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EXTENDED REPORT

Is cancer associated with polymyalgia rheumatica? A cohort study in the General Practice Research Database

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ABSTRACT**Objective** To investigate the incidence of new cancer diagnoses in a community sample of patients with polymyalgia rheumatica (PMR).**Methods** All incident cases of PMR in the UK General Practice Research Database (GPRD) (1987–99), without pre-existing cancer or vascular disease and treated with corticosteroids (n=2877) were matched with up to five age, sex and GP practice patients without PMR (n=9942). Participants were followed up until first cancer diagnosis, death, transfer out of the database or end of available records.**Results** The mean age of the sample was 71.6 years (SD 9.0), 73% were female. Median follow-up time was 7.8 years (IQR 3.4, 12.3). 667 (23.2%) people with a PMR diagnosis developed cancer compared with 1938 (19.5%) of those without PMR. There was an interaction between PMR status and time. In the first 6 months after diagnosis, those with a PMR diagnosis were significantly more likely to receive a cancer diagnosis (adjusted HR (95% CI): 1.69 (1.18 to 2.42)). The number of events was small, but occurrences of prostate, blood, lymph nodes, female reproductive and nervous system cancers may be more common in those with PMR in the first 6 months after PMR diagnosis.**Conclusions** An increase in the rate of cancer diagnoses was noted in the first 6 months of observation, but we were unable to determine whether the cancer incidence in PMR was different from controls, beyond this time point. Clinicians should ensure they fully exclude cancer as a cause of PMR-like symptoms and monitor patients for possible malignancies.conducted.¹⁰ Ji *et al*¹⁰ found a 19% increase in the risk of cancer in patients admitted to hospital with PMR and giant cell arteritis (GCA) in Sweden compared with the general population. This association diminished over time to a 6% increase after the first year. Smaller studies have considered the association of GCA or a combination of PMR and GCA with cancer in matched prospective cohorts,^{11–13} but have found no association. To date, however, no large-scale cohort study has investigated the potential association between PMR and cancer in the community, in which the majority of patients are exclusively diagnosed and managed.^{3 4}

Given the conflicting evidence, the true association between PMR and cancer in the community is unclear. This study uses the General Practice Research Database (GPRD) to prospectively assess the potential association between PMR and the subsequent diagnosis of cancer.

METHODS**General Practice Research Database**The GPRD contains the electronic medical records of patients registered with contributing general practices in England and Wales. Practices are broadly representative of all those in England and Wales for geographical distribution, list size and the age and sex distribution of registered patients. The GPRD includes demographic information, prescription details, clinical events, preventive care provided, specialist referrals, hospital admissions and their major outcomes, coded using the hierarchical system known as Read codes.^{14 15} Practices that contribute to the GPRD must meet strict quality criteria to provide ‘up-to-standard’ data.¹⁶ Recent reviews confirm the data to be of a good quality for research,¹⁵ although coding was better for chronic conditions, such as PMR and cancer, than for acute conditions.¹⁷**Participant identification**All patients with an incident PMR diagnosis (a single diagnostic Read code for PMR) between 1 January 1987 and 31 December 1999 were identified by GPRD staff and matched with up to five individuals without PMR for year of birth, sex and practice. The index date was taken as the date of the first PMR Read code for those with PMR and the corresponding matched date for those without. All participants included were aged ≥ 50 years at the index date, had no pre-index record of vascular**INTRODUCTION**With a lifetime prevalence of 2.4% for women and 1.7% for men,¹ polymyalgia rheumatica (PMR) is the commonest inflammatory rheumatological disease in adults aged ≥ 50 years.² It is usually diagnosed and managed in primary care.^{3 4} Classic symptoms are bilateral pain, aching and stiffness in the shoulders and pelvic girdle, usually accompanied by raised inflammatory markers. As the population ages,⁵ the number of cases of PMR is expected to rise.It has been known for some time that inflammatory rheumatological disorders such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) are associated with increased rates of certain forms of cancer (RA^{6 7}; SLE^{8 9}). Despite this, only one large-scale study investigating the association between PMR and cancer has beenOpen Access
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events and had at least 2 years of up-to-standard records before the index date.

