Skin Cancer, Rheumatoid Arthritis, and Tumor Necrosis Factor Inhibitors

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ABSTRACT. ***Objective.*** To determine the rates of reported non-melanoma skin cancer (NMSC) in a large cohort of patients with rheumatoid arthritis (RA) in comparison to patients with osteoarthritis (OA) and to determine risk factors for the development of NMSC in patients with RA.

Methods. Self-reported information from 15,789 patients with RA and 3,639 patients with OA were collected through semi-annual questionnaires since 1999. Survival analyses were used to determine incidence rates for NMSC among patients with RA and OA. Multivariate Cox proportional hazard models were used to estimate hazard ratios (HR) for the development of NMSC. Separate analyses were performed for patients with RA to explore associations between use of immunosuppressive medication and development of NMSC.

Results. The crude (unadjusted) incidence rate for reported NMSC among patients with RA and OA were 18.1 and 20.4 per 1000 patient years, respectively. OA patients were older, more likely to be Caucasian, and had higher past incidence of NMSC. Age, male sex, Caucasian race, and history of NMSC prior to entry into the database were associated with an increased risk of NMSC in multivariate Cox proportional hazard models. After adjustment for covariates, RA was associated with an increased risk of NMSC (HR 1.19, p = 0.042). Among RA patients, the development of NMSC was associated with use of prednisone (HR 1.28, p = 0.014) and tumor necrosis factor (TNF) inhibitors alone or with concomitant methotrexate (HR 1.24, p = 0.89 and HR 1.97, p = 0.001, respectively) in addition to established risk factors including fair skin, age, male sex, and previous history of NMSC. No association was found between use of methotrexate or leflunomide and development of NMSC (HR 1.12, p = 0.471, HR 0.83, p = 0.173, respectively).

Conclusion. In this large, national cohort, RA was associated with an increased risk for development of NMSC. Among patients with RA, use of TNF inhibitors and prednisone were associated with an increased risk of NMSC. (J Rheumatol 2005;32:2130–5)

Key Indexing Terms:
RHEUMATOID ARTHRITIS CANCER BASAL CELL CARCINOMA
SQUAMOUS CELL CARCINOMA INCIDENCE RATES
TUMOR NECROSIS FACTOR INHIBITORS

Many studies have confirmed that although rates of overall cancers are not increased substantially from the general population, certain types of cancers may be seen with higher frequency in patients with rheumatoid arthritis (RA)[1-3]. Most notably, an increased risk for the development of lymphoproliferative disorders, particularly non-Hodgkin's lymphoma, has been shown in patients with RA[4-6]. It is unclear whether this increased risk is due to aberrancies in the immune system from higher inflammatory activity in RA, from certain immunosuppressive agents used to treat RA, or a combination of the 2[5,6].

Several studies of European populations have suggested a slightly increased risk for the development of nonmelanoma skin cancers (NMSC), such as basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) in patients with RA when compared to rates in the general population[2,3]. Similar studies have generally not been performed on US populations as incidence rates of NMSC are not kept in national cancer registries.

BCC and SCC are among the most common types of malignancies, and although they rarely metastasize to distant sites or lead to death, their high prevalence and associated morbidity contribute to the overall public health burden. Studies have shown that the presence of NMSC may be associated with an increased risk for the subsequent devel-

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opment of internal malignancies[7,8]. Known risk factors for the development of NMSC include age, male sex, fair skin, sun exposure, and ionizing radiation[9]. Cigarette smoking is associated with an increase risk of SCC only[10,11]. Immune suppression may play a key role in the development of both SCC and BCC, although the incidence of SCC may be more affected by immunosuppression than BCC[9,12]. Data from renal transplant recipients have repeatedly shown an increased risk of both BCC and SCC in this population when compared to the general population[12,13]. In addition, patients with renal transplants develop SCC an average of 20 years younger than the general population[12].

The recent advent and widespread use of tumor necrosis factor (TNF) inhibitors to treat RA has raised additional concerns about the risk of NMSC with the use of these agents. Several case reports have described patients developing rapid onset of SCC after administration of TNF inhibitors[14,15]; however, another study found no increased risk for the development of SCC in patients participating in clinical trials of etanercept when compared to the general population[16,17].

We conducted a large cohort study to examine the incidence rates of NMSC in patients with RA compared to patients with osteoarthritis (OA) to identify possible risk factors for development of disease. Additionally, we sought to evaluate the role of several immunosuppressive medications on the development of NMSC.

