Psycho-Oncology
Psycho-Oncology **25**: 282–291 (2016)
Published online 6 August 2015 in Wiley Online Library (wileyonlinelibrary.com). **DOI**: 10.1002/pon.3909

Cancer-related symptoms predict psychological wellbeing among prostate cancer survivors: results from the PiCTure study

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Abstract

***Background*: Prostate cancer treatments are associated with a range of symptoms and physical side-effects. Cancer can also adversely impact on psychological wellbeing. Because many prostate cancer-related symptoms and side-effects are potentially modifiable, we investigated associations between symptoms and psychological wellbeing among prostate cancer survivors.**

***Methods*: Postal questionnaires were distributed to men diagnosed with prostate cancer 2–18 years previously identified through cancer registries. General and prostate cancer-specific symptoms were assessed using the EORTC QLQ-C30 and QLQ-PR25, with higher symptom scores indicating more/worse symptomatology. Psychological wellbeing was assessed by the DASS-21. Associations between symptoms and each outcome were investigated using multivariate logistic regression, controlling for socio-demographic and clinical factors.**

***Results*: A total 3348 men participated (response rate = 54%). Seventeen percent (95%CI 15.2%–17.9%), 16% (95%CI 15.1%–17.8%) and 11% (95%CI 9.5%–11.8%) of survivors scored in the range for depression, anxiety and distress on the DASS scales, respectively. In multivariate models, risk of depression on the DASS scale was significantly higher in men with higher urinary and androgen deprivation therapy (ADT)-related symptoms, and higher scores for fatigue, insomnia and financial difficulties. Risk of anxiety on the DASS scale was higher in men with higher scores for urinary, bowel and ADT-related symptoms and fatigue, dyspnoea and financial difficulties. Risk of distress on the DASS scale was positively associated with urinary, bowel and ADT-related symptoms, fatigue, insomnia and financial difficulties.**

***Conclusions*: Cancer-related symptoms significantly predict psychological wellbeing among prostate cancer survivors. Greater use of interventions and medications and to alleviate symptoms might improve psychological wellbeing of prostate cancer survivors.**

Received: 6 November 2014
Revised: 16 June 2014
Accepted: 16 June 2014

Introduction

More men are living with prostate cancer than with any other cancer. Five-year prevalence worldwide is 3.2 million, and almost three-quarters of survivors reside in countries with a very high human development index [1]. A range of treatment modalities is available including surgery (radical prostatectomy), radiotherapy (external beam radiotherapy and brachytherapy), androgen deprivation therapy (ADT; using a variety of regimes), active surveillance and chemotherapy. These treatments are associated with significant risk of specific physical side-effects (e.g. urinary incontinence, impotence, erectile dysfunction and osteoporosis) and more general cancer-related symptoms (e.g. fatigue, sleep disturbance and pain), both of which may persist long-term [2,3].

Cancer can also adversely affect psychological wellbeing. Across all cancers, 30%–50% of patients may have a mental health disorder [4]. For prostate cancer, a recent meta-analysis reported 18% prevalence of depression and 18% prevalence of anxiety post-treatment [5]. Moreover, anxiety and depression prevalence among survivors is higher than in the general population [6]. Considerable research has focussed on identifying which subgroups of patients and survivors are at increased risk of experiencing poor psychological health. Various predictors have been identified including socio-demographic (e.g. age and marital status) and clinical (e.g. tumour site, disease stage, treatment with palliative intent and previous treatment for psychological conditions) factors [7–9]. Many of these predictors are fixed (i.e. they are not modifiable). The identification of potentially modifiable predictors of psychological wellbeing would, therefore, be of considerable importance.

Medications, devices and supportive interventions are available to manage many of the general symptoms and specific physical side-effects of prostate cancer treatment [10–14]. Although these supports and interventions

appear under-utilised [14–18], their availability suggests that some symptoms and side-effects are modifiable. Therefore, to inform development of strategies to alleviate the psychological burden in prostate cancer survivors, we investigated whether cancer-related symptoms are associated with psychological wellbeing, after adjusting for socio-demographic and clinical predictors.

Methods

Setting

The PiCTure (Prostate Cancer Treatment—your experience) study was conducted in Ireland, which comprises the Republic of Ireland (RoI) and Northern Ireland (NI). The former has a complex mixed public–private healthcare system and the latter a predominantly publicly funded system. High-quality population-based cancer registries operate in each jurisdiction.

The PiCTure study was approved by the Irish College of General Practitioners in the RoI and the NI Office for Research Ethics. Participants provided informed consent.

