



# Pain, cancer-related distress, and physical and functional well-being among men with advanced prostate cancer

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## Abstract

**Purpose** Men with advanced prostate cancer (APC) experience high levels of pain, which contribute to poor psychosocial and functional outcomes. Cancer-related distress explains the relationship between pain severity and interference, yet specificity of distress characteristics (e.g., hyperarousal, intrusive, or avoidant symptoms) in explaining associations between pain experiences and well-being has not been explored within APC. This study examined men with APC entering a clinical trial and tested associations of baseline pain, cancer-related distress, and physical and functional well-being.

**Methods** One hundred ninety men with APC enrolled in a randomized-controlled trial and were assessed prior to randomization. The McGill Pain Questionnaire assessed pain severity, and the Functional Assessment of Cancer Therapy-General captures physical and functional well-being. The Impact of Events Scale-Revised measured cancer-specific distress symptoms, including hyperarousal, avoidance, and intrusion symptoms. Controlling for age, cancer stage at diagnosis, income, education, and race/ethnicity, mediation models (SPSS PROCESS, model 4) tested whether cancer-specific distress accounted for the associations between pain severity and physical and functional well-being.

**Results** Men were on average 68 years of age, White non-Hispanic, with stage IV cancer. Pain severity was related to poorer physical ( $p < .001$ ) and functional well-being ( $p < .001$ ). Associations between pain severity and physical and functional well-being were partially mediated by greater intrusive and hyperarousal symptoms but not avoidant symptoms.

**Conclusion** For men with APC, intrusive and hyperarousal symptoms may partially explain the relationship between pain severity and decrements in physical and functional well-being. APC pain management should attend to such distress symptoms, which may contribute to interference if left unaddressed.

**Trial registration** ClinicalTrials.gov Identifier: NCT03149185.

**Keywords** Cancer-related distress · Cognitive behavioral stress management · Functional well-being · Physical well-being · Prostate cancer

## Background

Pain is a debilitating symptom reported by up to 30% of patients with cancer [1]. Among men with advanced prostate cancer (APC), pain is particularly common and frequently related to metastatic cancer deposits in the bones; however, the pain experience is not fully accounted for by disease characteristics [2, 3]. APC pain is associated with multiple psychological symptoms, including elevated fatigue, anxious and depressive symptoms [4], poor adaptation to illness [5], and reduced quality of life [6, 7]. APC pain has also been associated with reduced physical and functional well-being, such as elevated urinary and sexual dysfunction, increased comorbidities, high interference with daily activities, and

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prolonged disability [8, 9]. While pharmacologic interventions aid in APC-related pain management, breakthrough pain (i.e., pain flare-ups during active pain management) is common and results in worse daily functioning [9, 10].

Cancer-related distress, which includes unwanted or distressing thoughts, images, sensations, or recurrent memories related to a cancer diagnosis and treatment [11], has also been linked to worse outcomes and poorer functioning across cancer types. Elevated levels of cancer-related distress (e.g., hyperarousal, intrusive, and avoidant symptomatology) may reach clinical significance for post-traumatic stress disorder (PTSD) because of the cancer experience, and clinically elevated symptoms are present in up to 13% of patients recovering from cancer [12]. Even among those who do not meet criteria for a PTSD diagnosis, elevated levels of depression, negative mood, treatment-related side effects, reduced quality of life, and greater physical impairment are often related to cancer-related distress [13–15].

