Pergamon

European Journal of Cancer Vol. 32A, No. 10, pp. 1753–1757, 1996

Printed in Great Britain
0959-8049/96 $15.00 + 0.00

PII: S0959-8049(96)00210-9

Original Paper

Rheumatoid Arthritis and Cancer Risk

L. Mellemkjær,[1] M. S. Linet,[2] G. Gridley,[2] M. Frisch,[3] H. Møller[4] and J. H. Olsen[1]

[1]Danish Cancer Society, Division for Cancer Epidemiology, Strandboulevarden 49, DK-2100 Copenhagen, Denmark; [2]Epidemiology and Biostatistics Program, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, Maryland, U.S.A.; [3]Danish Epidemiology Centre, Statens Seruminstitut, Copenhagen; and [4]Centre for Research in Health and Social Statistics, Copenhagen, Denmark

The aim of this study was to examine the cancer pattern in a large group of patients with rheumatoid arthritis (RA). A follow-up study of cancer incidence in RA was conducted within a cohort of 20 699 patients recorded in the Danish Hospital Discharge Register during 1977–1987 by linkage with the Danish Cancer Registry through 1991. There were consistent excesses of non-Hodgkin's lymphoma and Hodgkin's disease in both sexes and during both early and late periods of follow-up. Risks for lung cancer and non-melanoma skin cancer were also increased, with no predilection for any specific histological subtype, while risks for colorectal cancer and female breast cancer were reduced. The cancer pattern seen among Danish RA patients largely supports findings from two earlier Nordic investigations. Thus, there seem to be consistent positive associations between RA and non-Hodgkin's lymphoma, Hodgkin's disease and lung cancer and a consistent negative association with colorectal cancer. Copyright © 1996 Elsevier Science Ltd

Key words: rheumatoid arthritis, cancer risk, hospital discharge register, follow-up study

Eur J Cancer, Vol. 32A, No. 10, pp. 1753–1757, 1996

INTRODUCTION

RHEUMATOID ARTHRITIS (RA) is the most common systemic autoimmune disorder, characterised by chronic inflammation of the synovial membrane of multiple joints and a varying degree of systemic involvement. The aetiology is unknown but the female predominance, the tendency for remission during pregnancy, the involvement of the immune system (rheumatoid factor, antinuclear antibodies) and the association with HLA-DR4, indicate an interplay between hormonal, immunological and genetic factors [1, 2]. Viral infection has also been suggested to play an aetiological rôle. For example, cross-reacting proteins of the Epstein–Barr virus have been hypothesised to trigger the autoimmune process in genetically predisposed individuals [3].

During the last 20 years, several studies have described a potential association between RA and lymphatic and haematopoietic cancers [4–9]. Only two studies, both from Nordic countries, were large enough to analyse the risk of specific lymphatic and haematopoietic cancers [4, 5]. Increased risks were reported for non-Hodgkin's lymphoma, Hodgkin's disease, multiple myeloma and leukaemia in both Finland and Sweden, even though the association with multiple myeloma and leukaemia was significant only in the Finnish study [4, 5]. To further evaluate risks for the various lympho-haematopoietic malignancies as well as risks for other cancers, we conducted a study of cancer incidence in a cohort of more than 20 000 RA patients identified in the nationwide Danish Hospital Discharge Register.

MATERIALS AND METHODS

Patients with RA were identified in the Danish Hospital Discharge Register, which has recorded information on more than 99% of discharges from non-psychiatric hospitals in Denmark since 1977 [10]. The registration includes a personal identification number unique to every Danish citizen (encoding gender and date of birth), dates of admission and discharge and up to 20 diagnoses per discharge. Discharge diagnoses are coded according to a Danish version of the 8th International Classification of Diseases (ICD-8) [11]. All patients diagnosed during 1977–1987

Correspondence to L. Mellemkjaer at Danish Cancer Society, Division for Cancer Epidemiology, Strandboulevarden 49, DK-2100 Copenhagen Ø, Denmark.
Received 27 Feb. 1996; accepted 11 Apr. 1996.

with juvenile rheumatoid arthritis (ICD-8 code 712.09), Felty's syndrome (712.19), palindromic arthritis (712.29), other and unspecified rheumatoid arthritis (712.39) or rheumatoid fibrositis with chronic nodules (712.59), but not those with ankylosing spondylitis (712.49), were included in the cohort of 23 045 patients. Personal identification numbers of a cohort of patients with a discharge diagnosis of Sjögren's syndrome (734.90) in the Hospital Discharge Register were matched with those of the RA cohort to identify 216 patients who had both diseases.

