisms underlying this interaction are unknown. Literature searches yielded no previously published studies of hematological diseases and these medicines. The chemical components of the traditional Chinese medicines are complex, and more research should be carried out to determine the precise relationship between each of them and DLBCL.

As previously reported, significantly increased risk of DLBCL was also detected for the study participants who live on a farm. Additional farm-related risk factors (planting crops, animal husbandry, and agrochemicals) were also associated with increased DLBCL risk. In China, it is common for a single farmer to perform dual functions of planting crops and raising animals. Use of agrochemicals, including fertilizers, insecticides, and herbicides, is also common. Previous studies indicated that farm-related factors were positively associated with risk of NHL (Pearce and Bethwaite, 1992; Figgs et al., 1995; McDuffie et al., 2002; Chiu et al., 2004). In addition, animal husbandry is well-recognized for its increased risk of exposing a human to transmissible retroviruses, which are known to cause lymphoma (Tranah et al., 2008; Bouvard et al., 2009). In a population-based study, the risks of lymphoma were shown to be increased for individuals exposed to cattle, but decreased for individuals exposed to sheep and rabbits (Becker et al., 2004). In our study, the animal species was not taken into consideration, and when general animal exposure was analyzed, the increased risk of DLBCL was found. Other studies have reported an increased risk of NHL with agrochemicals, such as fertilizers, insecticides, and herbicides (Zahm and Blair, 1992; Kato et al., 2004; Pearce and McLean, 2005; Eriksson et al., 2008). Studies of individuals associated with the industrial production of agrochemicals have found increased risk of NHL (Kogevinas et al., 1997), but not more so than the farmers who are exposed to relatively lower concentrations. Long-term exposure and lack of effective protection allow toxicants to accumulate in the body, thereby increasing the risk of associated diseases. According to our research and that by others, farm-related exposures are particularly strong risk factors for NHL. Thus, farmers should be taught to protect themselves when using agrochemicals, and to carefully monitor the hygienic status of the farm.

The current study was carried out with a hospital-based case-control design, which provided many advantages. First, the study was conducted at multiple comprehensive hospitals, which represent the general hospital-based population of Shanghai. Second, the established DLBCL diagnostic standard used was uniform and accurate. Third, compared with some previous general studies of NHL, our study focused on the DLBCL type. Finally, the matched cases and controls were recruited from an inpatient setting, reflecting the fact that all of the DLBCL patients in China are administered in-hospital regimens of chemotherapy. Therefore, admission rate bias was restricted in our study. However, there are a few limitations to the study that should be considered when interpreting our results. As a hospital-based study, all of the controls were also inpatients, and many confounding factors are likely to exist in this group. Compared to a population-based study design, the sample size of our study was small.

Therefore, the results may not truly reflect the events at a population level.

In conclusion, we found that tuberculosis and living on a farm are risk factors for DLBCL, whereas use of traditional Chinese medicines is protective against this disease.

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