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The burden of depression in prostate cancer

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Abstract

Objective: **We sought to analyze the prevalence and incremental burden of depression among elderly with prostate cancer.**

Methods: **We adopted a retrospective cohort design using the Surveillance, Epidemiology and End Results-Medicare linked database between 1995 and 2003. Patients with prostate cancer diagnosed between 1995 and 1998 were identified and followed retrospectively for 1 year pre-diagnosis and up to 8 years post diagnosis. In this cohort of patients with prostate cancer, depression during treatment phase (1 year after diagnosis of prostate cancer) or in the follow-up phase was identified using the International Classification of Diseases-Ninth Revision depression-related codes. Poisson, general linear (log-link) and Cox regression models were used to determine the association between depression status during treatment and follow-up phases and outcomes–health resource utilization, cost and mortality.**

Results: **Of the 50,147 patients newly diagnosed with prostate cancer, 4285 (8.54%) had a diagnosis of depression. A diagnosis of depression during treatment phase was associated with higher odds of emergency room visits (odds ratio (OR)=4.45, 95% CI=4.13, 4.80), hospitalizations (OR=3.22, CI=3.08, 3.37), outpatient visits (OR=1.71, CI=1.67, 1.75) and excess risk of death over the course of the follow-up interval (hazard ratio=2.82, CI=2.60, 3.06). Health care costs associated with depression remained elevated compared with costs for men without depression, over the course of the follow-up.**

Conclusions: **Depression during the treatment phase was associated with significant health resource utilization, costs and mortality among men with prostate cancer. These findings emphasize the need to effectively identify and treat depression in the setting of prostate cancer.**

Keywords: depression; prostate cancer; cost; mortality; health resource utilization

Introduction

Prostate cancer is the most common cancer among older men with an estimated 217,730 new cases diagnosed in 2010 [1]. Prostate cancer has the highest annual Medicare expenditure than any other cancer affecting older men. Mortality due to prostate cancer is declining, and many men continue to live long after diagnosis with treatment-related morbidity [2]. Depression has serious implications for outcomes and recovery from prostate cancer as reflected in debilitating effects on health related quality of life, functional status, health resource utilization and cost [3–8]. Despite these troubling effects of depression on many patients with prostate cancer, the scope of the problem is largely unrecognized and underappreciated [9].

Prostate cancer care has evolved from a relatively straightforward mono-therapy model to a complex one with multi-modal treatment options. Depression among patients with prostate cancer has been linked to suicide, unpleasant lifestyle changes, poorer adherence to treatment and poorer long-term outcomes [10–12]. Moreover, studies of the outcomes of prostate cancer treatment have demonstrated deficiencies and variability in the quality of prostate cancer care across geographic region, age and racial and ethnic groups [1,2]. Depression in patients with prostate cancer may be an unidentified factor in the variability in care, contributing to poorer long-term treatment outcomes.

National samples have provided limited information regarding the prevalence of depression and its effects on health resource utilization and cost of care among older men with prostate cancer. Many earlier studies have highlighted the under-diagnosis of depression among older adults [3–5,8]. Among older patients with prostate cancer, inadequate attention has been given to the prevalence and impact of depression on outcomes of prostate cancer. The objective of this

study was to develop estimates of the diagnosis of depression among older men with prostate cancer and the association of depression with health resource utilization, cost of medical care and mortality. We used the Surveillance, Epidemiology and End Results (SEER)-Medicare linked data to examine the modifying effects of depression on health resource utilization, cost, and mortality among patients with prostate cancer. We hypothesized that depression would be associated with higher mortality, health resource utilization and costs in patients with prostate cancer, even after adjusting for potentially influential personal and clinical characteristics.

Methods

Data sources

The SEER-Medicare linked data of the National Cancer Institute bring together Medicare administrative claims data and clinical tumor registry data for Medicare recipients [13]. The SEER program collects data on cancer incidence, treatment and mortality from 13 SEER sites and encompasses 14% of the population of the USA. Of persons 65 years and older, diagnosed with cancer and enrolled in SEER registries, 93% have been matched with Medicare enrollment records.

