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

Pratibha Nayak, PhD, MPH,[1] Ruili, Luo, PhD,[2] Linda Elting, DrPH,[3] Hui Zhao, MD, PhD, [3] Maria E. Suarez-Almazor, MD, PhD[2]

**Affiliations:** 1. Georgia State University Tobacco Center of Regulatory Science, School of Public Health, Georgia State University, Atlanta, Georgia, 2. Department of General Internal Medicine, The University of Texas, MD Anderson Cancer Center, Houston, Texas, and 3. Department of Health Services Research, The University of Texas, MD Anderson Cancer Center, Houston, Texas.

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**Contact information for corresponding author:** Maria E. Suarez-Almazor, MD, PhD, Department of General Internal Medicine, Unit 1465, The University of Texas MD Anderson


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Cancer Center, 1515 Holcombe Blvd, Houston, TX 77030, USA; email: msalmazor@mdanderson.org phone: 713-745-4516

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**ABSTRACT**

OBJECTIVE. Comorbidity among cancer patients imposes additional risks for mortality. The possible impact of rheumatoid arthritis (RA) on cancer 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 years 2001-2010 were identified from the Texas Cancer Registry and Medicare-linked databases. The cohort was categorized into 3 groups according to whether patients had a claim with a diagnosis of RA in the year prior to the cancer diagnosis: (i) 2-RA (patients with ≥2 claims) (i) 1-RA (1 claim), and (iii) 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% 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 for cancers for shorter survival (colorectal or lung). Research is needed to determine whether the increased risk is related to comorbid burden, or differential utilization of cancer or rheumatoid therapies in patients with both diseases.

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**SIGNIFICANCE AND INNOVATION**

- 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 cancer have increased mortality risk compared to those with cancer alone, shortening their median life expectancy by 2 years
- This deleterious effect appears to primarily occur in patients with types of cancer expected to have longer survival.

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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 due to the disease itself, the side 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 gender, 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 anti-inflammatory 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 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

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survival in elderly patients with one of the four 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 two 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 (CERCIT) consortium has linked TCR and Medicare data collected by the Center of Medicare and Medicaid Services in the State of Texas. One of the largest statewide population-based cancer registries in the United States, the TCR maintains high-quality data standards and currently meets the standards of the National Program of Central Cancer Registries, Centers for Disease Control and Prevention, and 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 is reported to be 91% complete, and approximately 98% of TCR patients aged ≥65 years have been matched to Medicare beneficiary files. Medicare provides universal health insurance for people aged ≥ 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,

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we were able to estimate patients' census-level socioeconomic data by linking to 2000 United States 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 (NSCLC) cancer (Fig. 1). Other cohort selection criteria were: (i) index cancer was first cancer diagnosis in registry; (ii) Texas residency and age 66 or older at the time of cancer diagnosis; (iii) enrollment in Medicare Part A and B within 12 months before cancer diagnosis; and (iv) no simultaneous enrollment in a health maintenance organization at any time in the 12 months prior to the diagnosis, to ensure that all healthcare claims would be identifiable in Medicare data.

*Measures*

TCR provided demographic data on each patient's age, sex, and ethnicity. A comorbidity index (0, 1, 2, or ≥ 3) was estimated from the Medicare claims in the 12 months prior to the cancer diagnosis using the Klabunde's 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 others (including metro, urban, urban less, rural, and unknown). The patient's socioeconomic status information was not available at the individual level; therefore, the patients' zip codes were linked to the census data to obtain surrogate values at the census tract level and were measured as the percentage

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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) (http://www.texaspha.org/Resources/Documents/Hispaniccancerreport.pdf).

We used data from Medicare claims to assess whether participants may have RA, using the International Classification of Diseases 9$^{th}$ version code 714.0. Accordingly, we created three groups based on number of RA claims: (i) 2-RA, including patients with two or more RA claims at least 6 months apart, in the 12 months prior to cancer diagnosis; (ii) 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 (iii) patients with no RA claims. This approach was used to increase the diagnostic accuracy for identifying RA using administrative databases, which can be enhanced by requiring two 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 group 1-RA.

