

CASE-CONTROL STUDIES OF ACUTE MYELOID LEUKEMIA AND NON-HODGKIN LYMPHOID NEOPLASMS IN SHANGHAI: ENVIRONMENTAL AND OCCUPATIONAL RISK FACTORS BY SUBTYPES OF THE WHO CLASSIFICATION

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The case-control studies are part of the research projects of the China-US collaborative Shanghai Health Study (SHS).

Organizations participating in or contributing data to SHS:

- Fudan University, Shanghai,
- Shanghai Center for Disease Control & Prevention (CDCP),
- Shanghai Municipal Institute of Public Health Supervision (IPHS),
- Shanghai District Institutes of Public Health Supervision,
- University of Colorado,
- Applied Health Sciences,
- ExxonMobil Biomedical Sciences, and
- 29 hospitals in metropolitan Shanghai.

Objectives of the case-control studies

- To investigate potential environmental and occupational risk factors of acute myeloid leukemia (AML) and non-Hodgkin lymphoid neoplasms (NHLN*), and
- To explore the relationships between risk factors and AML or NHLN subtypes according to the 2001 World Health Organization (WHO) classification of neoplasms of the hematopoietic and lymphoid tissue.

* NHLN = all lymphoid neoplasms excluding Hodgkin lymphoma.

Epidemiologic study design

- Retrospective case-control (“trohoc”) studies based on hospital patients.
- Cases: patients aged 18 or older diagnosed with AML or NHLN according to WHO classification.
- Controls: 2 patients individually matched with gender and age at the same hospital (patients with lymphatic and hematopoietic diseases excluded).
- Patient enrollment:
 - AML (August 2003-June 2007 at 29 hospitals), and
 - NHLN (August 2003-January 2008 at 25 hospitals).

Enrollment of cases and controls

- Patients with a preliminary diagnosis of AML or NHLN were identified by clinical coordinators at participating hospitals.
- Biological samples (peripheral blood, bone marrow aspirates, tissue and core biopsies) were collected by the hospitals and sent to the Joint Sino-US Clinical and Molecular Laboratory (JCML) at Fudan University.
- Confirmation of diagnosis by JCML.
- Selection of controls by clinical coordinators.
- Interview of case and controls by interviewers from Fudan University.

Patient interviews and questionnaires

- Brief explanation of study to patients, but no mention of study hypothesis.
- Reassurance of privacy and security of data.
- Written informed consent.
- A 17-page structured primary questionnaire: demographics, medical & family history, lifestyle, employment history, residential history, environmental & occupational exposures.
- Second occupation-specific questionnaires (selected occupations): detailed information of jobs/tasks, materials used, and work environment.
- Interviewers were not told of the case/control status.

Classification of occupations and industries and exposure assessment

- Occupations and industries reported by patients were classified according to the official Chinese standard classification systems.
- Exposure assessment based on individual jobs was performed by a committee of local experts in Shanghai, with periodic reviews by a US-based industrial hygienist (both blinded with respect to case/control status).
- Sources for exposure data included: CDCP historical exposure database (50,000+ measurements since 1950s), data at District IPHS, data at factories, *ad hoc* walk-through surveys and measurements, and Chinese medical literature.

Data analysis

- To assess risk of individual factors, conditional logistic regression models taking matching into account were employed to calculate odds ratios (ORs) and 95% confidence intervals (95%CI).
- Multivariate models were used to adjust for potential confounding exposures, using the “noitanimile” procedure (at $p=0.20$, except for benzene).

Data analysis

Benzene exposure groups (EG) & exposure group scores (EGS)

- EG0: EGS=0 (non-exposed)
- EG1: EGS=1 (<1 mg/m³)
- EG2: EGS=2 (1-10 mg/m³)
- EG3: EGS=3 (10-100 mg/mg³)
- EG4: EGS=4 (100+ mg/m³)

Demographic and personal variables of AML cases and controls

Variable	AMLcases		Controls	
Number	722	100.00%	1444	100.00%
Male	406	56.23%	812	56.23%
Female	316	43.77%	632	43.77%
Mean age (SD) in years	49.92	(16.85)	49.98	(16.49)
Marital status - married	605	83.80%	1204	83.38%
Education - None	57	7.89%	60	4.16%
Primary school	137	18.98%	199	13.78%
Middle school	227	31.44%	448	31.02%
High school	183	25.35%	393	27.22%
University or higher	115	15.93%	340	23.55%
Smokers (ever)	277	38.37%	508	35.18%
Body mass index (SD)	22.6	(3.3)	23.1	(3.7)

Distribution of AML cases by subtypes of WHO classification

Category	Number	Percent
AML- total	722	100.00%
AML with current cytogenetic abnormalities (AML-RCA)	244	33.80%
AML with t(8;21)(q22;q22),(AML1/ETO)	64	8.86%
AML with inv(16)(p13q22) or t(16;16)(p13;q22),(CBE β /MYH11)	23	3.19%
Acute promyelocytic leukemia (APL)	124	17.17%
AML with 11q23 (MLL) abnormalities	33	4.57%
AML with multilineage dysplasia, with or without prior MDS (AML-MD)	186	25.76%
AML and MDS, therapy related	5	0.69%
AML not otherwise categorized (AML-noc)	269	37.26%
AML, minimally differentiated	26	3.60%
AML without maturation	64	8.86%
AML with maturation	48	6.65%
Acute myelomonocytic leukemia	60	8.31%
Acute monoblastic and monocytic leukemia	42	5.82%
Acute erythroid leukemia	19	2.63%

Summary of personal and lifestyle risk factors of AML by WHO subtypes

AML WHO subtype	Education	BMI	Blood transfusions	Chinese medicines	Smoking	Alcohol	Hair dyes
AML-total	⇓	⇓	↑	⇓	↑	⇑	~
AML-RCA	⇓	~	~	~	~	~	~
APL	~	⇑	~	~	~	~	~
AML-MD	⇓	~	~	↓	~	~	~
AML-noc	⇓	⇓	~	~	~	⇑	~

↑ (⇓) = significant increase (decrease); ↑ (↓) = borderline significant increase (decrease); ~ = no pattern.