For our retrospective cohort design, we employed SEER-Medicare data to obtain a sample of men, aged 66 years and older, diagnosed with prostate cancer (International Classification of Diseases (ICD) codes: 185, 233.4, 236.5) between 1995 and 1998 (n=50,147). Patients with prostate cancer who were less than 66 years of age at the time of diagnosis were excluded to ensure that the data file included sufficient claims for medical care prior to the diagnosis of prostate cancer to allow us to adjust for pre-diagnosis co-morbidity.

Sample selection

Data for men with prostate cancer were obtained for 1 year prior to diagnosis (pre-diagnosis phase or Phase 0) and for 5 years post diagnosis. The first year post diagnosis was considered the 'treatment-phase' (Phase 1), and the following 4 years were considered the 'follow-up phase' (Phase 2 to Phase 5). For men who died in the observed interval, we considered the 1 year prior to the date of death as the 'terminal phase'.

Measurement strategy

Diagnosis of depression

Depression diagnosis was the key independent stratification variable in our analyses. Primary and secondary diagnostic codes from Medicare inpatient and outpatient claims were used to identify men who had a diagnosis of depression. Depression diagnosis was classified as major (ICD-Ninth Revision Clinical Modification (9 CM)=296.2–major depressive disorder, single episode, and 296.3–major depressive disorder, recurrent episode) and minor depression (ICD-9 CM=300.4–neurotic depressive, 309.0–brief depressive reaction, 309.1–prolonged depressive reaction, 298.0–depressive type psychosis and 311–depressive disorder not classified). Men with a diagnosis of depression were categorized as diagnosed for depression during the treatment phase or in the subsequent follow-up phases.

Key dependent variables under study

Key dependent variables were health resource utilization, direct medical care cost and mortality. SEER-Medicare linked data include service codes categorized as inpatient (length of stay, number of admissions, surgical and diagnostic procedures), outpatient (laboratory testing and emergency room (ER) visits), durable medical equipment, home health services, skilled nursing facility use and hospice care. Direct medical care costs were defined as the reimbursements received from Medicare [14–16]. Total direct medical care costs included costs of care provided by physicians and other health professionals, care provided in hospitals, outpatient and ER costs, inpatient medications and laboratory services. All-cause mortality was obtained from the vital status variable in Medicare claims data. Time to death was calculated as the time between date of diagnosis and date of death, while patients alive at the end of 8 years of follow-up were censored.

Covariates

We obtained socio-demographic characteristics, disease severity, medical co-morbidity and prostate cancer treatment for use in adjusting our measures of association for potentially influential covariates. Age, ethnicity and income data were obtained from the Patient Entitlement and Diagnosis Summary File. Prostate cancer severity was assessed with information on prostate cancer stage, grade and histology provided in SEER. The Charlson co-morbidity index based on diagnostic information from the entire observation interval was used to measure medical co-morbidity using inpatient and outpatient Medicare claims data [17,18]. Primary and secondary procedure codes were searched to identify ICD-9 CM codes for prostate cancer treatments. Primary procedures were surgery (radical prostatectomy), radiation therapy (external beam or brachytherapy), hormone therapy and no treatment or watchful waiting.

Analytic strategy

We first tested for underlying differences in the demographic and clinical characteristics of patients with prostate cancer with and without depression,

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using standard *t*-tests and χ^2-tests, as appropriate. For categorical data on health resource utilization, we used χ^2-tests and odds ratios to compare the health resource utilization between men with and without depression.

The Poisson regression model (with zero inflation correction) was used to study the association between depression (coded separately as 'during treatment phase' or 'during subsequent follow-up phase') and health services utilization (number of ER visits, number of inpatient visits and number of outpatient visits) patterns [19–22]. Cox regression was used to study the association between depression and all-cause mortality. To analyze the association of diagnosis of depression with medical care cost, we used a generalized linear model with a log-link and gamma distribution variance function [19–22]. This approach uses log transformation to normalize the distribution of skewed costs and allows interpretation of the parameters directly on a dollar scale. All costs were standardized to 2009 figures using a 5% discount rate.

