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Association between cigarette smoking and the susceptibility of acute myeloid leukemia: a systematic review and meta-analysis

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Abstract. – OBJECTIVE: To elucidate the association between cigarette smoking and the susceptibility of acute myeloid leukemia (AML).

MATERIALS AND METHODS: We searched relevant articles from PubMed, Embase, and Cochrane by 1st December, 2018. This meta-analysis included 20 case-control studies, involving 7,538 AML patients and 137,924 healthy controls. Studies reported OR and 95%CI of the correlation between cigarette smoking and AML susceptibility were eligible. Subsequently, the included data were weighted by an inverse variance and analyzed using fixed-effects or random-effects model. Subgroup analysis was conducted based on ethnicities and sources of controls. Heterogeneity test was applied for the included articles. Data analyses were conducted using STATA 12.0.

RESULTS: Current smokers (OR=1.42, 95%CI= 1.28-1.57; *p*=0.392) and ever-smokers (OR=1.16, 95%CI=1.05-1.28; *p*=0.036) were associated with AML susceptibility. In the subgroup analysis by ethnicity, only current smokers (OR=1.45, 95%CI=1.29-1.63; *p*=0.371) and ever-smokers (OR=1.16, 95%CI=1.03-1.30; *p*=0.034) of the Caucasian population were associated with AML susceptibility. Stratified analysis based on SOC (source of controls) indicated increased susceptibility of AML in current smokers (OR=1.43, 95%CI=1.26-1.63; *p*=0.283) and ever-smokers (OR=1.20, 95%CI=1.07-1.35; *p*=0.078) of the population-based group. Nevertheless, only current smokers in the hospital-based group had increased susceptibility of AML (OR=1.45, 95%CI=1.19-1.76; *p*=0.198). The risks of AML in ever-smokers (OR=1.04, 95%CI = 0.81-1.35; *p*=0.054) of the hospital-based group did not remarkably changed.

CONCLUSIONS: In this meta-analysis, we confirmed the association between cigarette smoking and onset risk of AML, especially in the Caucasian population. High-quality, large-scale researches are required to be conducted in multi-center hospitals for verification.

Key Words:
Smoking, Susceptibility, AML, Meta-analysis.

Introduction

Acute myeloid leukemia (AML) is a malignant clonal disease originating from hematopoietic stem cells. AML is characterized by blocked differentiation, malignant proliferation, and apoptosis of normal hematopoietic cells, which is highly heterogeneous both in clinics and genetics[1-3]. AML is a multifactorial disease, and its complex process involves various potential risks, such as environmental factors, genetic factors, age, and races[4-6]. The specific pathogenesis of AML, however, is still unclear. Some epidemiological studies[3,6] have shown that smoking carcinogens, including benzene, formaldehyde, 1,3-butadiene, polycyclic aromatic hydrocarbons, and cesium, may increase the risk of AML. Meanwhile, a large number of candidate genes associated with AML have been identified[7]. Environmental factors, especially smoking, is proved to be reliable predictors of AML, which may contribute to primary prevention of AML[8].

Smoking is one of the biggest public health problems[9]. Globally, tobacco use causes nearly 6 million deaths and giant economic losses each year[9,10]. It is estimated that by 2030, more than 8 million people will die of smoking-induced diseases each year[10]. Smoking and drinking during pregnancy lead to the exposure of the fetus to carcinogens at the placental barrier, including benzene, polycyclic aromatic hydrocarbons, tobacco, and alcohol[11,12]. Smoking also affects spermatogenesis and damages sperm DNA by

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altering sperm morphology, activity, and concentration[13,14]. Maternal smoking during pregnancy does not show any correlation with childhood AML, although the risk of AML is relatively elevated[11,12]. Results on the correlation between paternal smoking and childhood AML are controversial[15,16].

To date, many studies[17-35] have been conducted to elucidate the relationship between smoking and susceptibility of AML. Some reports have demonstrated that smokers have a higher risk of developing AML than non-smokers. However, there are some studies that illustrated the inconsistent or even the opposite conclusions. It is necessary to verify whether smoking is the risk factor for AML. Here, we collected case-control studies to clarify the association between smoking and onset risk of AML.

