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Review Article

Depression and prostate cancer: A focused review for the clinician

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Abstract

Prostate cancer is the most common malignancy among men. Given its prevalence and relatively low mortality rates, several biopsychosocial survivorship issues have garnered recent attention. This article reviews the literature on the association between depression and prostate cancer, emphasizing key practice points relevant for clinicians. Depression is prevalent among men with prostate cancer, with approximately 1 in 6 patients experiencing clinical depression. Suicidal ideation is also not uncommon in this population and does not always present in those with other depressive symptoms. While choice of definitive cancer treatment (radiation or surgery) does not seem to affect depressive symptoms, receipt of androgen deprivation therapy appears to have a negative effect. Not only are patients at increased risk for depression following a prostate cancer diagnosis, but depression itself seems to adversely affect oncologic outcomes. We were not able to identify any clinical trials examining the efficacy of antidepressant medications for depressive symptoms in these patients, however population-based studies suggest antidepressant prescriptions are commonly utilized. Taken together, the literature on the intersection between urologic oncology and psychology/psychiatry affirms the importance of depression among men with prostate cancer. Clinicians should consider assessment of this symptom domain and treat or refer judiciously. Clinical trials represent a priority for future research.

Keywords: Prostate carcinoma; Major depressive disorder; Suicide; Quality of life; Patient-reported outcomes; Androgen deprivation therapy

1. Introduction

Prostate cancer is the most common male malignancy in North America [1]. At the same time, among all cancers and for all stages combined, prostate cancer carries the most favorable 5-year survival rate [1]. With a large number of men living for many years with a prostate cancer diagnosis, focus on survivorship issues and patient-reported outcomes has become increasingly important [2]. Decades of work have examined these in the context of the broad construct of "quality of life," solidifying the importance of prostate cancer patients' subjective experiences [3]. While they are a component of quality of life, mental health issues have received relatively less attention as standalone outcomes [4]. It is important to note that cancer is not only associated with biochemical changes, but in general is also associated with impairing psychological distress [5]. The present article focuses on depression as a psychological morbidity associated with prostate cancer and aims to highlight key points from the literature relevant to the practicing clinician (Table 1).

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Table 1
Clinical summary points.

- Approximately 1 in 6 men with prostate cancer will experience clinically significant depression.
- There is an increased risk of suicidal ideation and death by suicide in this population.
- Depression is associated with worse oncologic survival outcomes.
- Choice of definitive treatment modality (surgery vs. radiation) or active surveillance does not affect depression rates. However, receipt of androgen deprivation therapy may worsen depressive symptoms.
- Routine monitoring of depression is recommended.
- There exists overlap between the symptoms of depression and those related to cancer and its treatment (e.g., fatigue, weight loss).
- Treatment for depression can include antidepressant pharmacotherapy and/or psychotherapy and should be tailored to individual patients. Consultations with other health care providers should be utilized as necessary (e.g., social work, psychology).

2. Methods

Our aim for this review article was to review the literature on the association between depression and prostate cancer, and highlight key points relevant to practicing clinicians working with patients with prostate cancer (Table 1). This review article was not intended to be a comprehensive review of all studies on the topic. To identify relevant articles, an electronic search was carried out on PubMed (last search date: October 22, 2018) using the following search terms: *(prostate cancer) AND depress**. In terms of evidence hierarchy, preference was given to meta-analyses and systematic reviews. Narrative reviews focusing on depression or psychological outcomes among men with prostate cancer were also reviewed for references.

2.1. Defining depression

Similar to quality of life, depression itself is a multifaceted construct. It is comprised of a number of individual signs and symptoms each of which can vary dramatically in severity. These include those signs and symptoms on which a clinical diagnosis of major depressive disorder are based including low mood, anhedonia, cognitive deficits, and suicidal ideation (Table 2) [6]. Several of these individual symptoms such as fatigue and weight loss overlap with those associated with cancer and its treatment, suggesting a nuanced approach to patients and their symptomatology is required to guide clinical decision making related to any putative psychological concern [7]. This overlap can certainly lead to missed diagnoses of depression and cancer.

Within the prostate cancer literature, definitions of depression as an outcome have varied. This invariably complicates interpretation across studies. These definitions range from variability in single-item depression scores to a formal diagnosis of major depressive disorder. Most studies though have reported on clinically significant depression (i.e., a clinical diagnosis or depressive symptomatology suggestive of a diagnosis of major depressive disorder) as an outcome [8].

Table 2
Symptoms indexing a diagnosis of major depressive disorder.

