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Effect of more intense investigation and treatment of prostate cancer on survivor's physical symptoms, psychological wellbeing and health related quality of life: a two country cross-sectional study

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Keywords: Prostate cancer, survivors, patient reported outcomes, PSA testing

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Abstract

Aim

To investigate at population level effects on men's health and wellbeing of different intensities of Prostate cancer investigation and treatment.

Subjects

Prostate Cancer (PCa) survivors on the island of Ireland where since 1994, higher levels of PSA testing and prostate cancer in the Republic of Ireland (ROI) exist compared with Northern Ireland (NI).

Method

Postal questionnaires sent to PCa survivors 2-18 years post treatment, seeking information about physical symptoms and Health Related Quality of Life. Survivors were analysed separately for ROI and NI, for categories 'late disease' defined as stage III/IV and any Gleason Grade (GG) at diagnosis, and 'early disease' defined as stage I/II and GG 2-7.

Results

3,348 (54%) men responded (ROI, n=2567; NI, n=781). ROI responders were younger more likely to present asymptomatically, without comorbidities and with early disease. Current receipt of Androgen Deprivation Therapy (ADT) was 18% in NI and 9% in ROI. Similar levels for NI and ROI were recorded for current incontinence (weighted overall prevalence=16%) and impotence (56% in early disease, 67% in late disease). In early disease only bowel problems (ROI=12% NI=21%), remained significant.

In late disease NI men reported higher levels of breast changes (23% vs 9%,) and hot flashes (41% vs 19%), but when men on ADT were analysed separately no significant differences remained. Only QLQ C30 pain (early disease, NI>ROI)) and financial difficulties (late disease ROI>NI)) were significantly different between countries.

There were no significat differences in depression, anxiety, distress or index ED-5D score between ROI and NI..

Conclusion

In this population-based study, health outcomes among PCa survivors differed little between countries. However the higher intensity of investigation and treatment has resulted in many

additional men with ongoing prostate cancer-related physical symptoms in ROI, a risk for all areas with higher levels of testing.

Article summary

The island of Ireland has two separate jurisdictions and health care systems and since 1994, higher levels of PSA testing and prostate cancer in the Republic of Ireland (ROI) compared with Northern Ireland (NI). Age-standardised incidence rates have risen by 222% in ROI compared to 161% in NI since 1994.

This natural experiment has allowed us to investigate, at population level, effects on men's health and wellbeing of different intensities of prostate cancer investigation and treatment. This is a topical question as there are calls for increased PSA testing in younger men.

We sent postal questionnaires to prostate cancer survivors 2-18 years post treatment, identified from population-based cancer registries on the island of Ireland, seeking information about erectile dysfunction, urinary incontinence, bowel problems, libido loss, gynaecomastia and hot flashes/sweats), Health Related Quality of Life (HRQoL; using EQ-5D 5L, EORTC QLQ-C30) and psychological wellbeing (using DASS-21).

We analysed results separately for reaponders from ROI and NI, for categories 'late disease' defined as stage III/IV and any Gleason Grade (GG) at diagnosis, and 'early disease' defined as stage I/II and GG 2-7. Survey responses were weighted by age, jurisdiction and time since diagnosis. Between country differences were investigated using z-tests, chi-square tests, Anova and univariate and multivariate logistic and linear regression as appropriate. Significance was at the 5% level, with the Bonferroni correction to compensate for multiple comparisons.

3,348 (54%) men responded (ROI, n=2567; NI, n=781). ROI responders were younger (weighted average age at diagnosis 65 vs 67 years); more likely to present asymptomatically (66% vs 41%); without comorbidities (45% vs 58%), with early disease (56%, 35%); and less often with late disease (16%, 36%). This reflected increased PSA testing in younger men than occurred in NI.

Men in NI were more likely to report current Androgen Deprivation Therapy (ADT) (18% in NI and 9% in ROI.) Similar levels for NI and ROI were recorded for current incontinence (weighted overall prevalence=16%) and impotence (56% in early disease, 67% in late disease). In early disease, bowel problems (ROI=12% NI=21%), and fatigue (ROI=17% NI=29%), were significantly different between ROI and NI, and only bowel problems remained significant after adjusting for socio-demographic factors, clinical variables and treatment (mulitvariate odds ratio (OR) 1.8, (CI 1.26 - 2.56, P=0.001).

In late disease NI men reported higher levels of breast changes (23% vs 9%, OR 2.33 CI 1.41-3.73 p<0.001) and hot flashes (41% vs 19%, OR 2.30 CI 1.55- 3.51, p=0.001), but when men on ADT were analysed separately no significant differences remained. In multivariate analysis, only QLQ C30 pain (early disease) and financial difficulties (late disease) were significantly different between countries (pain: 19.4 NI vs 11.1ROI, risk estimate 5.829, CI. 2.349-9.308,p=0.001),financial difficulties: (7.9 NI vs 10.4 ROI, risk estimate -8.629, CI -12.770-4.488,p=0.0001).

There were no significat differences in depression, anxiety, distress or index ED-5D score between ROI and NI, in either univariate or adjusted analyses.

We concluded that In this population-based study, following twenty years of higher levels of prostate cancer detection in ROI than NI, health outcomes among PCa survivors differed little between countries. However the higher intensity of investigation and treatment has resulted in many additional men with ongoing prostate cancer-related physical symptoms in ROI, a risk for all areas with higher levels of testing. Caution should be exercised when advocating increased use of PSA testing in younger men and men should have the full facts about likely side effects of treatment explained before they have a PSA test.

'Strengths and limitations of this study'

Strengths

The same approaches were used in both areas for patient definition, recruitment, data collection and analysis. We used several validated instruments to assess patient-reported outcomes and categorised men by stage and grade of disease to help compensate for differences in the patient profile for the two populations. High-quality population-based cancer registries provided

the basis for sampling of survivors and this also allowed population representativeness to be assessed and proportions weighted to the entire survivor population.

Limitations

As with many questionnaire studies, older men were less likely to respond but weighted proportions allowed adjustment for this. We also recognise accuracy of recall as a potential limitation and this could be more of a problem with the older NI population and for men diagnosed longer ago. While the categorisation into early and late disease was loosely based on D'Amico criteria PSA levels at diagnosis were not systematically available and Gleason scores were recorded in the Registries as a categorical variable, with a cut off at 7. Finally, we did not collect data from men in the population without prostate cancer (i.e. normative data) so we cannot be sure that there the background prevalence of physical symptoms, or levels of Health Related Quality of Life or psychological wellbeing do not differ between N.Ireland and ROI.

- Prostate cancer is diagnosed almost 40% more commonly in Republic of Ireland than N. Ireland related to higher levels of PSA testing.
- After twenty years of higher levels of prostate cancer detection in ROI than NI, health outcomes among PCa survivors differed little between countries.
- The higher intensity of investigation and treatment has resulted in many additional men with ongoing prostate cancer-related physical symptoms in ROI,
- .Caution should be exercised when advocating increased use of PSA testing in younger men
- Men should have the full facts about likely side effects of treatment explained before they have a PSA test.

Introduction

Age standardised prostate cancer incidence has increased over the past two decades associated with increased use of PSA testing[1] so that now in many countries it is the most common cancer among males[2]. The debate about the value of PSA testing for the early detection of Prostate Cancer continues. While a simple blood test and the prospect of earlier cancer diagnosis are appealing, poor specificity leads to over diagnosis of clinically insignificant cancers[3]. To be considered effective, screening must reduce overall and disease specific mortality and morbidity and not just detect more disease. Only one large long term randomised

controlled trial has identified a significant reduction in deaths associated with PSA "screening", but this was accompanied with a high level of over diagnosis and associated treatment[4]. Despite this, marked international variations in Prostate Cancer incidence rates points to widespread use of PSA testing for unsuspected prostate cancer[2] and recent calls to offer men in their 40s access to the PSA test is likely to further increase numbers diagnosed. [5] In light of this, and in order to inform the PSA debate, it would be of value to determine whether more investigation and treatment improves men's self-reported health outcomes, especially in the long-term.

Circumstances exist in Ireland where different intensities of PSA testing and subsequent biopsy between its two jurisdictions, Republic of Ireland (ROI) and Northern Ireland (NI), exist in populations which are similar in lifestyle and ethnic and genetic makeup[6]. Both jurisdictions have high quality population-based cancer registries which have tracked prostate cancer incidence since the early 1990s[7-8]. The ROI has a complex mixed public–private healthcare system and in 2006 the National Cancer Forum recommended against the introduction of PSA screening, despite this the rates of PSA testing in men aged 50 and older rose by 23% per annum between 1993 and 2005[6] with high levels persisting[9]. In contrast NI has a predominantly publicly funded healthcare system similar to the NHS and has encouraged the following of NICE guidelines aimed at limiting the use of PSA testing in primary care[10]. Nevertheless, there is evidence of screening for prostate cancer in the NI population[11] although at markedly lower levels (annual percentage change 1993 to 2003 = +9.7%) than in ROI[6]. Consequently, since 1994, when Prostate Cancer incidence rates were similar, the age-standardised incidence rate has risen by 222% in ROI compared to 161% in NI. These unique circumstances allow us to investigate, at the population level, effects on men's health and wellbeing of different intensities of prostate cancer investigation and treatment.

Methods

The methods of the PiCTure (Prostate Cancer Treatment, *your experience*) study, which was conducted in ROI and NI, have been described previously[12].

Patient Involvement

Patients were involved in study steering group, piloting of questionnaire and interpretation of results.

Subjects/ patients

Briefly, after ethical approval, a population-based sample of all men diagnosed with invasive Prostate Cancer (ICD10 C61) between 1st January 1995 and 31st March 2010, and alive November 2011, was selected from the two population-based cancer registries (n=22,823). From this a country and time-since-diagnosis (under and over 5 years) stratified random sample of 12,322 men was selected.

Patients' General Practitioners (GP) / health care professionals were contacted to screen men for eligibility to participate in the study. Men were eligible if they were i) alive, ii) aware of their Prostate Cancer diagnosis, iii) well enough to receive and complete a questionnaire (in particular, had no cognitive impairment), iv) able to understand English and v) resident in ROI or NI. Following this process, 6,559 prostate cancer survivors were deemed eligible to be sent a questionnaire. Questionnaires were posted in 2012. Non-responders received up to two written reminders.