Using the personal identification number, the RA cohort was linked to the Danish Register of Deaths and the Danish Cancer Registry to ascertain deaths and cancer occurrence. All incident cases of malignant neoplasm, papilloma of the lower urinary tract and histologically benign tumour of the central nervous system in the Danish population have been reported to the Danish Cancer Registry for more than 50 years [12].

The first year of follow-up for cancer was excluded from the analysis to minimise the possibility of including cancer cases whose presenting symptoms of cancer overlapped substantially with those of RA [13, 14]. This exclusion affected 2346 patients for whom the period from RA diagnosis to death was less than one year. The analysis was performed on 20 699 patients who were followed from one year after the first discharge with a diagnosis of RA and continued until the date of death or end of December 1991. Person-years under observation were multiplied by sex-, age- and calendar-specific incidence rates in the Danish population to estimate the number of expected cancers. The relative risk (RR) was estimated as the ratio of observed-to-expected number of cancers, and the 95% confidence intervals were calculated assuming that the observed number of cancer cases follows a Poisson distribution. Exact Poisson limits were calculated when there were fewer than 10 observed cases; otherwise Byar's approximation was used [15].

RESULTS

The cohort consisted of more than twice as many women ($n = 14\,647$) than men ($n = 6052$) who had one or more hospitalisations with RA as a discharge diagnosis. The length of follow-up averaged 7 years (range 1–15 years) and a total of 144 421 person-years was accumulated. Characteristics of the cohort are shown in Table 1.

Table 1. Distribution of rheumatoid arthritis patients on selected characteristics

Characteristics	Number of persons (%)
Total (ICD-8 712.09-39, 712.59)	20 699
Men	6052 (29)
Women	14 647 (71)
Juvenile RA (712.09)	1007 (4.9)
Felty's syndrome (712.19)	94 (0.5)
Palindromic arthritis (712.29)	144 (0.7)
Other and unspecified RA (712.39)	19 387 (93.7)
Rheumatoid fibrositis with chronic nodules (712.59)	67 (0.3)
Secondary Sjögren's syndrome	216 (1.0)
Period of RA hospitalisation	
1977–1979	8091 (39)
1980–1982	5598 (27)
1983–1985	4432 (21)
1986–1987*	2578 (12)
Age at RA hospitalisation (years)	
0–19	939 (5)
20–39	1684 (8)
40–59	6069 (29)
60–79	10 518 (51)
≥80	1489 (7)

* Only two year period.

There was a significant excess of the combined group of lymphatic and haematopoietic cancers (Table 2). The risk of non-Hodgkin's lymphoma was more than 2-fold elevated among both genders and consisted of 71 (84%) nodal and 13 (15%) extranodal cases (5 of the latter in the stomach and the remaining at different sites with none in the brain) and one (1%) of unknown topography. The RR for non-Hodgkin's lymphoma was especially high in the subgroup of 216 patients registered with secondary Sjögren's syndrome (RR = 9.8; $n = 4$; 95% CI = 2.6–25). Patients of both genders had notably increased risks of Hodgkin's disease, although significantly elevated among females only, and 2-fold excesses of acute non-lymphocytic leukaemia. Overall, multiple myeloma and chronic lymphocytic leukaemia were

Table 2. Observed (Obs) numbers and relative risk (RR) for lymphatic and haematopoietic cancers among 20 699 patients followed 1–15 years after hospitalisation with rheumatoid arthritis

	Total				Men		Women	
Cancer site	Obs	Exp	RR	95% CI	Obs	RR	Obs	RR
All lymphatic and haematopoietic cancer	171	99.6	1.7	1.5–2.0	61	1.7†	110	1.7†
Non-Hodgkin's lymphoma	85	35.9	2.4	1.9–2.9	33	2.9†	52	2.1†
Hodgkin's disease	14	4.2	3.4	1.8–5.6	4	2.4	10	4.1†
Multiple myeloma	21	19.0	1.1	0.7–1.7	4	0.6	17	1.4
Leukaemia	50	39.8	1.3	0.9–1.7	19	1.2	31	1.3
Acute lymphocytic leukaemia	2	1.3	1.6	0.2–5.7	1	2.3	1	1.2
Chronic lymphocytic leukaemia	14	18.5	0.8	0.4–1.3	6	0.8	8	0.7
Acute non-lymphocytic leukaemia	25	13.1	1.9	1.2–2.8	11	2.4†	14	1.7
Chronic myeloid leukaemia	5	4.9	1.0	0.3–2.4	1	0.5	4	1.3
Other and unspecified leukaemia	4*	2.0	2.0	0.5–5.0	0	—	4	3.3
Mycosis fungoides	1	0.8	1.3	0.0–7.4	1	2.6	0	—

* One case of hairy cell leukaemia, one case of megakaryocitic leukaemia, one case of acute leukaemia NOS and one case of leukaemia NOS. † $P < 0.05$.

