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Factors associated with current and severe physical side-effects after prostate cancer treatment: What men report

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We identified patient and disease characteristics associated with (1) "current" physical side-effects of any severity; and (2) "severe" physical side-effects "ever" experienced by 3,348 (54%) prostate cancer (PCa) survivors in Ireland diagnosed 2–18 years previously. Postal questionnaires collected symptoms at diagnosis, post-biopsy complications, comorbidities, primary treatments and physical side-effects post-treatment (urinary incontinence, erectile dysfunction, libido loss, bowel problems, breast changes, hot flushes, and fatigue, "ever" and "current" at time of questionnaire completion). Men were grouped by "early" (localised) and "late" (locally advanced/advanced) disease at diagnosis. Multivariable logistic regression analysis identified patient and disease-related factors associated with post-treatment side-effects. Complications post-biopsy were associated with higher risk of "current" libido loss and impotence. Radical prostatectomy was associated with higher risk of "current" and "severe" incontinence, libido loss and impotence in both early and late disease. In early disease, brachytherapy was associated with lower risk of "current" fatigue and "severe" impotence. Comorbidities were associated with higher risk of "current" experience of four side-effects (incontinence, libido loss, bowel problems, fatigue). Men on active surveillance/watchful-waiting reported lower risk of sexual dysfunction. These findings could inform development of tailored information on side-effects, which, in turn, could inform treatment decision-making and post-treatment monitoring.

KEYWORDS
decision-making process, physical effects, PiCture study, prostate cancer, side-effects

1 | INTRODUCTION

Prostate cancer (PCa) is the second most commonly diagnosed cancer among men worldwide and mortality rates have been decreasing in most western countries (International Agency for Research on Cancer, 2012; Jemal, Center, Desantis, & Ward, 2010). This, with increased incidence, has resulted in a rise in prevalence (International Agency for Research on Cancer, 2012; Jemal et al., 2010).

Recommended clinical strategies for early (localised) PCa are radical prostatectomy (RP) or external beam radiotherapy (EBRT). For selected men, brachytherapy (BT), active surveillance (AS) and watchful-waiting (WW) are also suitable. AS; for example, can be used for men who may not yet benefit from definitive treatment (Mottet et al., 2015). Appropriate strategies for locally advanced and advanced disease are hormone therapy (HT), EBRT and WW. RP is appropriate for a highly selected group of men with locally advanced disease (Mottet et al., 2015).

While randomised controlled trials of treatment have been conducted, and there is little strong evidence that any of the treatment

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yield survival benefits over the other (Heidenreich et al., 2008; King et al., 2012; Wagner, Boelling, Hambruegge, Hartlapp, & Krukemeyer, 2011; Wilt & Ahmed, 2013). PCa treatment decisions are based on the consultation between the patient and the physician, aiming to find the best fit to the patient's personal and clinical characteristics (e.g. disease extent at diagnosis (Talcott et al., 2003; Wagner et al., 2011)). Patient preference should also be considered. All treatments for PCa carry a significant risk of side-effects and this information may play a role in the treatment decision. In a recent analysis, undertaken by the authors, of 3,348 PCa survivors, at least a 2 years post-diagnosis, 90% of men reported "ever" experienced at least one physical side-effect of treatment. In addition, 75% of men reported at least one "current" physical symptom (Gavin et al., 2015). The most common side-effects after PCa treatment are sexual dysfunction (in particular erectile dysfunction and libido loss) urinary incontinence, and bowel problems (Darwish-Yassine et al., 2014; King et al., 2012; Miller et al., 2005; Potosky et al., 2004).

Treatment-related side-effects or symptoms affect the health-related quality of life of PCa patients/survivors (Drummond, Kinnear, O'leary, et al., 2015). Thus, it would be valuable to identify what factors, if any, are associated with these side-effects. This information could be used to support and inform treatment decision-making, help prepare patients for what they can expect after their treatment and also facilitate post-treatment follow-up and monitoring by helping to determine if the patient is likely to need specific support or interventions to alleviate side-effects. Several factors associated with side-effects have been identified; treatment modality, age, comorbidities, pre-treatment function (e.g. already experiencing urinary incontinence) and the D'Amico risk groups based on Gleason score and Prostate Specific Antigen (PSA) level (Chen, Clark, & Talcott, 2009; D'Amico et al., 1998; Darwish-Yassine et al., 2014; Hoffman, 2012; Nam et al., 2014; Potosky et al., 2004; Sanda et al., 2008; Talcott et al., 2003). However, the majority of these studies focused on one specific side-effect with most of the data limited to urinary incontinence, sexual dysfunction and/or bowel problems and were restricted to the United States or Canada or health-care system. Little is known about other physical effects, such as hot flushes and fatigue, and their associated factors. Moreover, although, men are more likely to make decisions about treatment based on the possibility of severe, rather than milder side-effects (King et al., 2012), little is known about what factors are associated with either higher or lower risk of experiencing severe side-effects.

Therefore, the aim of this study was to identify patient-related factors and disease-related characteristics associated with a range of current and ever experienced severe, physical side-effects among PCa survivors diagnosed with either early or late disease in a population-based data set of PCa survivors across two jurisdiction, which operate under different health systems.

2 | METHODS

2.1 | Survivors

The study took place in the two countries on the island of Ireland—the Republic of Ireland (RoI) and Northern Ireland (NI). In both countries men were recruited with the same approach; full details are reported elsewhere (Drummond, Kinnear, Donnelly, et al., 2015). In brief, all men diagnosed with invasive PCa, between 1st January 1995 and 31st March 2010, were identified from the National Cancer Registry Ireland (NCRI) in RoI (n = 17,304) and the Northern Ireland Cancer Registry (NICR; n = 5,519) in November 2011. In both jurisdictions, a stratified random sample of 54% of all survivors (n = 12,322) was selected to ensure approximately equal numbers of survivors at <5 and >5 years post-diagnosis. Survivors were screened for eligibility by health care providers, general practitioners in the RoI and urology clinical nurses in NI. Eligible men had to be: (1) alive; (2) aware of their PCa diagnosis; (3) well enough to complete a survey; (4) usually a resident of RoI/NI and (5) able to understand English. Subsequently, 6,262 PCa survivors were considered eligible following questionnaire dispatch of whom 3,348 participated by completing the survey, a response rate of 54%.

