Antidepressant medication use and prostate cancer recurrence in men with depressive disorders

Reina Haque1,2 · Stephanie Reading1 · Michael R. Irwin3 · Lie Hong Chen1 · Jeff Slezak1

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Abstract

Purpose Whether treating prostate cancer survivors with a depressive disorder with antidepressants can affect their cancer outcomes is unknown. We evaluated the association between antidepressant use and prostate cancer recurrence, in survivors with comorbid depressive disorders.

Methods We conducted a longitudinal cohort study of 10,017 men with prostate cancer (stages I–II) diagnosed who also had a comorbid depressive disorder followed a maximum of 22 years, and examined rates of biochemical recurrence by antidepressant medication use. We conducted multivariable Cox models based on time-dependent antidepressant drug use status, and examined the risk of biochemical recurrence by cumulative duration of antidepressant use.

Results Of these 10,017 survivors, 1842 (18%) experienced biochemical recurrence over 69,500 person-years of follow-up. The prostate cancer biochemical recurrence rate was greater with antidepressant non-use (31.3/1000 person-years) compared to antidepressant use (23.5/1000 person-years). In Cox proportional hazards multivariable adjusted models, non-use of antidepressants was associated with a 34% increased risk of biochemical recurrence compared to antidepressant use (HR = 1.34, 95% CI: 1.24–1.44). Longer use of antidepressants was associated with a lower biochemical recurrence risk (P trend test < 0.001).

Conclusion Untreated depressive disorders in prostate cancer patients may be associated with an increased risk of biochemical recurrence.

Keywords Prostate cancer · Depression · Recurrence · Antidepressants

Introduction

Nearly 200,000 men are diagnosed with prostate cancer annually in the USA, and the population of survivors has surpassed 3 million [1, 2]. In prostate cancer survivors, depression prevalence is about threefold higher as compared to the general community of men [3–5] and depression is thought to contribute to adverse cancer outcomes. Indeed, one study found that depression history predicted increased mortality in prostate cancer survivors regardless of whether the depression diagnosis was made before or after cancer diagnosis and treatment [6]. In addition, in those with other cancers, depression and depressive symptoms are associated with worse outcomes such as higher cancer recurrence rates, more comorbidities, and a higher mortality risk than those without depression [7–9].

Less is known if antidepressant treatment can mitigate these risks. In women with metastatic breast cancer, antidepressant treatment was found to reduce depressive symptom severity over the first year after cancer diagnosis, and improvements in depression were associated with longer survival [9]. In 25 prostate cancer survivors, one small clinical trial found that antidepressant medication treatment with monoamine oxidase inhibitor (MAOI) decreased prostate specific antigen (PSA) levels 12 weeks after therapy; however, that study could not ascertain recurrence risk due to
its short follow-up [10]. In sum, no large population-based studies have specifically evaluated if antidepressant use can reduce biochemical recurrence risk in prostate cancer survivors with comorbid depressive disorders.

As antidepressants remain the cornerstone of depression treatment [11, 12], the objective of this cohort study was to evaluate the association between reported antidepressant medication use and recurrence of prostate cancer as defined by American Urological Association (AUA) guidelines in a sample of 10,017 prostate cancer survivors with a comorbid depressive disorder. In addition, we evaluated if cumulative duration of antidepressant use was associated with a lower risk of recurrence.

Methods

Study design, subjects and setting

Subjects were identified from the Kaiser Permanente Southern California (KPSC) health plan, a not-for-profit integrated healthcare delivery system comprised 15 community hospitals, over 220 medical offices and serving more than 4.7 million members. Patients receive virtually all of their medical care, including pharmacy prescriptions, within this system and medical procedures and diagnoses outside of the system are captured from claims databases. Patients were identified using the health plan’s U.S. National Cancer Institute’s Surveillance Endpoints & End Results (SEER)-affiliated cancer registry.

