Risk of Development of Lung Cancer Is Increased in Patients with Rheumatoid Arthritis: A Large Case Control Study in US Veterans

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ABSTRACT. ***Objective***. To investigate the occurrence of lung cancer in patients with rheumatoid arthritis (RA) in the US veteran population. Patients with rheumatic diseases appear to have an increased risk for the development of lymphoproliferative and some solid organ malignancies.

Methods. We conducted a retrospective case control study using prospectively collected data from the Veterans Integrated Service Networks (VISN) 16 Veteran Affairs (VA) database from 1998 to 2004. We studied the association of RA and lung cancer and analyzed data on 483,721 VA patients. Patients were identified by searching for the diagnoses of RA and lung cancer based on the International Classification of Diseases (ICD) codes. We identified 8768 (1.81%) patients with a diagnosis of RA (ICD code 714.0), 7280 (1.5%) patients with lung cancer (ICD code 162.0), 247 patients with lung cancer and RA, and 7033 patients with lung cancer but no RA. Logistic regression analysis was performed to adjust for age, gender, race, and tobacco and asbestos exposure. Statistical tests were conducted at a 5% level of significance.

Results. The diagnosis of RA was determined to have a significant association with lung cancer in this veteran population. Patients with RA are 43% (odds ratio 1.43) more likely to develop lung cancer than patients without RA, when adjusted for covariates.

Conclusion. Our study shows a significant positive association between RA and the development of lung cancer in the veteran population. Veterans with RA have an increased incidence of lung cancer when compared to the non-RA population. (First Release July 15 2008; J Rheumatol 2008;35:1704–8)

Key Indexing Terms:
RHEUMATOID ARTHRITIS
LUNG CANCER
SCREENING MEDICINE
DISEASE SUSCEPTIBILITY

Rheumatoid arthritis (RA) is a chronic, systemic, autoimmune disease of unknown etiology, characterized by symmetric polyarthropathy resulting in joint destruction, significant debility, and premature mortality, with a worldwide prevalence of 1–1.5%[1,2], a 2- to 3-fold excess in females[3,4], and a peak in prevalence between ages 45 and 54 years[5]. Efforts to ascertain the effects of a chronic immunologic disorder such as RA on cancer risk is limited by factors such as low power (related to small sample size), relatively low risk of malignancy in young patients, and the influence of immunomodulatory drugs used to treat autoimmune diseases on cancer expression. Nevertheless, an association between rheumatic diseases and malignancy has been asserted[6,7]. Three studies have been sufficiently large to analyze site-specific cancer risks[8-10]. Despite minor methodological differences, all reported increased risk for hematopoietic malignancies of 50% to 100% when compared to rates in the general population[10,11]. Further, several studies report an association between cancer and RA[8,12,13].

Lung cancer is currently the most common cause of cancer mortality in the United States and throughout the world[14,15]. The American Cancer Society estimates that lung cancer was responsible for about 172,000 deaths in the USA during 2005, in comparison to 125,000 deaths from colorectal, breast, and prostate cancer combined[16]. Exposure to tobacco, exposure to asbestos, arsenic, halo ethers, nickels, and polycyclic aromatic hydrocarbons are some identifiable risk factors for lung cancer. Genetic and dietary factors and the presence of underlying benign forms of parenchymal lung diseases such as pulmonary fibrosis[17] are other potential risk factors. We investigated whether US military veteran patients with RA have an increased risk of lung cancer.

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MATERIALS AND METHODS

Data source. The Veterans Health Administration (VHA) is organized into 21 administrative regions called Veterans Integrated Service Networks (VISN). VISN 16, or the South Central VA Health Care Network, provides health care to US military veterans in the 8-state region of Florida, Alabama, Mississippi, Louisiana, Arkansas, Missouri, Oklahoma, and Texas. This integrated health care system network includes 10 medical centers, 33 community-based outpatient clinics, 7 nursing homes, and 2 domiciliaries. It is one of the largest of the 21 VISN. Geographically, the network spans about 170,000 square miles and provides healthcare to more than 1.9 million veterans. The Veterans Health Information Systems and Technology Architecture (Vista)[18,19] is the integrated electronic medical record (EMR) system for the VHA that contains, among other information, records of inpatient stays, outpatient visits, diagnostic codes (according to International Classification of Diseases Codes), current procedural terminology codes, pharmacy records, and laboratory test results[20].

