Malignancies in Patients with Antineutrophil Cytoplasmic Antibody-associated Vasculitis: A Population-based Cohort Study

Caroline Heijl, Kerstin Westman, Peter Höglund, and Aladdin J. Mohammad

ABSTRACT. ***Objective.*** Patients with ANCA-associated vasculitides (AAV) exhibit higher rates of malignancy than the general population. We assessed whether the cancer risk is increased in a well-characterized population-based cohort of AAV in southern Sweden, followed for a median time of 8 years.

Methods. With case record review, the outcomes and malignancy development in a cohort of 195 patients with AAV [granulomatosis with polyangiitis (GPA), microscopic polyangiitis, and eosinophilic GPA] diagnosed between 1997 and 2010 were assessed. The patients were followed until death or December 31, 2015. The age- and sex-standardized incidence ratios (SIR) were estimated using the Swedish population data as a reference.

Results. During the observation period of about 1500 person-years, we found 60 cancers in 52 of the 195 patients. SIR (95% CI) was 2.8 (2.1–3.6) for cancers at all sites, 1.8 (1.3–2.5) for all cancers excluding squamous cell carcinoma (SCC), 12.9 (8.4–18.8) for SCC, 4.3 (1.4–10.0) for bladder cancer, and 7.0 (1.4–20.5) for pancreatic cancer. Cumulative doses of cyclophosphamide (CYC) < 10 g were not associated with higher incidence of cancers other than SCC (SIR 1.63, 95% CI 0.8–2.9).

Conclusion. In contrast to previous publications assessing malignancy risk in patients with AAV, we show in this population-based cohort of patients a persistent increased risk for overall malignancy, bladder cancer, and pancreatic cancer as well as a markedly increased risk for SCC. There was no increase in incidence of cancers other than SCC for those treated with < 10 g CYC. (J Rheumatol First Release March 15 2020; doi:10.3899/jrheum.181438)

Key Indexing Terms:
VASCULITIS ANTINEUTROPHIL CYTOPLASMIC ANTIBODIES
GRANULOMATOSIS WITH POLYANGIITIS POPULATION

Systemic small vessel vasculitides, comprising granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA), are in most cases associated with antibodies for proteinase 3 and myeloperoxidase in neutrophil granules[1]. GPA, MPA, and EGPA are grouped together under the name antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV)[2]. With the introduction of immunosuppressive agents such as glucocorticoids and cyclophosphamide (CYC), survival has improved substantially but is still low compared with the general population in the majority of patients[3]. The standard treatment regimens today consist of high-dose corticosteroids combined with CYC in the acute phase followed by lower doses of corticosteroids in combination with azathioprine (AZA) or methotrexate (MTX)[4]. Rituximab (RTX) is a drug that has been approved as an alternative to CYC in the acute phase as well as an option for treating relapses[5,6,7]. AAV often relapses, requiring repeated treatments with immunosuppression[8].

As survival of patients diagnosed with AAV has dramatically improved, the side effects of the immunosuppressive treatment have become a focus of interest, and the development of malignancies is a major concern[9]. Previously published observations suggested that the overall cancer incidence in patients treated for AAV is 1.6–2.4 times higher than in the general population, and the relationship between malignancy and cumulative dose of CYC has been highlighted in some of these studies[10,11,12,13,14,15].

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Interestingly, in a more recent study, patients treated with RTX did not show an increased malignancy risk compared with the general population[16].

Within the European Vasculitis Society (EUVAS), we previously assessed the longterm malignancy risk in patients with AAV who had participated in one of 4 randomized clinical trials[12,17,18,19,20]. Even though the EUVAS studies included patients with variable clinical manifestations and disease severity, patients with EGPA and those who had a known previous malignancy were excluded.

We investigated longterm malignancy risk in a population-based cohort of 195 patients with AAV without any referral or exclusion bias, including all the diagnoses within the AAV spectrum, and these patients were followed for a median time of 8 years.

MATERIALS AND METHODS

Study design and participants. The occurrence of malignancy was assessed in a cohort of all incident cases with AAV in a defined geographical area of about 0.7 million inhabitants in southern Sweden. Potential cases of AAV, diagnosed between 1997 and 2010, were identified through healthcare registries using a previously described validated search algorithm[21] and were reviewed using case records. Patients were considered to have AAV if they had symptoms and signs compatible with small vessel vasculitis supported by histopathology, radiology, and/or serological findings, and if they had been classified as having GPA, MPA, or EGPA according to the European Medicine Agency 2007 algorithm[22]. By review of each case record and pathology report for the 195 patients in the cohort, data of any malignancy occurring after the diagnosis of AAV were collected until December 31, 2015. If a patient developed several squamous cell carcinomas (SCC), only the first was reported. Likewise, if a patient developed several other cancers excluding SCC, only the first was reported. However, if a patient developed both SCC and any other cancer, the first of both malignancies was reported. In the Swedish Cancer Registry, basal cell carcinoma has been reported only since 2004; therefore, the study did not include this diagnosis as no data on this disease are available for the general population throughout the period of investigation.

The study was performed in accordance with the Declaration of Helsinki and was approved by the Ethical Review Board in Lund (2010-517).

Baseline evaluation and treatment. Results from laboratory investigations collected at the diagnosis of AAV included plasma creatinine and ANCA serotype analyzed with ELISA and capture ELISA. According to then-current guidelines used in southern Sweden, the majority of patients received CYC and glucocorticoids as induction treatment. CYC was given orally, intravenously (IV), or in many cases, both orally and IV at different times. Patients with creatinine ≥ 500 μmol/l or those with rapidly progressive glomerulonephritis or pulmonary hemorrhage received plasma exchange and/or IV methylprednisolone in addition to CYC as induction treatment. All patients who were treated with IV CYC also received mesna to protect the urinary bladder. For those without systemic involvement (i.e., exclusively upper respiratory involvement), induction therapy was MTX together with corticosteroids. After stable remission, the treatment continued with AZA in the majority of patients. Thirty-one patients were treated with RTX, of whom 4 did not receive any CYC, 11 received 1–10 g, and 16 received > 10 g. For all included patients, medical charts were reviewed, and the cumulative doses of CYC given throughout the entire followup period were calculated. In addition, information on immunosuppressive drugs other than CYC was gathered.

