Diet, Smoking, Incense and Lifestyle Risk Factors for Diffuse Large B-Cell Lymphoma: A Hospital-Based Case-Control Study

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Objective: The study assessed the impact of common modifiable lifestyle factors, such as smoking history, alcohol consumption, use of household insecticides, incense burning, body mass index (BMI), and other suspected variables, on the risk of diffuse large B-cell lymphoma (DLBCL).

Methods: We conducted a hospital-based case-control study in Southern Taiwan from October 2016 to August 2018 and used logistic regression analyses to assess the odds ratios (ORs) and 95% confidence intervals of DLBCL risk factors.

Results: A multivariate analysis of 41 DLBCL cases and controls revealed that DLBCL risk was associated with household insecticide use, patients with hepatitis, and plastic bags and container use to store hot food (OR = 4.73, *p* = 0.018; OR = 7.89, *p* = 0.012; OR = 8.18, *p* = 0.006, respectively).

Conclusions: Household insecticide usage, hepatitis virus infection, and use of plastic bags or containers to store hot food increase the risk of DLBCL. We found a weak correlation between DLBCL risk and incense burning (OR = 2.37, *p* = 0.089) and no significant association between DLBCL risk and smoking, alcohol consumption, ultraviolet light exposure, BMI, and dairy product intake.

Key words: DLBCL, risk factor, insecticide, plastic, case-control study

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Introduction

Lymphoid neoplasms are grouped into three major categories: B-cell neoplasms, T/NK-cell neoplasms, and Hodgkin lymphomas, with disease entities subdivided into > 80 subtypes based on their morphology, immunophenotype, genetic lesions, molecular profiles, clinical features, and cellular derivation.[1] Additionally, variations are based on age, sex, race, ethnicity, and regional trends in incidence and temporal patterns. Australia, New Zealand, Northern America, and Northern Europe are the regions with the highest incidence rates (13.5 – 16.4/100,000 persons), while the lowest rates are observed in Central Africa and America (3.2 – 4.6/100,000 persons).[2] However, racial and geographical variance remains unknown.

Diffuse large B-cell lymphoma (DLBCL), an aggressive B-cell lymphoid neoplasm, is the most prevalent subtype of non-Hodgkin lymphoma (NHL) worldwide. It represents approximately 30% of cases in Western countries and 50.7% of cases in Taiwan.[3-5] On average, there are seven new cases per 100,000 people per year in the United States.[6] In Taiwan, the incidence rate (age adjusted by the 2000 world standard population) increased from 3.12 to 4.06 per 100,000 between 2008 and 2020.[7,8]

The cause of DLBCL is still not entirely known. B-cell activating autoimmune disease, lifestyle, obesity, recreational sun exposure, and family history of NHL are a few suspected risk factors.[9-12] Although studies have highlighted environmental exposure factors related to the risk of lymphoma, such as pesticide exposure and having lived on a farm, few have focused on either the use of incense burning or plastic bags for stoking hot food.

Incense burning is a common ritual practice in Asia. In Taiwan, most people are either Buddhists or Taoists, and most worship every day at home and burn incense.[13,14] Incense burning can increase the concentration of particulate matter and the risk of lung cancer.[15,16] Additionally, incense burning was found to contribute to delayed developmental milestones in children.[17] Moreover, plastic bags or containers are frequently used to pack takeaway in the food industry in Taiwan and other Asian countries.[18] However, direct contact between heated food and plastic surfaces can result in the leaching out of chemicals into the food.

To the best of our knowledge, no thorough epidemiological study on lymphoma has been conducted in Taiwan till date, and the understanding of the etiology and prognosis of lymphoma is very limited. Here, we aimed to investigate the association between DLBCL and incense burning, use of plastic bags for storing hot food, and other common modifiable lifestyle factors, such as smoking, alcohol consumption, body mass index (BMI), diet, sun exposure, and other risk factors, using data from a hospital-based case-control study in Southern Taiwan.

