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Impact of Rheumatoid Arthritis on the Mortality of Elderly Patients Who Develop Cancer: A Population-Based Study

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Objective. **Comorbidity among cancer patients poses additional risks for mortality. The possible impact of rheumatoid arthritis (RA) on cancer patient survival is unclear. Our objective was to examine survival among elderly patients with RA who develop cancer.**

Methods. **Patients diagnosed with breast, prostate, colorectal, or lung cancer between 2001 and 2010 were identified from the Texas Cancer Registry and Medicare–linked databases. The cohort was categorized into 3 groups according to the number of claims patients had with a diagnosis of RA in the year prior to the cancer diagnosis: 2-RA (patients with ≥2 claims), 1-RA (1 claim), and no claims. Overall survival was estimated for these groups and for each cancer, using Cox proportional hazards models adjusting for covariates.**

Results. **The cohort included 139,097 patients with cancer (35,026 breast, 43,181 prostate, 31,103 colorectal, and 29,787 lung); 1.7% had 1 RA claim, and 1.1% had 2 or more. Adjusted hazard ratios for patients in the 2-RA group were 1.41 (95% confidence interval [95% CI] 1.21–1.65) for breast and 1.53 (95% CI 1.26–1.85) for prostate. No significant differences were observed for those with colorectal or lung cancer.**

Conclusion. **Mortality was increased by 40% and 50%, respectively, in elderly patients with RA who developed breast or prostate cancer, after controlling for other comorbidities. This association was not seen in cancers with shorter survival time (colorectal or lung). Research is needed to determine whether the increased risk is related to comorbid burden or to differential utilization of cancer or rheumatoid therapies in patients with both diseases.**

INTRODUCTION

There is an excess risk of mortality and morbidity in patients with cancer compared to the general population (1,2). Among cancer patients, premature mortality risk is heightened because of the disease itself, the adverse effects of cancer therapies, and the presence of other comorbid conditions, which are common in the elderly (3–5). The added deleterious effect of comorbid conditions remains after adjusting for age and sex, and has been observed for many different cancer types (6–9).

Patients with rheumatoid arthritis (RA) are at increased risk for certain cancers, possibly because of common genetic and/or environmental factors, the effects of sustained systemic inflammation, and the use of immunomodulating therapies (10–12). A recent meta-analysis reported that, compared with patients without RA, adult patients with RA have an increased risk of developing lung cancer (13) or lymphoma but may be at lower risk for colorectal and breast cancer, possibly because of the use of nonsteroidal antiinflammatory

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Significance & Innovations

- This is the largest study examining mortality risk in patients with both rheumatoid arthritis (RA) and cancer.
- Elderly patients with RA and breast and prostate cancers have an increased mortality risk compared to those with cancer alone, with their median life expectancy shortened by 2 years.
- This deleterious effect appears to occur primarily in patients with the types of cancer expected to have longer patient survival.

agents, which can be protective in colorectal tumors, and because of hormonal factors in the case of breast cancer (14).

Most previous studies that have examined the effect of comorbidity on survival among cancer patients use summary counts of comorbid conditions (weighted or unweighted) to determine the overall effect of comorbidity burden on survival (15–17). However, this approach assumes that each of the conditions assessed has an equal overall effect, which limits the revelation of the real effect for any single condition. Few studies have evaluated the independent effect of RA on the overall survival of cancer patients. This large population-based study examined overall survival in elderly patients with 1 of the 4 most common types of cancer, who had a prior diagnosis of RA, after adjusting for demographic factors and other comorbidities.

PATIENTS AND METHODS

Data sources. This study was approved by the institutional review boards at the University of Texas MD Anderson Cancer Center and the Texas Department of State Health Services, and by the privacy review board of the Centers for Medicare and Medicaid Services. We used 2 population-based data sources to conduct the study analyses: the Texas Cancer Registry (TCR) and Medicare claims data. The Comparative Effectiveness Research on Cancer in Texas consortium has linked TCR and Medicare data collected by the Center of Medicare and Medicaid Services in the state of Texas. The TCR is one of the largest statewide population-based cancer registries in the US, and it maintains high-quality data standards and currently meets the standards of the National Program of Central Cancer Registries, the Centers for Disease Control and Prevention, and the North American Association of Central Cancer Registries. The TCR collects data on age, sex, ethnicity, date of cancer diagnosis, cancer site, stage of disease, initial treatment, and survival. TCR data are reported to be 91% complete, and approximately 98% of TCR patients age ≥65 years have been matched to Medicare beneficiary files. Medicare provides universal health insurance for people age ≥65 years who do not have health insurance coverage. Medicare claims data include information on all services provided to Medicare beneficiaries, including hospital stays and physician services (part A) and supplemental services (part B) containing information on outpatient hospital visits. In addition, we were able to estimate patients' census-level socioeconomic data by linking to 2000 US Census files.