Outcome measures

The primary outcome variables for this analysis were determined by questionnaire and were

1. Prostate cancer related physical symptoms 'currently' experienced (i.e. present at time of questionnaire completion) (erectile dysfunction, urinary incontinence, bowel problems, loss of libido, gynaecomastia and hot flashes/sweats).
2. Health utility on the day of questionnaire completion, measured by the EQ-5D-5L which comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 possible levels of response: *no problems, slight, moderate, severe or unable to undertake the particular action.* The EQ-5D-5L health states were converted to EQ-5D-3L states and UK valuations applied to provide a single index value of up to 1 (since there are no valuations specifically for Ireland and NI is part of the UK)[13-14]; higher values indicate better/more health utility.
3. Health-related quality-of-life in the past week measured using the EORTC QLQ-C30[16] a general cancer questionnaire comprising a global health score (GHS), five functional subscales (measuring physical, role, emotional, cognitive, and social functioning) and nine general cancer symptom subscales (assessing fatigue, nausea/vomiting, pain, dyspnoea, sleep disturbance, loss of appetite, constipation, diarrhoea and financial

difficulties). Response options range from 1 (not at all) to 4 (very much), except for the two questions comprising the GHS, responses to which ranged from 1 (very poor) to 7 (excellent). Scores on each subscale were transformed to 0-100 as recommended, with higher scores indicating better HRQOL, higher functioning or worse symptoms)[15].

4. Psychological wellbeing during the past week, assessed by the 21 question version of the Depression, Anxiety and Stress Scale (DASS-21)[16] which contains three subscales which measure depression, anxiety and (di)stress. Each subscale is based upon seven questions with responses scored from 0 (did not apply) to 3 (applied to me very much, or most of the time). A summary score for each subscale was generated by doubling the sum of the individual responses. Possible scores on each scale range from 0-42, with higher scores indicating higher levels of depression, anxiety or stress.

Explanatory variables

Men were asked to report all treatments received, by answering yes/no to a list of treatments (radical prostatectomy, (RP), external bean radiotherapy (EBRT), Androgen deprivation therapy (ADT), active surveillance (AS), watchful waiting (WW) and brachytherapy (BT)). The Questionnaire also requested information on socio-demographic characteristics, method of diagnosis ("symptomatic clinically detected" or "asymptomatic PSA detected")[12] and health at diagnosis, in particular urinary (increase frequency, pain while urinating, blood in urine) or sexual (impotence/erectile dysfunction) symptoms (yes/no) and presence of comorbidities (which men were invited to select from a list comprising heart or lung disease, stroke, diabetes, high blood pressure, diverticular disease, bowel problems (eg constipation/diarrhoea), other cancer, depression or other).

Date of diagnosis, stage at diagnosis (Tumour-Lymph node-Metastasis (TNM) classification) and Gleason grade (GG) for all men who were sent questionnaires were extracted from the cancer registries. GG is collected by the ROI cancer registry (NCRI) as a categorical variable (low (GG 2-4), medium (GG 5-7) or high grade (GG 8-10), so these categories were used in analysis. Supplementary staging information was abstracted from medical records for NI respondents in early years when staging levels in the NI cancer registry (NICR) were low.

Statistical Analysis

The goal of the analysis was to compare health and wellbeing between men from ROI and NI. However the characteristics of the populations of prostate cancer patients and therefore the

populations of survivors and respondents differed between ROI and NI, notably in the proportions of early and late disease. To overcome this, and because disease extent at diagnosis is likely to be an important determinant of health and wellbeing, analyses adjusted for socio-demographic and clinical characteristics were undertaken and outcomes were analysed separately for two main categories: 'late disease' defined as stage III or IV and any GG at diagnosis and 'early disease' defined as stage I/II and GG 2-7 at diagnosis. A third group, 'other' which included those without stage or grade or with early stage and high grade was also created and summary findings are reported for completeness.

Survey responses were weighted by age, country and time since diagnosis to compensate for higher non-response in certain survivor subgroups[12] and increase representativeness of the results to the entire prostate cancer survivor population.

Differences in proportions of patient characteristics, symptom and functional scores and DASS-21 subscales between survivors from NI and ROI were tested using z-tests and chi-square tests for early and late disease separately. Multivariate regression models (logistic for physical symptoms and linear for health utility, HRQoL and psychological wellbeing) were developed using a staged approach. The first model adjusted for age at questionnaire completion, number of comorbidities at diagnosis, time since diagnosis and method of diagnosis ("model 1"). The second model ("model 2") then added treatments (RP, EBRT, BT, ADT) since treatment utilisation differs between ROI and NI. Records with missing treatment or method of diagnosis were dropped from all models (n=60).

Significance was at the 5% level with the Bonferroni correction applied to compensate for multiple comparisons (see table footnotes for details of significance levels for each analysis).

Results

3,348 men responded, providing a 54% overall response rate after adjustment for men who were discovered to be ineligible following questionnaire dispatch. 70% of responders were from ROI (n=2567) and 30% (n=781) from NI.

Almost half of respondents (48%) were surveyed 2- 4·9 years post-diagnosis, 32% were 5-9·9 years and 20% were ≥10 years after diagnosis. Respondents' average age at diagnosis was

64·9 years (standard deviation 7·6). Men from ROI were younger, more often reported asymptomatic PSA detection of their cancer and more often presented without urinary symptoms or without comorbidities compared to respondents from NI (all p < 0.001). Respondents from NI more often reported having ADT or EBRT, and less often having RP or BT compared to respondents from ROI (Table 1).

Table 1: Characteristics of men and treatment received by disease category and jurisdiction (weighted proportions)

	Early Disease**		Late Disease***		All Respondents- (includes those classified as 'other')	
	ROI	NI	ROI	NI	ROI	NI
Weighted numbers	1431	269	407	282	2567	781
Age at diagnosis > 70 years	27.6%	32.9%	30.3%	38.4%	32.4%*	40%*
Age at diagnosis < 60 years	25.2%	21.8%	25.6%*	15%*	22.8%*	17.4%*
Symptomatic clinically detected	28.3%*	51.4%*	37.5*	59.0*	32.3%*	58.2%*
Asymptomatic PSA detected	70.2%*	48.4%*	61.3%*	40.4*%	66.2%*	41.1%*
No symptoms at diagnosis	38.3%*	24.2%*	35.8%*	23.8%*	36.7%*	23.0%*
Urinating more frequently at diagnosis	45.9%*	64.3%*	45.0%*	58.3%*	47.5%*	62.7%*
No comorbidities at diagnosis	45.4%	39.0%	51.2%*	34.9%*	45.2%*	38.0%*
Radical prostatectomy	34.8%*	15.7%*	39.2%	10.5%*	30.9%*	13.9%*
External beam radiotherapy	51.5%*	64.4%*	64.1%*	79.1%*	55.7%*	64.1%*
Brachytherapy	7.4%	4.9%	3.2%	0%	6.6%*	1.8%*
Androgen Deprivation Therapy	27.9%*	60.0%*	52.5%*	87.1%*	37.3%*	71.9%*
Chemotherapy	1%	0.3%	3.8%	3.7%	2%	1.8%
Active Surveillance/	5%*	10.2%*	1.3%	0.2%	4.7%	5.7%

	Early Disease**		Late Disease***		All Respondents- (includes those classified as 'other')	
Watchful Waiting						
No treatment	2.9%	1.8%	2.0%	0.0%	3.2%	2.5%

Note: *Results are weighted by country, age at diagnosis and time since diagnosis*
** Significant difference at (notional p<0.05, p< 0.001with Bonferonni correction applied)*
*** Early = Stage I / II Gleason grade 2-7*
**** Late = Stage III / IV any Gleason grade*

Overall 51% of respondents (n=1700) were classified as early stage disease at diagnosis. Early disease survivors accounted for 56% of ROI respondents (n=1431) and 35% of NI respondents (n=269). Overall, 21% of respondents had late disease (n=689), and this comprised 36% of NI responders (n= 282) and 16% of ROI responders (n= 407). This left 959 (29% overall) in the 'other' group, representing an almost identical percentage of respondents from ROI (28%) and NI (29%).

Men with early disease at diagnosis

There were no differences between early disease patients in NI and ROI in terms of age or co-morbidities at diagnosis, current age, marital status, or (not shown) living alone and family history. Responders with early disease from ROI were more likely to have been diagnosed 5-10 years previously (46% vs 35%); more often asymptomatic PSA-detected; more often treated with RP; less often treated with EBRT, ADT or AS/WW and less likely to report no symptoms at diagnosis. Men from NI were more often diagnosed in the previous 2-5 years and more likely to report increased frequency of urination at diagnosis (all $p < 0.001$; Table 1).

There were no significant differences between early disease patients from NI and ROI in reported 'current' prostate cancer-related physical symptoms for urinary incontinence (overall weighted percentage, 15%), libido loss (42%), erectile dysfunction (56%), breast changes (5%), hot flashes (9%) or reporting at least one physical symptom (76%). Significant differences existed in univariate analysis for bowel problems and fatigue, both of which were more common in NI (Table 2). In multivariate analysis adjusting for age, comorbidities, time since diagnosis and method of diagnosis (model 1), these differences remained significant. When treatment was added (model 2) only bowel problems remained significant (OR 1.8, 95%CI 1.26 - 2.56 p=0.001) (Table 2).