The inclusion criteria for this longitudinal cohort study included: (1) all adult men (≥ 18 years) newly diagnosed with early stage prostate cancer (American Joint Committee on Cancer [AJCC] TNM stages I-II) from January 1996 to June 2017 (n = 36,335), and (2) those with an documented comorbid depressive disorder in their electronic health records (EHR), inclusive of year prior to their prostate cancer diagnosis through end of follow-up, and (3) at least six months of follow-up post cancer diagnosis. A combination of three data sources were used to identify the earliest documented depressive disorder; and the depression must have appeared in two of the three data sources. If dates of the depressive disorder were different in these data sources, we used the earliest date. The three data sources were: (1) having an inpatient or outpatient diagnostic code for a depressive disorder in the patient’s EHR (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 [13] – ICD-9-CM codes from the inpatient database were prioritized over outpatient database; (2) manual review of the current problem list within the patients’ EHR; and (3) manual review of documentation of a depressive disorder from a natural language-assisted review of clinicians’ notes within the patients’ EHR. We prioritized the information garnered from chart review of clinicians’ notes, then the problem lists. No other exclusions were applied. A total of n = 10,017 men fit the criteria, and we followed them through study’s end, 31 December 2018 (22 years maximum follow-up).

Prostate cancer biochemical recurrence

The main outcome, prostate cancer biochemical recurrence was based on the definitions of the American Urological Association (AUA) and the American Society for Therapeutic Radiology & Oncology (ASTRO) guidelines [14]. Briefly, these specifications define biochemical recurrence as occurring at least six months following the initial early stage prostate cancer diagnosis. This six-month window is based on the standard definitions of biochemical recurrence with prostate-specific antigen (PSA) data, which published reports agree are reliable in detecting early disease recurrence [15, 16]. Using this six-month window, the definition is further divided by type of prostate cancer treatment the patient receives. These treatment-based definitions are as follows [15]. For those who underwent radical prostatectomy, biochemical recurrence was defined as: (1) two consecutive PSA values ≥ 0.2 ng/ml at least six months after initial surgery date, or (2) a second treatment initiated six months or more after initial surgery date. For those who underwent radiation therapy (external beam or brachytherapy), biochemical recurrence was defined as either: (1) a rise in PSA by ≥ 2 ng/ml above the PSA nadir, or (2) a second treatment initiated six months or more after the initial radiation therapy. For those who received hormonal therapy, biochemical recurrence was defined as either: (1) three consecutive rising PSA values after initiation of hormonal therapy, (2) or a second treatment initiated six months or more after the initial hormonal therapy. For those who elected active surveillance or watchful waiting, which we defined as initiating no treatment within one year of the patient’s prostate cancer diagnosis, prostate cancer biochemical recurrence was defined as either: (1) three consecutive rising PSA values starting at least one year after diagnosis, or (2) a single value of at least 2 ng/mL above the PSA level at the time of diagnosis at least one year after diagnosis, or (3) initiation of treatment six months or more after the initial prostate cancer diagnosis. We used the earliest identified outcome as the date of the biochemical recurrence.

Antidepressant use

We examined antidepressant use starting from the drug’s date of initiation post prostate cancer diagnosis until the
earliest of one of the study endpoints (biochemical recurrence; disenrollment from health plan; death; study’s end in December 2018). Antidepressant use was extracted from the health plan’s pharmacy dispensing records; data elements included the drug names, initiation date, and days supplied. The study antidepressants were the following: selective serotonin reuptake inhibitors (SSRIs); serotonin antagonist and reuptake inhibitors (SARIs); serotonin modulator and stimulators (SMS); serotonin modulator and stimulators (SNRI); monoamine oxidase inhibitors (MOAIs); norepinephrine-dopamine reuptake inhibitors (NRI, NDRI); and tricyclic and tetracyclic antidepressants (TCA, TECA). We also searched for psychotherapy CPT-4 codes in the administrative and claims databases (e.g., 90832, 90834, 90837, 90838); however, we found few instances of psychotherapy (talk therapy) in the EHR.