Cohort selection. We included patients who had been diagnosed between 2001 and 2010 with histologically confirmed breast, prostate, colorectal, or non–small cell lung cancer (see Supplementary Figure 1, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.22997/abstract). Other cohort selection criteria were: index cancer was the first cancer diagnosis in the registry; Texas residency and age 66 years or older at the time of cancer diagnosis; enrollment in Medicare parts A and B within 12 months before cancer diagnosis; and no simultaneous enrollment in a health maintenance organization at any time in the 12 months prior to the diagnosis, to ensure that all health care claims would be identifiable in Medicare data.

Measures. TCR provided demographic data on each patient's age, sex, and ethnicity. A comorbidity index score (0, 1, 2, or ≥3) was estimated from the Medicare claims in the 12 months prior to the cancer diagnosis using the Klabunde adaptation of the Charlson Comorbidity Index (CCI), for Medicare claims (18–20). We excluded RA from the comorbidity list so that we could examine the specific effect of RA on survival. Tumor stage was categorized as in situ, localized, regional, distant, or unknown. The population density of the patient's area of residence was determined at the census-tract level and was categorized as big metro and other (with the category other including metro, urban, rural, and unknown). Information related to patient socioeconomic status was not available at the individual level; therefore, patient zip codes were linked to the census data to obtain surrogate values at the census-tract level and were measured as the percentage of median household income. Ethnicity was classified as white non-Hispanic, Hispanic, African American, and other. We were interested in controlling for the well-recognized "Hispanic paradox" in cancer mortality (Hispanics have a 20% lower cancer mortality rate after adjusting for demographic and clinical variables) (21,22).

We used data from Medicare claims to assess whether participants may have RA, using the International Classification of Diseases, Ninth Revision, code 714.0. Accordingly, we created 3 groups based on the number of RA claims: 2-RA, including patients with 2 or more RA claims at least 6 months apart, in the 12 months prior to cancer diagnosis; 1-RA, including patients with a single RA claim in the 12 months prior to cancer diagnosis, or not fulfilling criteria for 2-RA; and patients with no RA claims. This approach was used to increase diagnostic accuracy for identifying RA using administrative databases, which can be enhanced by requiring 2 diagnoses within a given time interval (23). Therefore, individuals in the 2-RA group are more likely to have a confirmed diagnosis of RA than those in the 1-RA group.

Statistical analysis. The characteristics of patients with and without RA claims were compared using a chi-square test for categorical variables and *t*-tests and analysis of variance for continuous variables. Kaplan-Meier curves and log rank tests

Table 1. Demographic and clinical characteristics of patients with and without RA claims (n = 139,097)*

Characteristic	1-RA	2-RA	No RA	*P*
Total	2,289 (1.7)	1,531 (1.1)	135,277 (97.2)	
Mean ± SD age, years	76.2 ± 7.0	75.1 ± 6.2	75.6 ± 7.0	< 0.0001
Sex				
Male	895 (39.1)	511 (33.4)	72,351 (53.5)	< 0.0001
Female	1,394 (60.9)	1,020 (66.6)	62,926 (46.5)	
Ethnicity				
Non-Hispanic white	1,548 (67.7)	1,172 (76.5)	101,809 (75.3)	< 0.0001
Hispanic	452 (19.7)	204 (13.3)	18,950 (14.0)	
African American	241 (10.5)	118 (7.7)	11,671 (8.6)	
Other	48 (2.1)	37 (2.4)	2,847 (2.1)	
Charlson Comorbidity Index				
0	952 (41.6)	725 (47.4)	76,642 (56.7)	< 0.0001
1	635 (27.7)	437 (28.5)	33,100 (24.5)	
2	331 (14.5)	209 (13.6)	13,672 (10.1)	
≥3	371 (16.2)	160 (10.4)	11,863 (8.8)	
Mean ± SD comorbidities	1.2 ± 1.5	1.0 ± 1.3	0.8 ± 1.2	< 0.0001
Stage				
In situ	109 (4.8)	78 (5.1)	6,056 (4.5)	< 0.0003
Localized	995 (43.5)	655 (42.8)	62,302 (46.1)	
Regional	472 (20.6)	346 (22.6)	26,549 (19.6)	
Distant	342 (14.9)	260 (17.0)	20,023 (14.8)	
Unknown	371 (16.2)	192 (12.5)	20,347 (15.0)	
Area of residence				
Big metro	1,022 (44.6)	653 (42.6)	61,141 (45.2)	0.12
Other	1,267 (55.4)	878 (57.4)	74,136 (54.8)	
Median annual income				
Q1 ($7–$30,048)	702 (30.7)	354 (23.1)	33,721 (24.9)	< 0.0001
Q2 ($30,049–$37,368)	570 (24.9)	393 (25.7)	33,865 (25.0)	
Q3 ($37,369–$50,366)	526 (23.0)	404 (26.4)	33,793 (25.0)	
Q4 (≥$50,367)	491 (21.4)	380 (24.8)	33,898 (25.1)	