All this information, except the content of narrative progress notes, can readily be accessed by means of automated queries. Prior to 1995 the various facilities maintained their Vista databases separately. At that time VISN 16 initiated a VISN-wide information system consolidation by standardizing the data from all the facilities in VISN 16. On October 1, 1996, VISN 16 consolidated each database. The VISN 16 data warehouse is an enriched administrative database and contains prospectively collected data of the patients treated in VISN 16.

The computerized records contain both clinical and administrative information such as all patient encounters (outpatient clinical visits), pharmacy, laboratory, vital signs, and financial and patient demographic data. In addition, several health care factors such as smoking and alcohol intake are recorded. All the diagnoses are coded according to International Classification of Disease (9th version, clinical modification; ICD9-CM). There are 750 million rows of data arranged in relational tables, which can be accessed by Microsoft® SQL server. The data from each facility are extracted monthly from the Vista, and tables are populated after standardization of the data from all the facilities in the VISN. Access to these data is monitored and controlled. The VISN 16 multi-site institutional review board authorized the study protocol, including access and use of the computerized patient clinical information. The informed consent requirement was waived for the study.

Study design. A retrospective case control study nested in a cohort was conducted using as subjects those included in the VISN 16 network with visits to the VA Health Care System between October 1, 1998, and June 1, 2004. A Microsoft® SQL server was used to identify these patients.

The VA administration defines a frequent VA Health Care System user as any person who was seen in a primary care clinic or was hospitalized in the VA Health Care System during the last 2 years. We used this definition to identify recent users of the system during the period between October 1, 1998, and June 1, 2004, for inclusion in our study. It excludes patients who utilize VA for prescriptions only. Thus, out of 1.4 million patients in the VISN 16 network, a total of 483,721 recent users of the VA Health Care System were included in the study. These patients were analyzed for presence of lung cancer, RA, age, race and gender, tobacco, and asbestos exposure. The incident cases that make up the case population consisted of patients diagnosed with lung cancer (with or without RA) during the time period for the study. Patients without lung cancer served as the control population.

Diagnosis of RA was based on physician recording in the electronic system, based on ICD-9 coding (714.0) in the computerized encounter forms.

Duration of disease activity of RA was not factored in the analysis because of the long lag time from the onset of the symptoms in these patients and the time to the initial diagnosis of RA. The temporal relationship between lung cancer and RA was not included in the analysis due to significant delay in the diagnosis of both conditions.

Also, data for treatment with anti-tumor necrosis factor (TNF) therapy in these patients were not available. The relationship of use of these drugs to the development of malignancy, irrespective of the original diagnosis of RA, is an area of much debate[19]. Also, during the study period October 1998 to June 2004, the use of anti-TNF inhibitors was not very common, and at least the duration of the therapy was insufficient to influence the result of development of malignancies secondary to these drugs.

The data were limited to subjects between the age of 18 and 100 years. A total of 173,431 patients without information about their smoking history were deleted from the analysis. Unfortunately, the database did not include duration and intensity of the patient's smoking, but all patients had a previous or current history of smoking.

Statistical analysis. Unconditional logistic regression analysis was performed on the data to determine the effect of RA on risk for developing lung cancer. A simple logistic regression model was used to calculate the crude odds ratio (OR) and its 95% confidence interval (CI), shown in Table 2. To adjust for the effects of confounding factors such age, gender, race, tobacco, and asbestos exposure, which were also significantly associated with lung cancer, multiple logistic regression analysis was performed to calculate the adjusted OR and its 95% CI (see Tables 1 and 2). A multiple logistic regression model with RA and other significant covariates as predictors for lung cancer was tested for goodness of fit to the data using the deviance and Pearson tests.

The OR compares the odds for lung cancer between RA and non-RA patients. For rare events like cancer, the OR and the relative risk (RR) are equivalent, so the OR calculated for our study also compares risk for lung cancer between the 2 groups of RA patients.

Cases and controls were compared for RA diagnosis and other significant covariates, with the adjusted OR shown in Table 1. They were also compared for different categories of the significant confounders with the crude and adjusted odds ratios shown in Table 2. The OR and its 95% CI were used universally in the data analysis.

SAS version 9.1.3 (Cary, NC, USA) was used for statistical computing.

RESULTS

The demographics of the case and control populations are shown in Table 1. The mean age of the case population was 68.9 (± 10.4) years and 61.2 (± 15.1) years for the controls. Men comprised 91.7% (443,556) of the total population. Of the 483,721 patients in the study population, 8768 (1.81%) had a diagnosis of RA and 7280 patients (1.5%) had lung cancer. Of the 7280 patients who had a diagnosis of lung cancer, 247 (3.4%) had RA compared to 8521 (1.8%) of the controls. Among those with available smoking data, a total of 184,517 patients (59.5%) had a history of smoking, 3623 (72.6%) and 180,894 (59.2%) for the cases and controls, respectively. A total of 3,233 patients (0.67%) had asbestos exposure. In addition to diagnosis of RA, other factors significantly associated with lung cancer were race, age, sex, asbestos exposure and tobacco. There was no significant interaction between RA and any of these other significant factors for lung cancer. Controlled for age, gender, tobacco and asbestos exposure, the odds of patients with RA for lung cancer are 1.43 times those without RA, as shown in Table 1.

