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Cancer risk in amyloidosis patients in Sweden with novel findings on non-Hodgkin lymphoma and skin cancer

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Background: Systemic amyloidoses include immunoglobulin light chain (AL) amyloidosis, serum amyloid (AA)-related amyloidosis and senile systemic amyloidosis (SSA). AL amyloidosis is associated with myeloma, and we showed recently that transthyretin-related hereditary amyloidosis was related to non-Hodgkin lymphoma (NHL). In SSA, amyloids constitute wild-type transthyretin. We wanted to analyze cancer risks in amyloidosis, particularly in SSA.

Patients and methods: Nonhereditary amyloidosis patients were identified from the Swedish Hospital Discharge and Outpatients Registers from years 1997 through 2010. Their cancer risk was assessed based on the Swedish Cancer Registry using standardized incidence ratio (SIR) between amyloidosis patients and the remaining population. To gain information about amyloidosis subtypes, we used the Swedish Prescribed Drug Register from years 2005 through 2010 to find out the specific medication prescribed.

Results: Among 1400 identified amyloidosis patients, cancer risk was increased for myeloma, NHL and squamous cell skin cancer. Myeloma and skin cancers were diagnosed 7–8 years earlier than in the population, whereas NHL was diagnosed in elderly patients. The SIR was 204 for myeloma in patients who received AL amyloidosis medication, and it was 17.22 in patients receiving rheumatoid arthritis medication, suggesting AA amyloidosis. In remaining patients, including

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SSA, NHL risk was 14.78, including lymphoplasmacytic lymphoma and Waldenstrom macroglobulinemia (51.41) and diffuse large B-cell lymphoma (18.69). In these patients, endometrial cancer (7.04) and cancer of unknown primary site (6.56) were also increased.

Conclusions: SSA is likely to be a main cause of NHL in the elderly population. The present findings suggest a novel mechanism for amyloidosis-related cancer, highlighting the role of chronic stimulation by amyloid.

Key words: non-Hodgkin lymphoma, senile amyloidosis, transthyretin, myeloma, cancer risk

introduction

Amyloidosis is a heterogeneous group of diseases but it is characterized by a homogeneous molecular disease mechanism of fibrillar protein (amyloid) deposition in a single organ or systematically in many organs [1, 2]. Systemic amyloidoses include immunoglobulin light chain-related AL amyloidosis, serum acute phase protein-related amyloid A (AA) amyloidosis and transthyretin-related senile systemic amyloidosis (SSA). Although AL amyloidosis is frequently referred to as being the most common systemic amyloidosis, SSA is more common at least in Sweden and Finland, and possibly even in the USA but it remains often unnoticed because of the slow progression in old patients [3–5]; right-sided heart failure and a history of carpal tunnel syndrome are the only clinical signs [6]. AA amyloidosis is a secondary condition in response to chronic inflammation. It has been estimated that some 20% of rheumatoid arthritis patients may have AA amyloidosis but the incidence has declined along a better control of inflammation [7, 8]. The most common and widespread hereditary amyloidosis is caused by transthyretin mutations and the disease is known as familial amyloid polyneuropathy (FAP) [9]. The difference between FAP and SSA is that a mutant protein is related to FAP while the wild-type form is the culprit in SSA. FAP is endemic in Sweden but we will limit the present study to nonhereditary amyloidoses [10]. The symptoms of amyloidosis arise in the critical organs where amyloids accumulate, including the heart, kidney, liver and peripheral nerves [2].

AL amyloidosis is associated with multiple myeloma, Waldenstrom macroglobulinemia and monoclonal gammopathy of unknown significance (MGUS). However, only some 10–20% of myeloma patients have AL amyloidosis [11, 12]. In a follow-up study of 1384 patients with MGUS for a median of 15 years, 10 primary amyloidosis and 75 myeloma cases were diagnosed giving relative risks of 8.4 and 25, respectively [11]. AL amyloidosis has been rarely associated with non-Hodgkin lymphoma (NHL), of mucosa-associated lymphoid tissue (MALT) or lymhoplasmacytic lymphoma types [13–15]. Other neoplasms that have been associated with amyloidosis include endocrine tumors of insulinoma, prolactinoma, medullary thyroid tumors and pituitary adenomas, all of which are rare, described in case reports and no risk estimates are available [1]. The endocrine tumors overproduce specific peptide hormones constituting the localized amyloid deposits [16–19]. Treatment of AL amyloidosis follows the same principles as are used for multiple myeloma with high-dose melphalan combined with prednisone or dexamethasone as the first-line chemotherapy [2].

