Risks of solid cancers in patients with rheumatoid arthritis and after treatment with tumour necrosis factor antagonists

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Background: Existing studies of solid cancers in rheumatoid arthritis (RA) reflect cancer morbidity up until the early 1990s in prevalent cohorts admitted to hospital during the 1980s. Objective: To depict the cancer pattern of contemporary patients with RA, from updated risk data from prevalent and incident RA populations. To understand the risk of solid cancer after tumour necrosis factor (TNF) treatment by obtaining cancer data from cohorts treated in routine care rather than trials. Methods: A population based study of three RA cohorts (one prevalent, admitted to hospital 1990–2003 (n = 53,067), one incident, diagnosed 1995–2003 (n = 3703), and one treated with TNF antagonists 1999–2003 (n = 4160)), which were linked with Swedish nationwide cancer and census registers and followed up for cancer occurrence through 2003. Results: With 3379 observed cancers, the prevalent RA cohort was at marginally increased overall risk of solid cancer, with 20–50% increased risks for smoke related cancers and >70% increased risk for non-melanoma skin cancer, but decreased risk for breast (−20%) and colorectal cancer (−25%). With 138 cancers, the incident RA cohort displayed a similar cancer pattern apart from non-decreased risks for colorectal cancer. TNF antagonist treated patients displayed solid cancer (n = 67) risks largely similar to those of other patients with RA. Conclusion: The cancer pattern in patients treated with TNF antagonists mirrors those of other contemporary as well as historic RA cohorts. The consistent increase in smoking associated cancers in patients with RA emphasises the potential for smoking cessation as a cancer preventive measure in RA.
The Inpatient Register RA cohort
The Swedish Inpatient Register contains individual-based information on inpatient care county wide since 1964 and nationally since 1987. For every hospital discharge, information on diagnoses and surgical procedures is recorded according to the International Classification of Diseases (ICD) versions 7–10. We identified all subjects above 16 years of age ever discharged with a diagnosis of RA (primary or contributory diagnosis) between 1 January 1990 and 31 December 2003. The ICD codes used were 714A-C, 714W (ICD 9), and M05–6 (ICD 10). We excluded subjects who were also discharged with systemic lupus erythematosus, ankylosing spondylitis, or psoriatic arthritis. For each patient, computerised information on the date of first hospital discharge with RA (1964–2003), discharge department, age, sex, and national registration number (NRN, unique to each resident and recorded in all health and census registers) was recorded (table 1). No information on drug treatment was available. Based on the estimated prevalence of RA in the general population, we calculate that the treatment was available. Based on the estimated prevalence of RA in the general population, we calculate that the

The Early Arthritis RA cohort
In Sweden, RA is normally diagnosed and followed up by rheumatologists. Centres reporting to the Early Arthritis Register contain a typical mix of small outpatient clinics and larger population based centres. The Early Arthritis Register contains information on subjects with incident (<1 year from onset) RA diagnosed at participating centres since the mid-1990s, with a geographically varying (40–100% in different regions, overall around 70%) but increasing coverage of the estimated number of cases of incident RA. From this register, we collected information on date of diagnosis of RA, date of birth, sex, and the NRN for 3703 patients with RA diagnosed from 1995 through 2003 (table 1). The TNF antagonist cohort of patients with RA
Within the context of a continuing Swedish structured post-marketing surveillance programme we assembled a cohort of 4160 patients with RA treated with etanercept, infliximab, or adalimumab between 1999 and 2003 (table 1). Details and patient identification methods have been described elsewhere. In brief, patients were identified through the Swedish Medical Products Agency in collaboration with the Swedish Society for Rheumatology, and through regional surveillance programmes of patients treated with TNF antagonists. A rough estimation from sales statistics suggests that at least 80% of all patients with RA treated with TNF antagonists in Sweden are included in this register. For each patient, we collected information on date of birth, sex, NRN, type of TNF antagonist, and date of treatment start and discontinuation (table 1).