Covariates

We captured the following covariates: age; stage; and year of prostate cancer diagnosis; baseline PSA; Gleason score; race/ethnicity; geocoded median household income (based on 2010 U.S. Census at the block level); body mass index (kg/m²) closest to prostate cancer diagnosis; smoking and alcohol misuse during follow-up (ICD-9-CM codes: 303.90–93 and 305.00–305.03); Charlson Comorbidity Index in the one-year before prostate cancer diagnosis using the Deyo method [16, 17]; anxiety disorder history (ICD-9-CM 293.84, 300.0, 300.01, 300.02, 300.09, 308); anti-anxiety medication use (alprazolam; clordiazepoxide; clonazepam; diazepam; lorazepam); and prostate cancer treatment type [radiotherapy; hormonal (androgen depriviation therapy); watchful waiting/active surveillance; surgery (prostatectomy)]. Statin and metformin use during follow-up were also captured. We also accounted for annualized number of outpatient visits, and prostate cancer diagnosis, hospital, tumor stage, tumor characteristics and with Schoenfeld residuals; no significant violations were found. We conducted stratified models to determine whether the association between antidepressant use and recurrence risk differed by the initial cancer treatment (surgery; hormonal; radiation; watchful waiting/active surveillance). We also conducted additional sensitivity analyses to assess the robustness of the multivariable results of the association between antidepressant use and biochemical recurrence on the subset of men who had grade codes (proxy of Gleason scores), baseline PSA, and statin and metformin use (n = 6,396).

Additionally, we conducted another analysis to examine risk of biochemical recurrence by cumulative duration (total days supplied prior to patients’ earliest study endpoint) in the subset of men who used antidepressants (n = 5,931). P-values for trend were calculated with the Cochran Mantel–Haenszel test. All analyses were performed using SAS 9.4 (SAS Institute Inc).

Results

Demographic and clinical characteristics

In the 10,017 prostate cancer survivors with documented depressive disorders, 5931 (59%) used antidepressants during study follow-up (Table 1). Records of depressive disorder diagnoses were mainly found after prostate cancer diagnosis (96%), and only 4% of the men had depression disorder at baseline (at time of prostate cancer diagnosis and up to one year prior). Among men aged 65–80 years at the time of prostate cancer diagnosis, 62% used antidepressant
medication compared to 55% in those aged 30–64 years \( (P < 0.0001) \). Men of color (i.e., Hispanic men [53%] and African American men [56%]) were less likely to use antidepressant medication compared to non-Hispanic white men (62%) \( (P = 0.0001) \). We found no significant differences in the antidepressant use by geocoded median household income \( (P < 0.09) \), nor by anxiety status, or at the time of prostate cancer diagnosis \( (p = 0.25) \). Men who used antidepressants were more likely to have been diagnosed with stage II disease (60%) compared with stage I disease (54%) and undergo prostatectomy, compared to men who did not use antidepressants, respectively \( (P < 0.05 \) for all variables). Antidepressant medication users were also more likely to be current smokers (66%) compared to non-antidepressant users (34%), as well as report alcohol misuse \( (P < 0.001 \) for both variables). Men who used antidepressants had a higher Charlson Comorbidity Index \( (P = 0.001) \), more likely to have had surgery or radiation \( (P < 0.001) \), and had a higher median annualized numbers of outpatient visits \( (17 \text{ visits, interquartile range [IQR]: 11–25 visits}) \) compared with non-antidepressant users \( (15 \text{ visits, IQR: 10–23 visits}) \) \( (p < 0.001) \).

Table 2 presents the distribution of antidepressant classes by the number of prescriptions and number of men who used antidepressants during study follow-up \( (n = 5931) \). As expected, the most common class was SSRIs \( (46\%) \) followed TCA \( (22\%) \) when examining the distribution by prescription type (left panel), and patients used multiple classes of antidepressants (right panel); thus, the total percent exceed 100% for both units of measurement. Overall, the mean cumulative duration of any antidepressant use was 2.42 years \( (\text{median: 1.32 years; IQR: 200 days–3.3 years}) \).