Patients with RA appear to have an increased incidence of lung cancer, 43% more (OR 1.43 with CI 1.23–1.65) when compared to patients without RA and controlled for age, gender, smoking and asbestos exposure (Table 1).

On further subgroup analysis, as shown in Table 2, RA as a significant risk factor for lung cancer increased with age, and risk was the highest in patients older than 75 (OR 1.61,

Table 1. Summary statistics on observed variables and adjusted odds ratios by lung cancer status. Values are expressed as number (%) or mean ± SD.

Variable	Cases (with lung cancer) n = 7280	Controls (without lung cancer) n = 476,441	Adjusted* OR[a]	95% CI for Adjusted OR
White	4,140 (56.8)	174,772 (36.7)		
Black	1,164 (16.0)	63,188 (13.3)	0.93	0.86, 1.01
Hispanic	72 (1.0)	5,709 (1.2)	0.61	0.47, 0.79
Am Indian/Alaskan	20 (0.3)	1,084 (0.2)	0.81	0.43, 1.52
Asian/Pacific Islander	4 (0.1)	360 (0.1)	0.88	0.33, 2.38
Unknown	1,880 (25.8)	231,328 (48.5)	0.49	0.46, 0.53
Male	7,124 (97.9)	436,432 (91.6)		
Female	156 (2.1)	40,009 (8.4)	0.71	0.59, 0.86
Age, yrs	68.9 ± 10.4	61.1 ± 15.1	1.041	1.039, 1.044
Rheumatoid arthritis	247 (3.4)	8,521 (1.8)	1.43	1.23, 1.65
Tobacco exposure	3,623 (72.6)	180,894 (59.2)	2.15	2.02, 2.30
No. missing info	2,286 (31.4)	171,145 (35.9)		
Asbestos exposure	110 (1.5)	3,123 (0.7)	1.77	1.43, 2.20

* Adjusted for effects of age, race, sex, smoking and asbestos exposure. [a] Versus White for race OR.

Table 2. Crude and adjusted* odds ratios for lung cancer by risk factors and rheumatoid arthritis (RA).

	RA	No. of Patients	No. of Controls	Crude Risk Estimate (OR)	95% CI	Adjusted Risk Estimate (OR)	95% CI	p[a]
Age, yrs								
< 55	Yes	18	1,690	2.24	1.40, 3.58	1.59	0.95, 2.67	0.08
	No	727	152,929					
55–65	Yes	47	2,118	1.58	1.18, 2.12	1.40	1.01, 1.95	0.047
	No	1,562	111,204					
65–75	Yes	87	2,262	1.64	1.32, 2.04	1.50	1.17, 1.93	< 0.01
	No	2,325	99,032					
> 75	Yes	95	2,451	1.68	1.36, 2.07	1.61	1.27, 2.05	< 0.01
	No	2,419	104,255					
Race								
Caucasian	Yes	162	4,449	1.56	1.33, 1.83	1.44	1.20, 1.73	< 0.01
	No	3,978	170,323					
Black	Yes	46	1,447	1.76	1.30, 2.37	1.46	1.05, 2.02	0.02
	No	1,118	61,741					
Unknown	Yes	35	2,412	1.80	1.29, 2.52	1.29	0.84, 1.98	0.24
	No	1,845	228,916					
Other	Yes	4	213	1.42	0.52, 3.89	1.27	0.46, 3.52	0.65
	No	92	6,940					
Asbestos								
Yes	Yes	6	100	1.74	0.75, 4.07	2.04	0.86, 4.85	0.11
	No	104	3,023					
No	Yes	241	8,421	1.92	1.69, 2.19	1.53	1.32, 1.78	< 0.01
	No	6,929	464,897					
Tobacco exposure								
Yes	Yes	153	4,233	1.84	1.56, 2.17	1.59	1.35, 1.88	< 0.01
	No	3,470	176,661					
No	Yes	38	2,387	1.46	1.05, 2.02	1.36	0.98, 1.88	0.07
	No	1,333	122,015					
Missing	Yes	56	1,901	2.24	1.71, 2.93	1.72	1.32, 2.26	< 0.01
	No	2,230	169,244					
Gender								
Males	Yes	232	7,393	1.83	1.60, 2.09	1.48	1.27, 1.73	< 0.01
	No	6,892	428,539					
Females	Yes	15	628	6.67	3.90, 11.43	2.91	1.63, 5.17	< 0.01
	No	141	39,381					

* Adjusted for effects of age, race, sex, tobacco and asbestos exposure. [a] For adjusted OR.

