A Cohort Study of Mortality in Individuals With and Without Schizophrenia After Diagnosis of Lung Cancer

Daniel W. Bradford, MD, MPH[a,b,*]; Joseph Goulet, PhD[c,e]; Marcia Hunt, PhD[d,e]; Natasha C. Cunningham, MD[b]; and Rani Hoff, PhD[d,e]

ABSTRACT

Objective: Individuals with serious mental illness have increased mortality relative to those without these illnesses. Although cancer is a leading cause of death, few studies have evaluated potential disparities relative to mortality for individuals with serious mental illness who are diagnosed with cancer. In this study, we evaluated mortality after diagnosis of a common malignancy (lung cancer) in a prototypical serious mental illness (schizophrenia).

Methods: Using administrative data in the Veterans Affairs system, we identified 34,664 individuals who were diagnosed with lung cancer between October 1, 2001, and September 30, 2005. We conducted a survival analysis comparing individuals with and without *ICD-9-CM* schizophrenia using data through September 30, 2010. Controlling variables were age, gender, smoking status, marital status, service connection, homelessness status, and presence of a substance use disorder.

Results: Our results demonstrated significantly poorer survival after lung cancer diagnosis for individuals with schizophrenia compared to those without schizophrenia. The hazard ratio for all-cause mortality associated with schizophrenia was 1.33 (95% CI, 1.22–1.44).

Conclusions: Individuals with schizophrenia are at higher risk of death after diagnosis of lung cancer than those without schizophrenia. Future studies should further characterize cause of death, quality of cancer care received, and barriers to care.

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[a]Durham VA Medical Center, Durham, North Carolina
[b]Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, North Carolina
[c]Pain, Research, Informatics, Multi-morbidities, and Education Center (PRIME), VA Connecticut Healthcare System, West Haven
[d]Mental Illness Research, Education, and Clinical Center, Veterans Health Administration, West Haven, Connecticut
[e]Department of Psychiatry, Yale University School of Medicine, New Haven, Connecticut
**Corresponding author:* Daniel W. Bradford, MD, MPH, Durham VA Medical Center, 1830 Hillandale Rd, Durham, NC 27705 (Daniel.bradford@duke.edu).

Individuals with serious mental illnesses have increased mortality relative to those without these illnesses.[1,2] Schizophrenia, one of the most debilitating of the mental illnesses, has been shown in several rigorous epidemiologic studies to be associated with increased mortality.[3,4] Disparities in mortality in individuals with schizophrenia could be a result of numerous factors including poverty, poor social support, unhealthy behaviors (eg, smoking, substance use), poor access to health care, and diminished quality of health care received,[5] all of which have been demonstrated in various studies to be associated with schizophrenia.

Understanding how various factors confer mortality disadvantage to individuals with schizophrenia and designing public health or health care interventions to mitigate these disparities are important priorities. In health care settings, process of care measures, mortality, or both have been studied in multiple acute and chronic illnesses associated with elevated mortality risk in populations that included individuals with schizophrenia. Several studies[6–9] have demonstrated increased mortality and reduced likelihood of potentially life-saving procedures in individuals with schizophrenia in the setting of acute myocardial infarction. Increased risk of death in individuals with schizophrenia among those who experienced a stroke was demonstrated in a large national database in Taiwan.[10] Among those admitted to a hospital in England, the impact of diabetes on mortality was significantly higher in individuals with schizophrenia than in matched controls.[11]

Even though cancer is the second leading cause of death in the US general population,[12] process of care and mortality of individuals with schizophrenia diagnosed with cancer in health care settings has been an understudied area. Most studies link health care facility databases to death registries to examine whether individuals with schizophrenia have higher rates of death due to cancer.

Studies of the rates of cancer death among individuals with schizophrenia have been conducted almost exclusively outside of the United States. These studies[4,13–15] have typically utilized health care facility databases to establish schizophrenia diagnosis and then compared mortality data obtained from death registries in this group to those of either other members of a retrospective cohort or matched controls. These types of approaches have demonstrated an increased risk of death due to cancer in individuals with schizophrenia. Lack of data on the timing of cancer diagnosis in these samples prevents comparison of survival in individuals with schizophrenia who are diagnosed with cancer with those without this mental illness. Therefore, these studies provide little basis for quantifying the potential contribution of disparities in health care services to differences in mortality in individuals with schizophrenia who are diagnosed with cancer.