Summary of environmental risk factors of AML by WHO subtypes

AML WHO subtype	Home renovation	Living near power lines	Living on a farm	Planting crops	Raising livestock
AML-total	↑	~	↑↑	↑↑	↑↑
AML-RCA	↑↑	~	↑↑	↑↑	~
APL	↑↑	~	↑	~	~
AML-MD	~	↑↑	↑↑	↑↑	↑↑
AML-noc	~	~	↑↑	↑↑	~

↑ (↓) = significant increase (decrease); ↑ (↓) = borderline significant increase (decrease); ~ = no pattern.

ORs (95%CI) of selected occupations by AML subtypes

AML WHO subtype	Farm workers	Metal workers	Rubber and plastic workers	Loading and unloading workers
AML-total	1.61 (1.27-2.03)	1.52 (0.87-2.66)	2.50 (0.99-6.33)	2.11 (1.22-3.64)
AML-RCA	1.53 (1.02-2.29)	2.86 (1.09-7.51)	5.99 (0.62-57.52)	3.00 (1.07-8.43)
APL	1.22 (0.69-2.15)	14.00 (1.72-113.77)	---	2.67 (0.60-11.91)
AML-MD	1.86 (1.19-2.91)	0.73 (0.18-2.91)	---	1.71 (0.58-5.10)
AML-noc	1.56 (1.07-2.29)	1.22 (0.51-2.90)	4.67 (1.21-18.05)	1.74 (0.76-3.96)

ORs (95%CI) of selected occupations by AML subtypes

AML WHO subtype	Chemical workers	Leather workers	Printers and related workers	Painters
AML-total	0.75 (0.29-1.92)	1.80 (0.73-4.43)	3.20 (1.05-9.77)	1.93 (0.98-3.79)
AML-RCA	0.80 (0.16-4.12)	1.20 (0.29-5.02)	3.00 (0.50-17.93)	2.80 (0.89-8.81)
APL	0.67 (0.07-6.41)	0.67 (0.07-6.41)	2.00 (0.13-31.97)	2.00 (0.58-6.91)
AML-MD	0.50 (0.06-4.47)	2.67 (0.60-11.91)	2.00 (0.40-9.91)	1.50 (0.34-6.70)
AML-noc	0.86 (0.22-3.32)	2.00 (0.28-14.20)	---	1.61 (0.58-4.49)

ORs (95%CI) of selected industries by AML subtypes

AML WHO subtype	Agriculture	Shoe manufacture	Metal milling and processing	Food and beverage industry
AML-total	1.57 (1.24-1.97)	1.75 (0.64-4.83)	1.40 (0.88-2.25)	1.61 (1.02-2.56)
AML-RCA	1.55 (1.04-2.32)	1.00 (0.18-5.46)	2.60 (1.14-5.93)	2.62 (1.24-5.53)
APL	1.21 (0.69-2.12)	---	2.33 (0.78-6.94)	2.11 (0.76-5.89)
AML-MD	1.77 (1.13-2.78)	8.00 (0.89-71.56)	0.75 (0.25-2.21)	1.18 (0.45-3.07)
AML-noc	1.54 (1.06-2.24)	0.67 (0.07-6.41)	1.22 (0.58-2.55)	1.13 (0.50-2.55)

ORs (95%CI) of selected exposures by AML subtypes

AML WHO subtype	Solvents	Benzene	Toluene	Xylene
AML-total	1.50 (0.95-2.71)	1.43 (1.05-1.93)	2.00 (0.79-5.04)	1.44 (0.71-2.95)
AML-RCA	2.50 (0.99-6.33)	1.61 (1.00-2.61)	3.33 (0.80-13.95)	2.00 (0.58-6.91)
APL	1.67 (0.51-5.46)	1.95 (0.98-3.88)	1.33 (0.22-7.98)	1.00 (0.18-5.46)
AML-MD	1.65 (0.63-4.32)	1.16 (0.60-2.24)	2.00 (0.28-14.20)	2.00 (0.40-9.91)
AML-noc	0.79 (0.30-2.08)	1.38 (0.83-2.28)	0.50 (0.06-4.47)	0.80 (0.25-2.55)

ORs (95%CI) of selected exposures by AML subtypes

AML WHO subtype	Petroleum fuels	Gasoline	Kerosene	Diesel
AML-total	1.16 (0.85-1.59)	1.07 (0.72-1.61)	0.94 (0.39-2.25)	1.23 (0.81-1.89)
AML-RCA	1.16 (0.69-1.95)	0.91 (0.76-2.07)	1.14 (0.34-3.90)	0.83 (0.36-1.96)
APL	1.17 (0.55-2.49)	1.07 (0.44-2.64)	2.00 (0.28-14.20)	0.79 (0.24-2.61)
AML-MD	0.92 (0.44-1.88)	1.09 (0.41-2.87)	0.40 (0.05-3.42)	0.75 (0.29-1.92)
AML-noc	1.35 (0.83-2.20)	1.31 (0.68-2.51)	1.28 (0.24-6.99)	1.92 (1.03-3.57)