Materials and Methods

Literature Search

We searched relevant articles from PubMed, Embase, and Cochrane by 1st, December, 2018. "Cigarette smoking" or "Tobacco", "Acute myeloid leukemia" or "Myelodysplastic syndrome", or "AML", and "Risk" or "Susceptibility" were used as key words. Citations in the enrolled eligible articles were manually searched. The latest and more comprehensive articles were selected if overlapping.

Inclusion and Exclusion Criteria

Only published articles on exploring the association between cigarette smoking and AML were enrolled. Inclusion criteria: (1) Independent case-control studies; (2) Explorations on the association between smoking and susceptibility of AML; and (3) OR and 95%CI or relative data that could be used to calculate OR were provided.

Exclusion criteria: (1) Non-case-control studies; (2) Retrospective studies; (3) Raw data on the association between smoking and AML were not provided; (4) Repeated published, low-quality articles. Review or abstract was excluded.

Data Extraction

Data acquisition was independently carried out by two reviewers using an accurate data acquisition table. A third reviewer was responsible for re-evaluating the disagreements of the previous two reviewers. Baseline data, including first author, year of publication, country, ethnicity, SOC, study period, patient age, case number, smoking evaluation, and Newcastle-Ottawa Scale (NOS) were extracted.

Statistical Analysis

OR and 95%CI were calculated to assess the strength of the association between smoking and onset risk of AML. Fixed-effect model (Mantel-Haenszel method) was used when $p<0.05$; otherwise, the random-effects model (Dersimonian-Laird method) was used. Subgroup analysis was conducted to explore potential sources of heterogeneity based on ethnic and control sources. Sensitivity analysis reflects the stability and reliability of the results by removing one individual study each time and recalculating their ORs. Publication bias was evaluated by Begg's funnel plot and Egger regression test. Statistical analysis was performed using Stata software (version 12.0, Stata Corporation, College Station, TX, USA). $p<0.05$ was considered statistically significant.

Results

Characteristics of the Studies

This meta-analysis included 20 case-control studies, involving 7,538 AML patients and 137,924 healthy controls[17-35]. Detailed characteristics and genotype distribution of selected studies reporting the relationship between cigarette smoking and onset risk of AML were illustrated in Table I. Flow diagram of literature search and selection process was detailed in Figure 1. Among the selected articles, 17 studies were conducted in Caucasians, and the remaining 3 studies were conducted in Asian populations. In addition, 13 population-based studies, 5 hospital-based studies, and 3 mixed studies were utilized to distinguish different SOCs.

Quantitative Synthesis Results

The overall results of this meta-analysis on elucidating the relationship between cigarette smoking and susceptibility of AMI were shown in Table II. Current smokers (OR=1.42, 95% CI=1.28-1.57; $p=0.392$) and ever-smokers (OR=1.16, 95% CI=1.05-1.28; $p=0.036$) had significant AML susceptibility (Figure 2).

Table I. Characteristics of studies that investigated the association between cigarette smoking and risk of acute myeloid leukemia.