In this study, we utilized a large retrospective cohort of individuals diagnosed with cancer within an integrated health care system in the United States to evaluate the potential impact of schizophrenia on survival among adults of all ages. Given the high rates of lung cancer[16,17] in this population, we chose to focus our study on this localization of

Clinical Points

- Individuals with schizophrenia were shown to be at increased risk of death after diagnosis of lung cancer than those without schizophrenia.
- The greatest disparity in risk of death in individuals with schizophrenia appears to occur within the first year after diagnosis of lung cancer.
- Additional research is needed to understand the cause of the mortality disparity in individuals with schizophrenia who are diagnosed with lung cancer.

malignancy. While administrative data are variably accurate in assigning psychiatric diagnoses, accuracy for a diagnosis of schizophrenia has been shown to be more accurate than diagnosis of other mental disorders.[18] For this reason, and because psychotic disorders have the greatest mortality risk[19] among the serious mental illnesses, we chose schizophrenia as our mental health condition of interest. Although numerous static and dynamic factors may confer differential risk of death in individuals with schizophrenia who are diagnosed with cancer in a health care setting, study of this cohort of individuals with incident lung cancer diagnoses provides an opportunity to evaluate potential disparities in the effectiveness of health care in improving survival in this population.

METHODS

The population of interest consisted of all veterans who used Veterans Health Administration (VHA) services between October 1, 2001, and September 30, 2005 (N = 6,788,470). Data were drawn from Veterans Affairs (VA) administrative databases, the general contents of which have been reviewed elsewhere.[20] This period corresponds to VHA fiscal years 2002–2005 and allows both for a substantial sample size and for at least 5 years of mortality follow-up (through fiscal year 2010) from the date of the initial lung cancer diagnosis on record during that period. We next identified veterans with an *ICD-9-CM* diagnosis code for lung cancer (162.xx). A veteran was considered to have a lung cancer diagnosis if the *ICD-9-CM* code occurred on 2 or more outpatient visits within 6 months or 1 or more inpatient visit(s) during the observation period. This methodology has been used in the identification of psychiatric disorders and HIV in Medicaid administrative data.[21–23] The date of first cancer diagnosis code was considered the start of observation for that patient. We identified 34,664 veterans with lung cancer.

Diagnoses of schizophrenia and substance use disorders were identified in a manner similar to the lung cancer diagnosis [ie, for schizophrenia, *ICD-9-CM* codes (295.xx) on 2 or more outpatient visits in 1 year or 1 or more inpatient visit(s) during the observation period]. Homelessness was defined as any use of VHA homeless services during the observation period.

We then linked the diagnoses data to patient demographic files for the veteran's sex, race/ethnicity, date of birth, and marital status. Age and marital status were determined at the time of cancer diagnosis. Additional VHA data included service-connected status, a measure of disability whereby a rating of 100% indicated the potential for total disability due to illness or injury sustained during or exacerbated by military service.

We derived smoking status from the VHA electronic medical record Health Factors dataset, a computerized clinical provider reminder and reporting system that periodically reminds clinicians (eg, physicians, nurses, physician assistants, mental health providers) to perform assessments of tobacco use and records the results of structured interviews; the methodology used has been further described elsewhere.[24] These assessments are performed at multiple patient encounters, and, therefore, an aggregate variable was derived, based on the most frequently reported smoking behavior, as we have found that this methodology has better agreement with self-reported smoking status derived from patient-completed surveys than does the single Health Factors smoking prevalence reported closest to the index date. This method has been validated against self-report in other VA datasets.[24] Smoking data from the Health Factors dataset were available for 75% of the patients in this sample. We dichotomized the result into "current" versus "never or past."

Next, we searched VHA mortality files to determine whether the patient died (all-cause mortality) at any point after the lung cancer diagnosis date until the end of fiscal year 2010. VHA mortality databases have been shown to be highly accurate,[25] comparing favorably with other national mortality databases in the United States. We retained information only on deaths that occurred within 5 years of the lung cancer diagnosis date to be consistent with other reports (5-year mortality rates). Time to death was calculated as days from the lung cancer diagnosis until death, or if the patient did not die in the 5 years following the diagnosis, they were censored in the survival analysis at the 5-year point. Each subject was followed prospectively until the date of last follow-up (5 years after diagnosis) or death.