Register linkages and follow up
Through linkage (of all subjects, using the NRN as linkage key) to the Swedish Cancer Register 1964–2003, we collected information on all registered solid malignancies, including the date of diagnosis. Reporting to this registry is mandatory for clinicians and pathologists, resulting in a completeness of around 99%. Only malignant (rather than, for example, atypical) lesions are registered. Non-melanoma skin cancer excludes basal cell cancer, which is not reported. Through linkage to the Cause of Death Register 1964–2003 and to the Register of Population and Population Changes 1969–2003, we collected information on marital status, and vital status, including date of death and date of emigration until 31 December 2003.

Statistics
We used standardised incidence ratios (SIRs, the ratio of the observed and expected numbers of cancers) as measures of relative risk. Expected numbers were calculated by multiplying sex-, age-, and calendar period-specific person-years of follow up with corresponding rates from the entire Swedish population. To avoid bias from misdiagnosis and selection for admission to hospital due to an incipient malignancy, we excluded observed and expected cancers during the first year of follow up in the Inpatient Register RA cohort, and stratified all cohorts by time of follow up. Ninety five per cent confidence intervals were calculated assuming a Poisson distribution of the observed cases. Trends were evaluated using Poisson regression. Because more than 80% of all observation time in the TNF antagonist cohort represented time during treatment, we present data based on the total follow up time. Sixty nine per cent of the TNF antagonist cohort had been admitted to hospital for their RA, and 27% of the Early Arthritis cohort had been admitted to hospital for their RA before 31 December 2003.

RESULTS
Relative risk of cancer in the prevalent Inpatient Register RA cohort 1990–2003
Based on 3379 observed cases of solid cancer, patients in the Inpatient Register RA cohort were at a minimally increased overall risk of solid cancer (SIR = 1.05, 95% CI 1.01 to 1.08; table 2). The overall relative risk was 1.19 (95% CI 1.13 to 1.26, n = 1311) among men and 0.97 (95% CI 0.93 to 1.02, n = 2068) among women. Much of this sex difference was explained by a reduced occurrence of breast cancer (SIR = 0.83, 95% CI 0.76 to 0.91, n = 471) but a risk of prostate cancer close to the expected (SIR = 0.98, 95% CI 0.89 to 1.09, n = 390).

Table 1 Characteristics of the three Swedish cohorts of patients with RA

<table>
<thead>
<tr>
<th></th>
<th>Inpatient Register</th>
<th>Early Arthritis</th>
<th>TNF antagonist</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>53067</td>
<td>3703</td>
<td>4160</td>
</tr>
<tr>
<td>Men</td>
<td>15185</td>
<td>1114</td>
<td>1048</td>
</tr>
<tr>
<td>Women</td>
<td>37882</td>
<td>2589</td>
<td>3112</td>
</tr>
<tr>
<td>Age at start of follow up (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16–44</td>
<td>4666</td>
<td>782</td>
<td>950</td>
</tr>
<tr>
<td>45–74</td>
<td>29900</td>
<td>2421</td>
<td>2986</td>
</tr>
<tr>
<td>75+</td>
<td>18501</td>
<td>500</td>
<td>224</td>
</tr>
<tr>
<td>Calendar period of entry into cohort</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1964–1979</td>
<td>6932</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1980–1989</td>
<td>11867</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1990–1999</td>
<td>20898</td>
<td>1176</td>
<td>11</td>
</tr>
<tr>
<td>1999–2001</td>
<td>7667</td>
<td>1478</td>
<td>2398</td>
</tr>
<tr>
<td>2002–2003</td>
<td>5703</td>
<td>1049</td>
<td>1751</td>
</tr>
<tr>
<td>Mean (min–max)</td>
<td>5.6 (0–13)</td>
<td>3.6 (0–8)</td>
<td>2.3 (0–4)</td>
</tr>
<tr>
<td>Person-years</td>
<td>297102</td>
<td>13292</td>
<td>9715</td>
</tr>
<tr>
<td>DAS28*</td>
<td>–</td>
<td>mean 3.5</td>
<td>mean 5.5</td>
</tr>
<tr>
<td></td>
<td>median 3.5</td>
<td>median 5.6</td>
<td></td>
</tr>
<tr>
<td>HAQ*</td>
<td>–</td>
<td>mean 0.6</td>
<td>mean 1.4</td>
</tr>
<tr>
<td></td>
<td>median 0.7</td>
<td>median 1.4</td>
<td></td>
</tr>
</tbody>
</table>

