



A hospital-based case-control study of acute myeloid leukemia in Shanghai: Analysis of personal characteristics, lifestyle and environmental risk factors by subtypes of the WHO classification

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ABSTRACT

Objectives: The objectives are (1) to investigate and identify potential risk factors (personal characteristics, lifestyle and environmental factors) of acute myeloid leukemia (AML), and (2) to explore the relationships between potential risk factors and AML subtypes according to the World Health Organization (WHO) classification of myeloid neoplasms.

Materials and methods: The investigation was a hospital-based case-control study consisting of 722 confirmed AML cases and 1444 individually gender-age-matched patient controls at 29 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 environmental and 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. Risk estimates (odds ratios and 95% confidence intervals) were calculated using conditional logistic regression models.

Results: Several potential risk factors of AML (all subtypes combined) and individual subtypes were identified; including low-level education, body mass index (BMI), blood transfusion, smoking, alcohol consumption, home or workplace renovation, living on a farm, planting crops, raising livestock or animals, employment as farm workers or in the agricultural industry, and exposures to insecticides or fertilizers. Some risk factors applied to all or several subtypes (such as low-level education and living on a farm), while others were limited to one or two specific subtypes (such as home/office renovation and acute promyelocytic leukemia). An inverse association was found between BMI and overall AML or the sub-category “AML not otherwise categorized”, whereas a positive association between BMI and the subtype acute promyelocytic leukemia was detected. An unexpected finding was the association between the use of traditional Chinese medicines and a reduced risk of AML in general as well as several major subtypes.

Conclusions: The study identified a number of risk factors for AML in general as well as for some specific subtypes. Some of the risk factors were subtype-specific. The difference in risk by subtype underscores the importance of investigating the etiologic commonality and heterogeneity of AML by subtype in epidemiologic research.

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1. Introduction

Acute myeloid leukemia (AML) is the most common type of leukemias in the United States and other western countries. The estimated number of newly diagnosed AML in the US for 2008 was 13,290, with a male-to-female ratio of 1.2:1.0 (Jemal et al., 2008).

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Based on the US National Cancer Institute's Surveillance Epidemiology and End Results (SEER) data for 2001–2005, the adjusted annual incidence rates for males and females were 4.5 per 100,000 and 2.9 per 100,000, respectively (Reis et al., 2008). 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 3.7 per 100,000 and 2.5 per 100,000, respectively, which are slightly lower than those for their white counterparts (4.6 per 100,000 and 3.0 per 100,000). Generally, the incidence of AML in adults is higher in developed countries

than in less developed nations. Incidence rates of AML in Asian countries such as China and Japan are generally lower than those in the US and European nations (Linnet and Cartwright, 1996).

Most early epidemiologic studies treated leukemia as a single diagnostic category, partly because of the lack of specific diagnostic information and partly because of the limited number of patients by subgroups of leukemia in individual studies. However, starting in the 1980s, following the clinical and pathological recognition of the heterogeneity of leukemias, epidemiologists began to appreciate the differences among the various subgroups within the broad category of malignancies collectively known as “leukemia”, and an increasing number of investigations focusing on specific major subgroups of leukemia (acute and chronic myeloid leukemias, and acute and chronic lymphocytic leukemias) began to appear in the literature (Linnet, 1985). A previous comprehensive review has identified a large number of potential risk factors of AML reported in epidemiologic investigations; including personal and family medical histories (such as blood transfusion, alkylating drugs for cancer treatment, diagnostic X-rays, rheumatoid arthritis, and family history of blood disorders), lifestyle (such as tobacco, alcohol, and hair dyes), environmental exposures (living on a farm, living near electrical power transmission lines), occupations and industries (such as farmers, painters, shoe and leather workers, chemical workers, printers, and grain workers), and exposures to chemical, physical or biological agents (such as benzene, solvents, radiation, and retroviruses) (Linnet and Cartwright, 1996). In addition, some recent studies have reported a positive association between anthropometric measurements (such as weight, height or body mass index) and lymphatic and hematopoietic malignancies including AML (Larsson and Wolk, 2008; Engeland et al., 2007; Kasim et al., 2005; Ross et al., 2004).

The findings of AML risk factors reported in epidemiologic studies, however, have not always been consistent. For example, while epidemiologic evidence generally suggests an increased risk of AML among smokers, no association between cigarette smoking and AML was found in some case-control studies (Flodin et al., 1986; Kabat et al., 1988; Spitz et al., 1990). Other studies have reported that cigarette smoking seems to affect certain subtypes of AML more than the others (Pogoda et al., 2002; Moorman et al., 2002). This observation of difference in risk by subtype underscores the fact that the diagnostic category of AML actually consists of several distinct subtypes and, hence, the need for epidemiologic studies of AML to treat these subtypes as separate diagnostic entities (Linnet and Cartwright, 1996). A new classification of myeloid neoplasms was introduced by the World Health Organization (WHO) in 2001 (Jaffe et al., 2001; Vardiman et al., 2002). At the present, there are no epidemiologic studies that systematically investigate the effects of personal, lifestyle, and environmental risks of individual AML subtypes based on the WHO 2001 classification. Epidemiologic studies to investigate the etiologic commonality and heterogeneity of AML subtypes using the new WHO classification are needed.

The objectives of the present study are twofold: (1) to investigate and identify potential risk factors (including personal characteristics, lifestyle, environmental factors, occupations, industries, and specific exposures) of AML in Shanghai, and (2) to explore the relationships between potential risk factors and specific AML subtypes according to the new WHO classification of myeloid neoplasms. In this report, we will present results based on an analysis of personal characteristics, lifestyle and environmental risk factors. Detailed analysis of occupations and specific exposures will be reported separately in the future.

2. Materials and methods

We conducted a hospital-based case-control study of AML in Shanghai. The study was one of several parallel but independent

research projects of the Shanghai Health Study (SHS) program, a collaborative research effort between investigators in the US and China. Participants of and contributors to the SHS program included both Chinese and US organizations: Fudan University, Shanghai Center for Disease Control and 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 Shanghai. A pilot study was carried out in 2001–2002 to assess the feasibility of the program. Study protocols and data collection instruments (such as questionnaires) of individual research projects as well as the overall SHS program organization were developed in 2002–2003. The study protocols were approved by Chinese and US Institutional Review Boards of respective organizations.

In designing the study, it was estimated that a sample size of approximately 500–600 AML patients would provide adequate statistical power to detect a modest risk of AML resulting from benzene exposure (one of the chemicals of primary interest). It should be noted that even though benzene was of primary interest in any investigation of AML including ours, other risk factors (personal, lifestyle, environmental and occupational) were also taken into consideration in the study protocol as reflected in the design of the questionnaire. Thus, the sample size was adequate to detect a modest risk for other factors that were as frequent as benzene exposure in the target population. Based on crude hospital admission data in Shanghai, it was anticipated the targeted sample size could be reached in 4–5 years.

For the AML case-control study, cases were defined as patients aged 18 or older and diagnosed with AML (“provisional diagnosis”) at any of the 29 participating hospitals in Shanghai between August 2003 and June 2007. The WHO 2001 classification of AML was used in the diagnosis (Jaffe et al., 2001). The WHO classification system utilizes not only morphologic findings but also genetic, immunophenotypic, biologic, and clinical features of the patients (Vardiman et al., 2002). To provide the equipment and facilities needed for the WHO diagnostic procedures, a new laboratory “the Joint Sino-US Clinical and Molecular Laboratory (JCML)” was built on the campus of Fudan University in Shanghai, staffed with scientists from both Fudan University and the University of Colorado. The JCML functioned as the centralized diagnostic laboratory for the participating hospitals in Shanghai and served as the clinical arm to provide diagnostic information to the research projects in the SHS program.

At each participating hospital, a designated clinical coordinator was responsible for identifying and recruiting eligible patients (i.e., patients with a provisional diagnosis of AML and aged 18 or older) for study participation. Each participant was asked to sign an informed consent according to the Declaration of Helsinki of 1975. Peripheral blood, bone marrow aspirates, tissue and core biopsies were collected in conjunction with diagnostic procedures and were sent to JCML for analysis. Details of diagnostic procedures at JCML have been described elsewhere (Bao et al., 2006; Gross et al., 2008). The clinical coordinators at the participating hospitals were also responsible for recruiting controls. For each case, two individually matched controls were randomly selected from patients admitted to the same hospital. Patients with any malignant or non-malignant diseases of the lymphatic and hematopoietic system were excluded from control selection. Matching criteria included gender and age. For each case, the clinical coordinators at the hospitals were asked to recruit two patients of the same gender within 5 years of age of the case. For some cases, suitable controls within 5 years of age were not available and the age requirement was relaxed. Because cases and controls were enrolled around the same time, hospital admission dates of the case and controls within each matched set (matched triplet) were quite similar.