The study was approved by the institutional review board of the local VHA facility. The study was granted an exemption of the need for informed consent given that the data were retrospective and final datasets were de-identified for analysis.

Analysis

We compared baseline characteristics by schizophrenia diagnosis of the cohort using the *t* test for normally distributed variables such as age and the χ^2 test for categorical variables such as race and comorbid disorders.

To avoid potential bias from missing smoking and race data, missing values were imputed via multiple imputation. We used a discriminant function with 20 imputations using the SAS PROC multiple imputation procedure.

We used Kaplan-Meier curves to display the unadjusted mortality experience, stratified by schizophrenia status.

We then used multivariable Cox regression to adjust for potential confounders in the association of schizophrenia status with mortality, including age, smoking status, and substance abuse disorders.

We used SAS 9.4 (SAS Institute, Cary, North Carolina) for all analyses.

RESULTS

Table 1 shows the clinical and demographic characteristics of the cohort veterans with lung cancer, by schizophrenia diagnosis. Consistent with a VHA sample, most were male, with similar proportions of male subjects in the groups with and without schizophrenia. Individuals with schizophrenia were younger at time of diagnosis with lung cancer (64.3 vs 70.0 years, $t = 15.15$, $P < .0001$). Patients with schizophrenia were significantly more likely to be white, smokers, and service-connected; be diagnosed with a substance use disorder; and have evidence of being homeless and less likely to be married.

Table 2 shows adjusted hazard rate ratios for death among veterans with lung cancer diagnoses. Figure 1 shows product-limit survival estimates for individuals with and without schizophrenia after diagnosis with lung cancer. In adjusted Cox models, individuals with schizophrenia had significantly higher hazard for death compared to those without schizophrenia (Cox hazard ratio [HR] = 1.33; 95% confidence interval [CI], 1.22–1.44). Increasing age was significantly associated with the likelihood of death, as was black race, current smoking at the time of cancer diagnosis, having 100% service connection, and substance abuse disorder diagnosis. Using homeless services was associated with a decreased risk.

Table 1. Clinical and Demographic Characteristics of the Sample of Veterans With Lung Cancer Diagnosis[a]

Characteristic	Total N = 34,664	Schizophrenia No n = 33,829	Schizophrenia Yes n = 835	*P* Value
Age, mean, y	69.8	70.0	64.3	< .0001
Female	546 (1.6)	521 (1.5)	25 (3.0)	.0009
Race				
Missing	13,883 (40.1)	13,771 (40.7)	112 (13.4)	< .0001
Other	642 (1.9)	612 (1.8)	30 (3.6)	
Black	3,074 (8.9)	2,892 (8.5)	182 (21.8)	
White	17,065 (49.2)	16,554 (48.9)	511 (61.2)	
Married	19,335 (55.8)	19,133 (56.6)	202 (24.2)	< .0001
Smoking				
Missing	8,663 (25.0)	8,465 (25.0)	198 (23.7)	.0018
Past/Never	13,171 (38.0)	13,047 (38.6)	124 (14.9)	
Current	12,830 (37.0)	12,317 (36.4)	513 (61.4)	
Service-connected disability of 100%	3,463 (10.0)	3,092 (9.1)	371 (44.4)	< .0001
Homeless	1,109 (3.2)	971 (2.9)	138 (16.5)	< .0001
Substance use disorder	8,865 (25.6)	8,428 (24.9)	437 (52.3)	< .0001
Fiscal year of cancer diagnosis				.9363
2002	7,708 (22.2)	7,517 (22.2)	191 (22.9)	
2003	8,704 (25.1)	8,492 (25.1)	212 (25.4)	
2004	8,968 (25.9)	8,759 (25.9)	209 (25.0)	
2005	9,284 (26.8)	9,061 (26.8)	223 (26.7)	
Years survived				
1	14,850 (42.8)	14,373 (42.5)	477 (57.1)	
2	3,127 (9.0)	3,051 (9.0)	76 (9.1)	
3	1,522 (4.4)	1,466 (4.3)	56 (6.7)	
4	917 (2.6)	898 (2.7)	19 (2.3)	
5	752 (2.2)	736 (2.2)	16 (1.9)	
≥ 6	13,496 (38.9)	13,305 (39.3)	191 (22.9)	

[a]Values are n (%) unless otherwise specified.

