Polymyalgia rheumatica (PMR) and temporal arteritis (TA) are common disorders in the elderly. In both conditions, the etiology is unknown, but inflammation of medium and large size arteries is characteristic of TA, while in PMR muscular and periarticular manifestations predominate. Malignant disorders may be associated with musculoskeletal symptoms or vasculitic syndromes. In some case reports, malignant disease presented as polymyalgia mimicking PMR or malignancy was discovered later in the course of PMR. However, no definite association between PMR and malignancy has been established. In biopsy proven TA, an increased risk of malignancy was found in one prospective controlled study, but other reports did not show enhanced susceptibility to malignancy in TA. Moreover, we recently found no difference in total mortality in patients with TA compared to population controls, suggesting no relationship between TA and fatal diseases such as cancer.

In this study we compared the prevalence and incidence of cancer in patients with PMR or TA with that of a matched control population in a prospective longitudinal study.

MATERIALS AND METHODS

In the county of Aust Ager, Norway, 338 patients with PMR or TA were enrolled in the period 1987–97 in a prospective population based study, as described. In addition, 60 cases were diagnosed at other departments in the same period, but were initially admitted to hospital for reasons not directly related to diagnosis of PMR or TA. Causes of referral included development of osteoporotic fractures due to treatment with corticosteroids and diagnostic evaluation of constitutional manifestations. All patients in the PMR group satisfied the criteria suggested by Bird, et al or those of Hamrin. Also, most patients with PMR fulfilled the criteria proposed by Chuang, et al. For TA, the American College of Rheumatology criteria were employed, but only those with histologically proven temporal arteritis were included. Patients with malignancy or cancer discovered around the time of the diagnosis of PMR or TA were included if the diagnostic criteria were satisfied. Cases with PMR and a positive temporal biopsy either at the time of diagnosis or later in the course of the disease were denoted PMR/TA. As there were no differences regarding age, sex, and occurrence
of malignancy between the 338 incident cases of PMR or TA and the 60 patients found by reviewing hospital records, all patients were regarded as one group, a total of 398 patients (Table 1).

From the Central Population Registry in Norway, all 398 patients were each randomly assigned 4 sex matched controls from the same county. The controls were born in the same year and month as the index case and were alive at the time of diagnosis of the index case.

The patients and their controls were cross-checked with the data files at the Cancer Registry of Norway. This registry includes all cases of cancer registered in Norway from 1953. When the study was undertaken, the registration of cancers was complete to the end of 1998. Time of diagnosis and types and sites of cancers were registered for each case identified. Further, the time intervals from diagnosis of malignant neoplasm to inclusion in the study (i.e., the date of diagnosis of PMR or TA), and from inclusion to diagnosis of cancer, were calculated. For subjects (12 patients and 40 controls) with 2 or more cancers, only the characteristics of the first detected neoplasm were used in the analysis. The followup thus started when diagnosis of PMR and/or TA was made and ended when the first cancer was diagnosed, or the patient died, or at end of followup at December 31, 1998. In the calculation of incidence, patients with cancer diagnosed prior to inclusion and their controls as well as all population controls with cancer detected before inclusion were excluded.

Causes of deaths were registered for all cases and their controls in the same period through linkage with Statistics Norway. Approval of the study was obtained from the data protection agency of Norway (Data Inspectorate) and the Board of Health of Norway (Statens Helsetilsyn). Statistics. Chi-square test and Student t test were used to compare characteristics between patients and controls. When the odds ratios were estimated, a conditional logistic regression model was applied. Stratified Cox proportional hazard regression analyses were used to compare the incidence of cancer between patients and their age and sex matched controls, thereby taking the matching into consideration when computing relative risks (RR) estimates and 95% confidence intervals. The standard multivariate Cox proportional hazard model was used when we compared survival after a cancer diagnosis in patients with PMR or TA with survival after cancer diagnosis in population controls. P values less than 0.05 indicated significant results. All statistical analyses were carried out using the SAS system*

RESULTS

Patients. Altogether, 398 patients with PMR and/or TA (273 women, 125 men) were enrolled in the study. Sex and diagnostic subgroups are shown in Table 1. Three women diagnosed at other departments could not be definitely classified, as they all met diagnostic criteria for PMR, but TA was not appropriately evaluated. In one case, biopsy of the temporal artery was performed, but the histological description could not be found. At the end of the study period in 1998, 301 patients (75.6%) were still alive.

Controls. The matched controls numbered 1592 subjects (1092 women, 500 men). At the end of the study period, 1106 of the controls (69.5%) were alive.