Patients and Methods

Study design

This case-control study included individual data from four hospitals in Southern Taiwan (Dalin Tzu Chi Hospital, E-Da Hospital, Liouying Chi Mei Hospital, and Pingtung Christian Hospital). The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of E-Da Hospital (protocol codes: B10504014, EMRP-105-046, 10512-L03, and IRB541B). All participants gave their informed consent before interviews were conducted.

Participants

From October 11, 2016, to August 31, 2018, inpatients or outpatients at a participating hospital who were hospitalized or treated for malignant lymphomas, including NHL,

Hodgkin lymphoma, acute lymphoblastic leukemia, chronic lymphocytic leukemia or small lymphocytic lymphoma, aggressive NK-cell leukemia, multiple myeloma, Waldenström's macroglobulinemia, plasmacytoma, and cutaneous lymphoma, and those who were 20 – 80 years of age at the time of initial diagnosis were considered eligible participants. Inpatients and outpatients at the collaborating hospitals served as control participants. Controls were matched to cases registered within the stated geographic area of the participating institutions (within three months) by hospital, age at diagnosis or admission (± 5 years), sex, and date of admission. Control groups included orthopedic patients, spouses of five cancer types (pancreatic, thyroid, gastric, colorectal, and brain cancers), and individuals undergoing general health examinations who did not present any type of lymphoma.

Data collection

After participants signed the informed consent form, a structured and validated questionnaire was provided (eQuestionnaire 1 in the Supplement). The questionnaire was designed by referring to the AsiaLymph study questionnaire, an international multicenter hospital-based case-control study of Chinese people in Eastern Asia, with minor revisions for Taiwanese people.[19] They could return the completed questionnaire during follow-up visits or via mail. We used some epidemiological survey methods to ensure the quality of the questionnaire and reduce research errors. If the participant did not return the questionnaire within two weeks, the researcher contacted the subject and filled out the questionnaire via a phone interview or in an interview during a follow-up visit, ensuring patient confidentiality. Moreover, if, despite getting the questionnaire, a participant did not complete it within 12 weeks, they were considered to have withdrawn from the trial.

Measure of exposure

The questionnaires were used to collect information on each participant's height, weight, and smoking history (whether you have used tobacco products for six months or more? No or Yes), alcohol consumption (whether you have consumed alcohol for ≥ 12 months? No or Yes), information about the use of household insecticide products, incense burning, and using plastic bags and containers to store hot foods (respondents indicated their usual frequency by choosing one of the following categories: never, once per day, over once per day, 1 – 3 times per week, 3 – 5 times per week, or 1 – 3 times per month), sun exposure (hours spent outdoors in sunlight per day, on average, in each season), exposure information in living and working (have you ever lived or worked on a farm > 1 year? No or Yes), frequency of dairy product intake (every day, 3 – 5 times per week, once per week, 1 – 3 times per month, almost never), frequency of physical activity per week, including vigorous, moderate, and mild (by selecting one of the following options: never, once, twice, three times, four times, five times, six times, or > 6 times), and duration of physical activity (how long on average for each exercise) two years before the interview. Data on each participant's family history of NHL (Has anyone in your family (among your direct-blood relatives) ever been diagnosed with NHL?) and health status (have you ever been diagnosed with hepatitis A, B, or C?) were also collected using questionnaires. Each participant's BMI (measure of a person's weight with respect to their height) was derived by dividing the reference weight in kilograms by the square of the height in meters. All malignant lymphoma cases were classified according to the World Health Organization classification.[1,20]

Statistical analysis

Although patients with diverse lymphoma subtypes were included in this trial, the risk factors for each lymphoma subtype were analyzed individually given the varying

etiology of the disease. This study mainly focused on risk factors associated with DLBCL, given the rarity of other subtypes. We used univariate logistic regression analyses to assess the odds ratios (ORs) and 95% confidence intervals (CIs) of risk factors for DLBCL. Those variables with p-values of < 0.20 were entered into a multivariate logistic regression model using backward selection. Participants with missing data for the exposure variable were excluded. Descriptive analyses of the quantitative data and participants' characteristics were performed. Continuous variables were reported as mean values and standard deviations (SDs) and compared using the independent-sample t-test. Categorical variables were presented as frequencies and percentages and compared using Fisher's exact test. A p-value less than 0.05 was considered statistically significant. All analyses were conducted using SPSS software (IBM Corp., 2016; IBM SPSS Statistics for Windows, version 24.0. Armonk, NY: IBM Corp.)

