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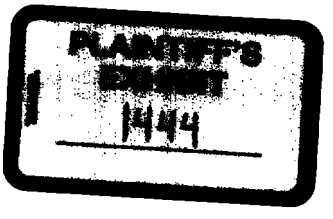
Abstract: Based on the incidence survey of leukemia and aplastic anemia (AA) from 1986 to 1988, Case control studies (1257 new leukemia cases and 339 new AA cases) were carried out according to the type of leukemia and AA in order to better understand the epidemiologic characteristics of the diseases. Controls were matched randomly (age, sex and ethnic group) from the same population. The data were analyzed with the conditional Logistic multi-regression model and calculated on an IBM-PC/XT. The risk factors of M2a were found to be X-rays, antipyretics, benzene, pesticides and bimolane; that of M3 was chloramphenicol; that of M5 was X-rays; and that of other ANLLs was phenylbutazone. The risk factors of ALL were chloramphenicol, phenylbutazone and family members with cancer: those of CML were X-rays and hepatitis; those of CLL were chloramphenicol and benzene; those of AAA were antipyretics and hepatitis; and that of CAA ws X-rays.

* Chinese version -
(English translation follows)



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全国白血病和再生障碍性贫血危险因素分析

全国白血病与再生障碍性贫血流行病学调查协作组*

提要 在白血病和再生障碍性贫血（再障）发病情况调查基础上，采用基于全人群 1:2 配对的病例对照研究，对新发白血病 1257 例和再障 339 例进行危险因素调查。按白血病和再障的类型对危险因素进行条件 Logistic 回归模型分析，平衡混杂因素后，发现与 M2a 有关的危险因素有 X 线、解热镇痛药、苯类物及农药化肥，乙双吗啉类药为高度可疑因素；与 M3 有关的因素有氯（合）霉素；与 M5 有关的因素有 X 线；与其它急性非淋巴细胞白血病（ANLL）亚型有关的因素有抗风湿类药；与急性淋巴细胞白血病（ALL）有关的因素有氯（合）霉素、抗风湿药及直系亲属患肿瘤史；与慢性粒细胞白血病（CML）有关的因素有 X 线与病毒性肝炎。与急性再障（AAA）有关的因素有解热镇痛药与病毒性肝炎。与慢性再障（CAA）有关的因素有 X 线。单因素分析表明，与慢性淋巴细胞白血病（CLL）有关的因素有氯（合）霉素及苯类药。

关键词 白血病 贫血再生障碍性 因素分析统计学

白血病为造血组织的恶性增生，再障则为造血组织的过度萎缩。两病均严重危及人类健康，其可疑致病因素均包括物理、化学、生物和遗传四个方面。全国白血病与再生障碍性贫血流行病学调查协作组于 1986 年～1988 年同时对白血病及再障的发病情况及危险因素进行调查，现将危险因素分析如下。

材 料 与 方 法

一、调查对象 白血病 1257 例、再障 339 例，皆为 1986 年～1988 年各调查点的新发病例。除北京、辽宁鞍山、吉林延吉、新疆石河子等调查点因条件所限未进行病例对照调查外，其它各调查点均进行了危险因素调查。各病例均按同年龄、同性别及同民族原则，在同一调查人群内以多次随机抽样法选取两名未患血液病和肿瘤的“健康人”为对照。

二、调查方法及内容 所有病例和对照均采用同一调查表，按同一调查法由各调查点负责调查。调查内容包括：一般情况、周围环境、患病史、理化因子接触史、服药史及家族史等。

三、统计方法 所有资料均贮存于 IBM PC-XT 的 dBASE-Ⅲ数据库内，首先按状态风险分析程序对连续变量进行切割聚类，初步筛选危险因素[1]，随后用条件 Logistic 回归模型进行单因素分析，最后采用逐步引入法进行多因素条件 Logistic 回归分析[2]。变量的选择采用似然比检验，求出最终的最佳非饱和模型（$^{*}P\leq 0.05$；$^{**}P\leq 0.01$）。

