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Rheumatoid Arthritis as a Risk Factor for Multiple Myeloma: A Case–Control Study

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This population-based case–control investigation was designed to study the importance of rheumatoid arthritis, other diseases and different types of treatment for the risk of developing multiple myeloma. In total, 275 cases with verified myeloma in northern Sweden were matched to as many control subjects. Information about different diseases, drug use, diagnostic X-ray investigations and radiotherapy was obtained through an extensive questionnaire mailed to all living subjects, i.e. cases and controls, and to the next of kin regarding deceased subjects. The study confirmed a suspected association with both rheumatic diseases in general and rheumatoid arthritis specifically. No other disease gave an increased risk for myeloma, but on the contrary, other diseases were in general more common among the controls. In accordance with this finding, use of medications and diagnostic X-ray investigations were also less common in cases than in controls. The study did, however, give some support to a recent finding that the number of X-ray investigations might be a risk factor for myeloma. Earlier radiotherapy on benign indications was more common in cases, whereas radiotherapy for malignant disease was more common among controls in this study.
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INTRODUCTION

An association between connective tissue diseases, e.g. rheumatoid arthritis (RA), and lymphoproliferative malignancies was first postulated in 1964 [1]. Subsequent investigations have been conflicting, with several studies not confirming this association [2–5]. Two different cohorts of RA patients have shown increased mortality [6] and morbidity [7] of lymphoproliferative malignancies, however. A third similar cohort revealed a significantly increased incidence of multiple myeloma (MM) only [8], whereas another did not find any association with malignant diseases [9].

A large Finnish study linked a nationwide computerised data register of patients with RA with the Finnish Cancer Registry [10, 11]. The results showed statistically significant increased incidence of various malignant lymphoproliferative diseases, i.e. MM, Hodgkin's disease, non-Hodgkin lymphoma and leukaemia, in the RA patients.

However, case–control studies on MM have not been able to confirm any association with RA [12–17], despite some of them revealing other probable autoimmune disorders as possible risk factors for MM. One case–control study demonstrated a significant excess of RA among the relatives of cases with multiple myeloma compared with controls [18].

Radiation is an established risk factor for MM, as demonstrated by significant dose responses in nuclear explosion survivors in Japan [19]. In a survey of different cohorts of persons exposed to radiation for which data on cancer-related mortality were available, Cuzick found an excess of MM in most cohorts [20]. This also included patients receiving therapeutic or diagnostic irradiation. Moreover, two recent American studies revealed X-ray therapy and diagnostic X-ray examinations, respectively, to be associated with MM [21, 22].

The present study will give data on different diseases and treatments in a popluation-based case–control study on MM in northern Sweden. Special emphasis will be placed upon the relation between RA and MM.

MATERIALS AND METHODS

Cases

Cases of multiple myeloma were derived from the Swedish Cancer Register, to which all physicians are obliged to report all incident cases of malignant tumours. The study area included the counties of Norrbotten, Västerbotten, Västernorrland and Jämtland in northern Sweden. The period from which cases were recruited was 1 July 1982 to 30 June 1986, i.e. all cases reported to the register during this time were selected regardless of age or gender. Out of 293 cases found in this way, 18 were omitted because scrutiny of their medical records revealed that they did not fulfil widely accepted diagnostic criteria proposed for use in therapeutic trials [23]. Of the 275 remaining cases 156 (57%) were alive and 119 (43%) were deceased. The study comprised 141 male and 134 female cases.

Controls

For each living case two persons were selected from the Swedish National Population Register by a matching procedure. This was based upon age, gender and county, so that the two persons living in the same county, with same sex and being closest in personal identity number, i.e. in age, with the respective case were chosen. One of these two was randomly selected as a control person.

In a corresponding way one deceased control person was chosen for every deceased case from the National Register for Causes of Death. In addition to the matching criteria described above the deceased controls were also matched on year of death. Persons who had committed suicide were not used as controls.

In total the study comprised 550 persons, 275 cases and as many controls.