Definition of cancer

A diagnosis of cancer was identified using Read codes. The same definition of cancer was adopted as that used in a previous study of cancer in the GPRD¹⁸: codes in chapter B (neoplasms), excluding subchapter B7 (non-malignant neoplasms). Read codes were converted into GPRD medcodes in order to identify consultations in the database.

Participant inclusion criteria

To provide further confidence of the accuracy of the PMR diagnosis, a method previously used by researchers using the GPRD was employed.¹⁶ Patients with PMR still registered with the practice 6 months or more after the index date were required to have at least two prescriptions for oral corticosteroids within that period. Patients who ceased to be registered with the practice within 6 months of the index date were required to have one or more prescriptions for oral corticosteroids between the index date and the end of their registration. Patients with a Read-coded diagnosis of PMR but not fulfilling these prescription criteria were excluded from further analyses. Individuals without PMR, but who were matched to excluded patients with PMR, were also excluded. Patients with a diagnosis of cancer before PMR diagnosis or matched date were excluded. The participant selection process is shown in figure 1.

Outcome measures

The outcome of interest was a diagnosis of cancer. Participants were followed up to the date of first cancer diagnosis, death, transfer out of the GPRD practice, or until the end of the data excerpt (latest date May 2011), whichever was the earliest.

Additional risk factors

Smoking status was defined according to the information provided directly by GPRD. Each person was classified as ever or never having smoked.

GPRD medcodes and associated definitions were used to define all other morbidities and are available from the authors, together with the definition of an oral steroid.

Statistical analyses

A post hoc power calculation was carried out to determine the power available in the sample to detect a 20% increased risk of cancer in the patients with PMR compared with patients without PMR.

The association between PMR and cancer was investigated using a Kaplan–Meier plot and was formally quantified using Cox proportional hazard models. Follow-up time was divided into intervals considered to be clinically relevant, (6 months, 1, 2, 5 and 10 years after PMR diagnosis) and a test for interaction with time performed. Analyses were adjusted for the potential cofounders of age, sex and smoking status.

Age group (50–59, 60–69, 70–79, ≥80 years), smoking and sex were also considered potential effect modifiers and such an effect was tested using a Mantel–Haenszel test.

Robust SEs (eg, White¹⁹) were used to adjust results for the matching of those with and without PMR. The proportional hazards assumption was tested using Schoenfeld residuals.

To investigate whether the types of cancer seen in those with and without PMR were similar, cancer diagnoses were grouped according to the anatomical systems affected. The distribution of these categories in those with and without PMR was then compared where differences were seen in rates of any cancer.

Analyses were performed using Stata V.12.1 and all point estimates were calculated with associated 95% CIs.²⁰

This study received approval from the Independent Scientific Advisory Committee for Medicines and Healthcare products Regulatory Agency database research (protocol number 10_109AR). People are included in an anonymised manner in the GPRD without explicit informed consent having been obtained.

RESULTS

A total of 3925 people with a PMR Read code and no pre-existing vascular disease were identified. Of these, the diagnosis