ORs (95%CI) of selected exposures by AML subtypes

AML WHO subtype	Paints and coatings	Paint thinners	Glues and adhesives	Inks and pigments
AML-total	1.71 (0.93-3.16)	2.00 (0.79-5.04)	3.96 (2.13-7.35)	3.50 (1.47-8.34)
AML-RCA	3.12 (1.12-8.65)	3.33 (0.80-13.95)	2.44 (0.97-6.15)	2.67 (0.60-11.91)
APL	2.94 (0.95-9.10)	2.67 (0.60-11.91)	1.40 (0.46-4.30)	---
AML-MD	1.20 (0.29-5.02)	1.50 (0.34-6.70)	3.50 (1.03-11.96)	3.33 (0.80-13.95)
AML-noc	1.18 (0.45-3.07)	1.00 (0.09-11.03)	8.67 (2.47-30.41)	5.00 (0.97-25.77)

ORs (95%CI) of selected exposures by AML subtypes

AML WHO subtype	Insecticides	Herbicides	Fertilizers	Metals at smelters and steel mills
AML-total	1.53 (1.16-2.04)	1.83 (0.99-3.38)	1.64 (1.23-2.19)	2.19 (1.09-4.39)
AML-RCA	1.44 (0.88-2.35)	1.94 (0.63-5.92)	1.61 (0.95-2.73)	4.67 (1.21-18.05)
APL	1.26 (0.65-2.44)	---	1.41 (0.70-2.82)	3.33 (0.80-13.95)
AML-MD	1.39 (0.80-2.43)	2.68 (0.74-9.68)	1.34 (0.79-2.27)	1.20 (0.29-5.02)
AML-noc	1.75 (1.11-2.78)	1.46 (0.59-3.62)	1.89 (1.17-3.03)	1.83 (0.63-5.29)

Multivariate analysis for AML subtypes

Because many individuals were exposed to multiple risk factors, multivariate logistic regression models were used to adjust for confounding factors.

Variables included in the multivariate models are:

Low-level education	Solvents
Traditional Chinese medicines	Benzene
Alcohol	Toluene
	Xylene
Home renovation	Petroleum fuels
Living on a farm	Gasoline
Planting crops	Kerosene
Raising livestock	Insecticides
	Herbicides
Farm workers	Fertilizers
Agricultural industry	Glues and adhesives
Metal milling and processing	Inks and pigments

ORs (95%CI) of variables remaining in multivariate models by AML subtypes

AML WHO subtype	Low –level education	Traditional Chinese medicines	Alcohol
AML-total	1.57 (1.19-2.08)	0.68 (0.45-1.02)	1.29 (0.97-1.73)
AML-RCA	1.65 (0.97-2.80)	✂	✂
AML with t(8;21)	✂	✂	✂
APL	1.78 (0.85-3.74)	✂	✂
AML-MD	2.01 (1.20-3.39)	0.42 (0.18-0.99)	✂
AML-noc	1.64 (1.03-2.60)	2.00 (1.19-3.35)	1.55 (1.07-2.23)

✂ = variables did not make the “cut” (i.e., eliminated from the multivariate model [p>20]).

ORs (95%CI) of variables remaining in multivariate models byAMLsubtypes

AML WHO subtype	Home renovation	Living on a farm	Raising livestock
AML-total	1.29 (0.95-1.76)	1.47 (1.18-1.85)	1.36 (0.92-2.10)
AML-RCA	1.91 (1.18-3.09)	1.63 (1.13-2.36)	✂
AML with t(8;21)	✂	✂	4.02 (0.76-21.22)
APL	2.01 (1.01-4.00)	1.58 (0.95-2.62)	✂
AML-MD	✂	1.64 (1.01-2.67)	2.32 (1.07-5.03)
AML-noc	✂	✂	✂

ORs (95%CI) of variables remaining in multivariate models byAMLsubtypes

AML WHO subtype	Benzene	Solvents	Toluene
AML-total	1.20 (0.84-1.71)		
AML-RCA	1.37 (0.76-2.50)	2.34 (0.76-7.18)	
AML with t(8;21)	4.26 (1.01-17.96)		
APL	1.85 (0.87-3.94)		
AML-MD	0.95 (0.45-1.98)		
AML-noc	0.99 (0.51-1.94)		0.17 (0.01-2.24)

ORs (95%CI) of variables remaining in multivariate models byAMLsubtypes

AML WHO subtype	Glues and adhesives	Inks and pigments	Insecticides
AML-total	2.76 (1.40-5.460)	2.39 (0.96-5.98)	✂
AML-RCA	✂	✂	✂
AML with t(8;21)	✂	✂	0.18 (0.02-1.39)
APL	✂	✂	✂
AML-MD	✂	2.89 (0.60-13.78)	0.55 (0.27-1.13)
AML-noc	7.67 (1.91-21.48)	3.86 (0.69-21.48)	✂