Identification and recruitment of survivors

All men diagnosed with invasive prostate cancer (ICD10 C61) 1/1/1995–31/03/2010 and alive at 31/03/2011 were identified through the two cancer registries (RoI = 17 304; NI = 5519). A country-stratified random sample was selected and screened for eligibility by healthcare providers (n = 12 322, 54% of sampling frame), GPs in RoI and hospital-based cancer research nurses in NI. To be eligible men had to: be aware of their diagnosis; understand English; be currently resident in NI or RoI; and be well enough to complete a questionnaire (in particular, they needed to have no cognitive impairment as judged by the healthcare provider from either personal knowledge or the man's medical records). Men who were designated ineligible by health professionals, and those whose eligibility could not be confirmed (e.g. because of GP non-response), were excluded, leaving 6559 men (53% of the sample) considered eligible.

Data collection

Eligible men were invited to complete a postal questionnaire. Non-responders were sent up to two reminders at approximately fortnightly intervals. Questionnaire responses were matched to cancer registry files to obtain date of diagnosis, Gleason score and clinical stage.

The questionnaire (available from the authors on request) included sections on socio-demographic characteristics (such as marital status and highest level of education completed) and clinical/medical factors (including presence of comorbid conditions at the time of prostate cancer diagnosis; mode of presentation (PSA-detected/asymptomatic or clinically-detected/symptomatic) and treatment for depression since the prostate cancer diagnosis). General cancer-related symptoms in the week before questionnaire completion were assessed using the EORTC QLQ-C30 which was developed to assess quality-of-life in cancer patients [19]. It has been shown to be valid and reliable in a range of cancers and clinical settings, including prostate cancer patients [20]. It includes nine symptom subscales (fatigue, nausea and vomiting, pain, dyspnoea, sleep disturbance, loss of appetite, constipation, diarrhoea and financial difficulties). Prostate cancer-specific symptoms and functioning were assessed using the EORTC QLQ-PR25, which contains five multi-item subscales (urinary symptoms, bowel symptoms, ADT-related symptoms, sexual activity and sexual function (conditional on being sexually active)) and a single-item relating to urinary bother which is conditional on using an incontinence aid [21]. The instrument has reasonable psychometric properties and discriminates between distinct clinical subgroups [21,22]. In addition, the factor structure, which was originally developed in patients undergoing active treatment, also applies to prostate cancer survivors [22]. Questions related to the week before questionnaire completion, with the exception of those on sexual function which related to the past four weeks. Response options for symptom-related questions on both instruments range from 'not at all' (scored as 1) and 'very much' (scored as 4). Raw scores were linearly transformed to values between 0 (lowest) and 100 (highest) and questions 20, 21 and 22 on the QLQ-PR25 were reverse scored [19,21]. Higher scores indicate more symptomatology or worse/poorer sexual activity.

Psychological wellbeing in the past week was measured using the 21 question version of the Depression, Anxiety and Stress Scales (DASS-21), which is a self-report scale designed to assess an individual's psychological state. It does not measure Generalized Anxiety Disorder (GAD) or Major Depressive Disorder (MDD) but rather is a screening instrument for identifying individuals who require further assessment for those disorders. It contains three (sub)scales, each containing seven questions [23]. The depression scale assesses unease or general dissatisfaction with life, hopelessness, devaluation of life, self-deprecation, lack of interest, inability to experience pleasure from activities usually found enjoyable and inertia; the anxiety scale assesses autonomic arousal, skeletal musculature effects and subjective experience of anxious affect; and the stress (henceforth 'distress') scale assesses difficulty relaxing, nervous arousal, and being agitated, irritable and impatient. The scales have high internal consistency and good convergent validity with other scales designed to assess depression and anxiety, and the factor structure is stable [23–25]. Question response options range from 'did not apply to me at all' (scored as 0) to 'applied to me very much, or most of the time' (scored as 3). A respondent's maximum score on each scale was 21; these totals were doubled for analysis [23].

DOI: 10.1002/pon

Statistical analysis

Some men (n = 297) were identified as ineligible after questionnaire dispatch (e.g. had recently died) and were removed from the response rate denominator. Men who returned the questionnaire but did not complete all questions on one of more of the DASS-21 scales were excluded from analysis; characteristics of included and excluded men were compared using chi-square tests.

Three binary outcome variables were created classifying men according to whether or not they scored in the range for (a) depression, (b) anxiety and (c) distress. The cut-offs used to define 'caseness' were: ≥10 on the depression scale; ≥8 on the anxiety scale; and ≥15 on the distress scale [23]. Multivariate logistic regression models of predictors of depression, anxiety and distress caseness were developed using a staged approach. Following the post-treatment survivorship framework of Given & Given [26], stage one involved building models of significant socio-demographic and clinical predictors. The candidate variables were: country of residence, age at diagnosis, marital status, highest level of education completed, whether lived alone, employment status, first degree family history of prostate cancer, mode of diagnosis, self-reported comorbidities at diagnosis, time since diagnosis, Gleason score at diagnosis, clinical stage at diagnosis and treatment for depression since prostate cancer diagnosis. Because treatment is strongly associated with cancer-related symptoms, to avoid collinearity treatment(s) received was not considered a candidate covariate. Initially, univariate associations between each socio-demographic and clinical variable and each outcome were assessed. Then variables were fitted simultaneously. Those which were statistically significant in the presence of the other variables were retained in the models (henceforth designated the 'core' models); those not significant were dropped and not considered further in the analysis. In stage two, each cancer-related symptom was fitted individually to the relevant core model. In stage three, those cancer-related symptoms which were significant at stage two were fitted simultaneously; the final models contained the socio-demographic and clinical variables from the relevant core model and those cancer-related symptoms which remained significant after the socio-demographic and clinical variables and other symptoms were included. The two QLQ-PR25 questions/subscales to which response was conditional (urinary bother and sexual function) were not analysed. A p value of <0.05 was considered statistically significant and significance of variables was determined using the likelihood ratio test (LRT). Final models had adequate fit.