Statistical analysis. Continuous variables are presented as medians and interquartile ranges (IQR). Categorical variables are expressed as counts and frequencies.

Estimation of cumulative cancer incidence and survival. Cumulative incidences of cancer, overall survival, and cancer-free survival were calculated using the Kaplan–Meier method. The calculations regarding cancer were performed both for all cancers and for SCC. Person-years (PY) of followup were calculated, starting from the date of diagnosis of AAV and ending at the earliest time of cancer of the selected kind, death, or the end of followup on December 31, 2015. The PY were calculated until the development of each specific cancer, regardless of a diagnosis of other cancers. To enable comparisons with our previous study[12] as well as many others in the calculation of cumulative incidence, the occurrence of cancer was considered an event, and patients were followed until death or the end of the study period. For calculation of cancer-free survival, the occurrence of cancer or death was considered an event, and patients were followed through the end of the study period[23].

Calculation of standardized incidence ratios (SIR). For each patient, PY of followup were calculated using the start and end dates described in the previous section; these calculations were made separately for each of the identified cancer endpoints. The PY risk was calculated by sex and by age in 5-year groups. SIR were calculated to compare the observed malignancies in the cohort with the expected numbers in the general population matched for sex, 5-year age groups, and 1-year calendar time period (i.e., for each year the patients grow older) and when appropriate, the corresponding 5-year age groups in the general population were changed. A published SAS macro[24] was modified and expressed in the MATLAB language for these calculations. The expected numbers of cases of cancers of each kind were calculated by multiplying the number of PY for each sex and age group by the corresponding cancer incidence rates as provided by the Swedish Cancer Registry[25]. Each healthcare provider in Sweden is obliged to report to the Swedish Cancer Registry every cancer case diagnosed at clinical, morphological, and other laboratory examinations as well as cases diagnosed at autopsy. SIR were calculated for cancers at all sites, for SCC and for each of the reported specific cancers in the cohort. SIR were stratified by disease phenotype, ANCA serotype, sex, and age group at entry (below vs above 60 yrs), chronic kidney disease group (CKD) at entry (CKD 1–2 vs CKD 3–5), previous malignancy (i.e., before diagnosis of AAV), and renal transplantation. We also performed a series of Poisson regressions to generate relative risks for cancer incidence in each subgroup.

RESULTS

Patients. One hundred ninety-five patients (98 female) with a median age of 69 years (IQR 55–77) at diagnosis of AAV fulfilled the inclusion criteria and were included in the study cohort. Among these patients, 94 (48%) were classified as having GPA, 90 (46%) as MPA, and 11 (6%) as EGPA. The followup time ranged between 0.3 and 18 years, with a median followup time of 8 years (IQR 4.0-11.9). Ninety-eight (50%) of the patients died during followup. Further demographic data are summarized in Table 1. Of the patients included in this cohort, 7 had also participated in the EUVAS longterm followup and malignancy studies[12]; of these 7 patients, 1 developed malignant melanoma and SCC and 1 developed lung cancer (both of whom participated in the MEPEX study)[20].

Numbers and characteristics of observed cancers. Fifty-two of 195 patients developed 60 malignancies during the followup time of 1300 PY. There were 26 SCC and 34 other types of cancers. The median time from the diagnosis of AAV to the first cancer diagnosis at any site was 5.13 years; to first SCC, 4.58 years; and to first malignancy of other types, 5.50 years. Overall survival rate at 1, 2, 5, and 10 years was 87%,

Table 1. Baseline and followup demographics in 195 patients with incident ANCA-associated vasculitis.

Characteristics	N = 195 (%)
Sex	
Male	97 (50)
Female	98 (50)
Age, yrs	69 (55–77)
Age quartiles, yrs	
0–55	49 (25)
55–70	57 (29)
70–80	53 (27)
80–100	36 (18)
P creatinine, μmol/l	152 (75–319)
eGFR, ml/min	40 (15–80)
CKD groups	
CKD 1–2	74 (38)
CKD 3	38 (19)
CKD 4	36 (18)
CKD 5	47 (24)
B hemoglobin, g/l	110 (96–123)
Platelets, 10^9/l	366 (283-450)
CRP, mg/l	87 (22–142)
ANCA	
PR3	100 (51)
MPO	84 (43)
Negative	11 (6)
Diagnosis	
GPA	94 (48)
MPA	90 (46)
EGPA	11 (6)
Renal transplantation	7 (4)
Previous malignancy	16 (8)
Followup, yrs	8.0 (4.0–11.9)
Deaths	98 (50)
CYC < 1 g	30 (15)
CYC 1–10 g	82 (42)
CYC > 10 g	83 (42)
CYC > 36 g	14 (7)

Data are presented in n (%) and median (IQR). ANCA: antineutrophil cytoplasmic antibodies; eGFR: estimated glomerular filtration rate; CKD: chronic kidney disease; CRP: C-reactive protein; PR3: proteinase 3; MPO: myeloperoxidase; GPA: granulomatosis with polyangiitis; MPA: microscopic polyangiitis; EGPA: eosinophilic GPA; CYC: cyclophosphamide; IQR: interquartile range.