ORs (95%CI) by benzene exposure variables andAMLsubtypes

WHO subtype	AML-total			AML-RCA		
Benzene exposure variable	OR (95%CI)	Ca	Co	OR (95%CI)	Ca	Co
Ever/never	1.43 (1.05-1.93)	78	113	1.61 (1.00-2.61)	33	43
Length of exposed jobs	1.00 (0.98-1.02)	78	113	1.00 (0.97-1.03)	33	43
Non-exposed	1.00 (reference)	644	1331	1.00 (reference)	211	445
≤10 years	1.99(1.29-3.07)	43	45	2.70 (1.42-5.14)	23	18
>10 to ≤20 years	1.44 (0.82-2.51)	21	30	1.01 (0.38-2.67)	6	13
>20 years	0.74 (0.39-1.39)	14	38	0.71 (0.23-2.22)	4	12
	P-trend=0.84			P-trend=0.89		
Maximum exposure (EGS)	1.25 (1.06-1.46)	78	113	1.36 (1.03-1.80)	33	43
Non-exposed	1.00 (reference)	644	1331	1.00 (reference)	211	445
EGS1	1.18 (0.79-1.76)	40	70	1.55 (0.86-2.79)	21	28
EGS2	1.63 (0.90-2.94)	20	25	1.05 (0.39-2.82)	6	12
EGS3&4	2.05 (1.05-3.98)	18	18	4.00 (1.00-15.99)	6	3
	P-trend=0.01			P-trend=0.03		
Decades of first exposure						
Non-exposed	1.00 (reference)	644	1331	1.00 (reference)	211	445
1940-1959	1.33 (0.54-3.26)	8	12	2.97 (0.50-17.80)	3	2
1960-1979	0.97 (0.57-1.62)	22	46	0.90 (0.37-2.19)	7	16
1980-1999	1.57 (1.00-2.46)	36	49	1.44 (0.70-2.94)	14	22
2000-	4.18 (1.56-11.15)	12	6	6.31 (1.79-23.46)	9	3
Cumulative EGS-years	1.01 (0.99-1.02)	78	113	1.01 (0.99-1.03)	33	43
	P-trend=0.38			P-trend=0.56		

ORs (95%CI) by benzene exposure variables and AML subtypes

WHO subtype	AML with t(8;21)(q22;q22)			APL		
Benzene exposure variable	OR (95%CI)	Ca	Co	OR (95%CI)	Ca	Co
Ever/never	1.26 (0.56-2.83)	10	16	1.95 (0.98-3.88)	18	20
Length of exposed jobs	0.97 (0.90-1.04)	10	16	1.01 (0.97-1.05)	18	20
Non-exposed	1.00 (reference)	54	112	1.00 (reference)	106	228
≤10 years	2.17 (0.83-5.63)	9	8	5.77 (1.86-17.92)	13	6
>10 to ≤20 years	---	0	4	0.89 (0.23-3.42)	3	8
>20 years	0.50 (0.06-4.47)	1	4	0.67 (0.14-3.3)	2	6
	P-trend=0.33			P-trend=0.79		
Maximum exposure (EGS)	1.36 (0.85-2.17)	10	16	1.29 (0.88-1.89)	16	20
Non-exposed	1.00 (reference)	54	112	1.00 (reference)	106	228
EGS1	1.00 (0.37-2.74)	6	12	2.68 (1.14-6.34)	13	10
EGS2	1.00 (0.37-2.74)	2	4	0.69 (0.14-3.36)	2	7
EGS3&4	---	2	0	2.00 (0.40-9.91)	3	3
	P-trend=0.20			P-trend=0.20		
Decades of first exposure						
Non-exposed	1.00 (reference)	54	112	1.00 (reference)	106	228
1940-1959	2.00 (0.50-17.80)	1	1	---	2	0
1960-1979	---	0	7	1.14 (0.34-3.90)	4	7
1980-1999	0.97 (0.25-3.81)	3	7	1.79 (0.69-4.61)	9	12
2000-	11.97 (1.44-99.64)	6	1	7.13 (0.72-70.61)	3	1
Cumulative EGS-years	1.01 (0.93-1.09)	10	16	1.00 (0.98-1.03)	18	20
	P-trend=0.85			P-trend=0.85		

ORs (95%CI) by benzene exposure variables andAMLsubtypes

WHO subtype	AML-MD			AML-noc		
Benzene exposure variable	OR (95%CI)	Ca	Co	OR (95%CI)	Ca	Co
Ever/never	1.16 (0.60-2.24)	16	28	1.38 (0.83-2.28)	27	40
Length of exposed jobs	0.99 (0.95-1.03)	16	28	1.00 (0.98-1.03)	27	40
Non-exposed	1.00 (reference)	170	344	1.00 (reference)	242	498
≤10 years	1.56 (0.64-3.81)	9	12	1.35 (0.60-3.06)	10	15
>10 to ≤20 years	1.95 (0.63-6.09)	6	6	2.00 (0.79-5.04)	9	9
>20 years	0.16 (0.02-1.39)	1	10	1.02 (0.42-2.47)	8	16
	P-trend=0.59			P-trend=0.95		
Maximum exposure (EGS)	1.22 (0.89-1.67)	16	28	1.17 (0.91-1.50)	27	40
Non-exposed	1.00 (reference)	170	344	1.00 (reference)	242	498
EGS1	0.58 (0.21-1.65)	5	17	1.08 (0.53-2.19)	12	23
EGS2	1.56 (0.47-5.15)	5	6	2.58 (0.96-6.94)	9	7
EGS3&4	2.40 (0.73-7.86)	6	5	1.22 (0.43-3.47)	6	10
	P-trend=0.22			P-trend=0.22		
Decades of first exposure						
Non-exposed	1.00 (reference)	170	344	1.00 (reference)	242	498
1940-1959	---	0	4	1.69 (0.51-5.53)	5	6
1960-1979	0.66 (0.23-1.92)	5	14	1.28 (0.57-2.87)	10	16
1980-1999	3.23 (1.18-8.87)	11	8	1.07 (0.47-2.43)	9	17
2000-	---	0	2	5.99 (0.62-57.52)	3	1
Cumulative EGS-years	1.01 (0.98-1.03)	16	28	1.00 (0.99-1.02)	27	40
	P-trend=0.65			P-trend=0.60		

Discussion of AML findings

- Low-level education:
Often as a surrogate measure for socioeconomic class.
Independent risk factor regardless of occupation in our study (e.g., farm workers).
- Traditional Chinese medicines:
Reduced risk of AML-MD (reduced use of western medicines such as antibiotics?).
Increased risk of AML-noc (especially AML without maturation).
- Home renovations:
Similar increases in risk of leukemia reported in previous studies in China.
Elevated levels of formaldehyde, benzene, toluene, xylene & VOCs in renovated homes.
- Living on a farm:
Consistent with increased risk reported in previous studies in China and US.
Independent risk factor (regardless of being employed as farm workers or not).