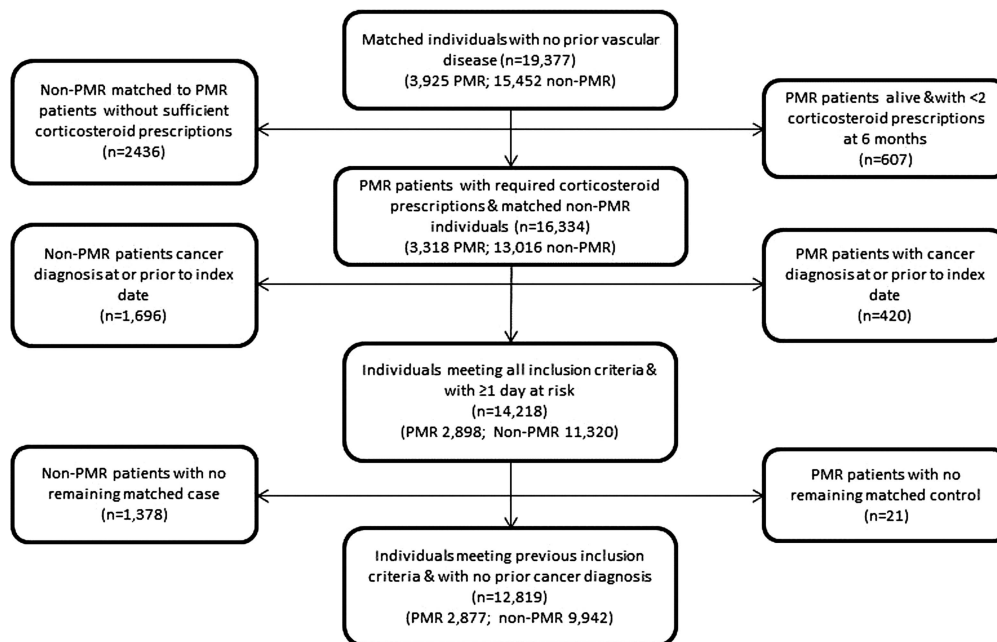


Figure 1 Flow chart of participant selection. PMR, polymyalgia rheumatic.

Table 1 Characteristics of sample, by PMR exposure status

Characteristic	PMR (n=2877)	No PMR (n=9942)
Age at index date, mean (SD), years	72.0 (8.9)	71.5 (9.1)
Female, n (%)	2091 (72.7)	7238 (72.8)
Ever smoker, n (%)*	1178 (44.1)	3531 (41.7)
Follow-up time at risk, median (IQR), years	8.4 (3.9, 12.3)	7.6 (3.3, 12.3)

*Contains missing data (10.3%) where smoking status was not recorded in the General Practice Research Database.
PMR, polymyalgia rheumatica.

of PMR could be validated in 3318 individuals who had received suitable steroid prescriptions and were matched to a total of 13 016 individuals without PMR (figure 1). After exclusion of those with a diagnosis of cancer before the date of their PMR diagnosis, 2877 individuals with a PMR diagnosis and 9942 without PMR were available for analysis.

Assuming a 5% significance level and a 20% cancer diagnosis rate over the course of the study, this sample size gives almost 97% power to detect a HR of 1.2 in a 1 : 4 matched sample.

As would be expected from the matched nature of the design, those with PMR were of similar age and sex to those without (table 1), although ever having smoked was more common in those with PMR (44.1% vs 41.7%).

Over the course of the study the median follow-up time was 7.8 years (IQR 3.4, 12.3). Cancer developed in 667 (23.2%) of those with PMR and 1938 (19.5%) of those without PMR over the follow-up period. This association is shown graphically in figure 2. There was a significant interaction between PMR status and time, meaning that the association between PMR and cancer was different in each time period (table 2). There was no evidence that the association between PMR status and cancer varied by age group, sex or smoking status. In the final model, residual checks indicated no violation of the assumption of proportional hazards.

Those with PMR were significantly more likely to develop cancer than those without the condition during the first 6 months after diagnosis (adjusted HR (95% CI): 1.69 (1.18 to

2.42)) (table 2). After this time, no statistically significant association was seen and although the CIs were wide, point estimates were close to the null value of 1.

Owing to small numbers, it is not possible to formally compare the rates of each type of cancer in the first 6 months in those with and without PMR. However, it appears that there was an increase in the rates of cancers of the prostate and lymph nodes (table 3). There is also a suggestion that there may be higher rates of cancers affecting the blood and female reproductive organs in those with PMR.

DISCUSSION

This study found a 69% increased risk of a cancer diagnosis within the first 6 months after a PMR diagnosis. It could not be established whether or not the risk in PMR was different from that of controls, beyond this point. No strong evidence was found to suggest what types of cancer are seen in patients diagnosed with PMR during these 6 months, though data suggested an excess of cancers of the genitourinary, lymphatic, haematological and nervous systems.

Prospective studies of the association of PMR and GCA with cancer are beginning to emerge. The emphasis in these studies is often on GCA, a condition that overlaps with PMR in about 25% of cases.²¹ Most of these studies were unable to definitively show whether or not there was an association between PMR/GCA and cancer,^{11–13} although they have tended to be small and to focus on patients with GCA. Ji *et al*¹⁰ conducted the largest study, comparing 36 918 people in Sweden hospitalised with PMR or GCA with population controls and, as in our study, found no increased risk of cancer in the long term, but an excess of cancer diagnoses within the first year. Kermani *et al*¹¹ also found a similar, but non-significant, trend suggestive of an early excess of cancer in patients with a primary diagnosis of GCA in secondary care.

