Cancer risk in hospitalized rheumatoid arthritis patients

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Objectives. Patients diagnosed with RA have been at an increased risk of many cancers and at a decreased risk of some cancers. We planned to revisit the theme by using a nation-wide population of RA patients.

Methods. An RA research database was constructed by identifying hospitalized RA patients from the Hospital Discharge Register and cancer patients from the Cancer Registry. Earlier studies from Sweden have shown that some 75% of RA patients have been hospitalized at some point. Follow-up of 42 262 RA patients was carried out from year 1980 to 2004 including separate follow-ups for shorter intervals. Standardized incidence ratios (SIRs) were calculated for cancer in RA patients by comparing with subjects without RA.

Results. Many cancers were in excess in RA patients, especially Hodgkin disease, non-Hodgkin lymphoma and squamous cell skin cancer; a novel association was found for non-thyroid endocrine tumours. Colon, rectal and endometrial cancers were decreased in RA patients. When RA patients were first hospitalized after 1999, the SIRs for melanoma, squamous cell skin and upper aerodigestive tract cancers and for leukaemia were increased compared with previous periods.

Conclusions. This study, the largest so far published, quantified the increased and decreased site-specific risks of cancer in RA patients. The recent increases in the risks of squamous cell skin and upper aerodigestive tract cancers, melanoma and leukaemia call for continuous vigilance and recording of changes in treatment.

KEY WORDS: Subsequent cancer, Changing risk, Age at onset, National databases.

Introduction
RA is a common autoimmune disease with an estimated population prevalence of 1% [1]. In these diseases, dysregulated lymphocytes react against self-antigens by producing autoantibodies and the normal immune function is suppressed; in RA synovial joints are particularly affected [1, 2]. Dysregulation of the host’s immune surveillance is a recognized cause of human cancer [3, 4]. Immunosuppression, i.e. the reduced capacity of the person’s immune system to respond to foreign antigens, is a risk factor of many cancers, as noted after organ transplantation and infections by immunodeficiency viruses [5–8]. Lymphoma risk has been consistently elevated in RA patients, and an increased risk of non-melanoma skin, lung and prostate cancers has also been noted [9–17]. Cigarette smoking is a risk factor for RA and in addition to lung cancer, even other smoking-related cancers such as bladder and renal cancers have been in excess in RA patients [18, 19]. The types of neoplasms increased in RA patients have featured those with the highest risks after immunosuppression, consistent with the notion that the immunosuppressed state rather than the previously used medication for RA underlies the risk of cancer. However, because the medication for RA has changed extensively, there is a need to follow the trends in cancer in the patients [20–22].

In the present study, we used the Swedish data resources on medically diagnosed RA and cancer, with a national coverage, to analyse risks of cancer in RA patients, with a specific aim to further characterize the spectrum of cancers and their time trends. The present report is based on 42 262 hospitalized RA patients and on all cancers diagnosed in them. It is the largest study so far published.

Materials and methods
The RA research database, used for this study, was constructed by linking several national Swedish registers. Statistics Sweden, the Swedish government-owned statistics bureau, provided the Multigeneration Register on the Swedish population. Linkages were carried out to national census data, in order to obtain individual occupational status. The final link was made by adding individual data from the Swedish Hospital Discharge Register that records data on all discharges with dates of hospitalization and diagnoses since the 1960s with a complete nation-wide coverage since 1987. All linkages were performed by the use of an individual national identification number that is assigned to each person in Sweden for their lifetime. This number was replaced by a serial number for each person in order to provide anonymity. The serial number was used to check that each individual was only entered once, for his or her first appearance with an RA diagnosis. Over 11.5 million individuals were included in this database.

Cancers were retrieved from the nationwide Swedish Cancer Registry from the period 1958 to 2004. A four-digit diagnostic code according to the seventh revision of the International Classification of Diseases (ICD-7) was used. The ethics committee at the Karolinska Institutet, Stockholm, Sweden, approved this study.