No cancers have been associated with SSA or AA amyloidosis. However, we recently described an excess of NHL in hereditary FAP and an obvious question is whether SSA would also be associated with NHL because the amyloidogenic precursor is the wild-type transthyretin [20]. With a 25% prevalence among those older than 70 years (Sweden) or 85 years (Finland) and with an ever-aging population, such an association would imply major population-level burden [3, 4]. In the present study, we assessed risks of all cancers through the Swedish Cancer Registry in nonhereditary amyloidosis patients based on hospital inpatient and outpatient data. Amyloidosis is a rare condition and the diagnostics are both demanding and time-consuming. Thus, the medical records often fail to specify the type of amyloidosis although hereditary amyloidoses have been recognized as distinct entities. In this study, we are able to mitigate the problem of defining amyloidosis subtype, by assessing the medication used by the patients and by considering comorbidities.

patients and methods

source of data

Amyloidosis patients were identified from the Swedish Hospital Discharge Register (1997–2010) or from the Outpatients Register (2001–2010). Cancers were identified from the Swedish Cancer Registry. Family data were obtained from the Multigeneration Register, to make the Family-Cancer Database [21]. Information from the registers was linked at the individual level via the national 10-digit civic registration number assigned to each person in Sweden for his or her lifetime. In the linked dataset, civic registration numbers were replaced by serial numbers to ensure the anonymity of each individual.

The 10th revision of the International Classification of Diseases (ICD-10) was used to identify all hospital or outpatient discharges using diagnostic codes for amyloidosis. The starting year 1997 was the first year when ICD-10 was used and distinguished hereditary and nonhereditary amyloidosis but the codes could not distinguish nonhereditary amyloidosis subtypes [22].

Data on medication were available from the Swedish Prescribed Drug Register, covering years 2005 through 2010 with 100% completeness. The following medication was considered specific for AL amyloidosis: melphalan, thalidomide and lenalidomide [2]. Medication suggestive of rheumatoid arthritis and AA amyloidosis included methotrexate, sulfasalazine, lefunomide, infliximab, anakinra, rituximab and abatacept; all patients for whom these drugs were prescribed were diagnosed as hospital patients with rheumatoid arthritis. Remaining patients included SSA.

statistical analysis

Person-years for amyloidosis patients were calculated starting from 1 January 1997, until diagnosis of first cancer, death, emigration or the closing date (31 December 2010). Age-specific incidence rates for cancer, divided into 5-year age bands. Standardized incidence ratios (SIRs) were used to measure the cancer risks among amyloidosis patients. SIRs were calculated as the ratio of observed (O) to expected (E) number of cases. The expected numbers were calculated from 5-year-age-, sex-, socioeconomic index-, geographical region of residence- and period-specific incidence rates for those not diagnosed with

amyloidosis, i.e. essentially the Swedish population. 95% Confidence intervals (95% CIs) were calculated assuming a Poisson distribution.

Ethical considerations: this study was approved by the Ethics Committee of the Lund University, Sweden.

results

Case numbers of hospitalized amyloidosis patients diagnosed as inpatients or outpatients were 1400, of whom 736 men and 664 women. During the follow-up from 1997 through 2010, 263 cancer were diagnosed, 141 in men and 122 in women, with respective SIRs of 1.37 and 1.98; for combined sexes, the SIR was 1.60 (Table 1). We show only cancers with at least five diagnosed cases. For all amyloidosis patients, the risk for myeloma was highest, 33.02, followed by 5.11 for NHL, 3.33 for squamous cell skin cancer and 2.52 for leukemia. Among NHL subtypes, the risk was highest for lymphoplasmacytic lymphoma and Waldenstrom macroglobulinemia (27.74). 'Other' NHL included unspecified NHL diagnoses. For leukemia, no individual subtype was significant. The higher overall risks in women compared with men were explained largely by their high risks for significantly increased tumor sites, particularly myeloma (45.92 versus 25.61) and NHL (6.40 versus 4.35); however, even for these the 95% CIs overlapped. Diagnostic ages for cancer are also shown. For myeloma (63.3 versus 70.9) and squamous cell skin cancer (69.2 versus 77.5), the mean age was significantly lower for amyloidosis patients than for cancer patients without amyloidosis.