Table 3. Observed (Obs) and expected (Exp) numbers and relative risks (RR) for lymphatic and haematopoietic cancers according to time since first known hospitalisation with rheumatoid arthritis

	Time since hospitalisation with RA (years)							
	1–4				5–15			
Cancer site	Obs	Exp	RR	95% CI	Obs	Exp	RR	95% CI
All lymphatic and haematopoietic cancers	101	49.2	2.1	1.7–2.5	70	50.4	1.4	1.1–1.8
Non-Hodgkin's lymphoma	41	17.0	2.4	1.7–3.3	44	18.9	2.3	1.7–3.1
Hodgkin's disease	6	2.1	2.8	1.0–6.1	8	2.0	3.9	1.7–7.8
Multiple myeloma	16	9.5	1.7	1.0–2.7	5	9.5	0.5	0.2–1.2
Leukaemia	38	20.2	1.9	1.3–2.6	12	19.6	0.6	0.3–1.1
Acute lymphocytic leukaemia	1	0.6	1.6	0.0–8.8	1	0.6	1.6	0.0–8.9
Chronic lymphocytic leukaemia	10	9.4	1.1	0.5–1.9	4	9.1	0.4	0.1–1.1
Acute non-lymphocytic leukaemia	20	6.7	3.0	1.8–4.6	5	6.5	0.8	0.3–1.8
Chronic myeloid leukaemia	3	2.5	1.2	0.3–3.6	2	2.4	0.8	0.1–3.0
Other and unspecified	4	1.0	4.0	1.1 10.3	0	1.0	—	—
Mycosis fungoides	0	0.4	—	—	1	0.4	2.6	0.1–14.4

not increased and only one case of mycosis fungoides was observed. All lymphomas occurred among patients in the largest subgroup, those with other and unspecified RA (Table 1). One case of leukaemia was seen in those with juvenile RA, one in those with Felty's syndrome and one in individuals with palindromic arthritis, while the remaining leukaemias arose in those with other and unspecified RA.

RRs for non-Hodgkin's lymphoma and Hodgkin's disease were 2- to 4-fold and significantly increased during both early and late follow-up (Table 3). In contrast, there was a reduction in the risk of acute non-lymphocytic leukaemia from a significant 3-fold excess within 5 years to no increase 5 or more years after the initial hospitalisation. No lymphatic or haematopoietic cancer was diagnosed among

Table 4. Observed (Obs) numbers and relative risks (RR) for cancer other than lymphatic and haematopoietic types among 20 699 patients followed 1–15 years after hospitalisation with rheumatoid arthritis

