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Cancer in Anti-Neutrophil Cytoplasm Antibody-Associated Vasculitis and Polyarteritis Nodosa in Australia: A Population-Based Study

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Objective. The study objective was to compare incident cancer rates among patients with anti-neutrophil cytoplasm antibody-associated vasculitis (AAV) and polyarteritis nodosa (PAN) in Western Australia (WA) with the general population and perform time-varying analyses to identify periods with greatest excess cancers.

Methods. Administrative health data from patients hospitalized with incident AAV/PAN from 1980 to 2014 were linked to the WA cancer registry, which holds compulsorily reported cancer data (excluding skin squamous cell and basal cell carcinomas). Incident cancer rates in patients with AAV/PAN were compared with age-, sex-, and calendar-year-matched WA population rates.

Results. Patients with AAV/PAN had higher overall rates of incident cancer compared with the matched population (standardized incidence ratio [SIR], 1.74; 95% confidence interval [CI], 1.42-2.10). In subgroup analyses, incident cancer rates in patients with granulomatosis with polyangiitis/eosinophilic granulomatosis with polyangiitis were approximately double the general population (SIR, 2.21; 95% CI, 1.73-2.78) but similar to the general population in patients with microscopic polyangiitis/PAN (SIR, 1.21; 95% CI, 0.85-1.68). Patients with AAV/PAN had higher rates of genitourinary, skin, hematological, and lung cancers. Excess rates of hematological and lung cancers peaked early after diagnosis, whereas excess skin and genitourinary cancer rates peaked at 5 and 10 years, respectively.

Conclusion. This study highlights the importance of long-term cancer surveillance in patients with AAV/PAN and defines time frames of excess risk for specific cancers, which may help inform guidance on cancer screening. Furthermore, it indicates the need for skin surveillance for melanoma in addition to nonmelanoma skin cancers in patients who have greater environmental ultraviolet exposure, such as in Australia.

INTRODUCTION

Anti-neutrophil cytoplasm antibody (ANCA)-associated vasculitis (AAV) is a life- and organ-threatening systemic vasculitis encompassing the following three subtypes with overlapping features: granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA). Early iterations of proposed classification criteria did not distinguish between the clinical presentations of the medium vessel vasculitis, polyarteritis nodosa (PAN), and MPA, which is reflected in International Classification of Diseases (ICD)

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SIGNIFICANCE & INNOVATIONS

- Cancer rates are higher in patients with anti-neutrophil cytoplasm antibody-associated vasculitis (AAV)/polyarteritis nodosa (PAN) compared with the general population.
- In this study, patients with AAV/PAN had a peak in new cancer diagnoses early after diagnoses of AAV/PAN, which was explained by lung and hematological cancers.
- Excess skin cancer rates peaked approximately 5 years after diagnosis of AAV/PAN, and excess genitourinary cancers peaked approximately 10 years after diagnosis of AAV/PAN.

codes. Historic trials investigating treatment approaches for AAV subtypes have included PAN (1–4).

A link between systemic vasculitides and malignancy has been proposed in several observational studies. Studies have focused on cancers related to medicines commonly used to treat vasculitis, namely, bladder cancer with cyclophosphamide (5–7) and skin cancer with methotrexate and azathioprine (8,9). Other proposed mechanisms include chronic immune activation, which is a shared pathogenesis of immune dysfunction and paraneoplastic phenomena.

Notably, the published risk of common cancers in the general population, such as breast and colorectal cancer, have not been greater among patients with AAV compared with population rates (10–17). In studies of patients with AAV, increased nonmelanoma skin cancers (NMSCs) have been consistently reported (6,10–12,14,15,17). This has largely been driven by squamous cell carcinomas (SCCs) of the skin (10,13,14,17), with no increase in the risk of melanoma or other skin cancers (10,14,17). In the Australian setting, the impact of AAV and PAN on cancer risk has not been examined. Moreover, a higher background risk exists for skin cancer in Australia.

In this study, we examined overall and time-varying rates of incident cancer in patients with AAV/PAN compared with the general population in Western Australia (WA).