Results

Patient characteristics

In this study, we included 41 DLBCL cases and 41 controls from the four collaborating hospitals. There were no significant differences in sex or age (p-values were 0.375 and 0.644, respectively) between DLBCL cases and controls. The proportion of males (61.0%) was higher than that of females (39.0%) in the DLBCL group; the proportions of males and females in the control group were 48.8% and 51.2%, respectively. The mean age of participants with DLBCL was 63.4 years (SD 11.2), and 56.1% of them were above 65 years of age. Similarly, the mean age in the control group was 62.4 years (SD 9.2), and 48.8% of them were greater than 65 years of age (Table 1). Sixty-six percent of participants smoked regularly for more than 6 months, and 73% of participants consumed alcohol at least once a month for more than 1 year. Patients who used house-hold insecticide products and incense at home were 34% and 63%, respectively. Twenty-two percent of participants were diagnosed with hepatitis A, B, or C. Seventy-eight percent of participants used plastic bags or containers to store hot foods. On average, 44% of participants were exposed to sun for more than 2 hours every day, whereas 22% were exposed to sun for less than 30 minutes. Approximately 30% of participants performed mild physical activity for more than 210 minutes each week, whereas 12% performed moderate physical activity for more than 150 minutes each week. Approximately 9% of participants performed vigorous physical activity for more than 75 minutes each week. Around 35% of participants had a BMI between 18.5 and 24; 38% had a BMI between 24 and 27; 22% had a BMI between 27 and 30; and 6% had a BMI between 30 and 35. Around 5% of participants had lived or worked on a farm for more than 1 year. Moreover, 60% of participants usually or always consumed dairy products every day.

Univariate logistic regression analyses

The potential risk factors for DLBCL are shown in Table 2, including smoking history, alcohol consumption, household insecticide use, incense burning, hepatitis virus infection (types A, B, or C), hot food storage in plastic bags and containers, sun exposure, physical activity (vigorous, moderate, and mild), BMI, family history of NHL, having ever lived or worked on a farm, and dairy product intake. According to the results of univariate logistic regression analyses, DLBCL risk is significantly associated with hepatitis virus infection, the use of plastic bags or containers to store heated food, and mild physical activity.

Compared to hepatitis-negative participants, hepatitis-positive participants were at higher risk for DLBCL (OR: 4.43; 95% CI: 1.27 – 15.47; p-value: 0.019). Compared to those who never keep hot food in plastic bags and containers, those who reported doing so

Table 1. Participant's characteristics.

