EXTENDED REPORT

Do steroids increase lymphoma risk? A case-control study of lymphoma risk in polymyalgia rheumatica/giant cell arteritis

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Background: Recent studies indicate increased risks of malignant lymphomas among individuals treated with corticosteroids, but have not taken into account the underlying reasons for steroid use, so the increased risks might be attributable to the underlying disease or concomitant treatments other than steroids. Polymyalgia rheumatica (PMR) and temporal arteritis (giant cell arteritis, GCA) are common inflammatory conditions treated with steroids as single immunosuppressive therapy, but data on lymphoma risk in GCA/PMR are limited.

Objective: To assess the risk of lymphoma associated with steroid treatment of GCA/PMR.

Methods: The association between GCA/PMR and malignant lymphomas (overall, and separately for non-Hodgkin lymphoma, Hodgkin lymphoma, and chronic lymphatic leukaemia) was examined in a nationwide, population based, case-control study of 42 676 lymphoma cases and 78 487 matched population controls, using prospectively recorded data on lymphomas from the Swedish cancer register 1964–2000 and data on pre-lymphoma hospital admissions for GCA/PMR from the Swedish inpatient register 1964–2000. Odds ratios (OR) associated with a pre-lymphoma hospital admission for GCA/PMR were calculated using conditional logistic regression.

Results: 153 lymphoma cases and 345 population controls had a history of GCA/PMR, resulting in an overall OR for malignant lymphomas of 0.81 (95% confidence interval, 0.67 to 0.98). The OR varied little with lymphoma type, sex, age, and calendar period. The OR for GCA was 0.67 (0.48 to 0.98) and for PMR, 0.83 (0.67 to 1.04).

Conclusions: Treated GCA is not associated with increased lymphoma risks, which suggests that even at considerable cumulative doses, steroids may not appreciably increase lymphoma risk.

Because of their pronounced anti-inflammatory properties, glucocorticoids ("steroids") belong to the most widely used drugs worldwide. Consequently, reports of their putative malignant side effects have public health implications and warrant serious attention. It is therefore of concern that a clear majority^{1–4} of all case-control studies^{1–6} that have included an assessment of the association between steroids and risk of malignant lymphomas, and a recent cohort study using a population based prescription database,⁷ have reported that steroid use is accompanied by increased lymphoma risks, with doubled risks in individuals reporting "long" duration of steroid treatment (more than two months,² more than 10 prescriptions,⁷ or not defined³). Common to all above studies, however, is the inability to take into account the conditions necessitating steroid treatment. Steroids are often used in the treatment of autoimmune or inflammatory conditions, many of which carry an increased lymphoma risk per se or through treatment with other potentially lymphoma inducing immunosuppressive drugs.^{8–15} This methodological problem is not trivial, and may even account for the observed dose-response-like association between steroids and lymphoma risk.^{4–7} Along with limited power and little information on treatments beyond a few months, such uncontrolled confounding by indication therefore hampers the interpretation of past studies. One way to reduce bias resulting from confounding by indication of an undefined array of underlying conditions and concomitant treatments is to assess the lymphoma risk in patients with a single medical condition, for which steroids have been the single therapy in homogeneous and clinically relevant dosages, and in which the duration of daily steroid use exceeds a few months.

Because of the dramatic effects of steroids in polymyalgia rheumatica (PMR) and giant cell arteritis (GCA), oral steroids—typically between 10 and 100 mg of prednisone daily tapered over one to two years—have long been the approved treatment of choice, with close to 100% of diagnosed individuals put on steroids as single immunosuppressive therapy.^{16–17} Cumulative doses above 10 g are not infrequent. Treatment with other immune suppressants is less effective and rare.^{16–18} GCA/PMR thus constitutes a near ideal proxy marker for considerable exposure to oral steroids in the absence of long standing inflammation of varying degree, as seen in, for example, rheumatoid arthritis, and in the absence of other immunosuppressive drugs. To assess the risk for lymphoma associated with steroids, we therefore undertook a population based nationwide case-control study of malignant lymphomas in relation to a history of GCA/PMR, taking advantage of the high quality Swedish health and census registers.