2.2 | Survey

The focus of this study was on men's self-reported physical side-effects after treatment. Two measures of physical side-effects were considered: "current" side-effects of any severity (i.e. at time of survey completion) and "severe" side-effects "ever" experienced (i.e. at any time since diagnosis and treatment for PCa). Survivors were asked to provide information about the experience of seven potential treatment-related side-effects: urinary incontinence, erectile dysfunction, libido loss, bowel problems, breast changes, hot flushes, and fatigue. They were asked to indicate whether they had ever experienced each side-effect and, if so, how severe the symptoms were at their worst (from 1 [very mild] up to 5 [very severe]) and whether they were currently experiencing the side-effect. Men were also asked to report all treatments received, including dates of commencement and completion for each treatment, and to provide information on their socio-demographic characteristics. Men were asked to indicate whether they had pre-treatment symptoms regarding urinary (increased frequency, pain urinating, blood in urine), bowel (diarrhoea, constipation) and/or sexual (erectile dysfunction) function. Additionally, they were asked to signify which comorbidities, if any, were present at diagnosis from a list of conditions (heart or lung disease, stroke, diabetes, high blood pressure, diverticular disease, bowel problems (e.g. constipation/diarrhoea), other cancer, depression or other) and, if they had a biopsy, whether they experienced any possibly related complications (bleeding into bladder/rectum and infection).

Surveys were posted to eligible men between April and September 2012. Up to two written reminders at two weekly intervals, with a second copy of the survey in the second reminder, were sent to non-responders.

2.3 | Cancer registry data

For respondents, information on date of diagnosis, stage at diagnosis (TNM classification) and Gleason Grade (GG) was extracted from the cancer registries. The NCRI collected GG as a categorical variable; low

(GG 2-4), medium (GG 5-7) or high grade (GG 8-10). Data on survivors in NI, diagnosed in early years, had low completeness of staging therefore supplementary staging information was abstracted from medical records of responders.

2.4 | Ethical approval

All procedures were in accordance with the ethical standards of the Irish College of General Practitioners, the Office for Research Ethics Committee NI and with the 1964 Helsinki Declaration and its later amendments. Research governance approval was obtained from the five NI Health Trusts. Informed consent was obtained from all individual participants included in the study through return of completed questionnaires and/or consent forms.

2.5 | Statistical analysis

Respondents were grouped into localised disease and locally advanced/advanced disease for analysis. Localised disease consisted of survivors with stage I/II and GG 2-7 at diagnosis, labelled as early disease (n = 1,700). Locally advanced/advanced disease survivors had stage III/IV and any GG at diagnosis, labelled as late disease (n = 689). Survivors with other combinations of stage and GG, or unknown stage or GG, were excluded from analysis (n = 959) leaving 2,389 PCa survivors for analysis.

Outcome variables were the seven physical side-effects investigated. Separate analyses were conducted for side-effects experienced currently and severe side-effects ever experienced. Potential explanatory variables were; age at diagnosis (<59/60–69/≥70 years), comorbidities at diagnosis (none/1–2/≥3), highest level of education completed (primary/secondary/≥tertiary), jurisdiction (RoI/NI), living alone (living alone/living with others), time since diagnosis (2–5/5–10/>10 years), pre-treatment function (urinating more frequently, pain while urinating, blood in urine, erectile dysfunction, loss of interest in sex and back pain [all no/yes]), complications after biopsy (bleeding into bladder/rectum/infection (no biopsy/yes/no), TURPs, no complications after biopsy (no biopsy/yes/no) and treatment "ever" had (RP, EBRT, HT, BT, AS/WW). HT was coded as having the treatment "previously," "currently" and "never"; other treatments were coded as received "yes" or "no."

Univariate and multivariate analyses were performed in the form of logistic regression to identify factors associated with (1) "current" side-effects of any severity and (2) "severe side-effects ever experienced." Analyses were weighted by age at diagnosis, jurisdiction, and time since diagnosis to assure representativeness for all PCa survivors in Ireland. A severe side-effect was defined as one that the survivor reported as severe or very severe at its worst. Multivariate analysis was performed initially including all variables which had a $p \leq 0.10$ in univariate analysis. Subsequently, backward selection was used to build the multivariate models with the $p \leq 0.05$ used as the criterion to include the variable in the model. Correlation between the variables included in the model was also assessed to ensure that collinearity was not an issue with the final models. Model goodness-of-fit of the different models were investigated with help of the Nagelkerke R^2 and the Hosmer–Lemeshow test. Missing data in explanatory variables were handled with a fully conditional specification multiple imputation method with five imputations and weighted for all PCa survivors in the population (n = 22,823). Missing data in outcome variables were coded as "never had the side-effect."

In addition, sensitivity analysis was performed for two "current" side-effects (urinary incontinence and erectile dysfunction) and early and late disease to explore the impact of the imputation of missing data. This was addressed by comparing the factors associated with the side-effect in the original data set with those obtained in analysis of the pooled data set generated by the multiple imputation method keeping the rest constant. The statistical analysis was carried out in SPSS version 20.

3 | RESULTS

3.1 | Survivors

Characteristics of the survivors and differences between early disease and late disease are shown in Table 1. Time since diagnosis, age at diagnosis, living alone and highest educational level achieved were equally distributed in early and late disease groups. In terms of treatment, HT (early: 33% vs. late: 66%) and EBRT (53% vs. 70%) were more common in the late disease group and BT (7% vs. 2%) and AS/WW (6% vs. 1%) were more common in the early disease group. Reasons for non-participation were administrative issues, queries regarding questionnaire content, being unaware of their PCa diagnosis or having data protection issues (Drummond, Kinnear, Donnelly, et al., 2015).

3.2 | Prevalence of side-effects

Prevalence of side-effects are shown in Figure 1A (early disease) and 1B (late disease). The prevalence of both "current" and "severe side-effects ever experienced" were higher in the late disease group. For "current" side-effects, the greatest difference were in; loss of libido (early: 42.4% vs. late: 57.0%), hot flushes (8.8% early vs. 27.9% late) and fatigue (18.8% early vs. 30.5% late). The biggest differences in the occurrence of "severe" side-effects between those with early and late disease were loss of libido (25.8% early vs. 41.0% late), impotence (39.6% early vs. 52.7% late) and fatigue (16.1% early vs. 29.1% late).

