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Incidence of cancer in a cohort of patients with primary Sjögren's syndrome

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***Objective*. To compare the incidence of subsequent cancers in a cohort of patients with primary Sjögren's syndrome (pSS) with that of the general population in the same region of England.**

***Methods*. A retrospective analysis was carried out on 112 patients who had attended the out-patients department at University College Hospital, London, from 1979 onwards. Patients were followed up from diagnosis of pSS to diagnosis of first subsequent cancer, death, loss to follow-up or 31 December 2003 (the censoring date) to determine the person-years at risk for each individual. The expected numbers of subsequent cancers were calculated from sex-/age-/period-specific rates for the general population of southeast England, derived from registrations at the Thames Cancer Registry. Standardized incidence ratios (SIRs) were then calculated as the ratio of observed to expected numbers of cancers, along with 95% confidence intervals (CIs). Separate analyses were performed for all malignant cancers combined, lymphomas and non-lymphoid cancers.**

***Results*. Among the 112 patients with pSS, 25 developed cancer (either before or after development of pSS), with lymphoma occurring in 11 cases. Nine patients had two cancers. There was a significantly elevated incidence of lymphomas in pSS patients compared with the general population (SIR 37.5, 95% CI 20.7–67.6). For non-lymphoid cancer, the observed increase in incidence was small and not statistically significant (SIR 1.5, 95% CI 0.9–2.6).**

***Conclusion*. This study confirms that there is an increased incidence of lymphoma in patients with pSS. An increase in the incidence of other cancers was not proven but the observation that some patients developed more than one cancer raises the possibility that there may be a subgroup of patients who are at greater risk of developing cancer.**

KEY WORDS: Sjögren's syndrome, Cancer.

Cancer has long been associated with systemic autoimmune diseases. One of the earliest and most notable associations recorded was that of dermatomyositis with adenocarcinoma of the stomach [1]. Since then a number of other cancers have also been observed to occur at higher than expected frequencies in patients with systemic autoimmune diseases [2–4].

The high incidence of lymphoma in primary Sjögren's syndrome (pSS) was first reported in 1963 by Bunim and Talal [5] and has been verified in several studies since [6–8]. There have been case reports of other cancers, including solid organ tumours, also occurring in patients with pSS [9–12]. Moreover, one study investigating possible predictors of lymphoma development in pSS noted that those patients who develop a lymphoma appear to have a greater risk of developing a second malignancy [13]. However, to our knowledge no study has fully investigated the incidence of non-lymphoid cancers in pSS.

The present study sought to examine further the relationship between pSS and cancer by documenting the incidence of all malignancies in a cohort of patients with pSS and comparing it with the incidence in the general population. This study also investigated the relationship between medication used for pSS and the development of cancer.

Patients and Methods

All patients seen at University College Hospital (UCH), London, between 1979 and 2003 with a diagnosis of pSS, as confirmed by the European classification criteria of 1993 [14], were eligible for the study. Data recorded on each subject included date of birth, age at diagnosis of pSS and of any recorded cancer, and age at death if relevant. Patients were matched against the database at the Thames Cancer Registry (TCR), which records data on all cancer cases occurring in the 14 million resident population of southeast England, in an attempt to elicit further details. Exact dates of death and cancer diagnosis were taken from the TCR database for these matched patients. For non-matched patients, dates of cancer diagnosis were calculated as (date of birth + age at diagnosis + 6 months), i.e. the assumption was made that diagnosis occurred half-way through the recorded year. Likewise, date of death was calculated as (date of birth + age at death + 6 months) for non-matched patients. For all patients, a similar calculation was used to define the date of diagnosis of pSS. If a patient was lost to follow-up, it was assumed that this also happened half-way through the stated year.

Patients were followed up from diagnosis of pSS to diagnosis of first subsequent cancer, death, loss to follow-up or 31 December 2003 (the censoring date) to determine the person-years at risk for each individual, and the expected numbers of cancers were calculated from sex-/age-/period-specific rates for the general population of southeast England, derived from registrations at TCR. Standardized incidence ratio (SIR) values were then calculated as the ratio of observed to expected numbers of cancers.

Separate analyses were performed for all malignant cancers combined (ICD-10: C00–C97, excluding non-melanoma skin cancer C44), for lymphomas (C82–C85), and for non-lymphoid cancers (including myelomas and leukaemias). Although

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TABLE 1. Characteristics of pSS patients in whom cancer was diagnosed