Our study is the largest community sample to date with anonymised individual patient data available. This allowed those with PMR to be matched with similar patients without the disease, more accurately accounting for the potentially confounding factors of age and sex than in the Swedish study of

Figure 2 Kaplan–Meier plot of the association between time from polymyalgia rheumatic (PMR) diagnosis and diagnosis of cancer. Truncated at 15 years.

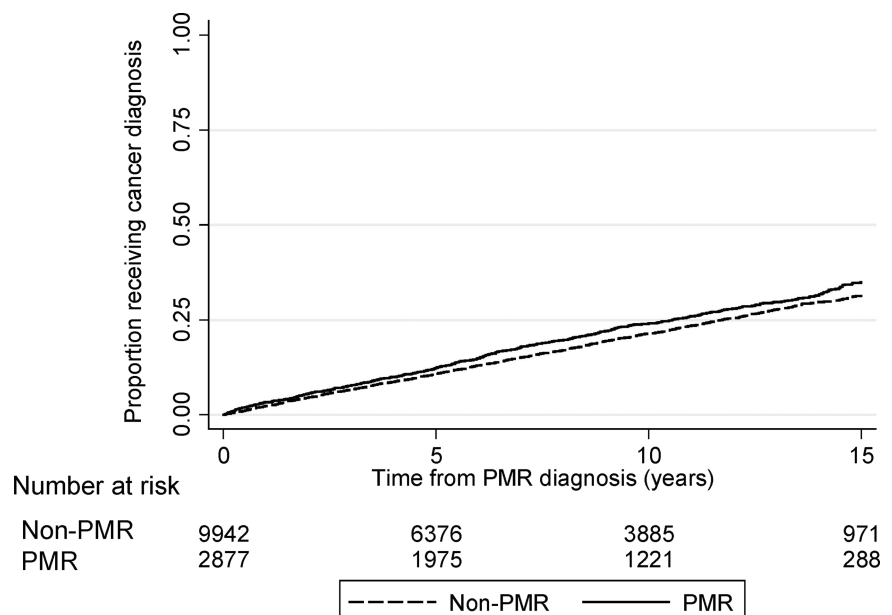


Table 2 Association between PMR exposure and all cancer diagnoses, by time period

	Cancer diagnoses per 1000 person years		HR (95% CI)	
	PMR	No PMR	Unadjusted	Adjusted*
0–6 months (n=159)	38.9 (29.9 to 50.7)	21.4 (17.6 to 25.9)	1.82 (1.31 to 2.52)	1.69 (1.18 to 2.42)
6–12 months (n=154)	27.9 (20.3 to 38.3)	25.0 (20.8 to 29.3)	1.12 (0.78 to 1.61)	1.03 (0.70 to 1.51)
1–2 years (n=263)	23.6 (18.4 to 30.3)	23.2 (20.2 to 26.6)	1.02 (0.76 to 1.35)	1.04 (0.77 to 1.40)
2–5 years (n=559)	24.6 (21.1 to 28.7)	22.0 (20.6 to 24.5)	1.10 (0.92 to 1.31)	1.04 (0.86 to 1.26)
5–10 years (n=866)	29.0 (25.5 to 33.0)	25.2 (23.3 to 27.2)	1.15 (0.99 to 1.34)	1.11 (0.95 to 1.30)
>10 years (n=504)	28.8 (24.1 to 34.4)	27.9 (25.3 to 30.9)	1.03 (0.84 to 1.27)	1.00 (0.82 to 1.23)

*Adjusted for age, gender and smoking status.
PMR, Polymyalgia rheumatica.

Ji *et al.*¹⁰ It also allowed testing for confounding by smoking history. However, as with many database studies, we were only able to consider basic demographic information and specific clinical diagnoses entered into the medical record, as more descriptive information, such as measures of disease activity are often not recorded.

Although a proportion of those with PMR in this study went on to develop the related condition of GCA, or other rheumatological conditions such as RA, exclusion of these patients from the study sample did not change our results.