Assessment of exposure

All living cases and control subjects received a comprehensive questionnaire by mail in 1987 or 1988. For deceased subjects

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the questionnaire was sent to the next of kin defined in the order of wife or husband, child, parent, sibling or other. An accompanying letter gave general information about the study, but did not reveal the specific aim of the investigation, i.e. multiple myeloma was not mentioned. Data obtained on questions regarding present and earlier diseases, medications, X-ray investigations and radiotherapy are published in this paper, analyses of other data are presented elsewhere.

Earlier and present diseases asked for included rheumatic disease, inflammatory bowel disease and diabetes; all with potential autoimmune pathogenesis. A question on metabolic disorder did probably capture most individuals with hyper- or hypothyroidism. Hypertension, tuberculosis, hyperlipidemia, thrombosis, allergy and nervous complaints were also inquired upon, as well as "other diseases" requesting a specification.

The questions were put in the following way: "Have you been treated for...?", or "Had he/she been treated for...?", in the questionnaires regarding living and deceased subjects, respectively. The time periods corresponding to the disease(s) in question were also defined.

The subjects' medications, past and present, were also recorded and in the analysis all drugs were grouped according to the Anatomical Therapeutic Chemical Classification recommended by WHO (ATC-codes). Furthermore, the approximate number, time and site of X-ray investigations experienced was questioned. Finally, an inquiry regarding radiotherapy of tumours, joint disorders and cutaneous diseases was also included.

In the coding of data, all "exposure", i.e. experienced diseases, medications and radiation, from the year of diagnosis of MM or later, was disregarded. For the controls, the year of MM diagnosis of the respective case was used. If the time of any exposure was unsure or omitted, however, that exposure was included with the exception of treatment with analgesics (ATC-codes NO2A, NO2B) or diagnostic X-ray of the skeleton, because of the expected connection of such factors with MM. Furthermore, all exposure to these two factors within 3 years before the diagnosis of the cases was also excluded, since an association with undiagnosed MM is probable. The same criterion was applied if the type of X-ray investigation was not clear.

Since the expression "rheumatic disease" may include different disorders and symptoms, a further step was taken to evaluate who had been diagnosed as suffering from a genuine RA. Thus, for all subjects who had answered yes on this question, available medical records from regional hospitals and/or district medical officers were requested.

The corresponding procedure was performed for all subjects for whom radiotherapy was reported, since this was shown to be surprisingly frequent according to answers in the questionnaires. This question was therefore suspected to have been misinterpreted.

On these grounds medical records were requested regarding 65 subjects (33 cases, 32 controls). Of 25 living subjects, 2 refused permission, 1 case and 1 control.

Statistical methods

Calculation of odds ratios for all exposure variables, including different types of medications, was done with sustained matching based on principles stipulated by Miettinen [24]. All incomplete pairs were thus omitted from the calculation. The total number of exposed cases and controls are given in Tables 1, 4 and 5 however. The 95% confidence intervals (CI) of the odds ratios was calculated with a test-based approximation method [25].

In addition, for all diseases, analyses were performed separately for living and dead subjects, in order to assess whether the status of the respondent influenced the answers.

RESULTS

For 36 cases (13.1%) and 55 control subjects (20.0%) no questionnaire was obtained, making the total refusal rate in this study 16.5%.

Results on disease experience calculated with sustained matching, are shown in Table 1. The four latter diseases in the table were specified in the answers as "other diseases". Specified diseases which appeared in less than 10 subjects are grouped together as "other diseases".

Rheumatic disease was accompanied by a non-significantly increased risk. When this factor was analysed with living and dead subjects separated the odds ratio (OR) did not differ greatly, but the CI became wider, since the number of subjects decreased. Thus, for living subjects rheumatic disease gave an OR of 1.67 (95% CI=0.73–3.80), and for dead subjects OR was 2.20 (95% CI=0.78–6.18). For most of the other diseases the differences between living and dead subjects were also small. In some instances, however, deviating OR produced CI not including unity in these separated analyses. This occurred for nervous complaints, which among living subjects gave an increased OR of 3.00 (95% CI=1.14–7.88), whereas a decreased OR of 0.42 (95% CI=0.15–1.15) was found among dead subjects.