3.3 | Factors associated with "current" side-effects in early disease

Factors significantly associated in multivariate analyses with "current" physical side-effects in early disease are presented in Table 2. Living with others was associated with a higher risk of "current" loss of libido (multivariate OR = 1.56; 95% CI: 1.13–2.11) and impotence (1.39; 1.01–1.91). Higher education was associated with a higher risk of erectile dysfunction and associated with a lower risk of hot flushes and fatigue. Being ≥10 years post-diagnosis was associated

TABLE 1 Characteristics of the survivors, overall and for early and late disease[a,b]

Variable	All survey participants (*n* = 3,348)[d]	Early disease (*n* = 1,700)	Late disease (*n* = 689)
Jurisdiction			
Republic of Ireland	2567 (76.7)	1431 (84.2)	407 (59.0)
Northern Ireland	781 (23.3)	269 (15.8)	282 (41.0)
Time since diagnosis at questionnaire completion			
2–4.99 years	1391 (76.7)	743 (43.7)	322 (46.7)
5–9.99 years	781 (23.3)	745 (43.8)	274 (39.8)
≥10 years	522 (15.6)	212 (12.5)	93 (13.5)
Age at diagnosis			
<59	721 (21.5)	420 (24.7)	147 (21.3)
60–69	1484 (44.3)	796 (46.8)	311 (45.1)
≥70	1143 (34.1)	484 (28.5)	232 (33.6)
Living alone			
Living alone	434 (13.0)	210 (12.4)	88 (12.7)
Living with others	2863 (85.5)	1463 (86.0)	593 (86.0)
Education			
Primary	1203 (35.9)	542 (31.9)	276 (40.0)
Secondary	1139 (34)	629 (37.0)	218 (31.6)
Tertiary or higher	860 (25.7)	452 (26.6)	178 (25.8)
Pre-treatment function			
Urinating more frequently	1708 (51.0)	830 (48.8)	348 (50.5)
Pain while urinating	256 (7.7)	101 (5.9)	56 (8.1)
Blood in urine	232 (6.9)	91 (5.4)	55 (8.0)
Erectile dysfunction	626 (18.7)	302 (17.8)	142 (20.6)
Loss of interest in sex	496 (14.8)	235 (13.8)	118 (17.2)
Back pain	498 (14.9)	227 (13.3)	134 (19.4)
Number of comorbidities			
None	1458 (43.5)	754 (44.4)	307 (44.5)
1–2	1682 (50.2)	863 (50.8)	324 (47.0)
3 or more	208 (6.2)	83 (4.9)	58 (8.5)
Biopsy complications			
No biopsy	367 (11)	139 (8.2)	79 (11.4)
Biopsy & bleeding into bladder	284 (8.5)	161 (9.5)	49 (7.1)
Biopsy & bleeding into rectum	203 (6.1)	102 (6.0)	36 (5.5)
Biopsy & infection	145 (4.3)	85 (5.0)	24 (3.5)
Biopsy & no complications	539 (16.1)	194 (11.4)	190 (27.5)
TURP	298 (8.9)	120 (7.1)	46 (6.7)
Treatment[c]			
Radical prostatectomy	842 (25.1)	503 (29.6)	181 (26.3)
External beam radiotherapy	1930 (57.6)	910 (53.5)	484 (70.3)
Hormone therapy			
No hormone therapy	1454 (43.4)	935 (55.0)	182 (26.4)
Previous hormone therapy	888 (26.5)	402 (23.7)	246 (35.6)
Current hormone therapy	632 (18.9)	159 (9.3)	214 (31.0)
Brachytherapy	184 (5.5)	119 (7.0)	13 (1.9)
Active surveillance/watchful-waiting	165 (4.9)	100 (5.9)	6 (0.8)

[a]Variables are weighted by age at diagnosis, jurisdiction and time since diagnosis to be representative of the entire PCa survivor population in Ireland.
[b]Localised disease is labelled as early disease, locally advanced/advanced disease is labelled as late disease.
[c]Patients could have had more than one treatment, so percentages for each treatment do not sum to 100%.
[d]Includes 959 survivors not classified as having early or late disease, largely because of unknown stage or grade.

with a lower risk of fatigue (0.55; 0.35–0.85) and being 5–10 years post-diagnosis was associated with a lower risk of hot flushes (0.60; 0.39–0.92). Living in NI was associated with higher risk of loss of libido, bowel problems and fatigue.

Treatments were associated with a higher risk of "current" side-effects. RP was associated with a higher risk of urinary incontinence (3.03; 2.28–4.03), loss of libido (1.72; 1.33–2.22) and erectile dysfunction (3.30; 2.56–4.23). EBRT was associated with a higher risk of bowel problems (3.35; 2.38–4.71) and hot flushes (1.93; 1.15–3.22). Any HT (previously and currently) was associated with a higher risk of loss of libido, breast changes and hot flushes while currently receiving HT was associated with a higher risk of fatigue (2.16; 1.44–3.26). BT was associated with a lower risk of fatigue (0.46; 0.24–0.89). AS/WW was associated with a lower risk of urinary incontinence (0.40; 0.16–0.99), loss of libido (0.37; 0.21–0.65), impotence (0.21; 0.12–0.34) and fatigue (0.16; 0.05–0.46).

Health at diagnosis was associated with a risk of "current" side-effects. Urinating more frequently was associated with urinary incontinence (1.72; 1.25–2.35), bowel problems (1.48; 1.08–2.02) and fatigue (1.45; 1.09–1.92). Loss of interest in sex was associated with a higher risk of loss of libido (1.79; 1.26–2.55). Post-treatment erectile dysfunction was associated with a higher risk of post-treatment loss of libido and erectile dysfunction. Back pain was associated with a higher risk of fatigue (1.78; 1.24–2.57). Multiple (>3) comorbidities at diagnosis was associated with a higher risk of urinary incontinence (2.34; 1.34–4.09), loss of libido (1.68; 1.03–2.75), bowel problems (3.29; 1.88–5.76) and fatigue (2.07; 1.21–3.53). Complications post-biopsy, in particular bleeding into the bladder, was associated with a higher risk of bowel problems (2.32; 1.08–4.96). Bleeding into the rectum was associated with a higher risk of breast changes (5.19; 1.76–15.29). Experiencing complications post-biopsy was associated with a higher risk of impotence (1.72; 1.17–2.54) and loss of libido (1.55; 1.05–2.31).