Author	Year	Country	Ethnicity	SOC	Period	Age (years)	No. of cases	No. of control	Smoking evaluation	Matching	NOS
Ugai	2017	Japan	Asian	PB	1990-1994	40-69	90	96,992	Self-administered questionnaire	Age, sex, and study area	7
Metayer	2016	USA	Caucasian	PB	1974-2012	-	1,330	13,169	Self-administered questionnaire	Age, sex, ethnicity, highest parental education, and study center	8
Orsi	2015	France	Caucasian	PB	2010-2011	-	100	1,421	Medical records	Age and gender	7
Musselman	2013	USA	Caucasian	PB	2005-2009	20-79	414	692	Self-administered questionnaire	Age, sex, and BMI	9
Strom	2012	USA	Caucasian	PB	2003-2007	18-80	638	636	Personal interviews	Age, sex, race, county of residence	7
Kim	2012	Korea	Asian	HB	1997-2008	50.5 ±16.9	415	1700	Medical records	Age, sex	5
Wong	2009	China	Asian	HB	2003-2007	≥18	722	1444	Personal blinded interviews	Age, sex	8
Bjork	2009	Sweden	Caucasian	PB&HB	2001-2004	≥20	104	278	Face-to-face interviews	Age, sex, county of residence	8
Richardson	2008	Germany	Caucasian	PB	1986-1998	53.5±14	120	266	Face-to-face interviews	Year of birth, sex, region	8
Kasim	2005	Canada	Caucasian	PB	1994-1997	20-74	307	5039	Mailed questionnaires with telephone follow-up	Age, sex, body mass index	8
Speer	2002	USA	Caucasian	HB	1984-1993	Median age (65)	604	7107	Medical records	Age, sex	5
Pogoda	2002	USA	Caucasian	PB	1987-1994	25-75	412	412	Non-blinded interviews	Birth year, sex, race	7
Stagnaro	2001	Italy	Caucasian	PB	1990-1993	20-74	223	1779	Blind interviews	Age, sex, area of residence, education level, type of interview	8
Bjork	2001	Sweden	Caucasian	PB	1976-1993	35-76	333	351	Structured telephone interview	Age, sex, county of residence	6
Mele	1994	Italy	Caucasian	HB	1986-1989	≥30	118	467	Personal interviews	Age, education, residence	6
Sandler	1993	USA/Canada	Caucasian	PB	1986-1989	18-79	423	618	Telephone interviews	Age, sex, race, region	7
Ciccone	1993	Italy	Caucasian	PB&HB	1989-1990	-	50	246	Structured interview	Age, region of birth, residence	7
Kane	1999	UK	Caucasian	PB	1991-1996	-	695	1593	Personal interview	Age, sex	7
Pasqualetti	1997	Italy	Caucasian	HB	Not specified	-	73	73	Medical record review	Age, sex, center	5
Brownson	1991	USA	Caucasian	PB	1984-1990	≥20	367	3641	Medical records	Age	7

SOC: Source of controls; PB: Population-based controls; HB: Hospital-based controls.

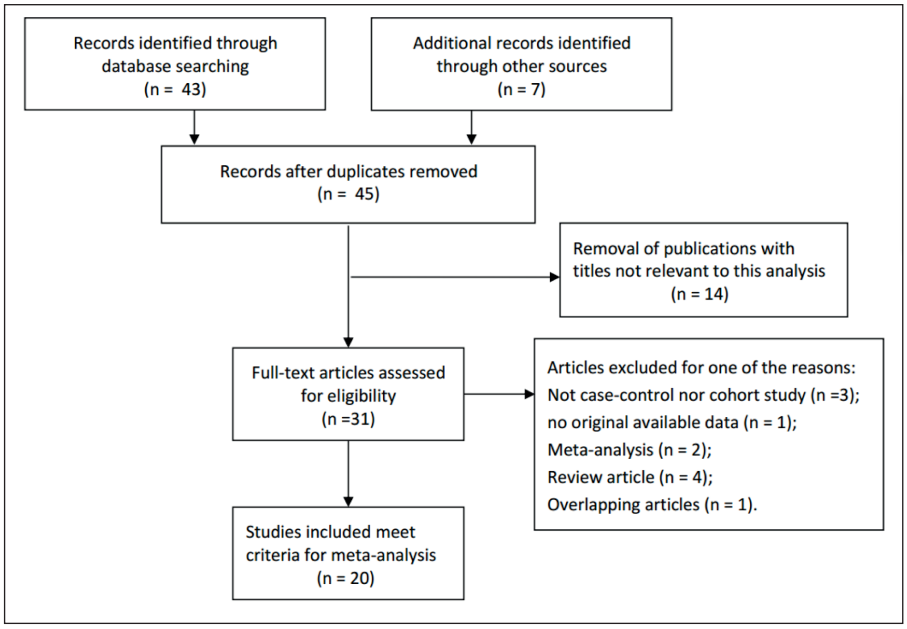

Figure 1. Flow diagram of literature search and selection process.

