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ORIGINAL REPORT

# Effect of Depression on Diagnosis, Treatment, and Mortality of Men With Clinically Localized Prostate Cancer

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Terms in blue are defined in the glossary, found at the end of this article and online at www.jco.org.

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## ABSTRACT

### Purpose
Although demographic, clinicopathologic, and socioeconomic differences may affect treatment and outcomes of prostate cancer, the effect of mental health disorders remains unclear. We assessed the effect of previously diagnosed depression on outcomes of men with newly diagnosed prostate cancer.

### Patients and Methods
We performed a population-based observational cohort study using Surveillance, Epidemiology, and End Results-Medicare linked data of 41,275 men diagnosed with clinically localized prostate cancer from 2004 to 2007. We identified 1,894 men with a depressive disorder in the 2 years before the prostate cancer diagnosis and determined its effect on treatment and survival.

### Results
Men with depressive disorder were older, white or Hispanic, unmarried, resided in nonmetropolitan areas and areas of lower median income, and had more comorbidities ($P < .05$ for all), but there was no variation in clinicopathologic characteristics. In adjusted analyses, men with depressive disorder were more likely to undergo expectant management for low-, intermediate-, and high-risk disease ($P \leq .05$, respectively). Conversely, depressed men were less likely to undergo definitive therapy (surgery or radiation) across all risk strata ($P < .01$, respectively). Depressed men experienced worse overall mortality across risk strata (low: relative risk [RR], 1.86; 95% CI, 1.48 to 2.33; $P < .001$; intermediate: RR, 1.25; 95% CI, 1.06 to 1.49; $P = .01$; high: RR, 1.16; 95% CI, 1.03 to 1.32; $P = .02$).

### Conclusion
Men with intermediate- or high-risk prostate cancer and a recent diagnosis of depression are less likely to undergo definitive treatment and experience worse overall survival. The effect of depression disorders on prostate cancer treatment and survivorship warrants further study, because both conditions are relatively common in men in the United States.

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## INTRODUCTION

Health care disparities by age, race, and socioeconomic status affect the diagnosis, treatment, and outcomes of men with prostate cancer.[1,2] In addition, longitudinal studies[3-8] have chronicled increased rates of anxiety, depression, cardiovascular events, and suicide that may result from uncertainties regarding treatment, cancer control (prostate-specific antigen [PSA] anxiety), erectile dysfunction, or urinary incontinence following treatment.[9] Whereas depression has been associated with an increased likelihood of receipt of noncurative treatment, as well as lower overall survival for other cancers, including breast cancer and hepatobiliary carcinoma,[10-12] little is known about the relationship between depression and diagnosis, treatment, and outcomes in prostate cancer.

Our objective was to use Surveillance, Epidemiology, and End Results (SEER)-Medicare linked data to assess the impact of recently diagnosed depressive disorders on prostate cancer choice. We hypothesized that men with a history of depressive disorder would present with higher-risk disease; would be less likely to receive definitive therapy (radical prostatectomy [RP] and radiotherapy [RT]) versus androgen deprivation therapy (ADT) alone or expectant management (EM), defined as watchful waiting or active surveillance; and have worse overall survival compared with men who did not have any of these.

## PATIENTS AND METHODS

SEER-Medicare was used to identify a cohort of men for investigating the hypothesized relationships. SEER-Medicare comprises demographic and cancer characteristics abstracted by the National Cancer Institute's tumor registry program linked to Medicare administrative data and encompasses approximately 28% of Medicare beneficiaries nationwide.[13] Our study was approved by the University of California at Los Angeles institutional review board, patient data were de-identified, and the requirement for consent was waived.

International Classification of Diseases, Ninth Revision (ICD-9) codes were used to identify disease categories, and Current Procedural Terminology, Fourth Edition (CPT-4) and Healthcare Common Procedure Coding System code sets were used to identify medical and surgical services. RP, RT, ADT, and EM were defined as previously described.[14] Frequency of doctors' visits was calculated by using provider claims data in the 24 months before prostate cancer diagnosis.

Patient age was obtained from the Medicare file, and the SEER registry provided information on clinical characteristics, race, population density, marital status, census measurements of median household income, and proportion of individuals with at least a high school education. Comorbidity using the Klabunde modification of the Charlson index was based on inpatient, outpatient, and carrier claims during the year before diagnosis.[15] A history of a depressive disorder was made by searching for the presence of diagnostic codes for depressive disorders (ICD-9-Clinical Modification [ICD-9-CM] 296.2, 296.3, 296.5, 296.6, 296.7, 298.0, 301.10, 301.12, 301.13, 309.0, 309.1, 311) in all outpatient, inpatient, and carrier files[16] in the 2 years before prostate cancer diagnosis.

### Study Population

We identified 103,809 men diagnosed with clinically localized prostate cancer from 2004 to 2007 and observed through December 31, 2009, by using SEER-Medicare linked data. To avoid potential confounding due to other concurrent cancers, we restricted our analyses to men with prostate cancer diagnosed as their only cancer, thus excluding 3,348 men with other cancers. Because diagnostic codes for depressive disorders were ascertained through Medicare data for the 2 years before prostate cancer diagnosis, we restricted our final study population to men age 67 years or older at the time of cancer diagnosis, excluding 13,772 men age 65 to 66 years. We excluded 29,295 men who were not continuously enrolled in Medicare Part A and B or were also enrolled in a health maintenance organization because claims were not reliably submitted for these men. We also excluded 4,624 men who had metastases at diagnosis, who died within 6 months of diagnosis, or who lost Medicare enrollment during the follow-up period. In addition, we excluded 11,034 men with incomplete clinical and demographic information. Finally, we excluded 460 men with a diagnosis of anxiety disorder (ICD-9-CM 293.84, 300.0, 300.01, 300.02, 300.09, 308). The final study cohort of 41,275 men was stratified into National Comprehensive Cancer Network (NCCN) risk groups.[17]

### Dependent Variable

We assessed the impact of a recent diagnosis of depressive disorder on tumor characteristics at presentation, prostate cancer treatment selection, and overall mortality.