3.4 | Factors associated with "severe side-effects ever experienced" in early disease

Table 2 shows the factors significantly associated, in multivariate analyses, with ever experiencing severe side-effects in early disease. Older age at diagnosis, especially being ≥70 years, was associated with a lower risk of loss of libido (0.48; 0.33–0.68) and impotence (0.71; 0.51–1.00). Higher education was associated with a higher risk of impotence and lower risk of hot flushes and fatigue. Being ≥10 years or more post-diagnosis was associated with a lower risk of fatigue (0.48; 0.28–0.82). Living in NI was associated with a higher risk of loss of libido, hot flushes and fatigue.

RP was associated with a higher risk of urinary incontinence, loss of libido, impotence, hot flushes and fatigue. EBRT was associated with a higher risk of bowel problems, hot flushes and fatigue. Previous and current HT was associated with a higher risk of loss of libido, breast changes, hot flushes and fatigue. BT was associated with a lower risk of impotence. AS/WW was associated with a lower risk of loss of libido and impotence.

Loss of interest in sex pre-treatment was associated with a higher risk of loss of libido (2.00; 1.43–2.78). Pre-treatment erectile dysfunction was associated with a higher risk of erectile dysfunction (1.62; 1.19–2.20). Back pain was associated with a higher risk of hot flushes

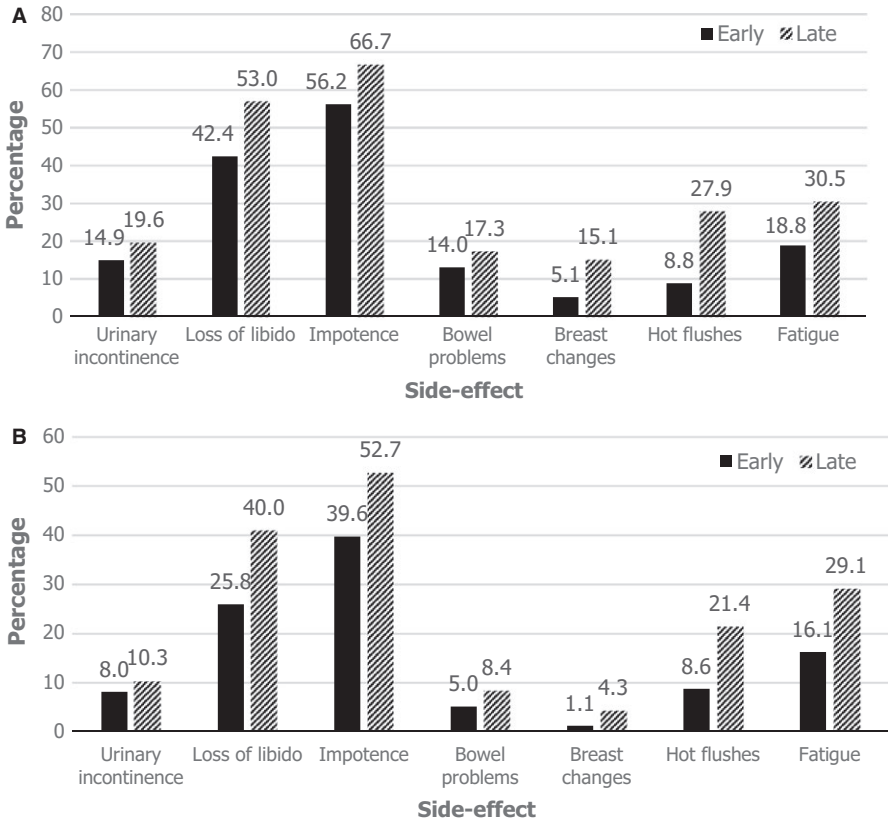

FIGURE 1 (A) "Current" side-effects in early and late disease (%). (B) "Severe side-effects ever experienced" in early and late disease (%)

TABLE 2 Multivariate analysis: factors significantly associated with current and severe side-effects in early disease[a,b]

	Current side-effects			Severe side-effects ever experienced		
Side-effect	**Variable**		**OR (95% CI)**	**Variable**		**OR (95% CI)**
Urinary incontinence	Radical prostatectomy	No	1.00	Radical prostatectomy	No	1.00
		Yes	3.03 (2.28–4.03)		Yes	3.62 (2.39–5.49)
	Comorbidities at diagnosis	None	1.00	Age at diagnosis	<59	1.00
		1–2	1.29 (0.96–1.72)		60–69	0.59 (0.39–0.88)*
		≥3	2.34 (1.34–4.09)*		≥70	0.68 (0.38–1.20)
	Active surveillance/ watchful-waiting	No	1.00			
		Yes	0.40 (0.16–0.99)			
	Urinating more frequently at diagnosis	No	1.00			
		Yes	1.72 (1.25–2.35)			
Loss of libido	Hormone therapy	Never	1.00	Hormone therapy	Never	1.00
		Previously	1.56 (1.19–2.05)		Previously	2.17 (1.58–2.98)
		Currently	2.24 (1.54–3.28)		Currently	2.53 (1.70–3.76)
	Jurisdiction	RoI	1.00	Jurisdiction	RoI	1.00
		NI	1.73 (1.05–2.86)		NI	1.43 (1.05–1.96)
	Impotence/erectile dysfunction at diagnosis	No	1.00	Age at diagnosis	<59	1.00
		Yes	1.47 (1.09–1.98)		60–69	0.81 (0.61–1.07)
	Radical prostatectomy	No	1.00		≥70	0.48 (0.33–0.68)*
		Yes	1.72 (1.33–2.22)	Radical prostatectomy	No	1.00
	Active surveillance/ watchful-waiting	No	1.00		Yes	1.51 (1.11–2.05)
		Yes	0.37 (0.21–0.65)	Active surveillance/ watchful-waiting	No	1.00
	Living alone	Alone	1.00		Yes	0.28 (0.10–0.46)
		With others	1.56 (1.13–2.11)	Loss of interest in sex at diagnosis	No	1.00
	Loss of interest in sex at diagnosis	No	1.00		Yes	2.00 (1.43–2.78)
		Yes	1.79 (1.26–2.55			
	Comorbidities at diagnosis	None	1.00			
		1–2	1.13 (0.91–1.40)			
		≥3	1.68 (1.03–2.75)*			
	No complications after biopsy	No biopsy	1.00			
		Yes	1.18 (0.62–2.26)			
		No	1.55 (1.05–2.31)*			
Erectile dysfunction	Radical prostatectomy	No	1.00	Radical prostatectomy	No	1.00
		Yes	3.30 (2.56–4.23)		Yes	2.56 (1.99–3.31)
	Active surveillance/ watchful-waiting	No	1.00	Age at diagnosis	<59	1.00
		Yes	0.21 (0.12–0.34)		60–69	1.00 (0.77–1.31)
	Living alone	Alone	1.00		≥70	0.71 (0.51–1.00)*
		With others	1.39 (1.01–1.91)	Education	Primary	1.00
	Education	Primary	1.00		Secondary	1.33 (1.02–1.72)
		Secondary	1.67 (1.29–2.16)		≥Tertiary	1.52 (1.14–2.02)
		≥Tertiary	1.67 (1.25–2.24)	Brachytherapy	No	1.00
	Erectile dysfunction at diagnosis	No	1.00		Yes	0.59 (0.38–0.92)
		Yes	1.96 (1.45–2.66)	Active surveillance/ watchful-waiting	No	1.00
	No complications after biopsy	No biopsy	1.00		Yes	0.13 (0.06–0.28)
		Yes	2.35 (1.46–3.78)	Urinating more frequently at diagnosis	No	1.00
		No	1.72 (1.17–2.54)		Yes	0.78 (0.62–0.98)
				Impotence/erectile dysfunction at diagnosis	No	1.00
					Yes	1.62 (1.19–2.20)
				Bleeding into bladder after biopsy	No biopsy	1.00
					Yes	2.25 (1.33–3.81)
					No	1.50 (1.00–2.25)