Results

A total of 3348 men returned questionnaires (adjusted response rate = 54%). Of these, 3044 (91%) completed one or more DASS-21 scale and were included in analyses (Table 1). Men who were excluded were more often older at diagnosis and unmarried, and more often had primary level education only, than included men (Supplementary Table 1).

A total of 2913 men completed all DASS depression scale questions; 2959 completed all DASS anxiety subscale questions and 2928 completed all DASS distress subscale questions. Overall 17% of men (n = 481; 95%CI 15.2%–17.9%) scored in the range for depression, 16% (n = 485; 95%CI 15.1%–17.8%) scored in the range for anxiety, and 11% (n = 310; 95%CI 9.5%–11.8%) scored in the range for distress on the DASS scales.

Table 2 shows the core models containing the significant socio-demographic and clinical predictors of depression, anxiety and distress on the DASS scales. In the core depression model, risk was significantly lower in men who were older and had higher educational attainment; it was significantly higher in unmarried men and those not working at diagnosis. Risk of depression was higher in men whose cancer was symptomatic at diagnosis, who reported having comorbid conditions at diagnosis and who had been treated for depression since prostate cancer diagnosis. Risk of scoring in the range for anxiety was significantly higher in men who were resident in Northern Ireland, unmarried, completed primary level education only, had symptomatic disease at diagnosis, reported comorbidities at diagnosis and had previously been treated for depression. Significant predictors of scoring in the range for distress were similar: younger age, lower educational attainment, symptomatic disease, comorbidities and treatment for depression.

Supplementary Table 2 shows mean scores (with standard deviations) for the nine general and four prostate-specific cancer symptom subscales investigated and the odds ratios for scoring in the range for depression, anxiety and distress for a unit increase in each subscale score, adjusted for the socio-demographic and clinical variables in the relevant core model. All of the symptoms were significantly associated with each outcome; p values were all <0.01. With the exception of sexual activity, for all symptoms, a higher score (i.e. more symptomatology) was associated with increased risk of poor wellbeing.

The final multivariate models are shown in Table 3; these models included the variables from the core models plus those symptoms which remained statistically significant when included simultaneously. With the exception of treatment for depression since prostate cancer diagnosis (all outcomes) and comorbidities (anxiety only), all of the socio-demographic and clinical variables became non-significant after multiple symptoms were included in the models. Risk of depression on the DASS scale was significantly higher for men with higher urinary and ADT-related symptom scores, and for those with higher scores for fatigue, insomnia and financial difficulties; it was

DOI: 10.1002/pon

Table 1. Characteristics of prostate cancer survivors included in analysis. Numbers and percentages

	No.	%
Total	3044	100.0
Socio-demographic variables		
Country of residence		
Republic of Ireland	2080	68.3
Northern Ireland	964	31.7
Age at diagnosis		
≤59	756	24.8
60–69	1494	49.1
70+	794	26.1
Marital status at diagnosis		
Married	2526	83.0
Not married	497	16.3
Not reported	21	0.7
Highest level of education completed		
Primary	1031	33.9
Secondary	1053	34.6
Tertiary	863	28.4
Not reported	97	3.2
Living alone at diagnosis		
No	2652	87.1
Yes	370	12.2
Not reported	22	0.7
Employment status[a]		
Working at diagnosis and questionnaire completion	1061	34.9
Working at diagnosis and not at questionnaire completion	355	11.7
Not working at diagnosis	1605	52.7
Not reported	23	0.8
Clinical variables		
First-degree family history of prostate cancer		
No	2240	73.6
Yes	726	23.9
Not reported	78	2.6
Mode of diagnosis		
PSA-detected/asymptomatic	1827	60.0
Clinically detected/symptomatic	1195	39.3
Not reported	22	0.7
Comorbid conditions at diagnosis[b]		
No	1346	44.2
Yes	1698	55.8
Time since diagnosis[c]		
2 to 5 years	1489	48.9
5 to 10 years	970	31.9
10+ years	585	19.2
Gleason score at diagnosis[c]		
2 to 6	187	6.1
7 or 8	2005	65.9
8 to 10	580	19.1
Not known/not graded	272	8.9
Clinical stage at diagnosis[c]		
Stage 1	15	0.5
Stage 2	1694	55.7
Stage 3	429	14.1
Stage 4	129	4.2
Not known/not staged	777	25.5
Treated for depression after prostate cancer diagnosis		
Yes	155	5.1
Other[d]	2889	94.9

