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Autoimmune diseases, asthma and risk of haematological malignancies: A nationwide case-control study in Sweden

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ABSTRACT

To investigate potential associations between several autoimmune diseases and haematological malignancies, we studied 39,908 cases of leukaemia, Hodgkin's disease, non-Hodgkin's lymphoma and myeloma that occurred during 1987–1999 in Sweden, and 149,344 controls. Hospital discharge diagnoses of psoriasis, Sjögren's syndrome, autoimmune haemolytic anaemia, idiopathic thrombocytopenic purpura, pernicious anaemia, multiple sclerosis, rheumatic fever or asthma from 1969 to 1999 were retrieved from the Swedish Hospital Discharge Registry. Psoriasis was positively associated with leukaemia, excluding chronic lymphocytic leukaemia, (odds ratio [OR] = 1.6, 95% confidence interval [CI] 1.1–2.3) and non-Hodgkin's lymphoma (OR = 1.6, 95% CI 1.3–2.1). Sjögren's syndrome increased the risks of all haematological malignancies combined (OR = 4.0, 95% CI 2.3–7.0), and of non-Hodgkin's lymphoma (OR = 6.4, 95% CI 3.5–12). These findings, together with increased risks of several haematological malignancies in autoimmune haemolytic anaemia and idiopathic thrombocytopenic purpura but not in asthma, suggest chronic autoimmunity and immune stimulation as mechanisms contributing to the development of haematological malignancies.

1. Introduction

The aetiology of both autoimmune diseases and haematological malignancies seems to be influenced by genetic predisposition as well as by the environment.[1] A familial aggregation of autoimmune conditions, immunologic abnormalities and haematological malignancies has been observed.[2,3] This implies that conditions that alter the normal function of the immune system may not only result in an impaired ability to suppress activation of autoimmune cells, but also lead to dysfunctional elimination of malignant haematological cells.

Several studies suggest a positive association between autoimmunity and haematological malignancies. The antigenic stimulation hypothesis proposes that immune-stimulating conditions may lead to an increased risk of malignancy. The suggested mechanism involves chronic stimulation induced by activated immune cells eventually leading to random mutations in dividing cells. However, there are also some studies where no associations with haematological malignancies were found.[4,5] Contradictory to the antigenic stimulation hypothesis, most studies on asthma have reported reduced risks or risks close to unity in association with haematological malignancies.[6,7] This would be in accordance with the immune surveillance hypothesis, which proposes that allergic conditions protect against malignancies by enhancing the ability of the immune system to detect

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and eliminate malignant cells.[8] However, in a recent study, no association between atopy and overall cancer risk was found, although among atopic men a slight excess of cases of Hodgkin's disease (HD) was found, and among atopic women, a slight excess of non-Hodgkin's lymphoma (NHL).[9]

T helper lymphocytes when activated become Th1 or Th2 effector cells identified by their production of key cytokines such as interferon-γ (Th1) and IL-4 (Th2). Th1 dominated immune responses contribute to the pathogenesis of autoimmune diseases such as psoriasis, Sjögren's syndrome, pernicious anaemia and multiple sclerosis (MS), diseases generally regarded as T cell mediated.[10] On the other hand excessive Th2 immune responses are associated with asthma, allergic conditions and autoimmune haemolytic anaemia (AIHA), idiopathic thrombocytopenic purpura (ITP) and rheumatic fever.[10] These Th2 disorders are characterised by activation of B cells and the production of pathogenic immunoglobulins.

The purpose of this study was to investigate the association between chronic immune cell activation in several Th1 and Th2 mediated autoimmune diseases, asthma and the risk of developing haematological malignancies, i.e. leukaemia, HD, NHL and myeloma. We chose to study chronic immune cell activation in several immune-mediated conditions in order to address the immune surveillance hypothesis and the antigenic stimulation hypothesis concerning immune defence and carcinogenesis.

