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Brief Correspondence

Variation and Trends in Antidepressant Prescribing for Men Undergoing Treatment for Nonmetastatic Prostate Cancer: A Population-based Cohort Study

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Abstract

Psychological distress is prevalent among men with prostate cancer (PCa). However, the variation in antidepressant use among individuals throughout the survivorship period is unknown. We sought to examine the variation and trends in receipt of antidepressants after PCa treatment, among patients with nonmetastatic PCa. Using population-based linked administrative data, we identified men ≥ 66 yr old who underwent surgery ($n = 4952$), radiotherapy ($n = 4994$), or surveillance ($n = 2136$), and these men were matched to general population controls ($n = 57\,127$). One year prior to PCa treatment, 7.7% of men received an antidepressant prescription, which increased to 10.5% in the year after treatment. In difference-in-differences analysis, adjusted for demographic and health characteristics, men had increased odds of antidepressant receipt up to 5 yr after surgery (odds ratio [OR] 1.49; 95% confidence interval [CI] 1.35–1.64; $p \leq 0.0001$) or radiotherapy (OR 1.33; 95% CI 1.21–1.47; $p \leq 0.0001$). Men did not have an increased risk of antidepressant receipt up to 5 yr after surveillance (OR 1.15; 95% CI 0.94–1.41; $p = 0.16$). Limitations include the potential for selection bias and misclassification due to the retrospective design of the study and the use of administrative databases. Thus, men with nonmetastatic PCa who initially receive surgery or radiotherapy, but not those who initially undergo surveillance, have an increased risk of antidepressant receipt after treatment.

Patient summary: In this report, we examined antidepressant prescription for men after treatment of nonmetastatic prostate cancer across the entire population of men ≥ 66 yr in Ontario, Canada, from 2002 to 2009. For men diagnosed with nonmetastatic prostate cancer, the risk of antidepressant receipt at 5 yr after treatment was significantly increased after surgery or radiotherapy, but not after surveillance. Providers and patients should consider the psychological effects of prostate cancer treatment during the survivorship period.

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Cancer diagnosis and treatment can cause psychological distress [1]. Prostate cancer (PCa) therapies may especially predispose patients to psychological distress due to adverse effects on urinary and sexual function [2] and physiological disturbances [3]. Previous reports on the incidence of depression following PCa treatment do not describe the intermittent and time-varying nature of depressive symptoms over the prolonged survivorship phase [4].

One way to measure the variability in clinically significant psychological burden is by assessing the use of antidepressants [5,6]. Thus, we evaluated the receipt of antidepressants among patients who underwent different initial treatments for nonmetastatic PCa.

Following institutional research ethics board approval, we performed a retrospective cohort study of all men aged ≥ 66 yr diagnosed with nonmetastatic PCa (Supplementary Table 3) between April 1, 2002 and December 31, 2009 in Ontario, Canada, using linked administrative data. Datasets were linked using unique encoded identifiers and analyzed at the Institute for Clinical Evaluative Sciences (ICES). We considered three initial treatment strategies for nonmetastatic PCa, including radical prostatectomy (RP), radiotherapy (RT), or surveillance. RP or RT (external beam or brachytherapy) was identified using physician billing codes within 1 yr of diagnosis. We excluded patients with metastases within 1 yr of diagnosis. Patients were classified as receiving surveillance if they did not receive treatment, including androgen deprivation therapy (ADT), within the 1st year after diagnosis. In the surveillance group, we excluded patients who died due to PCa within 5 yr or due to

metastatic disease within 1 yr (Supplementary Tables 1 and 2). Men were followed from the date of primary treatment until death or March 31, 2016.

We compared individuals undergoing these treatments to propensity-score-matched members of the general population, in a 1:5 ratio. Matching was performed based on a hard match of age and a propensity score comprising comorbidity (Aggregate Diagnostic Groups [ADG] score), hypertension, statin treatment, diabetes, previous myocardial infarctions and cerebrovascular accidents, and geographic region (Supplementary Table 4 for covariates). On the given index date for any PCa patient, we identified controls who matched appropriately. This date was assigned as their index date. We then looked back from the index date to ascertain “pre-index” windows, and we followed patients forward in time for their “post-index” windows. We did not directly match or compare rates of antidepressant prescriptions for patients between each PCa treatment, because antidepressant prescriptions are not a primary PCa treatment-related complication and the baseline risk of antidepressant use may differ between the groups.