*Analyses*

The characteristics of patients with and without RA claims were compared using a chi-squared test for categorical variables and a t-tests and analysis of variance for continuous variables. Kaplan–Meier curves and log rank tests were initially used to assess the overall survival differences for each group. Length of survival was calculated from the date of cancer diagnosis until death or to the end of follow-up on December 31, 2010 (censored). Multivariable Cox proportional hazard regression models were used to examine survival for each type of cancer in

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patients with or without RA claims, initially adjusting for socio-demographic characteristics and tumor stage, and in a second step, adjusting for comorbidity level (modified Charlson's index). We also conducted models which examined the independent effect of specific comorbid conditions including cardiovascular disease, diabetes and chronic obstructive pulmonary disease, which are often associated with RA. An *a priori* p-value of <.05 was considered statistically significant for all tests.

We used the Statistical Analysis Software 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 applying the exclusion criteria had 139,097 patients diagnosed with breast (35,026), prostate (43,181), colorectal (31,103), or lung (29,787) (Supplemental file - Figure 1). Patient characteristics according to prior RA claims are summarized in Table 1. Mean age was 76 years; 14% of the patients were Hispanic; 7% African-American. Overall, 3,820 (2.8%) cancer patients had a prior RA claim; 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 stage (1-RA, 36%; 2-RA, 40%) than patients without RA claims (34%) (p=0.0003). There were no significant differences in the distribution for size area of residence, but those with RA claims more often resided in areas with lower median incomes than those with no RA claims.

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The percent of patients having at least one claim for RA in the 12 months according to cancer type 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. Median survival for the total cohort was 5.6 years. Survival curves and logrank test results for each cancer type according to RA claims categories are presented in the supplemental electronic files (Supplemental file - Figure 2). Median patient survival for each cancer type comparing patients with no RA claims with those with 2-RA claims were as follows: (i) breast: 9.5 vs. 7.1 years ($p<0.0001$); (ii) prostate: 9.8 vs. 7.3 years ($p<0.001$); (iii) colorectal: 3.8 vs 2.8 years ($p=0.0009$); and (iv) lung: 0.7 vs. 0.9 years ($p=0.08$).

Table 2 shows overall survival among breast cancer patients across RA groups using Cox regression with hazard ratios (HR) and 95% confidence intervals (CI) for each variable. Results include (i) univariate (unadjusted) HR, (ii) HR for Model 1, adjusting for demographics and tumor staging, and (iii) HR for Model 2, adjusting for variables 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), 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 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, patients with 1-RA were on different from patients with no RA claims, but those in the 2-RA group had HR of 1.53 (95% CI 1.26-1.85).

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Associations between survival and other covariates were similar as those observed for breast cancer patients.

Having a 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: HR1.21; 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 a RA claim (Table 5). Similar covariates were associated with survival for all cancer types.

Table 6 examines the association of RA and other individual comorbidities with survival for each cancer type, adjusting for demographics and tumor stage. Diabetes and chronic obstructive pulmonary disease were independently associated with decreased survival for all cancer types. Cardiovascular disease was associated with decreased survival for breast, prostate and colorectal cancer but not for lung cancer. An independent mortality risk for RA persisted after these adjustments for breast and prostate cancer; HR for the 2-RA group were 1.44 (95%CI 1.23-1.68), and 1.51 (95% CI 1.25-1.83) respectively.

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**DISCUSSION**

We conducted a large population-based study of elderly patients diagnosed with one of four 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 – including over 139,000 patients, of whom, 2.8% had one or more prior claims of RA. Notably, patients with a diagnosis of RA and breast or prostate cancer respectively had 40% and 50% increased risk in mortality compared to patients without RA. A small non-significant 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 longer expected median survival. These differences persisted after controlling for age, gender, 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 survival for many cancer sites in patients with RA compared to those without RA; HR for breast, prostate and colon were 1.55, 1.18, and 1.30. No significant differences were observed for lung

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cancer. Results were adjusted for demographic variables and tumor stage, and for COPD, but the authors did not report adjustment for other comorbidities such as cardiovascular disease. not and without RA examined mortality in patients with both cancer and RA.(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 two-fold mortality risk was also observed in patients with RA and without cancer, compared to the general population.

To our knowledge, there is only similar study conducted in the Unites States (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.