Table 2: Prostate Cancer Related Physical Symptoms - Early disease patients

Stage I/II - Gleason 2-7			Univariate model	Multivariate model 1**	Multivariate model 2***
Ongoing side effect	**Weighted proportion**		**Odds ratio (NI vs. ROI)**	**Odds ratio (NI vs. ROI)**	**Odds ratio (NI vs. ROI)**
	ROI	**NI**	**(ROI as baseline)**	**(ROI as baseline)**	**(ROI as baseline)**
Urinary incontinence	14.3%	17.8%	1.26 (0.90,1.74) p=0.173	1.12 (0.81,1.56) p=0.485	1.43 (0.99,2.07) p=0.057
Loss of libido	41.3%	48.0%	1.27 (0.98,1.64) p=0.068	1.30 (1.00,1.69) p=0.046	1.20 (0.91,1.59) p=0.198
Erectile Dysfunction	56.1%	56.9%	1.01 (0.78,1.30) p=0.950	1.16 (0.88,1.52) p=0.289	1.24 (0.92,1.68) p=0.163
Bowel problems	11.5%*	21.1%*	**2.07*** (1.49,2.89) p<0.001	**1.87*** (1.32,2.64) p<0.001	**1.80*** (1.26,2.56) p=0.001
Breast changes	4.6%	7.9%	1.78 (1.12,2.83) p=0.015	1.63 (1.02,2.59) p=0.042	0.93 (0.56,1.54) p=0.772
Hot flashes	8.4%	10.9%	1.30 (0.87,1.94) p=0.199	1.15 (0.76,1.74) p=0.503	0.70 (0.44,1.13) p=0.144
Fatigue	17.0%*	28.7%*	**1.98*** (1.47,2.66) p<0.001	**1.76*** (1.30,2.39) p<0.001	1.53 (1.12,2.10) p=0.008

Note: *Results are weighted by country, age at diagnosis and time since diagnosis*
** Significant difference between countries*
*** Logistic regression model adjusted for age at questionnaire completion, number of comorbidities at diagnosis, time since diagnosis, method of diagnosis*
**** Logistic regression model adjusted for the above plus prostatectomy, External beam radiotherapy, Brachytherapy and Hormone Therapy Records with missing treatment or method of diagnosis dropped from all models (n=60) Significant difference at p<0.05 but with Bonferonni correction applied*

For health utility and HRQoL, better outcomes among men from ROI than NI were suggested in univariate analysis by higher scores for EQ-5D-5L, QLQ-C30 physical and role functioning and lower scores for QLQ-C30 fatigue, pain dyspnoea and insomnia. Apart from physical functioning and insomnia, these differences remained significant in multivariate model 1; however only pain (which was higher for men from NI) remained significant when treatment was added (model 2). (ROI: 11.1 NI: 19.4, risk estimate 5.829, CI. 2.349-9.308,p=0.001), (Table 2), In terms of psychological wellbeing, there were no significant differences between ROI and NI for depression, anxiety or distress scores in univariate or multivariate analysis (Table 3).

Table 3: Patient reported Health Utility, Health Related Quality of life and psychological Wellbeing outcomes - Early stage Prostate Cancer- ROI vs NI

Outcome and instrument/ subscale	Weighted mean		Univariate model NI vs. ROI				Multivariate model 1** NI vs. ROI				Multivariate model 2*** NI vs. ROI)			
	ROI	NI	Co-efficient	95% CI		p-value	Co-efficient	95% CI		p-value	Co-efficient	95% CI		p-value
Health Utility														
EQ-5D-5L score	0.9	0.8	-0.072	-0.103	-0.041	0.001	-0.052	-0.082	-0.022	0.001*	-0.040	-0.071	-0.008	0.013
Health Related Quality of Life														
QLQ-C30: Global health status	72.5	74.1	1.549	-1.367	4.466	0.298	3.318	0.400	6.237	0.026	4.063	1.024	7.101	0.009
QLQ-C30: Physical functioning	85.9	80.6	-5.297	-8.480	-2.114	0.001*	-3.357	-6.361	-0.352	0.029	-2.029	-5.103	1.046	0.196
QLQ-C30: Role functioning	85.7	77.3	-8.359	-12.335	-4.384	0.0001*	-6.781	-10.742	-2.821	0.001*	-5.218	-9.263	-1.174	0.011
QLQ-C30: Emotional functioning	84.8	82.0	-2.770	-5.682	0.141	0.062	-0.887	-3.745	1.970	0.543	0.097	-2.797	2.991	0.948
QLQ-C30: Cognitive functioning	83.9	81.3	-2.578	-5.278	0.122	0.061	-0.782	-3.515	1.952	0.575	-0.503	-3.316	2.311	0.726
QLQ-C30: Social functioning	86.1	81.1	-5.004	-8.488	-1.520	0.005	-3.283	-6.803	0.237	0.068	-2.437	-6.097	1.222	0.192
QLQ-C30: Fatigue	19.9	27.2	7.299	4.178	10.421	0.0001*	5.167	2.068	8.266	0.001*	3.893	0.703	7.082	0.017
QLQ-C30: Nausea and vomiting	3.1	3.8	0.717	-0.545	1.979	0.265	-0.115	-1.437	1.207	0.865	-0.732	-2.268	0.805	0.350
QLQ-C30: Pain	11.1	19.4	8.264	4.882	11.645	0.0001*	6.399	3.053	9.745	0.0001*	5.829	2.349	9.308	0.001*
QLQ-C30: Dyspnoea	12.2	19.9	7.711	3.962	11.461	0.0001*	6.125	2.382	9.869	0.001*	5.336	1.376	9.296	0.008
QLQ-C30: Insomnia	21.0	28.3	7.272	3.230	11.315	0.0001*	4.995	1.018	8.972	0.014	3.588	-0.565	7.741	0.090
QLQ-C30: Appetite loss	5.2	7.1	1.848	-0.580	4.276	0.136	0.451	-1.999	2.900	0.718	0.347	-2.241	2.934	0.793
QLQ-C30: Constipation	11.5	11.4	-0.155	-3.243	2.934	0.922	-1.868	-4.976	1.240	0.239	-1.731	-4.907	1.445	0.285
QLQ-C30: Diarrhoea	8.8	8.2	-0.624	-2.938	1.690	0.597	-1.585	-3.973	0.803	0.193	-1.954	-4.579	0.671	0.144
QLQ-C30: Financial difficulties	10.2	9.8	-0.392	-2.958	2.174	0.765	-1.454	-4.091	1.182	0.279	-1.713	-4.460	1.034	0.221
Psychological Wellbeing														
DASS: Distress	4.9	6.4	1.559	0.403	2.715	0.008	1.062	-0.095	2.219	0.072	0.652	-0.529	1.834	0.279
DASS: Anxiety	3.2	4.5	1.285	0.375	2.195	0.006	0.893	-0.010	1.797	0.053	0.828	-0.070	1.725	0.071
DASS: Depression	4.0	4.9	0.957	-0.089	2.002	0.073	0.620	-0.417	1.657	0.241	0.402	-0.688	1.492	0.469

Note: *Results are weighted by country, age at diagnosis and time since diagnosis with ROI as baseline*

** Significant difference between countries*

*** Linear regression model adjusted for current age, number of co-morbidities, time since diagnosis, method of diagnosis*

**** Linear regression model adjusted for above plus prostatectomy, External beam radiotherapy, Brachytherapy and Hormone Therapy*

Note: *higher symptom scores indicate more/worse symptoms or where appropriate better functioning or quality of life*

Men with late disease at diagnosis

There were no differences in current age, time since diagnosis, family history of prostate cancer or specific comorbidities at diagnosis between ROI and NI men with late disease (not shown). Responders with late disease from the ROI more often were under age 60 at diagnosis and reported no comorbidities at diagnosis. Men with late disease from NI more often reported urinating more frequently at diagnosis; they also more often presented symptomatically, were less often treated with RP and were more often treated with EBRT or ADT (All $p < 0.001$ Table 1).

In terms of physical cancer-related symptoms in men with late disease, there were no significant differences for ongoing urinary incontinence (overall weighted percentage 20%), erectile dysfunction (67%) or bowel problems (17%) between men from NI and ROI. Loss of libido, breast changes, hot flashes and fatigue were significantly more frequently reported in men from NI. These differences remained after adjustment for age, comorbidities, time since diagnosis and method of diagnosis (model 1); but when treatment was added to the model (model 2) only breast changes (OR 2.3, 95%CI 1.41-3.73) and hot flashes (OR 2.33, 95% CI 1.55- 3.51) remained significant although the odds ratios were attenuated (Table 4).

Table 4: Prostate Cancer Related Physical Symptoms – Late Disease Patients
Stage III/IV - Any Gleason

Ongoing side effect	Weighted proportion		Univariate model Odds ratio (NI vs. ROI)	Multivariate model 1** Odds ratio (NI vs. ROI)	Multivariate model 2*** Odds ratio (NI vs. ROI)
	ROI	NI	(ROI as baseline)	(ROI as baseline)	(ROI as baseline)
Urinary incontinence	22.2%	15.9%	0.65 (0.44,0.97) p=0.035	0.66 (0.44,0.99) p=0.047	0.88 (0.55,1.41) p=0.591
Loss of libido	51.6%*	64.7%*	1.68* (1.22,2.31) p=0.001	1.61* (1.16,2.23) p=0.005	1.32 (0.92,1.90) p=0.129
Erectile dysfunction	66.9%	66.4%	0.95 (0.68,1.33) p=0.784	1.09 (0.77,1.55) p=0.623	1.29 (0.87,1.89) p=0.202
Bowel problems	14.2%	21.7%	1.60 (1.07,2.39) p=0.021	1.40 (0.90,2.16) p=0.133	1.19 (0.75,1.87) p=0.458
Breast changes	9.4%*	23.3%*	2.80* (1.81,4.32) p<0.001	3.09* (1.94,4.91) p<0.001	2.30* (1.41,3.73) p=0.001
Hot flashes	18.8%*	41.1%*	2.95* (2.08,4.18) p<0.001	2.79* (1.95,3.99) p<0.001	2.33* (1.55,3.51) p<0.001
Fatigue	24.6%*	39.0%*	1.93* (1.39,2.70) p<0.001	1.71* (1.20,2.44) p=0.003	1.53 (1.05,2.23) p=0.028

Note: *Results are weighted by country, age at diagnosis and time since diagnosis.* Significant difference between countries with ROI as baseline*
*** Logistic regression model adjusted for current age, number of comorbidities, time since diagnosis, method of diagnosis*
**** Logistic regression model adjusted for above plus prostatectomy, External beam radiotherapy, Brachytherapy and Hormone Therapy Records with missing treatment or method of diagnosis dropped from all models (n=12) Significant difference at p<0.05 but with Bonferonni correction applied*

For health utility, HRQoL and psychological wellbeing, only QLQ-C30 financial difficulties scores differed significantly in multivariate analyses (ROI: 17.9 vs NI: 10.4; model 2: coefficient= 8.629, CI -12.770—4.488, P<0.001) (Table 5).