The cohort was followed a maximum of 22 years \( (\text{median: 6.2 years; IQR: 2.8–10.5 years}) \). Over the 69,500 person-years of follow-up, a total of 1842 men developed biochemical recurrence. The biochemical recurrence rate was higher for antidepressant non-use: 31.3/1000 person-years, compared to antidepressant use: 23.5/1000 person-years of follow-up, a total of 1842 men developed biochemical recurrence \( (\text{median: 6.2 years; IQR: 2.8–10.5 years}) \). Over the 69,500 person-years of follow-up, a total of 1842 men developed biochemical recurrence. The biochemical recurrence rate was higher for antidepressant non-use: 31.3/1000 person-years, compared to antidepressant use: 23.5/1000 person-years of follow-up, a total of 1842 men developed biochemical recurrence \( (\text{median: 6.2 years; IQR: 2.8–10.5 years}) \). Over the 69,500 person-years of follow-up, a total of 1842 men developed biochemical recurrence.

In another analysis, we examined the risk of biochemical recurrence by cumulative duration of antidepressant use in the subset of \( n = 5931 \) men exposed to such medications (Table 5). The risk of biochemical recurrence decreased with longer duration \( (\text{days supplied}) \) of antidepressant use; for example, compared to those who used antidepressants \( \leq 1 \text{ year} \), the risk of biochemical was 67% lower in those who used antidepressants > 3 years \( (\text{adjusted HR} = 0.33 \ [0.27–0.40]) \) even after adjustment for the aforementioned covariates. Moreover, the test for trend by number of years of use was statistically significant, \( P < 0.001 \).

**Discussion**

In the diverse cohort of 10,017 prostate cancer patients cared with documented depressive disorders followed over 20 years, the overall rate of prostate cancer biochemical recurrence was higher for antidepressant non-use \( (31.2/1000 \text{ person-years}) \) compared to antidepressant use \( (23.5/1000 \text{ person-years}) \). This corresponded to a 34% higher biochemical recurrence risk for antidepressant non-use compared to use \( (\text{adjusted HR} = 1.34, 95\% \text{ CI: 1.24–1.44}) \). Further, this increased risk was observed in all prostate cancer primary treatment groups \( (\text{surgery, radiation, hormonal, and watchful waiting/active surveillance}) \) even after accounting for demographics, comorbidity status, tumor characteristics, lifestyle variables, and healthcare utilization. Moreover, the biochemical recurrence risk decreased by longer cumulative duration of antidepressant use in the subset of men exposed to such medications.

These findings have public health implications and demonstrate that prostate cancer survivors should be prioritized for depression screening and treatment of depressive disorders, given that early recognition and treatment
Table 1  Demographics and clinical characteristics of prostate cancer survivors with depressive disorders by antidepressant use (n = 10,017)

