

# REPORTS

## Incidence of Cancer Among Patients With Rheumatoid Arthritis

Gloria Gridley, Joseph K. McLaughlin, Anders Ekblom, Lars Klareskog, Hans-Olov Adami, David G. Hacker, Robert Hoover, Joseph F. Fraumeni, Jr.\*

**Background:** To evaluate hypotheses about the relationship between immune alterations and cancer, several investigators have determined cancer incidence in groups of patients with rheumatoid arthritis (RA), a chronic autoimmune disease. The primary finding has been an increased risk of hematopoietic cancers. **Purpose:** In this study, we have attempted to refine estimates of the association between RA and subsequent development of specific cancers. **Methods:** We investigated site-specific cancer risk associated with RA in a population-based cohort study of 11683 Swedish men and women with a hospital (inpatient) diagnosis of RA. These case patients were identified from 1965 to 1983 and had follow-up through 1984 by computer linkage of the Swedish Hospital Inpatient Register to the National Swedish Cancer Registry (840 case patients with cancer) and the Swedish Registry of Causes of Death. Cancer risk was estimated by standardized incidence ratios (SIRs) for specific cancers. **Results:** For men and women overall, there were decreased risks for cancers of the colon (SIR = 0.63; 95% confidence interval [CI] = 0.5-0.9), rectum (SIR = 0.72; 95% CI = 0.5-1.1), and stomach (SIR =

0.63; 95% CI = 0.5-0.9) and an increased risk for lymphomas (SIR = 1.98; 95% CI = 1.5-2.6). **Conclusions:** The reduced risk for colorectal cancer in patients with RA is consistent with previous studies of RA patients and with reports which state that use of nonsteroidal anti-inflammatory drugs may protect against the development of large bowel cancers. The excess of lymphomas also confirms a number of earlier investigations of RA patients. [J Natl Cancer Inst 85:307-311, 1993]

Rheumatoid arthritis (RA) is a chronic autoimmune disease of worldwide distribution and unknown etiology. It strikes women more often than men and urban more than rural inhabitants (1). It affects about 1% of adults over 18 years of age. Because of the presence of altered immune function in RA patients, a number of investigators have studied the subsequent incidence of cancer in this population (2-11). In most studies (see Table 1), no increase in total cancer incidence was observed other than the reported increased risk for all types of hematopoietic cancer (lymphoma, multiple myeloma, and leukemia).

Only one study had more than 75 case patients (7), so the estimates of site-specific cancer risks have been mostly based on small numbers. While earlier reports suggested an overall deficit of cancer, which was later attributed to an artifact of study methodology (3,5), subsequent studies of RA showed a slight decrease of some cancer types, such as colorectal cancer (7,9,11). Clarification of these risks may shed light on the interplay between immune disorders, their treatment, and cancer risk. For example, reduced risks for colorectal cancer have been reported among regular users of nonsteroidal anti-inflammatory drugs

(NSAIDs) (12-14), which are employed extensively in treating RA patients.

In the present study, we have taken advantage of the ability to link a regional population-based registry of hospital discharge diagnoses with a nationwide cancer registry in Sweden to investigate the association of RA with subsequent cancer risk. The size and nature of this data resource allow a detailed evaluation of site-specific cancer risks following RA.

## Patients and Methods

### Patients

The six-county Uppsala Health Care Region is located in central Sweden and had, during the study period, a total population of 1.2-1.3 million people. Because there is almost no private inpatient treatment in Sweden, hospital-provided medical services are, in effect, population-based and referable to the county in which the patient lives. From 1965 through 1983, the Swedish National Board of Health and Welfare received annual reports from all inpatient medical institutions in Sweden and recorded data on individual hospital admissions and discharges in the Swedish Hospital Inpatient Register. Each record contained a national registration number (NRN), a unique personal identifier assigned to all Swedish citizens, and data on place of residence, dates of admission and discharge, surgical procedures, and up to eight discharge diagnoses. These diagnoses were coded according to the seventh revision of the Nordic edition of the International Classification of Diseases through 1968 (ICD7) and according to the eighth revision thereafter (ICD8). All records in the Inpatient Register with a diagnostic code for RA (ICD7 code 722.00 or ICD8 codes 712.20, 712.38, or 712.39) were considered for inclusion in this study. The NRN allowed us to select the first hospitalization with a diagnosis of RA for each individual for the study period. Excluded from the cohort were 125 patients with ankylosing spondylitis, a separate disease that has been linked to radiotherapy-induced leukemia and other cancers (15).