Table 2. Adjusted Hazard Rate Ratios for Death Among Veterans With Lung Cancer Diagnoses

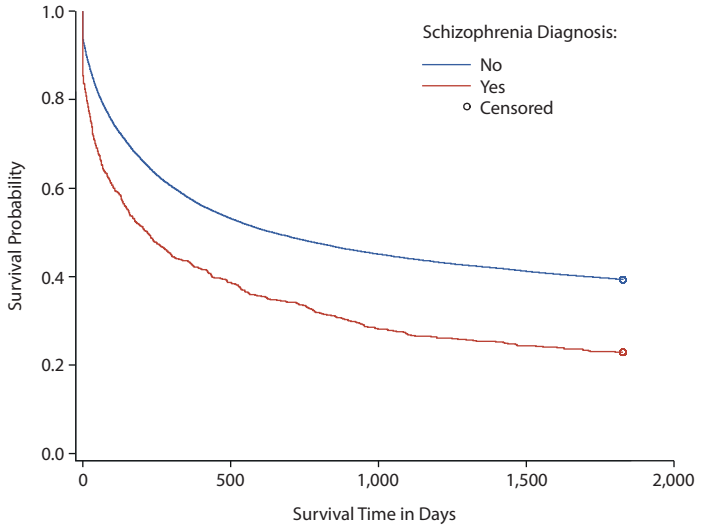
Characteristic	Hazard Ratio (95% CI)	*P* Value
Schizophrenia	1.33 (1.22–1.44)	< .0001
Age, per year	1.01 (1.01–1.02)	< .0001
Female	0.72 (0.64–0.81)	< .0001
Race (compared to white)		
Black	1.13 (1.07–1.19)	< .0001
Other	1.03 (0.91–1.17)	.601
Smoking at cancer diagnosis	1.13 (1.07–1.18)	< .0001
Married	0.82 (0.80–0.85)	< .0001
Service-connected	1.47 (1.41–1.54)	< .0001
Use of homeless services	0.83 (0.77–0.90)	< .0001
Substance use disorder	1.18 (1.13–1.22)	< .0001

DISCUSSION

This study is the first, to our knowledge, to compare survival of adults of all ages with schizophrenia after diagnosis of lung cancer to those without schizophrenia. Our results demonstrated significantly poorer survival after lung cancer diagnosis for individuals with schizophrenia compared to those without schizophrenia. The hazard ratio for all-cause mortality associated with schizophrenia in this study of 1.33 (95% CI, 1.22–1.44) was intermediate among those reported in prior studies. One unexpected finding was that use of homeless services was associated with a decreased risk of death. Given that the variable for homelessness is based on use of homeless services, rather than simply being homeless, it is possible that this variable selects for a group that is more engaged in health care services overall, given that VA homeless services have a focus on helping these veterans access overall health care services.

Several studies have examined the process and outcomes of care of individuals with schizophrenia from initial diagnosis of cancer. Mateen et al[26] conducted chart reviews in a US hospital sample to examine the care of 29 patients with schizophrenia who were diagnosed with lung cancer. Of 17 patients with a potentially curable cancer, 5 were identified with a potential disparity in care, but the researchers concluded that schizophrenia was never the sole reason that a therapy was not provided. Bergamo et al[27] examined lung cancer stage at diagnosis, diagnostic evaluation types, rates of stage-appropriate treatment, and survival in Medicare beneficiaries aged 66 years and older with and without schizophrenia who were diagnosed with non–small cell lung cancer. Although patients with schizophrenia presented with earlier stages of cancer, they were less likely to undergo diagnostic evaluation or receive