Other studies have successfully used the GPRD to identify patients with cancer.¹⁸ However, the GPRD comprises data collected in routine practice and can be vulnerable to delays, omissions and miscoding. Such failings, however, are likely to be similar in both groups in this study. It might be argued that the inclusion of the need for a corticosteroid prescription in the definition of PMR in this study altered the PMR–cancer association, either through masking or accentuating it. However, reanalysis of the data without this criterion did not alter the overall finding of an increase in cancer diagnoses in the early period after PMR diagnosis and no evidence of a long-term association. Although a previous study has described an increased risk of some skin cancers in patients receiving long-term corticosteroids,²² we think that the increased risk of all cancers in our study is unlikely to be explained by the use of

steroids, for a number of reasons. First, if steroids were responsible for this increase, it would probably persist beyond 6 months. Second, around a third of individuals in the study of Sørensen *et al.*²⁰ received stronger corticosteroids (betamethasone, triamcinolone) than the prednisolone received in our study and third, although based on small numbers, our data suggest that skin cancers occurred at very similar rates in the first 6 months after PMR diagnosis in our study.

The increased rate of cancer within the first 6 months after diagnosis of PMR might occur for several reasons; the most obvious of which is misdiagnosis. The difficulty in diagnosis of PMR is recognised in recent guidelines from the British Society for Rheumatology,² which cite active cancer as a core exclusion criterion. However, there is some evidence that systemic inflammation, as indicated by raised levels of C-reactive protein, may increase the risk of subsequent colon cancer (eg, Tsilidis *et al.*²³), although evidence for this in other cancers is lacking.²⁴ Furthermore, Ji *et al.*¹⁰ in agreement with our study, noted an increase in lymphatic and haematopoietic cancers, which might suggest a dysregulated immune system as a potential common cause of both PMR and these cancers. However, it seems unlikely that these biological factors would have such a time-limited effect. From these data, it is not possible to reach a conclusion about why there is an early increase in the diagnosis of cancer in those with PMR. More data are needed to clearly

Table 3 Rates of cancer diagnosis by anatomical system in the first 6 months after PMR diagnosis

Cancer diagnosis	PMR		No PMR	
	n	Rate per person-year (95% CI)	n	Rate per person year (95% CI)
Gastrointestinal	7	0.19 (0.09 to 0.40)	18	0.18 (0.12 to 0.29)
Skin	13	0.15 (0.09 to 0.26)	28	0.13 (0.09 to 0.19)
Prostate	5	0.26 (0.11 to 0.63)	4	0.07 (0.03 to 0.19)
Lung	5	0.28 (0.12 to 0.68)	13	0.28 (0.16 to 0.48)
Breast	3	0.13 (0.04 to 0.41)	9	0.10 (0.05 to 0.20)
Female reproductive	3	0.75 (0.24 to 2.34)	7	0.31 (0.15 to 0.64)
Blood	3	0.70 (0.23 to 2.18)	3	0.35 (0.11 to 1.07)
Lymphoma	1	3.32 (0.47 to 24.0)	1	0.09 (0.01 to 0.64)
Urinary tract	3	0.36 (0.12 to 1.12)	4	0.17 (0.07 to 0.46)
Nervous system	2	2.14 (0.54 to 8.57)	0	0.0*
Other†	10	0.36 (0.19 to 0.66)	17	0.36 (0.19 to 0.66)

*CI could not be estimated, as no nervous system cancers were recorded in the non-PMR group.

†Coding did not allow allocation of cancer to a body system. Examples include codes for 'Cancers', 'Malignant neoplasm of other and unspecified site', 'Disseminated malignancy not otherwise specified (NOS)'.

PMR, polymyalgia rheumatica.

delineate the types of cancer concerned, which might help to elucidate the reason for this association and lead to improved management strategies.

In the absence of a 'gold standard' diagnostic test and symptoms that are often vague and non-specific, making an accurate diagnosis of PMR in the community is challenging. Clinicians need to be aware of the possibility of alternative diagnoses, including cancer, and carefully monitor those diagnosed with PMR, especially in the months after the initial diagnosis, for management and surveillance for the development of cancer.

Contributors SM obtained funding for the study, managed the data, carried out data analysis, interpreted the findings, wrote the first draft of the paper and approved the final submitted draft. SLH conceived the idea for the study, obtained the data, interpreted the findings, critically revised the manuscript and approved the final submitted draft. JB advised on data management and analysis, critically revised the manuscript and approved the final submitted draft. TH, CDM conceived the idea for the study, interpreted the findings, critically revised the manuscript and approved the final submitted draft.

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Competing interests None.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement This study was conducted within the General Practice Research Database. Therefore, there are no unpublished data.

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