When scrutinising all available medical records regarding the subjects with rheumatic disease only 9 cases and 2 controls could be verified as having RA, producing an odds ratio of 8.00 (95% CI=1.39–46.12) in the matched analysis. Some clinical data on these subjects are presented in Table 2. If verified RA is calculated with dissolved matching, the odds ratio is 4.27.

Remaining subjects with rheumatic disease, i.e. 28 cases and 20 controls had suffered from a wide spectrum of osteoarthrosis, arthritis and arthralgia. The diagnoses found in the medical records are listed in Table 3.

Diabetes and inflammatory bowel disease were somewhat less common in cases than in controls, whereas other specified

Table 1. Reported diseases in cases and controls in the order they appeared in the questionnaire with odds ratios (OR) and 95% confidence intervals (CI) calculated with sustained matching

Disease	Cases (n = 239)	Controls (n = 220)	OR	95% CI
Hypertension	62	65	0.87	0.55–1.38
Diabetes	22	31	0.67	0.33–1.37
Tuberculosis	12	10	1.11	0.44–2.78
Inflammatory bowel disease	9	13	0.55	0.21–1.45
Rheumatic disease	37	22	1.86	0.98–3.54
Hyperlipidaemia	10	10	1.14	0.43–3.02
Thrombosis	19	20	0.76	0.36–1.59
Nervous complaints	24	20	1.18	0.61–2.29
Metabolic disorder	8	11	0.64	0.25–1.62
Allergy	20	16	1.08	0.51–2.30
Angina pectoris	6	10	0.75	0.26–2.14
Gastric ulcer	14	10	1.50	0.62–3.66
Gall bladder disease	10	11	1.00	0.37–2.67
Shingles	5	7	0.67	0.19–2.33
Other diseases	60	83	0.45	0.29–0.71

Table 2. Characteristics of cases and controls with rheumatoid arthritis verified in medical records

Case/control	Sex	Age at diagnosis RA	MM	RA-factor	RA-drugs	M-protein
Case	F	30	61	+	C,P	l.c.-k
Case	M	64	65	+	—	IgA-l
Case	F	68	74	—	Ph	l.c.-l
Case	F	48	82	+	C,P,Ph	IgG-?
Case	F	42	72	+	C,P	IgG-k
Case	F	24	70	+	G,P	IgG-l
Case	M	46	59	+	C	IgG-k
Case	M	70	83	+	P	IgG-k
Case	F	65	77	?	C,G,P,Ph	IgG-l
Control	M	23	—	—	C,G,A,S,P,Ph	—
Control	F	55	—	+	P,Ph	—

Anti-rheumatic drugs—C=chloroquine, G=gold salts, P=prednisone, A=azathioprine, S=sulphasalazine, Ph=phenylbutazone. Other drugs as salicylates and related drugs are not included in the Table.
F=female, M=male, l.c.=light chains, k=kappa, l=lambda.

diseases did not differ much between cases and controls. A history of "other diseases" gave a significantly decreased odds ratio for MM in this study.

A total of 116 controls and 107 cases had been using medication of some kind. In Table 4, calculations on different groups of drugs are listed, omitting groups with less than 10 subjects exposed. The only statistically significant finding was a decreased odds ratio for vasodilators, i.e. mainly nitrates.

In Table 5 it is demonstrated that exposure to diagnostic X-ray investigations were more common in controls than in cases. When grouping the subjects according to the total number of X-ray investigations experienced, however, this tendency was gradually weakened with increasing number, and there were more cases than controls in the category with more than 20 X-ray investigations.

Radiotherapeutic exposure was similar in cases and controls. Locations and/or indications for such treatment are listed in Table 6. Malignant tumours were more common in controls (9 cases vs. 1, respectively) whereas benign conditions were more common in MM cases (9 vs. 3, respectively). In 2 MM subjects but no controls, radiotherapy had been given to lumbar spine, 25 and 29 years prior to the MM diagnosis.