Factor	DLBCL No. (%)	Control No. (%)	Total No. (%)
Gender			
Male	25 (61.0)	20 (48.8)	45 (54.9)
Female	16 (39.0)	21 (51.2)	37 (45.1)
Age (mean ± SD)	63.4 ± 11.2	62.4 ± 9.2	62.9 ± 10.2
Smoking history			
No	15 (38.5)	12 (30.0)	27 (34.2)
Yes	24 (61.5)	28 (70.0)	52 (65.8)
Alcohol consumption			
No	8 (27.6)	8 (26.7)	16 (27.1)
Yes	21 (72.4)	22 (73.3)	43 (72.9)
Household insecticide			
Never	21 (56.8)	28 (75.7)	49 (66.2)
Sometimes/Usually[*]	16 (43.2)	9 (24.3)	25 (33.8)
Incense burning			
Never	10 (26.3)	18 (47.4)	28 (36.8)
Sometimes/Usually[*]	28 (73.7)	20 (52.6)	48 (63.2)
Hepatitis viruses positive (types A, B or C)			
No	23 (65.7)	34 (59.5)	57 (78.1)
Yes	12 (34.3)	4 (10.5)	16 (21.9)
Hot foods stored in plastic bags and containers			
Never	3 (7.7)	15 (37.5)	18 (22.8)
Sometimes/Usually[*]	36 (92.3)	25 (62.5)	61 (77.2)
Sun exposure (hours/day)			
≤ 0.5	10 (30.3)	5 (13.9)	15 (21.7)
0.5 − 2	12 (36.4)	12 (33.3)	24 (34.8)
> 2	11 (33.3)	19 (52.8)	30 (43.5)
Vigorous physical activity (min/week)[†]			
< 75	30 (90.9)	32 (91.4)	62 (91.2)
≥ 75	3 (9.1)	3 (8.6)	6 (8.8)
Moderate physical activity (min/week)[†]			
< 150	29 (85.3)	30 (90.9)	59 (88.1)
≥ 150	5 (14.7)	3 (9.1)	8 (11.9)
Mild physical activity (min/week)[†]			
< 210	29 (85.3)	22 (61.1)	51 (72.9)
≥ 210	5 (14.7)	14 (38.9)	19 (27.1)
BMI			
18.5 − 23.9	13 (40.6)	11 (29.7)	24 (34.8)
24 − 26.9	10 (31.3)	16 (43.2)	26 (37.7)
27 − 29.9	7 (21.9)	8 (21.6)	15 (21.7)
30 − 35	2 (6.3)	2 (5.4)	4 (5.8)
Family history of NHL			
No	34 (91.9)	40 (97.6)	74 (94.9)
Yes	3 (8.1)	1 (2.4)	4 (5.1)
Ever lived or worked on a farm			
No	23 (60.5)	23 (56.1)	46 (58.2)
Yes	15 (39.5)	18 (43.9)	33 (41.8)
Dairy products intake			
Almost none	12 (30.8)	20 (48.4)	32 (40.0)
Usually/always[§]	27 (69.2)	21 (51.2)	48 (60.0)

[*] Sometimes/Usually defined as the individual's option was once per day, more than once per day, 1 − 3 times per week, 3 − 5 times per week, or 1 − 3 times per month.

[†] Estimated by multiplying the frequency of physical activity per week by the time spent exercising each time.

§ Usually/always defined as the individual's option was every day, 3 – 5 times per week, once per week, or 1 – 3 times per month.
SD: standard deviation; BMI: body mass index; NHL: non-Hodgkin lymphoma;
DLBCL: diffuse large B-cell lymphoma.

sometimes and usually were more predisposed to DLBCL (OR: 7.20; 95% CI: 1.88 – 27.51; p-value: 0.004). People who engaged in mild physical activity for more than 3.5 hours per week had a considerably lower incidence of DLBCL (OR: 0.27; 95% CI: 0.08 – 0.87; p-value: 0.028).

Certain variables had a suggestive (no significance) relationship to DLBCL. A positive correlation between household insecticide use and the risk of DLBCL was found (OR: 2.37; 95% CI: 0.88 – 6.40, p-value 0.089). Long-term incense burning exposure may raise the risk of DLBCL (OR: 2.52; 95% CI: 0.96 – 6.60, p-value 0.060). There was a negative correlation between exposure to sunlight and DLBCL risk. More than two hours of sun exposure per day was associated with a lower risk of DLBCL than those who had less than thirty minutes of sun exposure daily (OR: 0.29; 95% CI: 0.08 – 1.07; p-value: 0.063).

Other variables did not exhibit a significant association with DLBCL, such as smoking history, alcohol consumption, vigorous or moderate physical activity, BMI, family history of NHL, history of living or working on a farm, and dairy product intake.

Multivariable logistic regression analyses

During the multivariate analysis, the final model indicated that only household insecticide use (OR: 4.73; 95% CI: 1.30 – 17.14; p-value: 0.018), hepatitis viruses A, B, or C (OR: 7.89; 95% CI: 1.59 – 39.30; p-value: 0.012), and the use of plastic bags and containers to store hot food (OR: 8.18; 95% CI: 1.84 – 36.48; p-value: 0.006) were significantly associated with DLBCL. Variables, including incense burning, sun exposure, and dairy product con-

sumption, calculated with a p-value < 0.20 in a univariable analysis showed no significance in the multivariate analysis. A noteworthy finding from the univariate analysis was a substantial correlation (p-value: 0.028) between mild physical activity and the risk of DLBCL; however, the multivariate analysis did not support this finding.

