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Original article

Case-Control Study of Occupational Acute Myeloid Leukemia in the Republic of Korea

Min Young Park [1], Hyoung-Ryoul Kim [1], Jun-Pyo Myong [1], Byung-Sik Cho [2,3], Hee-Je Kim [2,3,**], Mo-Yeol Kang [1,*]

[1] *Department of Occupational and Environmental Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea*
[2] *Department of Hematology, Catholic Hematology Hospital, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea*
[3] *Leukemia Research Institute, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea*

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A B S T R A C T

Background: We conducted a case-control study to identify high-risk occupations and exposure to occupational hazards for acute myeloid leukemia (AML).
Methods: When patients with AML admitted to the Department of Hematology in the study hospital for the first time are referred to the Department of Occupational and Environmental Medicine, data on occupation are collected by investigators to evaluate work-relatedness. Community-based controls were recruited through an online survey agency, and four controls per case were matched. Occupational information was estimated using structured questionnaires covering 27 specific occupations and 32 exposure agents. Conditional logistic regression analysis was performed by pairing cases and controls.
Results: In the analysis of the risk of AML according to occupational classification, a significant association was found in paint manufacturing or painting work (OR = 2.22, 95% CI: 1.03–4.81) and aircrew (OR = 6.00, 95% CI: 1.00–35.91) in males, and in pesticide industry (OR = 6.89, 95% CI: 1.69–28.07) and cokes and steel industry (OR = 2.00, 95% CI: 1.18–22.06) in $\geq$60 years old. Moreover, the risk of AML increased significantly as the cumulative exposure to thinners increased. In the analyses stratified by sex and age, the association between pesticide exposure and AML was significant in males (OR = 3.28, 95% CI: 1.10–9.77) and in $\geq$60 years old (OR = 6.22, 95% CI: 1.48–26.08).
Conclusion: This case-control study identified high-risk occupational groups in the Republic of Korea including paint manufacturers and painters, aircrew, and those who are occupationally exposed to pesticides or paint thinners.

1. Introduction

Cancer is the leading cause of death in developed countries, and there is a growing interest in understanding its causes. Although statistics vary, approximately 3–6% of all cancers worldwide are caused by exposure to carcinogens in the workplace [1], and, especially in the Republic of Korea, the incidence of cancer due to occupational hazards is estimated to be 5% of all cancer diagnoses [2].

Respiratory cancer is the most widely recognized occupational cancer, and additionally, bladder cancer, sinus cancer, leukemia, lymphoma, and skin cancer are well known as occupational cancers

Min Young Park: https://orcid.org/0000-0002-7812-7912; Hyoung-Ryoul Kim: https://orcid.org/0000-0001-7535-3140; Jun-Pyo Myong: https://orcid.org/0000-0001-8674-1034; Byung-Sik Cho: https://orcid.org/0000-0002-4524-6616; Hee-Je Kim: https://orcid.org/0000-0003-4098-3366; Mo-Yeol Kang: https://orcid.org/0000-0002-1682-865X

* Corresponding author. Department of Occupational and Environmental Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, 222, Banpo-daero, Seocho-gu, Seoul, 06591, Republic of Korea.
** Corresponding author. Department of Hematology and Leukemia Research Institute, Catholic Hematology Hospital, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, 222 Banpo-daero, Seocho-gu, Seoul 06591, Republic of Korea.
E-mail addresses: cumckim@catholic.ac.kr (H.-J. Kim), snaptoon@naver.com (M.-Y. Kang).

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with a relatively high incidence. According to an analysis of industrial accident compensation decisions and precedents of occupational cancer by the Korea Labor Welfare Service [3], cancer of the lymphohematopoietic system is the second most frequent occupational cancer source of claims and approvals for industrial accident compensation, after lung cancer. In a previous study, the attributable risk of cancer of the lymphohematopoietic system in the Republic of Korea was estimated to be approximately 15% [2].

