

# Patient-reported 'ever had' and 'current' long-term physical symptoms after prostate cancer treatments

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## Objective

To investigate the prevalence of physical symptoms that were 'ever' and 'currently' experienced by survivors of prostate cancer at a population level, to assess burden and thus inform policy to support survivors.

## Patients and Methods

The study included 3 348 men surviving prostate cancer for 2–18 years after diagnosis. A cross-sectional, postal survey of 6 559 survivors diagnosed 2–18 years ago with primary, invasive prostate cancer (ICD10-C61) identified via national, population-based cancer registries in Northern Ireland and Republic of Ireland. Questions included symptoms at diagnosis, primary treatments and physical symptoms (erectile dysfunction [ED]/urinary incontinence [UI]/bowel problems/breast changes/loss of libido/hot flashes/fatigue) experienced 'ever' and at questionnaire completion ('current'). Symptom proportions were weighted by age, country and time since diagnosis. Bonferroni corrections were applied for multiple comparisons.

## Results

Adjusted response rate 54%; 75% reported at least one 'current' physical symptom ('ever' 90%), with 29% reporting

at least three. Prevalence varied by treatment. Overall, 57% reported current ED and this was highest after radical prostatectomy (RP, 76%) followed by external beam radiotherapy with concurrent hormone therapy (HT, 64%). UI (overall 'current' 16%) was highest after RP ('current' 28%; 'ever' 70%). While 42% of brachytherapy patients reported no 'current' symptoms, 43% reported 'current' ED and 8% 'current' UI. 'Current' hot flashes (41%), breast changes (18%) and fatigue (28%) were reported more often by patients on HT.

## Conclusion

Symptoms after prostate cancer treatment are common, often multiple, persist long-term and vary by treatment method. They represent a significant health burden. An estimated 1.6% of men aged >45 years are survivors of prostate cancer and currently experiencing an adverse physical symptom. Recognition and treatment of physical symptoms should be prioritised in patient follow-up. This information should facilitate men and clinicians when deciding about treatment as differences in survival between radical treatments is minimal.

## Keywords

prostate cancer, population, patient-reported outcomes

## Introduction

Prostate cancer, the most common cancer in males in developed countries, has an estimated 900 000 new cases annually, 325 000 of which occur in Europe [1]. Driven by ageing populations, widespread PSA testing and improved survival, the prevalence of prostate cancer is predicted to rise in the UK from an estimated 255 000 cases in 2010 to 831 000 cases by 2040 [2]. In Ireland, prostate cancer currently accounts for 34% of male cancer survivors (excluding non-melanoma skin cancers) in Northern Ireland and ≈40% in the Republic of Ireland [3–4].

All prostate cancer treatments carry the potential for adverse effects, including erectile dysfunction (ED), urinary incontinence (UI), bowel problems, hot flashes and fatigue [5]. As studies have not conclusively shown survival benefits of one treatment over another for localised prostate cancer, robust population-based estimates of prevalence and duration of symptoms after treatment are valuable for informing treatment decision-making [6–10].

Most studies on side effects to date are from clinical trials that do not compare all treatment methods, exclude older men and do not extend beyond 10 years [11–13]. The aim of

the present study was to investigate the prevalence of physical symptoms that were 'ever' experienced and are 'currently' experienced at a population level, assess burden and inform policy to support medium to long-term survivors of prostate cancer.