Table 3. Diagnoses of rheumatic diseases among subjects without verified rheumatoid arthritis

Diagnosis	Cases	Controls
Osteoarthrosis	9	6
Gout	0	2
Rheumatic fever	2	2
Rheumatic erythema nodosum	1	1
Polymyalgia rheumatica	2	0
Psoriasisarthropathia	1	0
Becterew's disease	1	0
Unspecified arthritis	3	1
Other and unspecified joint disorders, e.g. arthralgia	11	8
No information on joint disorder found in records	3	3

33 diagnoses occurred in 28 cases, and 23 diagnoses in 20 controls.

Table 4. Reported medication use, divided in groups with ATC-codes, in cases and controls with odds ratios (OR) and 95% confidence intervals (CI) calculated with sustained matching

Medication groups (ATC-codes)	Cases (n=239)	Controls (n=220)	OR	95% CI
Antacids (A02A)	6	4	1.67	0.40–6.94
Insulin (A10A)	5	8	0.83	0.24–2.81
Oral hypoglycaemic drugs (A10B)	3	7	0.50	0.13–1.95
Potassium (A12B)	12	11	0.80	0.31–2.04
Anticoagulants (B01A)	7	8	0.43	0.12–1.60
Cardiac glycosides (C01A)	19	18	1.08	0.51–2.30
Vasodilators (C01D)	13	24	0.43	0.20–0.92
Calcium antagonists/hydralazine (C02D)	7	6	1.00	0.29–3.46
Thiazides and related diuretics (C03A,–B,–E)	23	28	0.76	0.40–1.46
High-ceiling diuretics (C03C)	17	12	1.10	0.48–2.54
Beta-adrenergic blocking drugs (C07A)	30	29	1.06	0.55–2.05
Corticosteroids (H02A)	8	5	2.33	0.63–8.67
Non-steroidal anti-inflammatory drugs (M01A)	9	11	1.00	0.35–2.89
Centrally acting muscle relaxants (M03B)	6	6	0.80	0.21–3.00
Salicylates and paracetamol (N02B)	13	8	2.00	0.70–5.74
Sedatives (N05B)	11	8	1.67	0.61–4.75

DISCUSSION

This study was mainly performed to test the hypothesis that RA is a risk factor for multiple myeloma, and therefore the results strongly support such an association, instead of being a result of multiple significance testing. The medium latency period from onset of RA symptoms to the diagnosis of MM was 21 years with a wide range. Most of the cases had a positive rheumatoid factor in serum.

Different theories regarding the connection between RA and lymphoproliferative neoplasms have been postulated, and the explanation favoured by most authors is that chronic immune stimulation, with its associated lymphocyte activation, predis-

Table 5. Exposure to diagnostic X-ray and radiotherapy prior to MM diagnosis in cases and controls, with odds ratios (OR) and 95% confidence intervals (CI) calculated with sustained matching

Exposure	Cases (n=239)	Controls (n=220)	OR	95% CI
⩾ 5 diagnostic X-ray investigations	65	82	0.58	0.32–1.06
5–10 X-rays	29	43	0.50	0.29–0.87
11–20 X-rays	20	27	0.77	0.41–1.46
> 20 X-rays	16	13	0.92	0.40–2.09
Radiotherapy	10	12	0.73	0.30–1.80

Calculations were also made according to the number of diagnostic X-ray investigations experienced; subjects with less than five were regarded as unexposed.

Table 6. Locations/indications for radiotherapy prior to diagnosis of MM in cases and controls

Location/indication	Cases	Controls
Benign conditions		
Spine (spondylosis)	2	1
Peripheral joints	3	1
Dermal (psoriasis)	2	0
Pituitary adenoma	1	0
Tuberculous glands	1	1
Malignant tumours		
Basal cell carcinoma	1	0
Breast carcinoma post operatively	0	4
Inguinal lymph nodes in melanoma	0	1
	0	1
Thyroid carcinoma		
Abdominal lymph nodes in seminoma	0	1
	0	1
Parotid tumour		
Cervix carcinoma (radium + external radiotherapy)	0	1

the subjects there is even a significantly decreased risk to develop MM. This finding may reflect that persons with malignant diseases may disregard less serious conditions.