Discussion of AML and benzene findings

- AML-total:

Significant risk based on univariate analysis, but reduced risk in multivariate analysis.

A similar finding reported in a previous case-control study of leukemia in Shanghai; OR=2.00 ($p<0.05$) reduced to 1.58 ($p>0.05$) in multivariate analysis (Lim 1991).

- AML with t(8;21)(q22;q22):

A 15-fold increase of t(8;21) levels in 22 benzene-exposed workers in Shanghai (Smith 1998), but no workers positive with t(8;21) in a second study in Tianjin (McHale 2008).

OR=1.58 ($p<0.05$) for FAB M2 in a nationwide Chinese study (Yang 1992).

OR=4.77 ($p<0.05$) for AML with t(8;21) in smokers (benzene?) in UK (Moorman 2002).

- Exposure variables with respect to AML-total and AML-RCA:

Elevated ORs for exposure <10 years, high exposure categories EGS3 & 4, and first exposure in or after 2000.

Risk not related to cumulative EGS-years.

Demographic and personal variables of NHLN cases and controls

Variable	NHLN 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 (SD) in years	52.5	(16.5)	52.7	(15.9)
Marital status - married	546	84.13%	1088	83.82%
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%
Smokers (ever)	272	41.91%	537	41.37%
Body mass index (SD)	22.6	(3.48)	22.8	(3.37)

Distribution of NHLN cases by subtypes of WHO classification

Category	Number	Percent
NHLN-total (all subtypes)	649	100.00%
B-cell neoplasms (all)	521	80.28%
Precursor B-cell neoplasms	134	20.65%
Mature B-cell neoplasms	387	59.63%
Chronic lymphocytic leukemia (CLL)	30	4.62%
Small lymphocytic lymphoma (SLL)	37	5.70%
Plasma cell myeloma	21	3.24%
Follicular lymphoma (FL)	45	6.93%
Diffuse large B-cell lymphoma (DLBCL)	186	28.66%
T- and NK-cell neoplasms (all)	118	18.18%
Precursor T-cell neoplasms	31	4.78%
Mature T-cell & NK-cell neoplasms	87	13.41%

Summary of personal and lifestyle risk factors of NHLN by WHO subtypes

NHLN WHO subtype	Education	BMI	Blood transfusions	Chinese medicines	Smoking	Alcohol	Hair dyes
NHLN-total	⇓	~	~	⇓	~	~	~
B-cell (all)	⇓	~	~	⇓	~	~	~
Precursor B-cell	⇓	~	~	~	~	~	~
Mature B-cell	⇓	~	~	↙	~	~	~
CLL/SLL	~	~	~	~	~	~	~
FL	~	~	~	~	~	~	~
DLBCL	⇓	~	~	⇓	~	~	~
T/NK-cell	⇓	~	~	~	~	~	~

↑ (↓) = significant increase (decrease); ↑ (↓) = borderline significant increase (decrease); ~ = no pattern.

Summary of environmental risk factors of NHLN by WHO subtypes

NHLN WHO subtype	Home renovation	Living near power lines	Living on a farm	Planting crops	Raising livestock
NHLN-total	↑↑	~	↑↑	↑↑	↑↑
B-cell (all)	↑↑	~	↑↑	↑↑	↑↑
Precursor B-cell	~	~	↑↑	↑	↑
Mature B-cell	↑↑	~	↑↑	↑↑	↑↑
CLL/SLL	~	~	~	~	~
FL	~	~	~	~	~
DLBCL	↑↑	~	↑↑	↑↑	↑↑
T/NK-cell	~	~	~	~	~

↑ (↓) = significant increase (decrease); ↑ (↓) = borderline significant increase (decrease); ~ = no pattern.

ORs (95%CI) of selected occupations by NHLN subtypes

NHLN WHO subtype	Teachers	Farm workers	Metal workers	Fabric sewing/ cutting workers
NHLN-total	0.72 (0.48-1.08)	1.43 (1.14-1.78)	0.75 (0.39-1.46)	3.89 (1.95-7.76)
B-cell neoplasms (all)	0.66 (0.42-1.03)	1.52 (1.19-1.96)	0.64 (0.29-1.42)	3.87 (1.81-8.25)
Precursor B-cell neoplasms	0.93 (0.37-2.33)	1.50 (0.89-2.25)	0.75 (0.20-2.83)	10.29 (2.77-46.66)
Mature B-cell neoplasms	0.60 (0.36-1.00)	1.53 (1.15-2.04)	0.59 (0.22-1.60)	2.29 (0.90-5.81)
CLL & SLL	0.72 (0.23-2.27)	0.83 (0.40-1.74)	0.40 (0.05-3.42)	4.00 (0.36-44.11)
FL	0.89 (0.27-2.89)	1.18 (0.53-2.50)	---	0.67 (0.07-6.41)
DLBCL	0.38 (0.16-0.94)	1.85 (1.24-2.76)	0.80 (0.16-4.12)	5.62 (1.14-27.75)
T/NK-cell neoplasms	1.00 (0.38-2.66)	0.88 (0.50-1.50)	1.14 (0.34-3.90)	8.00 (0.89-71.56)