Table 5: Patient reported Health Utility, Health Related Quality of life and psychological Wellbeing outcomes Late stage Prostate Cancer- ROI vs NI

Outcome scale	Weighted mean		Univariate model NI vs. ROI (i.e. ROI is baseline)				Multivariate model 1** NI vs. ROI (i.e. ROI is baseline)				Multivariate model 2*** NI vs. ROI (i.e. ROI is baseline)			
	ROI	NI	Coefficient	95% CI		p-value	Coefficient	95% CI		p-value	Coefficient	95% CI		p-value
Health Utilities														
EQ-5D-5L score	0.8	0.7	-0.061	0.102	0.020	0.004	-0.030	0.071	0.011	0.151	-0.027	0.071	0.017	0.233
Health Related Quality of Life														
QLC-C30: Global health status	67.8	71.2	3.405	-0.374	7.183	0.077	5.996	2.310	9.681	0.001*	5.472	1.525	9.420	0.007
QLC-C30: Physical functioning	78.6	75.2	-3.432	-7.457	0.594	0.095	0.476	-3.450	4.402	0.812	1.174	-3.174	5.522	0.596
QLC-C30: Role functioning	75.7	72.2	-3.520	-8.653	1.613	0.179	0.140	-5.055	5.335	0.958	1.355	-4.423	7.134	0.645
QLC-C30: Emotional functioning	81.0	82.1	1.091	-2.532	4.715	0.554	3.014	-0.614	6.643	0.103	3.750	-0.280	7.781	0.068
QLC-C30: Cognitive functioning	79.9	79.3	-0.538	-4.367	3.291	0.783	1.754	-1.990	5.498	0.358	1.818	-2.300	5.937	0.386
QLC-C30: Social functioning	76.4	76.6	0.231	-4.245	4.707	0.919	2.581	-1.991	7.154	0.268	2.915	-2.081	7.911	0.252
QLC-C30: Fatigue	27.1	31.6	4.542	0.322	8.762	0.035	0.838	-3.352	5.028	0.695	-0.607	-5.189	3.976	0.795
QLC-C30: Nausea and vomiting	6.2	5.3	-0.844	-3.227	1.540	0.487	-1.762	-4.426	0.903	0.195	-1.949	-4.800	0.902	0.180
QLC-C30: Pain	17.5	23.8	6.325	1.986	10.664	0.004	3.689	-0.715	8.094	0.101	2.638	-2.218	7.494	0.287
QLC-C30: Dyspnoea	20.3	22.9	2.611	-2.213	7.434	0.288	-1.720	-6.391	2.951	0.470	-3.083	-8.216	2.050	0.239

QLC-C30: Insomnia	26.2	26.7	0.518	-4.594	5.629	0.842	-2.442	-7.522	2.638	0.346	-3.823	-9.618	1.972	0.196
QLC-C30: Appetite loss	8.4	9.8	1.335	-1.990	4.661	0.431	-0.716	-4.357	2.926	0.700	-1.686	-5.641	2.268	0.403
QLC-C30: Constipation	14.4	14.3	-0.069	-4.036	3.898	0.973	-2.397	-6.641	1.847	0.268	-2.738	-7.258	1.783	0.235
QLC-C30: Diarrhoea	11.4	12.2	0.793	-2.844	4.430	0.669	-0.566	-4.298	3.165	0.766	-1.182	-5.181	2.817	0.562
QLC-C30: Financial difficulties	17.9	10.4	-7.454	-11.176	-3.731	0.0001*	-8.137	-11.772	-4.503	0.0001*	-8.629	-12.770	-4.488	0.0001*
Psychological Wellbeing														
DASS: Stress	5.7	6.3	0.644	-0.805	2.093	0.383	0.360	-1.062	1.781	0.620	0.743	-0.816	2.301	0.350
DASS: Anxiety	3.9	4.4	0.477	-0.641	1.596	0.402	-0.151	-1.292	0.991	0.796	-0.086	-1.342	1.170	0.893
DASS: Depression	5.1	5.7	0.581	-0.871	2.033	0.432	0.080	-1.366	1.526	0.914	0.172	-1.431	1.775	0.833

Note: *Results are weighted by country, age at diagnosis and time since diagnosis*

** Significant difference between countries*

*** Logistic regression model adjusted for current age, number of comorbidities, time since diagnosis, method of diagnosis*

**** Logistic regression model adjusted for age, number of comorbidities, time since diagnosis, method of diagnosis, Treatment type- prostatectomy, External beam radiotherapy, Brachytherapy and Androgen Deprivation Therapy*

Note: *higher symptom scores indicate more/worse symptoms or where appropriate better functioning or quality of life*

'Other' group

Of the 'Other' group (n=959) 300 had stage I/II, high grade (8-10) disease, and the remainder had either unknown stage (n=171) and/or unknown grade (n=372; for116 both were unknown). There were no significant differences between responders from NI and ROI for any outcomes in the fully adjusted multivariate model (model 2).

Discussion

Using data from this large population-based sample of prostate cancer survivors of all ages, and who had received all forms of treatment, we compared men's reported physical symptoms, psychological wellbeing, health utility, and HRQoL between two countries with different policies and practices in relation to prostate cancer detection. This unique set of circumstances - where clinicians in ROI undertake more PSA testing of asymptomatic men in primary care and refer more men onto hospital for prostate biopsy resulting in a considerably higher incidence of prostate cancer than in NI - has resulted in differences between countries in the profile of prostate cancer, in terms of the socio-demographic characteristics of the men diagnosed, the distribution of disease stage and grade, and patterns of treatment utilisation[6] By examining early and late disease patients separately we have been able to determine if more investigation and treatment affects patient reported outcomes. We found that, while survivors from ROI were younger, with earlier disease and fewer comorbidities than those from NI, patient reported outcomes were similar when stratified by disease extent at diagnosis; indeed very few significant differences were found once adjustment had been made for patient characteristics and treatment.

The prostate cancer specific symptom reported as most distressing to men is urinary incontinence[17-18]. In this study, current urinary incontinence was reported by 15% of men who had been diagnosed with early disease and 20% of those with late disease, irrespective of jurisdiction and thus intensity of investigation. Erectile dysfunction is reported as a long term irreversible side effect of treatment[19] especially following prostatectomy[20]. The levels of erectile dysfunction - 56% in early disease and 67% in late disease - were the same in responders from NI and ROI and are similar to those reported in other population based surveys[21]. In early disease patients, only bowel problems, a recognised side effect of radiotherapy[21-

22] remained significantly higher in NI than ROI, after adjustment for patient characteristics and treatments. Patients with cancers at other sites, including the colon and rectum, receive radiotherapy to the bowel area; however colorectal cancer incidence rates and use of radiotherapy as treatment for this cancer is higher in ROI than NI[23]. Physical symptoms associated with ADT - breast changes, hot flashes and libido loss - were reported with a similar frequency by men from NI and ROI with early disease but were significantly more common in late disease patients from NI compared to ROI. The almost two fold higher levels of current ADT reported by men from NI compared to men from ROI was taken into account in the multivariate analysis. We did not, however, have data on the duration, type or dose of ADT used which might have affected the patient-reported outcomes. We further note that no between country-difference was found when the subgroup of men currently on ADT were analysed separately (data not shown).

Outcomes related to HRQoL, including functioning, general cancer symptoms, health utility and psychological wellbeing, showed only minimal variations between survivors from ROI and NI; in multivariate analyses pain was reported as higher in NI in early disease patients however using internationally recognised scales the observed difference in scores (between 19.4 and 11.1) would be considered only minimally clinically significant[23]. Pelvic pain is an acknowledged side effect of radiation treatment[21-22] and this was more often reported by men from NI. This greater utilisation of radiation in NI however was accounted for in the multivariate analysis. The finding might be explained by higher levels of disease progression or poorer control of pain in NI. We did not collect information on recurrence or use of pain control so could not explore this further. The significantly higher level of financial difficulties identified by men from ROI is possibly a reflection of cancer-related out-of-pocket costs borne by patients in ROI. Previous work in ROI, which included prostate cancer survivors, found that cancer-related financial stress and strain is common[24], and this may be, in part, a function of the complex mixed public-private healthcare system in operation. Other studies have shown associations between financial burden and psychological wellbeing and HRQoL among cancer patients/survivors[25].This may in part explain the lower, although not significant,

global health scores reported by men in ROI compared with men from NI (although no differences were detected in DASS-21 outcomes).

Comparisons between countries with different policies and practices concerning prostate cancer detection can make a valuable contribution to the debate on use of PSA to test for prostate cancer. We have shown that patient reported outcomes are very similar in ROI and NI despite different levels of PSA testing and diagnosed prostate cancer. However, it is important to set these findings in the context of the wider population. It has been estimated that between 1994 and 2005, compared to the 1994 disease levels, there were 5938 “extra” cases of Prostate Cancer diagnosed in ROI and 763 in NI[4] Since 2005, the numbers of Prostate Cancers in the two jurisdictions have continued to rise. As we have shown here and elsewhere, physical side-effects, such as erectile dysfunction and incontinence, are common among prostate cancer survivors in Ireland[20], echoing studies in other settings[19] . These side-effects can be viewed, in part, as a consequence of widespread PSA testing since, in the absence of testing, many of the men with side-effects may never had been detected with prostate cancer or, if they had been detected, this may have been at an older age so they would have had to live less time with side-effects. The burden of side-effects, in terms of the numbers (and rates) of men in the population living with these, is greater in ROI than NI (i.e. higher in the population with higher levels of PSA testing). This important population-level health impact of more intensive PSA testing – and the little (at best) impact of PSA testing on mortality[4] - needs to be considered alongside the findings from the current analysis.

Strengths

The same approaches were used in both areas for patient definition, recruitment, data collection and analysis. We used several validated instruments to assess patient-reported outcomes and categorised men by stage and grade of disease to help compensate for differences in the patient profile for the two populations. High-quality population-based cancer registries provided the basis for sampling of survivors and this also allowed population representativeness to be assessed and proportions weighted to the entire survivor population.