In Table 2, cancer risks are shown by first recorded hospitalization age for amyloidosis. Overall, young diagnostic age associated with risk, which was 4.77 when amyloidosis was diagnosed before age 60 years. It decreased to 1.90 when diagnosis was at age 60–69 years and at higher ages, cancer risk was not significant. Myeloma risk declined from 186.92 (amyloidosis diagnosis before age 60 years) to 12.69 (80+ years). Lung cancer and other endocrine tumors and leukemia were increase only in patients diagnosed before age 60 years; for leukemia, two of four cases were polycythemia vera (SIR 60.06; 95% CI 5.66–220). NHL showed a deviant age dependence, and the risk was identical when amyloidosis was diagnosed before 60 years (6.55) or at 80+ years (6.45); in the former group, case numbers were 3 (4.6% of all cancer) while they increased to 9 (18.8%) in the latter.

Age-dependence of myeloma, NHL and skin cancer in amyloidosis patients and in the total Swedish population is shown in Figure 1. The patient numbers are shown in Table 1. The peak age for myeloma incidence in amyloidosis patients was 50–54 years but the incidence increased also toward advanced age (Figure 1A). For NHL, the prominent incidence maximum was at age 80–85 years (Figure 1B); of note, only three cases were diagnosed before age 60 years. Squamous cell skin cancer showed two incidence peaks, 60–64 and 80–84 years, both earlier than the background maximum at age 85+ years (Figure 1C).

Clues about the type of amyloidosis were acquired by analyzing the causes of death of cancer patients. Among myeloma patients of Table 1, 53 had died and of these 29 (55%) in cancer (all but one in myeloma), 6 (11%) in cardiovascular diseases and none in musculoskeletal diseases. Among NHL patients, 19 had died and of these 16 (84%) in cancer (mainly NHL but 2 in myeloma), 3 (16%) in cardiovascular diseases and none in musculoskeletal diseases. Among skin cancer patients, 11 had died and of these 3 (27%) in cancer (myeloma, leukemia and rectal cancer), 1 (9%) in cardiovascular diseases and 2 (18%) in musculoskeletal diseases.

In order to gain information on the specific type of amyloidosis, we were forced to narrow down the study period to 2005 through 2010 because the data on medication were available for that period. Of 540 amyloidosis patients, 94 (17%) had AL amyloidosis (or myeloma) medication, most commonly melphalan, 28 (5%) had a typical rheumatoid arthritis medication and all of them had been diagnosed with rheumatic arthritis as in- or outpatients. Table 3 shows the risk of cancer in 2005–2010 in amyloidosis patients with AL amyloidosis medication, with rheumatoid arthritis medication or with hospitalization for neither. Myeloma risk was 204 in AL amyloidosis patients, skin cancer risk was 17.22 in rheumatoid arthritis patients and NHL risk was 14.78 in patients not belonging to the two other groups. In NHL patients, the SIRs were significant for lymphoplasmacytic lymphoma and Waldenstrom macroglobulinemia (51.41) and diffuse large B-cell lymphoma (18.69). In the latter group, two deaths were due to NHL and one to myeloma. The non-AL and nonrheumatoid arthritis groups showed also increased risks of endometrial cancer (7.04) and unspecified primary (cancer of unknown primary site, 6.56).

Among the potential confounding factors, family history of NHL, myeloma and squamous cell skin cancer was checked among the first-degree relatives of patients in Table 1. Only myeloma and squamous cell skin cancer each had a sibling diagnosed with the same cancer (but no amyloidosis). The databases had no data on obesity, smoking or alcohol consumption but these are unlikely confounders because they are not essential risk factors of the three cancers. Moreover, based on proxy data, no possible associations could be found. None of the patients with the three cancers in Table 1 were diagnosed with obesity or alcoholism (among 74 024 and 171 114 identified patients) and only one NHL and skin cancer and three myeloma patients were diagnosed with chronic obstructive pulmonary disease, as proxy for smoking (among 413 255 identified patients).

discussion

Our recent data showing an increased risk of NHL after FAP urged us to assess possible cancer risks in wild-type transthyretin-related SSA, the most common systemic amyloidosis [20]. In the present dataset on NHL patients, the extraordinary high diagnostic age for maximal incidence (80–84 years) was the first clue that the associated disease was not AL amyloidosis which would typically be affecting younger patients. Further definition of the patient population appeared to confirm the hypothesis of an increased risk of NHL in SSA. The data additionally suggested that squamous cell skin cancer was associated with rheumatoid arthritis-related AA amyloidosis.