PATIENTS AND METHODS

Data source. Patients were identified in the Western Australia Rheumatic Disease Epidemiology Registry (WARDER), which collects compulsory reported hospitalization data from public and private hospitals in WA (from the Hospital Morbidity Data Collection [HMDC]) with emergency department data collection, WA cancer registry, and WA births, deaths and marriages registry and links the data via the WA Data Linkage System (WADLS). Linked emergency department data were not used in this analysis. This process is summarized in Figure 1. The high linkage accuracy (99.7%) of WADLS allows longitudinal follow-up for individuals across administrative health datasets (18).

The available HMDC dataset consists of data from 1980 to 2014, including demographic data, primary and up to 20 secondary diagnosis codes, and timing of hospitalization. Dates were provided as MM/YYYY to minimize the risk of reidentification of individuals. Data were available from the WA cancer registry from 1982 to 2014 and include diagnosis date, cancer topography, morphology, and behavior.

Study population. Patients were classified as having AAV/PAN using ICD-9 or ICD-10 codes from hospitalization or death diagnosis fields for AAV subtypes (Figure 1B). Patients with AAV/PAN were categorized into the following two subgroups using existing ICD code structures: GPA/EGPA or MPA/PAN, which reflect historic nomenclature and classification. Because of the nature of data linkage, additional clinical and laboratory data were not available to reclassify patients into alternative subgroup structures. Linked data for these patients in WARDER were used for analyses.

The date of first hospitalization listing ICD-9 or ICD-10 diagnosis codes for AAV/PAN was taken as the date of diagnosis. Patients were excluded if age at diagnosis was under 10 years. Patients were classified as having incident AAV/PAN if a prior hospitalization was identified without AAV/PAN, or if they were born after January 1980.

Outcome. The reporting of all cancers to state-based cancer registries is mandatory in Australia. All cancers are recorded in the WA cancer registry in accordance with World Health Organization ICD for Oncology codes, which are updated with each iteration of revisions. Solid organ malignancies were identified using topography codes and hematological malignancies using morphology codes. Where both were reported concurrently, morphology of the solid organ malignancy was reviewed to distinguish between concurrent cancers and occurrence of an extranodal or extra-medullary hematological malignancy. Reporting of recurrences is not mandatory, and because the objective of this study was to evaluate incident cancer, all recurrences in the same organ category or morphology for hematological malignancy were removed from analyses. The three most common skin cancers in Australia are melanoma, SCC, and basal cell carcinoma (BCC) (19). Both SCC and BCC of the skin are not included in Australian cancer registries, and skin cancers in Australian cancer registries are therefore predominantly melanoma, with other rare types such as Merkel cell included (19).

Statistical analysis. The study included patients who were diagnosed with AAV/PAN between January 1, 1983, and March 1, 2014, with an end date of December 31, 2014. Patients with a cancer diagnosis registered prior to AAV/PAN diagnosis or match date were excluded from analysis of incident cancer. The date of last linkage was used as the censor date (December