Cancer-related distress is frequently operationalized as a broad, unidimensional construct. However, within a psychotraumatic framework, cancer-related distress is comprised of three symptom subtypes (i.e., hyperarousal, intrusion, avoidance) that are independently related to health outcomes and psychosocial functioning [16, 17]. This framework posits that each symptom subtype operates uniquely within the stress response after a trauma. For example, among women with breast cancer, unique cancer-related distress subtypes have been primarily associated with worse general quality of life, fears of cancer progression, anxiety, depression, and adjustment to illness [18–20]. Prior studies have documented a relationship between pain and functional impairment by way of cancer-related distress among mixed cancer samples, including breast and hematologic cancers [21, 22]. However, only one study among men with PC found a positive relationship between intrusive symptoms and pain after inpatient cancer treatment but did not evaluate whether intrusive symptoms mediated pain effects on well-being [23]. The limited work that has been done has identified hyperarousal and intrusion as most strongly related to pain in cancer samples [24, 25] and other medical populations [26]. Through a cognitive behavioral lens, these symptom subgroups develop and are driven uniquely by emotional, cognitive, and behavioral stress responses. These subtypes are important to consider in the long-term development and maintenance of functional detriments via hyperarousal or intrusion symptoms, as pain may be a reminder of cancer-related experiences and distress [24]. However, no studies currently examine which subtype of cancer-related distress plays a role in the relationship between pain severity and functional and physical well-being in men with APC. Identifying associations between pain, cancer-related distress subtypes, and well-being may offer targeted intervention implications within this population.

The current study explored the association of pain severity with physical and functional well-being among men with APC presenting for a behavioral clinical trial. We examined symptoms of cancer-related distress, characterized as hyperarousal, avoidance, or intrusion, as symptoms that may help explain this relationship after initial treatment for prostate cancer. We hypothesized that hyperarousal and intrusive symptoms, but not avoidance, would be associated with the relationships of pain with physical and functional well-being.

## Methods

### Participants and procedures

A total of 190 participants consented and enrolled for a behavioral clinical trial (NCT03149185) between January 2013 and November 2016. Study staff recruited participants from Northwestern Memorial Hospital, the Robert H. Lurie Comprehensive Cancer Center of Northwestern University, Rush University Medical Center, the Jesse Brown Veterans Affairs Medical Center, Lake Forest Hospital, and the Graylake Outpatient Center. Eligible participants were 50 years of age or older, fluent in English ( $\geq 6$ th grade level), initially diagnosed with stage III or IV prostate cancer, and had undergone androgen suppression therapy at least once within the 12 months prior to enrollment. Participants were screened and, if eligible, provided written, Institutional Review Board-approved informed consent and completed a baseline psychosocial assessment during an in-person study visit before randomization. Detailed recruitment and data collection procedures have been published elsewhere [27].

### Measures

#### Pain severity

The McGill Pain Questionnaire – Short Form captured pain severity [28]. This measure consists of 15 pain descriptors (11 sensory; 4 affective) which are rated on a scale ranging from *none* (1) to *severe* (5). An example sensory item is “throbbing,” and the affective items include “tiring/exhausting,” “sickening,” “fearful,” and “cruel/punishing.” Affective items were assessed for overlap with cancer-related distress items and were determined to represent independent interpretations of the pain symptoms versus the experience of symptoms overall, as captured and described by the Impact of Events Scale below. Items were summed to create a total score, with higher scores indicating greater pain experiences. Two items were excluded from the present analysis, as has been done with prior use of this measure [27]. The measure has been well validated for use in oncologic

samples [29]. Internal consistency in the present sample was excellent ( $\alpha = 0.89$ ).

### Physical and functional well-being

Well-being constructs were measured with subscales from the Functional Assessment of Cancer Therapy – General (FACT-G) [30, 31]. Participants rated each item on a 5-point Likert scale ranging from *not at all* to *very much* to indicate the extent to which each item applied to them in the past 7 days. Scores from the physical and functional well-being subscales were used for the present analysis, with higher scores indicating better quality of life in these domains. The functional well-being subscale asked questions related to engaging in activities of daily living and professional or personal responsibilities. The physical well-being subscale included items related to specific physical symptoms. There is one item on the physical well-being subscale that assesses pain experiences. This item was retained and used to compute the subscale score prior to analysis and to ensure validity and reliability of the measure was maintained [32]. The present sample showed strong internal consistency in the physical and functional well-being subscales ( $\alpha = 0.81$  and  $0.77$ , respectively).