The number of occupational cancer compensation cases in the Republic of Korea is very small compared with that in European countries [4]. Therefore, compared with other countries, patients in the Republic of Korea with work-related cancer are more likely to suffer from the economic burden acquired during cancer treatment because they do not receive appropriate workers' compensation. In particular, lymphohematopoietic cancers are the second highest reported occupational cancer after lung cancer in the Republic of Korea, but there has been a lack of research and exploration. Therefore, it is urgent to identify those at risk for lymphohematopoietic cancers so that patients receive workers' compensation that allows them to receive appropriate treatment without financial difficulties.

Approximately 25% of all cases of adult leukemia are acute myeloid leukemia (AML) [5], and there have been just a few international attempts at epidemiologic studies of AML. Previous studies have identified a large number of potential risk factors for AML including personal and family medical histories; lifestyle; environmental exposures; occupations and industries; and exposure to chemical, physical, or biological agents [6]. In a case-control study conducted at 29 hospitals in Shanghai, China [7], benzene, diesel fuel, metals, pesticides, adhesives, paints, and coatings were associated with an increased risk of AML, and a study conducted at the Texas M.D. Anderson Cancer Center reported that occupational exposure to organic solvents above a moderate level significantly increased the risk of AML [8]. However, suspected factors were not found to significantly increase the risk of AML in a large-scale epidemiological study of occupational organic solvent exposure and AML conducted in Nordic countries [9]. As such, the potential relationships between multiple occupational hazard exposures and AML have been investigated in epidemiological studies, but different studies have had inconsistent results. Especially in the Republic of Korea, there has been little systematic approach to risk factors.

The Seoul St. Mary's Hospital operates a cooperative program in collaboration with the Department of Occupational and Environmental Medicine (OEM) and Department of Hematology for patients with AML to identify work-related AML [10]. From June 1, 2018 to December 31, 2020, 376 patients with AML who were newly hospitalized in the Department of Hematology at the study hospital were asked about their occupation and exposure histories. Based on this information, we conducted a case-control study to identify high-risk occupations and exposure to occupational hazards for AML in the Republic of Korea.

2. Materials and methods

2.1. Study design and data sources

The Seoul St. Mary's Hospital has established an occupational AML surveillance system in cooperation with the Department of OEM and the Department of Hematology in 2018. When patients with AML admitted to the Department of Hematology for the first time are referred to the Department of OEM, data on occupation are collected by investigators to evaluate work-relatedness. A trained investigator conducts an exposure assessment using a structured questionnaire, followed by detailed interviews on occupational processes and exposure to substances [10].