|                                | Antidepressants | No Antidepressants | P-value | Total  |
|--------------------------------|-----------------|--------------------|---------|--------|
|                                | n = 5,931       | n = 4,086          |         | n = 10,017 |
| Age at Prostate Cancer Dx (yrs)|                 |                    | <.0001  |        |
| 30–49                          | 199             | 188                | 3.4     | 387    |
| 50–64                          | 2,201           | 1,738              | 37.1    | 3,939  |
| 65–80                          | 3,083           | 1,876              | 52.0    | 4,959  |
| 80+                            | 448             | 284                | 7.6     | 732    |
| Race/Ethnicity                 |                 |                    | <.0001  |        |
| Non-Hispanic White             | 3,885           | 2,435              | 66.6    | 6,320  |
| Hispanic                       | 787             | 682                | 13.5    | 1,469  |
| African American/Black         | 878             | 689                | 15.1    | 1,567  |
| Asian/Pacific Islander         | 280             | 197                | 4.8     | 477    |
| Other/Unknown                  | 101             | 83                 | n/a     | 184    |
| Geocoded Median Household Income|                |                    | 0.09    |        |
| Lower 25%                      | 1,364           | 1,010              | 23.5    | 2,374  |
| >25–50%                        | 1,458           | 961                | 25.1    | 2,419  |
| >50–75%                        | 1,463           | 1,048              | 25.2    | 2,511  |
| Top 25%                        | 1,531           | 985                | 26.3    | 2,516  |
| Unknown/Missing                | 115             | 82                 | n/a     | 197    |
| Anxiety                        |                 |                    | 0.25    |        |
| No                             | 5,206           | 3,555              | 87.8    | 8,761  |
| Yes                            | 725             | 531                | 12.2    | 1,256  |
| Charlson Comorbidity Index     |                 |                    | 0.001   |        |
| 0                              | 3,320           | 2,381              | 56.9    | 5,701  |
| 1 to 2                         | 1,734           | 1,142              | 29.7    | 2,876  |
| 3+                             | 785             | 470                | 13.4    | 1,255  |
| Unknown/Missing                | 92              | 93                 | n/a     | 185    |
| Body mass index (kg/m²)        |                 |                    | 0.0013  |        |
| Underweight (<18.5)            | 22              | 12                 | 0.7     | 34     |
| Healthy (18.5–24.9)            | 650             | 545                | 19.7    | 1,195  |
| Overweight (25.0–29.0)         | 1,490           | 1,052              | 45.2    | 2,542  |
| Obese (≥30.0)                  | 1,136           | 792                | 34.5    | 1,928  |
| Unknown/Missing                | 2,633           | 1,685              | n/a     | 4318   |
| Smoking                        |                 |                    | <.0001  |        |
| Never smoker                   | 2,762           | 1,972              | 50.4    | 4,734  |
| Current smoker                 | 646             | 326                | 11.8    | 972    |
| Former smoker                  | 2,075           | 1,240              | 37.8    | 3,315  |
| Unknown/Missing                | 448             | 548                | n/a     | 996    |
| Alcohol misuse                 |                 |                    | <.0001  |        |
| No                             | 3,033           | 1,903              | 56.4    | 4,936  |
| Yes                            | 2,348           | 1,598              | 43.6    | 3,946  |
| Unknown/Missing                | 550             | 585                | n/a     | 1,135  |
| Stage at PC diagnosis          |                 |                    | 0.0003  |        |
| Stage I                        | 660             | 552                | 11.1    | 1,212  |
| Stage II                       | 5,271           | 3,534              | 88.9    | 8,805  |
| Prostate cancer treatment      |                 |                    | <.0001  |        |
| Surgery (Prostatectomy)        | 2,419           | 1,531              | 40.8    | 3,950  |
| Hormonal Therapy               | 556             | 420                | 9.4     | 976    |
| Radiation                      | 1,207           | 733                | 20.4    | 1,940  |
has the potential to influence prostate cancer recurrence risk. Furthermore, given that adherence to antidepressant medications is frequently poor, further research on whether monitoring adherence can potentially affect prostate cancer recurrence is needed. Dissemination of the favorable influence of antidepressant medications on prostate cancer recurrence, as well as depression outcomes, has the potential to increase clinician and patient awareness and improve adherence to antidepressant medication treatment.

A potential mechanism for our findings is that depression may increase biochemical recurrence risk through behavioral changes. For example, men with depression are at a greater risk of non-adherence to prescribed medications or healthcare provider treatment recommendations, or they may engage in fewer positive health behaviors [18]. Thus, these behavioral changes can lead to significant depression-associated morbidity (e.g., decreased treatment effectiveness, increased number of cancer-related complications, and/or the development of additional comorbidities [19–24] and mortality, which may also accelerate biochemical recurrence. Depression is associated with poor diet and lower physical activity, which are also risk factors for biochemical recurrence [25]. In all, the high depression prevalence among men diagnosed with early stage prostate cancer, and the negative consequent behavioral changes, warrants further examination of depression as a possible modifiable risk factor for altering prostate cancer outcomes.