The present results may suggest a novel mechanism for amyloidosis-associated cancers. While the mechanism for AL amyloidosis and endocrine peptide-related amyloidosis is the overproduction of the amyloid precursor protein or peptide by the tumors, it appears that for FAP- and SSA-related amyloidosis, malignant transformation may be caused by chronic stimulation or inflammation. In SSA, the accumulation of amyloid deposits in various organs, including connective tissue, may last for years, allowing ample time for chronic immune

Table 1. SIR and diagnostic age for cancer in amyloidosis patient in 1997–2010

Cancer site	Men				Women				All				Mean age at cancer diagnosis (years)		
	O	SIR	95% CI		O	SIR	95% CI		O	SIR	95% CI		Without amyloidosis	With amyloidosis	*P*-values for differences in ages
Upper aerodigestive tract	3	1.31	0.25	3.88	3	3.70	0.70	10.96	6	1.94	0.70	4.24	66.6	60.5	0.27
Colon	6	0.85	0.30	1.85	4	0.79	0.20	2.04	10	0.82	0.39	1.52	72.2	64.7	0.05
Rectum	2	0.45	0.04	1.64	3	1.33	0.25	3.94	5	0.74	0.23	1.75	70.8	68.6	0.68
Lung	4	0.50	0.13	1.29	3	0.68	0.13	2.00	7	0.56	0.22	1.16	69.2	65.7	0.38
Breast	0				15	0.85	0.47	1.40	15	0.84	0.47	1.39	63.7	61.2	0.48
Endometrium	0				6	1.36	0.49	2.98	6	1.36	0.49	2.98	68.9	69.2	0.95
Prostate	32	0.80	0.55	1.13	0				32	0.80	0.55	1.13	71.2	71.2	0.99
Urinary bladder	6	0.89	0.32	1.95	5	3.02	0.95	7.10	11	1.31	0.65	2.35	72.3	66.4	0.09
Melanoma	4	1.13	0.29	2.92	4	1.72	0.45	4.44	8	1.36	0.58	2.70	61.5	64.3	0.64
Skin, squamous cell carcinoma	16	**3.19**	**1.82**	**5.20**	9	**3.61**	**1.64**	**6.88**	25	**3.33**	**2.15**	**4.93**	77.5	69.2	<0.01
Endocrine glands	1	1.33	0.00	7.65	4	3.35	0.87	8.65	5	2.57	0.81	6.05	61.1	52.6	0.23
Non-Hodgkin lymphoma	14	**4.35**	**2.37**	**7.32**	12	**6.40**	**3.29**	**11.22**	26	**5.11**	**3.33**	**7.49**	67.1	69.7	0.40
Diffuse large B-cell	3	1.90	0.36	5.64	3	3.62	0.68	10.72	6	2.50	0.90	5.47	67.4	64.8	0.69
Lymphoplasmacytic/Waldenstrom	5	**23.07**	**7.28**	**54.28**	4	**37.14**	**9.66**	**96.04**	9	**27.74**	**12.58**	**52.89**	72.0	72.4	0.92
Others	6	**4.21**	**1.52**	**9.23**	5	**5.33**	**1.68**	**12.54**	11	**4.65**	**2.31**	**8.36**	66.5	70.2	0.46
Myeloma	34	**25.61**	**17.73**	**35.82**	35	**45.92**	**31.97**	**63.92**	69	**33.02**	**25.69**	**41.80**	70.9	63.3	<0.01
Leukemia	6	2.15	0.77	4.70	5	**3.19**	**1.01**	**7.50**	11	**2.52**	**1.25**	**4.53**	64.0	64.9	0.89
All	141	**1.37**	**1.15**	**1.61**	122	**1.98**	**1.64**	**2.36**	263	**1.60**	**1.41**	**1.80**			

Bold type: 95% CI does not include 1.00.
O, observed number of cases; SIR, standardized incidence ratio; CI, confidence interval.