82%, 70%, and 55%, respectively, and the cancer-free survival rate for cancer at any site at 1, 2, 5, and 10 years was 84% (95% CI 78–89), 77% (71–83), 61% (54–68), and 44% (37–52), respectively. The cancer-free survival at any site excluding SCC was 86% (95% CI 81–91), 80% (75–86), 66% (60–73), and 49% (42–57), respectively (Figure 1). The cumulative 5- and 10-year incidence for cancers at all sites was 17% (95% CI 11–23) and 30% (22–38), respectively (Figure 2). The respective incidence for cancers of types other than SCC was 10% (95% CI 5–15) and 20% (12–26; Figure 2).

Among the 52 patients with cancer at any site, 29 died and among the 34 patients with non-SCC, 18 died; 15 of the total 98 deaths were attributed to cancer. Sixteen patients had had malignancies prior to the diagnosis of AAV; 8 of these were diagnosed with cancer during the followup period of this study, and another 8 had no new cancer detected (p = 0.026). Seven patients underwent renal transplantation, and 4 of these were diagnosed with cancer.

SIR of malignancies. The SIR for all site cancers was 2.77 (95% CI 2.07–3.64, p < 0.001) and for all sites excluding SCC was 1.81 (95% CI 1.26–2.54, p = 0.001). Among the cancer site-specific analyses, incidences of SCC, bladder, and pancreatic cancers were significantly increased when compared with the general population. The SIR for SCC was 12.85 (95% CI 8.40–18.83, p < 0.001), the SIR for bladder cancer was 4.30 (95% CI 1.40–10.04, p = 0.003), and the SIR for pancreatic cancer was 7.00 (95% CI 1.44–20.45, p = 0.002; Table 2). During the first 5 years of followup, a total of 26 cancers were observed. The corresponding figures for SCC, for cancer at all sites excluding SCC, and bladder cancer were 14, 16, and 3, respectively. The cumulative followup time for the first 5 years was 735 PY, and SIR was 2.60 (95% CI 1.70–3.80) for all sites, 14.9 (8.14–25.0) for SCC, 1.66 (0.95–2.69) for other types, and 5.36 (1.11–15.7) for bladder cancer.

Table 3 shows subgroup analyses for SIR grouped by the predefined variables. The analysis indicates higher SIR for SCC in patients with EGPA, for those with negative ANCA, for patients younger than 60 years at diagnosis of AAV, and for those with renal transplants. The results for overall cancer excluding SCC indicate higher SIR for patients with previous malignancies and those with renal transplant, but a lower SIR for patients with EGPA and patients with negative ANCA.

Cumulative doses of CYC < 10 g were not associated with higher incidence of cancers other than SCC (SIR 1.63, 95% CI 0.8–2.9). Cumulative doses of CYC > 36 g exhibited SIR of 3.4 (95% CI 1.5–6.4) for cancers other than SCC. The risk for SCC was markedly increased in patients not receiving CYC (SIR 53.6 (95% CI 21.6–110.5). Among the 5 patients who developed bladder cancer, 3 were treated with cumulative CYC doses > 10 g (151, 31, and 17 g, respectively), and 2 patients were treated with doses < 10 g (7.5 and 8 g, respectively). Table 4 shows risk ratios calculated using Poisson regression, showing, for example, that patients with previous malignancies had a risk ratio of 3.9 (1.5–8.9, p < 0.001) compared with patients without previous malignancies.

DISCUSSION

In this population-based cohort of patients, which includes all 3 diagnoses within the AAV spectrum, we show that risk for overall malignancy, bladder cancer, pancreatic cancer, and SCC is still increased when compared with the general population.

A 2.77-fold increase in the risk for overall malignancy was seen in the AAV cohort compared with that in the general population. The highest risk was seen in SCC and was more than 12 times higher than that in the general population; the next highest risks were for pancreatic cancer, with a 7-fold