The primary outcome was receipt of antidepressants based on filled prescriptions, (selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, tricyclics, and monoamine oxidase inhibitors, Supplementary Table 6).

We identified 4952 (41.3%) men who received RP, 4994 (41.0%) who received RT, and 2136 (17.6%) who underwent surveillance with 1 yr of pre-/postindex follow-up available. Baseline characteristics are summarized in Table 1 with additional characteristics in Supplementary Table 7. Men who

Table 1 – Baseline demographic and clinical characteristics, compared by receipt of prostate cancer treatments to matched controls for the cohort with 5-yr observation period before and after index date

Characteristics	RP	RP controls	RT	RT controls	Surveillance	Surveillance controls
N	4595	18 998	4367	18 073	1150	4562
Age (yr)						
Mean (SD)	69.4 \pm 2.6	69.3 \pm 2.5	69.5 \pm 2.7	69.4 \pm 2.6	73.7 \pm 3.1	73.5 \pm 3.0
Median (IQR)	69 (67–71)	69 (67–71)	69 (67–71)	69 (67–71)	73 (71–76)	73 (71–75)
ADG comorbidity score						
Mean (SD)	8.6 \pm 3.0	8.2 \pm 3.1	8.6 \pm 2.9	8.2 \pm 3.1	7.6 \pm 3.1	7.3 \pm 3.1
Median (IQR)	8 (6–11)	8 (6–10)	8 (6–10)	8 (6–10)	7 (5–10)	7 (5–9)
Comorbidities, N (%)						
Myocardial infarction	53 (1.2)	116 (0.6)	53 (1.2)	102 (0.6)	19 (1.7)	39 (0.9)
CVA	16 (0.3)	26 (0.1)	17 (0.4)	33 (0.2)	≤ 5 (0.4)	17 (0.4)
Hypertension	3570 (77.7)	15 447 (81.3)	3441 (78.8)	14 789 (81.8)	946 (82.3)	3878 (85.0)
Diabetes	835 (18.2)	3148 (16.6)	800 (18.3)	3180 (17.6)	227 (19.7)	799 (17.5)
Adjuvant therapy						
Surgery, N (%)	–	–	30 (0.7)	90 (0.5)	30 (2.6)	9 (0.2)
Median time to RP (d, IQR)	–	–	679 (28–2186)	1382 (411–2242)	789 (578–1189)	1692 (1384–2251)
RT, N (%)	1075 (23.4)	605 (3.2)	–	–	381 (33.1)	102 (2.2)
Median time to RT (d, IQR)	571 (179–1442)	2104 (1080–2904)	–	–	1064 (651–1721)	2080 (1435–2678)
ADT, N (%)	744 (16.2)	230 (1.2)	1,826 (41.8)	234 (1.3)	178 (15.5)	45 (1.0)
Median time to ADT (d, IQR)	214 (–30 to 1178)	2077 (792–3060)	–56 (–104 to –1)	2021 (727–2947)	1440 (759–2214)	2119 (1434–2582)
ADT duration (mo), N (%)						
<6	268 (5.8)	167 (0.9)	608 (13.9)	161 (0.9)	109 (9.5)	42 (0.9)
6–12	394 (8.6)	196 (1.0)	794 (18.2)	186 (1.0)	103 (9.0)	32 (0.7)
>12	238 (5.2)	157 (0.8)	620 (14.2)	169 (0.9)	72 (6.3)	42 (0.9)
Antidepressant users preindex, N (%)	495 (10.8)	2999 (15.8)	534 (12.2)	2,825 (15.6)	137 (11.9)	689 (15.1)
Antidepressant supply per 1000-person days preindex (d), mean (SD)	29.8 \pm 143.7	47.6 \pm 184.2	33.7 \pm 148.9	46.3 \pm 176.2	33.0 \pm 141.5	50.2 \pm 197.5

ADG = Aggregate Diagnostic Group; ADT = androgen deprivation therapy; IQR = interquartile range; RP = radical prostatectomy; RT = radiotherapy; SD = standard deviation; CVA = cerebrovascular accident.