ORs (95%CI) of selected occupations by NHLN subtypes

NHLN WHO subtype	Chemical workers	Leather workers	Painters	Product testing workers
NHLN-total	1.60 (0.63-4.05)	1.67 (0.51-5.46)	0.60 (0.19-1.89)	1.54 (0.94-2.50)
B-cell neoplasms (all)	1.75 (0.64-4.83)	1.33 (0.38-4.73)	0.88 (0.26-2.99)	1.89 (1.11-3.21)
Precursor B-cell neoplasms	8.00 (0.89-71.56)	0.67 (0.07-6.41)	4.00 (0.36-44.11)	1.25 (0.41-3.82)
Mature B-cell neoplasms	0.86 (0.22-3.32)	2.00 (0.40-9.91)	0.47 (0.09-2.35)	2.14 (1.17-3.93)
CLL & SLL	---	---	4.00 (0.36-44.11)	0.80 (0.16-4.12)
FL	---	---	---	10.00 (1.17-85.58)
DLBCL	0.80 (0.16-4.12)	2.00 (0.28-14.20)	---	1.75 (0.64-4.83)
T/NK-cell neoplasms	1.00 (0.09-11.03)	---	---	0.57 (0.12-2.75)

ORs (95%CI) of selected industries by NHLN subtypes

NHLN WHO subtype	Agriculture	Garment	Leather & leather goods	Organic chemicals
NHLN-total	1.48 (1.18-1.85)	1.73 (1.01-2.97)	1.20 (0.44-3.30)	0.68 (0.35-1.32)
B-cell neoplasms (all)	1.54 (1.21-1.98)	1.65 (0.90-3.07)	1.33 (0.48-3.75)	0.68 (0.31-1.48)
Precursor B-cell neoplasms	1.49 (0.89-2.50)	1.55 (0.51-4.69)	1.33 (0.22-7.98)	1.00 (0.09-11.03)
Mature B-cell neoplasms	1.56 (1.18-2.07)	1.71 (0.82-3.58)	1.33 (0.38-4.73)	0.65 (0.29-1.48)
CLL & SLL	0.88 (0.43-1.79)	1.00 (0.18-5.46)	---	---
FL	1.26 (0.56-2.85)	0.77 (0.13-4.48)	---	---
DLBCL	1.99 (1.33-2.98)	2.55 (0.80-8.14)	1.50 (0.34-6.70)	0.31 (0.07-1.44)
T/NK-cell neoplasms	1.03 (0.59-1.78)	3.00 (0.85-10.63)	---	0.75 (0.20-2.83)

ORs (95%CI) of selected exposures by NHLN subtypes

NHLN WHO subtype	Solvents	Benzene	Toluene	Xylene
NHLN-total	1.15 (0.62-2.14)	1.06 (0.74-1.51)	1.00 (0.30-3.32)	1.08 (0.43-3.32)
B-cell neoplasms (all)	1.22 (0.63-2.37)	1.16 (0.77-1.73)	1.33 (0.38-4.73)	1.20 (0.44-3.30)
Precursor B-cell neoplasms	12.00 (1.45-99.67)	1.57 (0.63-3.94)	---	---
Mature B-cell neoplasms	0.73 (0.32-1.63)	1.07 (0.68-1.69)	0.33 (0.04-2.77)	0.80 (0.25-2.55)
CLL & SLL	1.20 (0.29-5.02)	2.05 (0.79-5.32)	2.00 (0.13-31.97)	1.33 (0.27-7.98)
FL	4.00 (0.36-44.11)	7.00 (1.45-33.70)	---	---
DLBCL	0.36 (0.08-1.64)	0.66 (0.31-1.42)	---	0.50 (0.06-4.47)
T/NK-cell neoplasms	0.77 (0.13-4.48)	0.55 (0.23-1.33)	---	0.67 (0.07-6.41)

ORs (95%CI) of selected exposures by NHLN subtypes

NHLN WHO subtype	Petroleum fuels	Gasoline	Kerosene	Diesel
NHLN-total	1.15 (0.80-1.64)	1.28 (0.83-1.96)	0.57 (0.19-1.74)	1.11 (0.68-1.82)
B-cell neoplasms (all)	1.06 (0.70-1.60)	1.25 (0.76-2.07)	0.62 (0.20-1.89)	1.09 (0.61-1.95)
Precursor B-cell neoplasms	1.32 (0.50-3.16)	1.12 (0.36-3.49)	---	1.00 (0.29-3.50)
Mature B-cell neoplasms	1.00 (0.63-1.60)	1.29 (0.73-2.26)	0.46 (0.13-1.62)	1.12 (0.56-21.60)
CLL & SLL	1.71 (0.63-1.60)	1.34 (0.37-2.26)	1.00 (0.09-11.03)	1.77 (0.50-6.24)
FL	6.61 (1.37-31.76)	[6 cases vs. 0 control]	---	1.62 (0.31-8.40)
DLBCL	0.67 (0.31-1.48)	0.76 (0.31-1.89)	---	0.50 (0.11-2.36)
T/NK-cell neoplasms	1.23 (0.57-2.65)	1.07 (0.45-2.57)	---	1.17 (0.46-2.96)