[a]'Working' includes employed and self-employed; not working includes retired and unemployed.
[b]Self-reported.
[c]From cancer registry/medical records.
[d]'Other' includes men who reported that they had not been treated and those who declined to answer the question.

lower for men with higher sexual activity symptom scores. Risk of anxiety on the DASS scale was higher in men with higher scores for urinary, bowel and ADT-related symptoms and fatigue, dyspnoea and financial difficulties and lower in men with higher sexual activity symptom scores. Risk of distress on the DASS scale was positively associated with urinary, bowel and ADT-related symptoms, fatigue, insomnia and financial difficulties and negatively associated with sexual activity symptoms.

Discussion

This study investigated whether cancer-related symptoms are independent predictors of psychological wellbeing in prostate cancer survivors. The rationale was that many of these symptoms are potentially modifiable by medical treatment or supportive interventions so, if associations exist, this suggests a route through which improvements in survivors' psychological wellbeing might be achieved. Several general and prostate-specific cancer-related symptoms were significantly associated with psychological wellbeing and, in the main, men with higher symptom scores (i.e. greater burden/more symptomatology) had higher risk of poor psychological wellbeing. Of note, once these symptoms were fitted in the models, most of the previously statistically significant socio-demographic and clinical predictors became non-significant. This suggests that cancer-related symptoms are more important determinants of survivors' psychological wellbeing than socio-demographic and (most) clinical factors.

There was considerable commonality in the general and prostate-specific cancer-related symptoms associated with each psychological outcome. In part, this is because of the fact that there was (as would be expected) some overlap between the men who scored in the range for each outcome. Of those with depression on the DASS scale, 62% also scored in the range for anxiety and 51% scored in the range for distress, while 52% of those with anxiety also scored in the range for distress. While most risk estimates were modest, they represented the change in risk per unit increase in the symptom score. The symptom scores were generally widely dispersed, and individual men's scores differed substantially. Differences of ≥5 in EORTC subscale scores have been designated as having clinical significance [27], but whether a difference of this magnitude in symptom scores corresponds to clinically significant differences in risk of negative psychological states is unknown.

Of the prostate cancer-specific symptoms, the strongest associations were between ADT-related symptoms and urinary symptoms and psychological wellbeing. Although concerns have been expressed about the psychological effects of ADT itself [10], in a large US study, after correcting for age and comorbidities, depressive disorders were not more common in men treated with ADT than

DOI: 10.1002/pon

Table 2. Univariate and multivariate associations between socio-demographic and clinical factors and depression, anxiety and distress. Numbers and percentages, crude and adjusted odds ratios (adj OR), 95% confidence intervals (CI) and p values