We performed a large case-control study by using data from the nationwide, population-based Swedish Hospital Discharge Registry and the Swedish Cancer Registry. By utilising high quality registries of the Swedish health care system, we had the possibility to avoid selection bias and recall bias. We obtained a larger number of exposed cases and longer periods of follow-up than most previous studies.

2. Materials and methods

2.1. Study base and selection of cases and controls

The study base consists of the entire Swedish population during the period 1987 through 1999. All cases of haematological malignancies that occurred from 1987 to 1999 were obtained from the Swedish Cancer Registry. We identified 39,908 individuals diagnosed with haematological malignancies; 2394 cases of HD (*International Classification of Diseases*[d], 7th revision, (ICD-7), code 201), 18,186 cases of NHL (ICD-7 200.0–200.3, 202.0–202.4), 7189 cases of myeloma (ICD-7 203) and 12,397 cases of leukaemia (ICD-8), codes 204.0–207.9). Table 1 displays the number of leukaemia cases subdivided into leukaemia subtypes. In order to minimise differential misclassification and reduce screening bias of outcome, only haematological malignancies that occurred at least 1 year after diagnosis of autoimmune disease or asthma were included.

Two controls per cancer case were randomly selected from the study base continuously throughout the study period using the nationwide population registry, stratified on sex, 5-year age groups, and year of diagnosis. For the youngest cases (<20 years), five controls for each cancer case were retrieved in order to increase the precision. Controls were selected simultaneously for parallel studies of pancreatic cancer and brain tumours, and the entire set of controls was used in the analyses; in total 149,344 controls. The median age at diagnosis of a haematological malignancy was 70 years (range 0–103 years), whereas the median age at selection of controls was 67 years (range 0–110 years). The study was approved by the Ethical Committee at Karolinska Institutet.

Table 1 – Number of haematological malignancies

Haematological malignancies	Total	Men	Women
Leukaemia (204–207)	12,397[a]	6936	5461
ALL (204.0)	1446	817	629
AML (205.0)	3490	1734	1756
CLL (204.1)	4744	2859	1885
CML (205.1)	1164	680	484
Unspecified leukaemia	1572	858	714
NHL (200, 202)	18,186	9960	8226
HD (201)	2394	1354	1040
Myeloma (203)	7189	3909	3280
All haematological malignancies combined (200–207)	39,908[b]	22,001	17,907
Controls	149,344	77,780	71,564

ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; CLL, chronic lymphocytic leukaemia; CML, chronic myeloid leukaemia; NHL, non-Hodgkin's lymphoma; HD, Hodgkin's disease.
a 19 individuals had two diagnoses of leukaemia.
b 275 individuals had two haematological malignancies, one person had three different haematological malignancies.

2.2. Autoimmune diseases

For all cases and controls, information about hospital discharges with immune-mediated diagnoses was obtained from the Swedish Hospital Discharge Registry. In 1964, the Swedish National Board of Health and Welfare started to collect data on individual discharges in the Swedish Hospital Discharge Registry, covering a small part of Sweden. The coverage of the Swedish population has gradually increased and encompassed 60% of the population in 1969, 85% by the end of 1983 and 100% in 1987.[11] We have retrieved information about all discharges between 1969 and 1999 that included a diagnosis of 36 different autoimmune diseases. Of these, psoriasis, Sjögren's syndrome, pernicious anaemia, MS, AIHA, ITP, rheumatic fever, and asthma were included in the present analysis. These autoimmune diseases are common and at least historically required hospital inpatient care. To focus on primary Sjögren's syndrome, we excluded individuals with a diagnosis of RA or systemic lupus erythematosus (SLE). The other most common autoimmune diseases; celiac disease, SLE, rheumatoid arthritis (RA), Crohn's disease and ulcerative colitis were not included in this article as they have previously been studied in the Swedish Hospital Discharge Registry with an equal length of follow-up in the Swedish Cancer Registry as in our material, e.g. Bjornadal (2002).[12] Also asthma and psoriasis have been followed up previously for malignancy, but only until 1987 and 1989, respectively,[13,14] and

[d] In the Swedish Cancer Registry, leukaemia is coded according to ICD-8 during the investigated period, while all other malignancies are coded according to ICD-7.

these two diagnoses were therefore also included in the present analysis. The remaining autoimmune diagnoses for which we had retrieved information were however not included, as analyses would have been based on too few cases to be meaningful. In the analyses we used the first date of registration with a specific diagnosis if the disease was registered on more than one occasion in the Hospital Discharge Registry.