The mapping of medications prior to the year of MM diagnosis did not reveal any drugs as related to this malignant disease. Thus, this study could not confirm the results in a few earlier studies of laxatives [13] and phenytoin [13, 41, 42] as risk factors for MM.

The decreased risk for MM found for both use of medications and for X-ray investigations, probably reflects increased disease reporting by controls. A biological explanation is hard to find.

However, it may be of interest that more cases than controls reported exposure to more than 20 X-ray procedures. This is in accordance with the findings of a recent American study [22]. It may also be noteworthy that 2 cases (but no controls) had received radiotherapy against the lumbar spine where bone marrow is abundant.

In conclusion, the substantial finding in this study was the association between RA, and perhaps also related disorders, and MM. No earlier case–control study has shown this connection, although several cohorts of RA patients have indicated the same association.

poses to the development of these malignancies [26]. Both increased humoral antibody production and decreased cell-mediated immunity may be of importance[11]. This hypothesis is supported by the fact that certain other diseases with chronic immune stimulation are established risk factors for malignant lymphoma, i.e. Sjögren's syndrome [27–29] and Hashimoto's thyroiditis [30–33].

In the present study other rheumatic diseases, some of which may be related to RA, also seemed to be more frequent in MM cases, but any association between other types of autoimmune diseases and MM was not found, in contrast to some earlier studies [14, 15, 27–34].

In the light of the known connection between the immunosuppressive drug azathioprine, used to prevent rejection of transplanted kidneys, and subsequent development of malignant lymphoma [35], it has been postulated that the use of immunosuppressive and cytotoxic drugs in RA may be partly responsible for the increased incidence of lymphoproliferative malignancies. However, the results in some studies are conflicting [5, 36, 37], and at present the risk of developing these neoplasms in RA is regarded to be independent of prior treatment with cytotoxic drugs [26]. The anti-inflammatory drug phenylbutazone has also been discussed because of its known haematological toxicity, with a suspected connection with leukaemia and malignant lymphoma [38, 39], but an association with MM has not been shown.

In this study the cases were too few to evaluate any possible association between anti-rheumatic drugs and the development of MM. 1 control, but no case subjects had used azathioprine or other immunosuppressive drugs. Phenylbutazone was used by 3 of the cases and each of the controls with RA, and furthermore by 2 non-RA cases and 2 additional controls with indications other than RA according to the questionnaire answers.

The prevalence of rheumatoid arthritis in adults in Sweden is about 1% [40], and is thus in agreement with the observation of 2 controls with the disease found in this study.

There are no indications that controls reported less diseases in general. On the contrary, most diseases were more common in the controls. For the category "other diseases" reported by