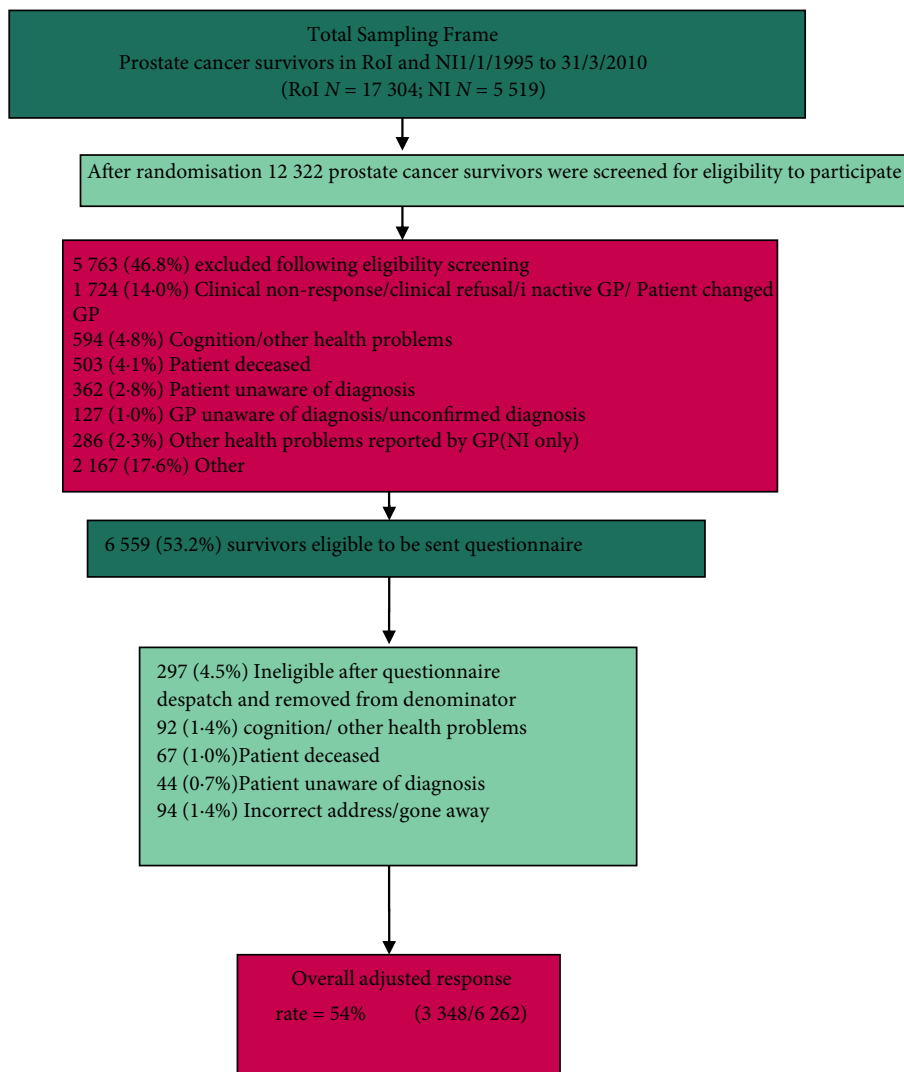
## Patients and Methods

The study took place in Ireland. Northern Ireland has a predominantly publically funded healthcare system, whereas the Republic of Ireland has a mixture of public and private healthcare. The same approach was used in both settings to identify and recruit participants. All men diagnosed with invasive prostate cancer (ICD10 C61) between 1 January 1995 and 31 March 2010 and alive at 31 March 2011 were identified through population-based cancer registries (Northern Ireland 5 519 men; Republic of Ireland 17 304 men). A random sample of survivors was screened for eligibility by healthcare providers ( $n = 12\ 322$ , 52% of total

sampling frame). Eligible survivors were: aware of their diagnosis, English speaking-resident in either Northern Ireland or the Republic of Ireland, and well enough to complete a questionnaire (in particular had no cognitive impairment).

In Northern Ireland, eligibility was checked by research nurses, or the patient's GP. In the Republic of Ireland, the patient's GP confirmed eligibility. In both areas, survivors whose eligibility was not confirmed (e.g. non-response of GP were excluded). After this process, 6 559 (53% of the random sample) were deemed eligible for invitation to complete a postal questionnaire (Fig. 1).

A questionnaire including the European Organisation for the Research and Treatment of Cancer (EORTC) QLQ C30, PR25, EQ5D-5L, DASS 21 and Decisional Regret Scale was developed following literature review with clinician and patient input [14–18]. Questions included sociodemographic characteristics and pre-diagnosis symptoms (urinary problems: increased



**Fig. 1** Recruitment of prostate cancer survivors. RoI, Republic of Ireland; NI, Northern Ireland.

frequency, pain urinating, blood in urine), bowel problems (diarrhoea, constipation), and/or sexual dysfunction (ED and loss of libido). Information on the last two were requested 'ever' after treatment, 'currently' at questionnaire completion and pre-diagnosis. A list of prostate cancer treatment methods was included and survivors were asked to indicate all treatments received, with dates. Specific questions were asked about seven potential disease- or treatment-related symptoms at two time-points; 'ever' (i.e. anytime since treatment) and 'current' (i.e. at time of questionnaire completion). The symptoms considered were UI, ED, loss of libido, bowel problems, breast changes, hot flashes and fatigue.

The draft questionnaire was pre-tested among 32 survivors of prostate cancer for acceptability, ease of understanding and face validity, and modified accordingly. Questionnaires were dispatched between April and September 2012. Each man received a cover letter, information sheet, consent form and freepost return envelope with their questionnaire. Non-responders received up to two written reminders. Date of diagnosis, clinical stage, and Gleason grade at diagnosis were extracted from cancer registry databases. The Gleason grade is collected and categorised as low (<5), medium (6–7) and high (>8) and not as raw data by the registry. Additional information was sourced for staging/Gleason grade for responders from Northern Ireland, as these data were incomplete in routine data for earlier years.

For survivors who answered some treatment or physical symptom questions, but omitted others from that section, a 'no' response was assumed. Non-response to all of five treatment questions (3%,  $n = 93$ ), or all 14 symptom questions (3%,  $n = 102$ ), were coded as 'missing' but retained in analyses.

To investigate whether symptoms varied by time since diagnosis, respondents were categorised into three groups: 2–4.9 years, 5–9.9 years and  $\geq 10$  years after diagnosis. To study symptoms by treatment, a variable was created based on a mutually exclusive hierarchy of treatments: each man was categorised once based on primary treatment(s) received: radical prostatectomy (RP) at any time following diagnosis (with or without other treatments); external beam radiotherapy (EBRT) with concurrent hormone therapy (HT) within 6 months; EBRT without HT; brachytherapy (BT), excluding survivors with previous EBRT or RP; HT alone without RP, EBRT or BT; chemotherapy alone; monitoring including active surveillance or watchful waiting.

Survivors were also categorised as: (i) currently on HT, (ii) previously received HT and (iii) never had HT. Pretreatment and post-treatment experience was compared for loss of libido and ED.

Comparisons of symptom proportions across treatment groups were tested for significance at the 5% level using two-sided

z-tests based upon weighted counts rounded to the nearest whole number, with differences in overall distributions tested using chi-square tests. Bonferroni corrections were applied to account for multiple comparisons. The Clopper–Pearson interval method was used to generate exact 95% binomial CIs for weighted proportion estimates [19].