ORs (95%CI) of selected exposures by NHLN subtypes

NHLN WHO subtype	Paints and coatings	Paint thinners	Glues and adhesives	Inks and pigments
NHLN-total	0.79 (0.35-1.83)	0.91 (0.32-2.62)	2.11 (1.11-4.40)	2.00 (0.50-8.00)
B-cell neoplasms (all)	0.93 (0.38-2.29)	1.00 (0.34-2.93)	2.47 (1.08-5.67)	2.00 (0.40-9.91)
Precursor B-cell neoplasms	2.67 (0.60-11.91)	2.00 (0.13-31.97)	6.61 (0.72-60.86)	---
Mature B-cell neoplasms	0.50 (0.14-1.77)	0.89 (0.27-2.89)	2.00 (0.79-5.04)	1.33 (0.22-7.98)
CLL & SLL	1.00 (0.18-5.46)	4.00 (0.36-44.11)	2.00 (0.13-31.97)	2.00 (0.13-31.97)
FL	2.00 (0.13-31.97)	4.00 (0.36-44.11)	2.00 (0.13-31.97)	---
DLBCL	---	--	3.50 (1.03-11.96)	---
T/NK-cell neoplasms	---	---	1.55 (0.43-5.58)	2.00 (0.13-31.97)

ORs (95%CI) of selected exposures by NHLN subtypes

NHLN WHO subtype	Insecticides	Herbicides	Fertilizers
NHLN-total	1.59 (1.22-2.07)	1.77 (1.02-3.05)	1.53 (1.17-2.00)
B-cell neoplasms (all)	1.66 (1.39-2.49)	1.98 (1.05-3.73)	1.68 (1.25-2.27)
Precursor B-cell neoplasms	1.96 (1.04-3.68)	0.57 (0.12-2.75)	1.62 (0.83-3.17)
Mature B-cell neoplasms	1.83 (1.32-2.55)	2.79 (1.33-5.82)	1.70 (1.22-2.37)
CLL & SLL	1.76 (0.76-4.08)	---	1.51 (0.63-3.64)
FL	1.64 (0.62-4.34)	---	0.84 (0.30-2.34)
DLBCL	2.20 (1.28-3.19)	3.00 (1.07-8.43)	1.97 (1.27-3.06)
T/ NK-cell neoplasms	0.57 (0.27-1.19)	1.00 (0.30-3.32)	0.74 (0.36-1.51)

Multivariate analysis for NHLN subtypes

Because many individuals were exposed to multiple risk factors, multivariate logistic regression models were used to adjust for confounding factors.

Variables included in the multivariate models are:

Low-level education	Solvents
Traditional Chinese medicines	Benzene
Alcohol	Toluene
	Xylene
Home renovation	Petroleum fuels
Living on a farm	Gasoline
Planting crops	Kerosene
Raising livestock	Insecticides
	Herbicides
Farm workers	Fertilizers
Fabric sewing/cutting workers	Glues and adhesives
Agricultural industry	Inks and pigments

ORs (95%CI) of variables remaining in multivariate models by NHLNsubtypes

NHLN WHO subtype	Traditional Chinese medicines	Home renovation	Living on a farm
NHLN-total	0.55 (0.35-0.85)	1.46 (1.05-2.05)	1.29 (1.01-1.65)
B-cell neoplasms (all)	0.59 (0.36-0.97)	1.16 (1.08-2.30)	1.26 (0.96-1.65)
Precursor B-cell neoplasms	✂	✂	✂
Mature B-cell neoplasms	0.66 (0.38-1.14)	1.86 (1.23-2.80)	✂
CLL & SLL	2.75 (0.82-9.24)	1.96 (0.74-5.17)	✂
FL	✂	✂	✂
DLBCL	0.24 (0.08-0.70)	1.91 (1.06-3.44)	✂
T/ NK-cell neoplasms	0.38 (0.11-1.27)	✂	1.47 (0.84-2.60)

ORs (95%CI) of variables remaining in multivariate models by NHLNsubtypes

NHLN WHO subtype	Fabric sewing/ cutting workers	Agricultural industry	Insecticides
NHLN-total	2.33 (1.19-4.56)		1.39 (0.94-1.79)
B-cell neoplasms (all)	3.98 (1.78-8.92)		1.69 (0.97-4.70)
Precursor B-cell neoplasms	24.59 (2.97-204.02)		2.13 (0.97-4.70)
Mature B-cell neoplasms	2.19 (0.84-5.71)		1.66 (1.15-2.39)
CLL & SLL	6.41 (0.55-75.22)	0.41 (0.12-1.36)	2.97 (0.73-12.09)
FL			
DLBCL	5.48 (1.05-28.44)	5.95 (1.36-25.98)	
T/ NK-cell neoplasms	6.40 (0.69-59.25)		0.34 (0.13-0.86)

ORs (95%CI) of variables remaining in multivariate models by NHLNsubtypes

NHLN WHO subtype	Benzene	Solvents	Glues and adhesives
NHLN-total	0.62 (0.35-1.10)	✂	2.16 (1.02-4.55)
B-cell neoplasms (all)	0.77 (0.42-1.42)	✂	2.13 (0.88-5.15)
Precursor B-cell neoplasms	0.88 (0.28-2.75)	19.47 (1.78-212.90)	✂
Mature B-cell neoplasms	0.60 (0.29-1.26)	✂	1.95 (0.73-5.22)
CLL & SLL	1.64 (0.58-4.67)	✂	✂
FL	7.00 (1.45-33.70)	✂	✂
DLBCL	0.56 (0.23-1.34)	✂	3.50 (0.93-13.11)
T/ NK-cell neoplasms	0.33 (0.09-1.22)	✂	2.72 (0.62-11.97)