* Values are the number (%) unless indicated otherwise. The 1-RA group specified at least 1 RA claim, and the 2-RA group specified at least 2 RA claims at least 6 months apart. RA = rheumatoid arthritis.

were initially used to assess the overall survival differences for each group. The length of survival was calculated from the date of cancer diagnosis until death or to the end of followup (December 31, 2010; censored). Multivariable Cox proportional hazards regression models were used to examine survival for each type of cancer in patients with and without RA claims, initially adjusting for sociodemographic characteristics and tumor stage and, in a second step, adjusting for comorbidity level (modified CCI). We also created models that examined the independent effect of specific comorbid conditions, including cardiovascular disease, diabetes mellitus, and chronic obstructive pulmonary disease, which are often associated with RA. An a priori *P* value of less than 0.05 was considered statistically significant for all tests. We used SAS, version 9.2, to perform the analyses.

RESULTS

A total of 697,734 patients with cancer were identified between 2001 and 2010 in the TCR Medicare database. The final study sample, after the exclusion criteria had been applied, was composed of 139,097 patients diagnosed with breast (n = 35,026), prostate (n = 43,181), colorectal (n = 31,103), or lung (n = 29,787) cancer (see Supplementary Figure 1, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.22997/abstract). Patient characteristics according to prior RA claims are summarized in Table 1. The mean age was 76 years; 14% of the patients were Hispanic, and 7% were African American. Overall, 3,820 cancer patients (2.8%) had a prior RA claim; 2,289 (1.7%) had 1 RA claim (1-RA group); 1,531 (1.1%) had 2 or more claims (2-RA group). Patients with RA claims were more likely to be female and had more comorbidities than those without RA claims. They were also more often diagnosed with regional or distant cancer (1-RA 36%, 2-RA 40%) than patients without RA claims (34%) ($P = 0.0003$). There were no significant differences in the distribution for area of residence (big metro versus other), but those with RA claims more often resided in areas with lower median incomes than those with no RA claims.

The percentage of patients having at least 1 claim for RA in the preceding 12 months was 3.3% for breast, 1.8% for prostate, 2.6% for colorectal, and 3.6% for lung cancer. Of the 139,097 patients, 65,002 (46.7%) died and 74,095 (53.3%) were censored at last claim. The median survival for the total cohort was 5.6 years. Survival curves and log

Table 2. Cox regression models for mortality risk among patients with breast cancer*

Characteristic	Univariate HR (95% CI)	Model 1 HR (95% CI)	Model 2 HR (95% CI)
Group			
No RA	Ref.	Ref.	Ref.
1-RA	1.28 (1.13–1.45)†	1.29 (1.14–1.46)†	1.17 (1.03–1.32)‡
2-RA	1.31 (1.12–1.54)§	1.49 (1.27–1.74)†	1.41 (1.21–1.65)†
Mean ± SD age	1.10 (1.10–1.10)†	1.09 (1.09–1.09)†	1.09 (1.08–1.09)†
Ethnicity			
Non-Hispanic white	Ref.	Ref.	Ref.
Hispanic	1.01 (0.95–1.07)	0.92 (0.86–0.98)‡	0.83 (0.78–0.89)†
African American	1.45 (1.36–1.55)†	1.27 (1.18–1.35)†	1.14 (1.07–1.22)§
Other	0.52 (0.42–0.66)†	0.55 (0.44–0.69)†	0.57 (0.45–0.71)†
Stage			
In situ	Ref.	Ref.	Ref.
Localized	1.57 (1.45–1.70)†	1.38 (1.28–1.50)†	1.36 (1.26–1.48)†
Regional	2.81 (2.59–3.05)†	2.53 (2.33–2.75)†	2.46 (2.27–2.67)†
Distant	11.84 (10.80–12.98)†	10.31 (9.40–11.31)†	10.35 (9.43–11.35)†
Unknown	7.42 (6.82–8.07)†	5.51 (5.06–6.00)†	5.18 (4.75–5.64)†
Area of residence			
Big metro	Ref.	Ref.	Ref.
Other	1.04 (0.99–1.08)	0.93 (0.89–0.97)‡	0.93 (0.90–0.97)‡
Median annual income			
Q1 ($7–$30,048)	Ref.	Ref.	Ref.
Q2 ($30,049–$37,368)	0.90 (0.86–0.95)†	0.98 (0.92–1.03)	0.99 (0.94–1.04)
Q3 ($37,369–$50,366)	0.81 (0.77–0.85)†	0.92 (0.87–0.97)‡	0.95 (0.90–1.00)
Q4 (≥$50,367)	0.70 (0.66–0.74)†	0.81 (0.76–0.86)†	0.85 (0.80–0.91)†
CCI			
0	Ref.	–	Ref.
1	1.61 (1.53–1.68)†	–	1.50 (1.43–1.57)†
2	2.57 (2.42–2.73)†	–	2.00 (1.88–2.12)†
≥3	3.79 (3.56–4.03)†	–	2.87 (2.70–3.06)†