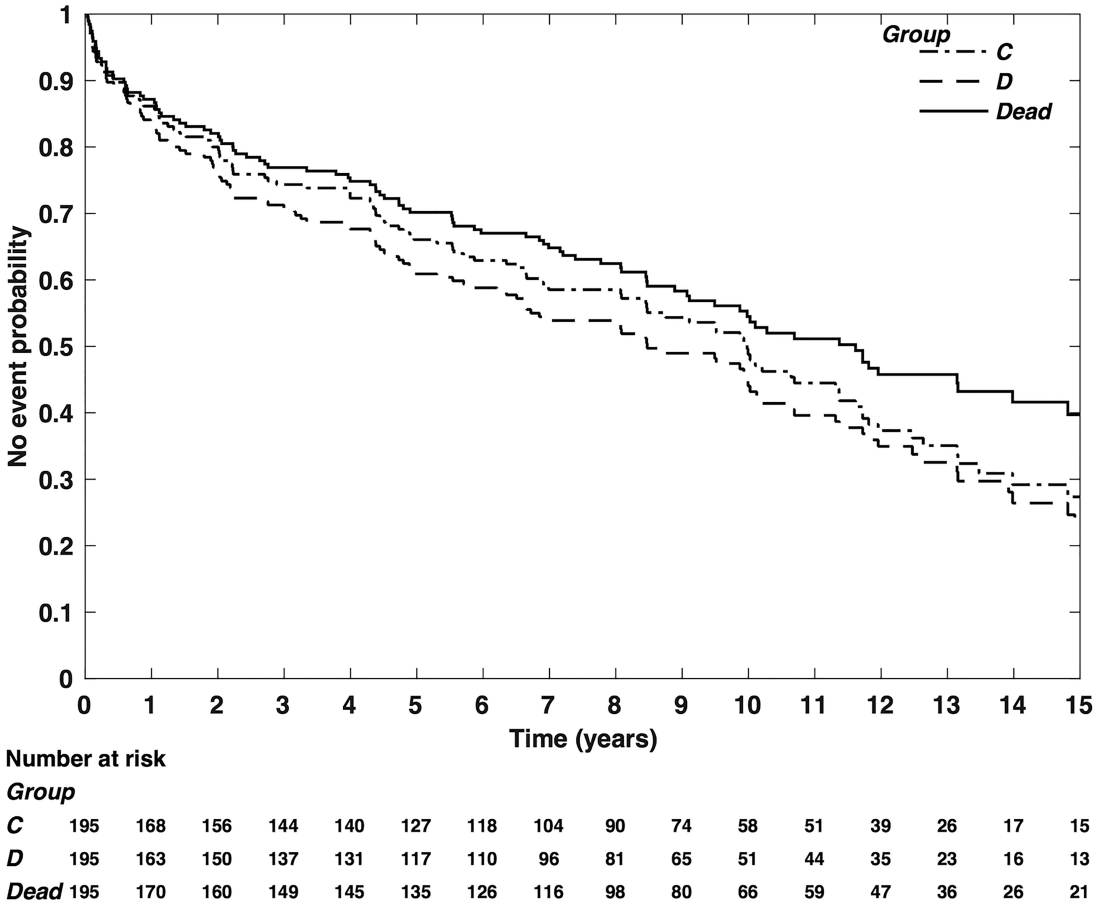

Figure 1. Overall survival (Dead), cancer-free survival for cancer at any site (D), and cancer-free survival for cancer at any site excluding squamous cell carcinoma (C).

increase, and bladder cancer, with a 4.3-fold increased risk compared to the general population. There were no other significantly increased risks for other reported malignancies.

Previous studies assessing malignancy risk in AAV have reported SIR for overall malignancy of different ranges. Earlier studies[26] have shown a 33-fold increased risk for bladder cancer, which was believed to be due to the use of higher doses of CYC for longer periods of time, but with current treatment protocols, these high risks are no longer seen. In more recent studies, the SIR for overall cancers range from nonsignificant[27] to 3.76[11,12,13], the SIR for bladder cancer ranges from nonsignificant to a 3.6-fold increase, the SIR for the nonmelanoma skin cancer (including SCC and basal cell carcinoma) ranges between a 2.8 and 4.7 increase, and the SIR for leukemia ranges from nonsignificant to a 5.9-fold increase.

Two studies, one the EUVAS followup study of multicenter clinical trials[12] with a followup time of almost 5 years, and the other a cohort of 138 patients identified through a pathology database[13] and followed for a median of 10 years, both stress that the malignancy risk in patients with AAV treated according to current protocols is increased but that this increase is solely driven by the increased risk for SCC. However, in our study, the risk for SCC as well as the risk for both bladder and pancreatic cancer is significantly increased. The increased risk for bladder cancer is consistent with other previous studies from 2002 and 2006, but pancreatic cancer has not been shown to be increased in other studies. However, the patients who developed bladder cancer were treated with high cumulative doses of CYC, and the interpretation of the finding of increased risks for pancreatic cancer must be made with caution, because the cohort is small. The treatment with cumulative doses of CYC < 10 g, corresponding to IV CYC for 3–6 months, was not associated with a higher risk for malignancies excluding SCC, indicating that the dosing of CYC with current treatment protocols is probably safe and not associated with an increased malignancy risk. However, cumulative doses of CYC of > 10 g were associated with higher incidence of cancers beyond SCC and an even higher risk was seen with doses > 36 g. The cutoff of 36 g was chosen for comparison with a previous study from Faurschou, *et al*, corresponding to treatment with 100 mg CYC/day for > 1 year[11].