\*See "Notes" section following "References."

**Table 1.** Published retrospective studies of cancer following rheumatoid arthritis\*

Study (year)	End point	Maximum years of follow-up	No. of RA patients	Total No. of cancers	Observed/expected						
					All cancers	Colorectal cancer	Lung cancer	Hematopoietic cancer	Lymphoma	Multiple myeloma	Leukemia
Monson and Hall (6) (1976)	Mortality	42	1035	72	1.36	1.3 <sup>†</sup>	1.2 <sup>‡</sup>	1.7	§	§	§
Isomaki et al. (7) (1978)	Incidence	7	46 101	1202	1.06	0.8	1.3 <sup>‡</sup>	2.2	2.7	2.2	1.7
Allebeck (8) (1982)	Mortality	7	1165	56	1.14	1.0	1.3	1.7	1.9	§	1.3
Katusik et al. (9) (1985)	Incidence	34	521	67	0.98	0.9	1.4	2.0	1.2	5.0	1.9
Prior (10) (1985)	Incidence	19	489	42	1.35	1.1 <sup>†</sup>	1.1 <sup>‡</sup>	8.7	20.0	0.0	4.3
Laakso et al. (11) (1986)	Mortality	10	1000	42	0.72	0.3	0.7	5.0	3.5	1/0	1/0

\*Studies with fewer than 25 case patients with cancer were not included.

<sup>†</sup>All digestive cancers (colorectal cancers not reported separately).

<sup>‡</sup>All respiratory cancers (lung cancer not reported separately).

§ Not reported.

## Statistical Methods

Newly diagnosed (incident) cancers were identified by computerized linkage of the hospital inpatient records to the National Swedish Cancer Registry for the years 1965 through 1984 (16). After linkage to the nationwide Swedish Registry of Causes of Death, person-years at risk in the cohort were calculated from the date of the first RA hospital admission until the occurrence of a diagnosis of cancer, death, or the end of the observation period (December 31, 1984).

Patients with incomplete NRNs or gender or date discrepancies among the three databases were excluded. The matching was performed only with a computer, and the NRN was the only item used for the match. NRNs in Sweden include date of birth, a unique code, and a validation digit. Names were not used for matching.

The first 60 days of follow-up were excluded from the analysis, a step that thereby eliminated patients who had a diagnosis of cancer or who died with less than 60 days of follow-up. Another effect of this procedure was to decrease the likelihood that a patient was included in the cohort because of prodromal cancer symptoms that mimic RA (17). Expanding the exclusion period up to 1 year did not change the results; thus, to increase statistical power, the analysis covered all subjects who had cancer or who survived 60 or more days after their first RA hospital visit.

Expected cancer incidence was computed by multiplying the observed person-years by the Uppsala Health Care Region cancer incidence rates, which were specific for sex, site, age, and calendar year in 5-year intervals. The measure used to evaluate risk was the standardized incidence ratio (SIR), which is the ratio of observed-to-expected cancers; 95% confidence intervals (CIs) were computed under the assumption that the number of observed cancers follow a Poisson distribution (18).