We used four sequential models to analyze the effect of depression on outcomes (health resource utilization, costs and mortality). Model 1 estimated the unadjusted association of depression with outcomes. In Model 2, we controlled for age, ethnicity, income, tumor, nodes and metastases stage, geographic area, SEER registry area, Charlson co-morbidity and marital status. Treatment of prostate cancer will have an effect on outcomes; however, in assessing the relationship of depression to prostate cancer outcomes, we must keep in mind that assignment to receive treatment is not random. To minimize the observed and unobserved bias because of treatment, we used propensity score analysis (Model 3) and instrumental variable analysis (Model 4). In all models, depression was operationalized as depression during treatment phase or depression in subsequent follow-up period, and no depression was the reference category.

In Model 3, we estimated, for each subject, the probability of receiving radical prostatectomy, external beam radiation therapy, hormone therapy or no treatment (i.e., the 'propensity score') based on age, race, tumor, nodes and metastases stage, geographic location, socio-economic status, marital status and Charlson co-morbidity score using multi-nomial logistic regression [21]. We then used this score as a control variable in modeling the outcomes as a function of the explanatory variable of interest (depression). To study the extent to which the prostate cancer treatment groups were matched, we compared the *t*-statistics for these covariates before and after adjusting with propensity score.

Model 4 employed an instrumental variable approach to address unmeasured bias, relying on an instrumental variable that is associated with the likelihood of particular type of treatment but is independent of the outcome [23,24]. Prior research indicated significant unexplained geographic variation in treatment. Based on proportion of patients receiving radical prostatectomy, the SEER regions were categorized as high or low radical prostatectomy regions, and this variable was used as an instrumental variable. To assess the validity of the instrumental variable, we performed the following analyses [22,23]. To begin with, we tested the association between the instrumental variable and treatment using multinomial logistic regression. We then confirmed the lack of association between the instrumental variable and outcomes using regression models. We compared observable attributes between patients from regions with a high proportion of radical prostatectomy treatment versus regions with a low proportion of radical prostatectomy treatment. Here, the characteristics of patients in the regions with a high proportion of radical prostatectomy treatment should be similar to those of patients in regions with a low proportion. Finally, we performed sensitivity analyses to test the validity of our findings by categorizing the depression diagnosis as major depression (ICD-9 CM=296.2 and 296.3) or minor depression (ICD-9 CM=300.3, 309.0, 309.1, 298.0 and 311). An additional sensitivity analysis was performed by excluding men with a diagnosis of depression in the pre-prostate and post-prostate cancer diagnosis. All analyses were conducted using Statistical Analysis System (SAS), Version 9.2 (SAS Institute, Cary, NC, USA).

Results

Sample characteristics

The study sample consisted of 50,147 fee-for-service elderly Medicare beneficiaries who were diagnosed with prostate cancer between 1995 and 1998. From this sample, we identified 4285 patients with a diagnosis of depression (1253 during treatment phase and 3032 in post-treatment phase) and 45,862 without a diagnosis of depression during the study period (Table 1). Men with a diagnosis of depression were older at the time of diagnosis of prostate cancer (75.8 years, standard deviation (SD)=6.4 years) compared with men without a diagnosis of depression (74.2 years, SD=6.2 years). Also, those with depression were more likely than those without depression to live in large metropolitan areas, less likely to be married and had lower annual income. With respect to clinical characteristics, men with depression had higher medical co-morbidity at the time of diagnosis of prostate cancer and were diagnosed at a later stage of cancer, compared with men without a depression. Finally, men with depression were more likely to have received radical prostatectomy than those without depression.