In the subgroup analysis by ethnicity, only current smokers (OR=1.45, 95%CI=1.29-1.63; p=0.371) and ever-smokers (OR=1.16, 95%CI=1.03-1.30; p=0.034) of the Caucasian population were associated with AML susceptibility (Figure 3A, 3B). Stratified analysis based on SOC (source of controls) indicated increased susceptibility of AML in current smokers (OR=1.43, 95%CI=1.26-1.63; p=0.283) and ever-smokers (OR=1.20, 95%CI=1.07-1.35; p=0.078) of the population-based group (Figure 3C, 3D). Nevertheless, only current smokers in the hospital-based group had an increased susceptibility of AML (OR=1.45, 95%CI=1.19-1.76; p=0.198). The susceptibility of AML in ever-smokers (OR=1.04, 95%CI=0.81-1.35; p=0.054) of the hospital-based group did not remarkably changed.

Sensitivity Analysis

The sensitivity analysis was performed by reviewing each study. The OR was re-calculated through the regression analysis. Figure 4 illustrated the sensitivity analysis of the association between smoking and susceptibility of AML, indicating that combined OR had no significant effect on study conclusions. We believed that our meta-analysis results were robust and stable.

Table II. Meta-analysis results of association between cigarette smoking and susceptibility of acute myeloid leukemia.

	N[a]	OR (95%CI)	I-squared	p[b]
Current smokers	11	1.42 (1.28-1.57)	5.4%	0.392
Ethnicity				
Caucasian	10	1.45 (1.29-1.63)	7.7%	0.371
Asian	1	1.28 (1.00-1.63)	–	–
SOC				
PB	6	1.43 (1.26-1.63)	20.0%	0.283
HB	3	1.45 (1.19-1.76)	38.2%	0.198
PB&HB	2	1.15 (0.76-1.74)	0.0%	0.822
Ever-smokers	17	1.16 (1.05-1.28)	41.9%	0.036
Ethnicity				
Caucasian	14	1.16 (1.03-1.30)	46.2%	0.034
Asian	3	1.16 (0.90-1.48)	46.8%	0.153
SOC				
PB	12	1.20 (1.07-1.35)	39.4%	0.078
HB	4	1.04 (0.81-1.35)	60.8%	0.054
PB&HB	1	1.06 (0.66-1.70)	–	–

[a]Number of studies; [b]p-value of Q test for heterogeneity

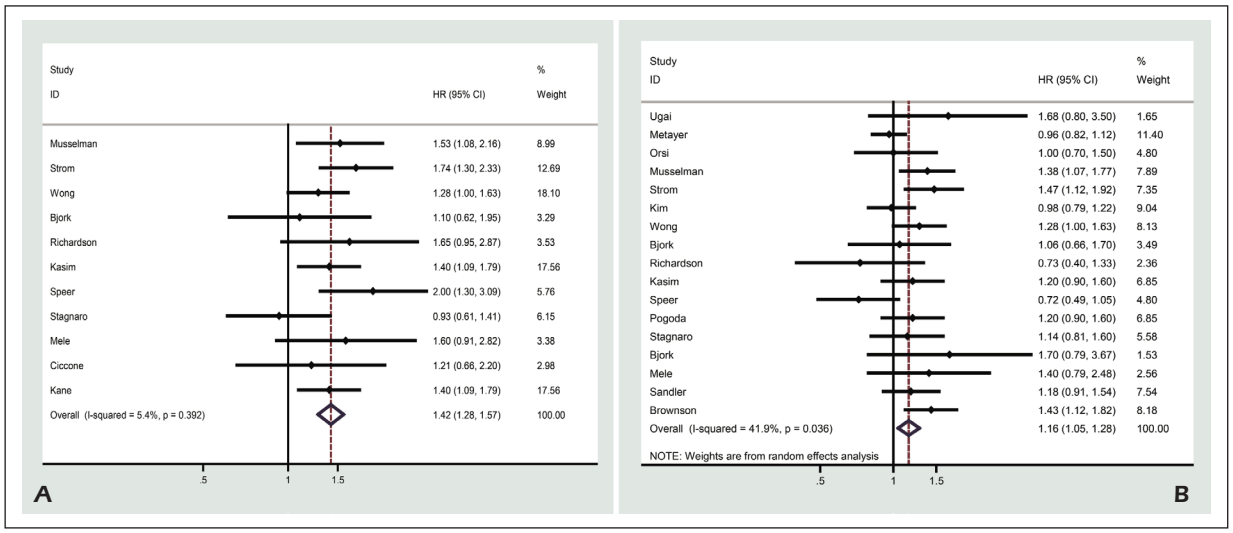

Figure 2. Forest plots of the association between cigarette smoking and AML susceptibility. **A**, Current smokers. **B**, Ever-smokers.