Discussion

In our study, we found that individuals who often kept hot foods in plastic bags or containers were more predisposed to DLBCL. Plastic products include ingredients such as bisphenol A (BPA), polybrominated diphenyl ethers (PBDE), and phthalates, which are hazardous to human health.[21-27] A multicentric case-control study in European countries found that cumulative exposure to phthalates was related to an elevated risk of NHL, while no association was observed between BPA and DLBCL.[23,28] Another study in Denmark reported a positive association between phthalate exposure and the incidence of NHL.[29] Although research on cell lines has shown that BPA exposure may lead to lymphomagenesis, this finding has not been verified in animal experiments or actual patient samples.[30] To the best of our knowledge, no epidemiologic study has reported associations between hot foods stored in plastic bags or containers and the risk of DLBCL.

Our results suggest that household insecticide usage may have contributed to increasing the risk of DLBCL, which is consistent with the findings of previous studies. Koutros et al. reported that the use of malathion, a commonly used insecticide, significantly pre-

Table 2. Univariate and multivariate analysis on the DLBCL.

Factor	Univariate		Multivariate	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Smoking history				
No	Ref			
Yes	1.46 (0.57 – 3.71)	0.429		
Alcohol consumption				
No	Ref			
Yes	1.05 (0.33 – 3.30)	0.937		
Household insecticide				
Never	Ref		Ref	
Sometimes/Usually[#]	2.37 (0.88 – 6.40)	0.089	4.73 (1.30 – 17.14)	0.018[*]
Incense burning				
Never	Ref			
Sometimes/Usually[#]	2.52 (0.96 – 6.60)	0.060		
Hepatitis viruses positive (types A, B or C)				
No	Ref		Ref	
Yes	4.43 (1.27 – 15.47)	0.019[*]	7.89 (1.59 – 39.30)	0.012[*]
Hot foods stored in plastic bags and containers				
Never	Ref		Ref	
Sometimes/Usually[#]	7.20 (1.88 – 27.51)	0.004[*]	8.18 (1.84 – 36.48)	0.006[*]
Sun exposure (hours/day)				
≤ 0.5	Ref			
0.5 – 2	0.50 (0.13 – 1.91)	0.310		
> 2	0.29 (0.08 – 1.07)	0.063		
Vigorous physical activity (min/week)[†]				
< 75	Ref			
≥ 75	1.07 (0.20 – 5.70)	0.940		
Moderate physical activity (min/week)[†]				
< 150	Ref			
≥ 150	1.72 (0.38 – 7.88)	0.482		
Mild physical activity (min/week)[†]				
< 210	Ref			
≥ 210	0.27 (0.08 – 0.87)	0.028[*]		
BMI				
18.5 – 23.9	Ref			
24 – 26.9	0.53 (0.17 – 1.63)	0.268		
27 – 29.9	0.74 (0.20 – 2.70)	0.649		
30 – 35	0.85 (0.10 – 7.04)	0.877		
Family history of NHL				
No	Ref			
Yes	3.53 (0.35 – 35.52)	0.284		
Ever lived or worked on a farm				
No	Ref			
Yes	0.83 (0.34 – 2.04)	0.690		
Dairy product intake				
Almost none	Ref			
Usually/always[§]	2.14 (0.86 – 5.35)	0.103		

[#] Sometimes/Usually defined as the individual's option was once per day, more than once per day, 1 – 3 times per week, 3 – 5 times per week, or 1 – 3 times per month.
[†] Estimated by multiplying the frequency of physical activity per week by the time spent exercising each time.
[§] Usually/always defined as the individual's option was every day, 3 – 5 times per week, once per week, or 1 – 3 times per month.
[*] Statistically significant.
OR: odds ratio; CI: confidence interval; Ref: reference category; BMI: body mass index;
NHL: non-Hodgkin lymphoma.