Limitations

As with many questionnaire studies, older men were less likely to respond but weighted proportions allowed adjustment for this[12]. We also recognise accuracy of recall as a potential limitation and this could be more of a problem with the older NI population and for men diagnosed longer ago. While the categorisation into early and late disease was loosely based on D'Amico criteria[27] PSA levels at diagnosis were not systematically available and Gleason scores were recorded in the Registries as a categorical variable, with a cut off at 7. Finally, we did not collect data from men in the population without prostate cancer (i.e. normative data) so we cannot be sure that there the background prevalence of physical symptoms, such as ED, or levels of HRQOL or psychological wellbeing do not differ between NI and ROI.

Conclusion:

In this population-based study, following twenty years of higher levels of PCa detection in ROI than NI, health outcomes among PCa survivors differed little between countries. However the increased intensity of investigation has resulted in many additional men with ongoing physical symptoms in ROI, a risk for all areas with higher levels of testing.

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Results were disseminated to participants on request and available via Prostate Cancer UK and NICR websites.

Competing Interest

Prof Linda Sharp received an unrestricted grant 2011-2012 from Sanofi-aventis for research into 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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Research Ethics Committees for NI (ORECNI), 10/NIR03/61

Data Sharing

Extra data are available by emailing a.gavin@qub.ac.uk

Author contribution

Achievement of funding AG, LS,CD, study design CD, AG, LS, FJD, GJG, data analysis DD, EM, AG, data interpretation and drafting AG, LS, FJD, CD, EM, DD. All authors approved the final version.

Licence

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Supplementary Table 1: Characteristics of 'other' category to be kept as a supplementary table

					Weighted		
					NI		Total
Stage I/II	High (8 to 10)				248	52	300
	Unknown	157			168	3	171
Unknown	Low (2 to 4)	34		46	32	8	40
	Intermediate (5 to 7)	147	100	247	164	101	265
	High (8 to 10)	36	32	68	41	25	67
	Unknown	65	43	108	76	39	116
Total Patients		664	258	922	730	229	959

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6,7,8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6,7,8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6,7
Bias	9	Describe any efforts to address potential sources of bias	*8*
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6,7,8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	8
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	8
		(*e*) Describe any sensitivity analyses	N/A
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	6
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	At bottom of tables
Outcome data	15*	Report numbers of outcome events or summary measures	Tables
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Tables
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	9,10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	24
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	21,22,23
Generalisability	21	Discuss the generalisability (external validity) of the study results	24
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	25

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Effect of more intense investigation and treatment of prostate cancer on survivor's physical symptoms, psychological wellbeing and health related quality of life: a two country observational study

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Effect of investigation intensity and treatment differences on prostate cancer survivor's physical symptoms, psychological wellbeing and health related quality of life: a two country cross-sectional study

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Keywords: Prostate cancer, survivors, patient reported outcomes, PSA testing

Abstract

Aim

To investigate effects on men's health and wellbeing of higher prostate cancer (PCa) investigation and treatment levels in similar populations.

Subjects

PCa survivors in Ireland where the Republic of Ireland (RoI) has 50% higher PCa incidence than Northern Ireland (NI).

Method

A cross-sectional postal questionnaire was sent to PCa survivors 2-18 years post-treatment, seeking information about current physical effects of treatment, health-related quality-of-life (HRQoL; EORTC QLQ-C30; EQ-5D-5L) and psychological wellbeing (DASS-21). Outcomes in RoI and NI survivors were compared, stratifying into 'late disease' (stage III/IV and any Gleason Grade (GG) at diagnosis), and 'early disease' (stage I/II and GG 2-7). Responses were weighted by age, jurisdiction and time since diagnosis. Between-country differences were investigated using multivariate logistic and linear regression.

Results

3,348 men responded (RoI n=2567; NI, n=781;reflecting population sizes, response rate 54%). RoI responders were younger; less often had comorbidities(45% vs 38%); were more likely to present asymptomatically(66%; 41%) or with early disease (56%; 35%); and less often currently used androgen deprivation therapy (ADT; 2%; 28%). Current prevalence of incontinence(16%) and impotence (56% early disease, 67% late disease) did not differ between RoI and NI. In early disease, only current bowel problems(RoI 12%; NI 21%) differed significantly in multivariate analysis. In late disease, NI men reported significantly higher levels of gynaecomastia (23% vs 9%), and hot flashes(41% vs 19%), but when ADT-users were analysed separately differences disappeared. For HRQoL, in multivariate analysis, only pain (early disease: RoI 11.1, NI 19.4) and financial difficulties (late disease: RoI 10.4, NI 7.9) differed significanty between countries. There were no significant between-country differences in DASS21 or index ED-5D-5L score.

Conclusion

Treatment side-effects were commonly reported and increased PCa detection in RoI has left more men with these side-effects. We recommended men are offered a PSA test only after informed discussion.

Strengths and limitations of this study

- This large study used the same approaches in both geographical areas for patient definition, recruitment, data collection and analysis with validated instruments used to assess patient-reported outcomes. Also men were categorised for analysis by stage and grade of disease to help compensate for differences in the patient profile of the two populations.
- High-quality population-based cancer registries provided the basis for sampling allowing population representativeness to be assessed and proportions weighted to the entire survivor population.
- Lack of information on baseline health at diagnosis and symptoms at diagnosis are potential limitation and we acknowledge this could be more of a problem with the older NI population and for men diagnosed longer ago however health and HRQol effects were measures as reported currently.
- While the categorisation into early and late disease was loosely based on D'Amico criteria PSA levels at diagnosis were not systematically available and Gleason scores were recorded in the Registries as a categorical variable, with a cut off at 7.
- We did not collect data from men in the population without prostate cancer (i.e. normative data) so we cannot be sure that there the background prevalence of physical symptoms, such as ED, or levels of HRQOL or psychological wellbeing do not differ between NI and ROI. (A normative study is however underway).

Introduction

Age standardised prostate cancer incidence has increased over the past two decades associated with increased use of PSA testing[1] so that now in many countries it is the most common cancer among males[2]. The debate about the value of PSA testing for the early detection of Prostate Cancer continues. While a simple blood test and the prospect of earlier cancer diagnosis are appealing, poor specificity leads to over diagnosis of clinically insignificant cancers[3]. To be considered effective, screening must reduce overall and disease specific mortality and morbidity and not just detect more disease. Only one large long term randomised

controlled trial has identified a significant reduction in deaths associated with PSA "screening", but this was accompanied with a high level of over diagnosis and associated treatment[4]. Despite this, marked international variations in Prostate Cancer incidence rates points to widespread use of PSA testing for unsuspected prostate cancer[2] and recent calls to offer men in their 40s access to the PSA test is likely to further increase numbers diagnosed. [5] In light of this, and in order to inform the PSA debate, it would be of value to determine whether more investigation and treatment improves men's self-reported health outcomes, especially in the long-term.

Circumstances exist in Ireland where different intensities of PSA testing and subsequent biopsy between its two jurisdictions, Republic of Ireland (ROI) and Northern Ireland (NI), exist in populations which are similar in lifestyle and ethnic and genetic makeup[6]. Both jurisdictions have high quality population-based cancer registries which have tracked prostate cancer incidence since the early 1990s[7-8]. The ROI has a complex mixed public–private healthcare system and rates of PSA testing in men aged 50 and older rose by 23% per annum between 1993 and 2005[6]. In 2006 the National Cancer Forum recommended against the introduction of PSA screening, however high levels of testing persisted [9]. In contrast NI has a predominantly publicly funded healthcare system similar to the NHS and has encouraged following of the National Screening Committee's advice in 2002 and NICE guidelines (2008) aimed at limiting the use of PSA testing in primary care[10,11]. Nevertheless, there is evidence of screening for prostate cancer in the NI population[12] although at markedly lower levels (annual percentage change 1993 to 2003 = +9.7%) than in ROI[6]. Consequently, since 1994, when Prostate Cancer incidence rates were similar, the age-standardised incidence rate has risen by 222% in ROI compared to 161% in NI. These unique circumstances allow us to investigate the effect of more intense investigation and treatment of prostate cancer on men's health and wellbeing.

Methods

This work was undertaken as part of the PiCTure (Prostate Cancer Treatment, *your experience*) study, which was conducted in ROI and NI, the methods of which have been described previously[13] and in short are described below.

Patient Involvement

Patients were involved in study steering group, piloting of questionnaire and interpretation of results.

Subjects/patients

Following ethical approvals, a population-based sample of all men diagnosed with invasive Prostate Cancer (ICD10 C61) between 1st January 1995 and 31st March 2010, and alive November 2011, was selected from the two population-based cancer registries (n=22,823). From this a country and time- with approximately the same numbers under and over 5 years since-diagnosis) stratified random sample of 12,322 men was selected. This was required as there were fewer survivors diagnosed in the earlier years for two reasons, one, the levels of prostate cancer diagnosed were lower and secondly as at least 50% of prostate cancer cases are over 70 when diagnosed so mortality would have reduced numbers.

Patients' General Practitioners (GP) / health care professionals were contacted to screen men for eligibility to participate in the study. Men were eligible if they were i) alive, ii) aware of their Prostate Cancer diagnosis, iii) well enough to receive and complete a questionnaire (in particular, had no cognitive impairment), iv)able to understand English and v) resident in ROI or NI. Following this process, 6,559 prostate cancer survivors were deemed eligible to be sent a questionnaire. Questionnaires were posted in 2012. Non-responders received up to two written reminders.

Outcome measures

The primary outcome variables for this analysis were determined by questionnaire and were

1. Prostate cancer related physical symptoms 'currently' experienced (i.e. present at time of questionnaire completion) (erectile dysfunction, urinary incontinence, bowel problems, loss of libido, gynaecomastia and hot flashes/sweats).
2. Health utility on the day of questionnaire completion, measured by the EQ-5D-5L which comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 possible levels of response: *no problems, slight, moderate, severe or unable to undertake the particular action*. The EQ-5D-5L health states were converted to EQ-5D-3L states and UK valuations applied to provide a single index value of up to 1 (since there are no valuations specifically for Ireland and NI is part of the UK)[14-15]; higher values indicate better/more health utility.