Health resource utilization

Comparisons of unadjusted health resource utilization patterns (ER visits, inpatient visits, outpatient

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Table 1. Personal and clinical characteristics of men aged 66 years and older who were diagnosed with prostate cancer between 1995 and 1998, according to depression status (n=50,147)

	No depression (n=45,862)	Depression (n=4285)
Age at diagnosis (years)		
Years, mean (SD)	74.20 (6.20)	75.80 (6.40)
Ethnicity (%)		
White	81.09	86.74
African American	11.97	8.32
Hispanic	6.94	4.94
Marital status (%)		
Married	69.38	62.99
Single/separated/divorced	23.28	30.29
Unknown	7.34	6.72
Geographic area (%)		
Metro	88.46	82.34
Urban	10.29	15.32
Rural	1.25	2.34
Charlson co-morbidity index (%)		
0	83.03	81.69
1–2	12.27	13.26
>3	4.70	4.79
Annual median income of census tract (dollars)		
Mean (SD)	39,206 (18,609)	37,189 (18,680)
Histology (%)		
In situ	0.04	0.13
Distant	6.63	5.47
Localized/regional	84.83	84.30
Unstaged	8.50	10.02
Grade (%)		
Well-differentiated	9.60	12.84
Moderately differentiated	58.70	55.42
Poorly differentiated/undifferentiated	21.00	20.38
Unknown	10.70	11.36
Tumor stage (%)		
≤T2a	40.57	40.65
T2b and T2c	35.71	35.55
≥T3a	23.72	23.80
Treatment (%)		
Radical prostatectomy alone or multi-modal therapy (radiation therapy+hormone therapy)	29.02	30.31
External beam radiation therapy alone or brachytherapy alone or multi-modal therapy (+hormone)	32.10	27.35
Hormone alone	12.34	13.80
No treatment or watchful waiting	26.54	28.54

Data from SEER-Medicare (1995–2003).
All p-values are <0.001.
SD, standard deviation.

visits and length of stay; Figure 1) showed significant variation in use of health services between men with and without depression across all phases of prostate cancer care. Men with a diagnosis of depression had higher ER, inpatient and outpatient visits and longer mean lengths of stay during all phases of care than did men without depression. Results of Poisson regression are presented in Table 2. Compared with men without depression, men with depression during treatment phase were more likely to have an ER visit (OR=4.45, 95% CI= 4.13, 4.80), inpatient visit or hospitalization (OR= 3.22, 95% CI=3.08, 3.37) and an outpatient visit (OR=1.71, 95% CI=1.67, 1.75). Comparable results were observed for men with depression in the follow-up phase, though the magnitude of the effect was lower. In sensitivity analysis, we examined the effect of major and minor depression on health service use in treatment phase and follow-up phase and observed comparable trend.

Medical care costs

Compared to men without depression, men with depression had higher inpatient pharmacy costs, physical therapy costs and laboratory costs across all phases of prostate cancer care. Medical and surgical supply costs were higher among those with depression during all phases of prostate cancer care, except for the terminal phase. Comparisons of unadjusted phase-specific total medical care costs are presented in Figure 2. Overall, costs were higher during the treatment phase compared to the pre-diagnosis phase and declined over follow-up phases. Among men who died, the costs were highest during the terminal phase for those with a diagnosis of depression.

Patients with prostate cancer with a diagnosis of depression during treatment phase had higher costs in the treatment phase (Table 3). The magnitude of the incremental cost associated with depression among patients with prostate cancer showed an increasing trend across the follow-up period. Comparable results were obtained by employing propensity score and instrumental variable analyses. Assessment of balance between treatment groups showed that the t-statistics varied between 0.67 and 2.9 for covariates (age, income, ethnicity, marital status and Charlson co-morbidity) indicating non-significant differences between groups after adjusting for propensity score. To conduct the two-stage regression for the instrumental variable method, we first ran a regression to obtain the predicted value of receiving treatment. The instrument of geographic region was significantly predictive of the likelihood of receiving a treatment (χ^2=7.306, p=0.0069). However, the instrumental variable was not associated with some outcomes such as number of ER visits and hospitalization. Demographic and clinical characteristics were comparable between regions of high radical prostatectomy and low radical prostatectomy. To examine the effects of major and minor depression (treatment phase and follow-up phase) on health service use, we performed a sensitivity analysis. The magnitude and direction of the results were comparable with earlier results.