95% CI 1.27 to 2.05). This could be secondary to the longer disease (RA) duration in these patients. At 5% statistical significance, RA did not increase the odds for lung cancer among patients younger than 55 years (OR 1.59, 95% CI 0.95 to 2.67) and it could have been due to the shorter duration of RA in these patients. Table 2 shows that the risk for lung cancer was found to be significantly increased for several subgroups of patients with RA: Caucasians and Blacks, those without asbestos and tobacco exposure, males and females.

The risk for lung cancer was found to be increased in patients with RA in general.

DISCUSSION

To date there are only a few studies to suggest that the risk for lung cancer is increased in patients with RA[21]. Our study is the largest investigation to date supporting this observation. Several mechanisms have been suggested for the association between RA and the increased risk of malignancies including tissue alteration and chronic lymphocyte stimulation. The action of immunosuppressive therapy with anti-TNF drugs may increase the risk of some malignancies, although risks have been observed in RA patients who have not received immunosuppressive therapy[22]. An alternative explanation may be that the 2 diseases share important immunologic and pathogenic factors that remain unidentified. This may reflect either decreased immune surveillance of neoplasms, increased systemic inflammation thus promoting gene rearrangements or increased susceptibility to neoplasm secondary to the fact that interstitial lung disease is more common in those with RA than in the regular population[17].

There have also been data reporting that patients developed arthropathy secondary to chemotherapy treatment for their malignancy, but no studies elucidate that lung cancer predisposes to the development of RA[23].

Our study suggests that risk of lung cancer is increased in patients with RA; increased risk was evident even after controlling for the significant effects of age, gender, tobacco and asbestos exposure. However, although thought provoking, the results of our study should be interpreted with caution. Because our study population was predominantly male (91%, reflecting the male predominance in the armed forces), our observations may not apply to all RA patients. The increased prevalence of RA in the US veteran population (1.8%) when compared to the general population worldwide (1-1.5%) can be well explained: Prevalence of RA is higher in the older population, and our subjects, being veterans, were elderly[24]. Alternatively, a higher prevalence of tobacco abuse among veterans results in increased prevalence of RA in this population[25-27].

Our study is a retrospective, case-control study. Therefore, we cannot rule out unknown biases or confounders. Although our study population was adjusted for tobacco and asbestos exposure, we did not adjust for other possible risk factors of lung cancer such as family history or exposure to halo ethers, polycyclic aromatic hydrocarbons, nickel, arsenic, passive smoke, and radon. Other potential risk factors, including genetic factors, and educational and financial status of the patients, were not included in our analysis.

One of the strengths of our study is the use of a computerized database, with prospective data gathering from patients, allowing for inclusion of 483,721 patients. Use of a computerized diagnosis database (with ICD coding methods) decreases misclassification and recall bias.

Based on our data, we speculate that more careful surveillance for lung cancer in patients with RA could lead to earlier detection and decreased mortality. Further, if chronic inflammation leads to risk of developing malignancies, the risk of lung cancer can be decreased with more aggressive treatment (e.g., TNF inhibitor therapy) of RA[28,29]. The possibility that RA and lung cancer have smoking as a common risk factor increases the importance of counseling for smoking cessation in patients and family members with RA. It may also be advisable that patients with RA have thoracic radiographs more frequently (because of RA itself, before major orthopedic surgeries or as a routine screening because of disease modifying antirheumatic drug treatment) than the normal population without RA. This may lead to an earlier diagnosis and better prognosis of lung cancer in patients with RA.

In conclusion, patients with RA appear to have an increased incidence of lung cancer when compared to matched non-RA subjects. Understanding the complex immunologic and host surveillance interrelationships between RA and malignancy may lead to better surveillance, as well as a better understanding of the pathogenesis of these conditions by health care providers.

Further investigation is warranted to study the magnitude of such an increased risk to further the prevention or early detection of lung cancer in patients with RA. We also conclude that males who had tobacco exposure and have RA are at a higher risk of developing lung cancer than patients who do not have RA. More detailed population studies are required to further our knowledge about the underlying mechanisms of increased risk in patients with rheumatic conditions and cancer.

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