### Statistical Analysis

Demographic and clinical characteristics associated with depressive disorder were assessed with the Pearson $\chi^2$ statistic and Fisher's exact tests. Ordinal variables such as risk group and age were assessed with the Mantel Haenszel $\chi^2$ test for trend. A multivariable logistic model was constructed to assess the effect of having a depressive disorder on the odds of receiving each treatment by risk group, adjusting a priori for potential confounders: year of diagnosis, age at prostate cancer diagnosis, Charlson score, race, marital status, SEER region, census measurements of median household income and education, residence in a metropolitan area, grade of tumor, and NCCN risk category. A Cox proportional hazards regression model was used to assess the effects of treatment and having a depressive disorder on survival. However, because the effect of treatment as well as the effect of having a depressive disorder on survival may have depended on risk group, we fit separate (stratified) Cox regression models by the three risk groups. All tests were considered statistically significant at $\alpha = .05$. Statistical analyses were performed with SAS version 9.1.3 (SAS Institute, Cary, NC).

## RESULTS

Between 2004 and 2007, 41,275 men received a new diagnosis of prostate cancer, and 1,894 (4.6%) also had a claim-associated diagnosis of depressive disorder by a physician in the 2 years before prostate cancer diagnosis (Table 1). Of the men categorized with a diagnosis of depressive disorder, 67% were diagnosed by mental health providers, and the remainder were diagnosed primarily by internal medicine and family practice providers. Men with diagnoses of depressive disorder were, on average, older, more likely to be non-Hispanic white and less likely to be black or Asian, less likely to be married, more likely to have lower median household income, more likely to have more comorbid illnesses, and more likely to reside in nonmetropolitan areas ($P < .05$ for all).

No statistically significant differences were noted in pretreatment disease characteristics between men with and without a diagnosis of depressive disorder (Table 2), except that men with a depressive disorder were more likely to have a poorly differentiated tumor ($P = .03$). Overall, men with a diagnosis of depression were more likely to have high-risk disease compared with men without a depression diagnosis ($P < .01$). Men with a diagnosis of depressive disorder, on average, saw a physician 43 times in the 2 years before prostate cancer diagnosis compared with men without these diagnoses who saw a physician 27 times during the same period ($P < .001$). There was no statistically significant difference between the median time from diagnosis of prostate cancer to treatment by status of diagnosis of depressive disorder (84 days for nondepressed men *v* 82 days for depressed men; $P = 1.0$).

### Multivariable Analysis

In adjusted analysis, depressive disorder was associated with 23% greater odds of undergoing ADT alone (odds ratio [OR] 1.23; 95% CI, 1.08 to 1.40; $P = .002$) and 29% greater odds of undergoing EM (OR, 1.29; 95% CI, 1.19 to 1.47; $P < .001$; Appendix Table A1, online only). Depressed versus nondepressed men were more likely to pursue EM in low-risk (OR, 1.15; 95% CI, 1.10 to 1.64; $P = .005$) and intermediate-risk (OR, 1.46; 95% CI, 1.17 to 1.81; $P < .001$) groups, and ADT alone was more likely to be chosen by depressed men with intermediate-risk (OR, 1.24; 95% CI, 1.01 to 1.52; $P = .04$) disease (Table 3). RT was less likely to be selected by depressed (*v* nondepressed) men with low-risk (OR, 0.76; 95% CI, 0.63 to 0.92; $P = .005$) and high-risk (OR, 0.82; 95% CI, 0.68 to 0.98; $P = .03$) disease, whereas surgery was less likely to be chosen by depressed men with intermediate-risk prostate cancer (OR, 0.72; 95% CI, 0.58 to 0.91; $P = .006$). Definitive therapy was less likely to be selected by depressed men in all risk groups (low: OR, 0.71; 95% CI, 0.59 to 0.86; $P < .001$; intermediate: OR, 0.68; 95% CI, 0.57 to 0.80; $P < .001$; high: OR, 0.77; 95% CI, 0.63 to 0.93; $P = .006$).

When stratified by risk group, younger age, fewer comorbidities, married status, and use of RP or RT (compared with EM) was associated with better overall survival in all three risk groups (Table 4). In adjusted analyses, overall survival was shorter for men with depressive disorders and all-risk (Fig 1A; $P < .001$), low-risk (Fig 1B; $P < .001$), intermediate-risk (Fig 1C; $P = .003$), and high-risk (Fig 1D; $P = .09$) prostate cancer.

  