Table 2. SIR for cancer in amyloidosis patients by age at amyloidosis diagnosis in 1997–2010

Cancer site	Age at diagnosis of amyloidosis <60 years				Age at diagnosis of amyloidosis 60–69 years				Age at diagnosis of amyloidosis 70–79 years				Age at diagnosis of amyloidosis ≥80 years			
	O	SIR	95% CI		O	SIR	95% CI		O	SIR	95% CI		O	SIR	95% CI	
Upper aerodigestive tract	2	5.87	0.55	21.60	2	2.22	0.21	8.16	2	1.71	0.16	6.30	0			
Colon	3	4.82	0.91	14.28	2	0.84	0.08	3.11	4	0.79	0.21	2.05	1	0.24	0.00	1.38
Rectum	1	2.38	0.00	13.66	1	0.64	0.00	3.67	2	0.71	0.07	2.61	1	0.52	0.00	2.96
Lung	4	**5.06**	**1.31**	**13.07**	0				2	0.36	0.03	1.33	1	0.33	0.00	1.89
Breast	6	1.74	0.63	3.82	4	0.68	0.18	1.76	3	0.55	0.10	1.64	2	0.65	0.06	2.39
Endometrium	1	2.27	0.00	13.03	2	1.51	0.14	5.54	1	0.60	0.00	3.46	2	2.02	0.19	7.43
Prostate	2	1.58	0.15	5.82	10	1.04	0.50	1.92	11	0.59	0.29	1.07	9	0.84	0.38	1.61
Urinary bladder	2	5.24	0.49	19.28	4	2.41	0.63	6.22	3	0.83	0.16	2.47	2	0.73	0.07	2.68
Melanoma	2	2.19	0.21	8.06	0				5	2.46	0.78	5.79	1	0.79	0.00	4.51
Skin, squamous cell carcinoma	2	8.80	0.83	32.34	12	**11.57**	**5.95**	**20.28**	6	2.20	0.79	4.83	5	1.42	0.45	3.35
Nervous system	0				1	0.84	0.00	4.80	2	1.64	0.15	6.04	1	2.01	0.00	11.51
Endocrine glands	3	**9.34**	**1.76**	**27.66**	2	3.33	0.31	12.24	0				0			
Non-Hodgkin lymphoma	3	**6.55**	**1.24**	**19.40**	8	**6.55**	**2.80**	**12.96**	6	**2.98**	**1.07**	**6.53**	9	**6.45**	**2.92**	**12.29**
Diffuse large B-cell	2	8.47	0.80	31.15	1	1.63	0.00	9.34	2	2.12	0.20	7.79	1	1.64	0.00	9.41
Lymphoplasmacytic/Waldenstrom	0				3	**46.22**	**8.71**	**136.83**	3	**21.69**	**4.09**	**64.21**	3	**29.27**	**5.52**	**86.64**
Others	1	4.12	0.00	23.64	4	**6.84**	**1.78**	**17.68**	1	1.06	0.00	6.10	5	**8.39**	**2.65**	**19.73**
Myeloma	24	**186.92**	**119.61**	**278.51**	20	**42.18**	**25.72**	**65.25**	17	**19.84**	**11.53**	**31.83**	8	**12.69**	**5.42**	**25.14**
Leukemia	4	**10.96**	**2.85**	**28.35**	3	3.05	0.58	9.04	3	1.71	0.32	5.07	1	0.79	0.00	4.53
All	65	**4.77**	**3.68**	**6.08**	77	**1.90**	**1.50**	**2.38**	73	1.10	0.86	1.38	48	1.08	0.80	1.44

Bold type: 95% CI does not include 1.00.
O, observed number of cases; SIR, standardized incidence ratio; CI, confidence interval.