	Depression						Anxiety						Distress					
			Univariate		Multivariate (core model)[a,b]				Univariate		Multivariate (core model)[b,c]				Univariate		Multivariate (core model)[b,d]	
Variable	**No.**	**%**	**Crude OR**	**95% CI**	**Adj OR**	**95%CI**	**No.**	**%**	**Crude OR**	**95% CI**	**Adj OR**	**95%CI**	**No.**	**%**	**Crude OR**	**95% CI**	**Adj OR**	**95%CI**
Socio-demographic variables																		
Country of residence																		
Republic of Ireland	298	15.1	1	—	—		296	14.7	1	—	1	—	187	9.4	1	—	—	
Northern Ireland	183	19.6	1.38	1.12–1.69	—		189	20.1	1.46	1.19–1.79	1.27	1.01–1.59	123	13.1	1.45	1.14–1.84	—	
			p = 0.002						*p < 0.001*		*p = 0.040*				*p = 0.003*			
Age at diagnosis																		
≤59	146	20.1	1	—	1	—	119	16.1	1	—	—		96	13.2	1	—	1	—
60–69	216	15.0	0.70	0.56–0.89	0.59	0.45–0.78	234	16.0	0.99	0.78–1.26	—		147	10.2	0.74	0.56–0.98	0.69	0.51–0.93
70+	119	16.0	0.76	0.58–0.99	0.54	0.39–0.75	132	17.3	1.09	0.83–1.43	—		67	8.9	0.64	0.46–0.89	0.57	0.39–0.81
			p = 0.011		*p < 0.001*				*p = 0.711*						*p = 0.021*		*p = 0.007*	
Marital status at diagnosis																		
Married	380	15.7	1	—	1	—	379	15.4	1	—	1	—	246	10.1	1	—		
Not married	99	20.9	1.42	1.11–1.82	1.39	1.06–1.81	103	21.5	1.51	1.18–1.92	1.43	1.10–1.86	62	13.2	1.35	1.00–1.82		
			p = 0.006		*p = 0.017*				*p = 0.001*		*p = 0.009*				*p = 0.054*			
Highest level of education completed																		
Primary	198	20.5	1	—	1	—	209	21.2	1	—	1	—	134	13.7	1	—	1	—
Secondary	160	15.7	0.72	0.58–0.91	0.79	0.61–1.01	152	14.7	0.64	0.51–0.81	0.76	0.59–0.96	95	9.4	0.65	0.49–0.86	0.69	0.51–0.93
Third level	110	13.1	0.59	0.46–0.76	0.60	0.46–0.79	103	12.1	0.51	0.40–0.66	0.54	0.41–0.71	68	8.1	0.55	0.40–0.75	0.53	0.39–0.74
			p < 0.001		*p = 0.001*				*p < 0.001*		*p < 0.001*				*p < 0.001*		*p = 0.001*	
Living alone at diagnosis																		
No	404	15.9	1	—	—		400	15.5	1	—	—		265	10.4	1	—	—	
Yes	76	21.5	1.45	1.10–1.91	—		82	22.9	1.62	1.24–2.12	—		44	12.6	1.25	0.89–1.76	—	
			p = 0.010						*p = 0.001*						*p = 0.210*			
Employment status[e]																		
Working at diagnosis and questionnaire completion	134	13.2	1	—	1	—	130	12.5	1	—	—		85	8.3	1	—	—	
Working at diagnosis and not at questionnaire completion	66	19.4	1.59	1.15–2.19	1.29	0.91–1.84	60	17.4	1.47	1.05–2.05	—		43	12.8	1.63	1.10–2.40	—	
Not working at diagnosis	276	18.0	1.45	1.16–1.82	1.50	1.15–1.97	291	18.7	1.60	1.28–2.00	—		179	11.6	1.45	1.11–1.90	—	
			p = 0.001		*p = 0.011*				*p < 0.001*						*p = 0.009*			
Clinical variables																		
First degree family history of prostate cancer																		
No	355	16.5	1	—	—		347	15.9	1	—	—		227	10.5	1	—		
Yes	112	16.2	0.98	0.78–1.23	—		122	17.3	1.10	0.88–1.38	—		74	10.7	1.02	0.77–1.35		
			p = 0.851						*p = 0.399*						*p = 0.891*			
Mode of diagnosis																		
PSA-detected/asymptomatic	243	13.8	1	—	1	—	243	13.6	1	—	1	—	153	8.7	1	—	1	—
Clinically detected/symptomatic	234	20.7	1.64	1.34–1.99	1.46	1.18–1.80	241	20.9	1.68	1.38–2.04	1.36	1.09–1.68	157	13.8	1.68	1.33–2.13	1.43	1.11–1.85
			p < 0.001		*p = 0.001*				*p < 0.001*		*p = 0.006*				*p < 0.001*		*p = 0.006*	

DOI: 10.1002/pon

Comorbid conditions at diagnosis[f]																		
No	154	11.9	1	—	1	—	135	10.3	1	—	1	—	89	6.8	1	—	1	—
Yes	327	20.3	1.89	1.54–2.32	1.63	1.31–2.04	350	21.2	2.35	1.89–2.90	2.07	1.65–2.59	221	13.6	2.14	1.66–2.77	1.99	1.51–2.62
			$p < 0.001$		$p < 0.001$				$p < 0.001$		$p < 0.001$				$p < 0.001$		$p < 0.001$	
Time since diagnosis[g]																		
2–5 years	234	16.4	1	—	—		228	15.6	1	—	—		154	10.7	1	—	—	
5–10 years	154	16.5	1.01	0.81–1.26	—		155	16.5	1.06	0.85–1.33	—		104	11.2	1.06	0.81–1.37	—	
10+ years	93	16.9	1.04	0.80–1.35	—		102	18.2	1.20	0.93–1.55	—		52	9.2	0.85	0.61–1.18	—	
			$p = 0.958$						$p = 0.380$						$p = 0.461$			
Gleason score at diagnosis[g]																		
2 to 6	28	15.9	1.00	0.65–1.52	—		30	16.9	1.00	0.72–1.63			19	10.6	1.00	0.61–1.65	—	
7 or 8	307	15.9	1	—	—		308	15.8	1	—	—		203	10.5	1	—	—	
8 to 10	96	17.3	1.10	0.86–1.42	—		96	16.9	1.09	0.84–1.40	—		61	11.0	1.05	0.78–1.42	—	
Not known	50	19.6	1.29	0.92–1.79	—		51	19.2	1.27	0.91–1.76	—		27	10.3	0.98	0.64–1.49	—	
			$p = 0.483$						$p = 0.542$						$p = 0.988$			
Clinical stage at diagnosis[g]																		
Stage 1	1	7.1	0.42	0.06–3.26	—		1	6.7	0.38	0.05–2.89	—		1	6.7	0.66	0.09–5.02	—	
Stage 2	248	15.4	1	—	—		261	15.9	1	—	—		159	9.8	1	—		
Stage 3	77	18.5	1.25	0.94–1.66	—		67	15.8	1.00	0.75–1.34	—		53	12.9	1.36	0.97–1.89	—	
Stage 4	25	20.8	1.45	0.91–2.30	—		24	19.4	1.27	0.80–2.03	—		18	14.5	1.56	0.92–2.64	—	
Missing	130	17.4	1.16	0.92–1.46	—		132	17.6	1.13	0.90–1.42	—		79	10.4	1.07	0.81–1.42	—	
			$p = 0.216$						$p = 0.519$						$p = 0.258$			
Treated for depression after prostate cancer diagnosis[h]																		
Yes	80	55.6	7.38	5.23–10.43	5.90	4.08–8.51	79	54.9	7.21	5.11–10.18	6.49	4.51–9.33	68	46.9	9.27	6.52–13.18	7.64	5.28–11.06
Other	401	14.5	1	—	1	—	406	14.4	1	—	1	—	242	8.7	1	—	1	—
			$p < 0.001$		$p < 0.001$				$p < 0.001$		$p < 0.001$				$p < 0.001$		$p < 0.001$	