Numbers indicate number of patients in each cohort unless otherwise specified.
*In the Early Arthritis cohort, values (means) refer to status at 6 months after diagnosis of RA. In the anti-TNF cohort, values refer to status at the start of anti-TNF treatment.

Register of Population and Population Changes
Gastrointestinal cancer risk was marginally reduced (SIR = 0.85, 95% CI 0.78 to 0.93, n = 554), made up by a decreased risk of colorectal cancer (SIR = 0.74, 95% CI 0.66 to 0.82, n = 342), which tended to decrease with increasing time of follow up (p for trend = 0.01; table 3). Respiratory tract cancers, essentially lung cancers, were more common than expected (SIR = 1.48, 95% CI 1.33 to 1.65, n = 330). The occurrence of non-melanoma skin cancer (SIR = 1.66, 95% CI 1.50 to 1.84, n = 374) was also increased, and increased with increasing time of follow up (p for trend = 0.001; table 3). A modestly increased occurrence of melanomas, kidney and bladder cancers was also noted (table 3). Age- and sex-specific incidences of selected solid cancer sites are tabulated in the appendix.


Overall, we observed 138 solid cancers in this cohort (SIR = 1.1, 95% CI 0.9 to 1.3), with a non-increased risk in women (SIR = 0.87, 95% CI 0.67 to 1.11, n = 64) and an increased risk among men (SIR = 1.42, 95% CI 1.12 to 1.79, n = 74). The sex difference was largely due to increased (prostate cancer, SIR = 1.6) and decreased (breast cancer, SIR = 0.6) risks for sex-specific cancers (table 2). Lung cancer occurred more often than expected (SIR = 2.4). When stratified by time since diagnosis of RA, the increased overall occurrence of cancer was confined to the first year after diagnosis of RA, and partly explained by prostate cancers diagnosed during this period (table 4).


We observed a total of 67 solid cancers in the TNF antagonist treated cohort (SIR = 0.9, 95% CI 0.7 to 1.2). The relative risk of solid cancer was non-significantly reduced among women (SIR = 0.87, 95% CI 0.63 to 1.16, n = 45) but 1.06 (95% CI 0.67 to 1.61, n = 22) among men, and varied little with time since the start of treatment (table 4). Contrary to the other RA cohorts, we did not observe any decreased occurrence of colorectal cancer (SIR = 1.2), but similar to the other RA cohorts, we noted an increased occurrence of lung cancer (SIR = 1.8), a markedly reduced occurrence of breast cancer (SIR = 0.4), but an increased occurrence of non-melanoma skin cancer (SIR = 3.6, table 2). Because of low numbers, trends in site-specific relative risks were difficult to evaluate (table 4).
DISCUSSION

To provide contemporary data on the risk of solid cancers in RA, we followed up the hitherto largest cohort of prevalent patients—admitted to hospital with RA during the 1990s—for cancer occurrence through 2003. To assess the generalisability of these cancer risks, we also followed up a recent cohort of incident patients with RA not necessarily admitted to hospital. In doing so, we made several important observations. Firstly, we confirmed the non-increased overall solid cancer risk in (female) RA and its composition of increased and decreased site-specific risks. Secondly, we found that the cancer patterns in the two cohorts were largely similar, with the exception that recently diagnosed patients with RA were neither at decreased risk of colorectal cancer nor at increased risk of non-melanoma skin cancer, but at particularly increased occurrence of cancer often detected during routine medical examinations (prostate cancer). To assess the safety of TNF antagonists we followed up a large cohort of patients with RA treated with TNF antagonists in routine care, but found (with the possible exception of non-melanoma skin cancer) no conspicuous occurrence of solid cancers. Finally, to aid future evaluation of drug safety we presented incidence rates for solid cancers in RA.