四、类型分布 白血病和再障均按型别分析。ANLL 主要亚型 M2a、M2b、M3 和 M5 单独进行分析；其它 ANLL 亚型 M1，M4，M6 及 M7 因例数较少，合为一类进行分析（表 1）。

本文于 1990 年 6 月 30 日收到；*张晓波、杨崇礼、邵宗鸿整理（血液学研究所，天津）

表 1 白血病及再生障碍性贫血类型分布

Table 1 Type distribution of the cases studied

	ANLL					ALL	CML	CLL	AAA	CAA
	M2a	M2b	M3	M5	Others					
No. of cases	193	12	171	178	208	309	152	34	72	367
No. of control	386	24	342	356	416	618	304	68	144	534

结 果

一、条件 Logistic 模型单因素分析结果

M2b 由于病例数太少，故未发现与其相关的危险因素：X 线、解热止痛药、乙双吗啉类药、苯类物及农药、化肥与 M2a 发病相关，氯（合）霉素与 M3 相关，X 线和抗风湿药与 M5 相关，抗风湿药与其它 ANLL 亚型相关。氯(合）霉素、抗风湿药及直系亲属肿瘤史与 ALL 相关，X 线、解热止痛药、苯类物和病毒性肝炎与 CML 相关，氯（合）霉素和苯类物与 CLL 相关。解热止痛药和病毒性肝炎与急性再障（AAA）相关，X 线和苯类物与慢性再障（CAA）相关（表 2）。

表 2 白血病与再生障碍性贫血危险因素分析的OR值（单因素分析）

Table 2 ORs of the risk factors of Leukemia and aplastic anemia[A]

	ANLL				ALL	CML	CLL	AAA	CAA
	M2a	M3	M5	Other					
X-ray	1.24'	1.15	1.47**	1.09	1.10	1.71**	1.23	0.93	1.82**
Chloramphenicol	0.96	1.90'	1.34	1.28	1.96**	1.52	2.83'	2.13	1.37
Antipyretics	1.70**	1.25	1.10	1.07	1.18	1.40*	1.17	2.22**	1.14
Antirheumatics	0.84	0.64	0.37*	1.64*	2.45*	1.43	1.00	—	1.18
Bimolane	4.00*	—	—	2.73	2.22	—	—	—	—
Benzene	1.58'	1.42	1.44	1.20	1.12	1.65*	3.07*	1.71	1.57
Fertilizer and insecticides	2.23*	—	—	—	—	—	—	—	—
Viral hepatitis	1.55	1.35	1.55	1.45	1.59	2.53*	3.00	4.00*	1.67
Familyhistory of malgnancy	1.63	0.61	0.81	1.15	1.78**	—	0.67	1.47	1.02

[A] : calculated with conditional logistic model for monovariable;

—: cancelled after screening

二、条件 Logistic 模型多因素分析结果

各类型白血病与再障均按逐步选入法对各危险因素进行条件Logistic 模型多因素分析，寻求各自的最佳非饱和模型。平衡混杂因素后，发现与 M2a 有关的危险因素有 X 线、解热止痛药、苯类物及农药化肥，与 M3 有关的因素有氯(合)霉素，与 M5 有关的因素有 X 线，与其它 ANLL 亚型有关的因素有抗风湿药；与 ALL 有关的因素有氯（合)霉素、抗风湿药及直系亲属患肿瘤史，与 CML 有关的因素有 X 线和病毒性肝炎，与 AAA 相关因素有解热止痛药和病毒性肝炎，与 CAA 有关因素有X 线（表 3）。CLL 病例数较少，多元分析，各因素均未达统计学意义。

表 3　白血病与再生障碍性贫血危险因素分析的OR值（多因素分析）

Table 3　ORs of the risk factors of leukemias and aplastic anemias[A]

