ORIGINAL ARTICLE

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Self-reported lack of energy or feeling depressed 12 months after treatment in men diagnosed with prostate cancer within a population-based registry

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Abstract

Objective: Feeling depressed and lethargic are common side effects of prostate cancer (PCa) and its treatments. We examined the incidence and severity of feeling depressed and lack of energy in patients in a population based PCa registry.

Methods: We included men diagnosed with PCa between 2015 and 2019 in Victoria, Australia, and enrolled in the Prostate Cancer Outcomes Registry. The primary outcome measures were responses to two questions on the Expanded Prostate Cancer Index Composite (EPIC-26) patient reported instrument: problems with feeling depressed and problems with lack of energy 12 months following treatment. We evaluated associations between these and age, cancer risk category, treatment type, and urinary, bowel, and sexual function.

Results: Both outcome questions were answered by 9712 out of 12,628 (77%) men. 981 patients (10%) reported at least moderate problems with feeling depressed; 1563 (16%) had at least moderate problems with lack of energy and 586 (6.0%) with both. Younger men reported feeling depressed more frequently than older men. Lack of energy was more common for treatments that included androgen deprivation therapy than not (moderate/big problems: 31% vs. 13%), irrespective of disease risk category. Both outcomes were associated with poorer urinary, bowel, and sexual functional domain scores.

Conclusions: Self-reported depressive feelings and lack of energy were frequent in this population-based registry. Problems with feeling depressed were more common in younger men and lack of energy more common in men having hormonal treatment. Clinicians should be aware of the incidence of these symptoms in these at-risk groups and be able to screen for them.

KEYWORDS

androgen deprivation, anxiety, cancer, depression, oncology, prostate cancer, prostatectomy, psycho-oncology, radiotherapy, registry

1 | BACKGROUND

There is a complex relationship between feeling depressed, the symptoms of depression (such as a lack of energy/low energy), the side effects of prostate cancer (PCa) treatment, and PCa itself.¹ Depression is multi-faceted and has probably been under-recognized in men diagnosed with PCa.² The treatments for PCa are also independently linked with depression, particularly androgen deprivation therapy (ADT) as primary or salvage treatment.^{3,4} We sought to quantify the incidence of these self-reported feelings in a large population-wide registry and to identify contributing patient and treatment factors.

The Victorian Prostate Cancer Outcomes Registry (PCOR-Vic) is a population-based clinical registry collecting clinicopathological details and patient-reported outcomes for men diagnosed with prostate cancer. PCOR-Vic currently covers approximately 80% of prostate cancer diagnoses in Victoria, Australia. This dataset enables patient outcomes to be related to men's characteristics at diagnosis, and many aspects of their prostate cancer care, in an unbiased unconfounded manner potentially providing information more validly applicable to the general population.

We used two questions from the validated Expanded Prostate Cancer Index Composite-26 (EPIC-26) instrument to measure the outcome, symptoms, and experiences of men diagnosed with PCa and how feeling depressed and lack of energy were associated with age at diagnosis, disease risk group, and treatment modality. Based on prior results, we also assessed how feeling depressed and a lack of energy correlated with urinary incontinence, urinary irritation, bowel, and sexual function.

2 | METHODS

2.1 | Patients

We analyzed data from PCOR-Vic, details of which have been previously described.⁵ Independent data collectors record clinicopathologic information regarding diagnosis, treatment, short-term follow up and administer the EPIC-26 patient reported outcome questionnaire 12 months after treatment commencement. The EPIC-26 is answered predominantly by phone or email. Men diagnosed between 2015 and 2019, and who completed the EPIC-26 between 2016 and 2020 were included in this study. Informed consent was obtained from patients and this project was approved by the Alfred Health Human Research Ethics Committee (Approval Number: HREC/16/ Alfred/98).

2.2 | Treatments and outcomes

The primary outcomes were responses to two questions on the EPIC-26: "How big a problem during the last 4 weeks, if any, has feeling depressed been for you?" and "How big a problem during the last 4 weeks, if any, has lack of energy been for you?." Responses are given on a five-point rating scale: no problem, very small, small, moderate, or big problem. Men were allocated to a treatment type by hierarchy starting with surgery, then radiation therapy (RT), ADT, and noninterventional management (active surveillance or watchful waiting). The small number of men with recorded surgery and RT, have been allocated to the surgery treatment type. The exception being men who had surgery and subsequent ADT who were classified into the ADT type due to expected effects on the outcome to be predominantly from hormonal treatment.