## Results

A total population of 4218 men and 8787 women with a diagnosis of RA was identified. Subjects were then

excluded from the study for the following reasons: (a) 266 men (6.3%) and 509 women (5.8%) because of an incomplete NRN; (b) 74 men (1.8%) and 131 women (1.5%) because of discrepancies in gender, age, or date of birth or date of death that preceded hospital admission date; and (c) 128 men (3.0%) and 214 women (2.4%) because they had fewer than 60 days of follow-up at diagnosis of cancer (61 subjects) or at death (281 subjects). The final cohort consisted of 11683 patients: 3750 men and 7933 women.

This cohort had follow-up to 20 years, for a total of 101000 person-years (average, 8.6 years per person). Both men and women averaged 60 years of age at first inpatient diagnosis of RA. RA was the primary diagnosis on at least one hospital visit for 82% of the patients, the sole diagnosis for 52%, and a secondary diagnosis for 18%. For those with a secondary RA diagnosis, the primary diagnosis was most often heart disease, diabetes, osteoarthritis, or bone fracture. Keeping only patients with RA as a primary diagnosis on at least one hospital visit (82%) or only those with RA as the sole diagnosis (52%) did not substantially affect the SIRs, so all patients were included in the analyses. There were 106 RA patients with accompanying Sjögren's (sicca) syndrome, which is known to predispose to lymphoma (19). Their exclusion had no effect on the SIRs for lymphoma, so they were kept in the analysis.

As shown in Table 2, the overall cancer incidence for the RA patients was close to expectation in both sexes (840 case patients with cancer; SIR =

0.95; 95% CI = 0.9-1.0). Reduced risks were found in both sexes for all digestive cancers combined (SIR = 0.70) and for specific sites including stomach (SIR = 0.63), colon (SIR = 0.63), rectum (SIR = 0.72), and liver (SIR = 0.35). For other digestive cancers (i.e., gallbladder and pancreas), reduced risks were seen only in women. A lower risk was also seen in both sexes for bladder cancer (SIR = 0.74) and in women for breast cancer (SIR = 0.79).

Men were at increased risk for all hematopoietic cancers (lymphoma SIR = 2.38, 95% CI = 1.5-3.6; multiple myeloma SIR = 1.83, 95% CI = 0.8-3.5; and leukemia SIR = 1.86, 95% CI = 1.0-3.1), while women were prone only to non-Hodgkin's lymphoma (SIR = 1.94; 95% CI = 1.2-2.9). Among women, the risks for Hodgkin's disease, multiple myeloma, and leukemia were slightly below expectation. The leukemia excess among men was comprised mainly of chronic lymphocytic leukemia (nine cases; SIR = 2.34; 95% CI = 1.1-4.4). The excess of acute nonlymphocytic leukemia was small and was based on few patients (three cases; SIR = 1.36; 95% CI = 0.3-4.0) (data not shown). In addition, elevated SIRs were seen in both sexes for cancers of the lung (SIR = 1.31), kidney (SIR = 1.33), and brain (SIR = 1.38). The excess of kidney cancer involved both renal cell (36 cases; SIR = 1.29) and renal pelvis cancers (four cases; SIR = 1.68).

We examined cancer risks stratified by several measures. Stratifying by number of years since first hospital RA diagnosis showed no increasing or

**Table 2.** Standardized incidence ratios (SIRs) for selected cancers in Swedish male and female rheumatoid arthritis patients