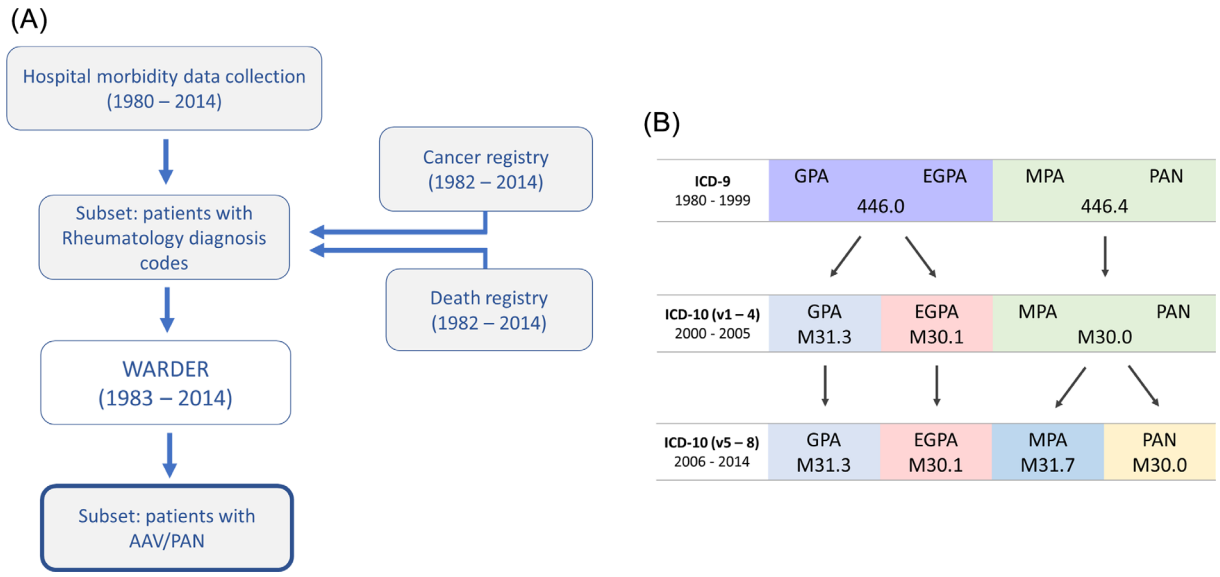

Figure 1. Data linkage flow chart and ICD codes for ANCA-associated vasculitis and PAN. **A**, Data linkage flowchart. **B**, ICD codes for ANCA-associated vasculitis and PAN. Patients with Rheumatological diagnoses from hospital admissions using ICD codes for the categories of chronic idiopathic arthritis, spondyloarthropathies, connective tissue disease, crystal induced arthritis, and osteoarthritis were identified from the HMDC. Data on all hospitalizations for these patients were linked to the WA Cancer registry and death registers from the Births, Deaths and Marriages registry to form the WARDER dataset. Patients with AAV/PAN were identified using ICD-9 and ICD-10 codes (Figure 1B), and linked WARDER data for these patients were used for analyses. The HMDC used ICD-9 until 1999, when ICD-10 was used for diagnosis classifications. The 5th edition was adopted in 2006. GPA and EGPA shared a diagnosis code in ICD-9 and had separate diagnosis codes in ICD-10. PAN and MPA shared a diagnosis code until the 5th edition ICD-10 update (adopted in HMDC in 2006) when separate codes were used. The distinction between PAN and the AAV subtypes (GPA, EGPA, and MPA) is therefore only possible from 2006 onward. AAV, ANCA-associated vasculitis; ANCA, anti-neutrophil cytoplasm antibody; EGPA, eosinophilic granulomatosis with polyangiitis; GPA, granulomatosis with polyangiitis; HMDC, Hospital Morbidity Data Collection; ICD, International Classification of Diseases; MPA, microscopic polyangiitis; PAN, polyarteritis nodosa; WARDER, West Australian Rheumatic Disease Epidemiology Registry; WA, Western Australia.

31, 2014). Follow-up times for participants were right censored at 25 years of follow-up or an attained age of 89 years.

Demographic data have been summarized as proportion (percentage) and median (interquartile range). Comparisons of age and year of diagnosis were analyzed using Wilcoxon rank sum test. Cancer risk in AAV/PAN was analyzed using time to event analysis performed using Stata version 16 (StataCorp LLC).

Cancer types selected for specific cancer analyses were based on existing literature for cancer in patients with AAV/PAN and included the most common cancers in Australia (6,7,10,12,13). Both incident cancer (any) and specific cancer rates were analyzed. Crude cancer incidence rates were calculated from the observed number of cancers and follow-up (exposure time). For comparison with population cancer rates, the expected number of cancers were calculated from age-, gender-, and calendar-year-matched WA population cancer rates using the Ederer II method (20). Expected cancers, observed cancers, and person-years follow-up were tabulated at half-yearly intervals using the Stata ado program strs (20). The standardized incidence ratio (SIR) was calculated from the ratio of the total observed to expected cancers (over 25 years of follow-up), with exact mid-*P* confidence intervals (CIs).