MATERIALS AND METHODS

Study participants. Patients in the study were participants in the National Data Bank for Rheumatic Diseases (NDB) longterm study of the outcomes of RA and OA. This database was designed to analyze health outcomes including morbidity, mortality, and comorbid conditions. Patients were recruited from the practices of 908 US rheumatologists as described[6,18,19] and are systematically followed up by NDB staff using semiannual questionnaires. The diagnoses of RA and OA were made by patients' rheumatologists. The NDB is an open cohort, and patients are added continuously. After initial assessment, approximately 8% of patients decline to participate each year. All patients with a diagnosis of RA or OA who had returned at least 2 completed semiannual questionnaires between January 1999 and January 2003 were included in the study. Data from 15,789 patients with RA (40,125 patient-years) and 3,639 patients with OA (9,988 patient-years) were available for analysis.

Questionnaire. For each questionnaire assessment, patients report demographic and clinical variables including the Health Assessment Questionnaire Disability Index (HAQ-DI), a validated tool for measuring functional disability that ranges from 0 (no disability) to 3.0 (inability to perform any common activities listed)[20]. Comorbid conditions including any malignancies, surgical procedures, medications, and side effects of treatment are additionally reported. At the time of enrollment into the NDB, patients report current (last 6 months) or past malignancies. Additionally, they report current malignancies in each biannual questionnaire completed. If a questionnaire is missed, patients are required to complete the past or "ever" questionnaire again.

Diagnosis of skin cancer. Each patient reporting NMSC was interviewed by an outcomes assessor to confirm the diagnosis of skin cancer versus a precancerous event, that the cancer was a new occurrence, and the date of diagnosis. The diagnosis of NMSC was accepted on determination that the report of the cancer was the result of a physician's diagnosis. In surrogate analyses, we have found that patient's report of illnesses are concordant with discharge diagnoses approximately 94% of the time[6,19]. From such data, we expect that patients report skin cancer with similar levels of accuracy. Validation processes for NMSC were instituted only recently, and could not be retrospectively obtained for earlier questionnaires. Because all reports could not be validated for the entire study period, patients' self-report of diagnosis of skin cancer was used as the dependent variable. We assume that any misclassification of diagnoses would be non-differential between RA and OA patients. NMSC could not be further divided into subsets of BCC and SCC.

Statistical analysis. Descriptive statistics including baseline demographics and cumulative reports of NMSC were compared between RA and OA groups at each patient's last observation within the databank. This captures all past NMSC reported in enrollment questionnaires as well as all reports of NMSC during the followup period. Variables including outdoor occupations, sun exposure, history of renal transplantation, and family history of NMSC were not collected for a significant proportion of patients, and could not be included in the analysis.

Survival analysis using Cox proportional hazard model were used for all analyses, with failure defined as a report of NMSC during the past 6 months (current) on a semi-annual questionnaire. Incidence rates of new NMSC were calculated for RA and OA groups. In the first analysis, all RA and OA patients were included. Univariate hazard ratios (HR) were computed for baseline demographics including age, disease duration, gender, race, marital status, education level, total income, smoking status, history of diabetes, HAQ-DI, and history of NMSC prior to enrollment in NDB. All clinically important variables were included in the multivariate analysis: diagnosis (RA vs OA), age, gender, race, marital status, high school graduate, history of NMSC prior to enrollment into the NDB, and HAQ-DI.

The second analysis was restricted to patients with RA only (15,789) in order to examine the effects of immunosuppressive medications upon the incidence of NMSC. Again, univariate analysis was performed for the same variables as in the first analysis with the addition of disease specific variables including disease duration, and any past or current use of prednisone, leflunomide, methotrexate (MTX), and TNF inhibitors (collectively). Subcategories of medication variables including average weekly dose, duration of use, or cumulative dose were not analyzed further. Development of a multivariate model was performed in the same fashion as in the first analysis. Covariates in the final model included age, gender, race, disease duration, marital status, high school graduate, history of NMSC prior to enrollment into the NDB, HAQ-DI, use of prednisone, leflunomide, MTX, TNF inhibitor without MTX, and combination TNF inhibitor plus MTX. All analyses were then repeated using only incident cases (15,191 patients with RA and 3,428 with OA), excluding patients with a reported history of NMSC prior to enrollment into the NDB.

RESULTS

Demographic variables for patients with RA and OA at their last observation are listed in Table 1. Patients with RA were younger than those with OA (62 vs 67 yrs, $p < 0.001$), were less likely to have diabetes (12% vs 16%, $p < 0.001$), and were more likely to have a history of smoking (56% vs 46%, $p < 0.001$). The majority of patients in both groups were Caucasian and women. Mean HAQ-DI scores were comparable between the 2 groups (1.09 vs 1.07, $p = 0.330$). Patients with RA were less likely to report NMSC prior to enrollment into the NDB (3.8% vs 5.8%, $p < 0.001$).