	Total				Men		Women	
Cancer site	Obs	Exp	RR	95% CI	Obs	RR	Obs	RR
All sites except lymphatic and haematopoietic cancers	1832	1701.8	1.08	1.03–1.13	653	1.15*	1179	1.04*
Buccal cavity and pharynx	36	29.5	1.2	0.9–1.7	18	1.2	18	1.2
Oesophagus	12	14.7	0.8	0.4–1.4	6	0.8	6	0.8
Stomach	58	57.9	1.0	0.8–1.3	22	0.9	36	1.1
Colo-rectum	204	249.3	0.8	0.7–0.9	55	0.7*	149	0.9*
Primary liver	20	17.0	1.2	0.7–1.8	4	0.6	16	1.6
Pancreas	62	57.7	1.1	0.8–1.4	14	0.8	48	1.2
Lung	308	205.4	1.5	1.3–1.7	170	1.5*	138	1.5*
Squamous cell carcinoma	79	56.2	1.4	1.1–1.8	52	1.4*	27	1.5*
Small cell carcinoma	52	38.9	1.3	1.0–1.8	27	1.4	25	1.3
Adenocarcinoma	61	45.7	1.3	1.0–1.7	27	1.4	34	1.3
Large cell carcinoma	23	16.7	1.4	0.9–2.1	13	1.5	10	1.3
Other and unspecified	93	47.9	1.9	1.6–2.4	51	2.0*	42	1.9*
Female breast	186	229.8	0.8	0.7–0.9	—	—	186	0.8*
Cervix uteri	40	36.9	1.1	0.8–1.5	—	—	40	1.1
Endometrium	50	61.1	0.8	0.6–1.1	—	—	50	0.8
Ovary	50	52.1	1.0	0.7–1.3	—	—	50	1.0
Other female genital organs	12	11.5	1.0	0.5–1.8	—	—	12	1.0
Prostate	90	78.1	1.2	0.9–1.4	90	1.2	—	—
Kidney	52	48.6	1.1	0.8–1.4	15	0.8	37	1.2
Urinary bladder	97	92.7	1.1	0.8–1.3	50	0.9	47	1.3
Melanoma	37	33.4	1.1	0.8–1.5	11	1.3	26	1.1
Non-melanoma skin	314	245.0	1.3	1.1–1.4	118	1.4*	196	1.2*
Squamous cell carcinoma	51	35.9	1.4	1.1–1.9	24	1.5	27	1.4
Basal cell carcinoma	253	202.0	1.3	1.1–1.4	91	1.4*	162	1.2*
Other and unspecified	10	7.1	1.4	0.7–2.6	3	1.3	7	1.4
Brain and nervous system	32	36.8	0.9	0.6–1.2	14	1.3	18	0.7
Other specified organs	110	93.4	1.2	1.0–1.4	46	1.3*	64	1.1
Secondary and unspecified organs	62	50.9	1.2	0.9–1.6	20	1.4	42	1.2

*$P < 0.05$.

patients less than 40 years of age (1.2 cases expected); the excess of cases was seen among patients in the age groups 40–59 and 60–79 years at cancer diagnosis.

The RR for cancers other than lymphatic and haematopoietic types was modest (8%) although significantly increased 1–15 years after first hospitalisation with RA (Table 4). The excess was accounted for by significantly increased risks of lung cancer and non-melanoma skin cancer. For these cancer sites, no specific relation to subgroup of RA was found, nor did risks differ by gender, age at cancer diagnosis or histological subtype of lung and non-melanoma skin cancer. Lung cancer of various types and basal cell skin cancer were in excess both during early and late follow-up, while the excess of squamous cell skin cancer was seen only during late follow-up. There was one case of Kaposi's sarcoma among females. Significant decreases in RR were observed for colorectal cancer among both genders and for breast cancer among females (Table 4).

DISCUSSION

The cancer pattern for RA patients found in the present study is quite consistent with the pattern found in previous register-based studies from Sweden and Finland [4, 5]. Accordingly, all three studies give evidence of increased risks for non-Hodgkin's lymphoma, Hodgkin's disease and lung cancer and of decreased risk for colorectal cancer. A minor difference between the studies exists for squamous cell skin cancer for which risk was significantly elevated among Danish RA patients, but just slightly, non-significantly elevated among Swedish and Finnish patients [4, 5]. In addition, only the Finnish study showed significantly increased risks for multiple myeloma and leukaemia, whereas ours and the Swedish study showed moderately, non-significantly increased risks. The overall excess of multiple myeloma and leukaemia in the Danish study was confined to the early years of follow-up, so the discrepancy between studies may, perhaps, be explained by a shorter follow-up in the Finnish study (maximum 7 years). Deficits of breast cancer were found in Danish and Swedish RA patients but not in Finnish patients, whereas a deficit of stomach cancer was not observed in our RA population, but did occur in the two other Nordic populations.

Positive associations between RA and lymphatic and haematopoietic cancers have been described in clinical reports, mortality studies and record linkage studies [4–8, 16–19], but only two of these were large enough to detect specifically significant excess of non-Hodgkin's lymphoma and Hodgkin's disease [4, 5]. Elevated risks for non-Hodgkin's lymphoma have also been found among patients with other systemic autoimmune diseases including systemic lupus erythematosus [20] and Sjögren's syndrome [21]; the latter is a secondary condition in some RA patients. Coexistence of Sjögren's syndrome with RA was associated with a 10-fold increase in the risk for non-Hodgkin's lymphoma in our population, but since this was based on only four cases it cannot explain the overall excess of non-Hodgkin's lymphoma. The underlying mechanisms for the increased incidence of lymphomas among RA patients, including both non-Hodgkin's lymphoma and Hodgkin's disease, are unknown but the disturbances of the immune system are likely to be involved. It has been suggested that an increased risk for non-Hodgkin's lymphoma due to RA *per se* may possibly be further increased if immunosuppressive therapy is initiated [22].

