Association of asthma with the risk of acute leukemia and non-Hodgkin lymphoma

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Abstract. An increasing incidence of hematological malignancies has been observed in children and adults worldwide over the last few decades. Asthma is a common chronic inflammatory disease. The aim of the present meta-analysis was to evaluate the potential association between a history of asthma and the risk of acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML) and non-Hodgkin lymphoma (NHL). A literature search was performed through PubMed and the Cochrane Database of Systematic Reviews and the Newcastle-Ottawa Scale was used to evaluate the quality of the selected studies. The I^2 index was used to evaluate heterogeneity and the outcome was measured as the odds ratio (OR) by the random-effects model. A total of 16 case-control studies were included. All the studies were of high quality. The OR for ALL was 0.90 [95% confidence interval (CI): 0.68-1.19; P=0.45; I^2=79%]. The OR for AML was 0.85 (95% CI: 0.67-1.08; P=0.19; I^2=8%). The OR for NHL was 0.91 (95% CI: 0.83-1.00; P=0.05; I^2=0%). Asthma was found to be inversely associated with the risk of NHL. A negative trend of association of asthma with ALL and AML was also observed. However, additional large prospective studies are required to confirm these findings.

Introduction

Acute leukemia and non-Hodgkin lymphoma (NHL) are the most common malignancies in children and adolescents (1,2), with an increasing incidence observed in children and adults worldwide over the last few decades (3-5). Although ionizing radiation, certain chemotherapeutic agents, certain infections, a family history of disease and certain genetic disorders have been reported to be associated with hematological malignancies, the etiology of acute leukemia and NHL has not been fully elucidated.

Severe autoimmune conditions, such as systemic lupus erythematosus and rheumatoid arthritis, have been found to be associated with acute leukemia and NHL; however, little is known on the role of subtle immune impairments in the development of diseases, such as asthma. Asthma is an aberrant chronic immune response due to a lack of infections during early childhood (6,7). The association of asthma with acute leukemia and NHL may be based on two hypotheses: One is the immune surveillance hypothesis, according to which the possible mechanism underlying the reduced the risk of asthma patients to develop acute leukemia and NHL is that asthma enhances the ability of the immune system to detect and destroy cancer cells (8). By contrast, the antigenic stimulation hypothesis suggests that immune-stimulating conditions may predispose to cancer, due to an increasing number of random mutations in activated dividing immune cells (9-12). Previous studies suggested that asthma was protective against leukemia and lymphoma (13-16), whereas other studies indicated asthma as a risk factor (17-19), or reported no association (20-23).

Given the conflicting results on the association of asthma with the risk of leukemia and NHL, a meta-analysis was conducted to elucidate this association. The objective of the present study was to evaluate the potential association between a history of asthma and the incidence of acute leukemia and NHL.

Materials and methods

Literature search. Two authors independently performed a literature search through PubMed and the Cochrane Database of Systematic Reviews through to April 20, 2014. The terms used in the search were 'asthma AND (leukemia or lymphoma)'. The title and abstract of every article were reviewed. According to the inclusion criteria, full-text articles were selected. The reference lists of the full-text articles were also searched for additional relevant studies.

Inclusion and exclusion criteria. An article was considered as useful if it reported original data on the association between asthma and the risk of acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML) or NHL from epidemiological studies. Only studies published in English were included. The

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articles included were required to provide sufficient information to calculate the odds ratio (OR). Any disagreements regarding inclusion or exclusion of a study were resolved by a joint review with other authors. Only the most recent articles were selected when the same study produced several publications.

Data extraction. Two authors independently performed the data extraction. The extracted data included name of first author, publication year, country, time of diagnosis of acute leukemia or NHL, age range of cases, number of samples (cases, controls, asthmatics and non-asthmatics), methods of assessment of asthma (medical records or interview questionnaires) and matching factors. Any disagreements were resolved by a joint assessment of the original study with other authors.

Quality assessment. Two authors independently evaluated the quality of the selected studies using the Newcastle-Ottawa Scale (NOS). The NOS for case-control studies includes three parameters, namely selection, comparability and exposure assessment. Any individual article may get the maximal NOS score of 4 points for selection, 2 for comparability and 3 for exposure. A NOS score of 1-3 was considered as low-quality, a score of 4-6 as intermediate-quality and a score of 7-9 as high-quality. Any disagreements on the NOS score of a study were resolved by a joint review of the original article.