**Table 1.** Demographic Characteristics of Study Population Stratified by Previous Diagnosis of Depressive Disorder

| Characteristic | Men Without Depressive Disorder (n = 39,381) No. | % | Men With Depressive Disorder (n = 1,894) No. | % | P |
|---|---|---|---|---|---|
| Year of diagnosis | | | | | .92 |
| 2004 | 10,334 | 26.2 | 492 | 26.0 | |
| 2005 | 9,925 | 25.2 | 482 | 25.5 | |
| 2006 | 9,829 | 25.0 | 463 | 24.5 | |
| 2007 | 9,293 | 23.6 | 457 | 24.1 | |
| Age at diagnosis, years | | | | | < .01 |
| 67-69 | 8,788 | 22.3 | 394 | 20.8 | |
| 70-74 | 13,407 | 34.0 | 593 | 31.3 | |
| ≥ 75 | 17,186 | 43.6 | 907 | 47.9 | |
| Charlson score | | | | | < .001 |
| 0 | 26,351 | 66.9 | 931 | 49.2 | |
| 1 | 8,462 | 21.5 | 503 | 26.6 | |
| ≥ 2 | 4,568 | 11.6 | 460 | 24.3 | |
| Race/ethnicity | | | | | < .001 |
| Non-Hispanic white | 31,467 | 79.9 | 1,588 | 83.8 | |
| Black | 3,863 | 9.8 | 144 | 7.6 | |
| Hispanic | 2,345 | 6.0 | 122 | 6.4 | |
| Asian | 1,706 | 4.3 | 40 | 2.1 | |
| Marital status | | | | | < .001 |
| Not married | 8,848 | 22.5 | 627 | 33.1 | |
| Married | 30,533 | 77.5 | 1,267 | 66.9 | |
| Percentage with high school education | | | | | .13 |
| < 75 | 8,691 | 22.1 | 420 | 22.2 | |
| 75-84.99 | 8,609 | 21.9 | 455 | 24.0 | |
| 85-89.99 | 7,509 | 19.1 | 351 | 18.5 | |
| ≥ 90 | 14,572 | 37.0 | 668 | 35.3 | |
| Median household income, $ | | | | | < .001 |
| < 35,000 | 14,715 | 37.4 | 835 | 44.1 | |
| 35,000-44,999 | 9,060 | 23.0 | 423 | 22.3 | |
| 45,000-59,999 | 8,352 | 21.2 | 364 | 19.2 | |
| ≥ 60,000 | 7,254 | 18.4 | 272 | 14.4 | |
| SEER registry site | | | | | < .001 |
| San Francisco | 1,634 | 4.2 | 72 | 3.8 | |
| Connecticut | 2,627 | 6.7 | 131 | 6.9 | |
| Detroit | 2,647 | 6.7 | 123 | 6.5 | |
| Hawaii | 593 | 1.5 | 15 | 0.8 | |
| Iowa | 2,476 | 6.3 | 167 | 8.8 | |
| New Mexico | 759 | 1.9 | 41 | 2.2 | |
| Seattle | 2,498 | 6.3 | 123 | 6.5 | |
| Utah | 1,396 | 3.5 | 101 | 5.3 | |
| Atlanta/rural Georgia | 1,286 | 3.3 | 53 | 2.8 | |
| San Jose | 1,080 | 2.7 | 43 | 2.3 | |
| Los Angeles | 2,785 | 7.1 | 121 | 6.4 | |
| Greater California | 7,604 | 19.3 | 358 | 18.9 | |
| Kentucky | 2,719 | 6.9 | 155 | 8.2 | |
| Louisiana | 3,240 | 8.2 | 167 | 8.8 | |
| New Jersey | 6,037 | 15.3 | 224 | 11.8 | |
| Population density | | | | | < .01 |
| Metropolitan | 35,561 | 90.3 | 1,672 | 88.3 | |
| Nonmetropolitan | 3,820 | 9.7 | 222 | 11.7 | |

**Table 2.** Tumor Characteristics Stratified by Previous Diagnosis of Depressive Disorder

| Characteristic | Men Without Depressive Disorder (n = 39,381) No. | % | Men With Depressive Disorder (n = 1,894) No. | % | P |
|---|---|---|---|---|---|
| Grade | | | | | .03 |
| Well/moderately | 16,277 | 41.3 | 736 | 38.9 | |
| Poorly/undifferentiated | 23,104 | 58.7 | 1,158 | 61.1 | |
| Clinical stage | | | | | .42 |
| T1 | 20,836 | 52.9 | 1,021 | 53.9 | |
| T2 | 16,414 | 41.7 | 770 | 40.7 | |
| T3 to T4 | 1,602 | 4.1 | 71 | 3.8 | |
| Gleason score | | | | | .42 |
| ≤ 6 | 15,403 | 39.1 | 691 | 36.5 | |
| 7 | 15,547 | 39.5 | 755 | 39.9 | |
| 8-10 | 8,248 | 20.9 | 438 | 23.1 | |
| Initial treatment by NCCN risk category | | | | | |
| Low risk | | | | | < .001 |
| All treatments | 10,860 | 27.6 | 487 | 25.7 | |
| ADT | 827 | 7.6 | 47 | 9.7 | |
| RT | 5,737 | 52.8 | 219 | 45.0 | |
| Cryotherapy | 203 | 1.9 | 13 | 2.7 | |
| RP | 1,458 | 13.4 | 54 | 11.1 | |
| EM | 2,635 | 24.3 | 154 | 31.6 | |
| Intermediate risk | | | | | < .001 |
| All treatments | 17,105 | 43.4 | 789 | 41.7 | |
| ADT | 2,338 | 13.7 | 152 | 19.3 | |
| RT | 8,033 | 47.0 | 330 | 41.8 | |
| Cryotherapy | 436 | 2.6 | 24 | 3.0 | |
| RP | 3,760 | 22.0 | 134 | 17.0 | |
| EM | 2,538 | 14.8 | 149 | 18.9 | |
| High risk | | | | | < .001 |
| All treatments | 11,416 | 29.0 | 618 | 32.6 | |
| ADT | 3,769 | 33.0 | 236 | 38.2 | |
| RT | 4,682 | 41.0 | 207 | 33.5 | |
| Cryotherapy | 178 | 1.6 | 10 | 1.6 | |
| RP | 1,355 | 11.9 | 54 | 8.7 | |
| EM | 1,432 | 12.5 | 111 | 18.0 | |
| PSA, ng/dL | | | | | |
| Mean | 11.4 | | 12.2 | | .47 |
| Median | 7.1 | | 7.1 | | 1.0 |
| Days from diagnosis to treatment | | | | | |
| Mean | 131 | | 134 | | .40 |
| Median | 84 | | 82 | | 1.0 |
| No. of physician visits in 2 years before diagnosis | | | | | < .001 |
| Mean | 26.8 | | 42.7 | | |
| Median | 22 | | 36 | | |

Abbreviations: ADT, androgen deprivation therapy; EM, expectant management; NCCN, National Comprehensive Cancer Network; PSA, prostate-specific antigen; RP, radical prostatectomy; RT, radiation therapy.