To obtain relevant information from study participants, face-to-face interviews at the hospitals were conducted by trained interviewers from Fudan University School of Public Health. To minimize recall bias, neither the patients nor the interviewers were informed about the specific objectives or hypotheses of the study. The interviewers were not informed of the patients' case/control status. A 17-page structured questionnaire, which was field-tested before the commencement of data collection, 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 (such as farm workers) triggered a second questionnaire, which was occupation-specific and asked for more details about jobs, tasks, materials used and work environment. Occupations and industries reported by the patients were coded according to the official Chinese standard classification systems (Chinese National Bureau of Census, 1982a,b).

Data from completed questionnaires were entered (double entry) in an Oracle database at the Fudan University computer system in Shanghai, with a periodically updated backup system at the University of Colorado in Denver. The two databases were maintained and managed by the JCML staff at Fudan University and the University of Colorado. After data collection of all study subjects has been completed, relevant diagnostic and questionnaire data were extracted from the JCML database and converted to SAS files for analysis in the case-control study. Data analysis was carried out with the SAS statistical software (SAS Institute, 2004). 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). In addition, analysis specific to gender (i.e., separately for males and females) was also performed. However, due to space limitation, only those results that are significantly different between males and females will be reported.

For variables with more than two categories, trend tests were also performed. For "education", the category "middle school" (equivalent to junior high school in the US), which is compulsory in China since 1986, had the largest number of patients and was used as the reference group for comparison. For both height and weight, five evenly spaced groups were created, and the middle categories (165–169 cm or 60–64 kg) with the largest numbers of patients were used as the reference groups for comparison. Body mass index (BMI) was calculated using the formula $[\text{weight}(\text{kg})/\text{height}(\text{m})^2]$. In our analysis, we used the BMI categories recommended for use in the Chinese population by the Working Group on Obesity in China (WGOC) in 2002 (Cooperative Meta-analysis Group of China Obesity Task Force, 2002). The Chinese BMI categories are as follows: underweight (<18.5), desirable (18.5–23.9), overweight (24.0–27.9) and obese (≥ 28.0). The "desirable" BMI category was used as the reference group. In the trend tests, the categories were ranked in ascending order. For BMI, for example, "underweight" = 1, "desirable" = 2, "overweight" = 3, and "obese" = 4.

3. Results

Twenty-nine hospitals in the Shanghai metropolitan area participated in 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 29 hospitals covered a sizable percentage of the cancer patient population of the city. Between August 2003 and June 2007, of all the patients with a provisional diagnosis of AML referred to JCML, 741 were subsequently confirmed with a diagnosis of AML according to the WHO 2001 criteria. Nineteen 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 722 confirmed AML patients with informed consents and completed questionnaires, representing a participation rate of 97%. For every AML case, two individually matched controls from the same hospital were subsequently recruited, resulting in a total of 1444 control patients with a variety of diagnoses (the most frequent ones 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 (94.60% cases and 99.03% controls) participated in the interviews (for cases, 68.56% patients only and 26.04% patients plus family members; for controls, 89.20% patients only and 9.83% patients plus family members). The reason for the higher percentage of "patients plus family members" among the cases was that more AML 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. The distribution of the 1444 controls by their age differences comparing with the cases was as follows: within 5 years ($n = 1255$ or 87%), 6–8 years ($n = 143$ or 10%), 9–10 years ($n = 34$ or 2%), and 11–13 years ($n = 12$ or 1%).

Although marital status was not part of the matching criteria, 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, slightly more controls than cases attended high schools (27.22% vs. 25.35%) and significantly more controls than cases received university or higher education (23.55% vs. 15.93%). Several anthropometric measures were included in the questionnaire, including height and weight, from which BMI were calculated. In Table 1, the distributions of cases and controls by the WGOC 2002 BMI categories are presented. The mean BMI of the controls (23.1) was slightly

Table 1
Distribution of demographic and personal variables of acute myeloid leukemia (AML) cases and controls.

Variable	Cases		Controls	
Number	722	100.00%	1444	100.00%
Male	406	56.23%	812	56.23%
Female	316	43.77%	632	43.77%
Mean age (standard deviation) in years	49.92	(16.85)	49.98	(16.49)
Marital status				
Married	605	83.80%	1204	83.38%
Divorced	10	1.39%	15	1.04%
Widowed	35	4.85%	70	4.85%
Never married	72	9.97%	147	10.18%
Missing data	0	0.00%	8	0.55%
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%
Missing data	3	0.42%	4	0.28%
Body Mass Index (BMI) ^a				
Mean BMI (standard deviation)	22.6	(3.3)	23.1	(3.7)
Underweight (<18.5)	66	9.14%	124	8.59%
Desirable (18.5–23.9)	434	60.11%	818	56.65%
Overweight (24.0–27.9)	179	24.79%	382	26.45%
Obese (≥ 28.0)	43	5.96%	120	8.31%

^a BMI categories recommended for use in the Chinese population by the Working Group on Obesity in China (2002).

Table 2

Distribution of acute myeloid leukemia (AML) cases by subtype according to the WHO 2001 classification.

Subtype	ICD-O code	Frequency	Percentage
AML with recurrent cytogenetic abnormalities			
AML with t(8;21)(q22;q22),(AML1/ETO)	9896/3	64	8.86
AML with inv(16)(p13q22) or t(16;16)(p13;q22),(CBF β /MYH11)	9871/3	23	3.19
Acute promyelocyte leukemia (AML with t(15;17)(q22;q12),(PML/RAR α) and variants)	9866/3	124	17.17
AML with 11q23 (MLL) abnormalities	9897/3	33	4.57
Subtotal		244	33.80
AML with multilineage dysplasia			
AML with multilineage dysplasia, with or without prior MDS	9895/3	186	25.76
AML and MDS, therapy related			
Alkylating agent related; Topoisomerase II inhibitor related	9920/3	5	0.69
AML not otherwise categorized			
AML, minimally differentiated	9872/3	26	3.60
AML without maturation	9873/3	64	8.86
AML with maturation	9874/3	48	6.65
Acute myelomonocytic leukemia	9867/3	60	8.31
Acute monoblastic and monocytic leukemia	9891/3	42	5.82
Acute erythroid leukemia	9840/3	19	2.63
Acute megakaryoblastic leukemia	9910/3	7	0.97
Acute basophilic leukemia	9870/3	1	0.14
Acute panmyelosis with myelofibrosis	9931/3	2	0.28
Myeloid sarcoma	9930/3	0	0.00
Subtotal		269	37.26
Acute leukemia of ambiguous lineage			
Acute leukemia of ambiguous lineage	9805/3	11	1.52
Other uncategorized cases			
Undifferentiated acute leukemia		3	0.42
AML, not otherwise specified		4	0.55
AML (total)		722	100.00

higher than that of the cases (22.6). There were proportionally more controls classified as either overweight or obese than cases.

The distribution of the 722 AML cases by WHO subtypes is given in Table 2. In the WHO classification, three unique subgroups are recognized: (1) AML with recurrent cytogenetic abnormalities (AML-RCA), (2) AML with multilineage dysplasia (AML-MD), and (3) therapy-related AML (t-AML) and myelodysplastic syndromes (MDS) (Vardiman et al., 2002). Cases that do not fit into any of these three categories or no genetic data are available are classified in a fourth residual category “AML, not otherwise categorized (AML-noc)”, which represents a heterogeneous group of subtypes of AML. It should be noted that some of the subtypes in the AML-noc group in the WHO classification resemble those in the previous French-American-British (FAB) classification (Vardiman et al., 2002). There were 244 (33.80%) cases of AML-RCA, with approximately half of them ($n = 124$, 17.17%) categorized as “acute promyelocytic leukemia” (APL). Classified in the category of AML-

MD were 186 (25.76%) patients, whereas only five (5) patients were categorized as t-AML. In the residual category AML-noc were 269 (37.26%) cases, of which four subtypes had more than 40 patients in each: AML without maturation ($n = 64$, 8.86%), AML with maturation ($n = 48$, 6.65%), acute myelomonocytic leukemia ($n = 60$, 8.31%), and acute monoblastic and monocytic leukemia ($n = 42$, 5.82%). There were 11 (1.51%) cases of acute leukemia of ambiguous lineage and 7 (0.97%) cases were uncategorized.