The discrepancies, however small, between our findings

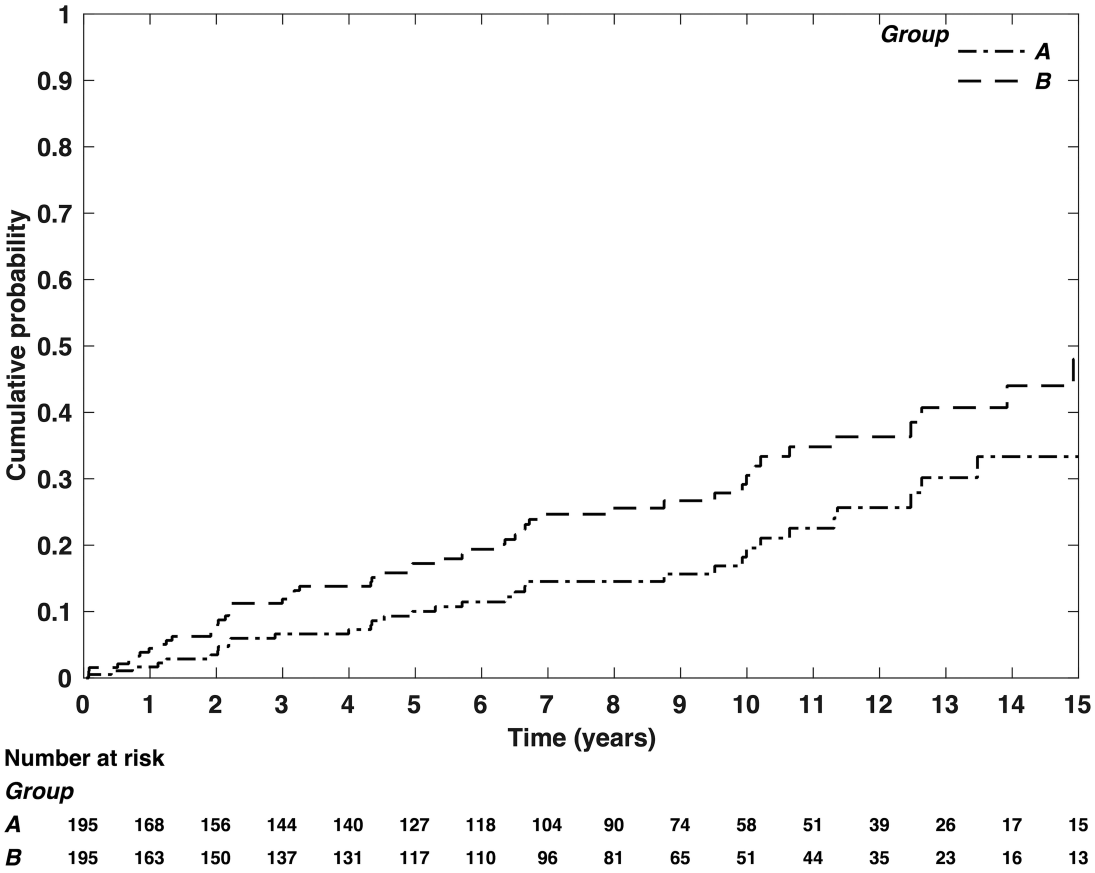

Figure 2. Cumulative incidence of cancer at any site (B), and cumulative incidence of cancer at any site excluding squamous cell carcinoma (A).

Table 2. Calculated age, sex, and calendar year SIR for observed cancers in 195 patients with ANCA-associated vasculitis.

Cancer Site*	Person-years	Observed	Expected	SIR (95% CI)	p
All sites	1300	52	18.7	2.77 (2.07–3.64)	< 0.001
All sites excluding SCC	1399	34	18.7	1.81 (1.26–2.54)	0.001
SCC	1375	26	2.02	12.85 (8.40–18.83)	< 0.001
Prostate	1468	7	4.21	1.66 (0.67–3.43)	0.129
Bladder	1485	5	1.16	4.30 (1.40–10.04)	0.003
Colorectal	1482	5	2.80	1.78 (0.58–4.17)	0.130
Lung	1502	3	1.70	1.77 (0.36–5.16)	0.186
Pancreas	1502	3	0.43	7.00 (1.44–20.45)	0.002
Breast	1491	2	2.51	0.80 (0.10–2.88)	0.919

* Ordered by decreasing numbers of observed cancer cases. SIR: standardized incidence ratios; ANCA: anti-neutrophil cytoplasmic antibody; SCC: squamous cell carcinoma.

and those in previous studies might have several explanations. The assessment of malignancies in Sweden is very thorough, and each healthcare provider is obliged to submit a report to the Swedish Cancer Registry for every cancer case diagnosed at clinical, morphological, and other laboratory examinations as well as in cases diagnosed at autopsy. The assessment of malignancies both in our cohort as well as in the general population is reliable, and the probability that any cancer case is missed is very low. In our current study we included patients with previous malignancies, and in this group the risk for additional malignancies is known to be higher[28]. In addition, the excess risk of SCC might be explained to some extent by the high risk in patients with EGPA who have not been included in previous studies, with the exception of the most recent one by van Daalen, *et al*[16]. In our study 7 patients received a renal transplant, and in

Table 3. Standardized incidence ratios (SIR) for cancer at all sites, all sites excluding SCC, and SCC according to selected subgroup variables.