[a]The core model for depression includes: age at diagnosis, marital status at diagnosis, highest level of education completed, employment status, mode of diagnosis, comorbid conditions at diagnosis and treated for depression after prostate cancer diagnosis. The Adj ORs in this column are adjusted for all of these variables.

[b]A dash (—) in the Adj OR column indicates that the variable was not significant in the multivariate analysis and was not included in the core model.

[c]The core model for anxiety includes: country of residence, marital status at diagnosis, highest level of education completed, mode of diagnosis, comorbid conditions at diagnosis and treated for depression after prostate cancer diagnosis. The Adj ORs in this column are adjusted for all of these variables.

[d]The core model for distress includes: age at diagnosis, highest level of education completed, mode of diagnosis, comorbid conditions at diagnosis and treated for depression after prostate cancer diagnosis. The Adj ORs in this column are adjusted for all of these variables.

[e]'Working' includes employed and self-employed; not working includes retired and unemployed.

[f]Self-reported.

[g]From cancer registry/medical records.

[h]'Other' includes men who reported that they were not treated and those who declined to answer the question.

DOI: 10.1002/pon

Table 3. Associations between general and prostate-cancer specific symptoms and depression, anxiety and distress, controlling for socio-demographic and clinical variables from core models[a] and other symptoms. Numbers and percentages, multivariate odds ratios (MV OR), 95% confidence intervals and p values from likelihood ratio tests

	Depression			Anxiety			Distress		
Variable/symptom	***MV OR*[b]**	***95%CI***	***p***	***MV OR*[b]**	***95%CI***	***p***	***MV OR*[b]**	***95%CI***	***p***
Socio-demographic and clinical variables from core models									
Country of residence									
Republic of Ireland	—			1	—		—		
Northern Ireland	—			0.78	0.54–1.11	0.166	—		
Age at diagnosis									
≤59	1	—	0.116	—			1	—	0.146
60–69	0.73	0.50–1.05		—			0.70	0.46–1.09	
70+	0.61	0.38–0.99		—			0.60	0.35–1.03	
Marital status at diagnosis									
Married	1	—	0.127	1	—	0.729	—		
Not married	1.36	0.92–1.99		1.08	0.71–1.65		—		
Highest level of education completed									
Primary	1	—	0.556	1	—	0.753	1	—	0.698
Secondary	1.03	0.73–1.46		1.02	0.71–1.49		1.21	0.77–1.89	
Third level	0.85	0.58–1.24		0.89	0.60–1.32		1.08	0.67–1.74	
Employment status[c]									
Working at diagnosis and questionnaire completion	1	—	0.706	—			—		
Working at diagnosis and not at questionnaire completion	0.89	0.54–1.44		—			—		
Not working at diagnosis	1.08	0.75–1.57		—			—		
Mode of diagnosis									
PSA-detected/asymptomatic	1	—	0.880	1	—	0.166	1	—	0.404
Clinically detected/symptomatic	1.02	0.76–1.39		0.79	0.57–1.10		0.85	0.58–1.25	
Comorbid conditions at diagnosis[d]									
No	1	—	0.503	1	—		1	—	0.153
Yes	1.11	0.82–1.51		1.48	1.06–2.06	0.021	1.33	0.90–1.96	
Treated for depression after prostate cancer diagnosis[e]									
Yes	3.21	1.87–5.50	<0.001	2.91	1.65–5.12	<0.001	3.65	2.08–6.41	<0.001
Other	1	—		1	—		1	—	
General cancer symptoms[f]									
Fatigue	1.03	1.02–1.04	<0.001	1.02	1.01–1.03	<0.001	1.03	1.02–1.04	<0.001
Nausea	—			—			—		
Pain	—			—			—		
Dyspnoea	—			1.02	1.01–1.03	<0.001	—		
Insomnia	1.01	1.01–1.02	<0.001	—			1.01	1.00–1.01	0.042
Appetite	—			—			—		
Constipation	—			—			—		
Diarrhoea	—			—			—		
Financial difficulties	1.01	1.00–1.02	0.003	1.01	1.00–1.02	0.001	1.01	1.00–1.02	0.004
Prostate-specific cancer symptoms[f]									
Urinary symptoms	1.02	1.01–1.02	<0.001	1.02	1.01–1.03	<0.001	1.02	1.01–1.03	<0.001
Bowel symptoms	—			1.01	1.00–1.02	0.039	1.01	1.00–1.03	0.026
ADT-related symptoms	1.03	1.02–1.04	<0.001	1.03	1.02–1.04	<0.001	1.03	1.01–1.04	<0.001
Sexual activity	0.99	0.99–1.00	0.002	0.99	0.99–1.00	0.015	0.99	0.99–1.00	0.047