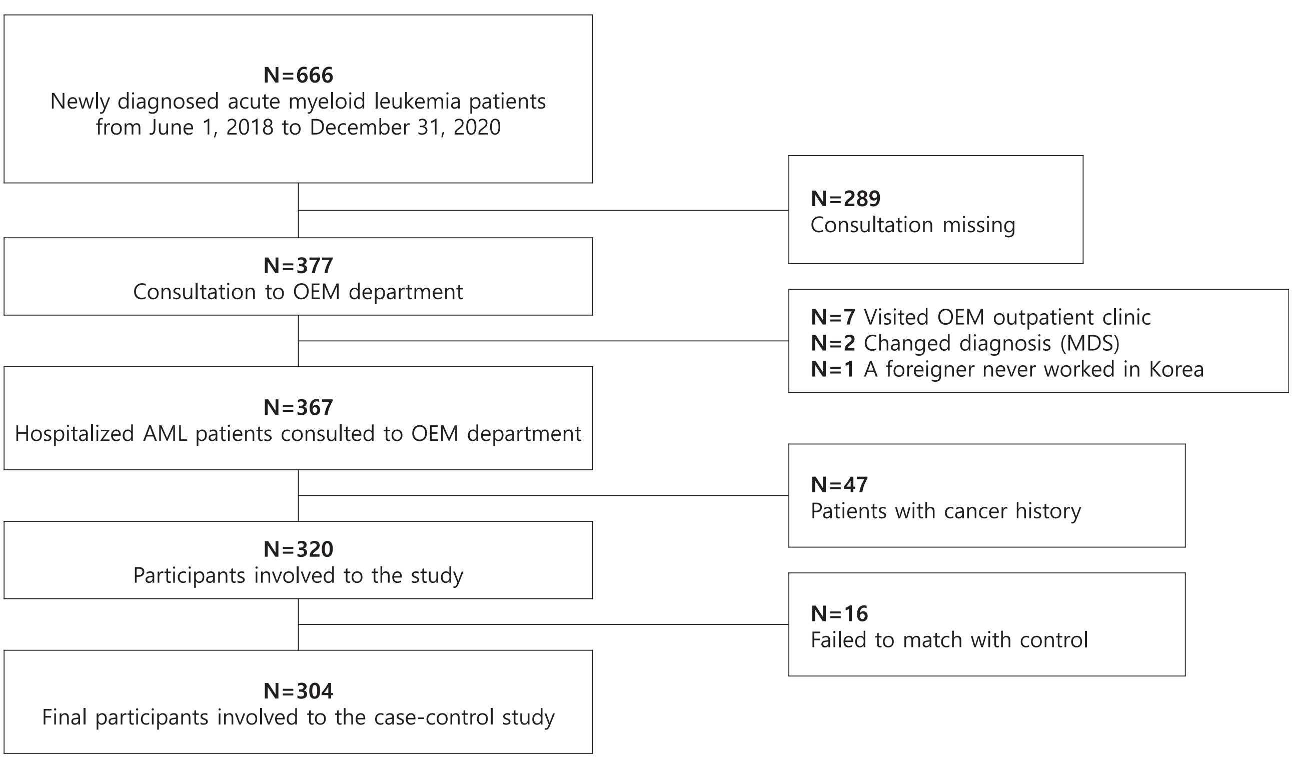

Fig. 1. A schematic diagram of participants with acute myeloid leukemia. MDS, Myelodysplastic syndromes; OEM, Occupational and Environmental Medicine.

The cases in this study were defined as all adults aged 19 years or older who were admitted to the Seoul St. Mary's Hospital with newly diagnosed AML and referred to the Department of OEM between June 1, 2018 and December 30, 2020. Patients who were initially diagnosed with AML but were subsequently diagnosed with other diseases through bone marrow examination and those who visited the Republic of Korea only for treatment were excluded. Patients who visited the Department of OEM as outpatients rather than as inpatients were excluded because they did not have an opportunity to complete the structured questionnaire. In addition, patients who had received chemotherapy or radiation therapy for other cancers before being diagnosed with AML were excluded from the study (Fig. 1).

Community-based controls without a history of AML or other malignant hematological diseases were recruited through an online survey agency. Four controls per case were matched for sex and age. A difference in age of up to 5 years was allowed between the cases and controls. Cases that could not be successfully matched to four controls due to a lack of recruitment in the community were matched with two or three controls. The matching age of the cases and controls was defined as the age at diagnosis and the age at survey participation, respectively.

For each case and control, occupational information had been collected using the same structured questionnaires covering 27 specific occupations and 32 exposure agents, which were based on the International Agency for Research on Cancer monograph and other previous studies for acute myeloid leukemia [7,8,11,12]. The cumulative exposure grade for the agents, especially formaldehyde, adhesives, thinners, and radiation, was estimated by evaluating the following logic:

$$\text{Exposure time grade} = \text{Period of use(years)} \times \text{Used per month (days)} \times \text{Exposure time per day(hours)} \times \text{Regularity of exposure} \quad (1)$$

$$\text{Exposure level grade} = (1) \times \text{Subjective exposure intensity} \quad (2)$$

$$\text{Cumulative exposure grade} = (2) \times \text{Personal protective equipment} \times \text{Ventilation status} \quad (3)$$

The exposure time grade was estimated by multiplying information on the period (years) of use of the agents, number of days of use per month, exposure time per day, and regular work status. The exposure level grade was evaluated by multiplying the exposure time grade by the subjective intensity level of exposure experienced by the workers. The subjective exposure intensity was chosen among “never exposed”, “almost not exposed”, “exposed but at a low level”, or “exposed at high concentration”. The participants could determine the intensity based on their individual experiences, such as their dirty coveralls after work, chemical splashes on their glasses, or smelling a strong odor. The cumulative exposure grade was evaluated by considering the exposure level grade, personal protective equipment, and ventilation status information. The cumulative exposure grade was classified as high, medium, or low. The items responded to as nominal variables (regularity of exposure, subjective exposure intensity, personal protective equipment, and ventilation status) and all grades (exposure time, exposure level, and cumulative exposure) were calculated using researcher-defined constants and weight values, respectively. All grade evaluation processes were derived through independent evaluations by two industrial hygiene experts.