	All Sites					All Sites Excluding SCC					SCC				
Group	PY	Obs	Exp	SIR (95% CI)	p	PY	Obs	Exp	SIR (95% CI)	p	PY	Obs	Exp	SIR (95% CI)	p
Diagnosis															
MPA	521	21	8.5	2.5 (1.5–3.8)	< 0.001	555	13	8.1	1.61 (0.86–2.75)	0.0726	537	10	1.0	10.05 (4.82–18.48)	< 0.001
GPA	696	28	9.2	3.0 (2.0–4.4)	< 0.001	778	20	9.9	2.02 (1.24–3.13)	0.0027	754	14	0.96	14.6 (7.98–24.50)	< 0.001
EGPA	83	3	1.1	2.7 (0.6–8.0)	0.0513	86	1	1.1	0.92 (0.02–5.15)	0.5883	85	2	0.1	28.9 (3.50–104)	< 0.001
ANCA serotype															
MPO	534	21	8.5	2.5 (1.5–3.8)	< 0.001	562	13	8.0	1.61 (0.86–2.76)	0.0723	552	10	1.0	10 (4.8–18.5)	< 0.001
PR3	690	26	9.5	2.7 (1.8–4.0)	< 0.001	746	19	9.8	1.95 (1.17–3.04)	0.0053	747	12	1.0	12.2 (6.3–21.4)	< 0.001
Negative	75	5	0.8	6.5 (2.1–15.1)	< 0.001	91	2	0.9	2.17 (0.26–7.85)	0.1325	77	4	0.05	81.1 (22.1–207.6)	< 0.001
Sex															
Women	697	21	8.0	2.6 (1.6–4.0)	< 0.001	743	14	8.0	1.8 (0.96–2.9)	0.034	726	10	0.68	14.8 (7.1–27.2)	< 0.001
Men	603	31	10.8	2.9 (2.0–4.1)	< 0.001	657	20	10.8	1.9 (1.1–2.9)	0.007	650	16	1.3	11.9 (6.8–19.3)	< 0.001
Age at entry, yrs															
< 60	627	12	4.1	2.9 (1.5–5.1)	< 0.001	657	9	4.3	2.09 (0.96–3.97)	0.0261	651	5	0.2	29.4 (9.6–68.7)	< 0.001
> 60	673	40	14.7	2.7 (1.9–3.7)	< 0.001	742	25	14.4	1.73 (1.12–2.56)	0.0077	724	21	1.9	11.3 (7.0–17.3)	< 0.001
CKD at entry															
CKD 1–2	645	19	7.8	2.4 (1.5–3.8)	< 0.001	672	14	7.8	1.80 (0.98–3.02)	0.0277	677	9	0.67	13.4 (6.1–25.4)	< 0.001
CKD 3–5	655	33	10.9	3.0 (2.1–4.2)	< 0.001	726	20	11.0	1.82 (1.11–2.82)	0.009	699	17	1.35	12.6 (7.3–20.2)	< 0.001
Previous malignancy															
No	1243	44	17.6	2.5 (1.8–3.4)	< 0.001	1327	28	17.6	1.59 (1.05–2.30)	0.0152	1309	23	1.9	12.4 (7.86–18.61)	< 0.001
Yes	57	8	1.1	7.1 (3.0–13.9)	< 0.001	72	6	1.2	5.11 (1.87–11.13)	< 0.001	66	3	0.17	17.73 (3.66–51.82)	< 0.001
Renal transplant															
No	1238	48	18.3	2.6 (1.9–3.5)	< 0.001	1321	30	18.0	1.67 (1.12–2.38)	0.0067	1308	24	2.0	12.0 (7.69–17.86)	< 0.001
Yes	62	4	0.5	8.2 (2.2–21.0)	< 0.001	78	4	0.7	5.52 (1.5–14.1)	0.0018	67	2	0.02	85.68 (10.38–309)	< 0.001
Immunosuppression															
CYC < 1 g	152	8	1.8	4.3 (1.9–8.5)	< 0.001	175	3	2.2	1.3 (0.3–3.9)	0.371	154	7	0.13	53.6 (21.6–110.5)	< 0.001
CYC 1–36 g	1008	34	14.6	2.3 (1.6–3.2)	< 0.001	1070	21	14.1	1.5 (0.9–2.3)	0.062	1049	18	1.7	10.8 (6.4–17.0)	< 0.001
CYC > 36 g	152	9	2.7	3.4 (1.5–6.4)	< 0.001	165	9	2.7	3.4 (1.5–6.4)	< 0.001	186	1	0.35	2.9 (0.1–16.0)	0.096
AZA, yes	414	14	6.11	2.3 (1.3–3.8)	0.003	439	8	6.1	1.3 (0.6–2.6)	0.319	426	9	0.7	12.6 (5.8–24.0)	< 0.001
AZA, no	913	37	13.3	2.8 (2.0–3.8)	< 0.001	986	25	13	1.9 (1.2–2.8)	0.002	977	17	1.5	11.6 (6.8–18.7)	< 0.001
RTX, yes	1081	47	17	2.8 (2.0–3.7)	< 0.001	1175	31	17	0.8 (0.1–3.1)	0.803	1153	24	2	12.0 (7.7–17.9)	0
RTX, no	246	4	2.4	1.7 (0.5–4.3)	0.185	250	2	2.3	1.83 (1.2–2.6)	0.001	250	2	0.17	11.5 (1.4–41.7)	0.002
MMF, yes	1047	41	15.5	2.6 (1.9–3.6)	< 0.001	1122	24	15.3	1.6 (1.0–2.3)	0.027	1105	23	1.8	12.8 (8.1–19.2)	0
MMF, no	280	10	3.9	2.6 (1.2–4.7)	0.005	303	9	4	2.3 (1.0–4.3)	0.015	298	3	0.38	7.9 (1.6–23.2)	0.001
MTX, yes	939	41	14.3	2.9 (2.1–3.9)	< 0.001	1005	27	14	1.9 (1.3–2.8)	0.001	997	19	1.7	11.2 (6.7–17.5)	< 0.001
MTX, no	388	10	5.1	2.0 (0.9–3.6)	0.032	420	6	5.3	1.1 (0.4–2.5)	0.571	406	7	0.5	14.7 (5.9–30.3)	< 0.001

SCC: squamous cell carcinoma; PY: person-years; Obs: observed; Exp: expected; MPA: microscopic polyangiitis; GPA: granulomatosis with polyangiitis; EGPA: eosinophilic GPA; ANCA: antineutrophil cytoplasmic antibodies; MPO: myeloperoxidase; PR3: proteinase 3; CKD: chronic kidney disease; CYC: cyclophosphamide; AZA: azathioprine; MMF: mycophenolate mofetil; MTX: methotrexate; RTX: rituximab.

Table 4. Relative risks (RR), calculated by Poisson regression, according to selected subgroup variables.