To extrapolate results to the entire prostate cancer survivor population, weighted proportions of symptoms were computed. Respondents' characteristics were compared with those of all prostate cancer survivors in Ireland (i.e. the total sampling frame) and the proportions with each symptom was adjusted with weights based on country, age at diagnosis and time since diagnosis.

## Results

In all, 3 348 men responded, representing a 54% response rate after adjusting for eligibility following questionnaire dispatch. Respondents' mean (SD) age was 64.9 (7.6) years. Compared with all prostate cancer survivors, respondents were younger at diagnosis (chi-square 49.6;  $P < 0.001$ ), diagnosed more recently (chi-square 164.8;  $P < 0.001$ ), had their cancer staged (chi-square 673.0;  $P < 0.001$ ) and graded (chi-square 653.1;  $P < 0.001$ ) (Table 1). Two-thirds of respondents (64%) had presented with early disease (stage I/II), while 65% had an intermediate Gleason grade (5–7) at diagnosis. Almost half (48%) were surveyed 2–4.9 years after diagnosis, 32% at 5–9.9 years and 20% at  $\geq 10$  years. Those in the  $\geq 10$ -year group were younger at diagnosis, less often had stage I/II disease and more often had low-grade disease compared with those diagnosed more recently (all comparisons  $P < 0.001$ ). They also more often reported RP treatment and less often BT or EBRT with HT (all comparisons  $P < 0.001$ ). At diagnosis over half (51.2%) of men reported urinary frequency, 18.8% ED and 14.7% loss of libido. There were no significant variations in pretreatment symptoms reported between groups diagnosed at different time-periods (Table 2). The responder's treatment categories were compared with data from both cancer registries taken in 2001. The levels of chemotherapy (2% responders, 1.4% registry;  $P = 0.11$ ), HT (45% responders, 44% registry;  $P = 0.46$ ) and RP (27% responders, 38% registry;  $P < 0.01$ ) were within the range of the overall prostate cancer population. The levels of radiotherapy were higher among responders at 58%, 24% registry ( $P < 0.01$ ), in keeping with, but not completely explained by increased use over time (Republic of Ireland average 41% for 2007–2011).

### 'Ever had' Physical Symptoms (Weighted Proportions)

Overall, 90% of respondents, reported 'ever' experiencing at least one of the seven possible physical symptoms investigated after treatment: 61% reported at least three, 20% reported

**Table 1** Characteristics of prostate cancer populations.

	All survivors (N = 22 823)	Random sample (n = 12 322)	Eligible for study (n = 6 559)	Responders (n = 3 348)	Non-responders (n = 3 211)
N (%)					
Age at diagnosis, years					
0–59	5 046 (22.1)	2 039 (16.5)	1 329 (20.3)	799 (23.9)	530 (16.5)
60–69	10 212 (44.7)	4 891 (39.7)	2 939 (44.8)	1 631 (48.7)	1 308 (40.7)
≥70	7 565 (33.1)	5 392 (43.8)	2 291 (34.9)	918 (27.4)	1 373 (42.8)
Time since diagnosis, years					
2–5	9 569 (41.9)	5 340 (43.3)	3 101 (47.3)	1 614 (48.2)	1 487 (46.3)
5–9.9	9 776 (42.8)	4 324 (35.1)	2 114 (32.2)	1 075 (32.1)	1 039 (32.4)
≥10	3 478 (15.2)	2 658 (21.6)	1 344 (20.5)	659 (19.7)	685 (21.3)
TNM stage*					
I/II	12 761 (55.9)	5 792 (47.0)	3 817 (58.2)	2 126 (63.5)	1 691 (52.7)
III	2 122 (9.3)	1 130 (9.2)	947 (14.4)	612 (18.3)	335 (10.4)
IV	690 (3.0)	445 (3.6)	267 (4.1)	141 (4.2)	126 (3.9)
Unknown	7 250 (31.8)	4 955 (40.2)	1 528 (23.3)	469 (14.0)	1 059 (33.0)
Gleason grade*					
2–4	1 578 (6.9)	923 (7.5)	472 (7.2)	212 (6.3)	260 (8.1)
5–7	11 766 (51.6)	4 996 (40.5)	3 609 (55.0)	2 186 (65.3)	1 423 (44.3)
8–10	2 865 (12.6)	1 594 (12.9)	1 060 (16.2)	625 (18.7)	435 (13.5)
Unknown	6 614 (29.0)	4 809 (39.0)	1 418 (21.6)	325 (9.7)	1 093 (34.0)

\*Further information was sourced for TNM stage and Gleason grade for Northern Ireland responders only. This is reflected in the lower percentage with stage unknown among responders compared with the other columns.