(Continues)

TABLE 2 (Continued)

	Current side-effects			Severe side-effects ever experienced		
Side-effect	**Variable**		**OR (95% CI)**	**Variable**		**OR (95% CI)**
Bowel problems	External beam radiotherapy	No	1.00	External beam radiotherapy	No	1.00
		Yes	3.35 (2.38–4.71)		Yes	2.25 (1.37–3.72)
	Comorbidities at diagnosis	None	1.00	Comorbidities at diagnosis	None	1.00
		1–2	1.20 (0.87–1.64)		1–2	1.28 (0.80–2.04)
		≥3	3.29 (1.88–5.76)*		≥3	2.80 (1.22–6.43)*
	Jurisdiction	RoI	1.00			
		NI	1.72 (1.21–2.45)			
	Urinating more frequently at diagnosis	No	1.00			
		Yes	1.48 (1.08–2.02)			
	Bleeding into bladder after biopsy	No biopsy	1.00			
		Yes	2.32 (1.08–4.96)*			
		No	1.42 (0.70–2.89)			
Breast changes	Hormone therapy	Never	1.00	Hormone therapy	Never	1.00
		Previously	3.80 (1.93–7.46)		Previously	4.27 (1.20–15.22)
		Currently	8.79 (4.45–17.36)		Currently	11.69 (3.29–41.53)
	Radical prostatectomy	No	1.00			
		Yes	0.33 (0.13–0.85)			
	Bleeding into rectum after biopsy	No biopsy	1.00			
		Yes	5.19 (1.76–15.29)*			
		No	1.43 (0.52–3.91)			
Hot flushes	Hormone therapy	Never	1.00	Hormone therapy	Never	1.00
		Previously	3.63 (2.04–6.44)		Previously	12.13 (6.19–23.76)
		Currently	34.61 (19.13–62.63)		Currently	14.23 (7.29–27.78)
	Time since diagnosis at survey completion	2–4.99	1.00	Jurisdiction	RoI	1.00
		5–9.99	0.60 (0.39–0.92)*		NI	1.81 (1.18–2.76)
		≥10	0.77 (0.42–1.39)	Radical prostatectomy	No	1.00
	External beam radiotherapy	No	1.00		Yes	2.45 (1.26–4.75)
		Yes	1.93 (1.15–3.22)	External beam radiotherapy	No	1.00
	Education	Primary	1.00		Yes	3.20 (1.85–5.55)
		Secondary	0.62 (0.40–0.98)	Education	Primary	1.00
		≥Tertiary	0.49 (0.28–0.84)		Secondary	0.90 (0.59–1.38)
					≥Tertiary	0.59 (0.36–0.99)*
				Back pain at diagnosis	No	1.00
					Yes	1.72 (1.02–2.89)
Fatigue	Hormone therapy	Never	1.00	Hormone therapy	Never	1.00
		Previously	1.13 (0.83–1.54)		Previously	4.60 (3.06–6.91)
		Currently	2.16 (1.44–3.26)*		Currently	4.91 (2.87–8.40)
	Jurisdiction	RoI	1.00	Jurisdiction	RoI	1.00
		NI	2.01 (1.43–2.82)		NI	1.68 (1.18–2.40)
	Time since diagnosis at survey completion	2–4.99	1.00	Radical prostatectomy	No	1.00
		5–9.99	0.84 (0.64–1.11)		Yes	3.07 (2.00–4.71)
		≥10	0.55 (0.35–0.85)*	External beam radiotherapy	No	1.00
	Urinating more frequently at diagnosis	No	1.00		Yes	2.51 (1.71–3.68)
		Yes	1.45 (1.09–1.92)	Time since diagnosis at survey completion	2–4.99	1.00
	Back pain at diagnosis	No	1.00		5–9.99	1.23 (0.92–1.66)
		Yes	1.78 (1.24–2.57)		≥10	0.48 (0.28–0.82)*

(Continues)

TABLE 2 (Continued)

Side-effect	Current side-effects			Severe side-effects ever experienced		
	Variable		OR (95% CI)	Variable		OR (95% CI)
	Comorbidities at diagnosis	None	1.00	Education	Primary	1.00
		1–2	1.18 (0.89–1.55)		Secondary	0.86 (0.62–1.20)
		≥3	2.07 (1.21–3.53)*		≥Tertiary	0.58 (0.39–0.85)*
	Brachytherapy	No	1.00	Back pain at diagnosis	No	1.00
		Yes	0.46 (0.24–0.89)		Yes	1.53 (1.13–2.08)
	Active surveillance/ watchful-waiting	No	1.00			
		Yes	0.16 (0.05–0.46)			
	Education	Primary	1.00			
		Secondary	0.84 (0.62–1.14)			
		≥Tertiary	0.57 (0.40–0.81)*			

NI, Northern Ireland; RoI, Republic of Ireland.
[a]Weighted by age at diagnosis, jurisdiction and time since diagnosis to assure representativeness for all PCa survivors in Ireland.
[b]Localised disease is labelled as early disease, locally advanced/advanced disease is labelled as late disease.
*$p < 0.05$.