### Cancer-specific distress

The three-factor model of the Impact of Events Scale – Revised (IES-R) assessed cancer-specific distress symptoms [33]. Participants rated the frequency of experiencing cancer-related hyperarousal, avoidance, and intrusion symptoms during the prior week. Items were non-specific to cancer-related pain or functioning. Example items are “I felt watchful and on-guard,” “I tried not to talk about it,” and “I felt irritable and angry.” Participants rate each statement on a five-point scale ranging from *not at all* to *extremely*. Higher scores reflect greater cancer-specific distress, and each subscale score is calculated by averaging the sum of all seven items corresponding to symptoms. The measure has been previously validated in cancer samples and shown to have adequate psychometric properties [34]. In the present sample, excellent internal consistency was found for the hyperarousal ( $\alpha = 0.81$ ), avoidance ( $\alpha = 0.82$ ), and intrusion ( $\alpha = 0.85$ ) subscales.

### Covariates

Sociodemographic covariates included age, education level, race/ethnicity, and family income. Medical covariates included cancer stage at diagnosis (III, IV) and years since diagnosis. Prior research has found that sociodemographic characteristics are related to psychosocial outcomes

of patients with APC [4, 23, 27], so analyses controlled for such effects.

### Data analytic strategy

Pairwise deletion accounted for missingness among participants (maximum: 15 cases missing cancer stage at diagnosis), and 153 complete cases were included in final analyses. Descriptive analyses were conducted to ensure that each variable had appropriate mean and standard deviation values, and minimum and maximum scores. Normality of variables was tested by assessing their skewness and kurtosis and internal consistency. Linear regression tested the effect of pain severity on functional and physical well-being without cancer-related distress to assess correlation of pain on well-being prior to testing associations.

IBM SPSS (version 27.0) PROCESS Macro (model 4) tested all proposed hypotheses with bootstrap sampling (5000 resamples). Separate models tested each subscale of the IES-R for cross-sectional associations with physical and functional well-being. IES-R subscales, FACT-G subscales (i.e., physical and functional well-being), McGill total pain scores, years since diagnosis, education, annual income, and age were included as continuous variables while stage (0: stage III, 1: stage IV), and race/ethnicity (0: non-Hispanic White, 1: Hispanic, Black/African American, Asian/Asian American, multiracial) were dummy coded. The cancer risk group, as captured through Gleason score (i.e., aggressiveness; low: less than 7, intermediate: 7, high: greater than 7) was evaluated as a covariate but ultimately not included due to homogeneity of the sample; 95.6% of men presented with disease classified as low risk (score of 1–6). Bootstrap estimates for the 95% confidence intervals indicate significance if the upper and lower confidence range do not include zero.

### Results

Data were assessed for normality and outliers, and all cases were included for subsequent analyses. Participant characteristics are presented in Table 1. The sample consisted of non-Hispanic White (59.5%) men on average 68 years old. Approximately one-quarter of the sample had attained a graduate degree (27.9% Masters or Doctoral degree) and had an annual household income of \$100,000 or greater (24.2%). On average, men presented approximately 4.69 years after initial APC diagnosis, and most had stage IV cancer (55.8%). On average, men reported mild to moderate levels of pain ( $M = 5.85$ ,  $SD = 7.47$ ; 43), although variability was high (range = 0–37). Baseline reports of hyperarousal ( $M = 0.38$ ,  $SD = 0.57$ ), avoidant ( $M = 0.65$ ,  $SD = 0.70$ ), and intrusive ( $M = 0.53$ ,  $SD = 0.63$ ) symptoms were generally low compared to symptoms reported by patients with other