Data synthesis and analysis. The primary result measured was OR with 95% confidence interval (CI) of developing ALL, AML or NHL in patients with a history of asthma. The Mantel-Haenszel method and the random-effects model were applied to measure the outcomes (24,25). The I^2 index was used to evaluate heterogeneity (26). I^2 values of 25, 50 and 75% were considered to reflect mild, moderate and severe heterogeneity, respectively. Meta-analyses were performed for ALL, AML and NHL using the Review Manager 5.2 software (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012). In the forest plots, OR values >1 suggested an increased risk, whereas OR values <1 suggested a decreased risk of cases among individuals with a history of asthma.

Results

Search results. The results of the literature search are summarized in Fig. 1. A total of 668 records were identified during our initial search. Following a review of the titles and abstracts, 618 articles did not pertain to the association between asthma and the risk of acute leukemia or NHL and were excluded. The remaining 50 articles were retrieved for full-text review. Following a detailed review, a further 34 articles were excluded (27 were irrelevant to the association between asthma and the incidence of acute leukemia or NHL, 1 was a case report and 6 were reviews). No additional articles were identified through searching the reference lists of the 50 articles. Finally, 16 case-control studies were included in our meta-analysis.

Characteristics of the studies. The main characteristics of the 16 studies included in our analysis are summarized in Table I. The studies were published between 1996 and 2012. A total of 7 studies originated from Europe, 6 from North
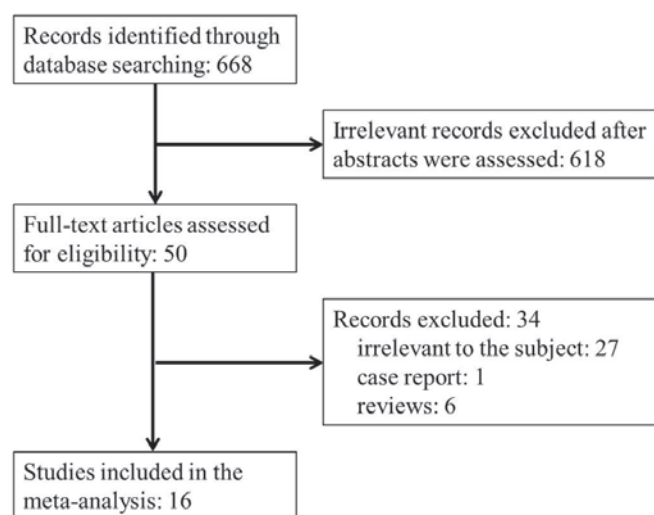

Figure 1. Flow diagram of the study selection process.

America, 2 from Australia and 1 from Asia. The time of diagnosis of the cases was between 1980 and 2008. The cases in the studies were children or adolescents in 9 studies, adults in 6 studies and both in 1 study. A total of 5,738 ALL patients, 4,362 AML patients, 22,048 NHL patients and 168,397 controls were included in our analysis. A history of asthma was identified by interviewing with questionnaires in 12 studies, reviewing medical records in 3 studies and using both methods in 1 study. In all the studies, the controls were matched to the patients by age and gender and 8 studies were adjusted by region of residence. As regards quality assessment, all the included studies were of high quality (NOS score ≥7).

Outcome results. A total of 8 studies reported outcomes on the association between asthma and the risk of ALL. The OR for ALL was 0.90 (95% CI: 0.68-1.19; P=0.45; I^2=79%; Fig. 2).

A total of 5 studies provided data on the association between asthma and the risk of AML. The OR for AML was 0.85 (95% CI: 0.67-1.08; P=0.19; I^2=8%; Fig. 3).

A total of 8 studies reported data on the association between asthma and the risk of NHL. The OR for NHL was 0.91 (95% CI: 0.83-1.00; P=0.05; I^2=0%; Fig. 4).

There was a significantly reduced risk of developing AML in asthmatic patients. In addition, there was an inverse association between asthma and acute leukemia, but this association was not statistically significant.

Discussion

In our meta-analysis, asthma was found to be associated with statistically significant reductions in the risk of NHL, whereas it was associated with non-statistically significant reductions in the risk of ALL and AML.

A hypothesis has been proposed with regard to the mechanism of the inverse association of asthma with NHL. According to the cancer immune surveillance hypothesis, the immune system identifies and eradicates aberrant cells in the body, thus averting the development of a number of potential

Table I. Characteristics of the 16 case-control studies included in the meta-analysis of the asociation of asthma with acute leukemia and non-Hodgkin lymphoma.