	All Sites					All Sites Excluding SCC					SCC				
Group	PY	Obs	Exp	RR (95% CI)	p	PY	Obs	Exp	RR (95% CI)	p	PY	Obs	Exp	RR (95% CI)	p
Diagnosis															
MPA	521	21	8.5	1 (ref)		555	13	8.1	1 (ref)		537	10	1.0	1 (ref)	
GPA	696	28	9.2	1.0 (0.57–1.78)	0.9	778	20	9.9	1.1 (0.55–2.3)	0.7	754	14	0.96	1.0 (0.45–2.3)	0.9
EGPA	83	3	1.1	0.90 (0.21–2.6)	0.8	86	1	1.1	0.50 (0.03–2.5)	0.5	85	2	0.1	1.3 (0.19–4.8)	0.7
ANCA serotype															
MPO	534	21	8.5	1 (ref)		562	13	8.0	1 (ref)		552	10	1.0	1 (ref)	
PR3	690	26	9.5	0.96 (0.54–1.7)	0.8	746	19	9.8	1.1 (0.55–2.3)	0.7	747	12	1.0	0.89 (0.38–2.1)	0.7
Negative	75	5	0.8	1.7 (0.57–4.2)	0.2	91	2	0.9	0.95 (0.15–3.4)	0.9	77	4	0.05	2.9 (0.79–8.6)	0.07
Sex															
Women	697	21	8.0	1 (ref)		743	14	8.0	1 (ref)		726	10	0.68	1 (ref)	
Men	603	31	10.8	1.7 (0.99–3.0)	0.05	657	20	10.8	1.6 (0.82–3.3)	0.1	650	16	1.3	1.8 (0.82–4.1)	0.1
Age at entry, yrs															
< 60	627	12	4.1	1 (ref)		657	9	4.3	1 (ref)		651	5	0.2	1 (ref)	
> 60	673	40	14.7	3.1 (1.7–6.2)	< 0.001	742	25	14.4	2.5 (1.2–5.6)	0.02	724	21	1.9	3.8 (1.5–11.3)	0.008
CKD at entry															
CKD 1–2	645	19	7.8	1 (ref)		672	14	7.8	1 (ref)		677	9	0.67	1 (ref)	
CKD 3–5	655	33	10.9	1.7 (0.98–3.1)	0.06	726	20	11.0	1.3 (0.67–2.7)	0.4	699	17	1.35	1.8 (0.83–4.3)	0.1
Previous malignancy															
No	1243	44	17.6	1 (ref)		1327	28	17.6	1 (ref)		1309	23	1.9	1 (ref)	
Yes	57	8	1.1	4.0 (1.7–8.0)	< 0.001	72	6	1.2	3.9 (1.5–8.9)	0.002	66	3	0.17	2.6 (0.6–7.4)	0.1
Renal transplantation															
No	1238	48	18.3	1 (ref)		1321	30	18.0	1 (ref)		1308	24	2.0	1 (ref)	
Yes	62	4	0.5	1.7 (0.50–4.1)	0.3	78	4	0.7	2.3 (0.67–5.7)	0.1	67	2	0.02	1.6 (0.26–5.5)	0.5

SCC: squamous cell carcinoma; PY: person-years; Obs: observed; Exp: expected; MPA: microscopic polyangiitis; GPA: granulomatosis with polyangiitis; EGPA: eosinophilic GPA; ANCA: antineutrophil cytoplasmic antibodies; MPO: myeloperoxidase; PR3: proteinase 3; CKD: chronic kidney disease.

these patients the SIR was higher, especially for SCC, also adding to the higher risk in our previous study compared to others assessing malignancy risk in AAV. The risk for SCC among those patients receiving transplants has in several studies been shown to exceed that in the AAV population[29]. The most probable explanation for the high risk for SCC that we see in patients not receiving CYC is that these patients received other oral immunosuppressive drugs such as AZA, known to increase the risk for nonmelanoma skin cancer including SCC[30].

The main limitation of our study is the relatively small number of patients. A larger number of patients would have strengthened the results, but the significantly increased malignancy risk seen already in a smaller cohort shows that this still is an important factor to keep in mind in the followup of patients with AAV. Unfortunately, it is not possible to make a firm conclusion on the pathogenesis of the malignancies in our patients. In our study, the main focus was on the relationship between malignancies and immunosuppression because no data are available on other potential risk factors for cancer in AAV.

Our study has important strengths. We used a population-based cohort of patients with AAV in which the diagnoses of AAV are scrutinized by reviewing case records, and all patients are classified according to a defined algorithm using the European Medicines Agency classification. Further, all diagnoses of malignancies in the patients have been collected through case records, pathology, histology, and cytology databases without any missing data. In addition, the number of PY of followup is about 1500 for a number of cancer diagnoses, and we were able to show important differences when comparing with the general population. Finally, the Swedish Cancer Registry, which includes data from the entire Swedish population, enables comparison with the general population.

In this population-based cohort of patients, which includes all 3 diagnoses within the AAV spectrum, we show that the malignancy risk is still increased when compared with the general population, but in patients receiving CYC doses of < 10 g, this is solely driven by the increased risk for SCC. In contrast to the most recent publications assessing malignancy risk in patients with AAV, we show a persistently increased risk for bladder cancer and pancreatic cancer in patients receiving CYC > 10 g, indicating that the risk for the development of solid tumors in patients treated for AAV should not be totally ignored.