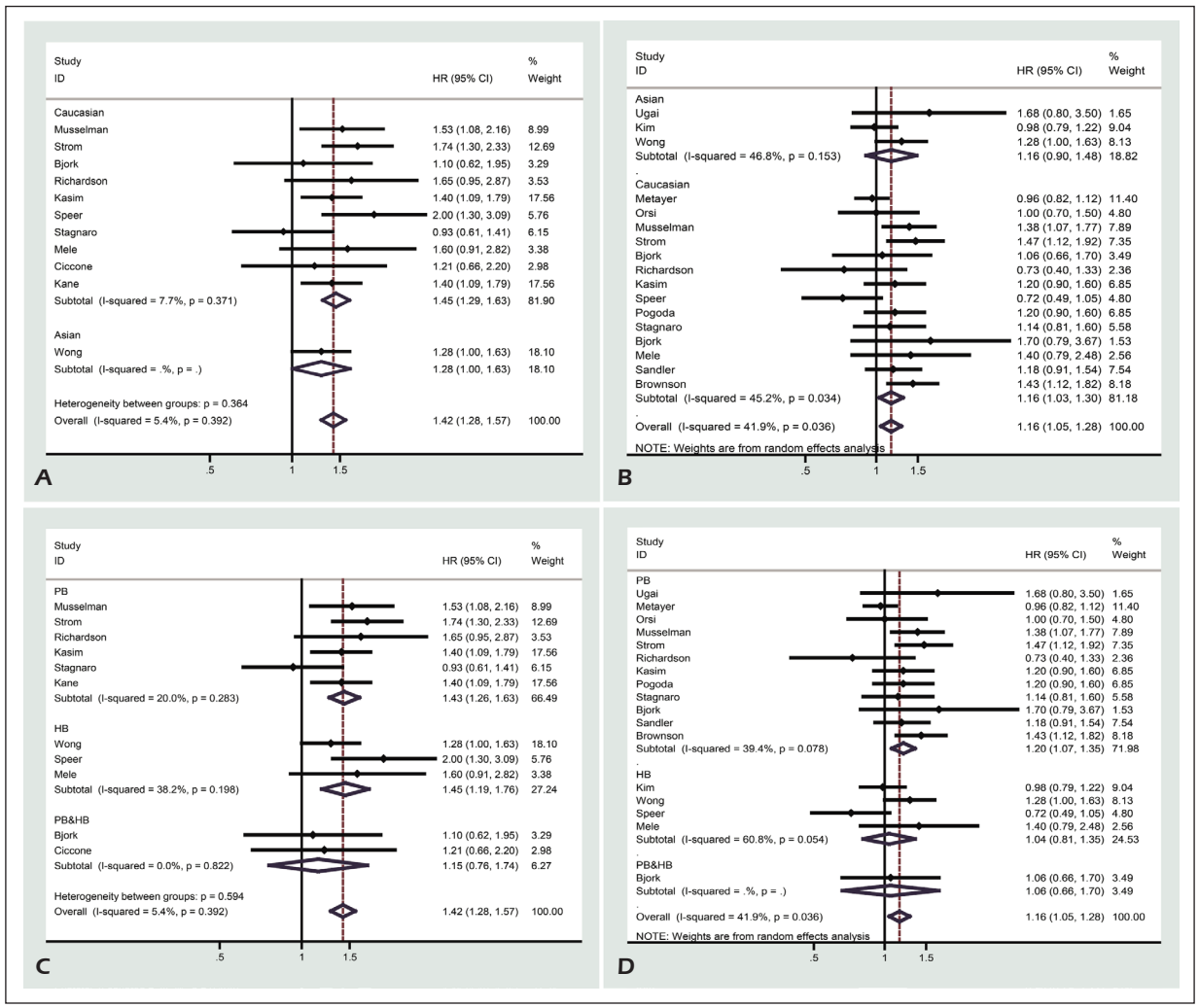

Figure 3. Forest plots of subgroup analysis of the association between cigarette smoking and AML susceptibility. **A**, Stratified by ethnicity in current smokers. **B**, Stratified by ethnicity in ever-smokers. **C**, Stratified by source of controls in current smokers. **D**, Stratified by source of controls in ever-smokers.