[a]The core model for depression includes: age at diagnosis, marital status at diagnosis, highest level of education completed, employment status, mode of diagnosis, comorbid conditions at diagnosis and treated for depression after prostate cancer diagnosis. The core model for anxiety includes: country of residence, marital status at diagnosis, highest level of education completed, mode of diagnosis, comorbid conditions at diagnosis, and treated for depression after prostate cancer diagnosis. The core model for distress includes: age at diagnosis, highest level of education completed, mode of diagnosis, comorbid conditions at diagnosis and treated for depression after prostate cancer diagnosis.

[b]MV ORs in this column are adjusted for the variables included in the relevant core model, plus those symptoms which were statistically significant when fitted simultaneously to a model already containing the core model variables. A dash (—) in this column indicates (1) for socio-demographic and clinical variables, that the variable was not included in the core model and hence not in the final multivariate model for the relevant outcome; and (2) for cancer-related symptoms, that the variable was not significant in the multivariate analysis and was not included in the final multivariate model for the relevant outcome.

[c]'Working' includes employed and self-employed; not working includes retired and unemployed.

[d]Self-reported.

[e]Other includes men who reported that they had not been treated and those who declined to answer the question.

[f]ORs are for unit increase in symptom score; higher symptom score indicates worse symptom burden/more symptomatology.

those who were not [28]. Because ADT may be used in the management of biochemical recurrence and metastatic disease, the observed association may be because of the presence of recurrent disease in men receiving ADT at questionnaire completion; shock, anger, fear and grief are common responses to a cancer recurrence [29] and

DOI: 10.1002/pon

may translate into depression, anxiety and distress. An alternative explanation follows from the content of the QLQ-PR25 ADT-related questions which include experience of hot flashes and presence of enlarged nipples/ breasts. These specific side-effects have been associated with feelings of loss of masculinity [30] suggesting that the threats that ADT-related symptoms pose to masculine identity could negatively impact on men's psychological wellbeing. Research exploring inter-relations between ADT, feelings of loss of masculinity and survivors' psychological wellbeing would shed further light on this issue.

As far as we are aware, this is the first study to report associations between urinary symptoms and psychological wellbeing. People with incontinence issues may fear urine leakage or smelling of urine and find using incontinence pads humiliating [31]. In prostate cancer survivors, these concerns and feelings may lead them to withdraw from social situations, and this isolation may, in turn, result in anxiety and depression [29]. This provides a potential explanation for our findings.

Sexual activity was the only subscale where a higher score (i.e. worse/poorer sexual activity) was related to lower risk of poor wellbeing. The explanation for this intriguing finding is not obvious. The QLQ-PR25 sexual activity subscale asks about interest in sex and the extent to which the respondent was sexually active in the past week, with less interest and less activity resulting in higher scores. Loss of interest in sex is a common sequelae of depression in older individuals, so men with depression would be expected to score more highly on the sexual activity subscale—which is inconsistent with our results. Greater loss of sexual desire has been associated with help-seeking for sexual problems after prostate cancer [32]. Men with poor psychological wellbeing may have more often sought and received supportive care or medications for sexual problems, leading them to have lower (i.e. 'better') sexual activity scores, but we cannot confirm this from our data.

After adjusting for cancer-related symptoms, treatment for depression following prostate cancer diagnosis and comorbidities at diagnosis were the only significant clinical predictors of psychological wellbeing. The positive association between comorbidities and anxiety on the DASS scale is consistent with a recent study of 377 mainly short-term prostate cancer survivors treated by radiotherapy [33]. Our findings extend these by showing that the association holds in longer-term survivors treated by a range of different modalities. Together, the studies highlight the need for health professionals to be alert to the heightened risk of poor psychological health in men with comorbidities. Similar, as regards previous treatment for depression and current risk of depression on the DASS scale, our findings confirm and extend those from a small series of 45 prostate cancer patients receiving ADT [34]. While perhaps an unsurprising finding, the strength of the associations in the current study suggests that it has important implications for development of strategies for psychological support for survivors.