Current knowledge of the risk of solid cancers in RA essentially rests upon data from historical cohorts of prevalent patients with RA who have been identified in hospital discharge registers and followed up for cancer occurrence in other health registers.2,45 Although the results of these studies have been internally consistent, their generalisability to current patients and clinical practice, and their ability to serve as reference rates (only relative risks have been presented) in the safety evaluation of new drugs must be judged in light of the following.

Firstly, the RA cohorts identified may neither reflect the burden of RA disease or treatment experience nor the distribution of other risk factors for cancer (for example, smoking among women) that characterise patients of today. Instead, the typical patient with RA has been identified on the basis of admission to hospital for RA dating 15 or more years back in time (1977–1987 in Mellemkjaer et al.,1965–1983 in Gridley et al.,4 1981–1996 in Thomas et al.,7 and from the 1960s until 1990 in Kauppi et al and Myllykangas-Luusujarvi et al.14). Secondly, the follow up of these cohorts has, with few exceptions,11,35 ended before the early 1990s, so there is little information on any changes in cancer risk related to the substantial changes in average RA disease status or treatment implemented during the past 10–20 years.

Thirdly, because these studies employed the same methodology and included a qualitatively similar subset of patients with RA, their consistent results come as little surprise, but leave unanswered the question of whether patients with RA ever-admitted to hospital differ from those never admitted to hospital. Likewise, entry into the cohorts in these studies was set to the date of the first discharge with RA, which may not necessarily equate to the date of diagnosis of RA. Although there are studies using other designs and follow up methods,11,35 these have often been limited to a few hundred patients diagnosed and/or followed up before the 1990s.

It follows from the above that we need not only updated cancer risks from large scale RA cohorts but also more information on how cancer risks in such prevalent cohorts compare with those of recent, incident—and largely outpatient—RA cohorts. Across all cohorts followed up—and as in previous studies—we noted a difference between the sexes, with higher overall relative risks among men than women. This difference between men and women was largely explained by a reduced risk of female breast cancer. This reduced breast cancer risk is not only consistent with some previous reports but also with recent data suggesting an inverse association between non-steroidal anti-inflammatory drug (NSAID) use (but not acetaminophen) and breast cancer.24 The non-increased risk of prostate cancer in the prevalent RA cohort in combination with the increased occurrence in early follow up in the incident cohort suggests that the latter risk may be due to increased detection rather than a true RA related risk increase.

In the Inpatient Register RA cohort, we not only observed an increased risk for non-melanoma skin cancer but also an increasing relative risk with increasing follow up time, which may explain the non-increased risk in the incident RA cohort, in which the average disease duration was shorter. The 70% increased risk in our study is higher than the 20% increased risk reported by Gridley et al who followed up patients with...
RA identified in the Swedish Inpatient Register during the 1960s up until the 1980s, suggesting increasing risks also by calendar period. Because immune suppression is an established risk factor for non-melanoma skin cancer, a causal association with an increasingly aggressive approach in the treatment of RA cannot be ruled out. The 25% reduced risk of colorectal cancer in the Inpatient Register RA cohort not only corroborates previous studies, but may be an effect of NSAID use.