ORs (95%CI) by benzene exposure variables and NHLN subtypes

WHO subtype	NHLN-total			B-cell neoplasms (all)		
Benzene exposure variable	OR (95%CI)	Ca	Co	OR (95%CI)	Ca	Co
Ever/never	1.06 (0.74-1.51)	50	95	1.16 (0.77-1.73)	40	70
Length of exposed jobs	1.00 (0.98-1.02)	50	95	1.00 (0.98-1.03)	40	70
Non-exposed	1.00 (reference)	599	1203	1.00 (reference)	481	972
≤10 years	1.12 (0.87-1.85)	24	43	1.29 (0.73-2.26)	20	31
>10 to ≤20 years	0.88 (0.43-1.83)	11	25	0.90 (0.38-2.14)	8	18
>20 years	1.12 (0.59-2.11)	15	27	1.15 (0.56-2.37)	12	21
	P-trend=0.80			P-trend=0.78		
Maximum exposure (EGS)	1.03 (0.85-1.26)	50	95	1.10 (0.89-1.37)	40	70
Non-exposed	1.00 (reference)	599	1203	1.00 (reference)	481	972
EGS1	1.14 (0.73-1.78)	32	56	1.18 (0.70-2.00)	23	39
EGS2	0.75 (0.35-1.64)	9	24	0.80 (0.35-1.85)	8	20
EGS3&4	1.21 (0.53-2.76)	9	15	1.64 (0.68-3.97)	9	11
	P-trend=0.76			P-trend=0.37		
Decades of first exposure						
Non-exposed	1.00 (reference)	599	1203	1.00 (reference)	481	972
1940-1959	0.69 (0.24-2.01)	5	14	0.88 (0.26-2.98)	4	9
1960-1979	1.37 (0.83-2.26)	27	40	1.51 (0.83-2.73)	20	27
1980-1999	0.95 (0.51-1.77)	15	32	0.98 (0.50-1.93)	13	27
2000-	0.67 (0.18-2.46)	3	9	0.86 (0.22-3.32)	3	7
Cumulative EGS-years	1.01 (0.99-1.02)	50	95	1.01 (0.99-1.03)	40	70
	P-trend=0.36			P-trend=0.23		

ORs (95%CI) by benzene exposure variables and NHLN subtypes

WHO subtype	Mature B-cell lymphoma			Follicular lymphoma		
Benzene exposure variable	OR (95%CI)	Ca	Co	OR (95%CI)	Ca	Co
Ever/never	1.07 (0.68-1.69)	31	58	7.00 (1.45-33.70)	7	2
Length of exposed jobs	1.00 (0.98-1.03)	31	58	1.42 (0.76-2.67)	7	2
Non-exposed	1.00 (reference)	356	716	1.00 (reference)	38	88
≤10 years	1.12 (0.58-2.16)	19	31	1.00 (0.09-11.03)	1	2
>10 to ≤20 years	1.01 (0.39-2.61)	5	18	---	1	0
>20 years	1.06 (0.49-2.31)	7	9	---	5	0
	P-trend=0.79			P-trend=0.27		
Maximum exposure (EGS)	1.04 (0.82-1.33)	31	58	2.10 (0.90-4.52)	7	2
Non-exposed	1.00 (reference)	356	716	1.00 (reference)	38	88
EGS1	1.12 (0.68-2.16)	19	31	---	5	0
EGS2	0.57 (0.21-1.52)	5	18	2.00 (0.13-31.98)	1	1
EGS3&4	1.57 (0.49-2.31)	7	9	2.00 (0.13-31.98)	1	1
	P-trend=0.74			P-trend=0.09		
Decades of first exposure						
Non-exposed	1.00 (reference)	356	716	1.00 (reference)	38	88
1940-1959	1.00 (0.29-3.50)	4	8	---	0	0
1960-1979	1.59 (0.84-3.01)	18	23	---	6	0
1980-1999	0.82 (0.36-1.87)	8	20	2.00 (0.13-31.98)	1	1
2000-	0.29 (0.04-2.32)	1	7		0	1
Cumulative EGS-years	1.01 (0.99-1.02)	31	58	1.26 (0.24-31.09)	7	2
	P-trend=0.35			P-trend=0.47		

Discussion of NHLN findings

- Traditional Chinese medicines (reduced risk):
Indirect effect (as a result of reduced use of western medicines such as antibiotics)?
- Home renovations:
Similar increases in risk of NHL reported in previous studies in China.
Elevated levels of formaldehyde, benzene, toluene, xylene & VOCs in renovated homes.
- Fabric sewing/cutting workers:
OR=2.4 for NHL for “apparel” industry in a US study (Blair 1993).
SMR=9.68 for NHL for fabric workers at Hill Air Force Base, Utah (Spirtas 1991).
- Insecticides:
Conflicting results in previous studies.
In current study, elevated risks for B-cell neoplasms, but not T/NK-cell neoplasms.
Independent risk factor (regardless of being employed as farm workers or not).
- Benzene:
RR=3.0 for NHL in CAPM-NCI cohort study (Hayes 1997).
SMR=1.00 for NHL in Pliofilm cohort study (Rinsky 2002).
OR=0.49-1.2 for NHL in case-control studies in US, UK, Canada & Italy (Wong 2005).
OR=1.9 (95%CI=0.7-5.3) for FL in a US case-control study (Blair 1993).

Limitations of the case-control studies

- Hospital and patient participations:

Hospitals: AML 29; NHLN 25.

Patient participation: AML 99%; NHLN 74%.

- Interviews:

Potential patient recall & interviewer biases.

- Multiple comparisons:

Need to take consistency into account in interpretation of results.

- Some risk estimates based small numbers:

Some ORs based on only 1 or 2 exposed cases or controls.

- Benzene exposure estimates:

Retrospective assessment and uncertainties in underlying data sources.

Conclusions

- Our studies confirmed several risk factors of AML and NHLN reported by other investigators in previous studies.
- Our studies identified some new etiologic factors and provided new information on risk factors by specific WHO subtypes.
- The results in our studies indicated that some risk factors were subtype-specific.
- The difference in risk by subtype underscores the importance of the etiologic commonality and heterogeneity of AML or NHLN subtypes.

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