	ANLL				ALL	CML	CLL /AAA	CAA
	M2a	M3	M5	Other				
X-ray	1.22*		1.46**			1.73**		1.76**
Chloramphenical		1.99*			1.87**			
Antipyretics	1.54*						2.42**	
Antireumatics				1.62*	2.89**			
Benzene	1.54*							
Fertilizer. insecticides	2.15*							
Viral hepatitis						2.73*	6.87*	
Family history of malignancy					1.96**			

[A] calculated with conditional logistic model for multiple variables

讨　论

以往危险因素调查因病例数所限，多未分析不同型别白血病和再障的主要致病因素。本调查在全国范围内进行，病例较多，故根据白血病和再障主要亚型分别对其危险因素进行分析。

医源性照射者、放射线工作者及日本原子弹爆炸幸存者的发病调查证实，电离辐射具有致白血病和再障作用[3~5]。本调查进一步表明，电离辐射主要引起 M2a、M5 及 CML 等髓系白血病及慢性再障，未发现电离辐射与淋巴细胞白血病明显相关。

乙双吗啉类药是近年来用于治疗银屑病的新药，然而自该药问世以来，中华血液学杂志已收到 80 多例由该药所致急性髓系白血病（多为 M2a 及 M3）的报告[6]。实验室观察表明，乙双吗啉是极强的致染色体畸变物[6]。本调查亦发现乙双吗啉类药与 M2a 发病有关，但由于人群中服用乙双吗啉类药的频率较低，故多因素分析尚不能确定该药与 M2a 的相关性。结合众多病例报告，笔者认为乙双吗啉与髓系白血病的关系应予肯定，我们已向卫生部建议禁用此类药物。氯（合）霉素对骨髓的损害作用十分明显，许多调查均表明，氯（合）霉素具有较强的致白血病和再障作用[3~5]。日本自 1975 年限用氯（合）霉素以来，再障死亡率明显下降[7]。本调查发现氯（合）霉素是 M3 和 ALL 的危险因素，对 CLL 也有一定作用，对其它类型白血病和再障的作用不明显。国内有关调查发现，解热镇痛药与再障发病有一定关系[8]。本调查结果亦显示，解热镇痛药与 M2a 及 AAA 发病有关。一般认为抗风湿类药（主要是保泰松）可引起急性白血病[3]，其致再障作用不如致白血病作用明显[5]。本调查亦未发现抗风湿类药与再障的关系，但该类药与 ANLL 及 ALL 具有一定关系。

苯对造血系统的危害早已证实，Aksoy 等[9]随访发现，土耳其苯作业工人白血病发病率明显高于普通人群。本调查发现苯与 M2a 有明显的相关关系，与 CML、CLL 及 CAA 也有一定关系。发病情况调查表明，油田白血病发病率较高，提示苯等化学物质污染环境使白血病发生。农药化肥与白血病和再障的关系偶有报道，本调查表明其可能与 M2a 发病有关。

已知病毒可引起鸡、狗和小鼠等多种动物白血病[10]，成人 T 细胞白血病由人类 T 细胞白血病病毒感染所致，Burkitt 淋巴瘤与 EB 病毒有关，人类细小病毒等多种病毒感染可胞

起急性造血功能停滞，病毒性肝炎则可能致急性再障。本调查结果表明，病毒性肝炎与CML、AAA有关，提示白血病和再障的发病与病毒感染有一定的相关关系。

以往家族和双生子调查表明，一部分白血病的发病受遗传因素影响[11]。本调查证实，ALL的发病与直系亲属患肿瘤史有密切关系，提示ALL有较强的遗传背景。

从本次调查结果可以看出，髓系白血病，尤其是M2a受外界环境致病因素的作用较淋巴细胞系统白血病明显，而遗传因素则与ALL密切相关。由于回顾性调查的局限性及白血病和再障的潜伏期尚不清楚，本调查结果尚不能表明危险因素与白血病和再障间的因果关系，只是为今后各类型白血病和再障的病因学研究提供线索。

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Risk Factors Analysis of Leukemia and Aplastic Anemia in China