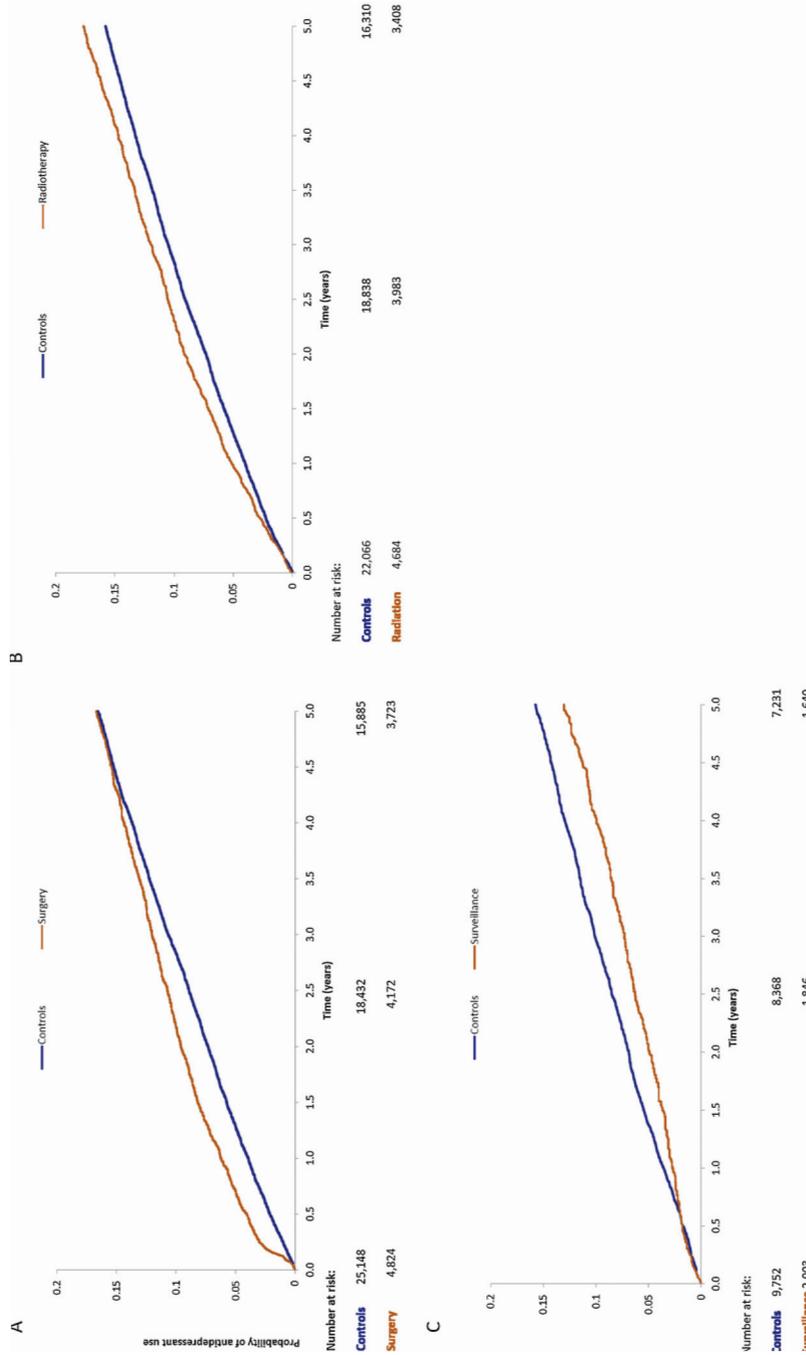


Fig. 1 – Cumulative probability of starting an antidepressant after (A) surgery, (B) radiotherapy, or (C) surveillance for localized prostate cancer.

underwent RP or RT were similar in age, but younger than those who underwent surveillance. The surgery and RT groups had comparable comorbidity but more than the surveillance group, as measured by mean ADG scores. Men were distributed similarly across income quintiles and geographic location. Frequencies of cardiovascular risk factors for depression were similar across all treatment groups.