**Table 2** Characteristics of responders by time since diagnosis.

	2–4.9 years after diagnosis (n = 1 614)	5–9.9 years after diagnosis (n = 1 075)	≥10 years after diagnosis (n = 659)	All respondents (n = 3 348)
N (%)				
Age at diagnosis, years				
0–59	340 (21.1)	255 (23.7)	204 (31.0)	799 (23.9)
60–69	750 (46.5)	534 (49.7)	347 (52.7)	1 631 (48.7)
≥70	524 (32.5)	286 (26.6)	108 (16.4)	918 (27.4)
Age at questionnaire completion, years				
0–59	186 (11.5)	45 (4.2)	12 (1.8)	243 (7.3)
60–69	637 (39.5)	346 (32.2)	102 (15.5)	1 085 (32.4)
≥70	791 (49.0)	684 (63.6)	545 (82.7)	2 020 (60.3)
Stage				
Stage I/II	1 120 (69.4)	670 (62.3)	336 (51.0)	2 126 (63.5)
Stage III	323 (20.0)	183 (17.0)	106 (16.1)	612 (18.3)
Stage IV	81 (5.0)	36 (3.3)	24 (3.6)	141 (4.2)
Unknown	90 (5.6)	186 (17.3)	193 (29.3)	469 (14.0)
Gleason grade				
Low (2–4)	66 (4.1)	51 (4.7)	95 (14.4)	212 (6.3)
Intermediate (5–7)	1 035 (64.1)	769 (71.5)	382 (58.0)	2 186 (65.3)
High (8–10)	356 (22.1)	170 (15.8)	99 (15.0)	625 (18.7)
Unknown	157 (9.7)	85 (7.9)	83 (12.6)	325 (9.7)
Symptom at diagnosis				
Frequency of urine	821 (50.9)	547 (50.9)	346 (52.5)	1 714 (51.2)
Pain while urinating	103 (6.4)	88 (8.2)	65 (9.9)	256 (7.6)
Blood in urine	94 (5.8)	72 (6.7)	53 (8.0)	219 (6.5)
ED	356 (22.1)	184 (17.1)	91 (13.8)	631 (18.8)
Loss of libido	247 (15.3)	163 (15.2)	83 (12.6)	493 (14.7)
Back pain	261 (16.2)	161 (15.0)	84 (12.7)	506 (15.1)
Primary treatment				
RP	374 (23.2)	305 (28.4)	255 (38.7)	934 (27.9)
EBRT with concurrent HT	383 (23.7)	179 (16.7)	68 (10.3)	630 (18.8)
EBRT without concurrent HT	484 (30.0)	391 (36.4)	213 (32.3)	1 088 (32.5)
BT	87 (5.4)	33 (3.1)	4 (0.6)	124 (3.7)
HT	147 (9.1)	91 (8.5)	72 (10.9)	310 (9.3)
Monitoring	102 (6.3)	44 (4.1)	18 (2.7)	164 (4.9)
Missing	34 (2.1)	31 (2.9)	28 (4.2)	93 (2.8)

Results are not weighted for survey non-response bias. Chemotherapy was omitted because there were <5 respondents. Respondents may have more than one symptom.

four, one in eight (12.5%) reported five, 6% reported six and 2% reported all seven. The most common were ED (68%), loss of libido (58%) and fatigue (55%). There was significant variation in 'ever' had symptoms by time since diagnosis. Loss of libido was more common in men 2–4.9 years since diagnosis compared with those  $\geq 10$  years after diagnosis (60% vs 54%, respectively;  $P = 0.010$ ). Bowel problems (26% of all respondents) and fatigue (55% of all respondents) were less common among those  $\geq 10$  years after diagnosis compared with other diagnosis periods, bowel (2–4.9 years,  $P < 0.001$ ; 5–9.9 years,  $P = 0.004$ ), fatigue (2–4.9 years,  $P < 0.001$ ; 5–9.9 years,  $P = 0.007$ ) (Table 3).

### 'Current' Physical Symptoms (Weighted Proportions)

Three-quarters of respondents reported at least one 'current' symptom with 29% reporting three or more symptoms and 4% at least five symptoms. About 65% reported currently having ED, UI and/or bowel problems, and 57% reported at least one of the following; loss of libido, breast changes, fatigue or hot flushes (Fig. 2). There was no significant

difference in proportions of 'current' symptoms between groups diagnosed during different periods. For each symptom, 'current' proportions were lower than 'ever'. The biggest differences were for fatigue (ever, 55%; current, 22%), hot flushes (ever, 39%; current, 6%) and UI (ever, 37%; current, 16%), and the smallest for ED (68% vs 57%). One-quarter of survivors (25%) reported no 'current' physical symptoms (Table 3).

### Pretreatment and Post-Treatment Comparisons

Pretreatment and post-treatment comparisons were possible for ED and loss of libido. Before diagnosis, 19% reported ED, increasing with age at diagnosis from 16% of those aged  $< 60$  years to 21% of men aged  $> 70$  years. ED as a new current symptom after treatment was reported by 43%, while 5% reported ED pretreatment, but not currently. This varied by primary treatment being highest after RP. Loss of libido was reported before diagnosis by 15% of survivors; 5% reported this pretreatment but not currently; and 46% report 'current' loss of libido but not pretreatment (Fig. 3).