**Table 1** Participant characteristics ( $N=190$ )

Characteristic	M (SD); N (%)
Age	68.72 (8.82)
Stage	
3	69 (36.3%)
4	106 (55.8%)
Unknown	15 (7.9%)
Years since diagnosis	4.69 (5.30)
Grade at diagnosis	
Low grade (Gleason < 7)	151 (95.6%)
Intermediate (Gleason = 7)	5 (2.6%)
High grade (Gleason > 7)	2 (1%)
Unknown	32 (16.7%)
Non-Hispanic White	113 (59.5%)
Education	
Less than 12 years	8 (4.2%)
High school or GED	51 (26.8%)
2-year technical degree	31 (16.3%)
4-year bachelor's degree	44 (23.2%)
Masters or doctoral degree	53 (27.9%)
Unknown	3 (1.6%)
Annual income	
Less than \$5000	12 (6.3%)
\$5,000–11,999	8 (4.2%)
\$12,000–15,999	11 (5.8%)
\$16,000–24,999	13 (6.8%)
\$25,000–34,999	23 (12.1%)
\$35,000–49,999	20 (10.5%)
\$50,000–74,999	23 (12.1%)
\$75,000–99,999	18 (9.5%)
\$100,000 and greater	46 (24.2%)
Unknown/not sure	16 (8.4%)

cancer types [35]. Approximately 15.3% ( $n=29$ ) reported elevated total scores on the IES-R suggestive of clinically meaningful levels of cancer-related distress (i.e., score of 24 or more) [33].

### Association of pain and well-being

Both functional ( $B = -0.23$ ,  $SE = 0.05$ ,  $p < 0.001$ ) and physical well-being ( $B = -0.41$ ,  $SE = 0.04$ ,  $p < 0.001$ ) were negatively correlated with pain severity at baseline. Controlling for covariates, pain severity accounted for 11.0% of functional well-being variance ( $\Delta R^2 = 0.110$ ) and 33.2% of physical well-being variance ( $\Delta R^2 = 0.332$ ).

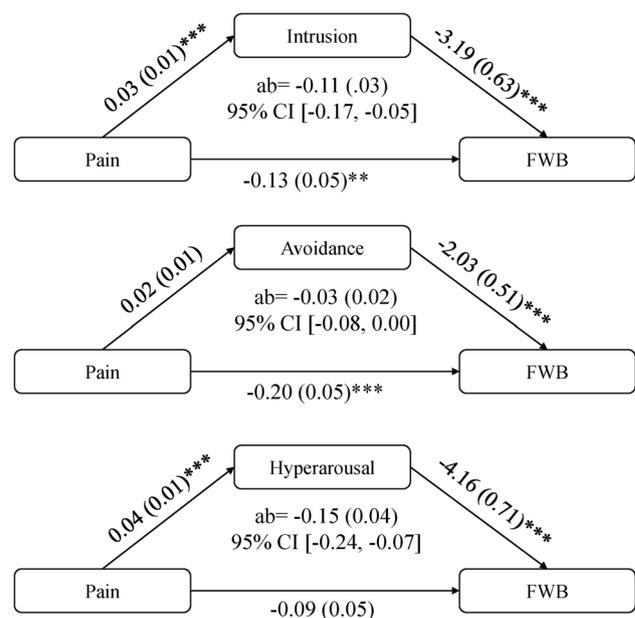
### Relationship among pain, cancer-related distress, and functional well-being

Pain had a negative indirect association with functional well-being by way of intrusive ( $B = -0.11$ ,  $SE = 0.03$ , bootstrapped 95% CI  $[-0.17, -0.05]$ ) and hyperarousal ( $B = -0.15$ ,  $SE = 0.04$ , bootstrapped 95% CI  $[-0.24, -0.07]$ ) but not avoidant symptoms ( $B = -0.03$ ,