1. Depressed mood
2. Decreased interest or pleasure in activities
3. Changes in weight or appetite (increase or decrease)
4. Changes in sleep pattern (increase or decrease)
5. Psychomotor retardation or agitation
6. Fatigue or loss of energy
7. Feelings of guilt/worthlessness
8. Changes in cognition (decreased concentration/indecisiveness)
9. Suicidal ideation

Adapted from the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) [6].

A diagnosis of major depressive disorder can be established if 5 or more of the above symptoms, including at least one of 1 or 2, are present during the same 2-wk period and cause significant distress or represent a change from previous functioning.

2.2. Evaluating depression

Numerous measures of depressive symptoms exist today, with several variants used with cancer patients [9]. However, there is not an extensive literature examining the validity and psychometric properties of these scales among prostate cancer patients, making it difficult to recommend a gold standard.

A single question is often used in clinical practice to quantify depression. Such an item is embedded into longer patient-reported outcome batteries such as the Edmonton Symptom Assessment System [10]. However, there are no validation studies of such an approach among men with prostate cancer. Studies with other populations however, suggest this may be a viable and valid option [11].

In regard to full scale measures, 1 analysis with Australian men with prostate cancer examined the inter-relationship between 3 commonly used depression self-report scales: the Hospital Anxiety and Depression Scale [12], the Zung Self-rating Depression Scale [13], and the Patient Health Questionnaire (PHQ-9) [14]. The study found significant correlations between scores from the 3 scales translating to approximately 33% to 55% shared variance [15]. Classification rates for clinically relevant depression also varied from 9% to 25%. This study highlights the variability across different depression assessment tools, which as mentioned above makes interpretation across studies difficult, but also underscores the need for more validation studies.

Table 3
Personal Health Questionnaire (PHQ-9).

Over the past 2 wk, how often have you been bothered by any of the following problems?	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed or hopeless	0	1	2	3
3. Trouble falling asleep, staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself—or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed. Or, the opposite—being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thought that you would be better off dead or hurting yourself in some way	0	1	2	3

The symptoms elicited on the PHQ-9 are those representing the diagnostic criteria of a diagnosis of major depressive disorder (Table 2). From the above questions, a total score can be calculated by summating the scores from the 9 questions [14].

Reprinted with permission from the Society of General Internal Medicine [14].

Although it is difficult to recommend 1 assessment tool over another, there is no evidence to our knowledge demonstrating the lack of validity of utilization of a single item measure asking patients to rate their depression. On the contrary, work in other populations supports this approach [16,17]. Although not specific to prostate cancer, the American Society of Clinical Oncology endorsed the Canadian Association of Psychosocial Oncology and Canadian Partnership Against Cancer guideline that all patients living with cancer and cancer survivors be evaluated for symptoms of depression and anxiety at baseline and at periodic times using validated instruments [18]. The guideline recommends initial screening with the first 2 items of the PHQ-9 index [14], with completion of the remaining 7 items if the patient achieves an initial score of 2 or higher (Table 3). The guideline suggests offering intervention if the total PHQ-9 score is 8 or higher, a score that corresponds to the detection of clinical depression [19].

2.3. Depression after a prostate cancer diagnosis

Several studies have been carried out exploring the variables associated with depression among men with prostate cancer, including both patient-related and disease-related variables. The underlying reasons for depression in this population may be multifold and can include the psychological distress related to the diagnosis both in the short-term and longer-term, physical symptoms, side effects of treatment, family and social concerns, as well as the cancer pathophysiology itself [20]. It is important to note that psychological distress, which includes depression as well as other mental health issues (e.g., anxiety), may occur at various time points in a cancer trajectory [21].

A meta-analysis including 27 studies with a pooled sample size of over 4,000 prostate cancer patients, with either localized or advanced disease, estimated a prevalence rate of clinically significant depression between 15% and 18% [8]. Notably, these rates were found to be similar for patients regardless of where they were along their treatment course. As a comparison, the global prevalence of depressive disorders has been estimated to be less than 5% [22]. Another study by Ravi et al. examined depression and other mental health issues in patients with clinically localized prostate cancer using the Surveillance, Epidemiology, and End Results-Medicare linked (SEER) database [23]. They found that approximately 20% of patients developed depression or other mental health issues following diagnosis of prostate cancer. Patients at risk included elderly patients, those with greater comorbidities, treatment in a rural setting, not being married, or experiencing urinary incontinence. Protective factors included black race, higher income, and definitive treatment (vs. watchful waiting).