2.3 | Statistical analyses

Primary analysis of the outcomes was performed using multivariable ordered logistic regression. The variables of age at diagnosis (as a restricted cubic spline with knots at the tertiles), mode of EPIC-26 completion, treatment type and cancer risk category were selected a priori and entered into the model simultaneously, with treatmentrisk category interactions also included. The predicted probability of each level of problem, by treatment and risk category, was expressed graphically. A secondary analysis to assess the relationship between response and age or treatment used multivariable logistic regression with the same covariates, and the outcomes defined as having at least a moderate problem reported. This level was selected as a response of "moderate" or "big" problem would be more likely to warrant further investigation and intervention. To investigate associations with the EPIC-26 functional domains of urinary incontinence, urinary irritation/obstruction, bowel, and sexual, responses pertaining to these domains were transformed into a 0-100 point scale with 100 indicating unimpaired function. The outcomes responses for this analysis were transformed into three levels: "no," "very small"/ "small," and "moderate"/"big" problems to examine the relationship between magnitude of domain with function. These were expressed graphically with box and whisker plots and tested with the Kruskal-Wallis test. Data was analyzed using Stata 14.0 (StataCorp) with $p \leq 0.05$ set as the two-sided significance level.

3 | RESULTS

12,628 men were diagnosed with PCa between 2015 and 2019 and enrolled in PCOR-Vic. Of these, 9712 patients (77%) completed the two questions and form the analytic sample (Table 1). The median age of the sample was 67.2 years with median time from diagnosis to EPIC-26 completion being 444 days, which incorporates time from diagnosis to treatment commencement, plus 12 months. Any magnitude of problem with feeling depressed was reported by 32% of men, and any problem with lack of energy by 46%. No problem with either outcome was reported by 47% of respondents. A "moderate" or "big" problem with feeling depressed was reported by 981 (10%) and 1563 (16%) reported a "moderate" or "big" problem with lack of energy (Table S1). No appreciable difference was noted in mode of collection (email, phone, mail) and outcome. The cross tabulation of the responses to the two outcome questions is shown in Table S2.

Within the intermediate and high/very high-risk categories, the estimated percentage of men reporting "small," "moderate," or "big" problems with lack of energy was considerably higher among those receiving ADT with RT compared to other modalities (Figure 1). For

TABLE 1 Characteristics of the sample

	N = 9712
Age at diagnosis, years	67.2 (61.4-72.4)
Age at diagnosis	
<65 years	3869 (40)
≥65 years	5843 (60)
Year of PROMs completion	
2016	1189 (12)
2017	1809 (19)
2018	2299 (24)
2019	2340 (24)
2020	2075 (21)
NCCN risk category	
Low	1763 (18)
High/Very high	4589 (47)
Intermediate	1905 (20)
Regional (cN1)	210 (2.2)
Metastatic	501 (5.2)
Not recorded	744 (7.7)
Primary treatment	
Surgery	5054 (52)
Radiation therapy - ADT	621 (6.4)
Radiation therapy + ADT	1007 (10)
ADT \pm chemotherapy	789 (8.1)
Non-interventional	2139 (22)
Other/Unknown	102 (1.1)
Days between diagnosis and EPIC-26	444 (407–516)
Mode of EPIC-26 completion	
Phone	4730 (49)
Email	4470 (46)
Post	505 (5.2)
Urinary incontinence domain score	94 (73-100)
Urinary obstruction/irritation domain score	94 (88-100)
Bowel domain score	100 (92-100)
Sexual domain score	21 (13-57)

Note: Median (IQR) or *n* (column %). Non-interventional = active surveillance or watchful waiting.

Abbreviations: ADT, androgen deprivation therapy; EPIC-26, Expanded Prostate Cancer Index Composite – Short Form; IQR, Inter-Quartile Range; NCCN, National Comprehensive Cancer Network; PROMs, patient reported outcomes measures.

intermediate risk disease, the percentage of ADT + RT patients reporting small, moderate, or big problems was 18%, 16%, and 7.8%, respectively. In contrast, the corresponding estimates for patients



FIGURE 1 Predicted percentage of men, on the vertical axis, reporting a level of problem with feeling depressed (left side of plots, circle markers) or lack of energy (right side of plots, square markers), according to treatment and National Comprehensive Cancer Network risk category. These have been adjusted for age and mode of questionnaire completion within an ordered logistic regression model. Estimated 95% confidence interval shows as spikes. Marker and spike colors indicate treatment type. Maroon = surgery without androgen deprivation therapy (ADT), Orange = active surveillance, Blue = radiation therapy, Navy = radiation therapy and ADT, Red = ADT alone. Only treatments given for more than 10% of patients in each risk category are included

receiving only RT was 15%, 11%, and 5.1%. For high-risk disease, ADT + RT patients reporting small, moderate, or big problems was 20%, 20%, and 11%, respectively. Conversely, the analogous estimates for those receiving surgery without ADT was 15%, 11%, and 4.9%. Minimal differences in estimated response frequency were observed between treatments for feeling depressed.