(1.72; 1.02–2.89) and fatigue (1.53; 1.13–2.08). Presence of multiple comorbidities at diagnosis was only associated with a higher risk of bowel problems (2.80; 1.22–6.43). Complications post-biopsy, especially bleeding into the bladder, was associated with a higher risk of impotence (2.25; 1.33–3.81).

3.5 | Factors associated with "current" side-effects in late disease

Table 3 indicates the factors which were significantly associated, in multivariate analyses, with "current" side-effects in late disease PCa. Older age at diagnosis, was associated with a lower risk of impotence, hot flushes and fatigue. Living with others and higher education were associated with a higher risk of impotence. Being >5 years post-diagnosis was associated with a lower risk of hot flushes and fatigue. Living in NI was associated with a higher risk of loss of libido, breast changes, hot flushes and fatigue.

RP was associated with a higher risk of urinary incontinence (4.45; 2.97–6.66) and erectile dysfunction (1.89; 1.18–3.04). EBRT was associated with a higher risk of bowel problems (2.66; 1.50–4.73) and breast changes (2.06; 1.13–3.78). Any HT was associated with a higher risk of loss of libido, bowel problems, breast changes and hot flushes. Currently receiving HT was associated with a higher risk of fatigue (2.33; 1.36–3.99). AS/WW was associated with a lower risk of erectile dysfunction (0.03; 0.00–0.62).

Urinating more frequently (1.66; 1.14–2.40) and back pain (1.76; 1.16–2.67) pre-treatment were associated with a higher risk of fatigue. Pre-treatment erectile dysfunction was associated with a higher risk of loss of libido (2.02; 1.36–3.01) and erectile dysfunction (1.87; 1.19–2.96). Having comorbidities at diagnosis was associated with a higher risk of urinary incontinence, bowel problems and fatigue. Bleeding into the rectum post-biopsy was associated with loss of libido (2.48; 1.06–5.83). Infection post-biopsy was associated with a higher risk of breast changes (3.17; 1.06–9.49). Having complications post-biopsy was also associated with a higher risk of erectile dysfunction (1.87; 1.10–3.18).

3.6 | Factors associated with "severe side-effects ever experienced" in late disease

Factors significantly associated in multivariate analyses with "severe side-effects ever experienced" are shown in Table 3. Older age at diagnosis was associated with a lower risk of erectile dysfunction, breast changes, hot flushes, fatigue and loss of libido. Living with others and a higher level of education were associated with higher risk of impotence. Living in NI was associated with a higher risk of loss of libido, erectile dysfunction, hot flushes and fatigue.

RP was associated with higher risk of urinary incontinence (4.47; 2.60–7.67) and erectile dysfunction (3.70; 2.15–6.36). EBRT was associated with a higher risk of bowel problems (5.46; 2.09–14.32). Any HT was associated with higher risk of loss of libido, hot flushes and fatigue. Previously receiving HT was associated with a higher risk of erectile dysfunction (1.81; 1.02–3.20).

Pre-treatment erectile dysfunction was associated with a higher risk of loss of libido (1.97; 1.36–2.84). Multiple comorbidities at diagnosis were associated with a higher risk of fatigue and bowel problems. Bleeding into the rectum post-biopsy was associated with hot flushes (3.02; 1.16–7.88) and fatigue (2.67; 1.12–6.36). Having complications post-biopsy was also associated with a higher risk of urinary incontinence (10.98; 1.04–115.53).

3.7 | Sensitivity analysis

There were no changes in the factors that were significantly associated with urinary incontinence between the original and pooled data sets (data not shown). For erectile dysfunction, modest differences

TABLE 3 Multivariate analysis: factors significantly associated with current and severe side-effects in late disease[a,b]