Table 3 shows the distribution of demographic and personal characteristics of all AML cases (AML-total) and by selected major WHO subtypes (AML-RCA, APL, AML-MD and AML-noc). The male-to-female ratio for AML-RCA was slightly higher than that for AML-total and even higher when compared with the other two major subtypes (AML-MD or AML-noc). AML-RCA patients (especially APL) also tended to be much younger than patients in the other two major subtypes (AML-MD and AML-noc). Furthermore, a higher percentage of AML-RCA patients attended university or post-graduate schools and/or never married. Compared with other AML patients, a higher proportion of APL patients tended to be overweight or obese.

In Table 4, we present ORs and 95% CIs for AML and selected major WHO subtypes by marital status, education and anthropometric measures (height, weight and BMI). Although based on relatively small numbers, being “divorced” seemed to carry a slightly higher risk of AML-total (OR = 1.35, 95% CI = 0.60–3.06) than being “married”. A similar increased risk was observed for being “divorced” across all four major subtypes in Table 4, but none of the increases was statistically significant. There was no clear pattern of risk between the other two marital categories (“never married” or “widowed”) and AML-total or the subtypes.

There was a consistent pattern that “education” was negatively associated with AML-total (p -trend < 0.01) and all the subtypes (p -trend < 0.05, except for APL). Compared with the “middle school” category, the category of “education, none” was associated with a significantly increased risk of AML-total (OR = 2.66, 95% CI = 1.66–4.25), AML-MD (OR = 2.24, 95% CI = 1.06–4.75), and AML-noc (OR = 4.72, 95% CI = 2.06–10.83). In contrast, individuals with a “university or higher” education were at a significantly reduced risk of AML-total (OR = 0.64, 95% CI = 0.48–0.84) and AML-noc (OR = 0.53, 95% CI = 0.33–0.84).

For AML-total, height appeared to be negatively associated with risk (p -trend < 0.01). There was a significant risk reduction in AML-total for the category “170–174 cm” when compared with the middle category “165–169 cm” (OR = 0.69, 95% CI = 0.52–0.93). A similar but stronger inverse association was also detected between height and AML-MD (p -trend = 0.02). Being shorter than 160 cm carried a significantly increased risk of AML-MD (OR of 2.23, 95% CI = 1.12–4.47). Little or no pattern was seen between height and AML-RCA or APL. For weight, using the middle category “60–64 kg” as the reference, there was a borderline significant excess risk for AML-total for patients weighing 55–59 kg (OR = 1.36, 95% CI = 1.00–1.84) but a significantly reduced risk for those weighing 70 kg or more (OR = 0.73, 95% CI = 0.55–0.96). The overall downward trend between weight and AML-total was significant (p -trend < 0.01). A similar inverse trend was also observed between weight and AML-MD (p -trend < 0.01); those weighing less than 60 kg experienced a significantly elevated risk of approximately twofold. In contrast, it is interesting to note that APL risk seemed to increase with weight (p -trend = 0.03). The significantly reduced risk of APL (OR = 0.39, 95% CI = 0.18–0.83) for the lowest weight category was in direct contrast to the significant increase of AML-MD (OR = 2.10, 95% CI = 1.22–3.61) in the same weight category. With respect to gender-specific analysis (results not presented in Table 4), the only difference between males and females was that males weighing 55–59 kg had a significantly elevated OR of 1.60 (95% CI = 1.02–2.49) for AML-total, whereas the

Table 3

Distribution of demographic and personal variables of AML cases by selected major WHO subtypes.

Variable	AML-total		AML-RCA		APL		AML-MD		AML-noc	
Number	722	100.00%	244	100.00%	124	100.00%	186	100.00%	269	100.00%
Male	406	56.23%	145	59.43%	70	56.45%	99	53.23%	145	53.90%
Female	316	43.77%	99	40.57%	54	43.55%	87	46.77%	124	46.10%
Mean age in years (standard deviation)	49.92	(16.85)	42.56	(14.49)	40.52	(13.43)	55.97	(16.68)	52.85	(16.45)
Education										
None	57	7.89%	9	3.69%	4	3.23%	21	11.29%	27	10.04%
Primary School	137	18.98%	36	14.75%	15	12.10%	48	25.81%	51	18.96%
Middle school	227	31.44%	77	31.56%	45	36.29%	50	26.88%	92	34.20%
High school	183	25.35%	78	31.97%	40	32.26%	38	20.43%	62	23.05%
University or higher	115	15.93%	43	17.62%	20	16.13%	27	14.52%	37	13.75%
Missing data	3	0.42%	1	0.41%	0	0.00%	2	1.08%	0	0.00%
Marital status										
Married	605	83.80%	200	81.97%	101	81.45%	155	83.33%	231	85.87%
Divorced	10	1.39%	6	2.46%	3	2.42%	1	0.54%	3	1.12%
Widowed	35	4.85%	4	1.64%	1	0.81%	18	9.68%	11	4.09%
Never married	72	9.97%	34	13.93%	19	15.32%	12	6.45%	24	8.92%
Body Mass Index (BMI) ^a										
Mean BMI (standard deviation)	22.6	(3.3)	22.9	(3.3)	23.3	(3.5)	22.8	(3.4)	22.3	(3.1)
Underweight (<18.5)	66	9.14%	23	9.43%	10	8.06%	16	8.60%	26	9.67%
Desirable (18.5-23.9)	434	60.11%	142	58.20%	65	52.42%	108	58.06%	167	62.08%
Overweight (24.0-27.9)	179	24.79%	59	24.18%	38	30.65%	48	25.81%	67	24.91%
Obese (>28.0)	43	5.96%	20	8.20%	11	8.87%	14	7.53%	9	3.35%

AML = acute myeloid leukemia, AML-RCA = AML with recurrent cytogenetic abnormalities; APL = acute promyelocytic leukemia; AML-MD = AML with multilinea AML-noc = AML, not otherwise categorized.

^a BMI categories recommended for the Chinese population by the Working Group on Obesity in China (2002).

OR for females of the same weight was lower (OR = 1.13, 95% CI = 0.74–1.74).

There was a negative association between BMI and AML-total (p -trend = 0.03). That is, as BMI increased, the risk for AML-total decreased. For the “obese” category, a significant reduction in risk of 33% (OR = 0.67, 95% CI = 0.46–0.97) for AML-total was found. A similar downward trend was also seen for AML-noc (p -trend < 0.01). For AML-RCA as a whole, BMI did not appear to have much effect on risk. On the other hand, APL seemed to be the only subtype with a positive trend of OR by increasing BMI (p -trend = 0.03); the risk for the “obese” category being more than twofold (OR = 2.15, 95% CI = 0.89–5.20).

Table 5 presents the results for medical history and lifestyle risk factors. There was little effect of family history (parents or siblings) of cancers (all types) on AML-total or the subtypes, except for a small non-significant increase of AML-noc (OR = 1.31, 95% CI = 0.92–1.86). Only a small number of cases or controls had a family history of blood diseases (9 cases vs. 15 controls) or hematopoietic cancers (7 cases vs. 12 controls). Even though the ORs for AML-RCA and AML-noc were elevated for patients with such a family history, the 95% CIs were relatively wide and the ORs were not significant. For example, for individuals with a family history of hematopoietic cancers, the risk for AML-noc was elevated (OR = 2.67), but the 95% CI (0.60–11.91) was wide. A history of blood transfusion (before the current illness) was associated with a small borderline significant increase of risk for AML-total (OR = 1.30, 95% CI = 0.99–1.71), and an upward trend by frequency of transfusion was apparent (p -trend = 0.05). In terms of subtypes, APL did not seem to be affected by blood transfusion. The use of traditional Chinese medicines (longer than one month) was associated with a significant protective effect on AML-total (OR = 0.63, 95% CI = 0.43–0.94), reducing the risk by almost 40%. Furthermore, all major subtypes seemed to show a similar reduction in risk, although some ORs were no longer significant because of reduced sample sizes. For AML-MD, the reduction in risk associated with the use of traditional Chinese medicines was more than 50% (OR = 0.44, 95% CI = 0.20–0.97).