Kaplan-Meier survival analysis demonstrated that the probability of first antidepressant receipt after surgery was greater than controls at 1 yr (6.2%; confidence interval [CI] 5.6–6.9% vs 3.9%; CI 3.7–4.2%; $p = 0.039$); by 5 yr, probabilities were similar (16.7%; CI 15.7–17.8% vs 16.6%; CI 16.1–17.1%; Fig. 1A). For patients undergoing radiation (Fig. 1B), probabilities of receiving an antidepressant were also greater than controls at 1 yr (5.1%; CI 4.5–5.8% vs 4.0%; CI 3.7–4.3%; $p = 0.25$) and 5 yr (17.6%; CI 16.6–18.8% vs 15.8%; CI 15.3–16.3%; $p = 0.25$), but this was not statistically significant. Patients undergoing surveillance (Fig. 1C) had a lower probability of receiving an antidepressant at 1 yr (2.7%; CI 2.1–3.5% vs 3.5%; CI 3.2–3.9%; $p = 0.01$) and 5 yr (13.0%; CI 11.6–14.6% vs 15.7%; CI 15.0–16.5%; $p = 0.01$) compared with controls. There were no differences between the different control cohorts (Supplementary Fig. 2).

To account for variable antidepressant receipt over time, including that prior to PCa treatment, we used multivariable logistic and negative binomial difference-in-differences (D-I-D) models for 1-, 2-, and 5-yr periods before and after treatment, looking at ever receipt of an antidepressant prescription and days of supply of antidepressants per 1000-person days. Parallel trend assumptions were confirmed (Supplementary Fig. 1). We adjusted our estimates for age, ADG score, geographic region, income quintile, and ADT treatment. In adjusted analysis, patients treated with surgery had greater odds of receiving antidepressants compared with controls, up to 5 yr (Table 2). The greatest

differential effect was seen at 2 yr (odds ratio [OR] 1.64; CI 1.46–1.79; $p < 0.0001$). There was also a significant increase in the supply of antidepressants received after surgery (Table 2), with a peak relative increase in supply of 33% at 2 yr after RP (rate ratio [RR] 1.33; CI 1.21–1.48; $p < 0.0001$).

For patients who underwent radiation, the odds of receiving antidepressants were increased compared with controls, with the peak at 2 yr (OR 1.36; CI 1.23–1.49; $p < 0.0001$; Table 2). Similarly, the relative quantity of antidepressants received was increased after treatment, with the peak rate ratio seen at 5 yr (RR 1.17; CI 1.04–1.32; $p = 0.0093$).

For patients who underwent surveillance, we failed to find a significant change in the odds of receiving antidepressants or in the supply of antidepressants received compared with controls.

To our knowledge, this is the first study to compare the receipt of antidepressants before and after the treatment of nonmetastatic PCa using a D-I-D estimation. The advantage of this technique is that we can control for background trends in antidepressant use among the general population. The D-I-D study design addresses the baseline increase in antidepressant use that would occur in the general population regardless of diagnosis and intervention by comparing the changes in the intervention group to a population-matched control group without the intervention [7]. Another advantage of this method is that we can include patients who receive antidepressants prior to the intervention of interest.

In the post-RP setting, a patient's erectile dysfunction [8], low sexual desire [9], and urinary incontinence [2] are associated with depression. RT for PCa also causes a transient loss to several quality-of-life domains [10], especially when combined with neoadjuvant ADT [11]. In our study, antidepressant receipt can act as a surrogate for psychological symptoms and their variation [5,6], and from that perspective our findings agree with previous knowledge. Active surveillance protocols may have important psychological effect on patients [12], although this varies depending on the comparator [13] and the heterogeneity of the surveillance cohort in this study may account, in part, for the difference in effects compared with active treatment groups.