	Current side-effects			Severe side-effects ever experienced		
Side-effect	**Variable**		**OR (95% CI)**	**Variable**		**OR (95% CI)**
Urinary incontinence	Radical prostatectomy	No	1.00	Radical prostatectomy	No	1.00
		Yes	4.45 (2.97–6.66)		Yes	4.47 (2.60–7.67)
	Comorbidities at diagnosis	None	1.00	No complications after biopsy	No biopsy	1.00
		1–2	1.17 (0.77–1.79)		Yes	13.42 (1.26–143.06)
		≥3	2.27 (1.16–4.44)*		No	10.98 (1.04–115.53)
Loss of libido	Hormone therapy	Never	1.00	Hormone therapy	Never	1.00
		Previously	1.71 (1.09–2.68)		Previously	1.71 (1.09–2.69)
		Currently	3.06 (2.00–4.70)		Currently	2.33 (1.50–3.63)
	Jurisdiction	RoI	1.00	Jurisdiction	RoI	1.00
		NI	1.53 (1.08–2.17)		NI	2.02 (1.42–2.87)
	Impotence/erectile dysfunction at diagnosis	No	1.00	Age at diagnosis	<59	1.00
		Yes	2.02 (1.36–3.01)		60–69	0.83 (0.55–1.26)
	Bleeding into rectum after biopsy	No biopsy	1.00		≥70	0.34 (0.21–0.53)*
		Yes	2.48 (1.06–5.83)	Impotence/erectile dysfunction at diagnosis	No	1.00
		No	1.63 (1.01–2.65)		Yes	1.97 (1.36–2.84)
Erectile Dysfunction	Radical prostatectomy	No	1.00	Radical prostatectomy	No	1.00
		Yes	1.89 (1.18–3.04)		Yes	3.70 (2.15–6.36)
	Active surveillance/ watchful-waiting	No	1.00	Age at diagnosis	<59	1.00
		Yes	0.03 (0.00–0.62)		60–69	1.11 (0.72–1.72)
	Living alone	Alone	1.00		≥70	0.48 (0.30–0.77)*
		With others	1.63 (1.01–2.63)	Education	Primary	1.00
	Education	Primary	1.00		Secondary	1.67 (1.12–2.48)
		Secondary	1.57 (1.04–2.36)		≥Tertiary	2.31 (1.52–3.49)
		≥Tertiary	1.99 (1.29–3.09)	Hormone therapy	Never	1.00
	Erectile dysfunction at diagnosis	No	1.00		Previously	1.81 (1.02–3.20)*
		Yes	1.87 (1.19–2.96)		Currently	1.38 (0.80–2.37)
	No complications after biopsy	No biopsy	1.00	Jurisdiction	RoI	1.00
		Yes	2.07 (1.17–3.66)		NI	1.81 (1.26–2.60)
		No	1.87 (1.10–3.18)	Living alone	Alone	1.00
	Age at diagnosis	<59	1.00		With others	1.66 (1.01–2.71)
		60–69	0.99 (0.61–1.60)			
		≥70	0.50 (0.30–0.83)*			
Bowel problems	External beam radiotherapy	No	1.00	External beam radiotherapy	No	1.00
		Yes	2.66 (1.50–4.73)		Yes	5.46 (2.09–14.32)
	Comorbidities at diagnosis	None	1.00	Comorbidities at diagnosis	None	1.00
		1–2	2.07 (1.31–3.26)		1–2	2.37 (1.22–4.63)
		≥3	3.84 (1.96–7.52)		≥3	7.31 (3.15–16.92)
	Hormone therapy	Never	1.00			
		Previously	1.53 (1.11–3.78)			
		Currently	2.05 (1.31–3.26)			

(Continues)

TABLE 3 (Continued)

	Current side-effects			Severe side-effects ever experienced		
Side-effect	**Variable**		**OR (95% CI)**	**Variable**		**OR (95% CI)**
Breast changes	Hormone therapy	Never	1.00	Radical prostatectomy	No	1.00
		Previously	2.84 (1.24–6.50)		Yes	0.11 (0.05–0.24)
		Currently	5.14 (2.30–11.52)	Age at diagnosis	<59	1.00
	External beam radiotherapy	No	1.00		60–69	0.41 (0.27–0.63)
		Yes	2.06 (1.13–3.78)		≥70	0.14 (0.05–0.43)
	Jurisdiction	RoI	1.00			
		NI	2.17 (1.38–3.42)			
	Infection after biopsy	No biopsy	1.00			
		Yes	3.17 (1.06–9.49)*			
		No	1.48 (0.70–3.12)			
Hot flushes	Hormone therapy	Never	1.00	Hormone therapy	Never	1.00
		Previously	2.49 (1.26–4.93)		Previously	12.90 (4.71–35.30)
		Currently	12.23 (6.30–23.76)		Currently	10.93 (4.06–29.42)
	Time since diagnosis at survey completion	2–4.99	1.00	Jurisdiction	RoI	1.00
		5–9.99	0.57 (0.37–0.86)		NI	1.99 (1.33–2.99)
		≥10	0.45 (0.24–0.84)	Age at diagnosis	<59	1.00
	Jurisdiction	RoI	1.00		60–69	0.49 (0.27–0.75)
		NI	2.82 (1.88–4.22)		≥70	0.43 (0.25–0.74)
	Age at diagnosis	<59	1.00	Bleeding into rectum after biopsy	No biopsy	1.00
		60–69	0.45 (0.27–0.76)*		Yes	3.02 (1.16–7.88)*
		≥70	0.60 (0.35–1.03)		No	1.31 (0.64–2.69)
Fatigue	Hormone therapy	Never	1.00	Hormone therapy	Never	1.00
		Previously	1.07 (0.62–1.84)		Previously	3.28 (1.95–5.52)
		Currently	2.33 (1.36–3.99)*		Currently	3.06 (1.81–5.18)
	Jurisdiction	RoI	1.00	Jurisdiction	RoI	1.00
		NI	1.99 (1.36–2.92)		NI	1.60 (1.11–2.31)
	Time since diagnosis at survey completion	2–4.99	1.00	Age at diagnosis	<59	1.00
		5–9.99	0.65 (0.44–0.95)		60–69	0.46 (0.30–0.73)
		≥10	0.52 (0.29–0.92)		≥70	0.33 (0.20–0.55)
	Urinating more frequently at diagnosis	No	1.00	Comorbidities at diagnosis	None	1.00
		Yes	1.66 (1.14–2.40)		1–2	1.23 (0.85–1.79)
	Back pain at diagnosis	No	1.00		≥3	1.93 (1.02–6.36)*
		Yes	1.76 (1.16–2.67)	Bleeding into rectum after biopsy	No biopsy	1.00
	Comorbidities	None	1.00		Yes	2.67 (1.12–6.36)*
		1–2	1.52 (1.04–2.22)*		No	1.00 (0.55–1.82)
		≥3	1.68 (0.88–3.23)			
	Age at diagnosis	<59	1.00			
		60–69	0.44 (0.28–0.69)			
		≥70	0.31 (0.19–0.52)			

NI, Northern Ireland; RoI, Republic of Ireland.

[a]Weighted by age at diagnosis, jurisdiction and time since diagnosis to assure representativeness for all PCa survivors in Ireland.

[b]Localised disease is labelled as early disease, locally advanced/advanced disease is labelled as late disease.

*$p < .05$.

were seen for the variable living alone in early disease; and variables AS/WW, living alone, education, no complications after biopsy and age at diagnosis in late disease. These differences related to the significance level of these variables; the odds ratio changed little (data not shown).

4 | DISCUSSION

This study was performed to provide information that could better inform treatment decision-making of patients with both early (localised) and late (locally advanced/advanced) PCa and their clinicians.