There was a small borderline significant risk increase of 28% for AML-total related to cigarette smoking (OR = 1.28, 95% CI = 1.00–

1.63). An analysis by gender (results not presented in Table 5) indicated that the excess risk related to smoking came from males as there were very few female patients who smoked (10 AML-total cases and 25 controls). The OR for male ever-smokers was significantly elevated (OR = 1.36, 95% CI = 1.04–1.77), whereas the OR for female ever-smokers was not. The effect of smoking in our study seemed to vary by subtype: little or no effect on AML-RCA or APL, but ORs were elevated for AML-MD (OR = 1.45, 95% CI = 0.92–2.30) and AML-noc (OR = 1.48, 95% CI = 0.96–2.26). The number of cigarettes consumed daily showed a non-significant upward trend with AML-MD (p -trend = 0.07) only; whereas duration of smoking (calculated based on ages starting and stopping smoking in years) seemed to be positively associated with the risk of developing AML-total (p -trend = 0.05) and AML-MD (p -trend = 0.08). Analysis by pack-years of smoking (i.e., packs per day multiplied by duration in years) suggested modest upward trends for AML-MD (p -trend = 0.08) and AML-noc (p -trend = 0.07). We also examined the effect of passive smoking, but did not find any for either AML-total or subtypes (Table 5).

Alcohol consumption of any kind increased the risk of AML-total significantly (OR = 1.53, 95% CI = 1.17–2.01). The risk of AML-RCA or APL was not affected by alcohol consumption, but the latter increased the risk of AML-noc by about twofold (OR = 2.13, 95% CI = 1.14–4.61). Overall, the effect of the specific type of alcoholic drinks (beer, rice or wheat wine, hard liquor) seemed to be relatively similar and consistent in the study as a whole. With respect to gender-specific analysis, rice or wheat wine seemed to have a greater effect on females (for AML-total, OR = 4.67 and 95% CI = 1.21–18.05) than males (for AML-total, OR = 1.33 and 95% CI = 0.92–1.93), although the number of female rice/wheat wine drinkers was small (7 cases and 3 controls).

We examined the risk of AML associated with the use of hair dyes. As Table 5 indicates, no increased OR was found for AML-total (OR = 0.98, 95% CI = 0.80–1.20) or any subtypes. We also examined AML risk by frequency of hair dye use (once every 6 months or less frequent, every 3 to 6 months, every 3 months or more often), and no trend or pattern was found (numerical results not presented).

In addition to lifestyle, the questionnaire asked for information on environmental and other non-occupational exposures; includ-

Table 4

Odds ratios and 95% confidence intervals for AML and selected major WHO subtypes by marital status, education and anthropometric measures.

Variable	AML-total OR (95% CI)	Ca	Co	AML-RCA OR (95% CI)	Ca	Co	APL OR (95% CI)	Ca	Co	AML_MD OR (95% CI)	Ca	Co	AML-noc OR (95% CI)	Ca	Co
Marital status															
Married (reference)	1.00 Reference	605	1204	1.00 Reference	200	392	1.00 Reference	101	196	1.00 Reference	155	315	1.00 Reference	231	461
Divorced	1.35 (0.60–3.06)	10	15	1.33 (0.4–3.90)	6	9	1.20 (0.29–5.02)	3	5	2.00 (0.13–31.97)	1	1	1.48 (0.33–6.62)	3	4
Never married	0.94 (0.59–1.50)	72	147	0.83 (0.43–1.61)	34	73	0.82 (0.34–1.97)	19	41	1.11 (0.36–3.41)	12	23	1.33 (0.54–3.28)	24	44
Widowed	1.00 (0.62–1.62)	35	70	0.56 (0.14–2.23)	4	12	0.40 (0.05–3.42)	1	5	1.26 (0.61–2.62)	18	31	0.82 (0.38–1.79)	11	26
Education															
None	2.66 (1.66–4.25)	57	60	1.80 (0.63–5.14)	9	14	1.91 (0.44–8.22)	4	6	2.24 (1.06–4.75)	21	26	4.72 (2.06–10.83)	27	18
Primary school	1.56 (1.17–2.09)	137	199	1.94 (1.12–3.35)	36	44	1.78 (0.82–3.87)	15	20	1.90 (1.10–3.27)	48	63	1.31 (0.82–2.08)	51	85
Middle school (reference)	1.00 Reference	227	448	1.00 Reference	77	171	1.00 Reference	45	101	1.00 Reference	50	103	1.00 Reference	92	163
High school	0.90 (0.74–1.14)	183	393	1.27 (0.85–1.91)	78	137	1.53 (0.87–2.70)	40	59	0.80 (0.49–1.33)	38	94	0.73 (0.49–1.07)	62	151
University or higher	0.64 (0.48–0.84)	115	340	0.77 (0.48–1.21)	43	122	0.74 (0.40–1.37)	20	62	0.61 (0.35–1.07)	27	85	0.53 (0.33–0.84)	37	120
	P-trend <0.01			p- trend = 0.02			p- trend = 0.14			p-trend <0.01			p-trend <0.01		
Height (cm)															
<160	1.25 (0.89–1.74)	167	298	0.95 (0.53–1.71)	45	89	1.01 (0.46–2.21)	24	46	2.23 (1.12–4.47)	55	82	1.01 (0.60–1.70)	62	123
160–164	1.06 (0.78–1.44)	154	304	0.93 (0.53–1.62)	49	97	0.90 (0.42–1.92)	25	52	1.29 (0.68–2.42)	37	79	1.04 (0.65–1.67)	65	120
165–169 (reference)	1.00 Reference	153	278	1.00 Reference	53	92	1.00 Reference	26	48	1.00 Reference	33	72	1.00 Reference	63	107
170–174	0.69 (0.52–0.93)	141	337	0.71 (0.43–1.16)	55	129	0.72 (0.35–1.50)	25	62	0.80 (0.44–1.46)	33	79	0.64 (0.40–1.04)	47	115
>175	0.77 (0.55–1.06)	107	227	0.85 (0.49–1.47)	42	81	1.07 (0.49–2.33)	24	40	0.84 (0.43–1.65)	28	60	0.69 (0.39–1.20)	32	73
	p-trend <0.01			p- trend = 0.63			p- trend = 0.93			p- trend = 0.02			p- trend = 0.16		
Weight (kg)															
<55	1.14 (0.86–1.51)	174	323	0.68 (0.41–1.13)	46	115	0.39 (0.18–0.83)	17	62	2.10 (1.22–3.61)	52	73	1.02 (0.64–1.63)	71	128
55–59	1.36 (1.00–1.84)	122	184	1.06 (0.63–1.80)	38	59	0.80 (0.39–1.62)	21	39	2.21 (1.20–4.07)	34	47	1.07 (0.65–1.78)	45	75
60–64 (reference)	1.00 Reference	140	279	1.00 Reference	53	91	1.00 Reference	27	44	1.00 Reference	30	85	1.00 Reference	52	91
65–69	1.06 (0.78–1.44)	110	199	0.90 (0.53–1.53)	35	68	1.15 (0.51–2.56)	17	27	1.51 (0.81–2.84)	25	43	0.98 (0.60–1.62)	49	81
>70	0.73 (0.55–0.96)	176	458	0.81 (0.51–1.27)	72	155	1.05 (0.56–1.96)	42	76	0.91 (0.53–1.58)	45	124	0.52 (0.32–0.84)	52	162
	p-trend <0.01			p- trend = 0.86			p- trend = 0.03			p-trend <0.01			p-trend <0.01		
Body Mass Index (BMI)^a															
Underweight (<18.5)	1.01 (0.73–1.40)	66	123	0.84 (0.49–1.43)	23	54	0.81 (0.35– 1.85)	10	26	1.22 (0.61–2.42)	16	25	1.13 (0.67–1.93)	26	41
Desirable (18.5– 23.9) (reference)	1.00 Reference	434	818	1.00 Reference	142	281	1.00 Reference	65	149	1.00 Reference	108	208	1.00 Reference	167	303
Overweight (24.0– 27.9)	0.87 (0.70–1.09)	179	382	1.04 (0.71–1.53)	59	113	1.55 (0.92–2.63)	38	60	0.89 (0.57–1.37)	48	103	0.79 (0.55–1.12)	67	154
Obese (>28.0)	0.67 (0.46–0.97)	43	120	0.99 (0.55–1.79)	20	40	2.15 (0.89–5.20)	11	13	0.75 (0.39–1.47)	14	36	0.42 (0.20–0.88)	9	39
	p-trend = 0.03			p- trend = 0.64			p- trend = 0.03			p- trend = 0.23			p-trend <0.01		

AML = acute myeloid leukemia; AML-RCA = AML with recurrent cytogenetic abnormalities; APL = acute promyelocyte leukemia; AML-MD = AML with multilineage dysplasia; AML-noc = AML not otherwise categorized. OR = odds ratio; 95% CI = 95% confidence interval; Ca = cases; Co = controls.

