Asthma and risk of myelodysplastic syndromes: a population-based cohort study

Henrik Frederiksen*,1,2, Dóra Kőrmendiné Farkas2, Erzsebet Horváth-Puhó2, Jan M Nørgaard3, Mette Nørgaard2 and Henrik T Sørensen2

1Department of Haematology, Odense University Hospital, Odense, Denmark; 2Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark and 3Department of Haematology, Aarhus University Hospital, Aarhus, Denmark

Background: Risk factors for the development of myelodysplastic syndromes (MDS) include age, exposure to ionising radiation, and cytotoxic drug treatment. Recently, asthma also has been suggested as a risk factor for MDS.

Methods: We undertook this nationwide population-based cohort study on patients with a first-time hospital-based asthma diagnosis during 2002–2013 and followed them for the development of MDS/chronic myelomonocytic leukaemia (CMML).

Results: We identified 75 995 patients with incident asthma and no previous MDS/CMML diagnosis. Seventy-eight patients subsequently developed MDS and nine patients developed CMML during 402 892 person-years. The cumulative risks of developing MDS/CMML among asthma patients were 0.02% (95% CI: 0.01–0.04%) and 0.07% (95% CI: 0.05–0.09%) during the first year and the first five years of follow-up, respectively. The standardised incidence ratio of MDS/CMML among asthma patients overall was 1.6 (95% CI: 1.3–2.0) with little variation across subgroups.

Conclusions: Asthma may be a risk factor for the development of MDS/CMML.

Myelodysplastic syndromes (MDS) constitute a group of related clonal hematopoietic disorders (Swerdlow et al, 2008). Risk factors for MDS include age, ionising radiation, smoking, occupational exposures, and cytotoxic drugs (Nisse et al, 1995; Andersen et al, 1998; Bjork et al, 2000; Dalamaga et al, 2002; Smith et al, 2003).

In a cohort of 22 601 women aged 55–59, self-reported asthma in 1997 was associated with a two-fold higher risk of MDS during the median follow-up of 14.8 years (RR = 2.0 (95% confidence interval (CI): 1.0–4.6)). Outcomes were MDS and other incident haematological malignancies identified in the State Health Registry of Iowa (Linabery et al, 2014). Although the underlying mechanism is unknown, immune dysregulation in MDS is evident, as some subtypes respond to the treatment with immunosuppressive or immunomodulatory agents (Saunthararajah et al, 2003; List et al, 2005; Mollgard et al, 2011; Duong et al, 2012). Some MDS patients also exhibit immune-mediated conditions such as vasculitis (Farah et al, 2010). We investigated the association between asthma and MDS/chronic myelomonocytic leukaemia (CMML) in a large cohort of adults.

MATERIALS AND METHODS

We conducted this cohort study using the Danish National Patient Registry (DNPR) and the Civil Registration System (CRS; Schmidt et al, 2014; Schmidt et al, 2015). The DNPR contains information on all inpatient discharges from hospitals since 1977, and on outpatient clinic and emergency department visits since 1995. The DNPR records patients’ civil registration numbers, dates of outpatient visits, hospitalisations, and up to 20 diagnoses coded by physicians according to the WHO’s International Classification of Diseases, Eighth Revision (ICD-8) until 1993 and Tenth Revision (ICD-10) thereafter. We identified all patients aged ≥18 years with a first-time hospital-based diagnosis of asthma (ICD-10 codes J45–46) in the DNPR during 2002–2013 (Byrjalsen et al, 2014) and subsequent diagnoses of MDS or CMML (MDS code: D46, CMML code: C93). We excluded patients whose MDS/CMML diagnosis preceded their asthma diagnosis. The CRS has recorded date of birth, sex, and vital status of all Danish residents since 1968. Follow-up for MDS/CMML began on the date of the asthma diagnosis.
Asthma and risk of MDS

We identified 75 995 patients with incident asthma and no previous diagnosis of MDS or CMML. Their median age was 48.9 years and median follow-up time was 5.0 years (IQR: 2.2–8.2 years). Seventy-eight patients developed MDS and nine patients developed CMML during 402 892 person-years of follow-up. During 1, 5, and 10 years of follow-up, the cumulative risks of developing MDS/CMML for asthma patients were 0.02% (95% CI: 0.01–0.04%), 0.07% (95% CI: 0.05–0.09%), and 0.12% (95% CI: 0.09–0.15%), respectively.

Asthma patients were at increased risk of developing MDS/CMML (SIR 1.6 (95% CI: 1.3–2.0); Table 1). SIR estimates across subgroups were similar (Table 1). When MDS and CMML patients were analysed separately, the SIR for MDS was identical to the overall SIR (1.6 (95% CI: 1.3–2.0)), whereas the SIR for CMML was imprecise (1.4 (95% CI: 0.6–2.6)) due to low numbers. The association was observed in all subgroups, as well as among patients without concurrent COPD (Table 1). As cancer treatment is a risk factor for MDS, we repeated our analyses excluding asthma patients with a previous cancer diagnosis, censoring follow-up if patients developed a cancer diagnosis before MDS/CMML, and also treating both the cancer and death as competing risks. These analyses resulted in virtually identical SIR estimates (data not shown).