Chinese Epidemiologic Study Group of Leukemia and Aplastic Anemia

Based on the incidence survey of leukemia and aplastic anemia **(AA)** from 1986 to 1988, Case control studies (1257 new leukemia cases and 339 new AA cases) were carried out according to the type of leukemia and AA in order to beffer understand the epidemiologic characteristics of the diseases. Controls mere matched randomly (age. sex and ethnic group) **from** the same population. The deta were analyzed with the conditional Logistic multiregression model and calculated on an IBM-PC/XT. The risk factors of M2a were found to be X-rays, autipyretics, benzene. pesticides and bimolane; that of M3 **was** chloramphenicol; that of M5 was X-rays: and that of other ANLLs was pheoylbutazone. The **risk** factors of ALL were choloramphenicol, phenylbutazone and family members with cancer: those of CML were X-rays and hepatitis; those of CLL **were** chloramphenicol and benzene;those of **AAA** were antipyretics and hepatitis; and that of **CAA** was **X-rays**.

Key words leukemia anemia, aplastic factor analysis, statisti—I

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Countrywide Analysis of Risk Factors for Leukemia and Aplastic Anemia

National Investigative Group for the Survey of Leukemia and Aplastic Anemia

Synopsis The foundation of our study of leukemia and apiastic anemia is a comparative survey using a 1:2 case ratio drawn from the entire population, surveying the risk factors in 1,257 cases of leukemia and 339 cases of aplastic anemia. Analyzing risk factors for leukemia and aplastic anemia types using conditional logistic model analysis, after accounting for extraneous factors, WC discovered risk factors associated with M2a include X-rays, antipyretic drugs, benzene type substances, arid insecticides arid chemical fertilizers. Bimolane type drugs is a high risk factor, Factors associated with M3 include chloramphenicol. Factors associated with M5 include X-rays. Factors associated with othcr forms of acute non-lymphatic leukemia (ANLL) include antireumatic type drugs. Factors associatcd with acute lymphatic leukemia (ALL) include chloramphenicol substances, antireumatics, and a family history of malignancy. Factors associated with chronic myelocytic leukemia (CML) include X-rays and viral hepatitis. Factors associated with acute aplastic anemia (AAA) include antipyretics and viral hepatitis. Factors associated with chronic aplastic anemia (CAA) include X-rays. Single factor analysis shows that significant factors associated with chronic lymphatic leukemia (CLL) include chloramphenicol and benzene.

Key terms leukemia aplastic anemia statistical analysis of risk factors

Leukemia is a malignancy of the blood production system; aplastic anemia is a degradation of the blood production system. Both illnesses are an equally grave threat to human health, Possible causes of these illnesses include four areas: physical, chemical, organic, and heredity. From 1986 to 1989, the National Investigative Group for the Study of Leukemia and Aplastic Anemia conducted research on tho pathology and risk factors of leukemia and aplastic anemia. The analysis of risk factors is presented below.

Materials and Methods

1. **Object of survey** 1,257 cases of leukemia and 339 cases of aplastic anemia. All were new cases from each survey site during the period 1986 to 1988. Except for Beijing, Yanji in Jilin, and Shihezi in Xinjiang, due to conditions restricting comparative analysis, survey of risk factors was undertaken at all

survey sites. Each case was placed in a sample group according to age, sex, arid nationality, and then compared with "healthy individuals" who had never experienced blood disease or malignancy and had been selected at random.

2. **Survey Method and Content** All cases and comparisons used the same survcy questionnaire. Each investigative site took responsibility for the survey according to a single survey method. The content of the survey included: general condition, environment, medical history, history of contact with physical and chemical factors, medication history, family history, etc..

3. **Statistical Method** All data was recorded on an IBM PC-XT using dBase-III. First we made an initial selection of risk factors by undertaking a process of isolation and grouping of successive variables according to an analytical processing of conditions and hazards.' We then used a conditional logistic model to analyze single factors. Last, we undertook multiple factor logistic analysis using a progressive selection method.' Variables were selected by the test of comparative likeness so as to obtain the best non-saturated model ($P<0.05$; $P<0.01$).