^a BMI categories recommended for use in the Chinese population by the Working Group on Obesity in China (2002).

ing home/workplace renovation, living within 100 m of high voltage electrical power transmission lines, living on a farm, planting crops, or raising livestock or animals. The results for environmental and non-occupational risk factors are presented in Table 6. Home/workplace renovation carried an increased risk for AML-total

(OR = 1.22, 95% CI = 0.92–1.63), AML-RCA (OR = 1.82, 95% CI = 1.16–2.85), and APL (OR = 2.02, 95% CI = 1.06–3.85), but no excess risk was associated with AML-MD (OR = 0.89, 95% CI = 0.46–1.74) or AML-noc (OR = 0.95, 95% CI = 0.59–1.54). Living within 100 meters of high voltage electrical power transmission lines

Table 5

Odds ratios and 95% confidence intervals for AML and selected major WHO subtypes by medical history and lifestyle risk factors.

	AML-total			AML-RCA			APL			AML-MD			AML-noc							
Variable	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
Family history of cancers	1.11	(0.88–1.38)	170	315	1.08	(0.72–1.61)	52	99	0.81	(0.47–1.42)	22	52	0.81	(0.52–1.28)	38	86	1.31	(0.92–1.86)	73	121
Family history of blood diseases	1.21	(0.52–2.82)	9	15	1.38	(0.36–5.29)	4	6	0.67	(0.07–6.41)	1	3	0.50	(0.06–4.47)	1	4	1.60	(0.43–5.96)	4	5
Family history of hematopoietic cancers	1.18	(0.45–3.07)	7	12	1.23	(0.27–5.75)	3	5	---		0	2	---		0	4	2.67	(0.60–11.91)	4	3
Blood transfusion (ever/never)	1.30	(0.99–1.71)	94	148	1.30	(0.78–2.18)	26	41	1.00	(0.46–2.16)	11	22	1.34	(0.81– 2.23)	28	43	1.18	(0.77–1.83)	36	62
Blood transfusion frequency																				
None (reference)	1.00	Reference	626	1290	1.00	Reference	218	444	1.00	Reference	113	225	1.00	Reference	158	328	1.00	Reference	231	474
Once	1.28	(0.94–1.74)	70	112	1.50	(0.86–2.62)	24	33	1.21	(0.52–2.84)	10	17	1.18	(0.65–2.14)	19	33	1.15	(0.70–1.91)	25	44
Twice or more	1.43	(0.85–2.40)	25	36	0.45	(0.10–2.10)	2	9	0.40	(0.05–3.42)	1	5	1.47	(0.59–3.65)	8	11	1.71	(0.80–3.68)	13	16
		P-trend = 0.05				p-trend = 0.72			p-trend = 0.76				p-trend = 0.34				p-trend = 0.17			
Traditional Chinese medicines (ever/never)	0.63	(0.43–0.94)	41	118	0.52	(0.23–1.18)	9	30	0.82	(0.27–2.44)	5	11	0.44	(0.20–0.97)	8	35	0.71	(0.39–1.30)	20	51
Smoking (ever/never)	1.28	(1.00–1.63)	277	508	1.10	(0.71–1.71)	94	182	1.00	(0.54–1.86)	44	88	1.45	(0.92–2.30)	71	121	1.48	(0.96–2.26)	103	181
Daily amount smoked (cigarettes/day)																				
0 cigarette/day (reference)	1.00	Reference	445	936	1.00	Reference	150	307	1.00	Reference	80	160	1.00	Reference	115	251	1.00	Reference	166	356
≤20 cigarettes/day	1.33	(1.03–1.71)	248	438	1.21	(0.78–1.88)	88	157	1.10	(0.59–2.05)	42	76	1.36	(0.84–2.21)	57	103	1.51	(0.98–2.33)	94	158
>20 cigarettes/day	0.96	(0.58–1.57)	27	65	0.47	(0.17–1.32)	5	23	0.16	(0.02–1.35)	1	12	1.92	(0.87–4.24)	14	18	1.01	(0.40–2.53)	8	20
		p-trend = 0.24				p-trend = 0.72			p-trend = 0.38				p-trend = 0.07				p-trend = 0.23			
Smoking duration (in years)																				
0 year (reference)	1.00	Reference	446	941	1.00	Reference	151	308	1.00	Reference	80	161	1.00	Reference	115	254	1.00	Reference	166	357
≤20 years	1.20	(0.84–1.73)	77	146	1.07	(0.61–1.89)	35	71	1.18	(0.55–2.54)	21	38	1.16	(0.53–2.57)	14	27	1.68	(0.86–3.26)	24	36
>20 years	1.33	(0.99–1.77)	189	347	1.13	(0.67–1.90)	55	107	0.97	(0.45–2.09)	22	48	1.59	(0.94–2.68)	54	89	1.42	(0.87–2.32)	75	139
		p-trend = 0.05				p-trend = 0.63			p-trend = 1.00				p-trend = 0.08				p-trend = 0.11			
Pack-years of smoking																				
0 pack-year (reference)	1.00	Reference	446	941	1.00	Reference	151	308	1.00	Reference	80	161	1.00	Reference	115	254	1.00	Reference	166	357
≤20 pack-years	1.27	(0.94–1.71)	122	223	1.17	(0.72–1.92)	51	96	1.48	(0.74–2.93)	29	44	1.43	(0.81–2.54)	30	50	1.40	(0.82–2.40)	36	63
>20 pack-years	1.29	(0.95–1.75)	142	267	1.01	(0.58–1.77)	38	81	0.57	(0.24–1.36)	13	42	1.49	(0.84–2.66)	38	66	1.56	(0.95–2.57)	62	110
		p-trend = 0.08				p-trend = 0.89			p-trend = 0.41				p-trend = 0.14				p-trend = 0.07			
Passive smoking	1.08	(0.83–1.41)	196	352	1.15	(0.71–1.87)	72	125	1.11	(0.61–2.03)	43	72	1.05	(0.65–1.71)	50	91	1.16	(0.74–1.81)	70	127
Alcohol consumption (all kinds)	1.53	(1.17–2.01)	139	209	1.07	(0.68–1.69)	44	83	0.96	(0.50–1.85)	19	38	1.48	(0.86–2.55)	34	53	2.13	(1.34–3.39)	54	66
Beer consumption	1.38	(0.95–2.00)	61	96	1.06	(0.60–1.86)	22	42	0.79	(0.34–1.83)	9	22	1.00	(0.42–2.38)	11	22	2.30	(1.14–4.61)	24	28
Rice/wheat wine consumption	1.47	(1.03–2.09)	65	95	1.00	(0.53–1.90)	17	34	1.62	(0.63–4.19)	9	12	1.52	(0.74–3.14)	16	23	1.66	(0.96–2.87)	28	37
Hard liquor consumption	1.26	(0.91–1.75)	70	116	0.83	(0.47–1.46)	4	49	0.80	(0.35–1.82)	10	24	1.04	(0.53–2.04)	15	29	1.94	(1.10–3.40)	30	36
Hair dyes	0.98	(0.80–1.20)	263	530	1.01	(0.72–1.40)	94	187	0.97	(0.60–1.56)	46	93	0.83	(0.55–1.25)	61	135	1.05	(0.75–1.46)	103	201

AML = acute myeloid leukemia; AML-RCA = AML with recurrent cytogenetic abnormalities; APL = Acute promyelocytic leukemia; AML-MD = AML with multilineage dysplasia; AML-noc = AML not otherwise categorized. OR = odds ratio; 95% CI = 95% confidence interval; Ca = cases; Co = controls.

did not increase the risk of AML-total (OR = 1.05, 95% CI = 0.82–1.34) or AML subtypes, except for AML-MD (OR = 1.71, 95% CI = 1.05–2.77).