Several risk factors for depression have been identified in the literature [24–26]. Drawing from this and our own experience, we highlight several factors that may place men with prostate cancer at greater risk for developing depression (Fig. 1). These risk factors can be classified as biological, psychological, and social, but it should be noted that these variables may interact variably to determine depression severity. Biologic variables that might place a man with prostate cancer at increased risk for depression include advanced stage, greater burden of physical symptoms, and elderly age to name a few. Psychosocial variables increasing risk include poor coping, helplessness, tendency to catastrophize, poor family support/being unmarried, lower income, and a personal history of psychiatric illness. Clinicians should be aware of these factors that place patients at risk for psychological morbidity.

2.4. Prostate cancer treatment and depression

The literature on whether treatment for prostate cancer has any effect on depressive symptoms has focused on 2 main questions.

The first question is whether the choice of definitive treatment (surgery, radiation, or active surveillance) is

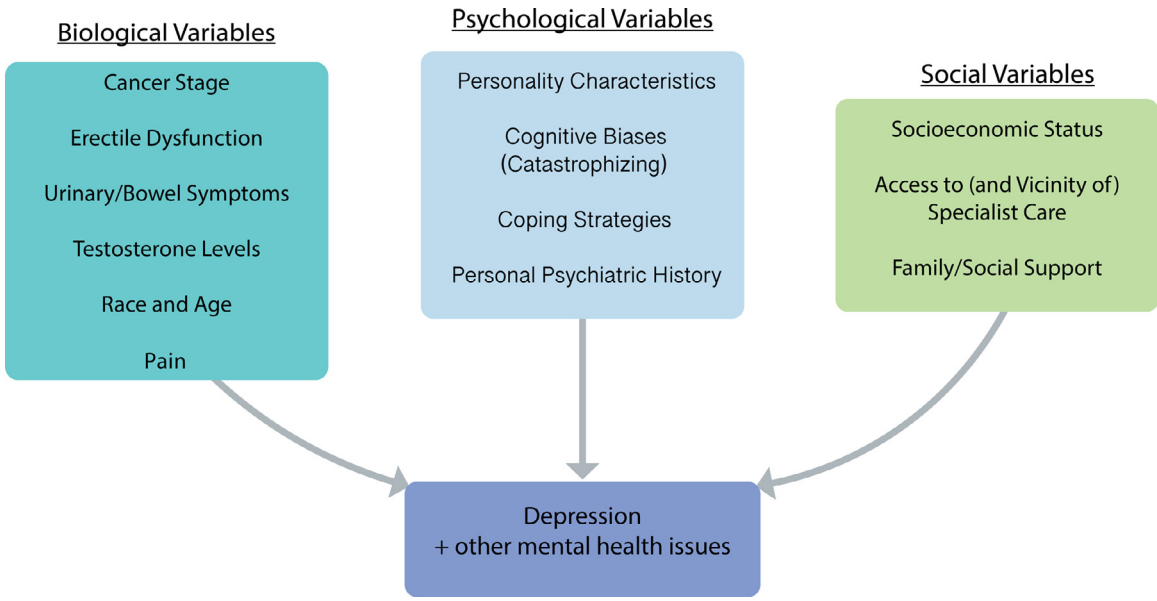

Fig. 1. Biopsychosocial factors associated with depression in men with prostate cancer.

associated with differential rates of depression. The study by Ravi et al. using the SEER database certainly suggested disadvantages to a lack of definitive treatment [23]. Another study examining a cohort of patients on active surveillance showed no changes in depression levels over time [27]. More recent evidence from a larger randomized clinical trial including 1,643 patients showed no differences in depression across the 3 main treatment modalities (active surveillance, surgery, or radiotherapy) [28].

The second question asks whether hormone-based treatment in particular influences depression outcomes. Several studies have been carried out to address this question, with some finding an association and others not. A recent systematic review and meta-analysis on the topic found that the use of androgen-deprivation therapy conferred an approximately 40% increased risk of depression [29]. This meta-analysis included over 150,000 individuals across 18 studies. Notably, most of these studies have taken on a retrospective study design, though findings are similar when limited to only prospective studies.

2.5. *Suicide among men with prostate cancer*

Population-based studies have shown that men with prostate cancer are at an increased risk of death by suicide [30–35]. While suicidal ideation can be a symptom of underlying depression, these 2 constructs are not synonymous, although they obviously share an association. A population based study in Florida highlighted that 30% of suicides among prostate cancer patients were completed by patients without a frank diagnosis of depression [36].