Outcome and adjustment variables
RA patients were retrieved from hospital discharges reported according to the seventh (1964–68), eighth (1969–86), ninth (1987–96) and 10th (1997–) ICD codes. A total of 50 354 RA patients were identified. However, because of the long follow-up, main results are only shown for RA patients hospitalized for the first time between years 1980 and 2004. The follow-up of cancer was also limited to that period. The individual variables controlled for in the analysis include gender, age at diagnosis (categorized <30, 30–39, 40–49, 50–59, 60–69 yrs), occupational status [six groups: (i) farmers, (ii) unskilled/skilled workers, (iii) white collar workers (iv), professionals (v), self-employed and (vi) all others] and region [three groups: (i) large cities, Stockholm, Gothenburg and Malmo, (ii) Southern Sweden and (iii) Northern Sweden], allowing adjustment for possible regional differences in hospitalization.
**Results**

Among 42,262 RA patients hospitalized for the first time during years 1980–2004, 4366 patients developed cancer after being hospitalized for RA, giving an overall SIR of 1.23 and an SIR of 1.17 for cancer diagnosed later than 1 yr of hospitalization (1+), as shown in Table 1. Only sites with at least 35 cases for the whole period were included; none of the rarer sites showed a significant difference. We separately show data for the whole period and 1+ because for some cancers the risks were very high during the first year, probably because of a concomitant diagnosis of RA and cancer; however, significant increases and decreases in SIRs agreed for the whole and 1+ periods for all cancer sites. The highest overall increase of 4.05 was noted for Hodgkin disease, followed by non-Hodgkin lymphoma (2.34), squamous cell skin cancer (1.89) and lung cancer (1.73); the increases at these sites were noted at all follow-up time since RA diagnosis. Other sites with increased SIRs for the whole period were the liver, prostate, kidney, bladder, skin (melanoma), non-thyroid endocrine glands (mainly parathyroid gland tumours) and haematopoietic system (leukaemia). SIRs for leukaemia were increased during the first year of RA diagnosis and the only leukaemia subtype that showed an overall increase was acute myeloid leukaemia with an SIR of 2.40 (n = 52; 95% CI 1.79, 3.15), thus ranking somewhat higher than non-Hodgkin lymphoma. The SIRs for sites with an increasing risk appeared not to be influenced by the length of the follow-up time (disregarding the first year after RA diagnosis), with the exception of Hodgkin disease, for which SIRs increased with follow-up time. The SIRs for some cancers were decreased, including colon (0.77), rectal (0.68) and endometrial (0.73) cancers. We also analysed the risk of RA after diagnosed cancer. Almost all significant results were limited to the first year of cancer diagnosis, suggesting a simultaneous diagnosis of the two conditions (data not shown).

The effect of age at RA diagnosis is shown in Table 2. For some cancer sites with an increased SIR (squamous cell skin and leukaemia), an early age (<50 yrs) of RA diagnosis was a risk factor for subsequent breast cancer. The other cancer sites included only 1 yr of cases. For most other sites, a late age at diagnosis (>64 yrs) correlated with a high risk; in the latter group, lung, prostate, kidney and bladder cancers were examples. For colon, rectal and endometrial cancers with an overall protective effect, the protection tended to be more extensive when the RA diagnosis was rendered before the age of 65 yrs.

In order to study periodic effects in respect to the changing therapeutic regimens, we analysed separately cancer risk in RA patients who were first hospitalized in the 1990s or after 1999 (Table 3). As only 5 yrs could be the follow-up after 1999, separate analyses were done for those diagnosed <1 and 1–4 yrs after hospitalization. The overall SIRs were higher for patients diagnosed after 1999 with those diagnosed earlier. The SIRs for squamous cell skin cancer (5.26 for <1 yr and 3.93 for 1–4 yrs), melanoma (1.81 for 1–4 yrs) and leukaemia (4.88 for <1 yr and 2.03 for 1–4 yrs) were particularly increased compared with the previous period. Among leukaemias, chronic lymphatic leukaemia was increased <1 yr after RA diagnosis (n = 6; SIR 9.84; 95% CI 3.54, 21.55 in the period 2000–04 compared with n = 2; SIR 1.98; 95% CI 0.19, 7.28 in the period 1990–99); acute myeloid leukaemia was increased in the 1- to 4-yr period (n = 8; SIR 6.90; 95% CI 2.95, 13.66 in the period 2000–04 compared with n = 9; SIR 2.51; 95% CI 1.14, 4.80 in the period 1990–99). Notably, the SIR for upper aerodigestive tract cancer was high in the latter period (7.22 for <1 yr); almost all these cancers were of squamous cell histology.