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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 *per se* increases mortality risk, much of this effect has been attributed to concomitant comorbidities which are increased in RA, especially cardiovascular disease.(28-33) In our study, we controlled for comorbidities, both as overall burden, and for individual conditions also, but found that the independent effect of RA remained for both breast and prostate cancer. Of interest, the impact of RA on survival was evident primarily for the malignancies with longest survival. Simard 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 claims. While this difference was small, and we adjusted for it in the multivariate analysis, 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 aged ≥ 65years have been matched to Medicare beneficiary files. The availability of this large, population-

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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 inherent to 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, at least 6 months apart. Higher diagnostic specificity could be obtained by including patient who received RA therapy or had claims by a rheumatologist. Part D data would be necessary 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 U.S. states, as it has one of the largest immigrant populations and is ethnically diverse. Therefore, the results may not be generalizable to other U.S. states. Nevertheless, our findings were similar to those reported by Patnaik 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 survival for

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all four cancer types we examined. Among elderly patients with colorectal 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.

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

| | | 1-RA* | 2-RA** | No RA | P-value |
|---|---|---|---|---|---|
| | | n (%) | n (%) | n (%) | |
| | | 2,289 (1.6) | 1,531 (1.1) | 135,277(97.2) | |
| Age | Mean (sd.) | 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) | |
| 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.) | 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) | |

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| | | | | | |
|---|---|---|---|---|---|
| | 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) | |

*Specified at least one RA claim (1-RA) or **at least two RA claims (2-RA) at least 6 months apart

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

| Characteristics | | Univariate | Model-1 | Model-2 |
|---|---|---|---|---|
| | | HR (95% CI) | HR (95% CI) | HR (95% CI) |
| Group | No RA | Reference | Reference | Reference |
| | 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)**† |
| Age | Mean (std.) | **1.10 (1.10-1.10)**† | **1.09 (1.09-1.09)**† | **1.09 (1.08-1.09)**† |
| Ethnicity | Non-Hispanic white | Reference | Reference | Reference |
| | 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 | Reference | Reference | Reference |
| | 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 | Reference | Reference | Reference |
| | Other metro | 1.04 (0.99-1.08) | **0.93 (0.89-0.97)**‡ | **0.93 (0.90-0.97)**‡ |
| Median | Q1: $7 - | Reference | Reference | Reference |

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| | | | | |
|---|---|---|---|---|
| | $30,048 | | | |
| annual | Q2: $30,049 - | **0.90 (0.86-0.95)**† | 0.98 (0.92-1.03) | 0.99 (0.94-1.04) |
| | $37,368 | | | |
| income | Q3: $37,369 - | **0.81 (0.77-0.85)**† | **0.92 (0.87-0.97)**‡ | 0.95 (0.90-1.00) |
| | $50,366 | | | |
| | Q4: $50,367+ | **0.70 (0.66-0.74)**† | **0.81 (0.76-0.86)**† | **0.85 (0.80-0.91)**† |
| CCI* | 0 | Reference | - | Reference |
| | 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)**† |

*CCI- Charlson Comorbidity Index; Model-1- controlling for demographic and medical factors, excluding CCI; Model-2: Model-2 + CCI; † ≤ 0.0001; § < 0.001; ‡ <0.05

[Type here]

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

| Characteristics | | Univariate HR (95% CI) | Model-1 HR (95% CI) | Model-2 HR (95% CI) |
|---|---|---|---|---|
| Group | No RA | Reference | Reference | Reference |
| | One RA | **1.26 (1.09-1.46)**[¥] | 1.09 (0.94-1.26) | 0.98 (0.84-1.13) |
| | Two RA | **1.38 (1.14-1.67)**[§] | **1.61 (1.33-1.95)**[†] | **1.53 (1.26-1.85)**[†] |
| Age | Mean (std.) | **1.13 (1.13-1.14)**[†] | **1.11 (1.11-1.11)**[†] | **1.10 (1.10-1.11)**[†] |
| Ethnicity | Non-Hispanic white | Reference | Reference | Reference |
| | 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 | Reference | Reference | Reference |
| | 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 | Reference | Reference | Reference |
| | Other metro | **1.05 (1.02-1.09)**[¥] | **0.89 (0.86-0.93)**[†] | **0.90 (0.86-0.94)**[†] |
| Median annual | Q1: $7 - $30,048 | Reference | Reference | Reference |
| | Q2: $30,049 - | **0.88 (0.84-0.92)**[†] | 0.96 (0.91-1.01) | 0.96 (0.91-1.01) |