The strengths of this study are its large, population-based nature and the extended period of survivorship examined. Moreover, we use D-I-D modeling to account for baseline risk of antidepressant receipt making our results more generalizable.

As with all studies using administrative databases, there is potential for misclassification bias. There is also potential for selection bias due to the retrospective design of the study. Although we adjust for geography within Ontario and income, the regional background might influence our results. The absence of information on surgical approach and extent of dissection, the modality and dose of RT delivered, and the surveillance protocols used are important limitations that may contribute to early and late morbidity. We could also not ascertain grade, stage, and prostate-specific antigen available for all patients in the study,

Table 2 – Difference-in-differences analysis: association between initial prostate cancer treatment strategy, ever use of antidepressants, and total antidepressant supply (adjusting for age, income quintile, LHIN, total ADG score, and ADT exposure throughout the observation period)

Observation period	Ever use of antidepressant			Antidepressant supply (d/1000-person days)		
	OR	95% CI	<i>p</i> value	RR	95% CI	<i>p</i> value
Surgery						
1 yr	1.54	1.39–1.70	<0.0001	1.26	1.14–1.38	<0.0001
2 yr	1.64	1.46–1.79	<0.0001	1.33	1.21–1.48	<0.0001
5 yr	1.49	1.35–1.64	<0.0001	1.27	1.11–1.44	0.0003
Radiotherapy						
1 yr	1.23	1.12–1.35	<0.0001	1.11	1.02–1.21	0.0115
2 yr	1.36	1.23–1.49	<0.0001	1.16	1.06–1.28	0.0018
5 yr	1.33	1.21–1.47	<0.0001	1.17	1.04–1.31	0.0093
Surveillance						
1 yr	1.04	0.91–1.20	0.5601	1.08	0.96–1.22	0.2116
2 yr	1.07	0.92–1.24	0.3973	1.01	0.88–1.16	0.8930
5 yr	1.15	0.94–1.41	0.1613	0.97	0.78–1.20	0.7727

ADG = Aggregate Diagnostic Group; ADT = androgen deprivation therapy; CI = confidence interval; LHIN = Local Health Integration; OR = odds ratio; RR = rate ratio.

although we know that following RP, men with higher-risk disease are more likely to report high anxiety at 1 yr [14]. The outcome of antidepressant receipt, rather than a diagnosis of depression or anxiety, may also include antidepressant prescription for other indications. This analysis cannot provide the indication for antidepressant prescription. To our knowledge, there are no reports regarding the distribution of indications for antidepressants after PCa treatment. Our cohort was limited to men aged ≥ 66 yr at diagnosis due to the eligibility for medical coverage in Ontario at age 65 yr; thus, these results may not be applicable to the antidepressant use of younger men. Finally, although we know that study participants received the antidepressant prescriptions, we cannot ascertain that they took the antidepressants.

In summary, men who were diagnosed and treated for nonmetastatic PCa with surgery or RT, but not those started on surveillance, have an increased risk of receiving antidepressants and an increased supply of antidepressants received per patient time compared with their general population-matched controls. These findings underscore the importance of providing psychological supports for PCa survivors.

Author contributions: Robert K. Nam had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Matta, Wallis, Goldenberg, Nam.

Acquisition of data: Matta, Wallis, Goldenberg.

Analysis and interpretation of data: Matta, Hird, Klaassen, Kodama, Herschorn, Nam.

Drafting of the manuscript: Matta, Nam.

Critical revision of the manuscript for important intellectual content: Matta, Wallis, Goldenberg, Klaassen, Hird, Kulkarni, Kodama, Herschorn, Nam.

Statistical analysis: Matta, Wallis, Nam.

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the Canadian Institution for Health information (CIHI). However, the analyses, conclusions, opinions and statements expressed in the material are those of the author(s), and not necessarily those of CIHI.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.eururo.2018.08.035>.

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