## RESULTS

We found an increased risk of MDS/CMML among patients with an asthma diagnosis. These findings are in line with the study by Linabery et al (2014). They reported no association between allergic diseases other than asthma and haematological malignancies. In a review of the previous studies, providing estimates of the association between allergic conditions and haematological myeloid neoplasms, Wang and Diepgen (2005) reported imprecise risk estimates around unity. In a case–control study that specifically included MDS patients and examined self-reported allergic conditions other than asthma, no differences in frequencies of allergies were observed between the MDS patients and their controls (Pekmezovic et al, 2006).

The mechanism linking asthma to MDS/CMML remains unknown. Although, epigenetic modifications are common to MDS/CMML and asthma (Yang and Schwartz, 2012; Bravo et al, 2014), they are unlikely to explain the association as the hallmark of MDS/CMML is clonal proliferation of neoplastic cells with subsequent epigenetic modifications, whereas asthma is a non-clonal disease.

Most previous studies of allergic conditions and risk of haematological cancers have focused on lymphoid malignancies (Wang and Diepgen, 2005; Turner et al, 2006; Melbye et al, 2007), with conflicting results. Some studies have found that allergic conditions and specific IgE titres were associated with the decreased risk of lymphoid haematological malignancies, (Wang and Diepgen, 2005), but one study suggested that these findings may be attributed to reverse causality, that is, immunological
response to IgE-specific allergens may be compromised among patients with the developing lymphomas (Melbye et al., 2007).

Despite its large size, and complete follow-up, our study has limitations. We included only asthma diagnosed in hospital-based settings. Some asthma patients may be diagnosed and followed by their general practitioner without a hospital contact (Hanania et al., 2011). However, asthma patients above 65 years of age (~10% of prevalent asthma cases) are most likely to be referred to hospital-based care (Hanania et al., 2011). As the incidence of MDS/CMML increases with age, (Dinmohamed et al., 2014) a larger proportion of MDS/CMML patients with a preceding asthma diagnosis would have had a hospital-based asthma diagnosis. During the first year following asthma diagnosis, the SIR estimate for MDS/CMML development was higher than in the following years. Heightened diagnostic effort probably explains part of the association in the short term. However, the increased risk was remarkably persistent many years after an asthma diagnosis.

In the DNPR, the completeness of the asthma diagnosis in conscripts has been found to be 0.44 and the specificity to be 0.98 (Jensen et al., 2010). Asthma patients with a hospital referral, however could have a higher risk of MDS/CMML than asthma patients treated only by general practitioners due to potentially, more severe asthma and higher levels of comorbidity. As well, because of our study’s registry-based design, we lacked detailed patient-specific information, such as smoking status. Still, when we used a concurrent COPD diagnosis as a proxy for smoking, we observed the association between asthma and MDS/CMML among the asthma patients without COPD.

We conclude that asthma may be a risk factor for the development of MDS/CMML.

**REFERENCES**

Andersen MK, Johansson SO, Pedersen-Bjergaard J (1998) Chromosomal abnormalities in secondary MDS and AML. Relationship to drugs and radiation with specific emphasis on the balanced rearrangements. *Haematologica* 83(6): 483–488.

Bjork J, Albin M, Mauritzson N, Stromberg U, Johansson B, Hagmar L (2000) Asthma and risk of hematopoietic malignancies in a cohort of postmenopausal women: a report from the Iowa Women’s Health Study. *Cancer Epidemiol Biomarkers Prev* 9(8): 1313–1319.

Dinmohamed AG, Visser O, van NY, Huijgens PC, Sonneveld P, van de Loosdrecht AA, Jongen-Lavrencic M, van de Loosdrecht AA, Jongen-Lavrencic M, van de Loosdrecht AA, Jongen-Lavrencic M (2014) Trends in incidence, initial treatment and survival of myelodysplastic syndromes: a population-based study of 5144 patients diagnosed in the Netherlands from 2001 to 2010. *Eur J Cancer* 50(5): 1004–1012.

Duong VH, Komrokji RS, List AF (2012) Efficacy and safety of lenalidomide in patients with myelodysplastic syndrome with chromosome 5q deletion. *Ther Adv Hematol* 3(2): 105–116.

Farah C, Bulai LG, Jego U, Paul C, Viraben L, Lamant L, Delavigne K, Adoue D, Laurent G, Beyne RO (2010) Prevalence and prognostic value of cutaneous manifestations in patients with myelodysplastic syndrome. *J Eur Acad Dermatol Venereol* 24(10): 1171–1175.