**Discussion**

Hospitalized cases of RA have been used in several previous Swedish studies analysing the risk of cancer. About 75% of the
Swedish RA patients have been estimated to be hospitalized at one time or another [12, 13, 23]. Probably the severity of disease is one factor contributing to hospitalization. Hospitalizations for RA and other conditions normally require a doctor’s pass from the primary care. Thus, each hospitalized patient is seen at least by two medical doctors, of which the one in the hospital is likely to be a rheumatologist. Thus, diagnostic accuracy is probably high for hospitalized RA patients. However, one problem with the hospitalized patients is that the first hospitalization may be several years after the onset of RA. Thus, even though we have analysed people entering hospitals for the first time, they may have been diagnosed and treated before the hospitalization. The Cancer Registry records all new cases of cancer and close to 100% of the cases are histologically or cytologically confirmed [24].

The spectrum of cancers that were increased after RA was not very different from earlier studies [9–17]. Because the present

### Table 2. SIR for subsequent cancer of patients with RA by age at diagnosis

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<th>Cancer site</th>
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| O: observed number of cases; bold type: 95% CI does not include 1.00.

### Table 3. SIR for subsequent cancer of patients with RA by follow-up time in periods 1990–99 and 2000–04

<table>
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<tr>
<th>Follow-up intervals (yrs), 1990–99</th>
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<td>Cancer site</td>
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O: observed number of cases; bold type: 95% CI does not include 1.00.
study is the largest one so far published, solid risk estimates were derived. The highest risks were noted for lymphomas and squamous cell skin cancer, in accordance with the spectrum of cancers observed after immunosuppression [5–8]. Increases in some of the less infrequently reported neoplasms included prostate cancer and melanoma. A novel observation was the increase in non-thyroid endocrine tumours, which was mainly explained by parathyroid adenomas. For all cancers, the highest risks were observed during the year of hospitalization for RA, which is likely to be due to lead time bias. However, these early cancers were so few that the SIRs calculated for the whole follow-up period and for the whole period minus the first year (1+) were not essentially different. Moreover, the lead time bias only shifts the diagnoses earlier but the diagnostic accuracy is not compromised; thus, even the early cases are true cancers. Thus, the 1+ risk is an underestimate of the true risk. The decreased risks of colorectal and endometrial cancers have been associated with anti-rheumatic therapies with agents such as NSAIDs [13].

The second aim of the present study was to follow the temporal trends of cancers. The caveat with present data on the RA patients is that we only know the first date of hospitalization but not the date of the initial diagnosis; moreover, we have no data on medication. The comparison of SIRs for those hospitalized in 2000–04 with those hospitalized in the 1990s showed increases for all cancers and particularly for squamous cell skin and upper aerodigestive tract cancers, melanoma and leukaemia. Upper aerodigestive tract cancers are predominantly squamous cell carcinomas, and lip and oral cavity cancers are vastly increased after immunosuppressive therapy [7, 8]. Among leukaemias, chronic lymphatic and acute myeloid leukaemias were in excess. Acute myeloid leukaemia, which was increased in the present analysis, is commonly found as a therapy-related side-effect [25].

In summary, the follow-up of RA patients showed the increased and decreased patterns of subsequent cancers many of which have been reported before. The recent increases in the risks of squamous cell skin and upper aerodigestive tract cancers, melanoma and leukaemia call for continuous vigilance and recording of changes in treatment.

**References**