Time-varying effects of AAV/PAN-related cancer risks were explored using the excess hazard rate (EHR), which is defined as the difference between the observed and expected cancer rates. This is an additive model of the effect of disease, is not confounded by an increase in the expected rates (the SIR denominator) that will occur during extended follow-up, and is not susceptible to distortions that may occur in the SIR with both small observed and expected rates. Spline-based modeling of the cancer EHR over follow-up time was performed using the Stata ado program stpm2 (21). The appropriate spline degrees of freedom were determined using the minimum Akaike information criterion, and knots were placed at default data centile positions determined by the degrees of freedom. The significance of differences in the time course of the excess hazards between AAV/PAN subgroups was determined by a multivariate Wald test of the time-varying regression coefficients.

Ethics. Ethical approval for linked data extraction was provided by the WA Health human research ethics committee (HREC) (WADOH HREC #2016.24).

RESULTS

In total, 564 incident patients with AAV/PAN were identified between 1980 and 2014. This included 342 (61%) patients with

Table 1. Demographics and incident cancer risk in patients with AAV/PAN

Characteristic	All AAV/PAN	GPA/EGPA	MPA/PAN
n	564	342	222
Females, *n* (%)	252 (45)	159 (46)	93 (42)
Age at Dx, median (IQR)	58 (45-69)	56 (44-67)	61 (58-65)
Year Dx, median (IQR)	2001 (1993-2007)	2002 (1996-2008)	1998 (1992-2005)
Maximum follow-up, y	25	25	25
Follow-up, person-years	4,882.249	2,836.339	2,045.91
Observed cancers	101	68	33
Expected cancers	58.13	30.84	27.29
Incident cancer rate[a] (95% CI)	2.07 (1.70-2.51)	2.40 (1.89-3.04)	1.61 (1.14-2.26)
SIR[b] (95% CI)	1.74 (1.42-2.10)	2.21 (1.73-2.78)	1.21 (0.85-1.68)

Abbreviations: AAV, antibody-associated vasculitis; CI, confidence interval; Dx, diagnosis; EGPA, eosinophilic granulomatosis with polyangiitis; GPA, granulomatosis with polyangiitis; IQR, interquartile range; MPA, microscopic polyangiitis; PAN, polyarteritis nodosa; SIR, standardized incidence ratio.
[a]Crude incidence rate/100 person-years.
[b]SIR relative to age-, gender-, and calendar-year-matched West Australian population cancer rates.

GPA/EGPA and 222 (39%) with MPA/PAN. Demographic details are summarized in Table 1. Compared with patients with GPA/EGPA, patients with MPA/PAN were older at diagnosis ($P < 0.05$).

A total of 101 incident cancers were identified over 4,882 person-years of follow-up. Of the 101 incident cancers, 68 occurred in patients with GPA/EGPA and 33 in patients with MPA/PAN. Overall, the incident cancer rate observed in patients with AAV/PAN was greater than WA population rates (SIR, 1.74; 95% CI, 1.42-2.10).

When analyzed by disease subgroups, the rate of any type of cancer after the diagnosis of GPA/EGPA was double that of the general population (SIR, 2.21; 95% CI, 1.73-2.78). Patients with MPA/PAN, however, did not have an increased rate of incident cancer over the general population (SIR, 1.21; 95% CI, 0.85-1.68). The incidence rate ratio of cancers (derived from the crude incidence rates reported in Table 1) for the GPA/EGPA group compared with MPA/PAN was 1.49 (95% CI, 0.99-2.28; exact mid-*P*, 0.059).