[Type here]

| | | | | |
|---|---|---|---|---|
| | $37,368 | | | |
| Income | 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 | Reference | - | Reference |
| | 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)†** |

*CCI- Charlson Comorbidity Index; Model-1- controlling for demographic and medical factors, excluding CCI; Model-2: Model-2 + CCI; † <0.0001; § < 0.001; ¥ <0.01; ‡ <0.05

[Type here]

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

| Characteristics | | Univariate HR (95% CI); | Model-1 HR (95% CI) | Model-2 HR (95% CI); |
|---|---|---|---|---|
| Group | No RA | Reference | Reference | Reference |
| | One RA | **1.23 (1.10-1.38)[§]** | **1.18 (1.05-1.33)[¥]** | 1.09(0.97-1.22) |
| | Two RA | 1.11 (0.95-1.29) | **1.21 (1.04-1.41)[‡]** | 1.15 (0.99-1.34) |
| Age | Mean (std.) | **1.06 (1.06-1.07)[†]** | **1.07 (1.07-1.07)[†]** | **1.06 (1.06-1.07)[†]** |
| Sex | Male | Reference | Reference | Reference |
| | Female | 1.00 (0.97-1.03) | **0.85 (0.82-0.87)[†]** | **0.86 (0.84-0.89)[†]** |
| Ethnicity | Non-Hispanic white | Reference | Reference | Reference |
| | 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 | Reference | Reference | Reference |
| | 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 | Reference | Reference | Reference |
| | Other metro | 0.97 (0.94-1.00) | **0.91 (0.88-0.95)[†]** | **0.91 (0.88-0.95)[†]** |

[Type here]

| | | | | |
|---|---|---|---|---|
| Median annual Income | Q1: $7 - $30,048 | Reference | Reference | Reference |
| | 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 | Reference | - | Reference |
| | 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)†** |

*CCI- Charlson Comorbidity Index; Model-1- controlling for demographic and medical factors, excluding CCI; Model-2: Model-2 + CCI; † <0.0001; § < 0.001; ¥ <0.01; ‡ <0.05

[Type here]

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

| Characteristics | Category | Univariate HR(95%CI) | Model-1 HR(95%CI) | Model-2 HR(95%CI) |
|---|---|---|---|---|
| Group | | Reference | Reference | Reference |
| | One RA | 0.97 (0.88-1.06) | 1.06 (0.97-1.17) | 1.03 (0.94-1.13) |
| | Two RA | **0.89 (0.81-0.99)**‡ | 1.03 (0.93-1.14) | 1.01 (0.92-1.12) |
| Age | Mean (SD) | **1.03 (1.02-1.03)**† | **1.03 (1.03-1.03)**† | **1.03 (1.03-1.03)**† |
| Gender | Male | Reference | Reference | Reference |
| | Female | **0.81 (0.79-0.83)**† | **0.80 (0.78-0.82)**† | **0.81 (0.79-0.83)**† |
| Ethnicity | Non-Hispanic White | Reference | Reference | Reference |
| | Hispanic or Latino | **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 | Reference | Reference | Reference |
| | 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 | Big Metro | Reference | Reference | Reference |
| Residence | Other Metro | **1.05 (1.02-1.07)**§ | **0.97 (0.94-1.00)**‡ | **0.97 (0.94-1.00)**‡ |
| Median | Q1: $7 - $30,048 | Reference | Reference | Reference |

[Type here]

| Characteristics | Category | Univariate HR(95%CI) | Model-1 HR(95%CI) | Model-2 HR(95%CI) |
|---|---|---|---|---|
| annual income | Q2. $30049 - $37368 | **0.93 (0.9-0.96)†** | 0.98 (0.94-1.01) | 0.98 (0.94-1.01) |
| | Q3. $37369 - $50366 | **0.88 (0.85-0.91)†** | **0.94 (0.90-0.97)§** | **0.94 (0.91-0.98)†** |
| | Q4. $50367+ | **0.79 (0.76-0.82)†** | **0.83 (0.80-0.86)†** | **0.84 (0.80-0.87)†** |
| CCI* | 0 | Reference | Reference | Reference |
| | 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)†** |