Significant risk excess for AML-total was associated with three non-occupational farm-related exposures: “living on a farm” (OR = 1.67, 95% CI = 1.37–2.03), “planting crops” (OR = 1.62, 95% CI = 1.27–2.06), and “raising livestock or animals” (OR = 1.84, 95% CI = 1.30–2.59). Similar increases in risk were consistently observed for all major subtypes, with the exception of APL and “raising livestock or animals” (Table 6). For example, the risk of AML-MD was 2.71 (95% CI = 1.44–5.10) for “raising livestock or animals”. As mentioned earlier, detailed analysis of occupations and specific exposures will be presented in a separate report in the future. However, to facilitate our discussion below of low-level education (as a surrogate for socioeconomic status) and living on a farm, included in Table 6 are several selected occupational risk factors related to farming. Significantly elevated risks for AML-total as well as several AML subtypes were associated with employment as farm workers or in the agricultural industry, and exposures to insecticides or fertilizers. For example, for farm workers the OR for AML-total was significantly elevated (OR = 1.61, 95% CI = 1.27–2.03).

Analysis similar to those presented in Tables 5 and 6 was carried out for other rarer AML 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. Instead, we will present results of selected combinations of risk factors and the other AML subtypes. ORs and 95% CIs for combinations with a *p*-value less than 0.10 (to include all significant as well as “suggestive” associations) are presented in Table 7. Alcohol consumption seemed to affect both “AML without maturation” and “AML with maturation”. Farm-related risk factors (“living on a farm”, “planting crops”, “raising livestock or animals”, “farm workers”, and “agricultural industry”) seemed to have an impact on acute erythroid leukemia, acute monoblastic and monocytic leukemia, and AML with t(8;21)(q22;q22), (AML1/ETO).

4. Discussion

This study represents an attempt to investigate the relationships between personal, lifestyle, and environmental risk factors and AML-total and AML subtypes according to the WHO 2001 classification of myeloid neoplasms. The case-control study design allowed us to systematically examine a wide variety of risk factors in relation to specific AML subtypes. Had we chosen the 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 (Wong, 2001). Because of the large number of ORs calculated (for the large number of combinations of risk factors and AML 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. As commented by Mantel and Haenszel in their 1959 landmark paper on the methodology of case-control studies: “The usual prescription for coping with this multiple comparison problem—requiring individual comparisons to test significant at an extreme probability level to reduce the number of associations incorrectly asserted to be true—would result only in making real associations difficult to detect. However, the

Table 6
Odds ratios and 95% confidence intervals for AML and selected major WHO subtypes by environmental exposures and occupational risk factors related to farming.

Risk factors	AML-total			AML-RCA			APL			AML-MD			AML-noc		
	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
Home/workplace renovation	1.22 (0.92–1.63)	84	141	1.82 (1.16–2.85)	40	47	2.02 (1.06–3.85)	20	21	0.89 (0.46–1.74)	15	33	0.95 (0.59–1.54)	27	57
Living within 100 m of power lines	1.05 (0.82–1.34)	128	245	1.06 (0.70–1.60)	44	82	1.05 (0.59–1.86)	22	41	1.71 (1.05–2.77)	38	50	0.73 (0.48–1.10)	42	106
Living on a farm	1.67 (1.37–2.03)	352	545	1.62 (1.16–2.26)	118	185	1.51 (0.96–2.38)	64	105	1.89 (1.26–2.82)	88	129	1.73 (1.25–2.41)	141	216
Planting crops	1.62 (1.27–2.06)	181	268	1.64 (1.09–2.48)	58	82	1.39 (0.78–2.49)	29	47	1.82 (1.16–2.88)	54	75	1.54 (1.03–2.30)	66	104
Raising livestock or animals	1.84 (1.30–2.59)	76	93	1.42 (0.76–2.68)	19	28	0.77 (0.28–2.13)	6	15	2.71 (1.44–5.10)	28	26	1.55 (0.87–2.74)	26	37
Farm workers	1.61 (1.27–2.03)	187	275	1.53 (1.02–2.29)	57	85	1.22 (0.69–2.15)	28	49	1.86 (1.19–2.91)	56	77	1.56 (1.07–2.29)	71	107
Agricultural industry	1.57 (1.24–1.97)	200	304	1.55 (1.04–2.32)	62	93	1.21 (0.69–2.12)	31	55	1.77 (1.13–2.78)	57	82	1.54 (1.06–2.24)	78	121
Insecticides	1.53 (1.16–2.04)	106	152	1.62 (0.63–4.19)	34	51	1.26 (0.65–2.44)	18	30	1.39 (0.80–2.43)	28	44	1.75 (1.11–2.78)	42	54
Fertilizers	1.64 (1.23–2.19)	104	141	1.61 (0.95–2.73)	31	43	1.41 (0.70–2.82)	17	26	1.34 (0.79–2.27)	29	46	1.89 (1.17–3.03)	41	50

AML = acute myeloid leukemia; AML-RCA = AML with recurrent cytogenetic abnormalities; APL = acute promyelocyte leukemia; AML-MD = AML with multilineage dysplasia; AML-noc = AML not otherwise categorized. OR = odds ratio; 95% CI = 95% confidence interval; Ca = exposed cases; Co = exposed controls.

multiple comparison problem exists only when inferences are to be drawn from a single set of data. ... The inferences will be based on a collation of evidence, the degree of agreement and reproducibility among studies, and their consistency with other types of available evidence, and not on the findings of a single study" (Mantel and Haenszel, 1959).

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 AML in a number of areas. First, we used the new WHO 2001 classification of AML, whereas most previous studies relied on the French–American–British (FAB) classification, which was introduced more than three decades ago. In the WHO classification, the blast threshold for the diagnosis of AML was reduced from 30% to 20% blasts in the blood or marrow. In addition, patients with certain recurrent cytogenetic abnormalities, regardless of the blast percentage, are considered to have AML (Vardiman et al., 2002). Therefore, the new WHO diagnostic criteria of AML are different from those used in the FAB classification, and some of the cases in our study would not have been classified as AML using the older FAB system. Second, we used a BMI classification that is more suitable for the Chinese population than the one used in western countries. The difference is that in the Chinese system the categories "overweight" (24.0–27.9) and "obese" (≥ 28.0) are both defined by lower BMI values.

One of the most consistent results in the present study was the inverse relationship between "education" and AML. Low-level education was consistently associated with an increased risk of not only AML-total but also all major WHO subtypes, although the magnitude of the increase varied by subtype. For the category of "education, none", the OR for AML-total was 2.66 and that for AML-noc was 4.72. In addition, not only AML-total demonstrated a significant downward trend by education level, but all three major WHO subtypes (AML-RCA, AML-MD and AML-noc) did as well. "Education" is often a surrogate measure for socioeconomic status or occupation, or a combination of the two. In a case-control study of AML in Los Angeles, AML cases had a lower socioeconomic status than did controls (Pogoda et al., 2002). On the other hand, AML risk was found to be unrelated to education in a study in Iowa (Sinner et al., 2005). In China, the education level of most farmers is not high, especially in the older age groups. In our study, farm workers were found to have an increased risk of AML-total (OR = 1.61, 95% CI = 1.27–2.03) as well as several major subtypes (Tables 6 and 7). Thus, the observed increased risk of AML associated with low education could be an indirect association through farm workers. To determine whether "education" had an independent effect on AML risk, we performed a logistic regression analysis of AML-total by education level stratified by the occupation "farm workers". Table 8 shows the risks of AML-total by education level separately for farm workers and non-farm workers. In either farm workers or non-farm workers, a clear inverse relationship between education level and AML risk was observed (p -trend < 0.01), with the "slope" being somewhat steeper among farm workers than among non-farm workers. That is, "education" and AML risk were negatively associated among farm workers and non-farm workers alike. Therefore, low-level education was an independent risk factor of AML-total in our study.