Hanania NA, King MJ, Braman SS, Saltoun C, Wise RA, Enright P, Felson AR, Mathur SK, Ramsdell JW, Rogers L, Stempel DA, Lima JF, Fish FE, Wilson SR, Boyd C, Patel KV, Irvin CG, Yawn BP, Halm EA, Wasserman SI, Sands MF, Ershler WB, Ledford FK (2011) Asthma in the elderly: current understanding and future research needs—report of a National Institute on Aging (NIA) workshop. *J Allergy Clin Immunol* 128(3 Suppl): S4–S24.

Jensen AO, Nielsen GL, Ehrenstein V (2010) Validity of asthma diagnoses in the Danish National Registry of Patients, including an assessment of impact of misclassification on risk estimates in an actual dataset. *Clin Epidemiol* 2: 67–72.

Linabery AM, Prizment AE, Anderson KE, Cerhan JR, Poynter JN, Ross JA (2014) Allergic diseases and risk of hematopoietic malignancies in a cohort of postmenopausal women: a report from the Iowa Women’s Health Study. *Cancer Epidemiol Biomarkers Prev* 23(9): 1903–1912.

List A, Kurtin S, Roe DJ, Buresch A, Mahadevan D, Fuchs D, Rimozza L, Heaton R, Knight R, Zeldis JB (2005) Efficacy of lenalidomide in myelodysplastic syndromes. *N Engl J Med* 352(6): 549–557.

Melbye M, Smedby KE, Lehtinen T, Rostgaard K, Glimmelius B, Munksgaard L, Schilinsky C, Sundström C, Chang ET, Koskela P, Adami HO, Hjalgrim H (2007) Atopy and risk of non-Hodgkin lymphoma. *J Natl Cancer Inst* 99(2): 158–166.

Mollgard L, Saft L, Treppenfeld MB, Dybedal I, Norgaard JM, Ahrenmark J, Ejerblad E, Garelius H, Dufva IH, Jansson M, Jandersten M, Kjeldsen L, Linder O, Nilsson L, Westergaard H, Porwit A, Grönbaek K, Hellström-Lindberg E (2011) Clinical effect of increasing doses of lenalidomide in high-risk myelodysplastic syndrome and acute myeloid leukemia with chromosome 5 abnormalities. *Haematologica* 96(7): 963–971.

Niise C, Lorthois C, Dorph V, Eloy F, Haguenoer IM, Fenaux P (1995) Exposure to occupational and environmental factors in myelodysplastic syndromes. Preliminary results of a case-control study. *Leukemia* 9(4): 693–699.

Pekmezovic T, Suvadjic VN, Kisic D, Grgurevic A, Bogdanovic A, Gotic M, Bakrac M, Brkic N (2006) A case-control study of myelodysplastic syndromes in Belgrade (Serbia Montenegro). *Ann Hematol* 85(8): 514–519.

Saunthararajah Y, Nakamura R, Wesley R, Wang QJ, Barrett AJ (2003) A simple method to predict response to immunosuppressive therapy in patients with myelodysplastic syndrome. *Blood* 102(8): 3025–3027.

Schmidt M, Pedersen L, Sorensen HT (2014) The Danish Civil Registration System as a tool in epidemiology. *Eur J Epidemiol* 29(8): 541–549.

Schmidt M, Schmidt SA, Sandegaard JL, Ehrenstein V, Pedersen L, Sorensen HT (2015) The Danish National Patient Registry: a review of content, data quality, and research potential. *Clin Epidemiol* 7: 449–490.

Smith SM, Le Beau MM, Hsu D, Karrison T, Sobecks RM, Anastassi J, Vardiman JW, Rowley JD, Larson RA (2003) Clinical-cytogenetic associations in 306 patients with therapy-related myelodysplasia and myeloid leukemia: the University of Chicago series. *Blood* 102(1): 43–52.

Swerdlov SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J, Vardiman JW (2008) WHO classification of tumours of haematopoietic and lymphoid tissues. International Agency for Research on Cancer (IARC): Lyon.

Turner MC, Chen Y, Krewski D, Ghadirian P (2006) An overview of the association between allergy and cancer. *Int J Cancer* 118(12): 3124–3132.

Wang H, Diepgen TL (2005) Is atopy a protective or a risk factor for cancer? A review of epidemiological studies. *Allergy* 60(9): 1098–1111.

Yang, Schwartz DA (2012) Epigenetic mechanisms and the development of asthma. *J Allergy Clin Immunol* 130(6): 1243–1255.

This work is published under the standard license to publish agreement. After 12 months the work will become freely available and the license terms will switch to a Creative Commons Attribution-NonCommercial-Share Alike 4.0 Unported License.