However, the risk of cancer was not constant over time. The time frame for any incident cancer risk for the two subgroups is illustrated in Figure 2. Following an initial spike in excess cancers in both groups, the EHR for patients with MPA/PAN falls close to

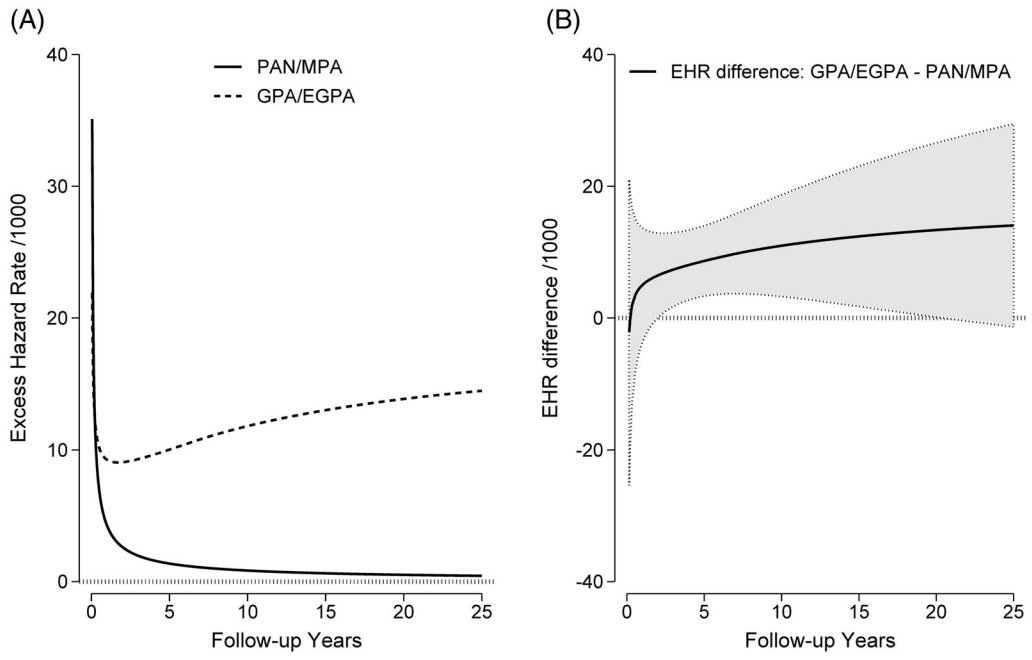

Figure 2. Spline based modelling of the cancer EHR, the difference between observed and expected rates, over follow-up time for both GPA/EGPA and MPA/PAN AAV subgroups. The EHR differed over time between the two AAV subgroups ($P = 0.011$). **A**, EHR for both GPA/EGPA and MPA/PAN subgroups. **B**, The difference in the EHR between AAV subgroups, with shaded areas representing 95% confidence interval. AAV, ANCA-associated vasculitis; ANCA, anti-neutrophil cytoplasm antibody; EGPA, eosinophilic granulomatosis with polyangiitis; EHR, excess hazard rate; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; PAN, polyarteritis nodosa.

Table 2. Specific cancer SIRs in patients with AAV/PAN and AAV/PAN subgroups

	AAV/PAN			GPA/EGPA			MPA/PAN		
Specific Cancer	Obs	Exp	SIR	Obs	Exp	SIR	Obs	Exp	SIR
Genitourinary	7	2.04	343 (1.50-6.79)	7	1.11	6.30 (2.76-12.47)	0	0.93	—
Breast	5	6.24	0.80 (0.29-1.78)	<5	3.97	0.76 (0.19-2.06)	<5	2.27	0.88 (0.15-2.91)
Lung	17	7.85	2.17 (1.30-3.40)	11	4.39	2.50 (1.32-4.35)	6	3.45	1.74 (0.71-3.62)
Colorectal	12	8.86	1.35 (0.73-2.30)	9	4.95	1.82 (0.89-3.34)	<5	3.92	0.77 (0.19-2.09)
Skin	22	6.56	3.35 (2.16-4.99)	15	3.73	4.02 (2.33-6.48)	7	2.83	2.48 (1.08-4.90)
Hematological	13	6.72	1.93 (1.08-3.22)	8	3.81	2.10 (0.98-4.00)	5	2.91	1.71 (0.63-3.80)
Prostate[a]	11	12.75	0.86 (0.45-1.50)	8	7.05	1.14 (0.53-2.16)	<5	5.70	0.52 (0.13-1.43)

Abbreviations: —, no data; AAV, antibody-associated vasculitis; EGPA, eosinophilic granulomatosis with polyangiitis; Exp, expected cancer rate; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; Obs, Observed cancer rate; PAN, polyarteritis nodosa; SIR, standardized incidence ratio; WA, Western Australia.
In accordance with WA Data Linkage policy, to minimize the risk of reidentification, cells with fewer than five individuals are reported as "<5."
[a]Men only.

zero, indicating that the cancer risk becomes similar to the population rate. For patients with GPA/EGPA, however, the EHR remains elevated and continues to increase over long-term follow-up.