* Model 1 controlling for demographic and medical factors, excluding the Charlson Comorbidity Index (CCI); Model 2 = Model 2 + CCI. HR = hazard ratio; 95% CI = 95% confidence interval; RA = rheumatoid arthritis.
† $P \leq 0.0001$.
‡ $P < 0.05$.
§ $P < 0.001$.

rank test results for each cancer type according to RA claims categories are shown in Supplementary Figure 2 (see Supplementary Figure 2, available on the Arthritis Care & Research web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.22997/abstract). The median patient survival for each cancer type, comparing patients with no RA claims to those with 2 RA claims, was as follows: breast, 9.5 versus 7.1 years ($P < 0.0001$); prostate, 9.8 versus 7.3 years ($P < 0.001$); colorectal, 3.8 versus 2.8 years ($P = 0.0009$); and lung, 0.7 versus 0.9 years ($P = 0.08$).

Table 2 shows overall survival among breast cancer patients across RA groups using Cox regression with hazard ratios (HRs) and 95% confidence intervals (95% CIs) for each variable. Results include the univariate (unadjusted) HR, the HR for model 1, adjusting for demographics and tumor staging, and the HR for model 2, adjusting for the same variables as in model 1 and, in addition, comorbidity levels. An increase in mortality risk with RA was observed for all models. When adjusting for demographic variables, tumor stage, and comorbidity (model 2), the HR for 1-RA patients compared to those without RA was 1.17 (95% CI 1.03–1.32), and for those with 2-RA, it was 1.41 (95% CI 1.21–1.65). Increasing age, being non-Hispanic, having advanced cancer, increasing comorbidities, and decreasing income were significantly associated with shorter survival. Results for patients with prostate cancer are shown in Table 3. No major differences were observed between models 1 and 2. For model 2, 1-RA patients were no different from patients with no RA claims, but those in the 2-RA group had an HR of 1.53 (95% CI 1.26–1.85). Associations between survival and other covariates were similar to those observed for breast cancer patients.

Having an RA claim resulted in a statistically significant decrease in survival among colorectal cancer patients in model 1, which adjusted for demographics and tumor stage (2-RA HR 1.21 [95% CI 1.04–1.41]) (Table 4); when controlling for other comorbid conditions, the HR decreased to 1.15 and did not reach statistical significance ($P = 0.07$). For lung cancer, no differences were observed among those with or without an RA claim (Table 5). Similar covariates were associated with patient survival for all cancer types.

Table 6 examines the association of RA and other individual comorbidities with patient survival for each cancer type, adjusting for demographics and tumor stage.

Table 3. Cox regression models for mortality risk among patients with prostate cancer*