In the Early Arthritis Register cohort, there was a non-significantly increased (+13%) colorectal cancer risk. Apart from poor precision because of the small number of observed colorectal cancers in this cohort (n = 18), possible explanations for the seemingly divergent risks include detection bias (colorectal cancer is often detected during investigation for anaemia or gastrointestinal bleeding, both of which are common medical problems in RA), insufficient time for NSAIDs to exert any protective effect, or a lower use of NSAIDs in the incident cohort.

Smoking is a risk factor for (seropositive) RA, and a risk factor for a wide array of cancers (for example, respiratory tract cancer, kidney, and urinary bladder cancer), which also displayed increased risks in our cohorts. However, like colorectal cancer, part of the immediate risk increase for lung cancer may be related to detection bias such as through chest x ray examinations, which at least in Sweden are common in the investigation for RA. It remains clear however, that stopping smoking would provide substantial cancer prevention in RA.

Information about the safety of new drugs can be derived from several sources: clinical trials offer a built-in comparator group, but the patients under study often differ substantially from those encountered in routine care. Patients at the highest risk of cancer—for example, those with anaemia for unknown reason, pathological liver enzyme tests, history of cancer, or precancerous lesion, are often excluded, and the trials are often too short to detect insidious adverse events like cancers. Open extensions of the treated arm of clinical trials may, if carefully monitored, provide good data on the occurrence of rare outcomes, but require readily available reference rates against which the experiences in the treated population (which is still a selected group) can be compared. Post-marketing surveillance which relies on physicians’ spontaneous reporting may result in underreporting and difficulties in determining the person-time experience.

Structured monitoring programmes of patients treated within the framework of routine care as in our study offer patients who have been less selected, and—if supplemented by qualitatively similar reference rates—provide a unique possibility of assessing the spectrum of comorbidity associated with treatment.

For TNF antagonists, analyses of clinical trials have shown an increased occurrence of malignant lymphomas, but inconspicuous risks for solid cancers, including a significant deficit of lung cancers, which may indicate patient selection.

Using regional data, and data from a previous national linkage, we have previously reported the occurrence of solid cancer after treatment with TNF antagonists. Although the number of observed cases was small (n = 118 and n = 167, both sets are included in the 67 cases observed in the current study), the relative risk for solid cancer overall in our three approaches is similar. Although still based on modest number of cancers, and although we cannot exclude the possibility that patients with a lower risk for cancer are directed towards treatment with TNF antagonists, our results suggest that TNF antagonists as actually used in practice are not associated with a cancer pattern that differs from that of other patients with RA (although the non-decreased colorectal cancer occurrence may be a concern). Prolonged follow up is necessary in order to detect or rule out cancer risks for which the induction time exceeds the currently available follow up times.

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<table>
<thead>
<tr>
<th>Table 5</th>
<th>Age- and sex-specific incidences (per 100 000) of solid cancers in the Swedish Inpatient Register RA cohort 1990–2003</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site [ICD-7]</td>
<td>Men</td>
</tr>
<tr>
<td>0-49</td>
<td>50-74</td>
</tr>
<tr>
<td>All solid (140–199)</td>
<td></td>
</tr>
<tr>
<td>Colorectal (153-154)</td>
<td>182 (97 to 312)</td>
</tr>
<tr>
<td>Hepatobiliary (155-156)</td>
<td>0 (0 to 52)</td>
</tr>
<tr>
<td>Lung (162)</td>
<td>0 (0 to 52)</td>
</tr>
<tr>
<td>Breast (170)</td>
<td>0 (0 to 52)</td>
</tr>
<tr>
<td>Prostate (177)</td>
<td>28 (3.4 to 102)</td>
</tr>
<tr>
<td>Melanoma (190)</td>
<td>28 (3.4 to 102)</td>
</tr>
<tr>
<td>Non-melanoma skin (191)</td>
<td>0 (0 to 52)</td>
</tr>
</tbody>
</table>

*Excludes cancers and person-years during the first year after entry into cohort.
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APPENDIX


REFERENCES


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