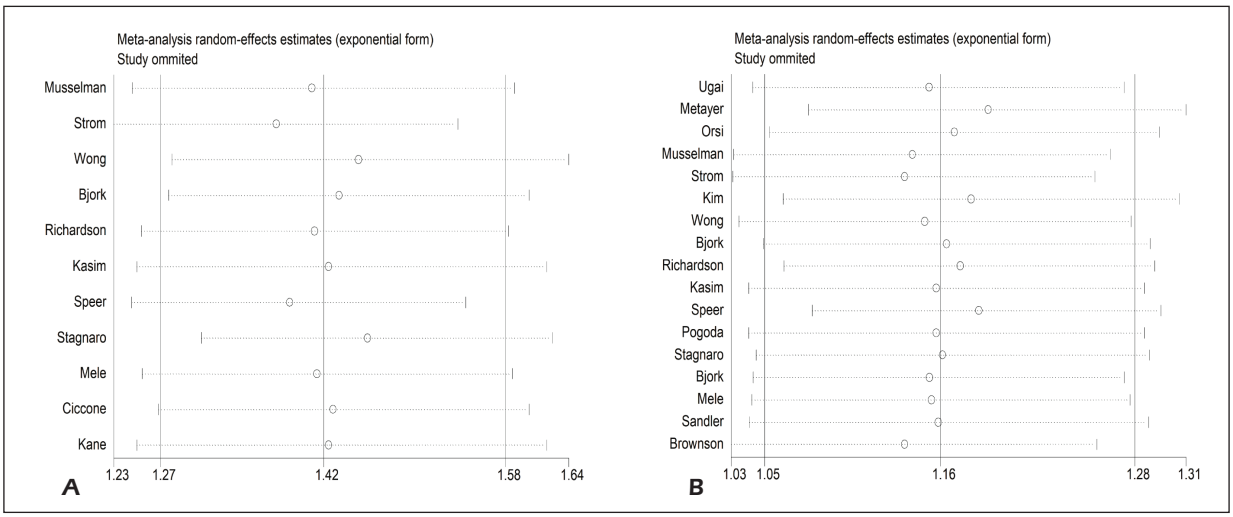

Figure 4. Sensitivity analysis about the association between cigarette smoking and AML susceptibility. **A**, Current smokers; **B**, Ever-smokers.

Publication Bias

Begg's funnel plot and Egger test were used to examine the publication bias of all data. Symmetrically distributed Funnel plot indicated no remarkable publication bias in this study. Egger test further confirmed our conclusion (Figure 5).

Discussion

The incidence of AML has strikingly increased, which has become one of the major diseases threatening human health. In population-based case-control studies[17-36], moderate evidence has supported that smoking during the pregnancy elevates the risk of childhood AML. In addition to the occupational exposure to benzene, active smoking is also an established risk for adult AML[15,23]. International Agency for Research on Cancer (IARC) proposed evidence that childhood leukemia is consistent with pre-existing and simultaneous smoking by parents[15,16]. Conversely, the influence of maternal smoking on childhood AML is controversial[16,17].

Previous studies[17-35] on investigating potential effects of cigarette smoking on the etiology of AML obtained conflicting results. The role of smoking in the risk of AML has not yet been