In our study, we found "height" to be negatively associated with AML-total and AML-MD, but not the other subtypes (AML-RCA, APL or AML-noc). An inverse relationship with "weight" was found for AML-total, AML-MD and AML-noc, but not for AML-RCA. In fact, the risk of APL (one of the subtypes of AML-RCA) increased with weight. Thus, our study indicated that the effect of weight might depend on the type of AML. In a study in Norway, height was found to be a significant risk factor of AML (all subtypes) (Engeland et al., 2007). Similarly, in a study in Iowa, weight was found to be posi-

Table 7

Odds ratios and 95% confidence intervals for selected combinations of medical history, lifestyle and environmental risk factors and other AML subtypes.^a

AML subtype and risk factor combination	OR (95% CI)	p-Value	Ca	Co
AML with t(8;21) (q22;q22),(AML1/ETO)				
Family history of cancers	2.22 (0.93–5.28)	0.07	19	26
Planting crops	2.20 (0.96–5.03)	0.06	16	18
Raising livestock or animals	5.75 (1.56–21.20)	0.01	10	5
Farm workers	2.26 (0.99–5.17)	0.05	16	18
Agricultural industry	1.97 (0.88–4.41)	0.10	16	20
AML with inv(16)(p13q22) or t(16;16)(p13;q22),(CBFB/MYH11)				
Home/workplace renovation	3.18 (0.92–11.00)	0.07	7	5
AML with 11q23 (MLL) abnormalities				
Blood transfusion	3.00 (0.85–10.63)	0.09	6	4
AML without maturation				
Alcohol consumption (all kinds)	2.71 (1.04–7.05)	0.04	15	17
AML with maturation				
Alcohol consumption (all kinds)	7.09 (1.53–32.90)	0.01	13	10
Beer consumption	4.96 (0.99–24.84)	0.05	7	5
Rice/wheat wine consumption	5.00 (0.97–25.77)	0.05	5	2
Hard liquor consumption	3.36 (0.83–13.55)	0.08	7	6
Acute monoblastic and monocytic leukemia				
Planting crops	5.62 (1.14–27.79)	0.03	9	8
Farm workers	4.64 (1.22–17.64)	0.02	11	10
Agricultural industry	5.00 (1.49–20.25)	0.01	13	11
Acute erythroid leukemia				
Living on a farm	4.64 (0.91–23.81)	0.07	10	12

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

^a Only combinations with $p < 0.10$ are presented.

tively associated with overall AML (no subtype break-down) (Ross et al., 2004). We are not aware of any epidemiologic studies of AML subtypes and height or weight.

For the composite measure BMI, our study demonstrated a negative association with AML-total and two major WHO AML subtypes (AML-MD and AML-noc). In contrast, APL showed a significant positive association with BMI. For the "obese" category, there was a significant reduction in risk for AML-total (OR = 0.67) and AML-noc (OR = 0.42), but a significant increase for APL (OR = 2.15). Other studies based on the overall category of AML reported an increased risk with increasing BMI (Engeland et al., 2007; Kasim et al., 2005; Ross et al., 2004). Although the exact mechanism is unclear, it has been hypothesized that the increased risk may be related to decreased immune response and increased plasma leptin hormone associated with obesity (Kasim et al., 2005). We are not aware of any epidemiologic studies of AML subtypes and BMI. In our study APL was the only subtype that showed an increased risk with BMI. It is not at all clear why our result of BMI and AML-total was not in agreement with other studies based on the overall category of AML. Ethnicity could have been a source of difference. One may also question the accuracy of the self-reported weight, since some patients might have undergone weight changes as a result of their illnesses. However, the questionnaire specifically asked for "weight before the current illness". In any event, our study indicated that the effect of BMI on AML was specific to subtypes, which may explain the partial agreement between our study and others.

Although previous studies have reported an increased risk of leukemia (not limited to AML alone) associated with a family history of blood diseases or hematopoietic cancers, our study showed only a weak and non-significant effect on AML-total. The number of patients (cases or controls) with such a family history was small and the statistical power to detect a modest risk was inadequate. Our study showed a relatively weak but borderline significant association between a history of blood transfusion (prior to the current illnesses) and the overall category AML-total, but no clear relationship with any subtype. In the Iowa study cited above, no increased risk of AML was associated with blood transfusion (Sinner et al., 2005). Another paper based on the same study population reported a slightly higher proportion of leukemia (all types) cases than noncases with a history of blood transfusion (31.6% vs. 25.4%, $p = 0.08$) (Ross et al., 2002). Additional studies of blood transfusion and specific leukemia subtypes are needed.

An interesting and unique finding in our study was the reduced risk for AML-total and subtypes associated with the use of traditional Chinese medicines (longer than one month), including 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 AML and traditional Chinese medicines. One possible explanation is that indeed some traditional Chinese medicines have a beneficial effect. Another explanation is that individuals in our patient population who regularly relied on traditional Chinese medicines for common ailments might have avoided or minimized the use of some western medicines such as chloramphenicol (an antibiotic) and phenylbutazone (an anti-inflammatory medication), which have been linked to an increased risk of AML (Linnet and Cartwright, 1996; Linnet, 1985; Shu et al., 1987). Obviously, the inverse relationship between traditional Chinese medicines and AML, regardless whether it is a direct or indirect one, requires additional investigations.

Similar to some previous studies, we have found a positive association with cigarette smoking and AML-total. However, there was no upward trend by number of cigarettes smoked per day, but those who smoked up to one pack a day experienced a significant increase of AML-total by 33%. When duration of smoking was considered, a borderline significant upward trend was observed for AML-total but not for individual subtypes. Analysis by pack-years of smoking suggested modest upward trends for AML-total and AML-noc. Overall, our data suggested that smoking might have a modest effect on AML-MD and AML-noc but little or no impact on AML-RCA or APL. Other studies have also reported smoking may affect only certain subgroups of AML. In a case-control study

in Los Angeles, only the FAB M2 (AML with maturation; OR = 2.3) and FAB M4 (acute myelomonoblastic leukemia; OR = 1.9) were related to cigarette smoking (Pogoda et al., 2002). In our study, according to the WHO classification, the risk associated with smoking was elevated for AML with maturation (OR = 1.53, 95% CI = 0.63–3.71) and acute monoblastic and monocytic leukemia (OR = 1.31, 95% CI = 0.52–3.31), but neither increase was statistically significant. In a case-control study in England, a small non-significant excess was reported for ever smokers (OR = 1.19), but when the data were analyzed by cytogenetic subgroups, only AML-t(8;21) was found to be related to smoking (OR = 4.77) (Moorman et al., 2002). In our study, there was a non-significant increase of risk for the subtype AML with t(8;21)(q22;q22),(AML1/ETO) for ever smokers (OR = 1.33, 95% CI = 0.61–2.90). The results of smoking in our study and other investigations underscore the importance of the etiologic heterogeneity of AML.

The results from our study indicated that alcohol consumption was a risk factor for AML-total and AML-noc, and the positive relationship appeared to be relatively consistent for all types of alcohol drinks. A twofold increase in AML-noc was associated with alcohol consumption of any kind (OR = 2.13, 95% CI = 1.34–3.39). Because AML-noc is a “residual” category in the WHO 2001 classification, individual subgroups within the category were examined. The analysis indicated that alcohol consumption of any kind was significantly associated with an increased risk of AML without maturation (OR = 2.71, 95% CI = 1.04–7.05). Furthermore, the subtype AML with maturation was most strongly associated with alcohol consumption: alcohol of any kind (OR = 7.09, 95% CI = 1.53–32.90), beer (OR = 4.96, 95% CI = 0.99–24.84), wine/wheat wine (OR = 5.00, 95% CI = 0.97–25.77), and hard liquor (OR = 3.36, 95% CI = 0.83–13.55). In a study in China, an elevated risk was observed for AML FAB M2 subtype (AML with maturation) among children under 18 months whose mothers drank alcohol during pregnancy (Shu et al., 1996). In our study, there appeared to be no association between alcohol consumption and AML-RCA. A population-based case-control study in Iowa and Minnesota reported no association between alcohol (any kind) and AML (OR = 0.8) (Brown et al., 1992). From Texas, a case-control study reported an AML risk of twofold associated with the consumption of hard liquor (OR = 2.2), but no increased risk for beer or wine was found (Crane et al., 1992). Additional studies of alcohol consumption and AML subtypes are needed.