A total of 738 patients with RA reported new cases of NMSC during followup within the NDB compared to 204 patients with OA, resulting in a crude incidence rate of 18.1 per 1000 person-years observation for RA patients (95%

Table 1. Baseline demographics of patients with RA versus OA at the last observation point. Results are expressed as percentages unless otherwise defined.

Variable	RA (N = 15,784)	OA (N = 3,639)
Age, yrs, mean ± SD	62 ± 13	67 ± 12
Disease duration, yrs, mean ± SD	15 ± 11	17 ± 11
Proportion male	23	17
Proportion Caucasian	91	94
Proportion married	68	63
Proportion with high school diploma	89	91
Total income, mean*	45.5	42.4
Proportion with diabetes	12	16
Proportion with smoking history	56	46
HAQ disability index, mean ± SD	1.09 ± 0.8	1.07 ± 0.7
Skin cancer before NDB,** no. (%)	596 (3.8)	211 (5.8)

* $1000 US. ** NDB: National Data Bank for Rheumatic Diseases.

confidence interval, CI: 16.8-19.4 per 1000 person-years) and 20.4 per 1000 person-years among OA patients (95% CI: 17.8-23.4 per 1000 person-years, p = 0.126). Age and gender adjusted incidence rates for RA and OA patients are shown in Table 2. After excluding prevalent cases of NMSC, crude incidence rates were reduced to 15.2 (95% CI: 14.1–16.5) and 15.8 (95% CI: 13.5-18.5) per 1000 person-years for RA and OA, respectively (p = 0.689). However, patients with OA tended to have more known risk factors for the development of NMSC: older age and Caucasian race.

Results from univariate and multivariate Cox proportional hazard model are summarized in Table 3. There appears to be an association between a small increase in risk for the development of NMSC and diagnosis of RA, with a HR of 1.19 (p = 0.042) in the multivariate model. As expected, the highest HR were seen with known strong risk factors for skin cancer: Caucasian ancestry (HR 5.05, p = 0.001) and prior history of NMSC (HR 6.62, p = 0.001). Surprisingly, smoking status did not have a statistically significant association with the development of skin cancer. Increasing HAQ-DI had only a minimal, nonsignificant impact on the development of NMSC. In the final multivariate model, diagnosis of RA, increasing age, male gender, Caucasian ancestry, married, and history of NMSC were associated with an increased risk of NMSC. The inclusion of total income and history of diabetes did not change results of the final model. Results of multivariate analysis restricted to patients without a history of reported NMSC prior to enrollment into the NDB were similar (data not shown).

Table 4 lists the results of the multivariate Cox proportional hazard analysis restricted to patients with RA. The same variables, including increasing age, Caucasian ancestry, male gender, being married, and history of prior NMSC were found to have similar effects when limited to RA patients. The use of prednisone was associated with an increased hazard (HR 1.28, p = 0.014) for the development of NMSC among RA patients; however, no association was seen with use of antimetabolite drugs (leflunomide and MTX) alone. The use of any TNF inhibitor (etanercept, infliximab, and adalimumab) alone showed a slightly increased risk of NMSC that did not reach statistical significance (HR 1.24, p = 0.089). An approximately 2-fold hazard for the development of NMSC was found among patients with RA using both MTX and any TNF inhibitor (HR 1.97, p = 0.001). These results were essentially unchanged when the analysis was restricted to incident cases only (patients without a reported history of NMSC) (data not shown).

DISCUSSION

BCC and SCC are among the most common types of malignancies, and although they rarely metastasize to distant sites or lead to death, their high prevalence and associated morbidity contribute to the overall public health burden. In the general population, SCC is less common than BCC by a ratio of approximately 1:4-5[12]. The estimated annual incidence of BCC in 1994 was approximately 200 to 500 per 100,000 people in the US in contrast to the estimated annual incidence of SCC of 25-130 per 100,000 persons[10]. Known risk factors for the development of NMSC include age, male sex, fair skin, sun exposure, and ionizing radiation[9]. Cigarette smoking is associated with an increase risk of SCC only[10,11].

Our results show that although crude incidence rates are

Table 2. Incidence rates of NMSC per 1000 person-years (95% CI) by age and gender among patients with RA or OA.