Although the effect was attenuated after considering cancer-related symptoms, in the core models risk of depression or anxiety on the DASS scales was higher in unmarried than married men. In terms of explanations, being married is associated with less loneliness and more social support [35,36] and loneliness and lack of social support have been related to poorer mental health among cancer survivors [37,38]. More generally, better understanding is needed for what underlies reported associations between socio-demographic factors and survivors' psychological wellbeing to inform development of psychological support services.

Prevalence of depression, anxiety and distress

Although studies have used different measures of psychological wellbeing and included different patient/survivor groups, the percentages with depression, anxiety or distress on the DASS scales in this study are broadly compatible with previous studies of prostate cancer patients on- and post-treatment [5]. This study adds information on longer-term prostate cancer survivors who have not previously been well studied. Moreover, of the men who completed all three DASS scales, 7.7% scored in the ranges for depression, anxiety and distress suggesting that this group may be in particular need of intervention or support.

Strengths and limitations

We considered a range of general and prostate-specific cancer-related symptoms, permitting us to investigate whether associations with an individual symptom persisted when adjusted for other symptoms; this is important because symptoms often occur simultaneously [39]. Although we identified subjects from population-based cancer registries, the number of participants was large, and we used well-validated measures of symptoms and wellbeing, the 54% response rate is a limitation. Compared to non-respondents, respondents were younger, diagnosed more recently and more often had cancer which was staged and graded. Among respondents, those who completed the DASS-21 and those who did not differed; respondents who did not complete the DASS-21 slightly more often stated that they had been treated for depression since diagnosis, suggesting that we may have underestimated prevalence of depression, anxiety and distress among survivors. Although we collected information on treatment for depression post-diagnosis, we did not know anything about psychological health pre-diagnosis. Nor did we have information on other psychological variables which impact psychological wellbeing, such as coping style or relationship satisfaction. In addition, the design was cross-sectional and, while we chose to analyse symptoms as predictors of psychological wellbeing, the

DOI: 10.1002/pon

possibility cannot be excluded that poor psychological health may predict higher actual or perceived symptom burden. Finally, scoring in the range for anxiety, depression or distress on the DASS-21 does not necessarily indicate presence of a clinically significant condition; and GAD and MDD were not assessed.

Implications

The potential importance of the findings of this study is underlined by the fact that medications, supports and interventions are available to manage many of the general and prostate-specific symptoms which were associated with psychological wellbeing. For example, the options for managing prostate cancer-related sexual problems include psychosexual therapy and counselling, phosphodiesterase type 5 inhibitors, vacuum erection devices and intracorporeal injections [14]; physical activity, psychosocial interventions and pharmacological agents may be beneficial for treating cancer-related fatigue [15]; incontinence may be treated with the transobturator sling or, potentially, oral medicines [40] and ADT-related symptoms such as hot flashes can respond to lifestyle changes, acupuncture or pharmacological agents [10]. However, these supports and interventions appear under-utilised [14–18]. Our findings suggest that placing a greater focus on identifying men with higher levels of cancer-related symptoms (perhaps through 'screening' for these at follow-up clinics or appointments), and more widespread provision of interventions to treat these symptoms, might help alleviate the psychological burden. As indicated by the lack of variation in prevalence of depression, anxiety and distress by time since diagnosis, this screening and intervention is likely to be needed throughout the survivorship continuum.

Conclusions

General cancer and prostate cancer-specific symptoms are significant predictors of psychological wellbeing among prostate cancer survivors. Greater attention should be paid to identifying and supporting survivors with a greater symptom burden; this may serve to improve psychological wellbeing among the growing population of prostate cancer survivors.

Acknowledgements

The study was funded by grants from the Health Research Board (HRA_HSR/2010/17), Prostate Cancer UK (NI09-03 & NI-PG13-001) and Northern Ireland R&D. The RoI National Cancer Control Programme provided additional support. The National Cancer Registry Ireland is funded by the Department of Health and the Northern Ireland Cancer Registry by the Public Health Agency, Northern Ireland. The authors thank the healthcare professionals who facilitated the study; members of Men Against Cancer (MAC) and local cancer support groups who assisted with survey pre-testing; Joanne Clooney, Claire O'Callaghan and Audrey Craven-Lynn for survey administration and clerical support; David Donnelly for statistical support; Jenalee Kennedy, Patricia McDowell and Jonathan Mitchell for data entry; Sandra Deady and Colin Fox for providing cancer registration data; registration, data and IT staff in the registries; and, most importantly, the men who participated. We also thank the study Steering Group for advice and input.

Conflict of interest

LS received an unrestricted project grant in 2011–2012 from Sanofi-aventis for research into the predictors of treatment receipt and survival in prostate cancer. None of the other authors have any conflicts of interest to declare.

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