## DISCUSSION

The Institute of Medicine defines health care disparities as "differences in the quality of healthcare that are not due to access-related factors or clinical needs, preferences, and appropriateness of intervention."[18] A

**Table 3.** Multivariable Analysis of Treatment Choice of Depressed Versus Nondepressed Men Stratified by Risk Group

| Variable | Low Risk | | | Intermediate Risk | | | High Risk | | |
|---|---|---|---|---|---|---|---|---|---|
| | OR | 95% CI | *P* | OR | 95% CI | *P* | OR | 95% CI | *P* |
| ADT | 1.15 | 0.84 to 1.59 | .39 | 1.46 | 1.17 to 1.81 | < .001 | 1.14 | 0.94 to 1.39 | .18 |
| EM | 1.34 | 1.10 to 1.64 | .005 | 1.24 | 1.01 to 1.52 | .04 | 1.27 | 1.00 to 1.63 | .05 |
| RT | 0.76 | 0.63 to 0.92 | .005 | 0.86 | 0.74 to 1.01 | .06 | 0.82 | 0.68 to 0.98 | .03 |
| RP | 0.91 | 0.67 to 1.23 | .53 | 0.72 | 0.58 to 0.91 | .006 | 0.86 | 0.62 to 1.20 | .38 |
| Definitive therapy (RT or RP) | 0.71 | 0.59 to 0.86 | < .001 | 0.68 | 0.57 to 0.80 | < .001 | 0.77 | 0.63 to 0.93 | .006 |

Abbreviations: ADT, androgen deprivation therapy; EM, expectant management; OR, odds ratio; RP, radical prostatectomy; RT, radiation therapy.

pre-existing diagnosis of a mental health disorder such as depression may lead to health care disparities because of biases, prejudices, or stereotypes held by providers that influence the recommended clinical care.[19] However, it may also be possible that depressed patients receive better primary care and more appropriate therapy. The contribution of health service providers to disparities (eg, race/ethnicity) in medical care has been investigated,[20,21] but little is known about the relationship between pre-existing mental health disorders and the primary treatment of prostate cancer. Given the various treatment options suggested by NCCN guidelines for low-risk (EM, RP, and RT), intermediate-risk (EM, RP, and RT ± ADT), and high-risk (RP and RT ± ADT) prostate cancer,[17] discerning appropriate treatment choices by risk strata is essential to understanding the impact of depression on prostate cancer management and outcomes.

Our study has several important and novel findings. To the best of our knowledge, this study is the first to demonstrate that a pre-existing diagnosis of depressive disorder is independently associated with treatment choice and outcomes of localized prostate cancer. Men with prostate cancer and a recent diagnosis of depression were less likely to undergo definitive treatment and experienced worse overall survival compared with men without a depressive disorder diagnosis. In contrast to NCCN guidelines for high-risk prostate cancer, our findings show that depressed men with intermediate- and high-risk prostate cancer were less likely to choose definitive therapy (RP or RT). Interestingly, depressed versus nondepressed men with low-risk disease were more likely to choose EM. The difference in overall survival between men with and without a depression diagnosis was independent of prostate cancer treatment type.

Although depression and prostate cancer treatment were independently associated with overall survival in our study, there are multiple factors that may contribute to a relationship between depressive disorder and prostate cancer treatment and outcome. For example, decreased use of RP and RT may be secondary to provider biases about appropriate therapy for depressed men or patient treatment preference. Indeed, depressed patients often display loss of interest and lack of motivation, which together may influence decision-making about more intensive treatments. Decreased overall survival in these men may reflect diminished capacity for appropriate self-care or presence and/or exacerbation of other comorbid illnesses, although this remains controversial.[22,23] Additional pathways such as smaller social networks and reduced social support in patients with depression may also influence overall survival.[24] Given that depression appears to be an independent risk factor for decreased survival following other medical conditions, including breast cancer,[16] hepatobiliary carcinoma,[12] hip fracture,[25] heart failure,[26] stroke,[27] and myocardial infarction,[28] this interaction merits additional investigation in light of additional evidence that depression is associated with change in other behavioral factors such as physical inactivity[29] and sleep,[30] which have been implicated in mortality outcomes. Finally, depression is associated with altered endocrine regulation,[31] heart rate variability,[32] inflammatory markers,[33] and mortality end points,[34] which together might represent a common mechanism of disease between depression and cancer.[35]

Men with a diagnosis of depressive disorder were more likely to receive ADT alone as treatment for their localized prostate cancer independent of age and clinical characteristics. ADT increases psychological distress and worsens quality of life in men with prostate cancer,[36] but its use does not appear to worsen depressive symptoms in men with prostate cancer and depression.[37] We also found that these men were more likely to receive EM compared with nondepressed men. Although the emotional consequences of a new prostate cancer diagnosis and the anxiety and distress of living with untreated cancer may exacerbate mental disorders, men on protocol-based surveillance actually report small and similar changes in depressive symptoms compared with men treated with RP or RT.[38,39] Although patient selection for ADT or EM should be optimized to patient preference, life expectancy, and disease characteristics, the use of these modalities appears to be appropriate in men with depressive disorders with appropriate screening and counseling.[40]

Men with prostate cancer and a depressive disorder were older, less likely to be married, had lower income, had more comorbidities, and were more likely to be white or Hispanic compared with men without such mental health disorders. In addition, we identified that race/ethnicity and depression were independently associated with overall survival following prostate cancer diagnosis. Age, marital status, income, and comorbidities have all been associated with worse outcomes following prostate cancer treatment,[41] and the correlation with these factors and depression only adds to the potential for diminished outcomes for depressed men with prostate cancer. Although the association between race/ethnicity and depression is inversely associated with poor prostate cancer outcomes, it is important to note that depression in black men, who experience worse outcomes in prostate cancer management, is more likely to be untreated, disabling, and chronic than in whites in the United States.[42] Mental health status disparities are closely related to racial and socioeconomic differences but have been found to display a different pattern than other known health care disparities associated with variation in prostate cancer treatment and outcomes (eg, African American race).[1,2] Whites have higher rates of mental disorders compared with Hispanics,[43] Asians,[43,44] and blacks[45] (although this finding may be related to