Among earlier studies, only the Swedish analysed risk of leukaemia by cytological subtype and noted that a small, non-significant overall increase was due primarily to an excess of chronic lymphocytic leukaemia [4] in disagreement with the excess of acute non-lymphocytic leukaemia in our RA population limited to years 1–4 of follow-up. Acute non-lymphocytic leukaemia may be related to alkylating agents that are used for severe cases of RA [23]. However, osteoarticular symptoms are sometimes seen in acute non-lymphocytic leukaemia, and the unequal time distribution of cases may indicate that the initial association occurred because the presenting symptoms of acute non-lymphocytic leukaemia were rheumatic and at first interpreted as an exacerbation of a known RA or as a new case of RA.

The observed 50% increase in lung cancer risk is compatible with the 1.3-fold increase found in two earlier linked registry studies [4, 5]. An excess of lung cancer has previously been observed among patients with autoimmune diseases other than RA such as systemic sclerosis [24] and systemic lupus erythematosus (Mellemkjær and coworkers, unpublished data). All three autoimmune disorders may involve lung manifestations and, at least in systemic sclerosis, the development of lung cancer is thought to be related to lung fibrosis [25, 26]. Another explanation may be a common risk factor for both RA and lung cancer such as cigarette smoking; smokers have been found to have a moderately higher risk for RA compared with non-smokers [27, 28]. However, if smoking is involved we would have expected a less pronounced excess of adenocarcinomas compared to other types of lung cancer since adenocarcinomas may be less strongly related to smoking than other types [29].

Reduced risks for colorectal cancer and female breast cancer were observed in the present investigation and in the Swedish study [4]. RA patients frequently use non-steroidal anti-inflammatory drugs (NSAIDs) which possibly have a protective effect on the development of colorectal cancer [30]. The female predominance in RA suggests that some unknown female factor increases the risk for RA; the same factor could possibly reduce the risk for female breast cancer.

Major strengths of the present investigation included the large size together with a high degree of ascertainment of malignancies in the Danish Cancer Registry [12]. The considerable number of observed cancers allowed us to look at histological subtypes of some malignancies. Possible limitations include lack of generalisability, since only hospitalised RA patients were included in the cohort, and potential selection bias if prevalent or undiagnosed RA cases are hospitalised due to symptoms of an unrecognised neoplastic disease [13, 14]. Exclusion of the first year of follow-up should have minimised selection bias, although this bias may not have been completely eliminated in relation to acute non-lymphocytic leukaemia. Patients with a chronic disease such as RA are followed more closely for health problems in general, which may produce surveillance bias in relation to less aggressive cancers with incomplete registration such as non-melanoma skin cancer; the excess of this cancer may partly reflect increased surveillance.

The present study provides evidence of an increased risk for specific lymphatic cancers such as non-Hodgkin's lymphoma and Hodgkin's disease. In line with previous reports, risk for lung cancer was increased while risks for colorectal cancer and female breast cancer were reduced. The positive association between RA and non-melanoma skin cancer must be interpeted with caution considering the possible influence from surveillance bias. Studies that ascertain detailed information about RA disease characteristics, medications, smoking habits, hormonal and reproductive factors would be necessary to further investigate the underlying explanation for the observed increases in the incidence of certain cancers among patients with RA.