	RA*		OA**	
Age, yrs	Male	Female	Male	Female
< 45	2.0 (0.3–14.0)	4.2 (2.6–6.9)	0	0
46–55	6.5 (3.4–12.5)	7.7 (6.0–10.4)	6.0 (0.9–43.0)	1.8 (0.5–7.3)
56–65	26.1 (20.2–33.8)	11.7 (9.5–14.4)	28.2 (15.2–52.4)	12.1 (8.4–17.5)
66–75	39.4 (32.4–48.0)	21.1 (18.0–24.8)	49.5 (33.2–73.9)	25.1 (19.3–32.7)
> 76	67.5 (54.6–83.5)	30.1 (25.0–36.2)	70.3 (49.4–99.9)	23.4 (17.2–31.7)

* Crude incidence rate 18.1 (16.8–19.4) per 1000 patient-years. ** Crude incidence rate 20.04 (17.8–23.4) per 1000 person-years.

Table 3. Univariate and multivariate Cox proportional hazard model analyses for risk factors for skin cancer among patients with RA and OA.

Variable	Univariate HR	p	Multivariate HR	95% CI	p
RA	0.90	0.194	1.19	1.01–1.41	0.042
Age	1.05	0.001	1.05	1.04–1.06	0.001
Male gender	2.23	0.001	1.83	1.56–2.14	0.001
Caucasian race	9.57	0.001	5.05	2.51–10.16	0.001
Smoking	0.7	0.009	0.99	0.86–1.15	0.938
Married	1.21	0.012	1.26	1.08–1.49	0.004
High school graduate	0.98	0.873	1.26	0.99–1.61	0.062
NMSC prior to NDB	8.01	0.001	6.62	5.58–7.85	0.001
HAQ	1.03	0.582	1.06	0.96–1.18	0.212
* Total income	1.00	0.842			
* Diabetes	0.92	0.451			

* Not included in multivariate model. NDB: National Data Base for Rheumatic Diseases.

Table 4. Multivariable Cox regression analysis for patients with RA only to determine risk factors for skin cancer.

Variable	HR	95% CI	p
Age	1.05	1.04–1.06	0.001
Caucasian	5.58	2.08–15.00	0.001
Male	1.61	1.30–2.00	0.001
Disease duration	1.01	1.00–1.02	0.004
Smoking	0.91	0.65–1.26	0.568
High school graduate	1.29	0.92–1.80	0.136
Married	1.3	1.04–1.62	0.021
HAQ	0.91	0.79–1.05	0.216
NMSC prior to NDB	6.71	5.31–8.50	0.001
Prednisone	1.28	1.05–1.55	0.014
Leflunomide	0.89	0.68–1.18	0.424
MTX without TNF	1.15	0.81–1.64	0.421
TNF inhibitor without MTX	1.24	0.97–1.58	0.089
Combination MTX and TNF	1.97	1.51–2.58	0.001

NDB: National Data Base for Rheumatic Diseases; NMSC: non-melanoma skin cancer; MTX: methotrexate; TNF: tumor necrosis factor.

similar, there appears to be a small but significant increased hazard of developing NMSC in patients with RA compared to OA (HR 1.19). Because national cancer registries do not collect incidence data of NMSC in the general population, we used a cohort of patients without inflammatory arthritis, OA patients, as a control group. Other studies have shown an increased incidence of NMSC among RA patients of similar magnitude when compared to the general population of Northern Europe, with standardized incidence ratios and relative risks ranging from 1.17[2] to 1.4[3], respectively. As expected, we found that age, male sex, and Caucasian ancestry were all associated with an increased hazard for the development of NMSC. In all analyses, married people were more likely to develop NMSC than those who were unmarried. This may be a reflection of increased detection of NMSC in married people rather than a true increased risk of the disease. Several studies have suggested that married people may be more likely to perform skin self-examinations than unmarried individuals[21]. Study results have been mixed about the association between education level and performance of skin self-examinations[21]. We did not find an association between smoking and NMSC. This is likely because cigarette smoking is associated with an increase in SCC only and we analyzed combined NMSC without analyzing separate subsets of BCC and SCC.

Immune suppression may play a key role in the development of both SCC and BCC. Data from solid organ transplant recipients has repeatedly shown an increased risk of NMSC when compared to the general population, and this risk appears to be related to the level of immunosuppression[22]. The main immunosuppressive medications studied in transplant recipients included prednisone, azathioprine, cyclosporine, and cyclophosphamide[22], which are less commonly used in the treatment of RA. Because transplant

recipients usually receive a combination of several immunosuppressants, it has been difficult to address the effect of any single agent upon the risk of NMSC. One study examined the role of prednisone upon the risk of NMSC in a group of heart transplantation recipients and found that the neither the average daily dose nor the cumulative dose of prednisone was associated with an increased risk of NMSC[23].