2.3. *Statistical methods*

We estimated the odds ratio (OR), and its 95% confidence interval (CI), of the haematological malignancies in relation to autoimmune diseases through unconditional logistic regression. All analyses were adjusted for sex, socioeconomic status and age at diagnosis (cases) or age at selection (controls). A socioeconomic variable with five categories was constructed according to Statistics Sweden's 13 categories of socioeconomic status from 1985 and 1990; blue-collar workers, lower and intermediate white-collar workers, senior white-collar workers and self-employed (excluding farmers), farmers and a fifth category of unclassifiable employees and those lacking information on profession. The categories were based on occupational status from the census of 1985 for controls and malignancies diagnosed 1987–1990 and from the census of 1990 for controls and malignancies diagnosed after 1990.

3. Results

In Table 2, the results for leukaemia are shown, while the results for NHL, myeloma and haematological malignancies combined are presented in Table 3. Results for acute lymphoblastic leukaemia (ALL) and HD are not presented separately because the number of exposed cases with these malignancies was too few for meaningful analyses, except for individuals with asthma which is the most common of the diseases in our study.

We found increased risks of leukaemia, excluding chronic lymphocytic leukaemia (CLL), and of NHL following a diagnosis of psoriasis (Tables 2 and 3). The risks of leukaemia, excluding CLL, following a diagnosis of psoriasis were 1.5 (95% CI 1.0–2.4, 20 exposed cases) after an induction period of 5 years and 1.4 (95% CI 0.8–2.5, 13 exposed cases) after an induction period of 10 years. For NHL, when induction periods of 5 and 10 years after the first diagnosis of psoriasis were introduced, the ORs were still elevated; 1.6 (95% CI 1.2–2.1, 58 exposed cases) and 1.6 (95% CI 1.1–2.2, 39 exposed cases), respectively.

Table 2 – Age-, sex- and socioeconomic status-adjusted odds ratio (OR) and 95% confidence interval (CI) for leukaemia among subjects with autoimmune diseases or asthma

Autoimmune disease	Controls	CLL (2041)			AML (2050)			CML (2051)			Leukaemia (excl. CLL)		
	No.	No.	OR	95% CI	No.	OR	95% CI	No.	OR	95% CI	No.	OR	95% CI
Psoriasis	360	12	0.9	(0.5–1.6)	12	1.3	(0.8–2.4)	4	1.4	(0.5–3.8)	28	1.6	(1.1–2.3)
Sjögren's syndrome	24	2	2.6	(0.6–11)	0		–	1	6.1	(0.8–45)	2	1.7	(0.4–7.0)
Primary Sjögren's syndrome	14	0		–	0		–	0		–	0		–
Pernicious anaemia	222	8	0.7	(0.3–1.4)	7	1.1	(0.5–2.4)	1	0.6	(0.1–4.4)	14	1.3	(0.8–2.3)
Multiple sclerosis	169	7	1.4	(0.7–3.1)	5	1.2	(0.5–3.0)	2	1.6	(0.4–6.6)	8	0.9	(0.5–1.9)
Autoimmune haemolytic anaemia	23	6	6.7	(2.7—17)	5	8.0	(3.0–21)	0		–	8	7.0	(3.1–16)
ITP	40	3	2.5	(0.8–8.1)	6	6.6	(2.8–16)	2	6.6	(1.6–27)	11	5.4	(2.8–11)
Rheumatic fever	489	21	1.0	(0.7–1.6)	7	0.6	(0.3–1.2)	3	0.8	(0.3–2.5)	17	0.7	(0.4–1.2)
Asthma	2176	70	0.9	(0.7–1.1)	46	0.8	(0.6–1.1)	16	1.0	(0.6–1.6)	98	0.9	(0.7–1.1)