*CCI- Charlson Comorbidity Index; Model-1- controlling for demographic and medical factors, excluding CCI; Model-2: Model-2 + CCI; † <0.0001; § < 0.001; ¥ <0.01; ‡ <0.05

[Type here]

**Table 6:** Effect of cardiovascular disease, diabetes and chronic obstructive pulmonary disease o in addition to rheumatoid arthritis on risk mortality

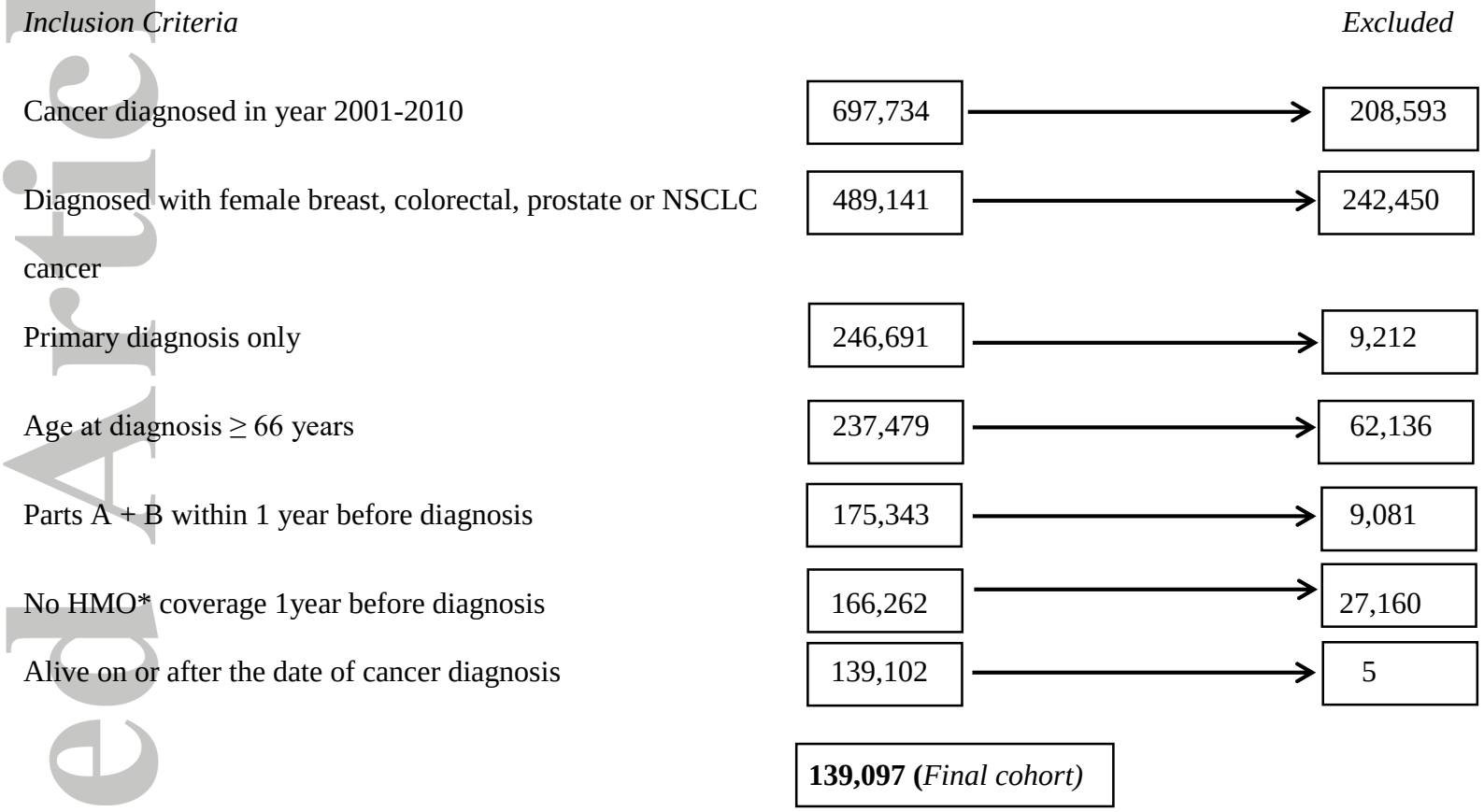
| Characteristics | Category | Univariate HR(95%CI) | p-value | Multivariate HR(95%CI) | p-value |
|---|---|---|---|---|---|
| **Breast** | | | | | |
| Group (ref=No RA) | One RA | **1.28 (1.13-1.45)** | **<0.001** | **1.17 (1.04-1.33)** | **0.013** |
| | Two RA | **1.31 (1.12-1.54)** | **<0.001** | **1.44 (1.23-1.68)** | **<.001** |
| Cardiovascular (ref=No ) | Yes | **2.77 (2.66-2.89)** | **<.001** | **1.32 (1.19-1.46)** | **<.001** |
| Diabetes (ref=No) | Yes | **1.46 (1.4-1.53)** | **<.001** | **1.29 (1.23-1.35)** | **<.001** |
| COPD (ref=No) | Yes | **1.78 (1.69-1.88)** | **<.001** | **1.42 (1.34-1.49)** | **<.001** |
| **Colorectal** | | | | | |
| Group (ref=No) | One RA | **1.23 (1.1-1.38)** | **<0.001** | 1.06 (0.95-1.22) | 0.31 |
| | Two RA | 1.11 (0.95-1.29) | 0.19 | 1.12 (0.96-1.30) | 0.16 |
| Cardiovascular (ref=No ) | Yes | **1.84 (1.78-1.91)** | **<.001** | **1.16 (1.08-1.25)** | **<.001** |
| Diabetes (ref=No ) | Yes | **1.15 (1.11-1.19)** | **<.001** | **1.12 (1.08-1.16)** | **<.001** |
| COPD (ref=No) | Yes | **1.48 (1.43-1.54)** | **<.001** | **1.28 (1.22-1.33)** | **<.001** |