The absolute risk of suicide among prostate cancer patients is relatively low. Nonetheless the relative risk appears to be increased, rendering this population vulnerable. One study estimated the rate of suicide among men with prostate cancer in a 10-year span to be approximately 1 in 1,000 men, a rate that is almost twice that of the general population [35]. The rates of suicidal ideation though are much higher in this population. One study estimated approximately 12% of patients endorse some degree of suicidal ideation [37].

2.6. *Effect of depression on cancer outcomes*

Studies discussed thus far have revolved around the notion of prostate cancer preceding depression and other psychological issues. The reverse proposition is much less explored. There is a suggestion that depression in and of itself may represent a risk factor for the development of cancer [38]. The pathophysiology of this link is hypothesized to relate to immune system dysfunction.

Besides frank risk of developing cancer, several studies have linked a baseline diagnosis of depression as a risk factor for worse outcomes among men with prostate cancer. Using the SEER database, Prasad et al. reported that patients with clinically localized prostate cancer and a diagnosis of a depressive disorder were less likely to undergo definitive treatment for the prostate cancer and experienced poorer survival outcomes [39]. Other analyses of the SEER database which have included patients with both clinically localized and advanced prostate cancer have corroborated an increased rate of mortality among prostate cancer patients with depression [40]. Baseline depression scores may also influence post-treatment quality of life impairments. Mohamed et al. reported that baseline depression significantly predicted worse post-treatment sexual and urinary quality of life [41]. These studies provide a clear signal that depression at the time of diagnosis of prostate cancer confers negative prognostic value.

2.7. Treatment of depression

Treatment guidelines for major depressive disorder are well developed and generally recommend first-line treatment with pharmacological agents (i.e., antidepressants) and/or psychotherapy (e.g., cognitive behavioral therapy) [42]. The evidence base for treatment of depression among patients with cancer is less well developed [43]. Numerous clinical trials have shown the efficacy of antidepressant medications for primary depression [44], however there are far fewer trials focused on cancer patients and the results and recommendations from these are more provisional [45,46].

Despite the paucity of data to guide treatment-related decisions, epidemiological data has shown that upwards of 14% of men with prostate cancer use antidepressant medications [47–49]. It is not clear what proportion of patients receiving antidepressant medication have a diagnosis of depression or what proportion of those with depressive symptoms do not receive these medications. Vigilance is required when using these medications in prostate cancer patients as they may confer side effects that overlap with those related to primary treatments for prostate cancer including sexual dysfunction [50]. Unfortunately, we are not aware of any clinical trials examining the efficacy of antidepressant medications for depressive symptoms in prostate cancer patients.

Vasomotor hot flushes are a common side effect of androgen deprivation [51]. Interestingly, antidepressant medications have shown efficacy in treating this symptom in this population [52,53]. This is noteworthy given the aforementioned association between androgen deprivation and depressive symptoms. Examination of these variables in concert may represent a promising area for future work.

Other interventions that have shown some efficacy for reducing depressive symptoms among men with prostate cancer include exercise and peer support [54]. Cognitive behavioral therapy is an effective first-line treatment among adults with major depressive disorder [42]. Studies with cancer patients provide a signal for efficacy of this treatment modality as well [55,56]. Well-designed prospective trials with prostate cancer patients specifically are lacking in the literature. Nonetheless, given a clear signal of benefit of psychotherapy for depression among cancer patients [57], clinicians should consider referring patients to mental health specialists for these treatments.

3. Conclusions

Prostate cancer is the most common malignancy among men. With most men living for years after their diagnosis, survivorship issues are of increasing importance in this population. Prevalence rates estimate 1 in 6 men with the diagnosis will experience clinically significant depression, with studies identifying numerous risk factors. While choice of definitive treatment does not seem to affect depressive symptoms, receipt of androgen deprivation therapy appears to have a negative effect. Not only are patients at increased risk for depression following a diagnosis of prostate cancer, but depression itself seems to adversely affect survival outcomes in this population. Taken together, the literature on the intersection between urologic oncology and psychology/psychiatry underscores the importance of depression among men with prostate cancer. Clinicians should routinely assess this symptom domain and treat judiciously. Most of the research on the topic stem from retrospective or post-hoc analyses which serves as a critical limitation to this area of work. Well-designed prospective studies are needed to clarify several ambiguities. Clinical trials in particular represent a priority for future research.

Conflicts of interest

The authors declare that they have no relevant conflicts of interest.

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