CLL, chronic lymphocytic leukaemia; AML, acute myeloid leukaemia; CML, chronic myeloid leukaemia; ITP, idiopathic thrombocytopenic purpura.

Table 3 – Age-, sex- and socioeconomic status-adjusted odds ratio (OR) and 95% confidence interval (CI) for non-Hodgkin's lymphoma, myeloma and all haematological malignancies among subjects with autoimmune diseases or asthma

Autoimmune disease	Controls	NHL (200 + 202)			Myeloma (203)			All haematological malignancies (200–207)		
	No.	No.	OR	95% CI	No.	OR	95% CI	No.	OR	95% CI
Psoriasis	360	78	1.6	(1.3–2.1)	20	1.0	(0.6–1.5)	142	1.4	(1.1–1.6)
Sjögren's syndrome	24	19	6.4	(3.5–12)	2	1.6	(0.4–6.7)	26	4.0	(2.3–7.0)
Primary Sjögren's syndrome	14	13	7.5	(3.5–16)	1	1.3	(0.2–9.8)	15	4.0	(1.9–8.2)
Pernicious anaemia	222	29	0.8	(0.6–1.2)	14	0.8	(0.5–1.4)	66	0.9	(0.7–1.2)
Multiple sclerosis	169	11	0.5	(0.3–1.0)	7	0.9	(0.4–1.9)	37	0.8	(0.6–1.2)
Autoimmune haemolytic anaemia	23	37	12	(7.1–20)	3	2.0	(0.6–6.8)	54	8.2	(5.0–13)
ITP	40	16	3.4	(1.9–6.2)	3	1.6	(0.5–5.4)	36	3.4	(2.2–5.4)
Rheumatic fever	489	68	1.0	(0.8–1.3)	34	1.1	(0.8–1.6)	140	1.0	(0.8–1.2)
Asthma	2176	254	0.9	(0.8–1.0)	125	1.0	(0.9–1.2)	561	0.9	(0.8–1.0)

NHL, non-Hodgkin's lymphoma; ITP, idiopathic thrombocytopenic purpura.

Increased risks of NHL and of all haematological malignancies combined were found for subjects earlier diagnosed with Sjögren's syndrome, which remained when individuals with RA and SLE were excluded (Table 3). The exclusion was performed in order to focus on persons with primary Sjögren's syndrome. The increased risks remained after introducing induction periods of 5 and 10 years after first diagnosis of Sjögren's syndrome; the ORs were 8.1 (95% CI 3.4–19.5, 10 exposed cases) and 6.0 (95% CI 2.1–17.5, six exposed cases) respectively, excluding subjects with RA and SLE.

The risk estimates associated with pernicious anaemia were close to unity (Tables 2 and 3). However, after an induction period of 5 years, the OR for NHL following pernicious anaemia was 0.3 (95% CI 0.1–0.7; four exposed cases). A tendency towards a decreased risk of NHL was seen in association with MS (Table 3), also evident when induction periods of 5 and 10 years were introduced.

AIHA and ITP were positively associated with an excess risk of leukaemia and NHL (Tables 2 and 3). In general, induction periods of 5 and 10 years resulted in less elevated risk estimates for the different types of haematological malignancies. After an induction period of at least 5 years the associations of all leukaemia combined to AIHA and ITP were still positive; the OR for AIHA was 5.7 (95% CI 2.5–13.4, eight exposed cases) and the OR for ITP was 2.1 (95% CI 0.8–5.4, five exposed cases). An elevated risk of haematological malignancies was observed following AIHA even after an induction period of at least 10 years (OR = 4.1; 95% CI 1.5–11.3). A similar tendency was noted also for ITP.