4. **Type Distribution** Both leukemia and aplastic anemia were analyzed according to respective types. (ANLL secondary types M2a, M2b, M3, and M6 were analyzed individually. Other ANLL secondary types, M1, M4, M6, and M7 had few cases and were combined for analysis.).

Table 1 Type Distribution of Cases Studied

	ANLL					ALL	CML	CLL	AAA	CAA
	M2a	M2b	M3	M5	Others					
No. of cases	193	12	171	178	208	309	152	34	72	267
No. of control	386	24	342	356	416	618	304	68	144	534

Results

1. **Conditional Logistic Model for Monovariables**

Since there were too few cases of M2b, it's associated risk factors wcre not discovered. X-ray, antipyretics, bimolane, benzene, chemical fertilizer arid insecticides were related to M2a illness. Chloramphenicol is related to M3. X-ray and antireumatics arc associated with M5. Chloramphenicol is associated with other ANLL types. Chloramphenicol, antireumatics, and a family history of malignancy is associated with ALL, X-rays, antipyretics, benzene, and viral hepatitis is associated with CML. Chloramphenicol and benzene is associated with

CLL. Antipyretics and viral hepatitis are associated with acute aplastic anemia (AAA). X-rays and benzene are associated with chronic aplastic anemia (CAA).

Table 2 ORs of the Risk Factors of Leukemia and Aplastic Anemia^

	ANLL				ALL	CML	CLL	AAA	CAA
	M2a	M3	M5	Others					
X-ray	1.24*	1.15	1.47**	1.09	1.10	1.71**	1.23	.93	1.82
Chloramphenicol	.96	1.90*	1.34	1.28	1.96**	1.52	2.83*	2.13	1.37
Antipyretics	1.70**	1.25	1.10	1.07	1.18	1.40*	1.17	2.22**	1.14
Antireumatics	0.84	0.64	0.37*	1.64*	2.45*	143	1.00	–	1.18
Bimolane	4.00*	--	–	2.73	2.22	–	–	–	–
Benzene	1.58*	1.42	1.44	1.20	1.12	1.65*	3.07*	1.71	1.57
Fertilizer & Insecticides	2.23*	–	--	--	–	--	–	–	–
Viral Hepatitis	1.55	1.35	1.55	1.45	1.59	2.53*	3.00	4.00*	1.67
Family History of Malignancy	1.63	0.61	0.8	1.15	1.78**	–	0.07	1.47	1.02

^: calculated with conditional logistic model for monovariable

--: cancelled after screening

2. Conditional Logistic Model for Multiple Variables

Each type of leukemia and aplastic anemia, according to a process of progressive selection, were analyzed for each risk factor using a conditional logistic model for multiple analysis, so as to find, the best non-saturated model for each. After accounting for extraneous variables, we discovered risk factors associated with M2a include X-rays, antipyretic drugs, benzene type substances, and pesticides and chemical fertilizers, Factors associated with M3 include chloramphenicol. Factors associated with M5 include X-rays. Factors associated with other secondary types of ANLL include antireumatics. Factors associated with ALL include chloramphenicol, antireumatics, and a family history of malignancy. Factors associated with CML include X-rays and viral. hepatitis. Factors associated AAA include antipyretics and viral hepatitis. Factors associated with CAA include X-rays (Table 3). Cases of CLL were relatively few and multiple analysis for each factor yielded no statistically significant results.

Table 3 ORs of the Risk Factors of Leukemias and Aplastic Anemias^

	ANLL				ALL	CML	CLL	AAA	CAA
	M2a	M3	M5	Others					
X-ray	1.22*		1.46**			1.73**			
Chloramphenicol		1.99*			1.87**				

Antipyretics	1.54*					2.42**
Antireumatics		1.62'	2.89*			
Benzene	1.54*					
Fertilizer & Insecticides	2.15*					
Viral Hepatitis				2.73*		6.87*
Family History of Malignancy			1.96*			

^: calculated with conditional logistic model for multiple variables

Discussion

Previous surveys of risk factors were limited by the number of cases, arid for the most part did not analyze major causes of different types of leukemia and aplastic anemia. This survey was carried out on a countrywide scale, with a relatively large number of cases, and analyzed the risk factors associated with the major types of leukemia and aplastic anemia.

