Supplementary material
Table S1. Subgroup analysis

	N patients	N observed malignancies	SIR (95% CI)*	SIR p value*	RR (95% CI)*	RR p value*
Gender						
Male	149	20	1.58 (0.96–2.44)	0.07	1 (reference)	
Female	174	25	2.25 (1.45–3.32)	<0.001	1.43 (0.76–2.71)	0.30
Age at diagnosis						
≥59 years	159	29	1.60 (1.07–2.29)	0.02	1 (reference)	
<59 years	164	16	2.84 (1.62–4.61)	<0.001	1.78 (0.90–3.38)	0.10
Clinical diagnosis						
Microscopic polyangiitis	160	23	1.59 (1.01–2.38)	0.05	1 (reference)	
Granulomatosis with polyangiitis	109	14	2.20 (1.20–3.68)	0.01	1.39 (0.66–2.81)	0.43
Eosinophilic granulomatosis with polyangiitis	54	8	2.75 (1.19–5.41)	0.02	1.73 (0.67–4.02)	0.27
ANCA serotype†						
MPO-ANCA	110	15	1.56 (0.87–2.58)	0.13	1 (reference)	
PR3-ANCA	152	24	2.18 (1.40–3.25)	<0.001	1.40 (0.70–2.87)	0.39
Renal transplantation						

No	311	41	1.79 (1.29–2.43)	<0.001	1 (reference)	
Yes	12	4	4.31 (1.17–11.04)	0.03	2.40 (0.62–6.62)	0.20
Follow-up						
0–5 years	156	16	2.38 (1.36–3.86)	<0.001	1 (reference)	
5–10 years	135	23	1.81 (1.15–2.72)	0.01	0.76 (0.39–1.54)	0.50
>10 years	32	6	1.38 (0.51 – 3.00)	0.55	0.58 (0.19–1.56)	0.35

* The standard incidence ratio (SIR) is the ratio of observed to expected malignancies and represents the malignancy risk compared to the general population, and the relative risk (RR) represents the malignancy risk compared to the reference group. Calculated by exact Poisson regression analysis.

† Unknown for 61 patients.

MPO-ANCA, myeloperoxidase ANCA; PR3-ANCA, proteinase 3 ANCA.

Table S2. Cyclophosphamide and rituximab treatment in the subgroups

	N patients treated with cyclophosphamide	Duration of cyclophosphamide treatment, months (SD)	Mean cumulative cyclophosphamide dose, g (SD)	N patients treated with rituximab	Duration of rituximab treatment, months (SD)	Mean cumulative rituximab dose, g (SD)
Gender						
Male	107	5.5 (5.5)	9.9 (6.5)	68	22.1 (14.9)	5.8 (3.4)
Female	116	6.4 (14.4)	8.4 (10.8)	85	20.9 (14.4)	5.9 (3.4)
Age at diagnosis						
≥59 years	114	6.5 (13.8)	6.8 (3.9)	63	20.2 (14.2)	5.2 (2.9)
<59 years	109	5.1 (4.2)	11.5 (11.8)	90	22.5 (14.9)	6.3 (3.6)
Clinical diagnosis						
Microscopic polyangiitis	116	6.3 (12.6)	8.1 (10.5)	65	18.7 (13.3)	5.2 (2.6)
Granulomatosis with polyangiitis	88	5.4 (4.4)	10.7 (7.3)	66	27.7 (15.0)	6.7 (4.0)
Eosinophilic granulomatosis with polyangiitis	19	4.5 (2.8)	7.8 (4.2)	22	22.6 (15.7)	5.3 (2.9)
ANCA serotype*						
MPO-ANCA	72	7.4 (16.1)	7.2 (4.7)	43	20.7 (16.9)	5.1 (2.9)

PR3-ANCA	121	5.0 (4.2)	9.2 (6.5)	82	20.9 (13.0)	6.1 (3.3)
Renal transplantation						
No	213	5.2 (4.9)	9.1 (9.0)	149	21.6 (14.4)	5.9 (3.4)
Yes	10	15.6 (37.3)	8.5 (8.6)	4	16.7 (19.4)	4.5 (2.4)
Follow-up						
0–5 years	102	4.7 (3.5)	7.0 (4.6)	52	17.5 (10.9)	4.6 (2.8)
5–10 years	101	7.2 (15.5)	10.8 (11.9)	82	23.5 (15.2)	6.3 (3.6)
>10 years	20	5.4 (5.1)	10.9 (6.8)	19	24.6 (19.6)	7.4 (3.1)

* Unknown for 61 patients.

MPO-ANCA, myeloperoxidase ANCA; PR3-ANCA, proteinase 3 ANCA.

Table S3. SIR for non-melanoma skin cancer according to cumulative cyclophosphamide and rituximab dose*

Cumulative dose (g)	N patients	N observed non-melanoma skin cancer	SIR (95% CI)†	SIR p value†
Cyclophosphamide				
0	89	3	2.17 (0.45 – 6.34)	0.16
0.1–20	207	18	4.89 (2.90 – 7.72)	<0.001
20–108	16	3	11.72 (2.42 – 34.25)	0.002
Rituximab				
0	167	23	8.47 (5.37 – 12.71)	<0.001
0.1–6	70	1	0.83 (0.02 – 4.64)	0.66
6–18	83	0	0 (0 – 2.47)	0.23

* SIR, standardised incidence ratio; the SIR is the ratio of the observed to expected malignancies adjusted for sex, age (per 5-year age group), and calendar time period (per 1-year calendar time period).

† Calculated by exact Poisson regression analysis.

Table S4. Cumulative cyclophosphamide and rituximab dose of each patient with a malignancy

Malignancy or malignancy site	N observed malignancies	Cumulative cyclophosphamide dose (g)*	Cumulative rituximab dose (g)*	Time to malignancy (years)†
Lung	4	36.0; 21.1; 4.9; 0.0	0.0; 7.0; 0.0; 5.0	3.7; 4.8; 0.5; 8.5
Breast	3	18.0; 6.0; 3.4	0; 4.0; 8.0	0.9; 1.1; 4.0
Colon or rectum	3	13.8; 9.5; 4.0	0.0; 0.0; 0.0	2.4; 4.5; 4.0
Prostate	2	10.0; 0.0	0.0; 0.0	7.4; 1.2
Bladder	1	0.0	1.0	2.4
Pancreas	1	0.0	0.0	1.4
Testis	1	7.0	5.0	4.6
Ovary	1	3.0	6.6	2.4
Melanoma	1	3.3	0.0	1.8
Tongue	1	0.0	0.0	4.5
Central nervous system	1	2.0	5.6	3.2
Kidney	1	7.0	4.0	2.4

* The cumulative doses of each patient with a malignancy is given. Patients with a cumulative dose of 0.0 did not receive the treatment. When more cases of the malignancy were observed, the first reported cumulative cyclophosphamide dose corresponds to the first reported cumulative rituximab dose, and to the first reported

time to malignancy.

† This is the time between the date of diagnosis of ANCA-associated vasculitis and the date of diagnosis of the malignancy.