Risk of specific cancer types in patients with AAV/PAN. Incident genitourinary, lung, skin (non-SCC/non-BCC), and hematological cancers were increased compared with age-, sex-, and calendar-year-matched population rates (Table 2). No increase in incident breast, prostate, or colorectal cancer was observed in patients with AAV/PAN compared with the population. Patients with GPA/EGPA had greater than expected rates of incident genitourinary cancer compared with matched population rates (Table 2), but no genitourinary cancers were observed in patients with MPA/-PAN. Skin cancer rates were increased in both GPA/EGPA and MPA/PAN subgroups of patients (Table 2). Incident lung cancer was increased in patients with GPA/EGPA compared with the general population, but not in patients with MPA/PAN (Table 2). Although the overall rate of hematological cancers was elevated, this was not statistically significantly in either subgroup.

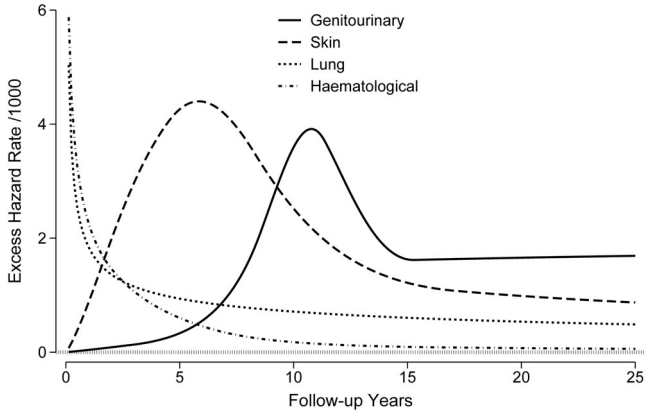

Figure 3. Spline based modelling of the excess hazard rate over time for specific cancers in patients with ANCA-associated vasculitis/polyarteritis nodosa. ANCA, anti-neutrophil cytoplasm antibody.

Timing of specific cancers after diagnosis. The EHR for cancers observed to be increased in patients with AAV/PAN (genitourinary, skin, lung, and hematological) in this dataset were modeled over time (Figure 3). A peak in EHR of skin and genitourinary cancers occurred at approximately 5 and 10 years, respectively, with a persistently increased rate observed thereafter. Lung and hematological cancer rates, however, peaked early after diagnosis and returned to rates similar to matched population rates in longer-term follow-up. Hematological cancers in the first 3 years included diagnoses of Hodgkin lymphoma, myelodysplastic syndrome, and myeloid sarcoma. Later hematological cancers included non-Hodgkin lymphomas, myeloma, and myelodysplastic syndrome.

DISCUSSION

With the success of induction therapy in the systemic vasculitides, longer-term outcomes have become an increasingly important focus in improving care. Treatment strategies to control disease activity and prevent relapses balance disease-related sequelae against treatment-related effects, including cancer. In this first study of cancer rates in Australian patients with AAV/-PAN, we observed higher rates of incident cancer in patients with AAV/PAN than the matched general population, explained by increased rates of genitourinary, skin, lung, and hematological cancers. We identified periods in the disease course with the greatest incidence of these cancers compared with the general population.

The estimated SIR for cancer in patients with AAV/PAN in this Australian cohort (1.74; 95% CI, 1.42-2.10) was comparable to a prior meta-analysis, which reported an overall SIR of 1.74 (95% CI, 1.37-2.21) (22). Cancer remains a significant contributor to mortality in patients with AAV and PAN (1,23,24). In a separate paper addressing mortality in the same cohort of patients with AAV/PAN included in this study, the risk of death related to malignancy was greater in patients with AAV/PAN than age-, sex-, and temporally matched hospitalized controls, increasing in longer-term follow-up (25).