  

**Table 4.** Cox Proportional Hazards Model of Overall Mortality by NCCN Risk Group

| Variable | Low Risk | | | Intermediate Risk | | | High Risk | | |
|---|---|---|---|---|---|---|---|---|---|
| | HR | 95% CI | *P* | HR | 95% CI | *P* | HR | 95% CI | *P* |
| Year of diagnosis (referent: 2004) | | | | | | | | | |
| 2005 | 0.92 | 0.78 to 1.08 | .31 | 0.87 | 0.78 to 0.96 | .01 | 1.03 | 0.95 to 1.12 | .49 |
| 2006 | 0.86 | 0.71 to 1.03 | .10 | 0.82 | 0.73 to 0.93 | .001 | 0.95 | 0.86 to 1.04 | .27 |
| 2007 | 0.74 | 0.59 to 0.93 | .01 | 0.75 | 0.65 to 0.87 | < .001 | 0.84 | 0.76 to 0.94 | .002 |
| Age at diagnosis, years (referent: ≥ 67-69) | | | | | | | | | |
| 70-74 | 1.24 | 1.02 to 1.51 | .03 | 1.33 | 1.14 to 1.54 | < .001 | 1.12 | 0.98 to 1.28 | .09 |
| ≥ 75 | 2.11 | 1.74 to 2.55 | < .001 | 1.96 | 1.69 to 2.27 | < .001 | 1.65 | 1.47 to 1.86 | < .001 |
| Charlson score (referent: 0) | | | | | | | | | |
| 1 | 1.46 | 1.25 to 1.71 | < .001 | 1.77 | 1.60 to 1.96 | < .001 | 1.30 | 1.20 to 1.41 | < .001 |
| ≥ 2 | 3.32 | 2.83 to 3.89 | < .001 | 2.76 | 2.48 to 3.07 | < .001 | 2.00 | 1.84 to 2.17 | < .001 |
| Race/ethnicity (referent: Asian) | | | | | | | | | |
| Non-Hispanic white | 1.28 | 0.82 to 2.02 | .28 | 1.20 | 0.92 to 1.57 | .18 | 1.53 | 1.24 to 1.89 | < .001 |
| Black | 1.86 | 1.15 to 3.03 | .01 | 1.23 | 0.91 to 1.65 | .17 | 1.67 | 1.32 to 2.11 | < .001 |
| Hispanic | 1.19 | 0.71 to 1.99 | .51 | 0.88 | 0.63 to 1.21 | .42 | 1.18 | 0.92 to 1.52 | .19 |
| Marital status (referent: married) | | | | | | | | | |
| Not married | 1.26 | 1.09 to 1.46 | .001 | 1.32 | 1.20 to 1.45 | < .001 | 1.29 | 1.20 to 1.39 | < .001 |
| Percentage with high school education (referent: ≥ 90) | | | | | | | | | |
| < 75 | 1.19 | 0.92 to 1.55 | .18 | 1.03 | 0.87 to 1.22 | .73 | 1.16 | 1.02 to 1.33 | .02 |
| 75-84.99 | 1.09 | 0.87 to 1.36 | .44 | 1.00 | 0.86 to 1.15 | .95 | 1.04 | 0.93 to 1.17 | .46 |
| 85-89.99 | 0.99 | 0.80 to 1.22 | .89 | 1.04 | 0.91 to 1.20 | .54 | 1.04 | 0.93 to 1.16 | .48 |
| Median household income, $ (referent: ≥ 60,000) | | | | | | | | | |
| < 35,000 | 1.13 | 0.84 to 1.50 | .43 | 1.52 | 1.25 to 1.85 | < .001 | 1.11 | 0.95 to 1.30 | .18 |
| 35,000-44,999 | 1.16 | 0.90 to 1.50 | .26 | 1.39 | 1.17 to 1.66 | < .001 | 1.21 | 1.06 to 1.39 | .006 |
| 45,000-59,999 | 1.13 | 0.90 to 1.44 | .30 | 1.17 | 0.99 to 1.39 | .07 | 1.14 | 1.00 to 1.30 | .05 |
| SEER registry site (referent: Atlanta) | | | | | | | | | |
| San Francisco | 0.38 | 0.21 to 0.69 | .002 | 0.54 | 0.37 to 0.77 | .001 | 1.00 | 0.78 to 1.29 | 1.00 |
| Connecticut | 0.84 | 0.55 to 1.29 | .42 | 0.66 | 0.49 to 0.89 | .007 | 0.86 | 0.69 to 1.09 | .22 |
| Michigan | 1.01 | 0.67 to 1.51 | .98 | 0.91 | 0.70 to 1.20 | .52 | 0.93 | 0.74 to 1.17 | .52 |
| Hawaii | 1.15 | 0.54 to 2.44 | .72 | 1.02 | 0.66 to 1.58 | .93 | 1.08 | 0.75 to 1.55 | .67 |
| Iowa | 0.93 | 0.60 to 1.47 | .77 | 0.76 | 0.56 to 1.03 | .08 | 1.06 | 0.84 to 1.35 | .63 |
| New Mexico | 0.77 | 0.42 to 1.41 | .39 | 0.82 | 0.57 to 1.18 | .28 | 1.05 | 0.76 to 1.44 | .77 |
| Seattle | 0.65 | 0.41 to 1.03 | .06 | 0.73 | 0.54 to 0.98 | .04 | 0.88 | 0.69 to 1.12 | .30 |
| Utah | 0.77 | 0.46 to 1.30 | .33 | 0.91 | 0.66 to 1.26 | .56 | 1.15 | 0.86 to 1.53 | .36 |
| San Jose | 0.98 | 0.60 to 1.60 | .93 | 0.70 | 0.48 to 1.01 | .06 | 0.88 | 0.67 to 1.17 | .39 |
| Los Angeles | 0.73 | 0.48 to 1.13 | .16 | 0.79 | 0.59 to 1.06 | .12 | 1.00 | 0.79 to 1.26 | .97 |
| Greater California | 0.72 | 0.49 to 1.05 | .09 | 0.65 | 0.50 to 0.85 | .001 | 0.90 | 0.73 to 1.12 | .34 |
| Kentucky | 0.96 | 0.62 to 1.46 | .84 | 0.69 | 0.51 to 0.93 | .02 | 1.11 | 0.87 to 1.41 | .39 |
| Louisiana | 0.87 | 0.58 to 1.29 | .48 | 0.82 | 0.62 to 1.08 | .16 | 0.89 | 0.71 to 1.11 | .30 |
| New Jersey | 0.73 | 0.50 to 1.06 | .10 | 0.79 | 0.61 to 1.03 | .09 | 0.89 | 0.71 to 1.10 | .27 |
| Population density (referent: metropolitan) | | | | | | | | | |
| Nonmetropolitan | 0.98 | 0.76 to 1.25 | .85 | 1.09 | 0.93 to 1.28 | .26 | 0.91 | 0.80 to 1.03 | .13 |
| Grade (referent: poorly/undifferentiated) | | | | | | | | | |
| Well/moderately | 0.80 | 0.52 to 1.23 | .31 | 0.87 | 0.79 to 0.96 | .006 | 0.59 | 0.53 to 0.67 | < .001 |
| Previous depressive disorder diagnosis (referent: no) | | | | | | | | | |
| Yes | 1.86 | 1.48 to 2.33 | < .001 | 1.25 | 1.06 to 1.49 | .01 | 1.16 | 1.03 to 1.32 | .02 |
| Treatment (referent: EM) | | | | | | | | | |
| RP | 0.49 | 0.36 to 0.66 | < .001 | 0.30 | 0.25 to 0.36 | < .001 | 0.23 | 0.19 to 0.28 | < .001 |
| RT | 0.67 | 0.58 to 0.78 | < .001 | 0.52 | 0.47 to 0.58 | < .001 | 0.41 | 0.37 to 0.46 | < .001 |
| ADT | 1.01 | 0.82 to 1.25 | .91 | 1.07 | 0.95 to 1.20 | .27 | 1.05 | 0.96 to 1.15 | .25 |