METHODS

Cases and controls

In the Swedish Cancer Register (with nationwide and nearly complete coverage^{19–20}) we identified as cases all individuals 50 years or older who were registered with a diagnosis of Hodgkin's lymphoma (HL), non-Hodgkin's lymphoma (NHL), or chronic lymphatic leukaemia (CLL) between 1964 and 1999, including information on dates of birth and

Abbreviations: CLL, chronic lymphatic leukaemia; GCA, giant cell (temporal) arteritis; HL, Hodgkin lymphoma; NHL, non-Hodgkin lymphoma; NSAID, non-steroidal anti-inflammatory drug; PMR, polymyalgia rheumatica

diagnosis of lymphoma, and sex. In the nationwide population register (the Swedish census register), two controls for each case were identified, matched on sex, year of birth, marital status (unmarried, married, widow), and county of residence at the year of lymphoma diagnosis in the case. After exclusion of cases and controls born outside Sweden, and of controls themselves diagnosed with lymphoma before their case, 42 676 cases and 78 487 controls remained (table 1). Through linkage with the register of total population, we also identified registered spouses of cases and controls up to the time of the diagnosis of lymphoma in the case.

Polymyalgia rheumatica/giant cell arteritis

Swedish inpatient care is public and population based. Referrals to hospital are based on geography rather than insurance or financial capacity. The Swedish Inpatient Register contains population based and individual information on inpatient care. Starting in 1964, the coverage encompassed 50% of all counties in the mid 1970s, and 100% since 1987.¹⁹ For each inpatient episode, information on discharge diagnoses (main and up to seven contributory diagnoses, coded according to the *International Classification of Diseases* (ICD)²¹) are recorded, together with the national registration number (NRN), a 10 digit number unique to each Swedish resident and recorded in all health and census registers.²² In this register, we identified all hospital discharges including discharge dates listing GCA/PMR (temporal arteritis ICD7: 456.00 ICD8: 446.30 ICD9: 446F ICD10: M31.6; polymyalgia rheumatica ICD8: 446.38, ICD9: 725 ICD10: M31.5) among cases and controls, and among their spouses.

Statistics

The relative risk of malignant lymphoma associated with GCA/PMR was expressed as odds ratios (OR), derived from conditional logistic regression (to account for the matched design) using PROC PHREG in SAS[®]. Personal history of GCA was assessed for cases and controls up until one year before the diagnosis of lymphoma in the index case (in order to reduce bias from misdiagnosis and reversed causality), and stratified according to time between the first discharge listing GCA/PMR and lymphoma diagnosis (1–4, 5–9, 10+ years), age at first discharge listing GCA/PMR (50–74, 75+ years), age at lymphoma diagnosis (50–74, 75+ years), calendar period of GCA/PMR (<1979, 1980–1999), decade of lymphoma diagnosis (1965–1979, 1980–1989, 1990–1999), and sex. To evaluate the significance of environmental factors

that could confound a statistical association between a personal history of GCA/PMR and lymphoma, we also calculated odds ratios for malignant lymphoma associated with having a spouse admitted to hospital with GCA/PMR.

RESULTS

Overall, 153 cases (0.4%) and 345 controls (0.4%) had been admitted to hospital with GCA/PMR one year or more before the lymphoma diagnosis in the index case, corresponding to a statistically significant 19% reduced risk (OR = 0.81 (95% confidence interval (CI), 0.67 to 0.98). The odds ratio varied little with time between the first discharge listing GCA/PMR and the lymphoma diagnosis (0.79 < OR < 0.87), calendar periods of GCA/PMR discharge (0.78 < OR < 0.88), age at GCA/PMR (OR 50–74 years = 0.84 (95% CI, 0.65 to 1.08); OR 75+ years = 0.78 (0.58 to 1.03)), age at lymphoma (OR 50–74 years = 0.95 (0.67 to 1.37); OR 75+ years = 0.76 (0.60 to 0.95)), and sex (ORs for males and females both = 0.81). The numbers of discharges and the distributions of time between first GCA/PMR discharge and lymphoma diagnosis were similar in cases and controls (data not shown). When stratified according to disease, the odds ratio for temporal arteritis (OR = 0.67 (0.48 to 0.98)) appeared somewhat lower than that for polymyalgia rheumatica (OR = 0.83 (0.67 to 1.04)). When the outcome was stratified according to lymphoma subtype, the odds ratios were essentially similar for NHL, HL, and CLL (table 2). In analyses from which all cases and controls who also had a registered discharge diagnosis of rheumatoid arthritis were excluded, the odds ratio remained similar (OR = 0.82 (0.67 to 1.00)). Having a spouse admitted to hospital with GCA/PMR was neither associated with any altered lymphoma risk overall (OR = 1.09 (0.88 to 1.35)) nor with lymphoma type (table 2). The odds ratio for spouses' PMR (1.09) was similar to that of spouses' GCA (1.10).