Surveys of medical radiation technicians, radiation workers, and Japanese atomic bomb survivors prove that leukemia and aplastic anemia is a side-effect of ionized radiation.[3,4,5] This survey further shows that ionized radiation is a major cause of M2a, M5 arid CML myelocytic leukemias and chronic aplastic anemia. Wc have not yet discovered a clear relation between ionized radiation and lymphatic leukemia.

Bimolane type drugs are new drugs which in recent years have been used to treat psoriasis. However, since it was introduced, the *Chinese Journal of Hematology* has received over 80 reports of this drug causing acute myelocytic leukemia (mostly M2a and M3).[4] Laboratory observations show that bimolane is a strong chromosome abnormality inducer.[6] This survey also discovered that bimolane is associated with M2a, but since the ratio of those who have used bimolane is relatively low, multiple variable analysis is unable to confirm the relationship between this drug and M2a. The aurhors believe that the many reports of illness, however, confirm a relationship between bimolane and myelocytic leukemia, arid we have already recommended to the Ministry of Health that the use of this drug be discontinued. The destructive effects of chloramphenicol on bone marrow is absolutely clear. Many studies have all showed that chloramphenicol has strong leukemia arid aplastic anemia effects?" Since Japan restricted the use of chloramphenicol in 1975, the death rate from aplastic anemia has noticeably declined.[7] This study discovered that chloramphenicol is a risk factor for M3 arid ALL. It also has some relationship with CLL. The effect on other types of leukemia and aplastic anemia is unclear. Related studies in China have discovered that there is a definite relationship between antipyretics arid aplastic anemia.[8] The results of this study also indicate that antipyretics are associatcd with M2a and AAA. It is generally considered that antireumatics (most importantly

phenylbutazene) can cause acute leukemia.[3] Its role as a cause of aplastic anemia is not as apparent.[5] This study also did not discover a relationship between antireumatics and aplastic anemia, but this kind of drug has sonic relationship with ANLL and ALL.

The destructive effect of benzene on the blood production system was early established, Aksoy et al discovered that the incidence rare of leukemia in Turkish benzene 'workers was clearly higher than for the general population.' Our research indicates that benzene has a strong cooperative relationship with M2a, arid some relationship with CML, CLL, and CAA. Surveys indicate that the incidence of leukemia at oil fields is relatively high, showing that an environment contaminated with benzene and other chemical pollutants can cause leukemia. A relationship between insecticides and chemical fertilizers, and leukemia and aplastic anemia has occasionally been reported. This study indicates there is a possible relationship with M2a.

We already know that viruses can cause leukemia in several animals such as chickens, clogs, and mice.[10] Adult T-cell leukemia *is* caused by viral infection. There is a relationship between Burkitt's lymphosarcoma and the EB virus, other viruses can also cause acute degradation of blood production capability, and viral hepatitis can lead to acute aplastic anemia. The results of this study indicate that there is a relationship between viral hepatitis and both CML and AAA, showing that there is some cooperative relationship between viral hepatitis and leukemia and aplastic anemia.

Previously, studies of families and twins indicated that a portion of leukemia cases are influenced by heredity." Our study proves that there is a close relationship between ALL and a family history of malignancy, showing that ALL has a relatively strong hereditary background.

From the results of this study we can see that myelocytic leukemia, especially M2a, is more clearly affected by environmental influences than lymphatic leukemia, and hereditary factors have a close relationship with ALL. Due *to* the limitations of retrospective. studies anti the fact that the incubation periods for leukemia and aplastic anemia arc still unclear, the results of this *study* still cannot indicate *the* cause and effect relationship between risk factor; and leukemia and aplastic anemia, and can only provide leads for future research on leukemia and aplastic anemia pathology.

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