We found risks close to unity for all haematological malignancies in association with rheumatic fever (Tables 2 and 3), remaining after induction periods of 5 and 10 years. Generally, ORs associated with asthma were below unity for most haematological malignancies (Tables 2 and 3). Following an induction period of 10 years after first asthma diagnosis, the OR for leukaemia, excluding CLL, was 0.6 (95% CI 0.4–0.9, 26 exposed cases) and for acute myeloid leukaemia (AML) 0.4 (95% CI 0.2–0.8, nine exposed cases), while the ORs for CLL and NHL were 0.8 (95% CI 0.6–1.2, 27 exposed cases) and 0.9 (95% CI 0.7–1.1, 101 exposed cases), respectively. The risks associated with asthma showed a tendency towards a decreased risk for ALL (OR = 0.6, 95% CI 0.3–1.0, based on 10 exposed cases) and a decreased risk was seen for HD (OR = 0.6, 95% CI 0.4–0.9, based on 18 exposed cases), which after an induction period of 10 years resulted in the OR 0.7 (95% CI 0.4–1.5, eight exposed cases).

4. Discussion

In our material, the autoimmune diseases psoriasis, Sjögren's syndrome, autoimmune haemolytic anaemia, and ITP were associated with increased risks for haematological malignancies, whereas no risk increases were found in association with pernicious anaemia and MS. None of the autoimmune diseases influenced the risk of myeloma. In accordance with the immune surveillance hypothesis slightly reduced risks of haematological malignancies were found in association with asthma, especially for asthma diagnosed at least 10 years prior to malignancy.[8]

One strength of the present case-control study is the non-differential ascertainment of outcome through population-based registers. Other strengths are the completeness of the Cause of Death Registry and the Swedish Cancer Registry and a long period of follow-up; up to 30 years. Another strength is the possibility to compare several diseases with immune responses skewed towards Th1 or Th2.

We have no reason to believe that selection bias is a problem as the study is population-based; all cases of haematological malignancies that occurred during the study period were retrieved and controls were randomly selected from the study base. It is required by law to report all incident cancer cases in Sweden to the Swedish Cancer Registry. New cases of cancer are reported by physicians in hospitals and other establishments as well as by pathologists.

Non-differential misclassification of outcome is unlikely to affect risks as the two independent notifications systems ensure a high coverage. As only hospitalised patients are included in the Hospital Discharge Registry, it is possible that subjects with autoimmune diseases have been subject to increased clinical surveillance, resulting in higher detection and diagnosis of malignancies, compared to the general population. To minimise differential misclassification and reduce screening bias of outcome, an induction period of at least 1 year after diagnosis of immune-mediated disease was required to include a case of haematological malignancy. Also, analyses with induction periods of at least 5 and 10 years, respectively, were performed which gave results in accordance with the analyses based on 1-year induction periods. Another strong argument against such bias is the lack of elevated risks in association with asthma; if anything, risk estimates for asthma were decreased.

Non-differential misclassification of immune-mediated diagnoses could dilute the risk estimates towards unity. Validations of the Hospital Discharge Registry by analysing medical records have demonstrated a correct ICD-code at the five-digit-level in 83% of all primary diagnoses.[15] We have controlled for confounding from age, sex and socioeconomic status. However, it cannot be completely ruled out that confounding from some other factor exists. Generalisability could be affected if hospitalised patients constitute a selection of individuals with more severe disease.