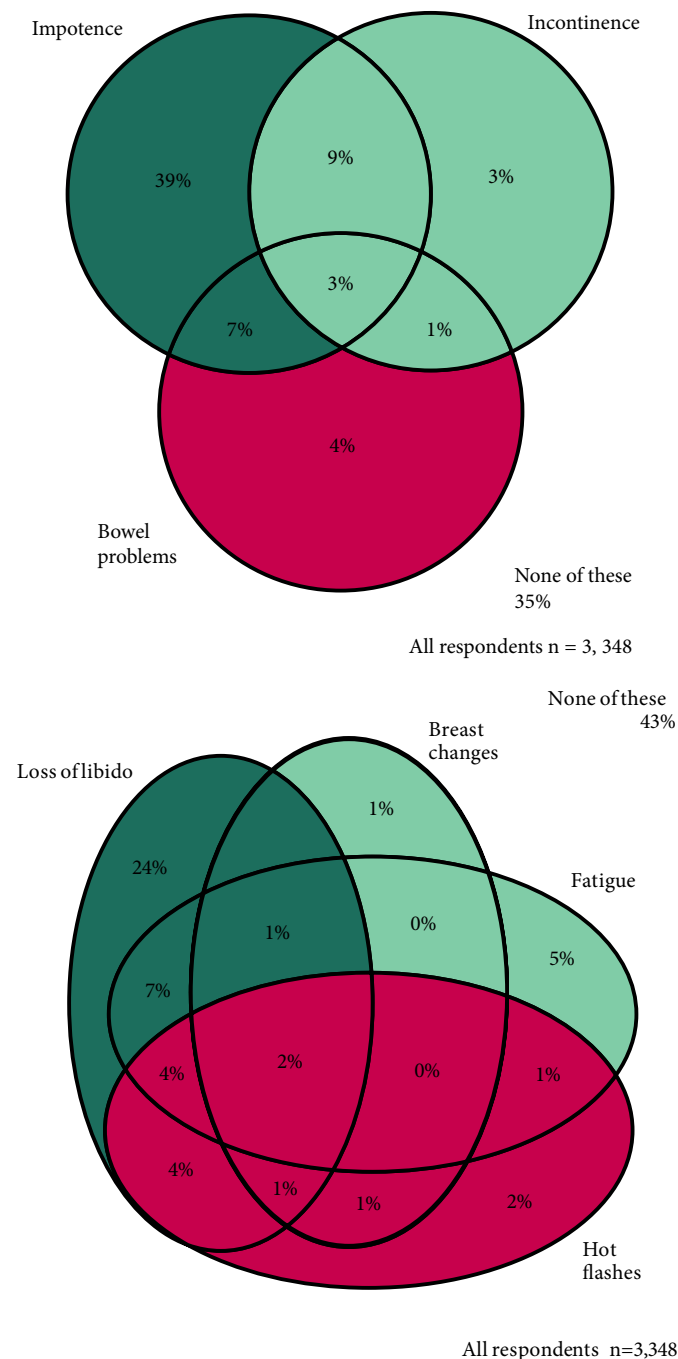
**Table 3** Symptoms ('current' and 'ever') reported by prostate cancer survivors, by primary treatment method (weighted for country, age at diagnosis and time since diagnosis).

	RP	EBRT with concurrent HT	EBRT without concurrent HT	BT	HT	Monitoring	Missing	All respondents
Percentage of men reporting symptom, (95% CI)								
Average age at diagnosis, years	60.5	66.4	67.1	61.7	73.5	67.9	69.0	64.9
UI								
Ever had	70.3 (67.2–73.3)	24.3 (20.8–28.0)	27.3 (24.7–30.0)	28.5 (20.7–37.3)	21.3 (17.1–26.1)	12.1 (7.6–18.1)	23.5 (15.7–33.0)	37 (35.4–38.7)
Current	27.8 (24.9–30.8)	10.7 (8.3–13.5)	11.8 (10.0–13.9)	8.1 (4.0–14.4)	14.5 (10.9–18.7)	6.7 (3.4–11.6)	12.7 (7.0–20.8)	15.8 (14.6–17.1)
Loss of libido								
Ever had	59.5 (56.2–62.7)	74.4 (70.6–77.9)	55.7 (52.8–58.7)	41.5 (32.7–50.7)	58.6 (53.1–63.9)	26.1 (19.5–33.5)	37.3 (27.9–47.4)	57.8 (56.1–59.5)
Current	47.0 (43.7–50.3)	58.0 (53.9–62.1)	43.1 (40.2–46.1)	26.0 (18.5–34.7)	51.5 (46.0–56.9)	21.8 (15.8–28.9)	29.4 (20.8–39.3)	45.5 (43.8–47.2)
ED								
Ever had	87.6 (85.3–89.7)	78.7 (75.1–81.9)	59.6 (56.7–62.5)	58.5 (49.3–67.3)	59.2 (53.7–64.5)	26.1 (19.5–33.5)	42.2 (32.4–52.3)	68.2 (66.6–69.8)
Current	75.5 (72.6–78.3)	64.2 (60.2–68.1)	50.2 (47.2–53.1)	43.1 (34.2–52.3)	50.9 (45.4–56.3)	20.6 (14.7–27.6)	29.4 (20.8–39.3)	57.2 (55.5–58.9)
Bowel problems								
Ever had	16.6 (14.2–19.2)	41.0 (36.9–45.1)	33.1 (30.4–36.0)	21.1 (14.3–29.4)	14.2 (10.7–18.4)	3.6 (1.3–7.7)	9.8 (4.8–17.3)	25.5 (24.1–27.1)
Current	9.2 (7.4–11.3)	22.0 (18.7–25.6)	19.2 (16.9–21.6)	7.3 (3.4–13.4)	9.2 (6.3–12.8)	2.4 (0.7–6.1)	4.9 (1.6–11.1)	14.2 (13.1–15.5)
Breast changes								
Ever had	6.2 (4.7–8.0)	39.6 (35.6–43.7)	17.7 (15.5–20.0)	1.6 (0.2–5.8)	22.8 (18.4–27.6)	2.4 (0.7–6.1)	4.9 (1.6–11.1)	17.2 (16.0–18.6)
Current	3.1 (2.1–4.5)	20.0 (16.8–23.5)	8.7 (7.1–10.4)	1.6 (0.2–5.8)	17.8 (13.8–22.3)	1.8 (0.4–5.2)	1.0 (0.0–5.3)	9.3 (8.3–10.3)
Hot flushes								
Ever had	15.7 (13.4–18.3)	79.9 (76.4–83.1)	40.4 (37.5–43.3)	11.4 (6.4–18.4)	60.1 (54.6–65.3)	6.1 (2.9–10.9)	5.9 (2.2–12.4)	38.7 (37.1–40.4)
Current	7.0 (5.4–8.8)	27.7 (24.1–31.5)	14.5 (12.5–16.7)	2.4 (0.5–7.0)	40.5 (35.3–46.0)	3.6 (1.3–7.7)	2.0 (0.2–6.9)	16.0 (14.8–17.3)
Fatigue								
Ever had	50.4 (47.1–53.7)	74.0 (70.2–77.5)	63.4 (60.5–66.2)	44.7 (35.7–53.9)	42.0 (36.7–47.5)	8.5 (4.7–13.8)	18.6 (11.6–27.6)	54.9 (53.2–56.6)
Current	18.1 (15.6–20.7)	31.5 (27.7–35.4)	22.8 (20.4–25.3)	13.0 (7.6–20.3)	28.4 (23.7–33.5)	4.2 (1.7–8.5)	4.9 (1.6–11.1)	21.7 (20.3–23.2)
No symptom								
Ever had	4.3 (3.1–5.9)	1.2 (0.5–2.5)	9.6 (8.0–11.5)	17.1 (10.9–24.9)	10.9 (7.8–14.8)	58.2 (50.3–65.8)	37.3 (27.9–47.4)	10.4 (9.4–11.4)
Current	15.5 (13.2–18.0)	16.5 (13.6–19.8)	29.4 (26.8–32.2)	41.5 (32.7–50.7)	19.5 (15.4–24.2)	63.6 (55.8–71.0)	49.0 (39.0–59.1)	25.2 (23.7–26.7)
Any symptom								
Ever had	95.7 (94.1–96.9)	98.8 (97.5–99.5)	90.4 (88.5–92.0)	82.9 (75.1–89.1)	89.1 (85.2–92.2)	41.8 (34.2–49.7)	62.7 (52.6–72.1)	89.6 (88.6–90.6)
Current	84.5 (82.0–86.8)	83.5 (80.2–86.4)	70.6 (67.8–73.2)	58.5 (49.3–67.3)	80.5 (75.8–84.6)	36.4 (29.0–44.2)	51.0 (40.9–61.0)	74.8 (73.3–76.3)