Cancer site (ICD7 code)	Men			Women			Total		
	Observed	SIR	CI	Observed	SIR	CI	Observed	SIR	CI
All (140-209)	331	1.08	1.0-1.2	509	0.88	0.8-1.0	840	0.95	0.9-1.0
Buccal (140-148)	1	0.13	0.0-0.7	16	1.77	1.0-2.9	17	1.03	0.6-1.7
Digestive (150-159)	73	0.79	0.6-1.0	108	0.65	0.5-0.8	181	0.70	0.6-0.8
Esophagus (150)	7	1.81	0.7-3.7	4	0.90	0.2-2.3	11	1.32	0.7-2.4
Stomach (151)	17	0.62	0.4-1.0	22	0.64	0.4-1.0	39	0.63	0.5-0.9
Colon (153)	15	0.70	0.4-1.2	29	0.60	0.4-0.9	44	0.63	0.5-0.9
Rectum (154)	11	0.74	0.4-1.3	17	0.73	0.4-1.1	28	0.72	0.5-1.1
Liver (155.0)	2	0.45	0.1-1.6	2	0.29	0.0-1.0	4	0.35	0.1-0.9
Gallbladder (155.1)	5	1.28	0.4-3.0	10	0.52	0.3-1.0	15	0.65	0.4-1.1
Pancreas (157)	15	1.12	0.6-1.8	17	0.68	0.4-1.1	32	0.83	0.6-1.2
Lung (162, 163)	39	1.19	0.9-1.6	29	1.50	1.0-2.2	68	1.31	1.0-1.7
Breast (170)	0	—	—	106	0.79	0.6-1.0	106	0.79	0.6-1.0
Cervix (171)	0	—	—	17	0.90	0.5-1.4	17	0.90	0.5-1.4
Uterine corpus (172)	0	—	—	27	0.86	0.6-1.1	27	0.86	0.6-1.3
Ovary (175)	0	—	—	30	0.96	0.7-1.4	30	0.96	0.6-1.4
Prostate (177)	90	1.16	0.9-1.4	0	—	—	90	1.16	0.9-1.4
Kidney (180)	16	1.25	0.7-2.0	26	1.38	0.9-2.0	42	1.33	1.0-1.8
Renal cell (180.0)	14	1.27	0.7-2.1	22	1.31	0.8-2.0	36	1.29	0.9-1.8
Pelvis (180.1)	2	1.62	0.2-5.9	2	1.74	0.2-6.3	4	1.68	0.5-4.3
Bladder (181)	14	0.73	0.4-1.2	10	0.74	0.4-1.4	24	0.74	0.5-1.1
Melanoma (190)	1	0.25	0.0-1.4	11	1.23	0.6-2.2	12	0.93	0.5-1.6
Other skin (191)	13	1.26	0.7-2.2	14	1.09	0.6-1.8	27	1.17	0.8-1.7
Brain and central nervous system (193)	8	1.20	0.5-2.4	22	1.46	0.9-2.2	30	1.38	0.9-2.0
Hematopoietic (200-209)	47	2.06	1.5-2.7	43*	1.18	0.9-1.6	90	1.52	1.2-1.9
Lymphoma (200-202, 205)	22	2.38	1.5-3.6	26	1.73	1.1-2.5	48	1.98	1.5-2.6
Hodgkins (201)	9	4.61	2.1-8.8	3	0.95	0.2-2.8	12	2.34	1.2-4.1
Non-Hodgkins (200, 202)	13	1.78	1.0-3.0	23	1.94	1.2-2.9	36	1.88	1.3-2.6
Multiple myeloma (203)	9	1.83	0.8-3.5	7	0.80	0.3-1.6	16	1.17	0.7-1.9
Leukemia (204-207)	15	1.86	1.0-3.1	9	0.79	0.4-1.5	24	1.23	0.8-1.8
CLL (204.0, 204.1)	9	2.34	1.1-4.4	2	0.52	0.1-1.9	11	1.43	0.7-2.6
Other†	30	1.13	0.8-1.8	57	0.90	0.7-1.2	87	1.02	0.8-1.3

\*This number includes one case with ICD7 code 208, polycythemia vera.

†Includes three small intestine, five secondary liver, three nose or middle ear, four larynx, two uterus (not otherwise specified), three vaginal and/or vulvar, one testis, one penis, two eye, six thyroid, 20 other endocrine, three bone, six connective tissue, and 28 other and/or not otherwise specified.

decreasing trend in SIRs for any cancer site. Age at first RA hospitalization also showed no consistent relationships to site-specific cancer risk. However, a greater rate of cancer was seen among patients with more than two hospital visits for RA; this increase was primarily caused by greater risks of all hematopoietic cancers (27 cases of lymphoma, SIR = 3.46, 95% CI = 2.3-5.0; 10 cases of leukemia, SIR = 1.63, 95% CI = 0.8-3.0; and seven cases of multiple myeloma, SIR = 1.58, 95% CI = 0.6-3.3). The risks of digestive cancers remained low regardless of number of visits.