Early observational studies of patients with GPA reported increased cancers compared with population rates, with estimated SIRs between 1.7 and 2.1 (6,10,17). Cancer studies including patients with MPA, EGPA, and PAN have produced mixed results. La Farage and colleagues reported no overall increase in malignancy in long-term follow-up of patients with AAV/PAN included in French vasculitis group studies (26). In contrast, Swedish, Dutch, United Kingdom, and Korean data suggest that an increased risk of cancer persists (13–16,27). Where cancer incidence has been compared among subgroups, rates were greater in patients with GPA compared with patients with MPA (13,15,16,27) and those with EGPA (16,27). In our subgroup analyses, patients with GPA/EGPA, but not MPA/PAN, also had increased rates of incident cancer compared with expected population rates. This may relate to the relapsing and refractory course of GPA and EGPA, resulting in repeated immune reactivation and consequently greater cumulative immunosuppressive therapy in these patients, and we note that increased cancer has been observed with greater cyclophosphamide (6,12,15,17) and methotrexate and azathioprine use (26,28). Disease activity and medication data were unfortunately not available in this linked dataset to address this hypothesis.

In analyses of specific cancer types in this study, the incidence of genitourinary, skin, lung, and hematological cancers were higher than general population rates. These cancers have been associated with AAV and PAN in prior studies (6,7,10–13,15–17,29), whereas rates of liver, pancreatic, and brain cancers identified in other studies were not increased (10,13). Whereas only patients with GPA/EGPA had increased rates of genitourinary and lung cancers, increased rates of skin cancer were identified in both patient groups. The long-term risk of genitourinary cancers is well recognized and attributed to the effects of cyclophosphamide, commonly used in treatment of AAV/PAN (5–7,10,11,17,27,30), with higher cumulative cyclophosphamide doses and with a diagnosis of GPA likely conferring greater risk (6,7). In this study, time-varying analyses of excess cancer rates revealed excess genitourinary cancer rates peaked approximately 10 years after diagnosis, consistent with the long latency periods noted in previous studies (6,7,10).

Prior studies have recognized the relatively common occurrence of skin SCCs and the substantial impact of SCCs on the overall risk of cancer (6,10–12,14,15). The association is most often attributed to azathioprine and methotrexate (6,26), which have been associated with NMSC in other settings (8,31–34). The high incidence of skin cancer in Australia is well-recognized, considering the high ultraviolet (UV) radiation exposure; although public health interventions have improved skin cancer rates, this effect has not changed skin cancer rates in the predominant age groups included in this study (35). The risk of skin cancers other than SCCs has not been significantly increased in European cohorts; whether patients with AAV/PAN with greater UV exposure in Australia were at greater risk of skin cancers has remained of interest. This study has confirmed the increased rate of incident skin cancer in Australian patients with AAV/PAN; importantly, this was predominantly driven by melanoma skin cancers as SCC and BCC are excluded from the cancer registry (19).

Few studies have evaluated the timing of cancer development in the follow-up of patients with AAV/PAN. Although not directly comparable, in contrast to the peak excess skin cancer rates observed in this study 5 years from diagnosis, a relatively stable SIR of NMSC was observed in two Scandinavian studies (6,10). Timing and behavior of melanoma compared with NMSC may explain this difference, or intensity and cumulative burden of immunosuppression may contribute. One study linking solid organ transplant with cancer registry data in the United States suggests a differing effect of short-term intense immunosuppression and longer-term immunosuppression; melanomas with regional or distant spread occurred early after transplantation, whereas in situ melanoma rates were consistently elevated over follow-up (36).

An early spike in excess cancers was observed soon after diagnosis in patients with AAV/PAN, with hematological and lung cancers contributing to this excess. This could be consistent with shared pathogenesis, short-term treatment effect or paraneoplastic effect. A paraneoplastic effect in AAV and PAN have been proposed by several reports [37-40]. Two case–control studies, however, have not identified an association between AAV diagnoses and preceding cancers (28,29). Patients with prior cancers were excluded from this study.