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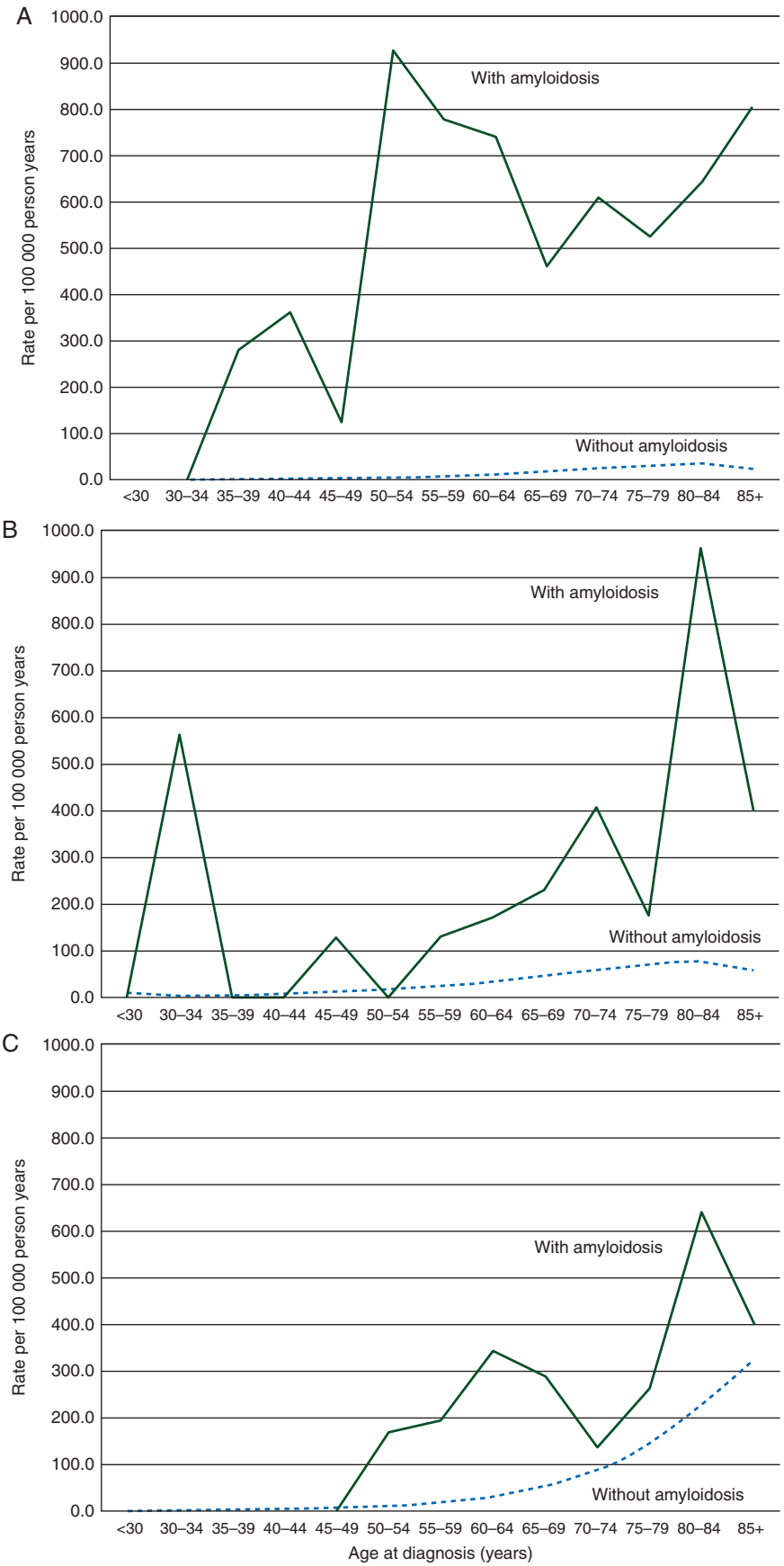

Figure 1. Age-specific incidence rate (per 100 000 person-years) of myeloma (A), non-Hodgkin lymphoma (B) and skin tumor (C) with and without amyloidosis.

Table 3. SIR for cancer in amyloidosis patients diagnosed and followed up from 2005 to 2010

Cancer site	With amyloidosis medication				With rheumatoid arthritis medication				No amyloidosis medication or rheumatoid arthritis medication/ hospitalization			
	O	SIR	95% CI		O	SIR	95% CI		O	SIR	95% CI	
Upper aerodigestive tract	0				0				2	5.90	0.56	21.72
Rectum	0				1	6.33	0.00	36.30	2	2.76	0.26	10.13
Breast	2	3.68	0.35	13.53	0				2	1.13	0.11	4.16
Endometrium	0				0				3	**7.04**	**1.33**	**20.83**
Prostate	2	0.98	0.09	3.61	2	2.89	0.27	10.64	6	1.18	0.43	2.59
Skin, squamous cell carcinoma	1	3.20	0.00	18.33	3	**17.22**	**3.25**	**50.98**	2	2.03	0.19	7.45
Non-Hodgkins lymphoma	1	6.67	0.00	38.22	0				9	**14.78**	**6.70**	**28.17**
Diffuse large B-cell	0				0				5	**18.69**	**5.90**	**43.97**
Lymphoplasmacytic/Waldenstrom	1	102.04	0.04	584.92	0				2	**51.41**	**4.85**	**189.08**
Other	0				0				2	8.65	0.82	31.80
Myeloma	17	**203.59**	**118.31**	**326.66**	0				10	**41.91**	**19.96**	**77.37**
Unknown primary site	0				0				3	**6.56**	**1.24**	**19.43**
All above	23	**5.98**	**3.79**	**8.99**	6	2.62	0.94	5.74	39	**3.67**	**2.61**	**5.02**