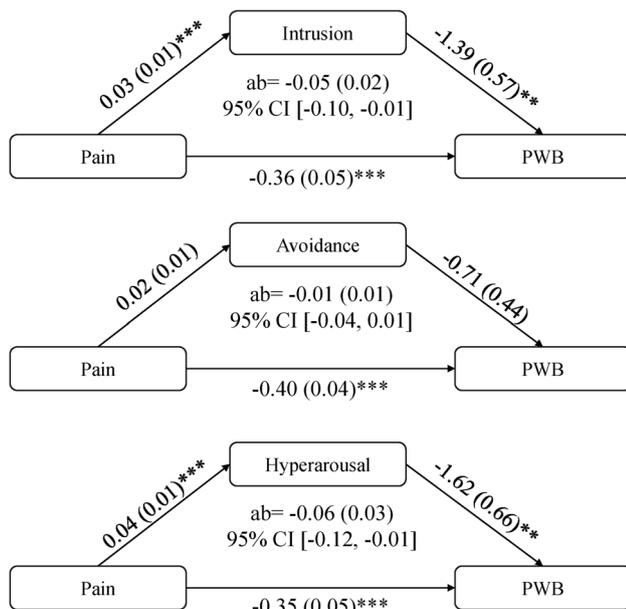
$SE = 0.02$ , bootstrapped 95% CI  $[-0.08, 0.00]$ ; Fig. 1). Additionally, pain exhibited direct associations with functional well-being while controlling for avoidant ( $B = -0.20$ ,  $SE = 0.05$ , bootstrapped 95% CI  $[-0.30, -0.10]$ ) and intrusive symptoms ( $B = -0.13$ ,  $SE = 0.05$ , bootstrapped 95% CI  $[-0.23, -0.03]$ ). No direct effects existed for total pain on functional well-being in the presence of the hyperarousal symptoms ( $B = -0.09$ ,  $SE = 0.05$ , bootstrapped 95% CI  $[-0.19, 0.02]$ ).

### Relationship among pain, cancer-related distress, and physical well-being

Total pain was negatively associated with physical well-being via indirect effects of intrusive ( $B = -0.05$ ,  $SE = 0.02$ , bootstrapped 95% CI  $[-0.10, -0.01]$ ) and hyperarousal symptoms ( $B = -0.06$ ,  $SE = 0.03$ , bootstrapped 95% CI  $[-0.12, -0.01]$ ; Fig. 2). No indirect association existed for pain on physical well-being via avoidant symptoms ( $B = -0.01$ ,  $SE = 0.01$ , bootstrapped 95% CI  $[-0.04, 0.01]$ ). A direct effect of total pain on physical well-being existed in all three models while controlling for hyperarousal ( $B = -0.06$ ,  $SE = 0.03$ , bootstrapped 95% CI  $[-0.12, -0.01]$ ), avoidant ( $B = -0.40$ ,  $SE = 0.04$ , bootstrapped 95% CI  $[-0.48, -0.31]$ ), and intrusive ( $B = -0.36$ ,  $SE = 0.05$ , bootstrapped 95% CI  $[-0.45, -0.27]$ ) indirect effects.



**Fig. 1** Indirect effects of pain on functional well-being via cancer-related distress. Note: FWB, functional well-being. \* $p < 0.05$ , \*\* $p < 0.01$ , \*\*\* $p < 0.001$ . Unstandardized coefficients reported. Indirect path represented by the product of a\*b coefficients. Covariates not pictured



**Fig. 2** Indirect effects of pain on physical well-being via cancer-related distress. Note: PWB, physical well-being.  $*p < 0.05$ ,  $**p < 0.01$ ,  $***p < 0.001$ . Unstandardized coefficients reported. Indirect path represented by the product of a\*b coefficients. Covariates not pictured

## Discussions

Within this sample of men with APC, hyperarousal and intrusive but not avoidant cancer distress symptoms partially explained the effects of pain severity on functional and physical well-being after treatment. Notably, hyperarousal explained the entirety of the relationship between pain and functional well-being, but not physical well-being. Findings support the proposed hypothesis that pain after treatment for APC is associated with specific types of cancer-related distress and physical and functional well-being decrements. These results are consistent with existing literature in other medical and cancer populations, in which hyperarousal and intrusive symptoms have been found to contribute to worse psychosocial and functional outcomes [24–26]. When conceptualized within a cognitive behavioral model, hyperarousal and intrusive symptoms alert the patient to their pain via physiological and cognitive reactions. Such responses may contribute to the observed changes in functional and physical well-being to in order to behaviorally alleviate pain and distress. To our knowledge, this is the first study to examine cancer-related distress symptom subtypes within the context of pain and functional and physical well-being for men with APC.