Characteristic	Univariate HR (95% CI)	Model 1 HR (95% CI)	Model 2 HR (95% CI)
Group			
No RA	Ref.	Ref.	Ref.
1-RA	1.26 (1.09–1.46)†	1.09 (0.94–1.26)	0.98 (0.84–1.13)
2-RA	1.38 (1.14–1.67)‡	1.61 (1.33–1.95)§	1.53 (1.26–1.85)§
Mean ± SD age	1.13 (1.13–1.14)§	1.11 (1.11–1.11)§	1.10 (1.10–1.11)§
Ethnicity			
Non-Hispanic white	Ref.	Ref.	Ref.
Hispanic	1.00 (0.95–1.05)	0.88 (0.84–0.92)§	0.83 (0.78–0.87)§
African American	1.50 (1.42–1.58)§	1.26 (1.19–1.34)§	1.18 (1.12–1.25)§
Other	0.28 (0.24–0.34)§	0.25 (0.21–0.29)§	0.25 (0.21–0.30)§
Stage			
In situ	Ref.	Ref.	Ref.
Localized	0.50 (0.27–0.93)¶	0.83 (0.45–1.54)	0.80 (0.43–1.49)
Regional	0.54 (0.29–1.02)	1.13 (0.60–2.11)	1.11 (0.59–2.07)
Distant	4.01 (2.15–7.46)§	4.41 (2.37–8.22)§	4.37 (2.35–8.15)§
Unknown	1.66 (0.89–3.09)	1.93 (1.04–3.59)¶	1.79 (0.96–3.33)
Area of residence			
Big metro	Ref.	Ref.	Ref.
Other	1.05 (1.02–1.09)†	0.89 (0.86–0.93)§	0.90 (0.86–0.94)§
Median annual income			
Q1 ($7–$30,048)	Ref.	Ref.	Ref.
Q2 ($30,049–$37,368)	0.88 (0.84–0.92)§	0.96 (0.91–1.01)	0.96 (0.91–1.01)
Q3 ($37,369–$50,366)	0.80 (0.76–0.84)§	0.93 (0.88–0.98)†	0.93 (0.88–0.98)†
Q4 (≥$50,367)	0.64 (0.61–0.67)§	0.77 (0.72–0.81)§	0.80 (0.75–0.84)§
CCI			
0	Ref.	–	Ref.
1	1.58 (1.51–1.65)§	–	1.46 (1.40–1.53)§
2	2.55 (2.41–2.69)§	–	2.02 (1.91–2.13)§
≥3	4.08 (3.87–4.31)§	–	2.88 (2.73–3.05)§

* Model 1 controlling for demographic and medical factors, excluding the Charlson Comorbidity Index (CCI); Model 2 = Model 2 + CCI. HR = hazard ratio; 95% CI = 95% confidence interval; RA = rheumatoid arthritis.
† $P < 0.01$.
‡ $P < 0.001$.
§ $P < 0.0001$.
¶ $P < 0.05$.

Diabetes mellitus and chronic obstructive pulmonary disease were independently associated with decreased patient survival for all cancer types. Cardiovascular disease was associated with decreased patient survival for breast, prostate, and colorectal cancers, but not for lung cancer. An independent mortality risk for RA persisted after these adjustments for breast and prostate cancers; the HRs for the 2-RA group were 1.44 (95% CI 1.23–1.68) and 1.51 (95% CI 1.25–1.83), respectively.

DISCUSSION

We conducted a large population-based study of elderly patients diagnosed with 1 of the 4 most frequent solid malignancies (breast, prostate, colorectal, and lung) to determine the potential association of RA with overall survival. We used data from the state of Texas TCR Medicare database, including more than 139,000 patients, 2.8% of whom had 1 or more prior RA claim. Notably, patients with a diagnosis of RA and breast or prostate cancer had a 40% and 50% increased risk in mortality, respectively, compared to patients without RA. A small nonsignificant risk was observed for colorectal cancer, and no differences were observed for lung cancer. These findings suggest that the additional cancer mortality risk from having RA is more pronounced for those tumors with a longer expected median patient survival. These differences persisted after controlling for age, sex, ethnicity, surrogate socioeconomic status, tumor stage, and other comorbidities.

While many studies have examined cancer mortality rates in RA compared to the general population, few have compared survival outcomes in cancer patients with or without RA. The first of such studies was published 3 decades ago, and compared 5-year survival rates in patients with cancer identified in the Finnish Cancer Registry, with and without RA, and found no significant differences in mortality (24). Two Swedish studies have reported survival rates in patients with cancer according to their RA status. The first one linked the Swedish hospital discharge register with the cancer registry, so only patients who had been previously hospitalized with RA were included. The authors reported a significant decrease in overall RA patient survival for many cancer sites,

Table 4. Cox regression models for mortality risk among patients with colorectal cancer*