| **Prostate** | | | | | |
| Group (ref=No RA) | One RA | **1.26 (1.09-1.46)** | **0.002** | 0.98 (0.84-1.13) | 0.76 |
| | Two RA | **1.38 (1.14-1.67)** | **0.001** | **1.51 (1.25-1.83)** | **<.001** |
| Cardiovascular (ref=No) | Yes | **2.70 (2.59-2.80)** | **<.001** | **1.22 (1.12-1.33)** | **<.001** |
| Diabetes (ref=No) | Yes | **1.32 (1.27-1.38)** | **<.001** | **1.21 (1.16-1.26)** | **<.001** |
| COPD (ref=No) | Yes | **2.25 (2.15-2.35)** | **<.001** | **1.56 (1.49-1.63)** | **<.001** |
| **Non-small cell lung cancer** | | | | | |
| Group (ref=No RA) | One RA | 0.97 (0.88-1.06) | 0.52 | 1.00 (0.91-1.09) | 0.93 |
| | Two RA | **0.89 (0.81-0.99)** | **0.028** | 0.99 (0.89-1.09) | 0.77 |
| Cardiovascular (ref=No ) | Yes | **1.22 (1.18-1.25)** | **<.001** | 0.98 (0.92-1.05) | 0.63 |

[Type here]

| | | | | | |
|---|---|---|---|---|---|
| Diabetes (ref=No) | Yes | **1.11 (1.07-1.14)** | **<.001** | **1.04 (1.01-1.08)** | **0.01** |
| COPD (ref=No) | Yes | **1.06 (1.03-1.09)** | **<.001** | **1.11 (1.08-1.14)** | **<.001** |

COPD: Chronic obstructive pulmonary disease. Multivariate model adjusted for demographic and clinical variables

**Figure 1.** Data source and cohort selection, data from 2001-2010 TCR-Medicare




*HMO* health maintenance organization; *NSCLC*- Non-small cell lung cancer

**Figure 2.** Product-limit survival curves for breast, prostate, colorectal and lung cancer