Home/workplace renovation seemed to increase the risk of AML-RCA, especially the specific subgroup APL (OR = 2.02, 95% CI = 1.06–3.85). There have been several investigations in China reporting an increased risk of acute leukemia (not further specified) associated with working in new or newly renovated workplaces or living in new or newly renovated homes (Wang and Jia, 2006; Yuan et al., 2004). 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 proper regulation or monitoring in China. For example, in China benzene levels in the range of several hundred mg/m³ associated with commercial painting have been reported (Wong, 2002,2003a,b; Zhu et al., 2004). 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 (Chen et al., 2002; Liu et al., 2002). Given the elevated risk found in our investigation and other studies, exposure to new or newly renovated homes or workplaces can be a serious public health issue in China. As many cities in China, especially large metropolitan areas such as Shang-

Table 8

Odds ratios and 95% confidence intervals for acute myeloid leukemia (all subtypes) by education level in farm workers and non-farm workers.

Education level	OR (95% CI)	Ca	Co
<i>Farm workers</i>			
None	2.93 (1.51–5.70)	35	28
Primary school	1.77 (1.12–2.79)	69	78
Middle school (reference)	1.00 Reference	60	115
High school	0.84 (0.45–1.59)	18	41
University or higher	0.58 (0.18–1.88)	4	13
Missing		1	0
	p -trend < 0.01		
<i>Non-farm workers</i>			
None	1.67 (0.91–3.06)	22	32
Primary school	1.24 (0.86–1.78)	68	121
Middle school (reference)	1.00 Reference	167	333
High school	0.92 (0.71–1.20)	165	352
University or higher	0.65 (0.49–0.87)	111	327
Missing		2	4
	p -trend < 0.01		

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

hai, 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.

The relationship between exposure to electromagnetic field (EMF) surrounding power transmission lines and leukemia has been a controversial issue for years (Linnet and Cartwright, 1996). Apart from the problem of defining and quantifying EMF exposure emitted from high voltage electrical power transmission lines, the type of leukemia also plays a role in the controversy. In our study, we did not find any increased risk associated with residential proximity to power transmission lines for AML-total, AML-RCA, APL or AML-noc. However, a significant association between residential proximity to high voltage power lines and AML-MD was found (OR = 1.71, 95% CI = 1.05–2.77). Future investigations of EMF and leukemia or AML need to take the heterogeneity of AML subtypes into consideration.

One of the most consistent findings in our study is the increased risks associated with farm-related exposures: “living on a farm”, “planting crops”, and “raising livestock or animals”. Of the 722 AML cases, 352 (48.75%) reported to have lived on a farm, compared with 545 of the 1444 controls (37.74%). Such a high proportion of patients admitted to Shanghai hospitals with a history of farm residence was somewhat unanticipated. One scenario we did anticipate was that, because of the high quality of the hospitals in Shanghai, many residents from neighboring provinces (especially rural areas) sought medical care in Shanghai. Another reason is that in 1958 large surrounding areas (including rural areas and farms) were annexed and incorporated into the City of Shanghai, which now covers 6340 km². Patients admitted to Shanghai hospitals, therefore, included residents from the rural areas or farming communities on the outskirts of the city. A third reason is the massive migration of villagers and farmers from inland rural regions into Shanghai in recent years. Finally, some older patients might have been assigned or relocated to rural areas of the country by the government during the Cultural Revolution in the 1960s and 1970s.

In our study, an increased risk of approximately 60–90% associated with “living on a farm” was observed for AML-total (OR = 1.67, 95% CI = 1.37–2.03) and the major subtypes (e.g., for AML-MD, OR = 1.89, 95% CI = 1.26–2.82). This finding was in agreement with previous studies. Living on a farm was found to be associated with a significantly increased risk of AML in a study in Iowa (risk ratio of 1.91) and in Texas (OR = 9.1) (Sinner et al., 2005; Crane et al., 1992). The other two farm-related variables “planting crops” and “raising livestock or animals” carried similar excess risks of AML and subtypes. “Planting crops” entails contacting and being exposed to agricultural chemicals including fertilizers and insecticides, and “raising livestock or animals” increases the opportunity of exposure to transmission of retroviruses, including bovine leukemia virus (Linnet and Cartwright, 1996). We will discuss these non-occupational farm-related variables further below in conjunction with the results of employment as farm workers or in the agricultural industry based on the analysis of occupations.

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 60% for AML-total (OR = 1.61, 95% CI = 1.27–2.03) and similar risks for all other major AML subtypes. However, it appeared that among farm workers the increased risk for AML-MD (OR > 2) was slightly higher than for other subtypes. Similar risks for AML-total and subtypes were observed for the agriculture industry. The increased risk for farm workers (occupation) or agriculture (industry) in our study was in agreement with many previous studies reporting an increased risk of either leukemia in general or, more specifically, AML in

the farming industry (Linnet and Cartwright, 1996; Lazarov et al., 2000). In a case-control study of AML in Novi Sad (Yugoslavia) and London, “farmers/gardeners” were found to have a significantly increased risk of AML (OR = 5.46, 95% CI = 1.11–26.69, based on 5 exposed cases and 5 exposed controls) (Lazarov et al., 2000). The advantage of our study was the large number of farm workers (187 AML cases and 275 controls classified as farm workers) and the 95% CIs were quite narrow. Another advantage of our study is the analysis by WHO subtypes. We are not aware of any other epidemiologic study that examined AML risk in farmers by WHO subtypes.

As stated above, a significantly increased risk of AML was also detected for “living on a farm” (OR = 1.67, 95% CI = 1.37–2.03) 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 897 patients (cases and controls) with a history of farm residence in our study, 452 (50.39%) 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 AML? 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 significantly increased risk of AML for “living on a farm” (OR = 1.51, 95% CI = 1.12–1.97), which was slightly smaller than the original OR = 1.67. 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 farm workers (but not matched triplets). The unconditional logistic regression model showed a similar result (OR = 1.50, 95% CI = 1.15–1.83). This analysis demonstrated that persons living on a farm, even if they did not work as farmers, were at an increased risk of AML. In other words, “living on a farm” was an independent risk factor for AML, apart from direct occupational exposures.

Several limitations of the study should be noted. First, in an interview-based case-control study such as ours, recall or reporting bias is always a potential concern. However, to minimize such bias, in our study neither the patients nor the interviewers were informed about the specific objectives or hypotheses of the study. Furthermore, the interviewers were not informed of the case/control status of the patients. Second, 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. Thirteen percent (13%) controls had an age difference of more than 5 years when compared to their corresponding cases. Nevertheless, the mean ages of all the cases (49.92 years) and controls (49.98) were almost identical (Table 1). 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. Third, our study was hospital-based and consisted of 29 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 AML) at these 29 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. Fourth, because of the large number of combinations of risk factors by AML subtypes, a large number of risk estimates were calculated and some might be statistically significant simply by chance alone. Therefore, consistency must be taken into consideration in the interpretation of the results, and, furthermore, our findings need to be replicated by other investigations in the future. Finally, some of the risk estimates were based on small numbers and the results need to be interpreted with caution.

On the other hand, our study has a few strengths as well. First, the participation rate among eligible AML patients in our study was extremely high (97%). Second, unlike some previous studies of leukemia in general, our study focused on only one specific type of leukemia, AML. Third, the number of AML patients was large not only in the overall disease category (all AML subtypes combined) but also in some major subtypes of AML. Fourth, another strength of the study is the detailed diagnosis based on the new WHO classification of myeloid neoplasms, which classified patients by individual AML subtypes based on a consideration of not only morphologic findings but also genetic, immunophenotypic, biologic, and clinical features of the patients. Many of the new WHO subtypes have never been investigated in an epidemiologic setting. With the large study size and the detailed diagnostic information, we were able to examine a wide spectrum of potential risk factors including personal, lifestyle and environmental exposures by subtype according to the new WHO classification. We believe our study is the first large-scale epidemiologic investigation of AML using the WHO classification.

5. Conclusion

In summary, we found several potential risk factors of AML (all subtypes combined) and individual subtypes; including low-level education, BMI, blood transfusion, smoking, alcohol consumption, home or workplace renovation, living on a farm, planting crops, raising livestock or animals, employment as farm workers or in the agricultural industry, and exposures to insecticides or fertilizers. Some risk factors applied to all or several subtypes (such as low-level education and living on a farm), while others were limited to one or two specific subtypes (such as home/workplace renovation and APL). An inverse association was found between BMI and overall AML or the sub-category “AML not otherwise categorized”, whereas a positive association between BMI and the subtype APL was detected. The difference in risk by subtype underscores the importance of investigating the etiologic commonality and heterogeneity of AML subtypes. An unexpected finding was the association between the use of traditional Chinese medicines and a reduced risk of AML in general as well as several major subtypes.

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