Additionally, proposed biologic pathways underlying prostate cancer biochemical recurrence are similar to molecular changes associated with depression, and include

### Table 1 (continued)

|                      | Antidepressants | No Antidepressants | P-value | Total |
|----------------------|-----------------|--------------------|---------|-------|
|                      | \( n = 5,931 \) | \( n = 4,086 \)    |         | \( n = 10,017 \) |
| N                    | %               | N                  | %       |       |
| Watchful waiting/active surveillance | 1,749 (29.5) | 1,402 (34.3) | <.0001 | 3,151 (31.5) |
| Year of PCa diagnosis |                 |                    |         |       |
| 1996–1999            | 614 (10.4)     | 513 (12.6)         | 1.127   | 11.3  |
| 2000–2004            | 1,696 (28.6)   | 965 (23.6)         | 2.661   | 26.6  |
| 2005–2009            | 1,929 (32.5)   | 1,260 (30.8)       | 3,189   | 31.8  |
| 2010–2014            | 1,260 (21.2)   | 1,008 (24.7)       | 2,268   | 22.6  |
| 2015–2017            | 432 (7.3)      | 340 (8.3)          | 772     | 7.7   |
| Annualized no. of outpatient visits | 16.9 (11.3–25.4) | 14.9 (9.6–22.8) | <.0001 |       |

**Subset* \( n = 3,764 \)**

|                      | Antidepressants | No Antidepressants | P-value | Total |
|----------------------|-----------------|--------------------|---------|-------|
|                      | \( n = 2,632 \) |                    |         |       |
| N                    | %               | N                  | %       |       |
| PSA baseline (quartiles) |               |                    | <.502   |       |
| Lower 25%            | 981 (26.1)     | 713 (27.1)         | 1.694   | 26.5  |
| > 25–50%            | 965 (25.6)     | 682 (25.9)         | 1.647   | 25.8  |
| > 50–75%            | 915 (24.3)     | 647 (24.6)         | 1.562   | 24.5  |
| Top 25%             | 903 (24.0)     | 590 (22.4)         | 1.493   | 23.4  |
| Grade group*         |                 |                    | 0.29    |       |
| 1                   | 2,062 (54.8)   | 1,455 (55.3)       | 3,517   | 55.0  |
| 2                   | 1,322 (35.1)   | 942 (35.8)         | 2,264   | 35.4  |
| 3                   | 380 (10.1)     | 235 (8.9)          | 615     | 9.6   |
| Metformin            |                 |                    | <.0001  |       |
| Yes                 | 516 (13.7)     | 260 (9.9)          | 776     | 12.1  |
| No                  | 3,248 (86.3)   | 2,372 (90.1)       | 5,620   | 87.9  |
| Statins              |                 |                    | <.0001  |       |
| Yes                 | 2,024 (53.8)   | 1,203 (45.7)       | 3,227   | 50.5  |
| No                  | 1,740 (46.2)   | 1,429 (54.3)       | 3,169   | 49.5  |

*Based on subset of \( n = 6,396 \) subjects with information on these variables: Grade group/Gleason score; PSA at baseline; metformin and statin use

*Grade group maps to Gleason scores: Grade code 1 = Gleason score \( \leq 6 \); Grade code 2 = Gleason score 7; Grade code 3 = Gleason score 8–10
chronic inflammation [24, 26–31]; DNA damage [32–37]; telomere shortening [38–42]; and genomic and epigenetic alterations [43, 44]. Combined, this indirectly suggests that depression treatment with antidepressants (which reduce pro-inflammatory cytokines) may affect cancer recurrence risk and warrants further investigation with clinical data.

Our study has several strengths. The maximum study follow-up was over 20 years, and the cohort was diverse; 35% of the group included African American/Black, Hispanic or Asian/Pacific Islander men similar to California’s