Mortality

Results of Cox regression models for all-cause mortality are displayed in Table 2, column 4. Mortality was associated with a diagnosis of depression during treatment phase among patients with prostate cancer

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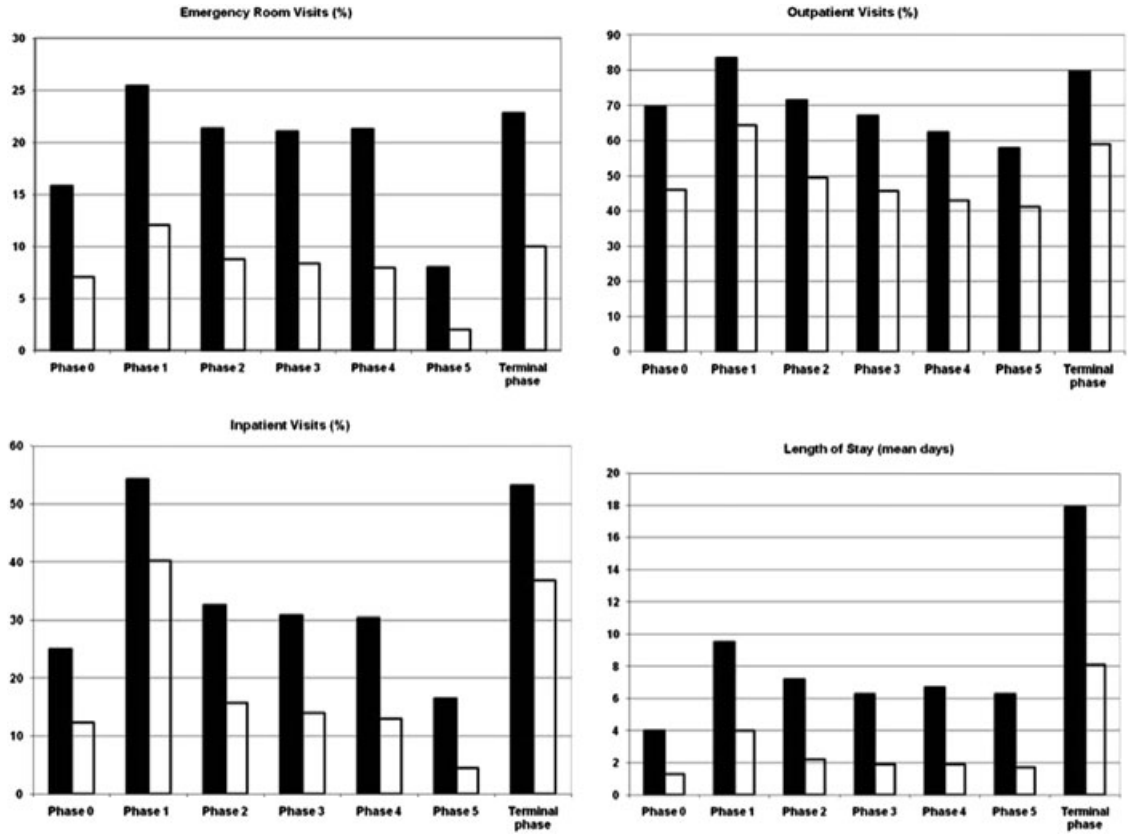

Figure 1. Health services utilization according to depression diagnosis present (dark bars) or absent (white bars). Phases signify years after prostate cancer diagnosis. Odds ratios represent the comparison of men with a diagnosis of depression and men without a diagnosis of depression. Data from SEER-Medicare (1995–2003)

based on the first two models, also the instrumental variable approach revealed increased mortality among patients with prostate cancer with a diagnosis of depression (hazard ratio=2.06, 95% CI=1.96, 2.16). Sensitivity analysis indicated comparable results; major depression in treatment phase was associated with higher mortality. Finally, among those with a diagnosis of depression, 5.4% had a diagnosis of depression in the year prior to and post diagnosis of prostate cancer. We reevaluated all models after excluding this cohort. Comparable results were obtained for health resource utilization, cost and mortality models.