Table 1
Demographic characteristics of acute myeloid leukemia cases and controls

Characteristic	Cases		Controls	
	N	%	N	%
Total	304	100	1170	100
Sex				
Male	172	56.58	662	56.58
Female	132	43.42	508	43.42
Age at index date*				
<30	37	12.17	125	10.68
30–39	43	14.14	174	14.87
40–49	53	17.43	167	14.27
50–59	69	22.70	271	23.16
60–69	80	26.32	372	31.79
70–79	18	5.92	55	4.70
≥80	4	1.32	6	0.51
Year of birth				
≤1950	27	8.88	52	4.44
1951–1960	91	29.93	366	31.28
1961–1970	65	21.38	265	22.65
1971–1980	45	14.80	182	15.56
1981–1990	44	14.47	171	14.62
≥1991	32	10.53	134	11.45

* Index date is defined as a date of diagnoses for cases and a date of survey for controls.

2.2. Statistical analysis

A descriptive statistical analysis was performed on the basic demographic characteristics of the case and control groups. Conditional logistic regression analysis was performed by pairing cases and controls according to sex and age, and the odds ratio (OR) and 95% confidence interval (CI) were calculated according to the exposure variables (occupations and exposure agents). In addition, stratified analyses were conducted by sex and age group (≥60 and <60 years) for each occupational classification and exposure agent to explore potential age-specific and sex-specific effect modification with occupations and exposures. Regarding the exposure agents, we estimated the exposure-response relationship according to the cumulative exposure grade by performing a simple linear regression as a test for trend. SAS 9.4 (SAS Institute Inc., Cary, NC, USA) was used for the statistical analysis.

3. Results

The demographic characteristics of the participants are shown in Table 1. A total of 320 patients with newly diagnosed AML were admitted to the study hospital during the study period; however, 16 patients (5%) were excluded from the study because of insufficient recruitment of controls (Fig. 1). Therefore, a total of 304 patients with AML and 1170 community controls were included in the study. The proportion of male participants was 56.58%, and the 60–69-year-old age group was the largest age group (26.32% of cases and 31.79% of controls) (Table 1).

Of the 27 occupations surveyed, 4 occupations (incineration plant, textile industry, asphalt manufacturing, and nuclear power plants) had no cases at all, while significant associations with AML were observed in paint manufacturing or painting (OR = 2.10, 95% CI: 1.01–4.35) and aircrews (OR = 6.00, 95% CI: 1.00–35.91) (Supplementary Table 1). The ORs of AML according to occupation stratified by sex and age are shown in Table 2, which shows a total of 10 occupational categories with ≥3 cases or significant results. In the analyses stratified by sex, AML was significantly associated with paint manufacturing or painting (OR = 2.22, 95% CI: 1.03–4.81) and aircrew (OR = 6.00, 95% CI: 1.00–35.91) in men. In the analyses stratified by age group, AML was significantly associated with paint manufacturing and painting in those under 60 years (OR = 3.11, 95% CI: 1.16–8.35) and working in the pesticide industry (OR = 6.89,

Table 2
Sex and age specific odds ratio (OR) and 95% confidence intervals (CI) of acute myeloid leukemia according to occupations