Although not significant in individual studies, a meta-analysis of early studies of cancer in patients with AAV identified increased lung cancer (22). Recent analyses of Korean health data have also identified an increased rate of lung cancer among patients with AAV (16,27). This has not, however, been found in recent European studies of patients enrolled in observational cohorts (13–15). Notably, this study and the Korean studies, both reporting increased lung cancer, have relied on administrative data for diagnoses, overcoming the difficulties in recruiting patients burdened with complex concurrent illnesses to observational cohorts.

The short latency to hematological cancers observed in this study is also congruent with the findings from data obtained from administrative data linkage studies from Korean and Sweden. Knight and colleagues report increased rates of both leukemias and lymphomas, with SIRs highest in the first year of follow-up (10). In the Korean studies, increased rates of hematological cancers were driven by increased non-Hodgkin lymphomas and myeloma in patients with AAV (16). These findings contrast with Faurschou and colleagues' report of myeloid leukemias in patients who received at least 36 g of cyclophosphamide, and after 5 years of follow-up (6).

Both AAV and PAN remain relatively uncommon, and collaboration among the vasculitis community has enabled recent large randomized controlled treatment trials (41–43). With the ability to better control initial disease activity, long-term and uncommon outcomes such as incident cancer, which can have a long

latency, need to be assessed by observational studies, including population-based studies. A population-based approach also enables the identification of outcomes for patients with early cancers and accounts for early deaths in patients who may not have the opportunity or ability to be included in observational cohorts and randomized controlled trials. The patients with AAV/PAN in this study were identified by ICD discharge codes. Although this represents real-world clinician-based diagnoses mandatorily audited by clinical coders, they are not validated against classification criteria through case-note review. A previous study from WA using the same discharge codes, however, reported a sensitivity of 91% for AAV diagnosis based on the European Medicines Agency classification algorithm (44).

Outpatient data are not included in WADLS, introducing possible bias because patients with AAV/PAN with less severe disease, never requiring hospitalization for AAV/PAN or complications, were not included. Moreover, because of the nature of data linkage in these patients, detailed clinical data and laboratory data including ANCA status were not available, limiting analyses on medication effects and analyses based on more contemporary understandings of patient subgroups.

Considering the early peak in excess cancers, including lung and hematological cancers, a degree of ascertainment bias was considered, owing to imaging and laboratory investigations required in the diagnosis of AAV/PAN. Rates of other commonly occurring cancers, including breast and colorectal cancers, were not increased, however. Moreover, the WA cancer registry consolidates mandatorily reported cancer data from pathology reports and radiation oncology records, which were available for all diagnosed lung and hematological cancers identified in this study. As highlighted earlier, the diagnosis of AAV/PAN is regularly and mandatorily audited. This study focused on incident cancer diagnoses because patients with prior cancer are more likely to have a second cancer and current standards in Australian cancer registries make the identification of recurrences unreliable. Larger scale studies may be helpful to study cancer outcomes in patients with a prior cancer, who may not have been included in clinical trials.

In conclusion, this study not only reiterates the importance of cancer monitoring in the follow-up of patients with AAV/PAN but also provides time frames for excess risk of specific cancers. These data help to inform future research as to whether, or when, cancer screening in patients with AAV/PAN is warranted, as skin and bladder cancers rates peaked at approximately 5 and 10 years, respectively. Furthermore, in addition to the increase in SCC skin cancers identified in European countries, this study has emphasized the need for vigilance for all skin cancers, including melanoma, in Australian patients.

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AUTHOR CONTRIBUTIONS

Dr. Tieu wrote the first draft of the manuscript. All authors contributed to article revisions and approved the submitted version.

Study conception and design. Tieu, Lester, Keen, Hill, Nossent.

Acquisition of data. Tieu, Lester, Raymond.

Analysis and interpretation of data. Tieu, Lester, Raymond, Keen, Hill, Nossent.

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