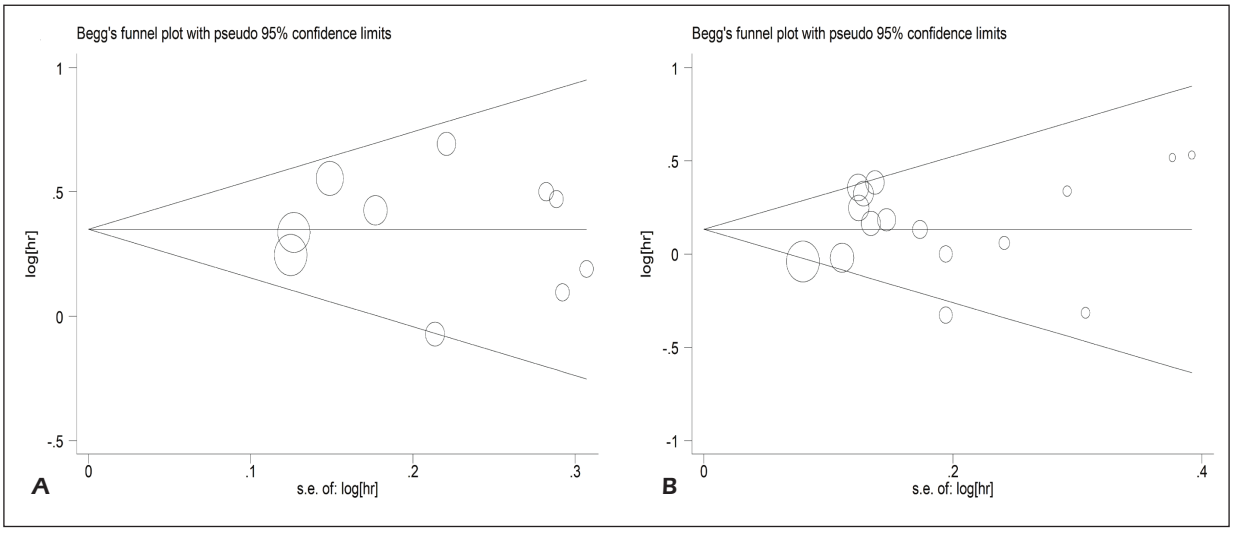

Figure 5. Begg's funnel plot of publication bias test. **A**, Current smokers. **B**, Ever-smokers.

concluded. Mattioli et al[19] suggested no evidence on the correlation between second hand smoking exposure and childhood AML. Nevertheless, Orsi et al[18] indicated that drinking during pregnancy may be related to AML, and parental smoking before pregnancy may be a risk factor for AML. In our meta-analysis, we aim to clarify whether smoking is associated with susceptibility of AML.

A meta-analysis is a powerful tool that makes conclusions more credible than individual studies, especially in analyzing unexplained associations[36-38]. Through subgroup analysis, we comprehensively elucidated the association between smoking and onset risk of AML. This meta-analysis included 20 case-control studies, involving 7,538 AML patients and 137,924 healthy controls.

The subgroup analysis was performed according to different ethnicities and SOCs. A correlation between smoking and the risk of AML was observed in the Caucasian population, rather than the Asian population. However, due to the relatively small sample size of the Asian population, this result may not be very conclusive. In addition, due to the mixed population from different geographical regions and other ethnic groups, there was significant heterogeneity in the Caucasian population, which may lead to negative results. Statistical significance of this correlation in the two different populations was also observed in a population-based group, rather than a hospital-based group. Besides, different individuals in the control group may have different risks of developing AML, which may affect the study quality. It is necessary to develop unified admission criteria and enlarge the sample size.

Some limitations should be noteworthy in this study. Firstly, the sample size in each stratified analysis was relatively small and may limit the statistical power. Secondly, the pathogenesis of AML is complex, involving both genetic and environmental factors. Gene-environment interaction is a vital factor for evaluating smoking risks. Further researches are needed to explore the potential genetic factors on influencing the susceptibility of the AML. Thirdly, pooled analysis on people with different ages and ethnicities may lead to bias. The incidence of AML is also varied in different ethnicities, which may result in heterogeneity. In our study, Caucasians accounted for the majority of research subjects, and it may affect the subgroup analysis based on different ethnicities. Large-scale, case-control or prospective study in different ethnic groups are required for further explorations.

Conclusions

In this meta-analysis, we observed the association between cigarette smoking and onset risk of AML, especially in the Caucasian population. High-quality, large-scale researches are needed to be conducted in multi-center hospitals for verification.

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Conflict of Interests

The authors declare that they have no conflict of interest.

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