Considering only the percentage of men having at least moderate problems with feeling depressed, as risk category at diagnosis increased, the predicted proportion increased from 8.5% for low-risk disease to 14% for regional and metastatic disease. No large differences were observed between treatment types within risk categories (Figure S1). A higher proportion of men receiving treatments that included ADT versus not ADT reported having at least moderate problems with lack of energy (31% vs. 13%). There was no appreciable difference in the proportions between men receiving ADT alone who had nodal (34%) or more disseminated metastatic disease (35%).

The relationship between feeling depressed, lack of energy and age at diagnosis, adjusting for other covariates, was modeled as a continuous function (Figure 2). As age increased, the predicted probability (95% CI) of at least moderate problems with feeling depressed was observed to halve, from 13% (11%–15%) at age 60 to 6.4% (5.3%–7.6%) at age 75. This general relationship was similar when considering the probabilities being 30% (28%–33%) at age 60 and 20% (18%–22%) at age 75. The relation for at least moderate problems with lack of energy was flatter with the predicted probabilities being 14% (12%–16%) at age 60 and 11% (9.5%–13%) at age 75 and for any problem: 35% (33%–38%) and 31% (28%–33%) at ages 60 and 75, respectively.

Statistically significant (p < 0.001) decreases in all functional domain scores were observed as problem with feeling depressed and lack of energy increased (Figure 3). The median score for urinary

incontinence declined from 100 (unimpaired function) for men reporting no problems with feeling depressed, to 85.5 and 79.3 for men reporting a "very small"/"small," and "moderate"/"big" problem, respectively.

4 | DISCUSSION

In this analysis using EPIC-26 patient reported outcome measures (PROM) data collected in the Prostate Cancer Outcomes Registry –



FIGURE 2 Predicted probability of any reported level of problem (solid lines) or moderate/big problem (dashed lines) according to age at diagnosis, adjusted for mode of questionnaire completion, National Comprehensive Cancer Network risk category and treatment. Dotted lines indicate 95% confidence interval. Histogram of the age distribution plotted below the line graphs

Victoria, we demonstrate that feeling depressed and having a lack of energy (lethargy) are frequently reported 12 months after treatment, with lethargy more common. These symptoms, particularly problems with feeling depressed, are more common amongst younger men. Reports suggest that older men are better able to moderate their own feelings of depression following a cancer diagnosis.⁶ This general pattern reflects what is seen in the contemporary Australian male population with 13.4% of men aged 55-64 and 7.0% of men over 75 years self-reporting any depression or feelings of depression lasting or expecting to last 6 months or more.⁷ These are lower than observed in our sample. The percentage of men reporting any problems with feeling depressed were estimated to be 30% at age 60 and 20% at age 75. However, our response outcome is measured on a different timescale hence these proportions are not directly comparable. More equivalent questions are part of the Kessler Psychological Distress Scale (K-10) where two questions ask: In the past four weeks, about how often did you "feel worn out for no real reason"? and "feel depressed"? Responses of "most" or "all of the time" for Australian adults were observed to be 11.3% for "worn out" and 4.0% for "depressed," respectively,⁸ considerably lower than our results from an older, male only sample (16% and 10%, respectively).

Feeling depressed was influenced by treatment modality with variation between disease risk group. Comparing men who received radiotherapy and ADT with men who received radiotherapy alone suggests ADT is a prominent factor in the frequency of lack of energy observed in this study, but with an attenuated effect on feeling depressed. ADT is effective in increasing overall survival, recurrence free survival, and managing metastatic disease.⁹ Testosterone has a role in the maintenance of normal psychological functioning.¹⁰ In the setting of medical castration, a large body of evidence pointing to an increase in fatigue, lack of interest in activities previously enjoyable,



Diamond indicates median score

FIGURE 3 Box and whisker plots of Expanded Prostate Cancer Index Composite-26 domain scores by response to the outcome questions

emotional liability, poorer cognition and decision making, loss of sexual desire, and diminished sexual function.¹¹ There is a natural decline in testosterone with advancing age in men, and lower serum testosterone is correlated with depression, this effect may be exacerbated in men receiving ADT.³ Disease stage is also correlated with depressive symptoms, with more severe depressive symptoms observed in more advanced disease.¹² Depression increases mortality in patients with PCa, especially with metastatic disease.¹³

The prominence of lack of energy may also relate to sexual dysfunction, relationship difficulties or fear of recurrence, and it should also be considered that men may not want to say they feel depressed but have symptoms that may be indicative of depression (such as lethargy).^{14,15} A strong relationship exists between sexual function and each man's notion of masculinity and how they respond to the initial diagnosis in terms of their personality and coping mechanisms, proposed or current treatment for their disease, pre-existing psychological conditions, and their relationship with their partner.¹⁶ There is evidence that depression and anxiety in partners can be just as severe as in the man with PCa.^{17,18} It may be appropriate to routinely use validated instruments to measure depression and anxiety in these men to monitor their mental health.