Figure 1. Product-Limit Survival Estimates for Individuals With and Without Schizophrenia After Diagnosis of Lung Cancer



stage-appropriate treatment. Survival was shorter for those with schizophrenia (22.3 vs 26.3 months, $P = .002$), although this difference was not present after controlling for stage-appropriate treatment. Schizophrenia was associated with an increased hazard ratio for death in Cox models with adjustment for potential confounders other than lung cancer treatment (Cox HR = 1.07; 95% CI, 1.01–1.13). Chang et al[28] examined stage at cancer diagnosis and all-cause mortality by linking 2 case register systems in the United Kingdom. They found no differences in stage at diagnosis, but found increased mortality in individuals with schizophrenia (Cox HR = 1.71; 95% CI, 1.38–2.11, adjusted for age and gender) as compared to those without this disorder. Kisely et al[15] linked mental health and cancer registries in Western Australia to evaluate cancer incidence, the presence of metastases at cancer diagnosis, mortality, and access to cancer intervention among those with and without mental illnesses. This study[15] showed similar incidence, but higher mortality for those with schizophrenia compared to the general population across all types of cancers. Among all types of cancer, individuals with schizophrenia had poorer survival (Cox HR = 1.96; 95% CI, 1.67–2.31) than the general population. Additionally, the study[15] demonstrated that individuals with a history of psychiatric treatment were less likely to get surgery, received fewer sessions of chemotherapy, and were more likely to have metastases at the time of diagnosis.

Our study is most comparable to the Bergamo et al study[27] given that both were in a US population and focused on individuals with and without schizophrenia who were diagnosed with lung cancer. The lower hazard ratio in the study of Bergamo and colleagues[27] (Cox HR = 1.07; 95% CI, 1.01–1.13) could be partially explained by the older age of the members of the cohort. The mean age in our study was 64.3 years for individuals with schizophrenia and 70.0 years for those without schizophrenia, while the mean age in the Bergamo et al study[27] was 73.9 years for individuals with schizophrenia and 75.1 years for those without schizophrenia. Death due to non-cancer causes in an older cohort would quite likely diminish the difference in survival among those with and without schizophrenia.

The contribution of schizophrenia to all-cause mortality after lung cancer diagnosis was smaller than that reported by Chang et al[28] and Kisely et al.[15] Both reported hazard ratios for all-cause mortality associated with schizophrenia that are notably larger than that in our study. Neither of these studies[15,28] reported hazard ratios specific to lung cancer. Differences in the hazard ratio associated with schizophrenia could also be due to differences in the health care systems in London, England, and Western Australia (in the Chang et al[28] and Kisely et al[15] studies, respectively) as compared to the VA health care system in the United States. While no direct comparisons between these systems and VHA are available, 1 study suggested improved survival after non–small cell cancer diagnosis in VHA as compared to the fee-for-service Medicaid system,[29] as well as higher rates of guideline concordant care for some treatments. It is possible that a higher overall quality of cancer care in VHA attenuates survival differences between individuals with and without schizophrenia.

Our study has several important limitations relative to the goal of understanding the impact of a diagnosis of schizophrenia on survival after diagnosis of lung cancer. The reliance of providers on coding for diagnoses, including the need to develop rules for reconciling contradictory diagnoses and missing data, introduces some uncertainty regarding the accuracy of diagnoses for both malignancy and psychiatric illness. Since the data are only from care received through VHA, it is possible that some individuals in the cohorts could have been diagnosed with malignancy prior to when lung cancer was documented in the VHA system. The present dataset lacks information on treatments offered and the cause of death, so we have no means of evaluating the quality of cancer care provided to those in the cohort or whether death is related to quality of cancer care received. Figure 1 shows that much of the disparity in mortality occurs within the first year after diagnosis, yet the current dataset does not allow us to further examine this issue. Given that disparities in survival could be interpreted as disparities in quality of cancer care for individuals with schizophrenia, the lack of information in this dataset on cancer staging and treatments received is a significant limitation. Without staging data, there is no way to assess whether disparities in survival may be due to late diagnosis, suggesting inadequate primary care rather than deficiencies in cancer care after diagnosis. Additionally, given that the latest date of follow-up in this cohort is September 30, 2010, this dataset would fail to capture any changes in treatment or delivery patterns for lung cancer that may have occurred since then.

Future research is needed to further characterize the disparities in mortality seen in individuals with schizophrenia

who are diagnosed with lung cancer relative to the general population. Using additional data sources available through the VHA would allow the incorporation of information such as cancer stage at diagnosis, receipt of treatment, follow-up care, and adherence to treatment. More detailed characterization of the causes of mortality disparities will inform development of targeted interventions for various phases of cancer care, ranging from screening[30] in the primary care or specialty mental health setting, to decision making after initial diagnosis, to addressing particular challenges that individuals with schizophrenia may have with various types of treatment for cancer.

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