1. Goust JM. Rheumatoid arthritis. *Immunol Ser* 1993, **58**, 451–464.
2. Hochberg MC, Spector TD. Epidemiology of rheumatoid arthritis: update. *Epidemiol Rev* 1990, **12**, 247–252.
3. Fox RI, Luppi M, Pisa P, Kang HI. Potential role of Epstein–Barr virus in Sjögren's syndrome and rheumatoid arthritis. *J Rheumatol Suppl* 1992, **32**, 18–24.
4. Gridley G, McLaughlin JK, Ekbom A, *et al.* Incidence of cancer among patients with rheumatoid arthritis. *J Natl Cancer Inst* 1993, **85**, 307–311.
5. Isomäki HA, Hakulinen T, Joutsenlahti U. Excess risk of lymphomas, leukemia and myeloma in patients with rheumatoid arthritis. *J Chron Dis* 1978, **31**, 691–696.
6. Katusic S, Beard CM, Kurland LT, Weis JW, Bergstralh E. Occurrence of malignant neoplasms in the Rochester, Minnesota, rheumatoid arthritis cohort. *Am J Med* 1985, **78** (Suppl. 1A), 50–55.
7. Prior P. Cancer and rheumatoid arthritis: epidemiologic considerations. *Am J Med* 1985, **78** (Suppl. 1A), 15–21.
8. Fries JF, Bloch D, Spitz P, Mitchell DM. Cancer in rheumatoid arthritis: a prospective long-term study of mortality. *Am J Med* 1985, **78** (Suppl. 1A), 56–59.
9. Pearce N, Porta M. Association of non-Hodgkin's lymphoma with rheumatoid arthritis [letter]. *Am J Med* 1986, **81**, 747–748.
10. Danish National Board of Health. *The Activity in the Hospital Care System.* Copenhagen, Danish National Board of Health, 1981 [in Danish].
11. Danish National Board of Health. *Classification of Diseases.* Copenhagen, Danish National Board of Health, 1976 [in Danish].
12. Storm HH, Manders T, Friis S, Bang S. *Cancer Incidence in Denmark 1989.* Copenhagen: Danish Cancer Society, 1992.
13. Brooks PM. Rheumatic manifestations of neoplasia. *Curr Opin Rheumatol* 1992, **4**, 90–93.
14. Butler RC, Thompson JM, Keat AC. Paraneoplastic rheumatic disorders: a review. *J R Soc Med* 1987, **80**, 168–172.
15. Rothman KJ, Boice JD. *Epidemiologic Analysis with a Programmable Calculator (DHHS Publication No (NIH) 79-1649).* Washington DC, US Government Printing Office, 1979.
16. Lewis RB, Castor CW, Knisley RE, Bole GG. Frequency of neoplasia in systemic lupus erythematosus and rheumatoid arthritis. *Arthritis Rheum* 1976, **19**, 1256–1260.
17. Monson RR, Hall AP. Mortality among arthritics. *J Chronic Dis* 1976, **29**, 459–467.
18. Allebeck P. Increased mortality in rheumatoid arthritis. *Scand J Rheumatol* 1982, **11**, 81–86.
19. Laakso M, Mutru O, Isomäki H, Koota K. Cancer mortality in patients with rheumatoid arthritis. *J Rheumatol* 1986, **13**, 522–526.
20. Pettersson T, Pukkala E, Teppo L, Friman C. Increased risk of cancer in patients with systemic lupus erythematosus. *Ann Rheum Dis* 1992, **51**, 437–439.
21. Kassan SS, Thomas TL, Moutsopoulus HM, *et al.* Increased risk of lymphoma in Sicca Syndrome. *Ann Intern Med* 1978, **89**, 888–892.
22. Kinlen L. Immunosuppressive therapy and acquired immunological disorders. *Cancer Res* 1992, **52** (Suppl.), 5474s–5476s.
23. Hazleman B. Incidence of neoplasms in patients with rheumatoid arthritis exposed to different treatment regimens. *Am J Med* 1985, **78** (Suppl. 1A), 39–43.
24. Rosenthal AK, McLaughlin JK, Linet MS, Persson I. Scleroderma and malignancy: an epidemiological study. *Ann Rheum Dis* 1993, **52**, 531–533.
25. Abu-Shakra M, Guillemin F, Lee P. Cancer in systemic sclerosis. *Arthritis Rheum* 1993, **36**, 460–464.
26. Peters-Golden M, Wise RA, Hochberg M, Stevens MB, Wigley FM. Incidence of lung cancer in systemic sclerosis. *J Rheumatol* 1985, **12**, 1136–1139.
27. Hernandez-Avila M, Liang MH, Willett WC, *et al.* Reproductive factors, smoking, and the risk for rheumatoid arthritis. *Epidemiology* 1990, **1**, 285–291.
28. Voigt LF, Koepsell TD, Nelson JL, Dugowson CE, Daling JR. Smoking, obesity, alcohol consumption, and the risk of rheumatoid arthritis. *Epidemiology* 1994, **5**, 525–532.
29. McDuffie HH, Klaassen DJ, Dosman JA. Determinants of cell type in patients with cancer of the lungs. *Chest* 1990, **98**, 1187–1193.
30. Buring JE, Lee IM, Hennekens CH. Nonsteroidal antiinflammatory drugs and colorectal cancer. A promising hypothesis but not yet proven [editorial; comment]. *Cancer* 1994, **74**, 1837–1839.

Acknowledgements—The authors thank Andrea Bautz at the Danish Cancer Society, Division for Cancer Epidemiology, Copenhagen, Denmark for computer assistance. This study was supported by research grant MAO NO1-CP-85639-04 from the National Cancer Institute, Bethesda, Maryland, U.S.A.