To examine possible associations between immunosuppression and NMSC in our cohort of patients with RA, we performed multivariate Cox regression including variables of the common immunosuppressive medications used by these patients (prednisone, MTX, leflunomide, and TNF inhibitors). Although we did not see an increased incidence of NMSC in patients using MTX or leflunomide, we found an increased hazard of developing NMSC among patients taking prednisone (HR 1.28) and a trend toward increasing risk with use of TNF inhibitors: HR 1.24 for TNF inhibitors without concomitant MTX and 1.97 for TNF inhibitor in combination with MTX. The association was still present when only patients without a history of NMSC were analyzed. This suggests that increasing immunosuppression, particularly with the use of TNF inhibitors, may be associated with increasing risk for the development of NMSC. It must be recognized, however, that we did not look for a dose-response relationship within each class of medication as duration of use or cumulative dose of medication was not included in the analysis. Additionally, we chose to analyze all TNF inhibitors together as a class rather than to examine them individually because any association seen is likely a class effect, either of the degree and type of immunosuppression, or alternatively, of the severity of underlying RA requiring aggressive treatment.

It is possible that the trend toward increased hazard of NMSC with increased immunosuppressive medications is actually confounding by indication: a function of the severity of underlying RA rather than direct effects of immunosuppression itself. We were not able to directly analyze disease inflammatory activity in this cohort with markers such as tender and swollen joint counts and laboratory data, as they were not available. The HAQ-DI is a patient-based composite score of function, which encompasses both the impact of current disease severity as well as accumulated chronic disability[20]. Increasing HAQ scores were not found to be associated with an increased risk of NMSC either in multivariate analysis of both RA and OA patients or in the subanalysis of RA patients alone. We can speculate that this composite index may reflect a combination of factors that may have different effects upon risk for NMSC including degree of inflammatory activity, requirement for aggressive immunosuppressive medications, and decreased function that may reduce patients' outdoor sun exposure.

There are several limitations inherent in our study. First, although all attempts were made to validate NMSC diagnosis, some reported diagnoses were unable to be validated, especially in earlier questionnaires. This is likely because skin cancer is common and many NMSC may be diagnosed and excised based on a clinical diagnosis without histological evaluation. It is possible that patients may have mistakenly reported a diagnosis of cancer when being treated for pre-malignant conditions of the skin including actinic keratoses. Conversely, patients may not have reported "likely" NMSC that did not have confirmatory pathologic diagnoses. Although it may affect absolute incidence rates, this potential misclassification bias is expected to be non-differential between OA and RA patients, and between patients treated with different antirheumatic regimens and, if anything, may bias results toward the null.

A second limitation of our study is that we were not able to separate NMSC into diagnoses of SCC and BCC and analyze them independently. Despite many similarities, these 2 types of NMSC are different in terms of incidence, risk factors such as cigarette smoking, and biology. The normal ratio of SCC to BCC (1:4) appears to be reversed in solid organ transplant recipients, suggesting that the immunopathogeneses of these cutaneous malignancies are distinct[22]. It is possible that RA or immunosuppressive medications affect the incidence of one type of NMSC more than the other, and that estimated HR may be diluted by combining them. Additionally, we were not able to compare the SCC to BCC ratio between patient subsets.

A third limitation surrounds the possibility that unmeasured variables related to the development of NMSC including outdoor occupation, sun exposure, history of solid organ transplantation, or family history of NMSC may be confounders and may introduce bias into the results. We do not expect that the distribution of such variables would be differential between large cohorts of patients with RA or OA; however, the absence of data on these variables precludes our ability to account for them in the final model.

To our knowledge, this is the first large cohort study of the associations between NMSC, RA, and immunosuppressant medications. The increased hazard for the development of NMSC in patients with RA is in concert with that found in other studies of European populations. It is unclear if our finding of an increased hazard of NMSC with the use of prednisone and TNF inhibitors is a function of immunosuppression itself, of increased inflammatory activity of underlying disease, or their combination. Together, these findings suggest that skin cancer screening at regular intervals may be warranted for all patients with RA, especially those receiving chronic immunosuppressive therapy. Further studies examining different subsets of NMSC, rates of metastases, and the effect of increased inflammatory activity are needed to further define associations between RA and skin cancer.

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