Results were weighted for survey non-response bias. Chemotherapy was omitted because there were  $< 5$  respondents. Respondents may have more than one symptom.



**Fig. 2 (a)** 'Current' ED, UI and bowel problems. **(b)** 'Current' loss of libido, breast changes, fatigue and hot flashes.



### Variations in 'current' Physical Symptoms by Primary Treatment

Among men treated with RP proportions of 'current' ED (76%) and UI (28%) were higher than the average for all respondents (weighted proportions;  $P < 0.001$ ) while bowel problems (9%), hot flashes (7%) and breast changes (3%)

after RP were lower than average ( $P < 0.001$  for all three comparisons).

Men treated with EBRT with concurrent HT reported the highest proportions of current bowel problems (20%) compared with HT (9%), RP (9%), BT (7%) or monitoring (2%). Survivors treated by EBRT with concurrent HT, compared with those who had EBRT without concurrent HT, reported more 'current' loss of libido (58% vs 43%,  $P < 0.001$ ), ED (64% vs 50%,  $P < 0.001$ ), breast changes (20% vs 9%,  $P < 0.001$ ), hot flashes (28% vs 15%,  $P < 0.001$ ) and fatigue (32% vs 23%,  $P < 0.001$ ).

Those treated with BT reported lower than average proportions of 'current' ED (43%), loss of libido (26%), hot flashes (2%), and breast changes (2%); 42% of this group reported no 'current' problems.

Men treated with HT alone reported high proportions of 'current' loss of libido (52%), ED (51%), hot flashes (41%) and fatigue (28%), while 20% reported no 'current' physical symptoms.

Of the men on monitoring, 64% reported no 'current' physical symptoms, higher than other groups ( $P < 0.001$ ). One in five men on monitoring reported loss of libido or ED (21%, only slightly higher than pretreatment average level of 19%) or loss of libido (22%). Other symptoms were less common in the monitoring group [UI (7%), hot flashes (4%), fatigue (4%), bowel problems (2%) and breast changes (2%)] (Table 3).