Characteristic	Univariate HR (95% CI)	Model 1 HR (95% CI)	Model 2 HR (95% CI)
Group			
No RA	Ref.	Ref.	Ref.
1-RA	1.23 (1.10–1.38)†	1.18 (1.05–1.33)‡	1.09 (0.97–1.22)
2-RA	1.11 (0.95–1.29)	1.21 (1.04–1.41)§	1.15 (0.99–1.34)
Mean ± SD age	1.06 (1.06–1.07)¶	1.07 (1.07–1.07)¶	1.06 (1.06–1.07)¶
Ethnicity			
Non-Hispanic white	Ref.	Ref.	Ref.
Hispanic	0.99 (0.95–1.03)	0.95 (0.91–0.99)§	0.91 (0.87–0.96)¶
African American	1.24 (1.18–1.30)¶	1.16 (1.10–1.23)¶	1.08 (1.03–1.14)‡
Other	0.66 (0.58–0.76)¶	0.74 (0.64–0.85)¶	0.74 (0.64–0.85)¶
Stage			
In situ	Ref.	Ref.	Ref.
Localized	1.21 (1.10–1.34)†	1.15 (1.04–1.27)‡	1.15 (1.04–1.27)‡
Regional	1.85 (1.67–2.04)¶	1.76 (1.59–1.94)¶	1.78 (1.61–1.96)¶
Distant	6.40 (5.78–7.07)¶	6.61 (5.98–7.31)¶	6.85 (6.19–7.57)¶
Unknown	4.61 (4.17–5.10)¶	3.97 (3.58–4.39)¶	3.89 (3.51–4.30)¶
Area of residence			
Big metro	Ref.	Ref.	Ref.
Other	0.97 (0.94–1.00)	0.91 (0.88–0.95)¶	0.91 (0.88–0.95)¶
Median annual income			
Q1 ($7–$30,048)	Ref.	Ref.	Ref.
Q2 ($30,049–$37,368)	0.90 (0.87–0.94)¶	0.94 (0.90–0.98)†	0.95 (0.91–0.99)‡
Q3 ($37,369–$50,366)	0.87 (0.84–0.91)¶	0.91 (0.87–0.95)¶	0.91 (0.87–0.95)¶
Q4 (≥$50,367)	0.81 (0.78–0.85)¶	0.83 (0.79–0.87)¶	0.84 (0.80–0.88)¶
CCI			
0	Ref.	–	Ref.
1	1.29 (1.24–1.33)¶	–	1.26 (1.22–1.31)¶
2	1.62 (1.55–1.70)¶	–	1.51 (1.44–1.58)¶
≥3	2.23 (2.14–2.34)¶	–	2.10 (2.01–2.20)¶

* Model 1 controlling for demographic and medical factors, excluding the Charlson Comorbidity Index (CCI); Model 2 = Model 2 + CCI. HR = hazard ratio; 95% CI = 95% confidence interval; RA = rheumatoid arthritis.
† $P < 0.001$.
‡ $P < 0.01$.
§ $P < 0.05$.
¶ $P < 0.0001$.

compared to those without RA; HRs for breast, prostate, and colon cancers were 1.55, 1.18, and 1.30, respectively. No significant differences were observed for lung cancer. The results were adjusted for demographic variables and tumor stage, and for chronic obstructive pulmonary disease, but the authors did not report adjustment for other comorbidities, such as cardiovascular disease (25). A more recent study also using Swedish register data compared mortality rates in patients with RA (with or without cancer), patients with cancer and no history of RA, and the general population (26). They reported that, in patients with RA and no cancer, the mortality risk was doubled, compared to the general population. When comparing patients with RA and cancer to those with cancer alone, the results varied by cancer stage. For patients with cancer at earlier stages (I and II), the mortality risk was also doubled for those with RA, but for patients diagnosed with advanced cancer, this effect decreased (HR 1.2). The authors concluded that the increased mortality rates in patients with RA and cancer was probably attributable to RA alone, independently of the cancer, since the 2-fold mortality risk was also observed in patients with RA and without cancer, compared to the general population.

To our knowledge, there is only 1 similar study conducted in the US. Patnaik et al used the Surveillance, Epidemiology, and End Results (SEER) Medicare database to evaluate the individual comorbidity effects on survival in 64,034 patients with breast cancer between 1992 and 2000 (27). The SEER registry has data from several states but does not include the state of Texas, so our results are derived from a different population. They examined 13 comorbid conditions, including RA, and found that each one was independently associated with poorer survival compared to no comorbidities. For RA, the fully adjusted HR was 1.27.