Occupational categories (10)	Sex-specific								Age-specific							
	Male				Female				<60				≥60			
	Case	Control	OR*	95% CI	Case	Control	OR*	95% CI	Case	Control	OR*	95% CI	Case	Control	OR*	95% CI
Motor vehicle maintenance and repair	4	14	1.09	0.36–3.33	1	2	2.00	0.18–22.06	2	8	0.97	0.21–4.57	3	8	1.84	0.46–7.42
Chemical, plastics, adhesives manufacturing	4	18	0.87	0.29–2.64	2	6	1.16	0.23–5.83	4	18	0.86	0.29–2.58	2	6	1.13	0.21–5.97
Paint manufacturing or painting	10	18	**2.22**	**1.03–4.81**	1	3	1.33	0.14–12.82	8	9	**3.11**	**1.16–8.35**	3	12	1.20	0.33–4.36
Cleansing, washing, or degreasing using solvents	3	6	2.00	0.50–8.00	1	0	—		3	5	2.40	0.57–10.04	1	1	4.00	0.25–63.95
Sterilization of medical devices	1	21	0.18	0.02–1.32	4	21	0.74	0.26–2.17	5	32	0.61	0.24–1.59	0	10	—	
Pesticide industry (including spraying)	6	13	1.81	0.67–4.88	1	1	4.00	0.25–63.95	1	8	—		6	6	**6.89**	**1.69–28.07**
Cokes and steel industry	2	9	0.89	0.19–4.11	0	1	—		1	8	—		1	2	**2.00**	**1.18–22.06**
Printing industry	3	20	0.56	0.17–1.91	0	6	—		1	15	0.27	0.04–2.02	2	11	0.62	0.13–2.89
Interior construction	5	16	1.21	0.44–3.32	0	1	—		1	11	0.36	0.05–2.82	4	6	2.52	0.71–8.93
Aircrew	3	2	**6.00**	**1.00–35.91**	0	0	—		1	1	4.00	0.25–63.95	2	1	8.00	0.73–88.23

* Cases with too wide confidence intervals due to no or very few patients were deleted.

95% CI: 1.69–28.07) and in the cokes and steel industry (OR = 2.00, 95% CI: 1.18–22.06) in those over 60 years. The results of all surveyed occupations are shown in Supplementary Tables 3 and 4.

Among the 32 exposure agents investigated, 16 agents showed no exposure in the case group, and no agents were found to have a statistically significant association with AML (Supplementary Table 2). AML was significantly associated with pesticide exposure in males (OR = 3.28, 95% CI: 1.10–9.77) and in those aged 60 years and older (OR = 6.22, 95% CI: 1.48–26.08) (Table 3). Adhesives, formaldehyde, radiation, and thinners were identified as exposure agents for which the exposure-response relationship could be examined according to the cumulative exposure grade, as the exposure of both the patient and control groups could be classified as high, medium, or low. All these substances showed a tendency for the OR values to increase as the cumulative exposure grade increased from low to high, but the exposure dose-response relationship was statistically significant only for thinners (p for trend = 0.02) (Table 4). The results of all surveyed exposure agents are shown in Supplementary Tables 5 and 6.

4. Discussion

This case-control study attempted to identify high-risk occupations and exposure to occupational hazards associated with AML using data from a general hospital in the Republic of Korea. The case-control study design allowed us to systematically explore a large number of factors associated with AML. In the analysis of the risk of AML according to occupational classification, a significant association was found in paint manufacturing or painting work and aircrew. Although none of the results of the analysis were based on the presence or absence of occupational exposure to specific substances, according to the cumulative exposure level of occupational exposure to substances, the risk of AML was significantly higher in the group with a high (top) cumulative exposure level to thinners. Moreover, the risk of AML increased as the cumulative exposure to adhesives, formaldehyde, radiation, and thinners increased, although the test for trend was not statistically significant. In the analyses stratified by sex and age, the association between pesticide exposure and AML was significant in males and those aged 60 years or older.

Airline cabin crew are exposed to levels of ionizing radiation of 2 to 4 mSv annually [13]. This dose is almost twice the typical annual dose that people in the general population receive from natural and medicinal sources. Gamma and neutron radiation dominate the cosmic radiation at typical cruising altitudes (8,000–10,000 m), with a small number of heavy nuclei. In 1990, the International Commission on Radiological Protection suggested that exposure of aircrew to radiation during flights should be considered an occupational exposure [14]. However, protection against exposure to cosmic radiation is insufficient in the Republic of Korea. Previous research on the incidence of cancer in airline pilots found an elevated prevalence of skin, prostate, and brain cancers [15]. Other studies have reported a higher risk of leukemia in airline cabin crew [16]. Given its large relative excess risk and the lack of other risk factors, leukemia (apart from chronic lymphocytic leukemia) is a cancer that can serve as a good indicator of the health impact of