## Discussion

This cohort study of 3750 Swedish men and 7933 women with a hospital diagnosis of RA revealed a reduced risk for several digestive cancers (large bowel, stomach, and liver), which is noteworthy since the known risk fac-

tors for these cancers are quite different from one another (20). The low risk of colon and rectal cancer in our study is consistent with results from previous studies of RA patients (7,9,11) and with reports (12-14) of significant reductions in the risk of large bowel cancers following use of NSAIDs, mainly aspirin, although one study (21) did not find a lowered risk.

In addition, studies in laboratory animals (22,23) have reported an inhibitory effect of NSAIDs on colon cancer development, with a dose-response relationship. Although the mechanisms of action are unclear, the use of NSAIDs in humans has been shown to inhibit tumor growth (24,25), heighten immune response (26), and interfere with prostaglandin synthesis (27,28). Also, chronic immune stimulation associated with RA may decrease the risk for highly antigenic tumors such as colorectal cancer (29) and limit their progression by enhancing the reactivity

of T-lymphocytes against stress proteins expressed by tumor cells (30,31). Furthermore, patients with inflammatory joint diseases sometimes change their diets, particularly to vegetarian fare (32), which might decrease their risk of colon cancer (33).

The low SIR for stomach cancer is consistent with the Finnish cohort of RA patients (7), although in that study only women had a substantially reduced risk. The deficits of digestive cancers that we found could not be attributed to competing risks, since (a) age-specific cancer incidence rates were used and (b) mortality from nonmalignant gastrointestinal disease among RA patients is not greatly elevated (34). We also found lowered risks for liver and breast cancers, but deficits of these tumors have not been reported among RA patients elsewhere.

In contrast, the incidence of lymphomas was increased, in agreement with the excess risks reported in

previous studies of RA patients (5,7,8,10,11,35). This finding was not explained by the inclusion of patients with Sjögren's syndrome. Since rheumatic symptoms may be an early manifestation of lymphoma or leukemia (17), we excluded the first 60 days of follow-up to rule out misdiagnoses of RA. In our study, however, the distinction between Hodgkin's disease and non-Hodgkin's lymphoma may be problematic, since 36% of the diagnoses of Hodgkin's disease from one of the counties in the Uppsala region were changed to non-Hodgkin's lymphoma after a recent pathologic review (36).

The findings of our study and others (7,8,10) suggest a stronger association of RA with lymphoma than with multiple myeloma or leukemia, although it is difficult to evaluate what fraction of these excesses may be due to treatment. Frequent diagnostic x rays may play a role in the risk of multiple myeloma (37). A relationship was reported between the NSAID phenylbutazone and leukemia, but it was attributed to the use of this drug for early rheumatic symptoms of leukemia (38).

Since the late 1960s, various cytotoxic or immunosuppressive drugs have been available as treatment alternatives for patients with severe RA. In cancer patients, alkylating agents such as cyclophosphamide have been linked to bladder cancer and acute nonlymphocytic leukemia (39), while azathioprine has been associated with non-Hodgkin's lymphoma in kidney transplant recipients (40). Several surveys of RA patients given alkylating or immunosuppressive agents have shown excesses of leukemia (41), non-Hodgkin's lymphoma, and bladder cancer; however, these surveys were generally based on few cancer cases (42-45).