Abbreviations: ADT, androgen deprivation therapy; EM, expectant management; HR, hazard ratio: NCCN, National Comprehensive Cancer Network; RP, radical prostatectomy; RT, radiation therapy.

access and stigma regarding mental health disorder diagnosis in minority groups).[46,47] Therefore, bias resulting from mental health may more commonly apply to racial groups traditionally less affected by health care disparities.

In addition, we found that men with a diagnosis of a depressive disorder had a significantly higher number of doctor visits in the 2 years before diagnosis of prostate cancer. Although depressed men were more likely to have T1 prostate cancers, they were also more likely to be diagnosed with high-risk disease. This finding—that depressed men were more likely to present with aggressive disease despite an increased number of physician visits—may potentially be rooted in provider (decreased focus on preventative screening during

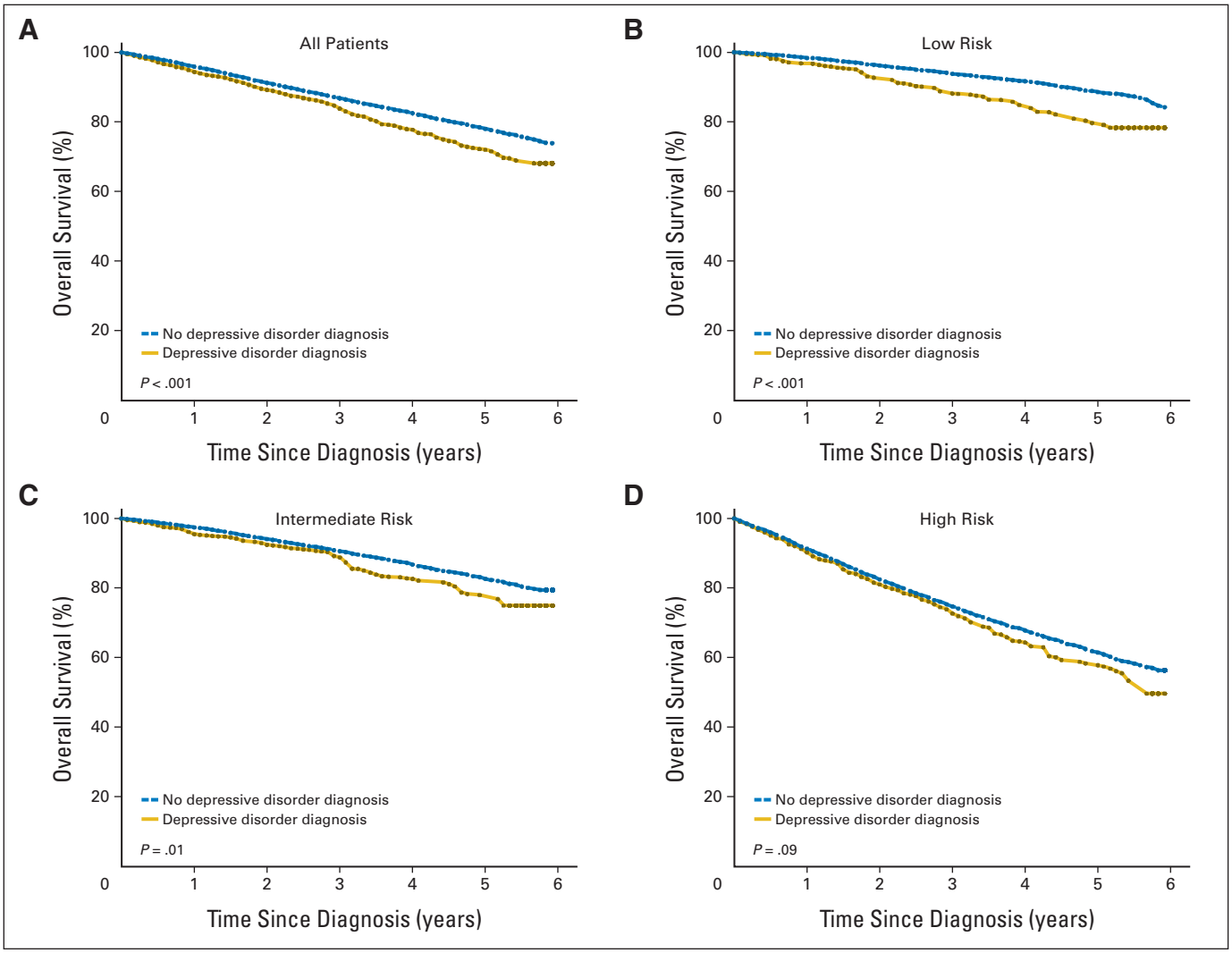


**Fig 1.** Cox proportional hazard model for overall survival by depressive disorder status in (A) all, (B) low-risk, (C) intermediate-risk, and (D) high-risk men.

mental health visits) or patient (disinterest in prostate cancer screening) behavior. In addition, individuals diagnosed with more aggressive disease are at increased risk of psychological deterioration, because men with advanced prostate cancer demonstrate a decline in vitality, social functioning, and mental health following diagnosis.[48] It is critically important that, in addition to their oncologic management, these men be monitored for progression of their mental health symptoms during treatment because intervention and improvement of symptoms is associated with improved survival in patients with metastatic cancer.[10,49] Urologists counseling men with newly diagnosed prostate cancer should be aware that the diagnosis is associated with greater psychological distress and a 2.5-fold increased risk of suicide within 1 year of diagnosis compared with men in the general population and persistently increased risks after that period.[8] The risk of suicide in men with prostate cancer was higher in those with locally advanced disease, metastatic disease, and Gleason score 8 to 10 disease.[7]

Our study must be interpreted in the context of the study design because the associations from this cross-sectional study are observations and do not confirm causation. First, analyses were restricted to Medicare beneficiaries older than age 67 years who resided in SEER regions. Therefore, our findings may not be generalizable to younger men or to those with other cancers; however, depression symptoms are more common in aging patients with prostate cancer, although younger patients with cancer are more likely to report increased levels of psychological distress that may affect subsequent treatment decisions.[50] Second, the effect of anxiety or other mental health disorders such as post-traumatic stress disorder on prostate cancer treatment and outcomes may differ from these findings associated with depression alone. We included anxiety disorders in a prior analysis and found that inclusion of these mental health disorders did not significantly affect the findings in this study. Third, a diagnosis of depression was based on diagnosis codes and is reliant on physicians screening for and accurately coding for the disease. Although there may be underreporting of these conditions, the 5% prevalence rate seen in this study is similar to rates reported in population-based reports for men and the elderly.[51] However, our use of diagnosis codes likely does not fully capture the true incidence of depressive disorders, and this likely leads to underestimation of the magnitude of our findings. In addition, our methodology does not enable us to explore the effects of depression

  