For psoriasis, the majority of previous studies have also found relative risk estimates for haematological malignancies above unity, although most studies are based on small numbers of exposed cases which have resulted in statistically unstable risk estimates. There are studies showing increased risks,[7,16,17] and also studies that found no association with haematological malignancies.[4,18] Our study includes a considerably larger number of exposed cases than previous studies, with the exception of one study on AML.[7] Similar to our results, previous studies have not found an increased risk of myeloma associated with psoriasis. Our findings for Sjögren's syndrome are in accordance with most previous studies.[19–21]

Pernicious anaemia and MS did not increase the risk of developing haematological malignancies. Instead, a decreased risk was found for NHL in association with pernicious anaemia after an induction period of 5 years. This is partly in contrast to two previous studies considering pernicious anaemia and risk of myeloid leukaemia and myeloma.[22,23] In our

material, subjects with MS showed a tendency towards a decreased risk of NHL. Only a few previous studies have assessed the risk of NHL among individuals with MS; in those studies the risk of NHL has been close to unity or only slightly increased.[5,24,25]

For AIHA and ITP, our results are in accordance with the literature. AIHA and ITP have mostly been discussed as a secondary phenomenon to lymphoproliferative disorders, such as CLL.[26] However, our findings of increased risks also after induction periods as long as 10 years imply that either AIHA and ITP may precede the development of haematological malignancy or that malignancy has been present as long as 10 years before being diagnosed.

Some case-control studies have been conducted to examine the association between rheumatic fever and haematological malignancies. Most of them found no associations. However, elevated risks for myeloma and CLL, respectively, have been observed in two studies.[27,28] Our study is based on a larger number of cases with rheumatic fever than previous studies. Rheumatic fever did not influence the risks of NHL, myeloma or leukaemia.

Most previous studies have observed risks below or close to unity for haematological malignancies following asthma,[6,7,13] which are in accordance with our findings. To our knowledge, no previous studies have used induction periods as long as at least 10 years, which resulted in statistically significantly reduced risks for leukaemia, excluding CLL, and in particular for AML. There are studies where decreased risks in association with AML and lymphatic leukaemia have been found.

In conclusion, our results suggest that the influence of autoimmune diseases on the development of haematological malignancies is complex. In accordance with the literature and proposed hypotheses, we found increased risks of haematological malignancies following a diagnosis of Sjögren's syndrome and psoriasis. A noteworthy finding is that even when AIHA and ITP were diagnosed at least 10 years prior to diagnosis, increased risks of haematological malignancies were found. Our findings indicate that several autoimmune diseases are associated with increased risk of NHL. These findings, together with increased risk estimates following a diagnosis of psoriasis and Sjögren's syndrome lend support to the antigenic stimulation hypothesis for these Th1-mediated diseases in combination with chronic inflammatory processes, whereas we did not find elevated risks following the Th1-mediated diseases pernicious anaemia, where pathogenesis does not involve chronic inflammation, and MS, where inflammation is intermittent. Also, these two diseases destroy their target organs, leading to lack of exposed antigen and thereby ceased antigenic stimulation. As chronic inflammation is generally a minor symptom in rheumatic fever, its lack of influence on risk of developing haematological malignancies supports that the antigenic stimulation hypothesis may be of importance in autoimmune diseases when chronic inflammation is part of the pathogenesis. Asthma was associated with a reduced risk of haematological malignancies, most pronounced after induction periods of 10 years following asthma diagnosis, which lend some support to the immune surveillance hypothesis. The autoimmune diseases do not seem to affect the risk of myeloma.

It is likely that the pathogenesis differs between subtypes of leukaemia, HD, NHL and myeloma which may explain the conflicting results between subgroups of haematological malignancies. Also, the risk of developing cancer may be affected by type of medical treatment. Furthermore, different immunological mechanisms may be implicated in the various types of autoimmune diseases, which may affect the risk of haematological malignancies differently. This is a reason for not combining the various types of autoimmune diseases into large groups. Further studies are needed to resolve these issues. Preferentially, carefully collected prospective epidemiological data from persons with distinct immunological disorders should be combined with clinical information about haematological malignancies that are defined according to modern classifications, including information about genotype and immunophenotype.

Conflict of interest statement

None declared.

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