In our study, there was a deficit of bladder cancer and only a small increase of acute nonlymphocytic leukemia. These findings were consistent with our clinical impression that few RA patients in Sweden were treated with cytotoxic drugs. In England, the increased risks of lymphoma and leukemia in RA patients were not related to cytotoxic or immunosuppressive therapy (10), suggesting a role for immunologic alterations accompanying

RA, such as chronic immune stimulation, reduced lymphokines and natural killer cell activity, or susceptibility to Epstein-Barr virus (5,46).

Our study also revealed moderate excesses of lung, kidney, and brain cancers. Four previous studies (6-9) of RA patients have reported an excess of respiratory cancer, two (7,9) an excess of brain cancer, and one (6) an excess of kidney cancer. We have no information on smoking habits, but RA patients tend to be more often urban (1), which may contribute to slightly higher lung cancer rates. Also, rheumatoid interstitial lung disease may predispose to lung cancer, based on case reports (47), and an association has been reported between rheumatoid factor positivity and lung cancer (48). Renal pelvis cancers and, to some extent, renal cell cancers have been linked to heavy consumption of phenacetin-containing analgesics (49,50), which were used in the past to treat RA patients.

There are several strengths and limitations of our study. The advantages include the large size of the cohort, its population-based nature, the quality of the cancer registry data, and the nearly complete ascertainment of cancer and death. One limitation is that the computerized hospital records used in the analysis lacked information on treatment. Another concern is the uncertainty of RA diagnoses reflected by periodic changes in definition (51). Moreover, this cohort was composed of hospitalized patients, who probably tended to have more severe RA disease or an intervening major illness, so the results may not be generalizable to all RA patients. While there was some evidence that severity of disease (as measured by number of hospital visits for RA) was associated with increased risk of hematopoietic cancers, direct markers of severity (e.g., erosions or nodules) were not available in this study.

Nevertheless, this large study of RA patients confirmed an increased risk of hematopoietic cancer, particularly lymphoma, and also revealed a significant reduction in the incidence of digestive cancers, including colon and rectal. The latter finding lends support to reports of lowered colorectal cancer risk among users of NSAIDs.

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## Notes

*Author affiliations:* G. Gridley, J. K. McLaughlin, R. Hoover, J. F. Fraumeni, Jr., Division of Cancer Etiology, National Cancer Institute, Rockville, Md.

A. Ekbom, L. Klareskog, H.-O. Adami, Cancer Epidemiology Unit, University Hospital, Uppsala, Sweden.

D. G. Hacker, Information Management Services, Silver Spring, Md.

*Correspondence to:* Gloria Gridley, Division of Cancer Etiology, National Cancer Institute, 6130 Executive Blvd., EPN 443, Rockville, MD 20852.

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## Enhancement of Cellular Accumulation of Cyclosporine by Anti-P-glycoprotein Monoclonal Antibody MRK-16 and Synergistic Modulation of Multidrug Resistance

*Mikihiko Naito, Harumi Tsuge, Chie Kuroko, Tomoko Koyama, Akihiro Tomida, Tohru Tatsuta, Yuji Heike, Takashi Tsuruo\**

**Background:** Drug resistance is a major obstacle to successful cancer chemotherapy. P-glycoprotein, which transports certain antitumor agents out of resistant tumor cells, is known to be a major factor in some types of multidrug resistance. Studies have shown that verapamil and the immunosuppressors cyclosporine and FK-506 can reverse multidrug resistance in vitro and in vivo and that the P-glycoprotein monoclonal antibody MRK-16 increases drug toxicity in multidrug-resistant tumors. **Purpose:** The purpose of this in vitro study was to establish effective treatment modalities for overcoming multidrug resistance. We assessed the synergistic effects of verapamil, cyclosporine, or FK-506 in combination with MRK-16 and antitumor agents. **Methods:** Human myelogenous leukemia K562 cells and multidrug-resistant K562/ADM cells were treated with vincristine or doxorubicin combined with MRK-16 and cyclosporine alone or together; MRK-16 and verapamil alone or together; or MRK-16 and FK-506.

\*See "Notes" section following "References."