Table 3
Sex and age specific odds ratio (OR) and 95% confidence intervals (CI) of acute myeloid leukemia according to exposure agents

Exposure agents (8)	Sex-specific								Age-specific							
	Male				Female				<60				≥60			
	Case	Control	OR*	95% CI	Case	Control	OR*	95% CI	Case	Control	OR*	95% CI	Case	Control	OR*	95% CI
Benzene	7	31	0.83	0.36–1.94	2	7	1.14	0.24–5.50	7	18	1.56	0.63–3.84	2	20	0.34	0.08–1.52
Pesticides	6	7	**3.28**	**1.10–9.77**	0	3	—		1	7	—		5	3	**6.22**	**1.48–26.08**
Adhesives	5	88	0.20	0.08–0.49	2	38	0.19	0.05–0.79	4	80	0.17	0.06–0.48	3	46	0.23	0.07–0.78
Formaldehyde	6	27	0.87	0.35–2.11	1	8	0.48	0.06–3.86	6	20	1.18	0.47–2.98	1	15	0.28	0.04–2.16
Radiation	4	32	0.47	0.16–1.36	1	17	0.23	0.03–1.74	3	35	0.32	0.10–1.07	2	14	0.58	0.13–2.58
Gasoline	5	73	0.26	0.10–0.65	1	9	0.41	0.05–3.23	4	47	0.24	0.08–0.78	2	35	0.23	0.05–0.97
Thinner (for paint)	14	90	0.57	0.32–1.03	2	12	0.67	0.15–2.98	10	55	0.62	0.30–1.30	6	47	0.47	0.19–1.16
Styrene	3	11	1.09	0.30–3.91	0	2	—		2	8	0.97	0.21–4.57	1	5	0.58	0.06–5.30

* Cases with too wide confidence intervals due to no or very few patients were deleted.

Table 4
The odds ratio (OR) and 95% confidence intervals (CI) of acute myeloid leukemia according to exposure agents by cumulative exposure grade

Exposure agents	Cumulative exposure grade	Cases	Controls	OR	95% CI	*p*-value for trend
Adhesives						0.30
	low	1	57	0.06	0.01–0.46	
	medium	1	16	0.20	0.03–1.58	
	high	3	4	2.22	0.47–10.40	
Formaldehyde						0.22
	low	2	8	1.00	0.21–4.71	
	medium	1	2	1.56	0.14–17.75	
	high	1	1	4.00	0.25–63.95	
Radiation						0.21
	low	2	18	0.50	0.12–2.18	
	medium	1	9	0.63	0.22–1.79	
	high	1	2	1.16	0.52–2.61	
Thinner (for paint)						**0.02**
	low	4	42	0.41	0.15–1.14	
	medium	5	13	1.21	0.72–2.03	
	high	4	2	**1.91**	**1.08–3.37**	

ionizing radiation. There have also been reports of an increased prevalence of chromosomal abnormalities in flight attendants that could indicate cancer risk [17]. A population-based cohort study of Danish pilots revealed that increasing flight hours in jets increased the risk of AML [18].

Paint manufacturing and painting have previously been reported to increase the risk of AML [19]. A case-control study of patients with AML in Novi Sad (Yugoslavia) and London found that painters had a significantly higher risk of developing AML (OR 4.57) [20]. Exposure to organic solvents such as benzene, toluene, xylene, degreasers, adhesives, and glues containing organic solvents is common in these jobs, raising the possibility that one or more of these exposures leads to a higher risk of AML. We found a statistically significant increase in the risk of AML among those who had occupational exposure to paint thinners, and the risk of AML increased according to the cumulative exposure grade. Our findings are consistent with those of a previous meta-analysis of industry-based cohorts that found that exposure to benzene at work increased the incidence of AML in a dose-dependent manner [21]. The association between solvents and AML has been investigated in several previous case-control studies. In a case-control study of AML in Italy, there was no association between exposure to any solvent and AML [22]. However, a hospital-based case-control study of AML in Shanghai found that exposures associated with an increased risk of AML included benzene, diesel fuel, metals, insecticides, fertilizers, glues and adhesives, paints and other coatings, and inks and pigments [7]. As the most researched solvent in relation to leukemia risk, benzene, which is sometimes mixed as an impurity in thinner, is recognized to be hemotoxic even at low levels of exposure [23]. However, evidence supporting an elevated risk of AML due to exposure to organic solvents other than benzene is mixed [7,20,22,23].