Our results are in agreement with what has been observed in the Scandinavian studies and the SEER Medicare data (25–27). Yet the reasons for the increased mortality risk from RA in cancer patients remains unclear. While RA alone increases mortality risk, much of this effect has been attributed to concomitant comorbidities that are increased in RA,

Table 5. Cox regression models for death among patients with lung cancer*

Characteristic	Univariate HR (95% CI)	Model 1 HR (95% CI)	Model 2 HR (95% CI)
Group			
No RA	Ref.	Ref.	Ref.
1-RA	0.97 (0.88–1.06)	1.06 (0.97–1.17)	1.03 (0.94–1.13)
2-RA	0.89 (0.81–0.99)†	1.03 (0.93–1.14)	1.01 (0.92–1.12)
Mean ± SD age	1.03 (1.02–1.03)‡	1.03 (1.03–1.03)‡	1.03 (1.03–1.03)‡
Ethnicity			
Non-Hispanic white	Ref.	Ref.	Ref.
Hispanic	1.17 (1.13–1.22)‡	1.01 (0.97–1.05)	0.99 (0.95–1.04)
African American	1.21 (1.16–1.26)‡	1.09 (1.04–1.14)§	1.08 (1.03–1.13)¶
Other	0.92 (0.83–1.03)	0.88 (0.78–0.98)†	0.88 (0.79–0.98)†
Stage			
In situ	Ref.	Ref.	Ref.
Localized	0.5 (0.35–0.73)§	0.53 (0.37–0.76)§	0.53 (0.37–0.77)§
Regional	0.86 (0.6–1.24)	0.91 (0.63–1.31)	0.93 (0.64–1.33)
Distant	2.01 (1.39–2.89)§	2.12 (1.47–3.05)‡	2.18 (1.52–3.14)‡
Unknown	1.29 (0.89–1.85)	1.3 (0.9–1.87)	1.31 (0.91–1.89)
Area of residence			
Big metro	Ref.	Ref.	Ref.
Other	1.05 (1.02–1.07)§	0.97 (0.94–1.00)†	0.97 (0.94–1.00)†
Median annual income			
Q1 ($7–$30,048)	Ref.	Ref.	Ref.
Q2 ($30,049–$37,368)	0.93 (0.9–0.96)‡	0.98 (0.94–1.01)	0.98 (0.94–1.01)
Q3 ($37,369–$50,366)	0.88 (0.85–0.91)‡	0.94 (0.90–0.97)§	0.94 (0.91–0.98)‡
Q4 (≥$50,367)	0.79 (0.76–0.82)‡	0.83 (0.80–0.86)‡	0.84 (0.80–0.87)‡
CCI			
0	Ref.	–	Ref.
1	1.02 (0.99–1.05)	–	1.09 (1.06–1.12)‡
2	1.11 (1.07–1.15)‡	–	1.19 (1.15–1.24)‡
≥3	1.36 (1.3–1.41)‡	–	1.44 (1.38–1.49)‡

* Model 1 controlling for demographic and medical factors, excluding the Charlson Comorbidity Index (CCI); Model 2 = Model 2 + CCI. HR = hazard ratio; 95% CI = 95% confidence interval; RA = rheumatoid arthritis.
† $P < 0.05$.
‡ $P < 0.0001$.
§ $P < 0.001$.
¶ $P < 0.01$.

especially cardiovascular disease (28–33). In our study, we controlled for comorbidities, both the overall burden and for individual conditions, but found that the independent effect of RA remained for both breast and prostate cancers. Of interest, the impact of RA on survival was evident primarily for the malignancies with the longest patient survival. Simard et al also reported that the survival disadvantage was only observed for patients in early stages and not for those diagnosed with advanced disease (26). In our study, patients with RA claims had been diagnosed with cancer, on average, at later stages than those without RA claims. While this difference was small, and we adjusted for it in the multivariate analysis, the stage was unknown in many cases. Delayed cancer diagnosis could possibly result in worse outcome, not fully accounted for through statistical adjustment. The potential differential utilization of cancer therapies was not examined in our study but could also be related to the findings. For instance, patients with RA may be less likely to receive certain therapies, such as radiotherapy (34), because of fear of complications (35–38) or may discontinue therapy early. Likewise, the effect of immunomodulatory agents used in the treatment of RA could also interfere with tumor immunity and possibly result in worse outcomes. Additional research is needed to determine whether differences exist between patients with and without RA with respect to cancer screening, early diagnosis, and therapy.

The data quality of this study is high, as approximately 98% of the TCR patients age ≥65 years have been matched to Medicare beneficiary files. The availability of this large population-based sample and information on tumor histology and stage allowed us to conduct our analyses by cancer subtype and to control for important factors that are known to influence survival.