REFERENCES

1. Jayne D, Rasmussen N. Twenty-five years of European Union collaboration in ANCA-associated vasculitis research. Nephrol Dial Transplant 2015;30 Suppl 1:i1-7.
2. Jennette JC, Falk RJ, Bacon PA, Basu N, Cid MC, Ferrario F, et al. 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. Arthritis Rheum 2013;65:1-11.
3. Flossmann O, Berden A, de Groot K, Hagen C, Harper L, Heijl C, et al; European Vasculitis Study Group. Long-term patient survival in ANCA-associated vasculitis. Ann Rheum Dis 2011;70:488-94.
4. Mukhtyar C, Guillevin L, Cid MC, Dasgupta B, de Groot K, Gross W, et al; European Vasculitis Study Group. EULAR recommendations for the management of primary small and medium vessel vasculitis. Ann Rheum Dis 2009;68:310-7.
5. Stone JH, Merkel PA, Spiera R, Seo P, Langford CA, Hoffman GS, et al; RAVE-ITN Research Group. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. N Engl J Med 2010;363:221-32.
6. Guillevin L, Pagnoux C, Karras A, Khouatra C, Aumaitre O, Cohen P, et al; French Vasculitis Study Group. Rituximab versus azathioprine for maintenance in ANCA-associated vasculitis. N Engl J Med 2014;371:1771-80.
7. Jones RB, Tervaert JW, Hauser T, Luqmani R, Morgan MD, Peh CA, et al; European Vasculitis Study Group. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. N Engl J Med 2010;363:211-20.
8. Westman KW, Bygren PG, Olsson H, Ranstam J, Wieslander J. Relapse rate, renal survival, and cancer morbidity in patients with Wegener's granulomatosis or microscopic polyangiitis with renal involvement. J Am Soc Nephrol 1998;9:842-52.
9. Mahr A, Heijl C, Le Guenno G, Faurschou M. ANCA-associated vasculitis and malignancy: current evidence for cause and consequence relationships. Best Pract Res Clin Rheumatol 2013;27:45-56.
10. Knight A, Askling J, Ekbom A. Cancer incidence in a population-based cohort of patients with Wegener's granulomatosis. Int J Cancer 2002;100:82-5.
11. Faurschou M, Sorensen IJ, Mellemkjaer L, Loft AG, Thomsen BS, Tvede N, et al. Malignancies in Wegener's granulomatosis: incidence and relation to cyclophosphamide therapy in a cohort of 293 patients. J Rheumatol 2008;35:100-5.
12. Heijl C, Harper L, Flossmann O, Stucker I, Scott DG, Watts RA, et al; European Vasculitis Study Group (EUVAS). Incidence of malignancy in patients treated for antineutrophil cytoplasm antibody-associated vasculitis: follow-up data from European Vasculitis Study Group clinical trials. Ann Rheum Dis 2011;70:1415-21.
13. Rahmattulla C, Berden AE, Wakker SC, Reinders ME, Hagen EC, Wolterbeek R, et al. Incidence of malignancies in patients with antineutrophil cytoplasmic antibody-associated vasculitis diagnosed between 1991 and 2013. Arthritis Rheumatol 2015;67:3270-8.
14. Knight A, Askling J, Granath F, Sparen P, Ekbom A. Urinary bladder cancer in Wegener's granulomatosis: risks and relation to cyclophosphamide. Ann Rheum Dis 2004;63:1307-11.
15. Le Guenno G, Mahr A, Pagnoux C, Dhote R, Guillevin L; French Vasculitis Study Group. Incidence and predictors of urotoxic adverse events in cyclophosphamide-treated patients with systemic necrotizing vasculitides. Arthritis Rheum 2011;63:1435-45.
16. van Daalen EE, Rizzo R, Kronbichler A, Wolterbeek R, Bruijn JA, Jayne DR, et al. Effect of rituximab on malignancy risk in patients with ANCA-associated vasculitis. Ann Rheum Dis 2017;76:1064-9.
17. De Groot K, Rasmussen N, Bacon PA, Tervaert JW, Feighery C, Gregorini G, et al. Randomized trial of cyclophosphamide versus methotrexate for induction of remission in early systemic antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheum 2005;52:2461-9.
18. Jayne D, Rasmussen N, Andrassy K, Bacon P, Tervaert JW, Dadoniene J, et al; European Vasculitis Study Group. A randomized trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies. N Engl J Med 2003;349:36-44.
19. de Groot K, Harper L, Jayne DR, Flores Suarez LF, Gregorini G, Gross WL, et al; EUVAS (European Vasculitis Study Group). Pulse versus daily oral cyclophosphamide for induction of remission in

antineutrophil cytoplasmic antibody—associated vasculitis: a randomized trial. Ann Inter Med 2009;150:670-80.
20. Jayne DR, Gaskin G, Rasmussen N, Abramowicz D, Ferrario F, Guillevin L, et al; European Vasculitis Study Group. Randomized trial of plasma exchange or high-dosage methylprednisolone as adjunctive therapy for severe renal vasculitis. J Am Soc Nephrol 2007;18:2180-8.
21. Mohammad AJ, Jacobsson LT, Westman KW, Sturfelt G, Segelmark M. Incidence and survival rates in Wegener's granulomatosis, microscopic polyangiitis, Churg-Strauss syndrome and polyarteritis nodosa. Rheumatology 2009;48:1560-5.
22. Watts R, Lane S, Hanslik T, Hauser T, Hellmich B, Koldingsnes W, et al. Development and validation of a consensus methodology for the classification of the ANCA-associated vasculitides and polyarteritis nodosa for epidemiological studies. Ann Rheum Dis 2007;66:222-7.
23. Hakulinen T. Cancer survival corrected for heterogeneity in patient withdrawal. Biometrics 1982;38:933-42.
24. Udaltsova. SAS macros for standard incidence ratio calculation. [Internet. Accessed January 28, 2020.] Available from: www.lexjansen.com/wuss/2014/33_Final_Paper_PDF.pdf
25. Swedish Cancer Registry. [Internet. Accessed February 21, 2020.] Available from: www.socialstyrelsen.se/statistik-och-data/register/alla-register/cancerregistret
26. Hoffman GS, Kerr GS, Leavitt RY, Hallahan CW, Lebovics RS, Travis WD, et al. Wegener granulomatosis: an analysis of 158 patients. Ann Intern Med 1992;116:488-98.
27. Holle JU, Gross WL, Latza U, Nolle B, Ambrosch P, Heller M, et al. Improved outcome in 445 patients with Wegener's granulomatosis in a German vasculitis center over four decades. Arthritis Rheum 2011;63:257-66.
28. Hellstrom V, Lorant T, Dohler B, Tufveson G, Enblad G. High posttransplant cancer incidence in renal transplanted patients with pretransplant cancer. Transplantation 2017;101:1295-302.
29. Hellstrom VC, Enstrom Y, von Zur-Muhlen B, Hagberg H, Laurell A, Nyberg F, et al. Malignancies in transplanted patients: multidisciplinary evaluation and switch to mTOR inhibitors after kidney transplantation — experiences from a prospective, clinical, observational study. Acta Oncol 2016;55:774-81.
30. Maddox JS, Soltani K. Risk of nonmelanoma skin cancer with azathioprine use. Inflamm Bowel Dis 2008;14:1425-31.