diagnosed before our 24-month window before prostate cancer diagnosis. However, given that the majority of men had more than 25 physician visits during this period, we believe that a diagnosis of depression would be documented, even if diagnosed earlier for the purposes of medication refill or treatment assessment. Fourth, although men with incomplete clinical and demographic information were excluded from analysis (which may be a potential source of bias), the stage and grade of this excluded population did not significantly differ from that of the study cohort. Fifth, we did not control for some known confounding factors that may have been diagnosed and treated before enrollment in Medicare such as cardiovascular disease, which has been shown to interact with depression and survival.[52] Similarly, we were unable to examine rates of PSA screening before Medicare enrollment. Finally, there may be other unexplained social[34] or genetic[53] pathways that may directly influence processes that affect overall survival.

In summary, these results point toward a newly identified disparity in the management of men with incident prostate cancer. Men diagnosed with depression and intermediate- or high-risk prostate cancer are less likely to undergo definitive therapy. Conversely, depressed men were more likely to choose EM for low- and intermediate-risk disease. Although EM may be appropriate for elderly men with low-risk disease, depression may blunt the aggressiveness of treatment for intermediate- and high-risk disease. Considering the marked prevalence of both prostate cancer and depression, additional efforts are needed to better understand and ameliorate the decreased survival following prostate cancer diagnosis in the depressed male patient.

## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

## AUTHOR CONTRIBUTIONS

**Conception and design:** Sandip M. Prasad, Scott E. Eggener, Michael R. Irwin, Jim C. Hu
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## GLOSSARY TERMS

**active surveillance:** an approach to management of suspected or proven malignancy felt to pose a low risk of progression in the short to intermediate term. Tumors are observed closely with blood tests, imaging, and/or serial biopsy, and intervention is undertaken if/when there is evidence of tumor growth or progression.

**Cox proportional hazards regression model:** a statistical model for regression analysis of censored survival data, examining the relationship of censored survival distribution to one or more covariates. This model produces a baseline survival curve, covariate coefficient estimates with their standard errors, risk ratios, 95% CIs, and significance levels.

**prostate-specific antigen (PSA):** a protein produced by cells of the prostate gland. The blood level of prostate-specific antigen (PSA) is used as a tumor marker for men who may be suspected of having prostate cancer. Most physicians consider 0 to 4.0 ng/mL to be the normal range. Levels of 4 to 10 and 10 to 20 ng/mL are considered slightly and moderately elevated, respectively. PSA levels have to be complemented with other tests to make a firm diagnosis of prostate cancer.

**Surveillance, Epidemiology, and End Results (SEER):** a national cancer registry that collects information from all incident malignancies in multiple geographic areas of the United States.