3. Health-related quality-of-life in the past week measured using the EORTC QLQ-C30[16] a general cancer questionnaire comprising a global health score (GHS), five functional subscales (measuring physical, role, emotional, cognitive, and social functioning) and nine general cancer symptom subscales (assessing fatigue, nausea/vomiting, pain, dyspnoea, sleep disturbance, loss of appetite, constipation, diarrhoea and financial difficulties). Response options range from 1 (not at all) to 4 (very much), except for the two questions comprising the GHS, responses to which ranged from 1 (very poor) to 7 (excellent). Scores on each subscale were transformed to 0-100 as recommended, with higher scores indicating better HRQOL, higher functioning or worse symptoms)[16].
4. Psychological wellbeing during the past week, assessed by the 21 question version of the Depression, Anxiety and Stress Scale (DASS-21)[17] which contains three subscales which measure depression, anxiety and (di)stress. Each subscale is based upon seven questions with responses scored from 0 (did not apply) to 3 (applied to me very much, or most of the time). A summary score for each subscale was generated by doubling the sum of the individual responses. Possible scores on each scale range from 0-42, with higher scores indicating higher levels of depression, anxiety or stress.

Explanatory variables

Men were asked to report all treatments received, by answering yes/no to a list of treatments (radical prostatectomy, (RP), external bean radiotherapy (EBRT), Androgen deprivation therapy (ADT), active surveillance (AS), watchful waiting (WW) and brachytherapy (BT)). The questionnaire also requested information on socio-demographic characteristics, method of diagnosis ("symptomatic clinically detected" or "asymptomatic PSA detected")[13] and health at diagnosis, in particular urinary (increase frequency, pain while urinating, blood in urine) or sexual (impotence/erectile dysfunction) symptoms (yes/no) and presence of comorbidities (which men were invited to select from a list comprising heart or lung disease, stroke, diabetes, high blood pressure, diverticular disease, bowel problems (eg constipation/diarrhoea), other cancer, depression or other).

Date of diagnosis, stage at diagnosis (Tumour-Lymph node-Metastasis (TNM) classification) and Gleason grade (GG) for all men who were sent questionnaires were extracted from the cancer registries. GG is collected by the ROI cancer registry (NCRI) as a categorical variable (low (GG 2-4), medium (GG 5-7) or high grade (GG 8-10), so these categories were used in

analysis. Supplementary staging information was abstracted from medical records for NI respondents in early years when staging levels in the NI cancer registry (NICR) were low.

Statistical Analysis

The goal of the analysis was to compare health and wellbeing between men from ROI and NI. However the characteristics of the populations of prostate cancer patients and therefore the populations of survivors and respondents differed between ROI and NI, notably in the proportions of early and late disease. To overcome this, and because disease extent at diagnosis is likely to be an important determinant of health and wellbeing, analyses adjusted for socio-demographic and clinical characteristics were undertaken and outcomes were analysed separately for two main categories: 'late disease' defined as stage III or IV and any GG at diagnosis and 'early disease' defined as stage I/II and GG 2-7 at diagnosis. A third group, 'other' which included those without stage or grade or with early stage and high grade was also created and summary findings are reported for completeness.

Survey responses were weighted by age, country and time since diagnosis to compensate for higher non-response in certain survivor subgroups[13] and increase representativeness of the results to the entire prostate cancer survivor population.

Differences in proportions of patient characteristics, symptom and functional scores and DASS-21 subscales between survivors from NI and ROI were tested using z-tests and chi-square tests for early and late disease separately. Multivariate regression models (logistic for physical symptoms and linear for health utility, HRQoL and psychological wellbeing) were developed using a staged approach. The first model adjusted for age at questionnaire completion, number of comorbidities at diagnosis, time since diagnosis and method of diagnosis ("model 1"). The second model ("model 2") then added treatments (RP, EBRT, BT, ADT) since treatment utilisation differs between ROI and NI. Records with missing treatment or method of diagnosis were dropped from all models (n=60).

Significance was at the 5% level with the Bonferroni correction applied to compensate for multiple comparisons (see table footnotes for details of significance levels for each analysis).

Results

3,348 men responded, providing a 54% overall response rate after adjustment for men who were discovered to be ineligible following questionnaire dispatch. 70% of responders were from ROI (n=2567) and 30% (n=781) from NI reflecting the different country population numbers.

Almost half of respondents (48%) were surveyed 2- 4·9 years post-diagnosis, 32% were 5-9·9 years and 20% were ≥10 years after diagnosis. Respondents' average age at diagnosis was 64·9 years (standard deviation 7·6). Men from ROI were younger, more often reported asymptomatic PSA detection of their cancer and more often presented without urinary symptoms or without comorbidities compared to respondents from NI (all $p < 0.001$). Respondents from NI more often reported having ADT or EBRT, and less often having RP or BT compared to respondents from ROI (Table 1).

Table 1: Characteristics of men and treatment received by disease category and jurisdiction (weighted proportions)

	Early Disease**		Late Disease***		All Respondents- (includes those classified as 'other')	
	ROI	NI	ROI	NI	ROI	NI
Weighted numbers	1431	269	407	282	2567	781
Age at diagnosis > 70 years	27.6%	32.9%	30.3%	38.4%	32.4%*	40%*
Age at diagnosis < 60 years	25.2%	21.8%	25.6%*	15%*	22.8%*	17.4%*
Symptomatic clinically detected	28.3%*	51.4%*	37.5*	59.0*	32.3%*	58.2%*
Asymptomatic PSA detected	70.2%*	48.4%*	61.3%*	40.4*%	66.2%*	41.1%*
No symptoms at diagnosis	38.3%*	24.2%*	35.8%*	23.8%*	36.7%*	23.0%*
Urinating more frequently at diagnosis	45.9%*	64.3%*	45.0%*	58.3%*	47.5%*	62.7%*
No comorbidities at diagnosis	45.4%	39.0%	51.2%*	34.9%*	45.2%*	38.0%*
Radical prostatectomy	34.8%*	15.7%*	39.2%	10.5%*	30.9%*	13.9%*
External beam	51.5%*	64.4%*	64.1%*	79.1%*	55.7%*	64.1%*

	Early Disease**		Late Disease***		All Respondents- (includes those classified as 'other')	
radiotherapy						
Brachytherapy	7.4%	4.9%	3.2%	0%	6.6%*	1.8%*
Androgen Deprivation Therapy (ever)	27.9%*	60.0%*	52.5%*	87.1%*	37.3%*	71.9%*
Chemotherapy	1%	0.3%	3.8%	3.7%	2%	1.8%
Active Surveillance/ Watchful Waiting	5%*	10.2%*	1.3%	0.2%	4.7%	5.7%
No treatment	2.9%	1.8%	2.0%	0.0%	3.2%	2.5%

Note: *Results are weighted by country, age at diagnosis and time since diagnosis*
** Significant difference at (notional p<0.05, p< 0.001with Bonferonni correction applied)*
*** Early = Stage I / II Gleason grade 2-7*
**** Late = Stage III / IV any Gleason grade*

Overall 51% of respondents (n=1700) were classified as early stage disease at diagnosis. Early disease survivors accounted for 56% of ROI respondents (n=1431) and 35% of NI respondents (n=269). Overall, 21% of respondents had late disease (n=689), and this comprised 36% of NI responders (n= 282) and 16% of ROI responders (n= 407). This left 959 (29% overall) in the 'other' group, representing an almost identical percentage of respondents from ROI (28%) and NI (29%).

Men with early disease at diagnosis

There were no differences between early disease patients in NI and ROI in terms of age or co-morbidities at diagnosis, current age, marital status, or (not shown) living alone and family history. Responders with early disease from ROI were more likely to have been diagnosed 5-10 years previously (46% vs 35%); more often asymptomatic PSA-detected; more often treated with RP; less often treated with EBRT, ADT or AS/WW and more likely to report no symptoms at diagnosis. Men from NI were more often diagnosed in the previous 2-5 years and more likely to report increased frequency of urination at diagnosis (all $p < 0.001$; Table 1).

There were no significant differences between early disease patients from NI and ROI in reported 'current' prostate cancer-related physical symptoms for urinary incontinence (overall weighted percentage, 15%), libido loss (42%), erectile dysfunction (56%), breast changes (5%),

hot flashes (9%) or reporting at least one physical symptom (76%). Significant differences existed in univariate analysis for bowel problems and fatigue, both of which were more common in NI (Table 2). In multivariate analysis adjusting for age, comorbidities, time since diagnosis and method of diagnosis (model 1), these differences remained significant. When treatment was added (model 2) only bowel problems remained significant (OR 1.8, 95%CI 1.26 - 2.56 p=0.001) (Table 2).

Table 2: Prostate Cancer Related Physical Symptoms - Early disease patients

Stage I/II - Gleason 2-7			Univariate model	Multivariate model 1**	Multivariate model 2***
Ongoing side effect	**Weighted proportion**		**Odds ratio (NI vs. ROI)**	**Odds ratio (NI vs. ROI)**	**Odds ratio (NI vs. ROI)**
	ROI	**NI**	**(ROI as baseline)**	**(ROI as baseline)**	**(ROI as baseline)**
Urinary incontinence	14.3%	17.8%	1.26 (0.90,1.74) p=0.173	1.12 (0.81,1.56) p=0.485	1.43 (0.99,2.07) p=0.057
Loss of libido	41.3%	48.0%	1.27 (0.98,1.64) p=0.068	1.30 (1.00,1.69) p=0.046	1.20 (0.91,1.59) p=0.198
Erectile Dysfunction	56.1%	56.9%	1.01 (0.78,1.30) p=0.950	1.16 (0.88,1.52) p=0.289	1.24 (0.92,1.68) p=0.163
Bowel problems	11.5%*	21.1%*	**2.07*** (1.49,2.89) p<0.001	**1.87*** (1.32,2.64) p<0.001	**1.80*** (1.26,2.56) p=0.001
Breast changes (Gynaecomastia)	4.6%	7.9%	1.78 (1.12,2.83) p=0.015	1.63 (1.02,2.59) p=0.042	0.93 (0.56,1.54) p=0.772
Hot flashes	8.4%	10.9%	1.30 (0.87,1.94) p=0.199	1.15 (0.76,1.74) p=0.503	0.70 (0.44,1.13) p=0.144
Fatigue	17.0%*	28.7%*	**1.98*** (1.47,2.66) p<0.001	**1.76*** (1.30,2.39) p<0.001	1.53 (1.12,2.10) p=0.008

Note: *Results are weighted by country, age at diagnosis and time since diagnosis*

** Significant difference between countries*

*** Logistic regression model adjusted for age at questionnaire completion, number of comorbidities at diagnosis, time since diagnosis, method of diagnosis*

**** Logistic regression model adjusted for the above plus prostatectomy, External beam radiotherapy, Brachytherapy and Hormone Therapy Records with missing treatment or method of diagnosis dropped from all models (n=60) Significant difference at p<0.05 but with Bonferonni correction applied*

For health utility and HRQoL, better outcomes among men from ROI than NI were suggested in univariate analysis by higher scores for EQ-5D-5L, QLQ-C30 physical and role functioning and lower scores for QLQ-C30 fatigue, pain dyspnoea and insomnia. Apart from physical functioning and insomnia, these differences remained significant in multivariate model 1; however only pain (which was higher for men from NI) remained significant when treatment was added (model 2). (ROI: 11.1 NI: 19.4, co-efficient5.829, CI. 2.349-9.308,p=0.001), (Table 2), In terms of psychological wellbeing, there were no significant differences between ROI and NI for depression, anxiety or distress scores in univariate or multivariate analysis (Table 3).