Patient no.	Sex	Age at diagnosis of pSS (yr)	Tumour 1 type	Age at diagnosis of tumour 1 (yr)	Tumour 2 type	Age at diagnosis of tumour 2 (yr)
1	F	45	NHL MALT (parotid)	47		
2	F	46	NHL MALT (parotid)	54	Renal granular cell carcinoma (bilateral)[c]	57
3	F	53	Lung adenocarcinoma	57		
4	M	57	Plasma cell myeloma	70	BCC[b,c]	73
6	M	43	B cell leukaemia	48		
7	F	25	NHL MALT	32		
8	F	64	NHL high grade	69		
10	F	42	NHL MALT (palate)	52	BCC[b,c]	67
11	F	77	BCC[b]	74	NHL	87
13	F	58	Squamous cell carcinoma[a,c]	47	BCC[b]	59
14	F	57	Cervical cancer[a]	55		
15	F	64	Melanoma	65		
17	F	78	NHL MALT (stomach and bone marrow)	79	BCC[b,c]	82
18	F	47	Breast adenocarcinoma (ductal)	54		
19	F	74	Bowen's disease of skin[b]	71	Lung carcinoma	82
20	F	72	Breast adenocarcinoma	79		
21	F	47	NHL MALT (neck)	66		
22	F	51	Melanoma	55	NHL MALT (parotid and stomach)[c]	58
23	F	85	Bladder transitional cell carcinoma[a]	80	Cervical cancer[a]	80
26	M	36	Salivary adenocarcinoma	40		
27	F	80	Pancreatic adenocarcinoma	81		
64	F	51	NHL MALT[c]	58		
68	M	50	NHL (neck)[c]	55		
85	F	54	Ovarian adenocarcinoma	71		
111	F	45	Breast cancer	52		

NHL, non-Hodgkin's lymphoma.
[a]Patients with cancer diagnosed prior to diagnosis of pSS, and hence not included in main analysis; [b]excluded from main analysis, as non-melanoma skin cancers not routinely recorded at the Thames Cancer Registry; [c]cancers not confirmed at the Thames Cancer Registry.

precancerous lesions (e.g. epithelial dysplasias) were present in some cases, these were ignored and only malignant cancers were included in the analysis as corresponding incidence rates were available only for these cancers.

Results

A total of 112 patients with pSS (six males, 106 females) were available for analysis. Eighty-seven (78%) had positive lip biopsies. The mean age at diagnosis of pSS was 53.6 yr, with a range of 21–85 yr. Patients were followed up for an average of 10.8 yr. Table 1 lists the 25 patients in whom cancer occurred, either prior to or subsequent to the development of pSS. Lymphoma was present in 11 cases, of which eight were of the mucosa-associated lymphoid tissue (MALT) type, one a high-grade non-Hodgkin's lymphoma and two of unknown subtype. Nine cases had two cancers, five of whom had a lymphoma as one of the cancers. Three cases (cases 13, 14 and 23) had cancer diagnosed prior to the diagnosis of pSS and were excluded from the subsequent analysis. In addition, non-melanoma skin cancers such as basal cell carcinoma (BCC) were not included in the analysis as TCR does not routinely register these tumours. All bar four of the 24 tumours included in the final analysis (three lymphomas and a renal cell carcinoma) were confirmed on the TCR database.

Table 2 shows the observed and expected numbers of first cancers subsequent to the diagnosis of pSS, with the corresponding SIRs and 95% confidence intervals (CIs). Two patients (patients 2 and 22) had both a lymphoma and a non-lymphoid cancer and hence contributed to the observed numbers in each of these categories. However, only their first cancer (lymphoma or otherwise) was counted in the 'all cancers' category. There was a significant increase in all cancers subsequent to the diagnosis of pSS (SIR 2.6, 95% CI 1.7–4.0). As expected, there was a large excess of lymphomas in pSS patients when compared with the general population (SIR 37.5, 95% CI 20.7–67.6). For non-lymphoid cancers, the observed increase was small and not statistically significant (SIR 1.5, 95% CI 0.9–2.6).

Table 3 shows the relationship between the use of the drugs hydroxychloroquine, prednisolone, azathioprine and methotrexate and the development of cancer. The cells show the numbers and percentages of patients who developed a lymphoma or any cancer amongst patients taking a particular drug *vs* those not taking it. Thus, for example, of the 58 patients treated with hydroxychloroquine, seven (12%) developed lymphoma and 14 (24%) any kind of cancer. In the 54 patients not taking the drug, four (7%) developed lymphoma and 11 (20%) any cancer. Although the incidence of cancer was higher in those taking these drugs, the difference was statistically significant only in the case of methotrexate and lymphomas (33% in users *vs* 8% in non-users).

Discussion

This study confirms that patients with pSS have an increased risk of developing lymphomas. The incidence was calculated as being 37.5 times that in the general population, similar to previous studies, which have calculated relative risks between 33 and 44 in populations of similar age, race and sex [6, 8].

The overall incidence of all cancers was 2.6 times that in the general population, but this was almost entirely due to the excess occurrence of lymphoma. The SIR for non-lymphoid malignancy was 1.5, but this was based on a small number of excess cases and was not statistically significant.

Nine patients (8%) developed two malignancies. Of the 11 patients with lymphoma, five developed additional cancers: one developed a bilateral renal granular cell carcinoma and four developed skin cancers (three BCCs and one melanoma).