4.1 | Clinical implications

It was unexpected that self-reported feeling depressed and lack of energy were so frequent among younger men and it is important that these men are evaluated for and receive effective psychological and psychosocial care,¹⁹ and support, for example, in the form of vigorous monitored exercise.²⁰ Feeling depressed and a lack of energy were less common in men diagnosed at an older age, but these men should still be considered for routine mental health screening and interventions when clinically indicated, given an increased risk of suicide.²¹

The management of patients who feel depressed or who have lethargy can be challenging as these are frequent side effects of necessary and definitive treatments for prostate cancer. This is particularly a problem for men with metastatic disease treated with ADT alone, and RT with ADT. Pre-rehabilitation,²² exercise, pelvic floor interventions, Phosphodiesterase type 5 inhibitors to improve erectile function, and mindfulness interventions are effective in improving symptoms, body image, sexual functioning, and pain measures.²³ It should be noted that these interventions may have potential adverse effects such as increased anxiety, so the patient should still be monitored appropriately as with other interventions.²⁴ Vigorous monitored exercise is particularly effective in treating the side effects of ADT in men with metastatic disease.²⁵ It is also important to consider the experience of partners, who can suffer profound depression and anxiety because of a PCa diagnosis in a loved one and may need assistance in identifying depression or anxiety and accessing appropriate care. It may be appropriate for individual patients and couples to be referred for psychosexual therapy and sexual rehabilitation.²⁶

We observed lower urinary and bowel functional domain scores in men reporting higher problems with feeling depressed and lack of energy. While we are uncertain of causality, it is known that poor urinary symptoms following treatment are associated with poorer patient reported outcomes in terms of overall quality of life,^{27,28} depression,²⁹ regret over treatment decisions,³⁰ sexual functioning,^{31,32} and relationship quality.³³

4.2 | Study limitations

The primary limitation of this work is that we used only two questions from the EPIC-26 instrument in a sample that were all treated for PCa. Consequently, we are unable to determine the clinical severity of the depressive symptoms reported by these men compared to a reference population, although the general pattern in our sample reflect what would be expected in relevant age groups of Australian males.⁷ In practice, clinicians may incorporate other validated instruments that give greater insight into mental health, such as the Hospital Anxiety Depression Scale (HADS) or Patient Health Questionnaire-9 (PHQ-9).¹⁷ This would allow interpretation of the clinical relevance of the approach utilized in this study. It should be emphasized that EPIC-26 has demonstrated excellent performance when compared head-to-head with other instruments to measure prostate cancer outcomes. The feeling depressed and a lack of energy questions in EPIC-26 have good loading as a function of the whole score, acceptable reliability, and good internal correlation.³⁴ Further, the use of a single question within a larger tool has been shown to be clinically useful in patients with cancer.³⁵ A single question of the Edmonton Symptom Assessment System (where the patient answers on a one to 10 ordinal scale from not depressed to worst possible depression) demonstrated acceptable performance in screening of depression detected by the HADS³⁶ or the depression subscale of the PHO-9.37

This study only examined a single time point, 12 months after treatment. Other work has shown anxiety,³⁸ depression,³⁹ and adverse psychosocial outcomes change over time in men with PCa, and with disease severity, treatments, and changes in personal relationships.⁴⁰ We are unaware of what, if any, psychological therapy or interventions were offered to or accessed by patients. Further, testosterone levels were not available from the registry, which may correlate better with symptomatology in men receiving ADT. On the other hand, this is a large dataset, representing the entire population of Victoria and the results can probably be validly generalized to Victoria and Australia. Additionally, the responses come from the men themselves, and from a valid, reliable, and standardized survey instrument.

5 | CONCLUSION

Using two questions from the EPIC-26 patient reported outcome measures instrument, we observed a frequent incidence of feeling

depressed and lack of energy reported by men diagnosed with prostate cancer. Moderate to big problems with feeling depressed were more common in men diagnosed at a younger age. The frequency of moderate to big problems with lack of energy increased with advancing disease state, primarily due to the use of ADT (with or without radiotherapy). Clinicians should be aware of the incidence of this symptomatology in these at-risk groups, screen men for these symptoms, and refer those in need to appropriate support services.

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CONFLICT OF INTEREST

None of the authors declare any relevant conflicts of interest.

ETHICS STATEMENT

This project was approved by the Alfred Health Human Research Ethics Committee (Approval Number: HREC/16/Alfred/98).

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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