Table 3: Patient reported Health Utility, Health Related Quality of life and psychological Wellbeing outcomes - Early stage Prostate Cancer- ROI vs NI

Outcome and instrument/ subscale	Weighted mean		Univariate model NI vs. ROI				Multivariate model 1** NI vs. ROI				Multivariate model 2*** NI vs. ROI)			
	ROI	NI	Co-efficient	95% CI		p-value	Co-efficient	95% CI		p-value	Co-efficient	95% CI		p-value
Health Utility														
EQ-5D-5L score	0.9	0.8	-0.072	-0.103	-0.041	0.001	-0.052	-0.082	-0.022	0.001*	-0.040	-0.071	-0.008	0.013
Health Related Quality of Life														
QLQ-C30: Global health status	72.5	74.1	1.549	-1.367	4.466	0.298	3.318	0.400	6.237	0.026	4.063	1.024	7.101	0.009
QLQ-C30: Physical functioning	85.9	80.6	-5.297	-8.480	-2.114	0.001*	-3.357	-6.361	-0.352	0.029	-2.029	-5.103	1.046	0.196
QLQ-C30: Role functioning	85.7	77.3	-8.359	-12.335	-4.384	0.0001*	-6.781	-10.742	-2.821	0.001*	-5.218	-9.263	-1.174	0.011
QLQ-C30: Emotional functioning	84.8	82.0	-2.770	-5.682	0.141	0.062	-0.887	-3.745	1.970	0.543	0.097	-2.797	2.991	0.948
QLQ-C30: Cognitive functioning	83.9	81.3	-2.578	-5.278	0.122	0.061	-0.782	-3.515	1.952	0.575	-0.503	-3.316	2.311	0.726
QLQ-C30: Social functioning	86.1	81.1	-5.004	-8.488	-1.520	0.005	-3.283	-6.803	0.237	0.068	-2.437	-6.097	1.222	0.192
QLQ-C30: Fatigue	19.9	27.2	7.299	4.178	10.421	0.0001*	5.167	2.068	8.266	0.001*	3.893	0.703	7.082	0.017
QLQ-C30: Nausea and vomiting	3.1	3.8	0.717	-0.545	1.979	0.265	-0.115	-1.437	1.207	0.865	-0.732	-2.268	0.805	0.350
QLQ-C30: Pain	11.1	19.4	8.264	4.882	11.645	0.0001*	6.399	3.053	9.745	0.0001*	5.829	2.349	9.308	0.001*
QLQ-C30: Dyspnoea	12.2	19.9	7.711	3.962	11.461	0.0001*	6.125	2.382	9.869	0.001*	5.336	1.376	9.296	0.008
QLQ-C30: Insomnia	21.0	28.3	7.272	3.230	11.315	0.0001*	4.995	1.018	8.972	0.014	3.588	-0.565	7.741	0.090
QLQ-C30: Appetite loss	5.2	7.1	1.848	-0.580	4.276	0.136	0.451	-1.999	2.900	0.718	0.347	-2.241	2.934	0.793
QLQ-C30: Constipation	11.5	11.4	-0.155	-3.243	2.934	0.922	-1.868	-4.976	1.240	0.239	-1.731	-4.907	1.445	0.285
QLQ-C30: Diarrhoea	8.8	8.2	-0.624	-2.938	1.690	0.597	-1.585	-3.973	0.803	0.193	-1.954	-4.579	0.671	0.144
QLQ-C30: Financial difficulties	10.2	9.8	-0.392	-2.958	2.174	0.765	-1.454	-4.091	1.182	0.279	-1.713	-4.460	1.034	0.221
Psychological Wellbeing														
DASS: Distress	4.9	6.4	1.559	0.403	2.715	0.008	1.062	-0.095	2.219	0.072	0.652	-0.529	1.834	0.279
DASS: Anxiety	3.2	4.5	1.285	0.375	2.195	0.006	0.893	-0.010	1.797	0.053	0.828	-0.070	1.725	0.071
DASS: Depression	4.0	4.9	0.957	-0.089	2.002	0.073	0.620	-0.417	1.657	0.241	0.402	-0.688	1.492	0.469

Note: *Results are weighted by country, age at diagnosis and time since diagnosis with ROI as baseline*
** Significant difference between countries*
*** Linear regression model adjusted for current age, number of co-morbidities, time since diagnosis, method of diagnosis*
**** Linear regression model adjusted for above plus prostatectomy, External beam radiotherapy, Brachytherapy and Hormone Therapy*
Note: *higher symptom scores indicate more/worse symptoms or where appropriate better functioning or quality of life*

Men with late disease at diagnosis

There were no differences in current age, time since diagnosis, family history of prostate cancer or specific comorbidities at diagnosis between ROI and NI men with late disease (not shown). Responders with late disease from the ROI more often were under age 60 at diagnosis and reported no comorbidities at diagnosis. Men with late disease from NI more often reported urinating more frequently at diagnosis; they also more often presented symptomatically, were less often treated with RP and were more often treated with EBRT or ADT (All $p < 0.001$ Table 1).

In terms of physical cancer-related symptoms in men with late disease, there were no significant differences for ongoing urinary incontinence (overall weighted percentage 20%), erectile dysfunction (67%) or bowel problems (17%) between men from NI and ROI. Loss of libido, breast changes, hot flashes and fatigue were significantly more frequently reported in men from NI. These differences remained after adjustment for age, comorbidities, time since diagnosis and method of diagnosis (model 1); but when treatment was added to the model (model 2) only breast changes (OR 2.3, 95%CI 1.41-3.73) and hot flashes (OR 2.33, 95% CI 1.55- 3.51) remained significant although the odds ratios were attenuated (Table 4).

Table 4: Prostate Cancer Related Physical Symptoms – Late Disease Patients
Stage III/IV - Any Gleason

			Univariate model	Multivariate model 1**	Multivariate model 2***
Ongoing side effect	**Weighted proportion**		**Odds ratio (NI vs. ROI)**	**Odds ratio (NI vs. ROI)**	**Odds ratio (NI vs. ROI)**
	ROI	**NI**	**(ROI as baseline)**	**(ROI as baseline)**	**(ROI as baseline)**
Urinary incontinence	22.2%	15.9%	0.65 (0.44,0.97) p=0.035	0.66 (0.44,0.99) p=0.047	0.88 (0.55,1.41) p=0.591
Loss of libido	51.6%*	64.7%*	1.68* (1.22,2.31) p=0.001	1.61* (1.16,2.23) p=0.005	1.32 (0.92,1.90) p=0.129
Erectile dysfunction	66.9%	66.4%	0.95 (0.68,1.33) p=0.784	1.09 (0.77,1.55) p=0.623	1.29 (0.87,1.89) p=0.202
Bowel problems	14.2%	21.7%	1.60 (1.07,2.39) p=0.021	1.40 (0.90,2.16) p=0.133	1.19 (0.75,1.87) p=0.458
Breast changes (Gynaecomastia)	9.4%*	23.3%*	2.80* (1.81,4.32) p<0.001	3.09* (1.94,4.91) p<0.001	2.30* (1.41,3.73) p=0.001
Hot flashes	18.8%*	41.1%*	2.95* (2.08,4.18) p<0.001	2.79* (1.95,3.99) p<0.001	2.33* (1.55,3.51) p<0.001
Fatigue	24.6%*	39.0%*	1.93* (1.39,2.70) p<0.001	1.71* (1.20,2.44) p=0.003	1.53 (1.05,2.23) p=0.028

Note: *Results are weighted by country, age at diagnosis and time since diagnosis.* Significant difference between countries with ROI as baseline*
*** Logistic regression model adjusted for current age, number of comorbidities, time since diagnosis, method of diagnosis*
**** Logistic regression model adjusted for above plus prostatectomy, External beam radiotherapy, Brachytherapy and Hormone Therapy Records with missing treatment or method of diagnosis dropped from all models (n=12) Significant difference at p<0.05 but with Bonferonni correction applied*

For health utility, HRQoL and psychological wellbeing, only QLQ-C30 financial difficulties scores differed significantly in multivariate analyses (ROI: 17.9 vs NI: 10.4; model 2: coefficient= 8.629, CI -12.770—4.488, P<0.001) (Table 5).