Yet our study has limitations, primarily those inherent in the use of administrative data for outcomes research. Medicare coverage is restricted to individuals ≥65 years of age; therefore, the results may not be generalizable to a younger population. However, cancer is mostly prevalent among the elderly population. Medicare claims may not be sufficiently sensitive or specific to diagnose RA. To address this limitation, we analyzed data separately for patients who had 2 or more hospital or outpatient claims related to RA

Table 6. Effect of cardiovascular disease, diabetes mellitus, and COPD, in addition to RA, on mortality risk*

Characteristic	Univariate HR (95% CI)	*P*	Multivariate HR (95% CI)	*P*
Breast†				
1-RA	1.28 (1.13–1.45)	< 0.001	1.17 (1.04–1.33)	0.013
2-RA	1.31 (1.12–1.54)	< 0.001	1.44 (1.23–1.68)	< 0.001
Cardiovascular‡				
Yes	2.77 (2.66–2.89)	< 0.001	1.32 (1.19–1.46)	< 0.001
Diabetes mellitus‡				
Yes	1.46 (1.4–1.53)	< 0.001	1.29 (1.23–1.35)	< 0.001
COPD‡				
Yes	1.78 (1.69–1.88)	< 0.001	1.42 (1.34–1.49)	< 0.001
Colorectal†				
1-RA	1.23 (1.1–1.38)	< 0.001	1.06 (0.95–1.22)	0.31
2-RA	1.11 (0.95–1.29)	0.19	1.12 (0.96–1.30)	0.16
Cardiovascular‡				
Yes	1.84 (1.78–1.91)	< 0.001	1.16 (1.08–1.25)	< 0.001
Diabetes mellitus‡				
Yes	1.15 (1.11–1.19)	< 0.001	1.12 (1.08–1.16)	< 0.001
COPD‡				
Yes	1.48 (1.43–1.54)	< 0.001	1.28 (1.22–1.33)	< 0.001
Prostate†				
1-RA	1.26 (1.09–1.46)	0.002	0.98 (0.84–1.13)	0.76
2-RA	1.38 (1.14–1.67)	0.001	1.51 (1.25–1.83)	< 0.001
Cardiovascular‡				
Yes	2.70 (2.59–2.80)	< 0.001	1.22 (1.12–1.33)	< 0.001
Diabetes mellitus‡				
Yes	1.32 (1.27–1.38)	< 0.001	1.21 (1.16–1.26)	< 0.001
COPD‡				
Yes	2.25 (2.15–2.35)	< 0.001	1.56 (1.49–1.63)	< 0.001
Non–small cell lung†				
1-RA	0.97 (0.88–1.06)	0.52	1.00 (0.91–1.09)	0.93
2-RA	0.89 (0.81–0.99)	0.028	0.99 (0.89–1.09)	0.77
Cardiovascular‡				
Yes	1.22 (1.18–1.25)	< 0.001	0.98 (0.92–1.05)	0.63
Diabetes mellitus‡				
Yes	1.11 (1.07–1.14)	< 0.001	1.04 (1.01–1.08)	0.01
COPD‡				
Yes	1.06 (1.03–1.09)	< 0.001	1.11 (1.08–1.14)	< 0.001

* Multivariate model adjusted for demographic and clinical variables. COPD = chronic obstructive pulmonary disease; RA = rheumatoid arthritis; HR = hazard ratio; 95% CI = 95% confidence interval.
† Ref. = no RA.
‡ Ref. = no.

that were at least 6 months apart. Higher diagnostic specificity could be obtained by including patients who received RA therapy or had claims filed by a rheumatologist. Part D data would be necessary in order to accurately address medication use. In addition, we did not have access to physician specialty codes for claims. We believe, nevertheless, that potential misclassification would have increased the number of individuals without RA among the RA group, in which case the mortality effect we observed would be underestimated. Finally, the population of Texas may vary from that of other US states, as it has one of the largest immigrant populations and is ethnically diverse. Therefore, the results may not be generalizable to other US states. Nevertheless, our findings were similar to those reported by Patnaik et al for breast cancer using SEER data, which includes several states other than Texas (27).

In conclusion, we used a Texas population-based cancer registry linked to Medicare claims data to examine the independent effect of RA on survival among individuals diagnosed with specific cancer types. We observed that socioeconomic and comorbidity factors influenced patient survival for all 4 of the cancer types we examined. Among elderly patients with breast and prostate cancer, having RA increased the risk of a poor prognosis, decreasing survival by 2 years. Additional research is needed to identify potentially modifiable determinants of this effect.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Suarez-Almazor

had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study conception and design. Nayak, Elting, Suarez-Almazor.
Acquisition of data. Elting, Suarez-Almazor.
Analysis and interpretation of data. Nayak, Luo, Zhao.

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