First author, year (Refs.)	Country	Time of diagnosis	Age range, years	No. of cases	No. of controls	Assessment of asthma	Matching factors	NOS score
Chang, 2012 (17)	Taiwan	2000-2008	1-10	846 ALL	3,674	Medical records	Gender, birth date, diagnosis time	8
Cooper, 1996 (20)	USA/Canada	1986-1990	18-79	121 ALL, 622 AML	637	Interview	Age, gender, race, residence	8
Cozen, 2007 (22)	USA	1998-2000	20-74	604 NHL	464	Interview	Age, gender	8
Dikalioti, 2012 (15)	Greece	1996-2008	0-14	166 NHL	166	Interview	Age, gender	7
Grulich, 2005 (27)	Australia	2000-2001	20-74	699 NHL	691	Interview	Age, gender, residence	8
Hughes, 2007 (19)	UK	1991-1996	≤14	720 ALL, 101 AML	1,337	Interview and medical records	Age, gender, residence	7
Jourdan-Da Silva, 2004 (13)	France	1995-1998	≤15	400 ALL, 63 AML	565	Interview	Age, gender, residence	8
Lee, 2004 (28)	USA	1980-1986	≥21	872 NHL	2,336	Interview	Race, age, gender, vital status	8
Lee, 2006 (29)	USA	1998-2000	20-74	668 NHL	543	Interview	Age, gender, race, residence	8
Rudant, 2010 (14)	France	2003-2004	1-15	633 ALL, 86 AML	1,493	Interview	Age, gender	8
Rudant, 2011 (30)	France	2003-2004	2-14	164 NHL	1,311	interview	Age, gender	8
Schuz, 2003 (31)	Germany	1980-1994	≤14	996 ALL	2,441	Interview	Age, gender, residence	8
Soderberg, 2006 (21)	Sweden	1987-1999	0-103	18,186 NHL, 3,490 AML	149,344	Medical records	Age, gender, year of diagnosis	9
Spector, 2004 (18)	USA	1985-1999	0.23-6.86	180 ALL	718	Medical records	Age, gender, diagnosis time	8
Vajdic, 2007 (32)	Australia	2000-2001	20-74	689 NHL	691	Interview	Age, gender, residence	8
Wen, 2000 (33)	USA	1989-1993	≤15	1,842 ALL	1,986	Interview	Age, gender, race, residence	8

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; NHL, non-Hodgkin lymphoma; NOS, Newcastle-Ottawa scale.
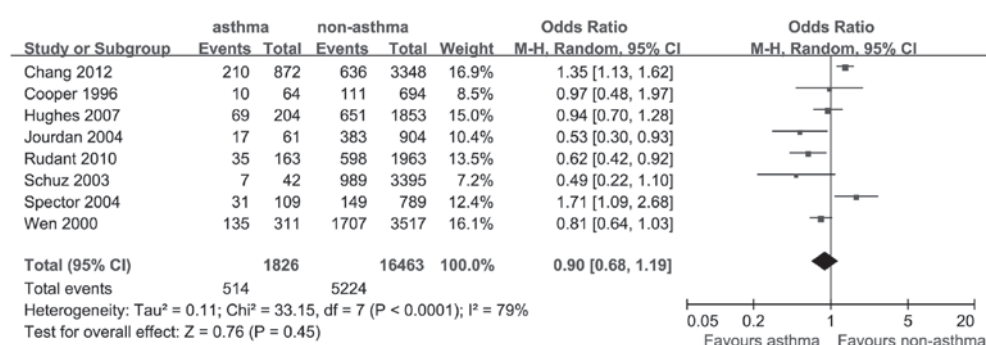
Study or Subgroup	asthma Events	asthma Total	non-asthma Events	non-asthma Total	Weight	Odds Ratio M-H, Random, 95% CI
Chang 2012	210	872	636	3348	16.9%	1.35 [1.13, 1.62]
Cooper 1996	10	64	111	694	8.5%	0.97 [0.48, 1.97]
Hughes 2007	69	204	651	1853	15.0%	0.94 [0.70, 1.28]
Jourdan 2004	17	61	383	904	10.4%	0.53 [0.30, 0.93]
Rudant 2010	35	163	598	1963	13.5%	0.62 [0.42, 0.92]
Schuz 2003	7	42	989	3395	7.2%	0.49 [0.22, 1.10]
Spector 2004	31	109	149	789	12.4%	1.71 [1.09, 2.68]
Wen 2000	135	311	1707	3517	16.1%	0.81 [0.64, 1.03]
Total (95% CI)		1826		16463	100.0%	0.90 [0.68, 1.19]
Total events	514		5224			

Heterogeneity: Tau² = 0.11; Chi² = 33.15, df = 7 (P < 0.0001); I² = 79%
Test for overall effect: Z = 0.76 (P = 0.45)

Figure 2. Estimates of the odds ratio of developing acute lymphoblastic leukemia in patients with a history of asthma.