Bold type: 95% CI does not include 1.00.
O, observed number of cases; SIR, standardized incidence ratio; CI, confidence interval.

response [6]. Amyloid deposits from wild-type transthyretin express partially the same epitopes as the common V30M mutant of FAP but these epitopes are not expressed by native transthyretin, implying that the protein has undergone structural changes upon tissue deposition [23]. NHL is associated with many autoimmune and inflammatory conditions [24]. Diffuse large B-cell lymphoma is known to arise in response to chronic inflammatory stimulation by metallic or other surgical implants [25]. Also the risk of lymphoplasmacytic lymphoma and Waldenstrom macroglobulinemia is increased in response to personal history of many types of infections and autoimmune manifestations [26]. The present data also gave an indication that endometrial and unknown primary cancers were increased in SSA patients but this needs to be confirmed.

The risks of diffuse large B-cell NHL of 18.69 and lymphoplasmacytic lymphoma/Waldenstrom macroglobulinemia of 51.41 were remarkably high for the assumed SSA population in Table 3. Yet these risk estimates are probably underestimates for true SSA because the population at risk for SSA (Table 3) was defined as 'no AL amyloidosis medication in 2005–2010' and 'no rheumatoid arthritis medication or hospitalization'. The designated SSA population certainly also covered amyloidosis types other than SSA. In fact, among the deaths in this group, two were due to NHL and one was due to myeloma, suggesting that some AL amyloidosis patients were also included in this group. Recent incidence estimates of systemic amyloidosis have been 8/million for Sweden and the UK, both sources accounting an incidence of 3/million to AL amyloidosis [22, 27]. Neither source gave estimates for the incidence of SSA because the degree of underdiagnosis is difficult to assess.

AA amyloidosis is a response to chronic inflammation for which rheumatoid arthritis is a common course in developed countries. Rheumatoid arthritis and many other autoimmune diseases are associated with various cancers and to what extent the present SIR of 17.22 for on skin cancer was related to the underlying autoimmune disease or AA amyloidosis cannot be resolved; however, the extraordinary risk of skin cancer supports a role for amyloidosis [28]. In our previous study on autoimmune diseases and subsequent squamous cell skin cancer, the risk in rheumatoid arthritis patients was 1.72 but the risk was even higher in some other autoimmune diseases, particularly in Wegener granulomatosis (9.29) [29]. Among the skin cancer patients from Table 1, two patients had died of musculoskeletal causes, providing further evidence that this group included AA amyloidosis.

The SIR of 203 for myeloma among patients with AL amyloidosis medication is likely to be inflated. Among 540 amyloidosis patients identified in period 2005–2010, 94 (17%) were treated with amyloidosis (or myeloma) medication and thus the likelihood of AL amyloidosis is high but many cases were missed apparently because they did not receive treatment during the relevant period. Our previous estimate on AL amyloidosis was 39% of all Swedish nonhereditary amyloidosis patients [22]. The SIR would also be influenced by surveillance bias: diagnostic activity for myeloma and AL amyloidosis is likely to lead to concomitant diagnoses of the two, resulting in an artificially elevated incidence.

In conclusion, we found at least a 15-fold increase in NHL risk in a designated SSA population. Consistently, the incidence of NHL in these patients peaked at a high age of 80–84 years. The present findings may propose a novel mechanism for amyloidosis related cancer, positing that fragmented and aggregated transthyretin amyloids cause chronic stimulation which eventually precipitates NHL. SSA is an underdiagnosed disease but *ad hoc* studies have shown that it may affect 25% of the elderly population [3, 4]. Thus, SSA is likely to be a main cause of NHL in the elderly population, the proportion of which is increasing in the developed countries. Squamous cell skin cancer

was associated with rheumatoid arthritis related amyloidosis but the relative contribution of AA amyloidosis, autoimmune disease and/or their interaction cannot be resolved.

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disclosure

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