Several epidemiologic studies have investigated the relationship between pesticide exposure and AML, but the results have been inconsistent. In a systematic review, 17 cohort studies yielded a meta-rate ratio estimate of 1.21 for occupational pesticide exposure, but there was significant heterogeneity among the studies, largely due to the different occupational groups evaluated [24]. A statistically significant increase in risk was observed in studies targeting manufacturing workers and pesticide applicators, but not among farmers or agricultural workers. In a recent meta-analysis of 14 case-control studies including 3,955 cases and 9,948 controls, occupational pesticide exposure was found to be associated with an increased risk of AML (OR 1.51), which was not affected by sensitivity analyses [25]. However, although age was adjusted or matched in most studies, the researchers did not conduct an analysis of the risk of AML stratified by age as in this study.

As a case-control study, our study has some inherent limitations. The first is the potential for misclassification of exposure caused by recall bias, which is inherent in all case-control studies. To reduce this effect, OEM experts conducted an occupational history interview using a structured questionnaire. The reliability and applicability of self-reported occupational histories in determining exposure history were reviewed by two independent occupational hygiene experts for both cases and controls. Second, owing to the large number of ORs estimated (for a large number of risk factors and AML combinations), some ORs may have been statistically significant by chance alone. Although the observed age-specific and sex-specific variation in risk estimates may be because of physiological changes caused by age and sex on toxicokinetics, it is also possible due to the potential of coincidental observations. Third, patients were recruited in our study from one Korean hospital. Therefore, the patients included in the study may not be representative of the entire population of patients with AML in the Republic of Korea. However, the study hospital was a large university hospital that treats patients with AML from throughout the country. Thus, the patient population may be somewhat representative of the Korean AML patient population. Fourth, we were unable to consider other known risk factors or potential confounders associated with AML such as income, educational level, smoking, and genetics [6]. Because the data of cases for this study were obtained from hospital care and treatment settings, there is a limitation in that additional demographic information was not investigated. It is also not possible to rule out the possibility of residual confounding due to measurement error or unknown confounding factors. Finally, many of the risk estimates were based on small sample sizes; thus, caution should be exercised when interpreting the results. We plan to perform an updated analysis once we have recruited more patients with AML.

On the other hand, this study also has several strengths. To our knowledge, this is the first case-control study in the Republic of Korea to investigate occupation and occupational exposures as risk factors for newly diagnosed AML. Moreover, we were able to estimate overall occupational exposure more accurately by collecting lifetime occupational history rather than limiting the analyses to the most recent job.

In conclusion, this case-control study identified high-risk occupational groups in the Republic of Korea including paint manufacturers and painters, aircrew, and those who are occupationally exposed to pesticides or paint thinners. The research methodology used in this study serves as a reference for follow-up studies including multicenter hospital. The methods of this study, using data from the cooperative system established at the study hospital, are expected to influence the establishment of surveillance systems at other hospitals in the Republic of Korea in the future.

Once knowledge based on real-world experience is established to identify high-risk occupations and occupational hazard exposure for AML, it will affect the awareness of medical staff in hospitals and the operation of surveillance systems for occupational health services. Thus, more patients with AML and occupational cancers are expected to receive adequate treatment opportunities through compensation for occupational diseases. In addition, this study could be used to establish a policy basis for worker health protection and play an expanded role in disease prevention by raising awareness regarding risk factors for occupational cancers among workers and the general public.

Ethical approval

This study was conducted in accordance with the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board of the Seoul St. Mary's Hospital, the Catholic University of Korea (IRB number: KC21RISI0551).

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Conflicts of interest

The authors declare that they have no competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.shaw.2023.10.010.

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