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Table 2. SIRs for first subsequent occurrence of cancer in pSS patients

	Observed	Expected	SIR	95% CI
All cancers	22	8.38	2.63	1.73–3.99
Lymphomas	11	0.29	37.46	20.74–67.64
Non-lymphomas	13	8.52	1.53	0.89–2.63

Table 3. Use of drugs and development of cancer

	All cancers		Lymphoma		
Drug type	No	Yes	No	Yes	Total
Hydroxychloroquine					
No	43 (79.6%)	11 (20.4%)	50 (92.6%)	4 (7.4%)	54
Yes	44 (75.9%)	14 (24.1%)	51 (87.9%)	7 (12.1%)	58
Prednisolone					
No	66 (81.5%)	15 (18.5%)	75 (92.6%)	6 (7.4%)	81
Yes	21 (67.7%)	10 (32.3%)	26 (83.9%)	5 (16.1%)	31
Azathioprine					
No	77 (80.2%)	19 (19.8%)	87 (90.6%)	9 (9.4%)	96
Yes	10 (62.5%)	6 (37.5%)	14 (87.5%)	2 (12.5%)	16
Methotrexate					
No	84 (79.3%)	22 (20.7%)	97 (91.5%)	9 (8.5%)[a]	106
Yes	3 (50.0%)	3 (50.0%)	4 (66.7%)	2 (33.3%)	6
Total	87	25	101	11	112

[a]Difference statistically significant at 5% level.

There was also one patient who developed a plasma cell myeloma followed by a BCC.

There is concern that the use of disease-modifying medication in autoimmune diseases might increase the risk of cancer and therefore this was also analysed. This subanalysis showed that the use of methotrexate was significantly linked with the development of lymphoma. However, this finding needs to be interpreted with caution as the use of methotrexate may correlate with more active disease and other systemic complications associated with the development of lymphoma. Also, the number of patients taking methotrexate was small and the association may simply be due to chance.

It has been shown in two previous studies that patients with pSS have a lifespan not significantly different from that of the normal population [15, 16]. A subanalysis in the Swedish study showed, however, that there was an excess mortality in patients with lymphoproliferative malignancy [16]. An earlier multicentre study followed 33 patients with pSS who had developed lymphomas [17]. It recorded nine deaths. Only four deaths were directly related to the lymphoma and one to the treatment given. Four deaths, all in the low-grade group, were unrelated to the lymphoma but there was no comment as to the cause of death in these cases. It should be noted that in our study, of the five patients with lymphoma who developed an additional cancer, one appeared to have died as a result of this. Additional cancers could therefore be contributing to the excess mortality in patients with lymphomas.

The potential link between the development of lymphoma and the subsequent development of additional cancers suggests that there may be a common aetiology. One study has shown evidence of defective repair of a promutagenic DNA base lesion, O^6-methylguanine, in the lymphocytes of patients with pSS predisposed to lymphoma [18]. This raises the possibility that pSS patients, pre-disposed to lymphoma, may have defective DNA repair mechanisms in other cell types. A number of oncogenes, cell surface molecules and viruses have also been implicated in the development of lymphomas [19–22] and these could also possibly have a role in causing additional cancers. An alternative explanation could be that the lymphomas in pSS patients are associated with suppressed immunity [23], thus possibly making patients more susceptible to other malignancies. It is also possible that the cytotoxic treatments given for lymphomas could contribute to the development of further cancers. In our study, four of the eleven patients with lymphoma were documented as being given chemotherapy: two were given chlorambucil alone, one was given cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP), and in one the treatment was not stated. Interestingly, two of these four patients later developed BCCs.

The lack of a statistically significant association between pSS and non-lymphoid cancer in this study is possibly a result of the small cohort size. This study is also limited by being dependent on the reporting of cancers to either the Centre for Rheumatology at UCH or the TCR. A larger prospective study would provide a more accurate result. An alternative would be to encourage other centres to perform a study similar to this and to pool the results.

Currently, a large multicentre study is investigating the incidence of malignancy in patients with SLE [4]. A subanalysis looking at patients with overlapping Sjögren's syndrome may also help to establish whether patients with Sjögren's syndrome have a greater risk of developing non-lymphoid cancer.

Overall, this study does not show conclusively that patients with pSS have a greater risk of non-lymphoid cancer but suggests that there may be certain subgroups, such as those who develop lymphomas, who are at higher risk. Non-lymphoid cancer might contribute to the higher mortality that has been observed in those patients who develop lymphomas. The pathogenic factors that may be involved in the development of lymphoma, such as genetic polymorphisms and infectious organisms, could also be involved in the development of non-lymphoid cancer. Patients are also occasionally exposed to immunosuppressant/cytotoxic medications that have the potential for causing cancer. Our findings should therefore encourage clinicians to remain vigilant with patients with pSS, in particular those who develop lymphomas.

The authors have declared no conflicts of interest.

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