Prevalence of cancer. Malignancy was registered in 32 patients (8.0%) and 153 controls (9.6%) before inclusion in the study (Table 2) (OR 0.82, 95% CI 0.55–1.22, p = 0.3).

In cases with cancer prior to PMR or TA, the time until inclusion in the study was 8.4 years on average (range 17 weeks to 33.5 years) in patients and 9.4 years (2 weeks to 39.5 years) in controls. The difference was not statistically significant (p = 0.5).

Incidence of cancer. A total of 366 patients and 1324 controls were enrolled in the incidence study of malignancy discovered after diagnosis of PMR or TA. The patients were followed for a total of 2596 person-years and their controls for 9391 person-years. As shown in Table 2, malignant neoplasms were diagnosed in 34 patients (9.3%) compared to 143 controls (10.8%) after inclusion. Among women, there were 19 patients (7.5%) and 83 controls (9.1%) with cancer. In men, cancers were discovered in 15 patients (13.4%) and 60 controls (14.5%). The relative risk of cancer in patients was 0.86 (95% CI 0.59–1.26, p = 0.4) compared to controls. Patients with biopsy proven TA with or without PMR had a relative risk of cancer of 1.48 (95% CI 0.65–3.40, p = 0.4) compared to controls. In patients with PMR only, the relative risk of cancer was 0.75 (95% CI 0.47–1.16, p = 0.2). Patients with positive biopsy had a relative risk of cancer of 1.40 (95% CI 0.63–3.12, p = 0.4) compared to patients with PMR only.

Age at inclusion and the time interval from inclusion to diagnosis of malignant neoplasm. In patients whose malignant neoplasms were discovered after inclusion, the mean age at the time of diagnosis of PMR or TA was 73.1 (SD 7.3) years (60–84 yrs) compared to 71.7 (SD 7.2) years (51–91 yrs) in patients without cancer. The difference was not statistically significant (p = 0.3).

The interval from diagnosis of PMR or TA to diagnosis of malignant neoplasm was on average 3.8 (SD 2.7) years (7 weeks–12.2 yrs) in controls who contracted cancer. The difference was statistically significant (p = 0.001).

Table 2. Number (%) of cases with malignant neoplasms in patients before and after diagnosis of PMR or TA and in controls.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Before Inclusion</th>
<th>After Inclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients</td>
<td>Controls</td>
</tr>
<tr>
<td>PMR</td>
<td>25 (7.9)</td>
<td>127 (10.1)</td>
</tr>
<tr>
<td>TA</td>
<td>5 (9.3)</td>
<td>17 (7.9)</td>
</tr>
<tr>
<td>PMR/TA</td>
<td>2 (7.7)</td>
<td>9 (8.7)</td>
</tr>
<tr>
<td>Not classified</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Total</td>
<td>32 (8.0)</td>
<td>153 (9.6)</td>
</tr>
</tbody>
</table>

*Thirty-two patients with cancer diagnosed before inclusion and their controls (n = 128, including 13 controls with cancer prior to inclusion), as well as remaining controls with cancer detected before inclusion (n = 140) were excluded from calculation of incidence.
differences in intervals between patients and controls were not statistically significant (p = 0.4). The proportion of patients with PMR or TA and population controls who are free of cancer during followup is illustrated in Figure 1.

Types and localization of malignant neoplasms. No significant differences in types and localization of malignant neoplasms were found between patients and controls. Cancers in colon and rectum were discovered in 6 (1.5%) patients (3 cases diagnosed after inclusion) compared to 44 (2.8%) cases among the controls (22 cases diagnosed after inclusion) (p = 0.2). The localization of the malignant neoplasms was similar in subjects diagnosed with cancer before and after diagnosis of PMR or TA (Table 3). A total of 2 cases of hematological malignancy were reported in the patients and 11 in controls. Apart from patients with cancer in the prostate, no clustering of cases near inclusion was found. However, 5 of 16 patients (31%) with prostate cancer were discovered in the period from 6 months before to one year after inclusion, compared to 3 out of 39 cases (8%) in the controls (p = 0.04).

Survival in cases with malignant neoplasms diagnosed after inclusion. Among incident cancer cases (34 patients, 143 controls), 7 patients (20.6%) and 51 controls (35.7%) died of cancer during the followup through 1998. After adjusting for age at inclusion and sex, Cox proportional hazards regression analysis may suggest a better survival of cancer in our patients than in population controls (RR 0.46, 95% CI 0.21–1.02, p = 0.05).