1. Lea AJ. An association between the rheumatic diseases and the reticuloses. *Ann Rheum Dis* 1964, **23**, 480–484.
2. Oleinick A. Leukemia or lymphoma occurring subsequent to autoimmune disease. *Blood* 1967, **29**, 144–153.
3. Miller DG. The association of immune disease and malignant lymphoma. *Ann Intern Med* 1967, **66**, 507–521.
4. Owen DT, Waller M, Toone E. Rheumatoid arthritis and malignancy. *Arthritis Rheum* 1967, **10**, 302–303.
5. Lewis RB, Castor CW, Kinsley RE, *et al.* Frequency of neoplasia in systemic lupus erythematosus and rheumatoid arthritis. *Arthritis Rheum* 1976, **19**, 1256–1260.
6. Monson RR, Hall AP. Mortality among arthritis. *J Chronic Dis* 1976, **29**, 459–467.
7. Prior P, Symmons DPM, Hawkins CF, *et al.* Cancer morbidity in rheumatoid arthritis. *Ann Rheum Dis* 1984, **43**, 128–131.
8. Katusic S, Beard CM, Kurland LT, *et al.* Occurrence of malignant neoplasms in the Rochester, Minnesota rheumatoid arthritis cohort. *Am J Med* 1985, **78**, 50–55.
9. Fries JF Bloch D, Spitz P, Mitchell DM. Cancer in rheumatoid arthritis: A prospective long-term study of mortality. *Am J Med* 1985, **78**, 56–59.
10. 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.
11. Hakulinen T, Isomäki H, Knekt P. Rheumatoid arthritis and cancer studies based on linking nationwide registries in Finland. *Am J Med* 1985, **78**, 29–32.
12. Gallagher RP, Spinelli JJ, Elwood JM, Skippen DH. Allergies and agricultural exposure as risk factors for multiple myeloma. *Br J Cancer* 1983, **48**, 853–857.
13. Linet MS, Harlow SD, McLaughlin JK. A case–control study of multiple myeloma in whites: Chronic antigenic stimulation, occupation and drug use. *Cancer Res* 1987, **47**, 2978–2981.
14. Koepsell TD, Daling JR, Weiss NS, *et al.* Antigenic stimulation and the occurrence of multiple myeloma. *Am J Epidemiol* 1987, **126**, 1051–1062.
15. Boffetta P, Stellman SD, Garfinkel L. A case–control study of multiple myeloma nested in the American cancer society prospective study. *Int J Cancer* 1989, **43**, 554–559.
16. Cohen HJ, Bernstein RJ, Grufferman S. Role of immune stimulation in the etiology of multiple myeloma: A case–control study. *Am J Hematol* 1987, **24**, 119–126.
17. Cuzick J, De Stavola B. Multiple myeloma—a case–control study. *Br J Cancer* 1988, **57**, 516–520.
18. Linet MS, McLaughlin JK, Harlow SD, Fraumeni JF. Family history of autoimmune disorders and cancer in multiple myeloma. *Int J Epidemiol* 1988, **17**, 512–513.