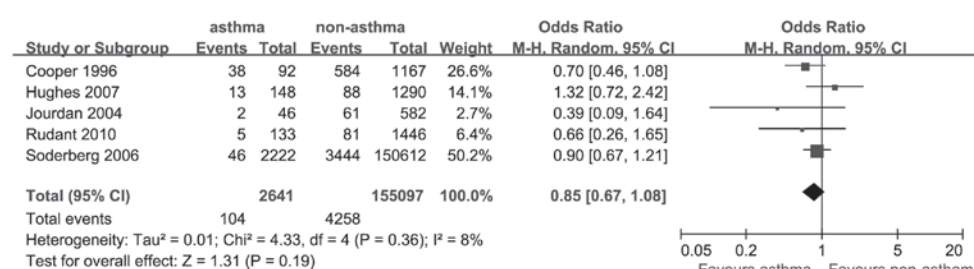| Study or Subgroup	asthma Events	asthma Total	non-asthma Events	non-asthma Total	Weight	Odds Ratio M-H, Random, 95% CI
Cooper 1996	38	92	584	1167	26.6%	0.70 [0.46, 1.08]
Hughes 2007	13	148	88	1290	14.1%	1.32 [0.72, 2.42]
Jourdan 2004	2	46	61	582	2.7%	0.39 [0.09, 1.64]
Rudant 2010	5	133	81	1446	6.4%	0.66 [0.26, 1.65]
Soderberg 2006	46	2222	3444	150612	50.2%	0.90 [0.67, 1.21]
Total (95% CI)		2641		155097	100.0%	0.85 [0.67, 1.08]
Total events	104		4258			

Heterogeneity: Tau² = 0.01; Chi² = 4.33, df = 4 (P = 0.36); I² = 8%
Test for overall effect: Z = 1.31 (P = 0.19)

Figure 3. Estimates of the odds ratio of developing acute myeloid leukemia in patients with a history of asthma.

Study or Subgroup	asthma Events	asthma Total	non-asthma Events	non-asthma Total	Weight	Odds Ratio M-H, Random, 95% CI
Cozen 2007	60	108	544	960	5.7%	0.96 [0.64, 1.43]
Dikalioti 2012	16	48	150	284	2.2%	0.45 [0.23, 0.85]
Grulich 2005	113	239	586	1151	11.6%	0.86 [0.65, 1.14]
Lee 2004	45	177	827	3031	7.5%	0.91 [0.64, 1.29]
Lee 2006	66	123	602	1088	6.5%	0.93 [0.64, 1.36]
Rudant 2011	10	130	154	1345	2.0%	0.64 [0.33, 1.26]
Soderberg 2006	254	2430	17932	165100	52.9%	0.96 [0.84, 1.09]
Vajdic 2007	113	239	576	1141	11.6%	0.88 [0.67, 1.16]
Total (95% CI)		3494		174100	100.0%	0.91 [0.83, 1.00]
Total events	677		21371			

Heterogeneity: Tau² = 0.00; Chi² = 6.58, df = 7 (P = 0.47); I² = 0%
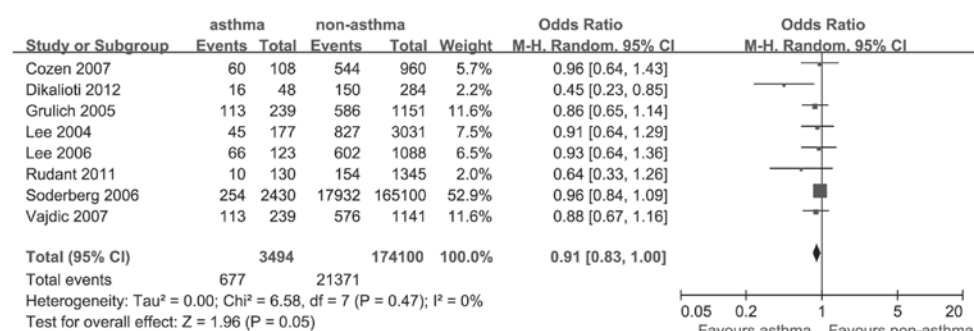Test for overall effect: Z = 1.96 (P = 0.05)

Figure 4. Estimates of the odds ratio of developing non-Hodgkin lymphoma in patients with a history of asthma.

malignancies (34). The occurrence of asthma may be a surrogate marker of an increased ability of the immune system to recognize and destroy malignant cells (23). By contrast, the antigenic stimulation hypothesis suggests that the chronic inflammatory state in asthmatic patients may result in an inflammatory cytokine cascade and lead to tissue damage and, ultimately, lymphoid malignancies (35). Asthma was associated with a reduced risk of NHL, which supports the immune surveillance hypothesis.