Discussion

Employing National Cancer Institute SEER-Medicare linked data, we show that a diagnosis of depression among older patients with prostate cancer was associated with increased use of health care services and costs, compared with men who did not have a diagnosis of depression. The association of depression with increased use of services and costs was consistent across the different phases of treatment, with the periods shortly after diagnosis and the year before death showing the most use of services and costs. Our estimates of association were statistically

Table 2. Association between depression diagnosis, health services use and mortality

	Emergency room visit	Hospitalization	Outpatient visit	Mortality
Model 1: unadjusted				
Treatment phase depression	4.45 [4.13, 4.80]	3.22 [3.08, 3.37]	1.71 [1.67, 1.75]	2.82 [2.60, 3.06]
Post treatment depression	1.66 [1.55, 1.79]	1.42 [1.36, 1.47]	1.58 [1.56, 1.60]	0.86 [0.79, 0.92]
Model 2: adjusting for clinical and demographic covariates				
Treatment phase depression	3.46 [3.21, 3.74]	2.76 [2.63, 2.88]	1.80 [1.76, 1.85]	2.01 [1.85, 2.18]
Post treatment depression	1.64 [1.52, 1.77]	1.34 [1.29, 1.39]	1.52 [1.50, 1.80]	0.75 [0.70, 0.81]
Model 3: propensity score adjusted				
Treatment phase depression	3.44 [3.18, 3.72]	2.89 [2.76, 3.02]	1.69 [1.66, 1.73]	2.09 [1.92, 2.27]
Post treatment depression	1.66 [1.54, 1.78]	1.38 [1.33, 1.45]	1.54 [1.52, 1.56]	0.76 [0.71, 0.80]
Model 4: instrumental variable adjusted				
Treatment phase depression	3.44 [3.35, 3.66]	2.94 [2.86, 3.00]	1.71 [1.69, 1.73]	2.06 [1.96, 2.16]
Post treatment depression	1.65 [1.58, 1.72]	1.38 [1.35, 1.42]	1.53 [1.51, 1.54]	0.76 [0.73, 0.79]

Data from SEER-Medicare (1995–2003).
Odds ratios represent the comparison of men with a diagnosis of depression and men without a diagnosis of depression. 95% CI shown in brackets.