## Clinical implications

Cancer-related distress subtypes operated differently in relation to physical and functional well-being among men with APC and supported evidence that patient distress characteristics and their relationship to pain are crucial to consider upon clinical presentation. While patients with APC may experience pain throughout the course of their illness, the level to which this pain impacts their daily functioning may be modifiable. Specifically, hyperarousal and intrusive symptoms may be targeted through psychosocial intervention, such as cognitive behavioral stress management [36]. CBSM offers relevant skill building, such as thought awareness and cognitive restructuring for intrusive thoughts and relaxation and stress psychoeducation for hyperarousal symptoms [36]. Notably, participants of this current trial were presenting for a randomized-controlled trial testing CBSM for prostate cancer; therefore, this sample was willingly recruited and aware of potentially receiving this intervention at the time of baseline assessment. Furthermore, assessment and treatment of pain and psychosocial factors are critical for optimal patient outcomes, and current APC pain management guidelines recommend the inclusion of psychosocial interventions in addition to traditional pharmacologic treatments [37].

## Study limitations

The current study included primarily white, non-Hispanic, middle-aged men with of socioeconomic status who with low-risk disease characteristics who were recruited from large academic medical settings, most men presented. Therefore, conclusions may not generalize to patients with more aggressive APC. Additionally, avoidance and intrusion symptoms have been identified as psychological constructs that fluctuate overtime [20], so the findings of this cross-sectional study may be limited in application throughout the trajectory of cancer care. Lastly, pain presents often in tandem with several negative psychosocial outcomes for men with APC [4]. This study is limited by its cross-sectional nature and may not suggest causation within these associations. Overall, this study solely assessed participants at presentation for a clinical trial and therefore findings should be viewed as preliminary. It is plausible that greater cancer distress could exacerbate pain intensity suggesting that the pain is an intermediary between distress and well-being. Alternatively, poorer sense of well-being could increase distress. Future longitudinal analysis of this relationship would better evaluate and decipher the role of cancer-related distress in predicting well-being for men with APC-related pain overtime. While found to have some impact on cancer pain presentation [2, 3, 9, 10], prostate cancer metastasis location and pharmacologic pain treatments were not captured or tested

in the present study, and future research in this area should consider if these biologic and physiologic characteristics impact these associations.

## Conclusion

This cross-sectional study identified components of cancer-related distress as modifiable targets underlying the relationship between pain and well-being, which has not been previously explored within APC. Men with APC who present with elevated hyperarousal and intrusive subtypes of cancer-related distress may experience worse pain-related functional and physical well-being. Ultimately, these patient-level factors are important to evaluate and incorporate into treatment for men presenting with APC to limit consequences on physical and functional well-being.

**Author contribution** Conceptualization: Emily A. Walsh, Frank J. Penedo

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Writing—original draft: Emily A. Walsh, Patricia B. Pedreira

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**Code availability** Deidentified data is available from the authors upon reasonable request.

## Declarations

**Ethics approval** Approval was obtained from the ethics committee of Northwestern University. The procedures used in this study adhere to the tenets of the Declaration of Helsinki.

**Consent to participate** Informed consent was obtained from all individual participants included in the study.

**Conflict of interest** M. Antoni and F. Penedo are consultants for Blue Note Therapeutics. E. Walsh, P. Pedreira, P. Moreno, P. Popok, R. Fox, and B. Yanez declare they have no financial or non-financial interests.

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