### Table 2 Distribution of psychiatric drugs use in the subset of prostate cancer survivors treated with such medications during follow-up (n = 5931 men)

|                          | N  | %   | N** | %** |
|--------------------------|----|-----|-----|-----|
| **Unit of observation = prescription** |
| Anti-anxiety drugs*      | 5,999 | 6.6 | 1,046 | 17.6 |
| Antidepressants          |     |     |     |     |
| Monoamine oxidase inhibitors | 360  | 0.4 | 32 | 0.5 |
| Norepinephrine dopamine reuptake inhibitor/ Norepinephrine reuptake inhibitor | 8,551 | 9.3 | 962 | 16.2 |
| Serotonin antagonist and reuptake inhibitors | 89  | 0.1 | 14 | 0.2 |
| Serotonin modulator and stimulator | 144 | 0.2 | 8 | 0.1 |
| Serotonin and norepinephrine reuptake inhibitors | 6,704 | 7.3 | 834 | 14.1 |
| Selective serotonin reuptake inhibitors | 41,652 | 45.5 | 3,623 | 61.1 |
| Tricyclic antidepressants | 20,112 | 22.0 | 2,679 | 45.2 |
| Tetracyclic antidepressants | 4,835 | 5.3 | 707 | 11.9 |
| Other                    | 3,113 | 3.4 | 406 | 6.9 |
| **TOTAL**                | 91,559 | 100.0 | 10,311 | 173.9 |

*Alprazolam; chlordiazepoxide; clonazepam; diazepam; lorazepam

**Not mutually exclusive; exceeds 100%

### Table 3 Biochemical recurrence in 10,017 prostate cancer survivors by antidepressant use

|                          | Person-years | Rate per 1,000 PYs |
|--------------------------|--------------|-------------------|
| **Biochemical recurrence (N)** | 42,311     | 23.45             |
| All men (n = 10,017)      | 992          | 23.45             |
| Antidepressant use        | 992          | 23.45             |
| Antidepressant non-use    | 850          | 31.26             |

### Table 4 Overall and adjusted risk of prostate cancer progression by prostate cancer treatment and antidepressant use

|                          | Overall HR | Adjusted HR |
|--------------------------|------------|-------------|
| **HR**                   | 95% CI     | HR*         | 95% CI   |
| All men (n = 10,017)     |            |             |
| Antidepressant use       | 1.00 (ref) | 1.00 (ref)  |
| Antidepressant non-use   | 1.14 1.06 1.22 | 1.34 1.24 1.44 |
| Surgery (n = 3950)       |            |             |
| Antidepressant use       | 1.00 (ref) | 1.00 (ref)  |
| Antidepressant non-use   | 1.27 1.10 1.46 | 1.56 1.34 1.81 |
| Hormonal (n = 976)       |            |             |
| Antidepressant use       | 1.00 (ref) | 1.00 (ref)  |
| Antidepressant non-use   | 1.14 1.00 1.31 | 1.38 1.19 1.60 |
| Radiation (n = 1940)     |            |             |
| Antidepressant use       | 1.00 (ref) | 1.00 (ref)  |
| Antidepressant non-use   | 1.17 1.01 1.36 | 1.26 1.07 1.47 |
| Watchful waiting/Active surveillance (n = 3151) | | |
| Antidepressant use       | 1.00 (ref) | 1.00 (ref)  |
| Antidepressant non-use   | 1.07 0.95 1.20 | 1.23 1.08 1.39 |

*Adjusted for all variables in Table 1 including medical center

chronic inflammation [24, 26–31]; DNA damage [32–37];
distribution. This enhances the study’s generalizability. Importantly, we conducted additional analyses based on initial prostate cancer treatment groups to address the fact that antidepressant use could make more of a difference for patients on active surveillance/watchful waiting where depression might affect their compliance with cancer surveillance more so than for patients who underwent surgery. Further, the analysis based on the subset of \( n = 5931 \) men who used antidepressants demonstrated that longer cumulative duration of antidepressant use was associated with lower risk of biochemical recurrence; this enhances the biologic plausibility of the association. Study medication use was extracted from pharmacy dispensing records mitigating recall bias. Further, patients had similar healthcare access in this managed care organization, and therefore, bias resulting from variable medical coverage was reduced. We were able to account for multiple covariates rarely accounted for in prior studies, such as cancer treatments, tumor characteristics, comorbidity, and sociodemographics, which were captured from electronic health records. We also adjusted for annualized outpatient office visits because men with more clinic visits might have had a greater likelihood of being diagnosed with biochemical recurrence or depressive disorders. Also, we handled pharmacy data as time-dependent variables in the main multivariable model to address immortal time bias. All these features enhanced our study design.