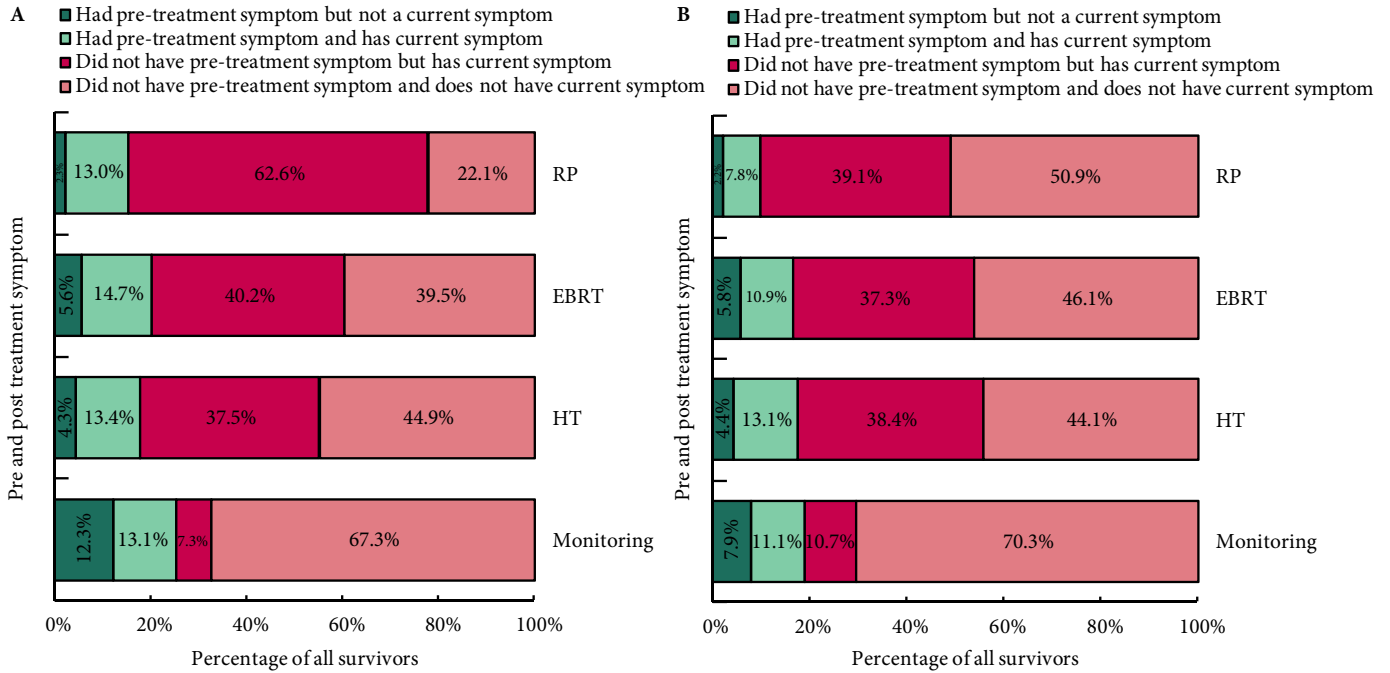
### Variation in 'current' Symptoms by HT

Overall, 45% reported receiving HT at some point after diagnosis. Current use of HT (19%) compared with past use (26%), and never used (55%) was associated with more hot flashes, (54% current vs 15% past vs 4% never), loss of libido (62% current vs 50% past vs 38% never), breast changes (23% current vs 14% past vs 2% never) and fatigue (38% current vs 23% past vs 16% never) (all comparisons  $P < 0.001$ ) (Fig. 4).

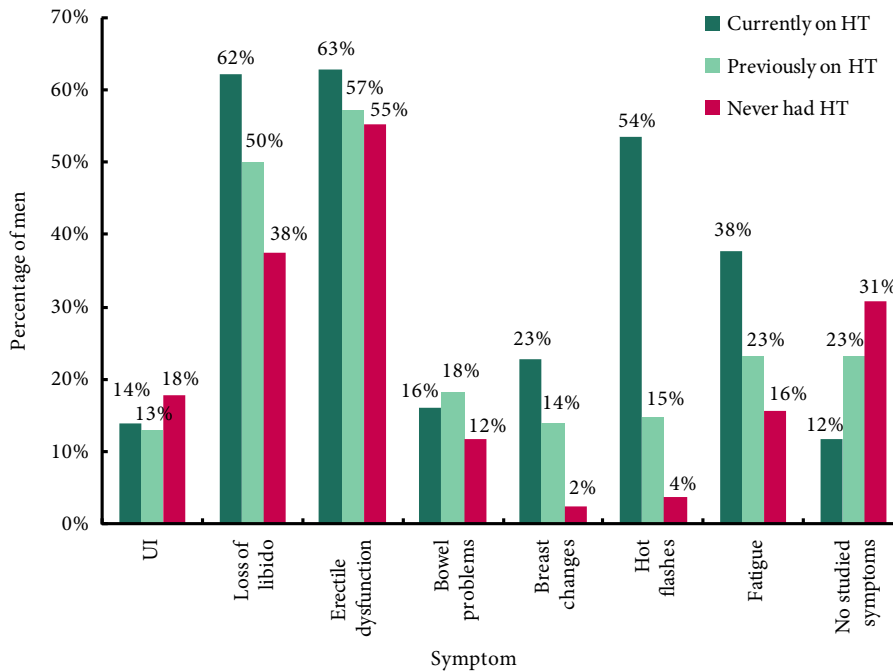
### Discussion

This large population-based study adds to the literature in this area by examining seven disease-specific physical symptoms of men of all ages with prostate cancer up to 18 years after diagnosis. All treatment methods were included in two countries with high standards of services and patient care. This has allowed us to estimate the population burden of physical symptoms as reported by men, their patterns following different treatments and their 'persistence'. Considering the uncertainties about optimal treatment from a clinical outcome perspective, this type of information on patients-reported outcomes is potentially extremely valuable for informing treatment decision-making.

**Fig. 3** (A) ED pretreatment and currently. (B) Loss of libido pretreatment and currently. Note, only ED and loss of libido are compared before and after treatment as definitions for other conditions differed before and after treatment.



**Fig. 4** Current symptoms reported by the survivors of prostate cancer using HT.



The burden of symptoms is high, with many survivors reporting multiple symptoms. Nine out of 10 men reported at least one of the seven possible symptoms at some point after diagnosis and three-quarters reported at least one as ‘current’. However, about one in 10 survivors reported no symptoms at any time and 25% were currently symptom free.