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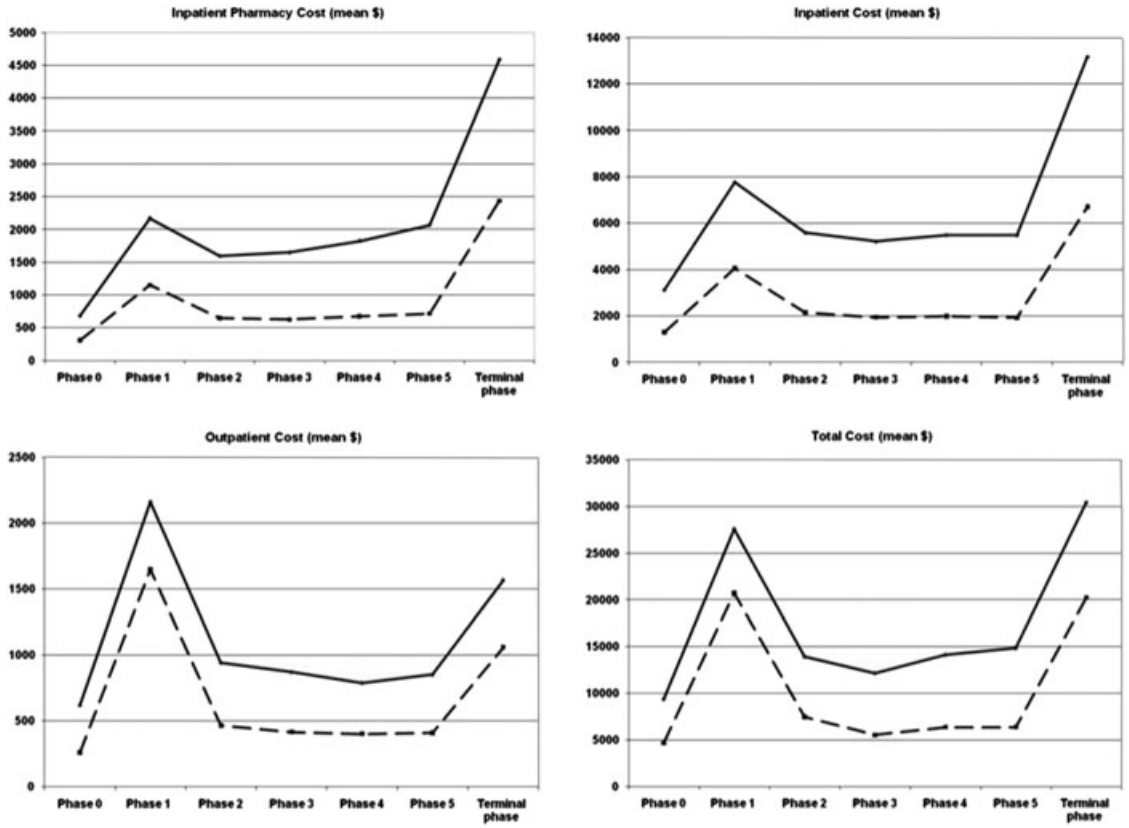

Figure 2. Costs according to depression diagnosis present (dark bars) or absent (white bars). Phases signify years after prostate cancer diagnosis. Odds ratios represent the comparison of men with a diagnosis of depression and men without a diagnosis of depression. Data from SEER-Medicare (1995–2003)

adjusted for observed and unobserved characteristics, including stage and histological grade of prostate cancer. Depression diagnosis during treatment phase was associated with greater risk of death over the follow-up period. We believe our study results have implications for clinical care, research and policy.

Before discussing the implications of our findings, we note certain limitations of our study. SEER-Medicare linked data have been used to study cancer-related health services and costs, including for prostate cancer [13–15]. In our study, the sample consists only of men aged 66 years and older, not enrolled in a health maintenance organization and living in an SEER region. Furthermore, whereas the age and sex distribution for persons 66 years and older is comparable with that of older adults in the USA, the SEER regions have a higher proportion of non-white persons. Mortality rates derived from SEER data may not be representative of national data on cancer mortality rates [13]. Administrative data have become an important source of information for public health and health services research but are subject to error [25]. Studies employing medical records used as a validation criterion for administrative data show generally good agreement for medical conditions (e.g., MI [26], diabetes [27], osteoarthritis [28], Parkinson's disease [29], medical co-morbidity [30]) and for procedures (e.g., colonoscopy [31], mammography [32]). Although threshold for depression diagnosis may vary from physician to physician [33], studies of the use of claims data for depression have shown generally good agreement, with some potential for misclassification and false positives [34,35]. Our estimates of the association of depression with health services use and costs may be conservative because men with milder forms of depression are likely to be misclassified into the comparison group as not being depressed.

Despite limitations, our study draws attention to a largely silent problem: depression among patients with prostate cancer. Himelhoch and colleagues found that, among men with prostate cancer, depression was associated with three-fold higher odds of emergency department use and hospitalization over the course of 1 year when compared with men without depression [36]. In our study, a diagnosis of depression was associated with increased health services use, costs and mortality among men with prostate cancer in the follow-up period. Depression could be a direct consequence of treatment (e.g., hormonal therapy that decreases testosterone levels [37,38]), a direct effect of disease (e.g., pain or fatigue in advanced prostate cancer [39,40]) or an indirect result of functional loss because of treatment (e.g., sexual dysfunction after radical prostatectomy [41]). Although the prevalence of depression diagnosis among patients with prostate cancer in our sample was comparable with other estimates employing