Certain limitations also need consideration. Although this was an observational study, the cohort was longitudinally followed a maximum of 22 years, and we considered a comprehensive set of covariates. Thus, unlike randomized clinical trials that are susceptible to disenrollment, we were able to track patients for a long period. While other classifications for prostate cancer recurrence exist, we selected definitions based on the AUA and ASTRO which were employed in other major urologic studies [14, 15]. Further, although we used the AUA’s definition of biochemical recurrence that did not distinguish between rising PSA or additional treatment, we cannot fully hypothesize on the mechanisms how antidepressant use and depression influence prostate cancer outcomes; however, our application of this definition of biochemical recurrence has been applied in several publications [45–52]. Additionally, because we did not find records on depression severity nor on psychotherapy (“talk therapy”) utilization in this health plan, we cannot address if or behavioral health interventions may also reduce the possible depression-induced risk of biochemical recurrence. Another limitation is that we could not examine the biochemical risk by individual antidepressant drug classes due to the potential low numbers of recurrences for some of these classes. Even larger cohorts are needed to confirm the individual effects of the antidepressants, and if the association between non-use of antidepressants and biochemical recurrence risk is stronger in men with more severe depressive disorders. Residual confounding from physical activity is possible; however, we controlled for body mass index, which may be a proxy. Further, studying effect of various combinations of the nine types of antidepressants, their heterogeneous biologic mechanisms, and mechanisms following drug switching was beyond the scope of this study.

In summary, only 60% of prostate cancer survivors with documented depressive symptoms received antidepressant therapy in this managed care system; this is consistent with a recent meta-analysis that determined half of cancer patients who screen positive for depressive symptoms undergo pharmacologic treatment [53]. Further, this is the first large population-based observational study to suggest that untreated depressive disorders in prostate cancer survivors is associated with an increased risk of biochemical recurrence. Antidepressant medications are not appropriate for all patients. Even though both pharmaceutical and non-pharmacological treatments are available, antidepressants are used more frequently than psychological interventions given inadequate resources in managed care organizations. Notwithstanding the study’s limitations, our findings highlight that depression screening is needed as a part of cancer survivorship care plans given that early identification of depression and its treatment (via medications, psychotherapy, or other

### Table 5: Risk of biochemical recurrence by cumulative duration of antidepressant use in men treated with antidepressants (\( n = 5931 \) subset)

| Cumulative duration of antidepressant use | Biochemical recurrence\( n = 992 \) | No recurrence\( n = 4939 \) | Crude HR (95% CI) | Adjusted HR (95% CI)* |
|-----------------------------------------|--------------------------------------|-----------------------------|------------------|-----------------------|
| \( \leq 1 \) year                       | 483                                  | 2016                        | 1.00 (ref)       | 1.00 (ref)            |
| > 1–2 years                             | 254                                  | 894                         | 1.21 (1.04–1.44) | 1.09 (0.93–1.27)     |
| > 2–3 years                             | 108                                  | 550                         | 0.79 (0.64–0.97) | 0.70 (0.57–0.87)     |
| > 3 years                               | 147                                  | 1479                        | 0.34 (0.28–0.41) | 0.33 (0.27–0.40)     |

*Adjusted for variables listed in Table 1
behavioral interventions) has the potential to improve both depression and cancer outcomes.

**Author contributions** All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by RH, LHC, and JS. The first draft of the manuscript was written by RH, SR, LHC, MRI, and JS. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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**Data availability** The study datasets are available upon reasonable request. De-identified data are available from the corresponding author. Data use agreements may be required.

**Declarations**

**Conflict of interest** The authors have no relevant financial or non-financial interests to disclose.

**Ethical approval** This retrospective study was reviewed and approved by the internal review board of the Kaiser Permanente. The IRB waived the right to obtain written or verbal consent.

**Consent to participate** The KPSC IRB waived the right to obtain written or verbal consent due to the de-identified nature of the dataset.

**Consent to publication** Not applicable.

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