disposed people to DLBCL. Other analyses have reported that organochlorine insecticides, including lindane and Dichloro-Diphenyl-Trichloroethane (DDT), also significantly predispose people to DLBCL.[31,32] Pyrethroids, such as cyphenothrin, metofluthrin, and prallethrin, are also common pesticide components. Although they are less toxic to humans, their artificial preparations frequently contain organic solvents, which can damage the human body. Several studies have found that organic solvents contribute to lymphomagenesis.[33-35]

We observed a strong association between hepatitis viruses and DLBCL risk, which is in line with the findings of previous studies. Wang et al. reported that patients with DLBCL had a significantly higher serum hepatitis B virus positivity rate than the general population.[36] A retrospective study conducted between 2012 and 2019 reported that HBsAg, anti-HBc IgG, HBeAg, anti-HBe, and hepatitis C virus seropositivity rates were higher in patients with DLBCL than in those with HL.[37] A case-control study using the Surveillance, Epidemiology, and End Results (SEER)-Medicare database in the US elderly population also demonstrated that hepatitis B virus was a significant risk factor for DLBCL with an odds ratio of 1.24 (95% CI: 1.06 – 1.46).[38]

We found evidence of a weak positive association between the risk of DLBCL and incense use. Several studies have reported that the use of household incense is associated with the incidence of specific illnesses, including lung cancer and asthma; however, these findings are not consistent.[39,40] Furthermore, burning incense is associated with leukemia. A study on childhood leukemia showed a significantly increased risk for children whose parents burned incense at home before pregnancy and during the nursing period.[41] However, no prior evidence indicated a relationship between incense and DLBCL risk.

Unexpectedly, there were no significant associations between DLBCL and the other variables investigated. Some studies have shown that other risk factors for DLBCL include the family of NHL, BMI, and alcohol consumption.[12,42] A population-based case-control study in Canada found that obesity increases DLBCL risk. Conversely, higher levels of recreational physical activity were associated with a reduced risk of DLBCL.[10] A pooled study from the International Lymphoma Epidemiology Consortium (InterLymph) indicated an increased DLBCL risk if the relative with NHL was a male; however, no significant risk for DLBCL was found in those with a female relative with NHL.[12] Another pooled analysis from InterLymph studies found that hepatitis C virus seropositivity, family history of NHL, and higher young adult BMI were associated with increased DLBCL risk, whereas more recreational sun exposure was associated with decreased risk.[42] In another study, total fat intake (a component of dairy products) was significantly associated with DLBCL.[43]

Limitations

Our study had certain limitations. First, the sample size was insufficient, as there were too few cases for the analysis of several other potential variables, including Sjögren's syndrome and the human immunodeficiency virus. Second, our findings may only apply to patients with less aggressive tumors or healthier individuals due to the bias of our data (individuals who were unable to participate include those whose conditions were rapidly deteriorating and those who refused to participate). Third, the recall bias, which is a prevalent and unavoidable bias in all case-control studies.

In summary, our hospital-based case-control study identified the use of household insecticides and the use of plastic bags or containers to store heated food as significant risk factors for DLBCL. Since these two lifestyle-related exposure variables are modifiable, the incidence of DLBCL could be reduced by interventions that reduce such exposures.

Supplementary Material

eQuestionnaire 1. Questionnaires: Lymphoma epidemiology and outcomes.

Author Contributions

Study Design, Yu-Chieh Su and Sheng-Fung Lin; Data Collection, Yu Chang, Wen-Tsung Huang, Szu-Chin Li, Erh-Jung Hsueh, and Yu-Chieh Su; Statistical Analysis, Hung-Ju Li; Data Interpretation, Hung-Ju Li, Hui-Ming Lee and Yu-Chieh Su; Manuscript Preparation and Literature Search, Hung-Ju Li and Hui-Ming Lee. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement

The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of Dalin Tzu Chi Hospital (protocol code B10504014-1), E-Da Hospital (protocol code EMRP-105-046), Liouying Chi Mei Hospital (protocol code 10512-L03), and Pingtung Christian Hospital (protocol code IRB541B).

Informed Consent Statement

Not applicable.

Data Availability Statement

Reasonable requests for data will be considered by the corresponding author.

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Conflicts of Interest

The authors declare no conflict of interest.

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