DISCUSSION

Despite GCA/PMR being one of the most common rheumatic inflammatory diseases in the general population, and the fact that several other inflammatory diseases have been linked to increased lymphoma risk, the occurrence of cancer—including malignant lymphomas—following GCA/PMR has been little studied apart from the follow up of groups of patients too small (n = 50–400) to allow proper assessment of lymphoma risk.^{23–28} Our large, population based, nationwide case–control study resting on prospectively recorded data suggests that neither PMR nor GCA is associated with any increased short or long term occurrence of malignant lymphomas. Instead, we unexpectedly observed a moderate but statistically significantly 19% reduced lymphoma risk associated with GCA/PMR. Importantly, from a public health point of view, this unremarkable occurrence of lymphomas has wider implications. Because of the uniform and single treatment of GCA/PMR with steroids, our results imply that daily oral corticosteroids in moderate to high cumulative doses over one to three years do not increase the occurrence of malignant lymphomas.

Steroids have been implicated in lymphoma development in several recent moderate sized case–control studies of NHL,^{1–4} (although exceptions exist^{5–6}) and in a recently published cohort study from a prescription database.⁷ Inference on causality of the reported associations between steroids and lymphomas is, however, hampered by the lack of information on the underlying conditions necessitating treatment with steroids. Indeed, the chronic conditions (for example, rheumatoid arthritis, systemic lupus erythematosus, post-transplantation) that may lead to the highest cumulative doses of steroids are often—in themselves or through treatment with immunosuppressive drugs—associated with an increased occurrence of lymphomas.^{8–15} In

Table 1 Number of cases with malignant lymphoma diagnosed in Sweden 1964–2000, and their matched controls

	Cases	Controls
Overall	42 676	78 487
Sex		
Male	23 994	44 156
Female	18 682	34 331
Age at lymphoma diagnosis		
50–74	26 363	48 702
75+	16 312	29 783
Type of malignant lymphoma*		
Hodgkin's lymphoma	4 037	7 394
Non-Hodgkin's lymphoma	28 355	52 164
Chronic lymphocytic leukaemia	10 555	19 391
Year of lymphoma diagnosis		
1964–1979	14 147	26 042
1980–1989	13 282	24 722
1990–2000	15 247	27 723
Number of identified spouses	31 758	58 458

*Numbers exceed total because of overlap.

Table 2 Number of cases and controls with a personal or spouse's history of temporal arteritis or polymyalgia rheumatica, with corresponding odds ratios and 95% confidence intervals

Outcome												
Exposure												
GCA/PMR												
Case	Cont	OR (95% CI)	Case	Cont	OR (95% CI)	Case	Cont	OR (95% CI)				
Personal history												
Overall*	153	345	0.81 (0.67 to 0.98)	114	256	0.82 (0.65 to 1.02)	5	21	0.42 (0.16 to 1.14)	35	72	0.89 (0.59 to 1.32)
GCA	42	112	0.67 (0.48 to 0.98)	29	85	0.63 (0.41 to 0.96)	2	6	0.55 (0.11 to 2.76)	11	21	0.96 (0.46 to 1.99)
PMR	114	250	0.83 (0.67 to 1.04)	88	187	0.86 (0.67 to 1.11)	3	15	0.38 (0.11 to 1.33)	24	52	0.83 (0.51 to 1.36)
Spouse's history												
Overall	132	220	1.09 (0.88 to 1.35)	86	153	1.01 (0.77 to 1.31)	9	19	0.84 (0.38 to 1.87)	37	56	1.24 (0.81 to 1.89)
Data stratified by lymphoma type (all lymphomas, HL, NHL, CLL), type of history (personal or spouse's), and (personal history only) type of exposure (Overall, GCA, PMR). *Sum of GCA and PMR exceeds "Overall" as some patients had both diagnoses. CI, confidence interval; CLL, chronic lymphatic leukaemia; Cont, control; GCA, giant cell (temporal) arteritis; HL, Hodgkin lymphoma; NHL, non-Hodgkin lymphoma; OR, odds ratio; PMR, polymyalgia rheumatica.												

contrast, GCA/PMR can typically be brought into remission by steroids, and although relapses may occur during tapering of the steroids, GCA/PMR typically subsides after a few years of treatment with steroids as single therapy.