We found that treatment was the strongest factor associated with both "current" and "severe" physical side-effects in both early and late disease, which is consistent with other studies (Darwish-Yassine et al., 2014; Nam et al., 2014; Potosky et al., 2004; Sanda et al., 2008). In particular, RP was associated with a higher risk for side-effects in early disease; associations were strong for "current" side-effects and even more pronounced for "severe" side-effects. In contrast, our results suggest that AS/WW may be associated with a lower risk of physical side-effects. Thus, more widespread use of AS/WW (which was only received by 5% of men in this study) among suitable men with localised PCa could provide an opportunity to avoid, minimise or delay physical side-effects. This strategy might be of particular interest to those men anxious to avoid incontinence and impotence (Chapple et al., 2002). BT was associated with a lower risk of "current" fatigue and "severe" erectile dysfunction. Consistent with this, in another small study BT was found to be the treatment with the highest probability of maintaining erectile function (Robinson, Moritz, & Fung, 2002). The men who underwent BT in our study were a small and highly select group (mostly resident in RoI and treated privately). Nonetheless, it is an important finding and more research should be done to determine if these results can be replicated in populations where BT is more widely available. Treatments, which were not included in the model could be regarded as unimportant with respect to the predictive value of a side-effect.

Our findings suggest that, in terms of patient-related factors, being younger at diagnosis is more frequently associated with physical side-effects in late disease and with "severe" physical side-effects. Men ≥70 years were less likely to report physical side-effects ("current" and "severe") compared to younger men (<59). This could be explained by the fact that younger men are more likely to present without symptoms and via PSA testing. They are more likely to have early disease and with less co-morbidities, therefore more likely to have RP with all its known side-effects and less likely to be in the WW group. An alternative explanation could be that older men have a different view of life than younger men and may perceive some "side-effects" to be due to ageing instead of treatment (Korfage, Hak, de Koning, & Essink-Bot, 2006). Living with others was associated with a higher risk of sexual dysfunction (erectile dysfunction and loss of libido). This could be due to the fact that most men living with others likely live with a partner and may be more likely to be—or want to be—sexually active, and therefore more alert to sexual problems. For both "current" and "severe" physical side-effects, men with tertiary or higher education were less likely to have hot flushes and fatigue—after adjusting for treatment—than men with primary education. This could be a because higher education is a marker for other socio-economic factors or the fact that less well educated men may have poorer health literacy and know less about options to alleviate side-effects (Knight et al., 2007). Men with higher education are more likely to present for PSA testing, and to be diagnosed with earlier stage disease (Nordstrom et al., 2016).

Pre-treatment function had an impact on risk of experiencing physical side-effects after treatment; in most cases men already experienced the "side-effect" before treatment. Another study found that pre-treatment function was the strongest predictor of post-treatment function (Talcott et al., 2003). We did not find pre-treatment function to be as important and this difference is possibly due to the fact that men in our study were at least 2, and up to 18 years post-diagnosis, while those in the other study were only 2 years after treatment; accuracy of recall may be poorer, or some side-effects may have resolved by the time of the survey, in our study. Presence of comorbidities was particularly associated with a higher risk of "current" physical side-effects with an association evidence for four of seven physical side-effects. As (Hoffman, 2012) suggests men of older age are more likely to have comorbidities and this can affect PCa treatment tolerance and possible benefits of aggressive cancer treatment. Therefore, this finding has important implications both for treatment decision-making among men with other conditions and for follow-up services post-diagnosis.

An interesting finding was that post-biopsy complications were associated with side-effects after PCa treatment, although it is not known how severe these complications were. However, this may be, as (Loeb, Carter, Berndt, Ricker, & Schaeffer, 2011) have suggested, due to the selection of patients for biopsy. These authors also suggested that individualised assessment of the risk-benefit ratio is important to determine if the potentially risky procedure of a biopsy should be performed. This is confirmed by the prospective study of (Rosario et al., 2012) who found that a significant percentage of men experience problems during or after biopsy. Our findings emphasise the potential importance of choices made long before treatment on patients' outcomes after treatment and suggest better selection of patients for biopsy might lead to improved post-treatment outcomes. However, men who have had a bad experience starting with their biopsy, could be are more likely to respond to the questionnaire. Further research is necessary to investigate the association between biopsy complications and post-treatment side-effects, taking into account the advances in biopsy surgery that have been made over the years.

The following limitations should be considered when interpreting the results. Firstly, the side-effects questions used for analyses were not formally validated against a gold standard and their psychometric properties were not examined. However, they were pretested among men with PCa so have face validity. The measures for pre- and post-treatment symptoms differed and the measure of side-effect severity did not include timing or duration. Also, if men received more than one treatment, they were included more than once. Fourthly, there were reasonable levels of missing response to the side-effects questions.

These men were categorised as "never had the side-effect" so the estimates of prevalence are likely to be conservative. In addition, a notable proportion of respondents had unknown stage and grade, even after checking medical records and were excluded from the analysis. This means that it is possible that the men of a particular stage/grade included in the analysis may not be entirely representative of all men with that stage/grade. Sixth, the study had a response rate of 54%. In order to address for the excluded respondents and the difference between respondents and non-respondents, which is described elsewhere (Drummond, Kinnear, Donnelly, et al., 2015), analyses were weighted for age at diagnosis, jurisdiction and time since diagnosis, so that results would be representative of all PCa survivors in Ireland. However, it is possible that differences between ineligible and eligible survivors and respondents and non-respondents consisted of other variables and may have affected the outcome (Drummond, Kinnear, Donnelly, et al., 2015). Seventh, in this study men reported their pre- and post-treatment symptoms and these men were up to 18 years post-diagnosis, and it is not certain whether, or how, accuracy of recall of pre-treatment symptoms (for example) differs by time since diagnosis. In addition, clinical practice has changed over the time window during which the study participants were diagnosed and treated (e.g. advances have been made in the ways biopsies are taken) and these could have influenced the likelihood of experiencing side-effects. Lastly, the Nagelkerke R^2 indicated that the models had relatively low predictive value, suggesting that there are other important factors associated with treatment-related side-effects which have not been identified.

In conclusion, in this large, population-based study, treatment is the most important factor associated with post-treatment side-effects. After treatment, various other factors such as pre-treatment function, comorbidities and biopsy complications were strongly associated with a higher risk of side-effects. These findings may be used to better inform PCa patients and physicians about the potential side-effects associated with specific treatments and which patients may be at risk of these, as well as informing strategies for post-treatment follow-up and monitoring. This could ultimately lead to better informed treatment decision-making and better support after treatment.

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