Our results revealed a non-significant odds ratio of 0.90 and 0.85 for the association of a history of asthma with ALL and AML, respectively,. The literature on asthma and acute leukemia is heterogeneous. In the present analysis, a ~10% reduction in the risk for NHL in patients with a history of asthma was observed. An IgE-mediated anticancer response in asthma patients may be a possible explanation for the protective effect of asthma against the development of NHL (22). In addition, histamine, an inflammatory mediator in asthma, was reported to have the ability to defend normal cells by suppressing oxygen radical-induced damage and activating protective lymphocytes (36).

Asthma is considered as an overactive state of the immune response, characterized by a shift towards a Th2-dominant immunity. The persistence of a Th2-dominant immune system in asthmatic patients is inversely associated with the risk of NHL, of which the mechanism has not been fully elucidated. Other unmeasured factors associated with asthma may contribute to the reduced risk of NHL. Elucidating the mechanism of this negative association may provide valuable information on the effect of asthma on the immune response and the subsequent risk of developing NHL. The true underlying mechanism was not determined in the present analysis; however, our results support the immune surveillance hypothesis. We also hypothesize that genetic or exposure factors underlying the development of asthma may also be protective against NHL.

When analyzing the association between asthma and ALL, a high degree of heterogeneity was observed among the studies. A possible explanation for this severe heterogeneity may be the differences in the included studies regarding age range, country, number of cases and controls, diagnosis time

and matching factors. Major differences in baseline characteristics largely account for the heterogeneity. By contrast, only mild heterogeneity and no heterogeneity were observed in the analysis of AML and NHL, respectively. Consequently, the results of the inverse association between asthma and NHL may be considered as credible.

The results of the meta-analysis should be interpreted with caution due to certain limitations. First, in the majority of the studies, the history of asthma was obtained from interview by telephone or questionnaire and recall bias may exist in the self-reported data (37,38). Although the information bias appeared to be inevitable, the inverse association of asthma with acute leukemia and NHL (significant in NHL and non-significant in ALL and AML) was notable, provided that patients are more likely to pay attention to disease history, leading to information bias of a false-positive association (27). The positive association between asthma and the risk of developing acute leukemia or NHL was reported in previous studies (17,18). Shared etiological factors may account for the results. However, as the reference date, corresponding with the date of diagnosis in cancer patients, is not well-defined in the controls, a history of asthma may be over-reported (31). This may lead to a higher incidence of asthma in the controls, from whom the data were obtained by interview. Previous studies reported only a moderate consistency between the medical reports and interview data (19). Second, there was no sufficient information on the morphological, immunological, genetic, molecular or pathological subtypes of acute leukemia and NHL in previous studies; therefore, further analysis of the association between asthma and the subtypes of these diseases was not feasible. Third, there was also a possible information bias in the data based on the medical records, as less severe cases of asthma may be not documented in medical records. This misclassification may exist equally among cases and controls, or more frequently in controls, resulting in a positive association trend of asthma with acute leukemia and NHL. Fourth, asthma-related medications may modulate the immune system, affecting the association of asthma with acute leukemia and NHL. The medical treatment of asthma may affect the risk of developing cancer due to cellular and humoral immunosuppression. In addition, the duration and severity of asthma, should also be taken into consideration. Fifth, confounding factors including age, gender and region of residence were controlled in the majority of the included studies, but other confounding factors, such as genetic characteristics, individual lifestyle, other immune-related diseases and infection exposure cannot be completely ruled out.

There were also several strengths in our study. First, the number of included cases and controls was sufficiently large to obtain a reliable association between asthma and ALL, AML and NHL. Second, the studies in our analysis included a diversity of countries and races, enabling the generalization of the outcomes. Third, with regard to NOS, all the studies included in our analysis were of high quality, ensuring reliable results. Fourth, in all the included studies, the cases and controls were matched by age and gender; region of residence and race were also matched in some studies, minimizing the potential information bias between cases and controls. Fifth, in the majority of the studies, a history of asthma was identified shortly before the diagnosis of acute leukemia or NHL.

Therefore, asthma during the early or indolent course of these diseases was excluded.

In conclusion, this study demonstrated that asthma is inversely associated with the incidence of NHL. A negative trend in the risk of ALL and AML in subjects with a history of asthma was also observed. Additional large prospective studies are required to elucidate the association between asthma and hematological malignancies.

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