Over half (57%) reported ‘current’ ED, almost half (46%) reported loss of libido and one in six reported ‘current’ UI, with fatigue a common complaint. UI and ED were more common after RP compared with other treatments, and bowel problems were most common after EBRT. The pattern of these symptoms was as documented in smaller studies

reporting on specific treatments [7,10,20–21]. However, the present study, which looks at survivors at population level, allows an estimate of total burden.

For ED, ‘current’ levels of 57% and ‘ever’ levels of 68% were reported. This work extends that of Korfage *et al.* [22], who found that at 52 months after treatment, 88% of men treated with RP and 64% of those who had EBRT with concurrent HT reported ED. We found similar high levels by examining men up to 15 years after diagnosis supporting the Korfage *et al.* assertions that ED is likely to be permanent if present 12 months or more after treatment.

The effect of HT in improving survival has been documented, but at a cost of symptoms such as loss of libido, fatigue, hot flushes and breast changes [10,23]. Consistent with this, and reported for a large cohort, those currently on HT were  $\approx 10$ -times more likely to report breast changes and hot flushes than those who never had HT. High levels of fatigue for those on HT is similar to clinical studies [24].

An important part of our present analysis related to the prevalence of symptoms at different times since diagnosis. The lower proportion of bowel problems reported by survivors diagnosed  $\geq 10$  years ago probably reflects lower rates of EBRT in that cohort (confirmed by cancer registry data), as well as improvements in technologies. The fact that the proportions who reported ‘ever’ and ‘current’ symptoms were similar in each survival period indicates a need for ongoing support after treatment for prostate cancer.

## Implications

Current UK guidelines recommend that survivors and their partners are given opportunities to discuss psychosexual problems and that counselling on sexual problems and UI is available as long as needed [6]. Our present results suggest there is likely to be a large need, with three-quarters of men reporting at least one physical symptom, almost 60% ‘current’ ED and one in six reporting ‘current’ UI.

Based on the present work, of the 22 823 prostate cancer survivors resident in Ireland at the time of the study, we estimate that  $17\ 100 \pm 300$  had at least one ‘current’ physical symptom, including ED ( $13\ 100 \pm 400$ ) loss of libido ( $10\ 400 \pm 400$ ), fatigue ( $5\ 000 \pm 300$ ) and UI ( $3\ 600 \pm 300$ ). Based upon the 2011 Censuses in both countries, we estimate that 1.6% of the male population aged  $\geq 45$  years is a prostate cancer survivor with a ‘current’ physical symptom: 1.2% with ED and 1% with loss of libido. This represents a significant number of men who require ongoing care. The information in the present study could also be used to help inform decisions about investigation and treatment of prostate cancer and survivors’ expectation of symptoms [6]. Recognition and

treatment of physical symptoms should be prioritised in patient follow-up.

## Strengths

Unlike other similar patient-reported outcome studies in prostate cancer, the present study included men of all ages, treated with all available methods [25–26]. It also covered a longer period since diagnosis [7,20]. High-quality cancer registries provided the basis for sampling and this allowed population representativeness to be assessed and proportions to be weighted, so that estimates are of the symptom burden in the entire survivor population. Self-reported treatment was compared with treatment information from each registry; congruence for RP was 86% in Northern Ireland and 70% in the Republic of Ireland, and for EBRT was 96% in Northern Ireland and 75% in the Republic of Ireland. Weighting allowed us to address some demographic aspects of non-response.

## Limitations

As with many questionnaire studies, older persons were less likely to respond but weighted proportions allowed adjustment for this [5]. In addition, as a cross-sectional study, comparisons between groups diagnosed at different time-periods have limitations owing to changing treatment, investigation patterns and different patient profiles. We recognise that accuracy of recall as a potential limitation, for example, the 4% of survivors in the monitoring group reporting ‘current’ hot flushes may represent contamination of treatment recall with survivors not recognising that they are having HT.

While we have documented symptoms reported by survivors of prostate cancer, we recognise that not all can be attributed to prostate cancer treatments, e.g. ED increases with age [27,28]. We have reported pretreatment and post-treatment levels of ED and these increased with age from 16% in men aged  $< 60$  years, to 18.7% in men aged 60–69 years and 20.4% in men aged  $\geq 70$  years. The same men responded with to post-treatment levels of ED of 66.4% aged  $< 60$  years, 61.5% aged 60–69 years and 45.9% aged  $\geq 70$  years. These figures reflect the higher rates of RP in younger men and monitoring in older men. UI in general male populations, without prostate cancer, has been estimated to be between 3% and 11% [29]. UI among the Irish population has been reported at 4.5% for men aged  $> 50$  years, ranging from 2 to 4% for men aged 50–64 years to 4–7% for men aged 65–74 years and 6–11% for those aged  $> 75$  years [30], which is lower than the 16% ongoing UI reported after treatment. Some of the reported physical symptoms may, however, be caused by co-morbidities, or other treatments such as breast changes caused by commonly used medications [29]. Future studies should collect normative data for the male population to better determine treatment effects.



In conclusion, physical symptoms after prostate cancer treatment are common, often multiple and persist years after diagnosis, representing a large health burden.

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## Conflicts of Interest

The authors declare that they have no conflicts of interest.

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**Abbreviations:** BT brachytherapy; EBRT external beam radiotherapy; EORTC European Organisation for the Research and Treatment of Cancer; ED erectile dysfunction; HT hormone therapy; RP radical prostatectomy; UI urinary incontinence.