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Table 3. Association between depression diagnosis and costs

	Phase 1	Phase 2	Phase 3	Phase 4	Phase 5	Terminal phase
Model 1: unadjusted						
Treatment phase depression	1.19 [1.08, 1.31]	1.32 [1.16, 1.51]	1.37 [1.20, 1.56]	1.37 [1.19, 1.56]	1.02 [0.89, 1.17]	1.29 [1.15, 1.45]
Post treatment depression	1.01 [0.95, 1.07]	1.41 [1.32, 1.51]	1.69 [1.58, 1.78]	1.76 [1.66, 1.87]	1.88 [1.78, 2.00]	1.15 [1.06, 1.24]
Model 2: adjusting for clinical and demographic covariates						
Treatment phase depression	1.52 [1.39, 1.66]	1.41 [1.24, 1.60]	1.39 [1.22.1.58]	1.34 [1.18, 1.53]	1.01 [0.88, 1.15]	1.43 [1.28, 1.60]
Post treatment depression	1.03 [0.97, 1.09]	1.51 [1.41, 1.62]	1.69 [1.59, 1.79]	1.74 [1.64, 1.85]	1.89 [1.78, 2.00]	1.26 [1.17, 1.37]
Model 3: propensity score adjusted						
Treatment phase depression	1.25 [1.14, 1.38]	1.35 [1.19, 1.54]	1.40 [1.23, 1.59]	1.38 [1.22, 1.58]	1.03 [0.90, 1.18]	1.34 [1.20, 1.51]
Post treatment depression	1.05 [0.99, 1.11]	1.47 [1.38, 1.58]	1.71 [1.60, 1.78]	1.70 [1.60, 1.80]	1.87 [1.76, 1.98]	1.18 [1.09, 1.27]
Model 4: instrumental variable adjusted						
Treatment phase depression	1.44 [1.37, 1.52]	1.41 [1.31, 1.52]	1.42 [1.32, 1.52]	1.36 [1.26, 1.48]	1.02 [0.94, 1.10]	1.42 [1.34, 1.52]
Post treatment depression	1.02 [0.98, 1.05]	1.51 [1.45, 1.57]	1.72 [1.66, 1.78]	1.74 [1.67, 1.78]	1.89 [1.84, 1.96]	1.26 [1.20, 1.32]

Data from SEER-Medicare (1995–2003).

Phases signify years after prostate cancer diagnosis. Odds ratios represent the comparison of men with a diagnosis of depression and men without a diagnosis of depression. 95% CI shown in brackets.

diagnostic interviews (e.g., Structured Clinical Interview for DSM-IV [37]) or scales (e.g., Center for Epidemiologic Studies Depression Scale [42], Hospital Anxiety and Depression Scale [43–45]), these reported prevalence estimates of depression in prostate cancer were derived from small (100 men or fewer) outpatient or hospitalized samples [10,46,47]. Three population-based studies reported that rates of suicide among men with prostate cancer were markedly elevated compared with men without prostate cancer [11,48,49]. Despite the development of effective management strategies that reduce the burden of depression among older adults [50–52], many studies describing interventions directed at psychosocial issues associated with the diagnosis of prostate cancer have focused on providing information about the disease rather than specifically addressing depression [10,46,47].

The widespread use of prostate-specific antigen for screening has led to increased awareness and detection of prostate cancer. Rates of depressive symptoms associated with prostate cancer appear to increase with advancing age [45], when many factors may combine to make diagnosis of depression more difficult [11,49,53–55]. Depression may contribute as much to mortality as cardiovascular disease and diabetes [56], and among men with prostate cancer, depression was associated with as much erectile dysfunction and poor sexual health as was diabetes [3]. As most men with prostate cancer may not develop clinically significant depression, more research on identification of depression and development of effective intervention approaches is needed to alleviate the burden of depression among men with prostate cancer, their families and society.

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