  

## *Appendix*

**Table A1.** Multivariable Analysis of Odds of Receiving ADT or EM

| Variable | ADT | | | EM | | |
|---|---|---|---|---|---|---|
| | OR | 95% CI | *P* | OR | 95% CI | *P* |
| Year of diagnosis (referent: 2004) | | | | | | |
| 2005 | 0.91 | 0.84 to 0.99 | .02 | 1.16 | 1.07 to 1.25 | < .001 |
| 2006 | 0.85 | 0.78 to 0.93 | < .001 | 1.15 | 1.07 to 1.25 | < .001 |
| 2007 | 0.79 | 0.72 to 0.86 | < .001 | 1.08 | 1.00 to 1.17 | .06 |
| Age at diagnosis, years (referent: ≥ 67-69) | | | | | | |
| 70-74 | 1.20 | 1.08 to 1.33 | < .001 | 1.19 | 1.10 to 1.30 | < .001 |
| ≥ 75 | 3.34 | 3.05 to 3.66 | < .001 | 2.09 | 1.94 to 2.26 | < .001 |
| Charlson score (referent: 0) | | | | | | |
| 1 | 1.21 | 1.13 to 1.31 | < .001 | 0.97 | 0.90 to 1.04 | .39 |
| ≥ 2 | 1.56 | 1.44 to 1.70 | < .001 | 1.30 | 1.20 to 1.42 | < .001 |
| Race (referent: Asian) | | | | | | |
| Non-Hispanic white | 1.03 | 0.87 to 1.22 | .74 | 1.16 | 0.99 to 1.37 | .07 |
| Black | 1.17 | 0.96 to 1.42 | .13 | 1.79 | 1.49 to 2.15 | < .001 |
| Hispanic | 1.35 | 1.10 to 1.66 | .004 | 0.99 | 0.81 to 1.20 | .89 |
| Marital status (referent: married) | | | | | | |
| Not married | 1.29 | 1.21 to 1.38 | < .001 | 1.37 | 1.29 to 1.46 | < .001 |
| Percentage of patients with high school education (referent: ≥ 90) | | | | | | |
| < 75 | 1.11 | 0.99 to 1.26 | .08 | 1.05 | 0.93 to 1.17 | .45 |
| 75-84.99 | 1.03 | 0.93 to 1.15 | .53 | 1.04 | 0.94 to 1.14 | .45 |
| 85-89.99 | 1.04 | 0.94 to 1.14 | .48 | 1.07 | 0.98 to 1.17 | .15 |
| Median household income, $ (referent: ≥ 60,000) | | | | | | |
| < 35,000 | 1.41 | 1.23 to 1.61 | < .001 | 1.10 | 0.98 to 1.25 | .11 |
| 35,000-44,999 | 1.31 | 1.16 to 1.48 | < .001 | 1.03 | 0.93 to 1.14 | .60 |
| 45,000-59,999 | 1.16 | 1.04 to 1.30 | .009 | 0.97 | 0.88 to 1.07 | .50 |
| SEER registry site (referent: Atlanta) | | | | | | |
| San Francisco | 0.94 | 0.74 to 1.20 | .63 | 2.09 | 1.69 to 2.58 | < .001 |
| Connecticut | 1.04 | 0.84 to 1.30 | .70 | 1.61 | 1.32 to 1.96 | < .001 |
| Detroit | 1.28 | 1.03 to 1.59 | .02 | 1.57 | 1.29 to 1.92 | < .001 |
| Hawaii | 0.83 | 0.59 to 1.18 | .30 | 1.32 | 0.96 to 1.82 | .09 |
| Iowa | 1.48 | 1.18 to 1.85 | < .001 | 1.17 | 0.94 to 1.46 | .15 |
| New Mexico | 1.17 | 0.88 to 1.56 | .27 | 1.60 | 1.23 to 2.09 | < .001 |
| Seattle | 0.87 | 0.69 to 1.10 | .26 | 1.52 | 1.24 to 1.86 | < .001 |
| Utah | 0.58 | 0.44 to 0.77 | < .001 | 1.67 | 1.33 to 2.08 | < .001 |
| San Jose | 1.96 | 1.53 to 2.50 | < .001 | 1.93 | 1.53 to 2.43 | < .001 |
| Los Angeles | 1.19 | 0.95 to 1.47 | .13 | 1.38 | 1.13 to 1.69 | .002 |
| Greater California | 1.24 | 1.02 to 1.51 | .03 | 1.58 | 1.32 to 1.90 | < .001 |
| Kentucky | 0.99 | 0.79 to 1.24 | .95 | 1.23 | 1.00 to 1.52 | .05 |
| Louisiana | 1.57 | 1.28 to 1.94 | < .001 | 1.19 | 0.98 to 1.45 | .08 |
| New Jersey | 1.33 | 1.09 to 1.63 | .005 | 1.04 | 0.87 to 1.26 | .66 |
| Population density (referent: metropolitan) | | | | | | |
| Nonmetropolitan | 1.31 | 1.17 to 1.46 | < .001 | 0.87 | 0.77 to 0.97 | .01 |
| Grade (referent: poorly/undifferentiated) | | | | | | |
| Well/moderately | 0.87 | 0.80 to 0.95 | .001 | 1.98 | 1.83 to 2.14 | < .001 |
| D'Amico risk category (referent: low) | | | | | | |
| Intermediate | 1.37 | 1.23 to 1.52 | < .001 | 0.72 | 0.66 to 0.78 | < .001 |
| High | 3.73 | 3.34 to 4.17 | < .001 | 0.60 | 0.55 to 0.67 | < .001 |
| Previous depressive disorder diagnosis (referent: no) | | | | | | |
| Yes | 1.23 | 1.08 to 1.40 | .002 | 1.29 | 1.19 to 1.47 | < .001 |

Abbreviations: ADT, androgen deprivation therapy; EM, expectant management; OR, odds ratio.