19. Preston DL, Kato H, Kopecky KJ, Fujita S. Studies of the mortality of A-bomb survivors. 8. Cancer mortality 1950–1982. *Radiat Res* 1987, **111**, 151–178.
20. Cuzick J. Radiation-induced myelomatosis. *N Engl J Med* 1981, **304**, 204–210.
21. Friedman GD. Multiple myeloma: Relation to propoxyphene and other drugs, radiation and occupation. *Int J Epidemiol* 1986, **15**, 423–425.
22. Boice JD, Morin MM, Glass AG, *et al.* Diagnostic X-ray procedures and risk of leukemia, lymphoma and multiple myeloma. *JAMA* 1991, **265**, 1290–1294.
23. Committee of the chronic leukemia-myeloma task force. NCI: Proposed guidelines for protocol studies. II. Plasma cell myeloma. *Cancer Chemother Rep* 1968, **1**, 17–39.
24. Miettinen OS. Estimation of relative risk from individually matched series. *Biometrics* 1970, **26**, 75–86.
25. Miettinen OS. Estimability and estimation in case-referent studies. *Am J Epidemiol* 1976, **103**, 226–235.
26. Symmons DPM. Neoplasia in rheumatoid arthritis (editorial). *J Rheumatol* 1988, **15**, 1319–1322.
27. Rothman S, Block M, Hauser FV. Sjögren's syndrome associated with lymphoblastoma and hypersplenism. *Arch Dermatol Syphiol* 1951, **63**, 642–643.
28. Tatal N, Bunim JJ. The development of malignant lymphoma in the course of Sjögren's syndrome. *Am J Med* 1964, **36**, 529–540.
29. Kassan SS, Thomas TL, Moutsopoulos HM, *et al.* Increased risk of lymphoma in sicca syndrome. *Ann Intern Med* 1978, **89**, 888–892.
30. Lindsay S, Dailey ME. Malignant lymphoma of the thyroid gland and its relation to Hashimoto disease: a clinical and pathologic study of 8 patients. *J Clin Endocrinol Metab* 1955, **15**, 1332–1353.
31. Holm L-E, Blomgren H, Löwhagen T. Cancer risks in patients with chronic lymphocytic thyroiditis. *N Engl J Med* 1985, **312**, 601–604.
32. Kato I, Tajima K, Suchi T, *et al.* Chronic thyroiditis as a risk factor of B-cell lymphoma in the thyroid gland. *Jpn J Cancer Res* 1985, **76**, 1085–1090.
33. Fukuda A, Hirohata T, Noguchi S, Ikeda M, Matsuo K, Yoshida A. Risks for malignancies in patients with chronic thyroiditis: a long-term follow-up study. *Jpn J Cancer Res* 1987, **78**, 1329–1334.
34. Brinton LA, Gridley G, Hrubec Z, Hoover R, Fraumeni JF Jr. Cancer risk following pernicious anaemia. *Br J Cancer* 1989, **59**, 810–813.
35. Penn I, Hammond W, Brettschneider I, *et al.* Malignant lymphomas in transplantation patients. *Transplant Proc* 1969, **1**, 106–112.
36. Farber SS, Sheon RP, Kirsner AB, et al. Incidence of malignant disease in patients receiving cytotoxic therapy for rheumatoid arthritis. *Arthritis Rheum* 1979, **22**, 608.
37. Balthus JAM, Boersma JW, Hartman AP, et al. The occurrence of malignancies in patients with rheumatoid arthritis treated with cyclophosphamide: A controlled retrospective follow-up study. *Ann Rheum Dis* 1983, **42**, 368–373.
38. Jensen MK, Roll K. Phenylbutazone and leukemia. *Acta Med Scand* 1965, **178**, 505–513.
39. Bean RHD. Phenylbutazone and leukemia: a possible association. *Br Med J* 1960, **2**, 1552–1555.
40. Svensson B. *Inflammerade Leder*. Södertälje, Syntex Nordica AB, 1991. (In Swedish)
41. Matzner Y, Polliack A. Lymphoproliferative disorders in four patients receiving chronic diphenylhydantoin therapy: etiologic correlation or chance association? *Isr J Med Sci* 1978, **14**, 865–869.
42. Aymard JP, Lederlin P, Witz F, et al. Multiple myeloma after phenytoin therapy. *Scand J Haematol* 1981, **26**, 330–332.

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Prognosis of Rectal Cancer in France

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We studied changes in the prognosis of cancer of the rectum (excluding the rectosigmoid junction) from 1978 to 1986 in the French department of Calvados on the basis of the 616 cases in the cancer registry. Taken as whole, survival has improved slightly with time ($P < 0.01$), but the improvement is only significant for men ($P < 0.02$), patients under 70 years ($P < 0.01$) and patients living in urban areas ($P < 0.05$). With regard to tumour characteristics, the improvement was significant only for patients with Dukes' stage C tumours at surgery ($P < 0.02$). To determine the reasons for the improvement in survival, the year of diagnosis and all other prognostic factors were studied in a multivariate model. Diagnostic conditions such as age and tumour stage did not vary from 1978 to 1986; in contrast, the rates of tumour resection and adjuvant radiation therapy increased, possibly explaining at least part of the improvement, particularly for patients with Dukes' stage C tumours.
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INTRODUCTION

CANCER OF the rectum is frequent in both France and in Europe as a whole [1]. In France, cancer of the rectum (excluding the rectosigmoid junction), represents about one third of all colorectal cancers [2, 3]. On the basis of registries, the average 5-year survival rate is between 35 and 40% [4, 5]. In the last 10 years, the use of endoscopy has become widespread and attempts to improve survival have involved tumour resection and adjuvant therapy [6–9]. The aim of this study was to assess possible changes in the prognosis of rectal cancer in a well-defined population, together with the impact of changes in medical practice in this setting.

PATIENTS AND METHODS

Between 1 January 1978 and 31 December 1986, 616 cancers of the rectal ampulla, excluding cancers of the anus and those of