DISCUSSION

The 2 comprehensive public registries in Norway (the Central Population Registry and the Cancer Registry) provide excellent opportunities to identify cases with malignancy in a cohort of a defined geographic region. Further, the design of this study allowed us to follow a population of patients from a county with a high incidence of PMR or TA, and in the observation period no patient or control was lost. Thus, the design of the study and the characteristics of the population evaluated offered unique opportunities to determine the true incidence of malignancy in PMR and TA. On the other hand, patients enrolled and regularly controlled in a hospital based study seem more likely to undergo extensive tests and examinations. Consequently, serious diseases such as cancer are probably discovered more rapidly in such patients. In a prospective study like the present one, it was up to the population controls themselves to establish contact with a general practitioner if symptoms or signs of illness appeared. With regard to referral for more comprehensive examinations and diagnosis of diseases such as cancer, a delay in the final diagnosis is expected and cases with malignant neoplasms might remain undiagnosed. Thus, in this study there existed a risk of overestimating the incidence of cancer in the patient population compared to controls. However, the incidence of cancer in the PMR/TA patients was, if anything, lower than in controls.

We found no increased frequency of cancer in patients with PMR or TA compared to population controls. This is in agreement with the low number of cancers discovered in earlier followup studies. A 2.35-fold higher risk of cancer was found in patients with a positive temporal artery biopsy compared to controls. In these patients, the authors also found a hazard rate of cancer 4.40 times higher than the rest of the patients studied. This is in contrast to our findings, where the relative risk of cancer in biopsy proven TA or PMR/TA was 1.48 (95% CI 0.65–3.40) compared to their controls. Moreover, in patients with positive biopsy we found a relative risk of cancer of 1.40 (95% CI 0.63–3.12) compared to patients with negative biopsy or where biopsy was not taken (i.e., PMR). The difference in the risk of cancer within patients might be explained by a combination of a higher frequency of cancer in patients with biopsy proven TA and a smaller number of cancers in patients with PMR in the study of Haga and coworkers. In that study, the patient population was based on medical records from 2 hospitals, in contrast to our study based on...
cases selected from general practitioners. In general, subjects with symptoms of serious diseases have a greater chance of being referred to hospital and undergo comprehensive examinations such as biopsy of the temporal artery than cases with milder disease. Thus, important differences in study design might explain the contradictory results in the 2 surveys. In Southern Europe, where the incidence of PMR and TA is much lower, cases of cancer presenting with PMR-like manifestations have been described. However, in that part of Europe the mortality of isolated PMR was similar to the control population. This was also the case when mortality in patients with biopsy proven giant cell arteritis, with or without associated PMR, was assessed.

In TA, associations with leukemia, lymphoma, Waldenstrom’s macroglobulinemia, and lung cancer have been suggested. Furthermore, symptoms resembling PMR have been described in metastatic cancers, myeloma, lymphoma that later transformed into subsequent acute lymphoblastic leukemia, and in renal cell carcinoma and thyroid carcinoma before surgical removal of the tumor. In PMR, followup studies have described a wide range of malignant neoplasms mainly developing long before or after the diagnosis of PMR. Thus, it is unlikely to consider PMR as a paraneoplastic syndrome, but evidently many types of cancer may present with polymyalgic symptoms.

We found no differences in types and sites of malignant neoplasm between patients and controls. However, among men there was a clustering of patients with cancer in the prostate close to the time of inclusion. Among these 5 patients, only one had symptoms from the urinary system at the time of inclusion resulting in further examination. In the other cases, referral to a department of urology was done by the general practitioners. Thus, the simultaneous manifestation of cancer in the prostate seemed to be coincidental, and is conceivably not explained by improved medical surveillance.

Finally, no tendency to increased frequency of cancer throughout the observation period appeared in patients compared to controls (Figure 1). The interval from diagnosis of PMR or TA to diagnosis of cancer was on average 3.8 years, and this may speak against previous suggestions of these diseases representing paraneoplastic disorders. As PMR and TA are relatively low prevalence diseases, and due to the paucity of cancer in our patients, we have limited statistical power to detect statistically significant differences in cancer prevalence and incidence between our patients and the controls. It may, however, be argued that the 95% confidence intervals do indicate that a clinically significant increased cancer risk is rather unlikely.

No differences in frequencies and types of malignant neoplasms between patients with PMR or TA and population controls were found in this study. Thus, neither PMR nor TA as defined by present diagnostic criteria appears to be associated with cancer in general. However, cancer by itself may present with polymyalgic manifestations and the older ages of patients with PMR and TA should always alert the clinician to the possible coexistence of malignancy. It is the experience of many rheumatologists that patients with biopsy negative TA and cases with inadequate responses to corticosteroid are those at highest risk of having a concomitant malignant disease.

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REFERENCES