During the entire study period, oral steroids have represented the drug of choice in the treatment of GCA/PMR.^{16 17} Doses and duration of treatment may vary but add up to a minimum of one year of treatment/3 grams of prednisone, and often reach two years of treatment or more than 10 grams of prednisone, particularly during the decades covered by our study (1964 to 2000). Accordingly, although we lacked individual data on steroid exposure, few if any of our individuals with GCA/PMR may have been exposed to less than 3 grams of steroids. Our observation of a 20–30% significant decrease in risk of malignant lymphomas in GCA/PMR therefore strongly suggests that oral steroids do not increase lymphoma risk. One should not uncritically generalise our results to all settings in which steroids are used, including the partial suppression of inflammation in rheumatoid arthritis. The absence of risk increase associated with steroids in our study is, however, in line with findings from ongoing studies of rheumatoid arthritis, although in this group steroids have not been studied in the absence of disease modifying antirheumatic drugs and the underlying chronic rheumatoid disease.^{29 30} Although we could not separate any effects of GCA/PMR from the effects of steroids, the proposed doubling of lymphoma risk associated with steroids⁷ would only be compatible with our odds ratio of 0.81 if untreated GCA/PMR by itself were somehow associated with a lymphoma risk that was reduced by two thirds or more, which must be considered highly unlikely. Only a small fraction of our patients with GCA/PMR (fewer than 10%) will ever have received immunosuppressive treatment in addition to steroids,^{16 18} but some may have used non-steroidal anti-inflammatory drugs (NSAID) as symptom control. Most previous studies of NSAIDs have, however, either observed no risk increase^{1 3} or an increased lymphoma risk,^{2 4 31} although there are exceptions.⁵ We therefore consider co-medication unlikely to explain our results.

A particular strength of our study is its nationwide and population based setting, which provided the by far hitherto largest study population for the assessment of steroid associated lymphoma risks. The design allowed assessment of long term effects, changes in the association over calendar periods of GCA/PMR or lymphoma diagnosis, and permitted risk assessments not only for NHL, but also for HL and CLL. Within the framework of our study, we did not have access to tissue specimens to validate the lymphoma diagnoses. Despite this, we consider misclassification of lymphomas to be low. In an ongoing case-control study of 378 lymphomas registered at the Cancer Register among patients with rheumatoid arthritis, only 2% of the registered lymphomas turned out to be incorrect upon validation.³⁰ With respect to GCA/PMR, the overall diagnostic validity of the Swedish Inpatient Register is around 90%.¹⁹ Validations of the discharge diagnoses of, for example, rheumatoid arthritis and Wegener's granulomatosis indicate an overall validity close to 90% for these diagnoses as well.^{30 32 33} We were unable to validate the diagnoses of GCA/PMR among cases and controls in our study. However, any misclassification of GCA/PMR is likely to affect cases and controls equally and would therefore result in a bias towards 1.0, and thus cannot explain our significantly reduced risks. To reduce the risk of reversed causality, we excluded GCA/PMR during the last year before lymphoma diagnosis. Inclusion of this year resulted in a virtually unchanged odds ratio for temporal arteritis and an odds ratio for polymyalgia rheumatica of 1.0 (data not shown).

The incomplete ascertainment of GCA/PMR (no information on GCA/PMR occurring before the start of the inpatient register in each county) applied equally to cases and controls,

who were matched for geography, and does not in itself introduce measurable bias. Patients with symptoms suggestive of polymyalgia rheumatica may go on to develop rheumatoid arthritis. Whereas erroneous inclusion of such misdiagnosed rheumatoid arthritis might have biased our odds ratios, we observed almost no change in the odds in analyses from which cases and controls who also had a discharge listing of rheumatoid arthritis had been removed.

Our results apply to patients who had been admitted to hospital with GCA/PMR at some time. Although many patients with PMR/GCA are never admitted to hospital, we think it unlikely that the observed associations would be different in patients who were not admitted to hospital, as these would be likely to have less severe disease and to receive lower doses of steroids. In any case, the requirement for hospital admission applied equally to cases and controls.

In contrast to previous questionnaire based case-control studies, our design rules out recall bias. Although adjustment for confounding was difficult, few risk factors for GCA/PMR and malignant lymphomas are established. The matched design and analysis ensured adjustment for the effects of sex, age, marital status, area of residence, and calendar period. Some studies have described a cyclic onset of GCA/PMR,^{34, 35} and an infectious aetiology has been proposed.³⁶ To assess any possible effects of such environmental exposures or undefined lifestyle factors that may have confounded an individual association between GCA/PMR/steroids and lymphoma, we included assessments of the spouses' history of GCA/PMR, as spouses tend to share lifestyle and environmental exposures, only to find associations close to 1.0.

In conclusion, the results of our nationwide case-control study suggest that neither treated GCA/PMR nor the corticosteroids used as its treatment increases lymphoma risk.

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