Table 5: Patient reported Health Utility, Health Related Quality of life and psychological Wellbeing outcomes Late stage Prostate Cancer- ROI vs NI

Outcome scale	Weighted mean		Univariate model NI vs. ROI (i.e. ROI is baseline)				Multivariate model 1** NI vs. ROI (i.e. ROI is baseline)				Multivariate model 2*** NI vs. ROI (i.e. ROI is baseline)			
	ROI	NI	Coefficient	95% CI		p-value	Coefficient	95% CI		p-value	Coefficient	95% CI		p-value
Health Utilities														
EQ-5D-5L score	0.8	0.7	-0.061	0.102	0.020	0.004	-0.030	0.071	0.011	0.151	-0.027	0.071	0.017	0.233
Health Related Quality of Life														
QLC-C30: Global health status	67.8	71.2	3.405	-0.374	7.183	0.077	5.996	2.310	9.681	0.001*	5.472	1.525	9.420	0.007
QLC-C30: Physical functioning	78.6	75.2	-3.432	-7.457	0.594	0.095	0.476	-3.450	4.402	0.812	1.174	-3.174	5.522	0.596
QLC-C30: Role functioning	75.7	72.2	-3.520	-8.653	1.613	0.179	0.140	-5.055	5.335	0.958	1.355	-4.423	7.134	0.645
QLC-C30: Emotional functioning	81.0	82.1	1.091	-2.532	4.715	0.554	3.014	-0.614	6.643	0.103	3.750	-0.280	7.781	0.068
QLC-C30: Cognitive functioning	79.9	79.3	-0.538	-4.367	3.291	0.783	1.754	-1.990	5.498	0.358	1.818	-2.300	5.937	0.386
QLC-C30: Social functioning	76.4	76.6	0.231	-4.245	4.707	0.919	2.581	-1.991	7.154	0.268	2.915	-2.081	7.911	0.252
QLC-C30: Fatigue	27.1	31.6	4.542	0.322	8.762	0.035	0.838	-3.352	5.028	0.695	-0.607	-5.189	3.976	0.795
QLC-C30: Nausea and vomiting	6.2	5.3	-0.844	-3.227	1.540	0.487	-1.762	-4.426	0.903	0.195	-1.949	-4.800	0.902	0.180
QLC-C30: Pain	17.5	23.8	6.325	1.986	10.664	0.004	3.689	-0.715	8.094	0.101	2.638	-2.218	7.494	0.287
QLC-C30: Dyspnoea	20.3	22.9	2.611	-2.213	7.434	0.288	-1.720	-6.391	2.951	0.470	-3.083	-8.216	2.050	0.239

QLC-C30: Insomnia	26.2	26.7	0.518	-4.594	5.629	0.842	-2.442	-7.522	2.638	0.346	-3.823	-9.618	1.972	0.196
QLC-C30: Appetite loss	8.4	9.8	1.335	-1.990	4.661	0.431	-0.716	-4.357	2.926	0.700	-1.686	-5.641	2.268	0.403
QLC-C30: Constipation	14.4	14.3	-0.069	-4.036	3.898	0.973	-2.397	-6.641	1.847	0.268	-2.738	-7.258	1.783	0.235
QLC-C30: Diarrhoea	11.4	12.2	0.793	-2.844	4.430	0.669	-0.566	-4.298	3.165	0.766	-1.182	-5.181	2.817	0.562
QLC-C30: Financial difficulties	17.9	10.4	-7.454	-11.176	-3.731	0.0001*	-8.137	-11.772	-4.503	0.0001*	-8.629	-12.770	-4.488	0.0001*
Psychological Wellbeing														
DASS: Stress	5.7	6.3	0.644	-0.805	2.093	0.383	0.360	-1.062	1.781	0.620	0.743	-0.816	2.301	0.350
DASS: Anxiety	3.9	4.4	0.477	-0.641	1.596	0.402	-0.151	-1.292	0.991	0.796	-0.086	-1.342	1.170	0.893
DASS: Depression	5.1	5.7	0.581	-0.871	2.033	0.432	0.080	-1.366	1.526	0.914	0.172	-1.431	1.775	0.833

Note: *Results are weighted by country, age at diagnosis and time since diagnosis*

** Significant difference between countries*

*** Logistic regression model adjusted for current age, number of comorbidities, time since diagnosis, method of diagnosis*

**** Logistic regression model adjusted for age, number of comorbidities, time since diagnosis, method of diagnosis, Treatment type- prostatectomy, External beam radiotherapy, Brachytherapy and Androgen Deprivation Therapy*

Note: *higher symptom scores indicate more/worse symptoms or where appropriate better functioning or quality of life*

'Other' group

Of the 'Other' group (n=959) 300 had stage I/II, high grade (8-10) disease, and the remainder had either unknown stage (n=171) and/or unknown grade (n=372; for116 both were unknown). There were no significant differences between responders from NI and ROI for any outcomes in the fully adjusted multivariate model (model 2) (see supplementary Table 1).

Discussion

Using data from this large sample of prostate cancer survivors of all ages, and who had received all forms of treatment, we compared men's reported physical symptoms, psychological wellbeing, health utility, and HRQoL between two countries with different policies and practices in relation to prostate cancer detection. This unique set of circumstances - where clinicians in ROI undertake more PSA testing of asymptomatic men in primary care and refer more men onto hospital for prostate biopsy resulting in a considerably higher incidence of prostate cancer than in NI - has resulted in differences between countries in the profile of prostate cancer, in terms of the socio-demographic characteristics of the men diagnosed, the distribution of disease stage and grade, and patterns of treatment utilisation[6] By examining early and late disease patients separately we are able to compare patient reported outcomes between two similar populations with different levels of investigation and treatment . We found that, while survivors from ROI were younger, with earlier disease and fewer comorbidities than those from NI, patient reported outcomes were similar when stratified by disease extent at diagnosis; indeed very few significant differences were found once adjustment had been made for patient characteristics and treatment.

The prostate cancer specific symptom reported as most distressing to men is urinary incontinence[18-19]. In this study, current urinary incontinence was reported by 15% of men who had been diagnosed with early disease and 20% of those with late disease, irrespective of jurisdiction and thus intensity of investigation. Erectile dysfunction is reported as a long term irreversible side effect of treatment[20] especially following prostatectomy[21]. The levels of erectile dysfunction - 56% in early disease and 67% in late disease - were the same in responders from NI and

ROI and are similar to those reported in other population based surveys[22]. In early disease patients, only bowel problems, a recognised side effect of radiotherapy[22-23] remained significantly higher in NI than ROI, after adjustment for patient characteristics and treatments. Patients with cancers at other sites, including the colon and rectum, receive radiotherapy to the bowel area; however colorectal cancer incidence rates and use of radiotherapy as treatment for this cancer is higher in ROI than NI[24]. Physical symptoms associated with ADT - breast changes, hot flashes and libido loss - were reported with a similar frequency by men from NI and ROI with early disease but were significantly more common in late disease patients from NI compared to ROI. The almost two fold higher levels of ever ADT reported by men from NI compared to men from ROI was taken into account in the multivariate analysis. We did not, however, have data on the duration, type or dose of ADT used which might have affected the patient-reported outcomes. We further note that no between country-difference was found when the subgroup of men currently on ADT were analysed separately (data not shown).

Outcomes related to HRQoL, including functioning, general cancer symptoms, health utility and psychological wellbeing, showed only minimal variations between survivors from ROI and NI; in multivariate analyses pain was reported as higher in NI in early disease patients however using internationally recognised scales the observed difference in scores (between 19.4 and 11.1) would be considered only minimally clinically significant[25]. Pelvic pain is an acknowledged side effect of radiation treatment[22-] and this was more often reported by men from NI. This greater utilisation of radiation in NI however was accounted for in the multivariate analysis. The finding might be explained by higher levels of disease progression or poorer control of pain in NI. We did not collect information on recurrence or use of pain control so could not explore this further. The significantly higher level of financial difficulties identified by men from ROI is possibly a reflection of cancer-related out-of-pocket costs borne by patients in ROI. Previous work in ROI, which included prostate cancer survivors, found that cancer-related financial stress and strain is common[26], and this may be, in part, a function of the complex mixed public-private healthcare system in operation. Other studies have shown associations between financial burden and psychological wellbeing and HRQoL among cancer

patients/survivors[27].This may in part explain the lower, although not significant, global health scores reported by men in ROI compared with men from NI (although no differences were detected in DASS-21 outcomes).

Comparisons between countries with different policies and practices concerning prostate cancer detection can make a valuable contribution to the debate on use of PSA to test for prostate cancer. We have shown that patient reported outcomes are very similar in ROI and NI despite different levels of PSA testing and diagnosed prostate cancer. However, it is important to set these findings in the context of the wider population. It has been estimated that between 1994 and 2005, compared to the 1994 disease levels, there were 5938 “extra” cases of Prostate Cancer diagnosed in ROI and 763 in NI[4] Since 2005, the numbers of Prostate Cancers in the two jurisdictions have continued to rise. As we have shown here and elsewhere, physical side-effects, such as erectile dysfunction and incontinence, are common among prostate cancer survivors in Ireland[21], echoing studies in other settings[20]. These side-effects can be viewed, in part, as a consequence of widespread PSA testing since, in the absence of testing, many of the men with side-effects may never had been detected with prostate cancer or, if they had been detected, this may have been at an older age so they would have had to live less time with side-effects. The burden of side-effects, in terms of the numbers (and rates) of men in the population living with these, is greater in ROI than NI (i.e. higher in the population with higher levels of PSA testing). This important population-level health impact of more intensive PSA testing – and the little (at best) impact of PSA testing on mortality[4] - needs to be considered alongside the findings from the current analysis.

Conclusion

Following twenty years of higher levels of PCa detection in ROI than NI, when stage at presentation is taken into account health outcomes among PCa survivors differed little between countries. However the increased intensity of investigation has resulted in a population impact with many additional men in ROI having ongoing prostate cancer-related physical symptoms, a risk for all areas with higher levels of testing.

Based on this evidence the use of PSA to test high numbers of asymptomatic men as occurred in ROI has not reduced mortality compared to NI but has left many more men with side effects. We recommended that men are offered a PSA test only after informed discussion as recommended by current guidelines.

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Contributorship Statement

Conception of study, funding and ethics AG, LS, CD. Data analysis AG and DD. Study organisation FJD, AG, LS and GG. All authors involved in data interpretation and write up.

Competing Interest

Prof Linda Sharp received an unrestricted grant 2011-2012 from Sanofi-aventis for research into 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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Research Ethics Committees for NI (ORECNI), 10/NIR03/61.

Results were disseminated to participants on request and available via Prostate Cancer UK and NICR websites.

Data sharing statement

Data from this research is available in anonymised format for specified research proposals by emailing a.gavin@qub.ac.uk. The release of data will be conditional on assurance from the secondary researcher that the proposed use of the data is compliant with the MRC Policy on Data Preservation and Sharing regarding scientific quality, ethical requirements and value for money. A minimum requirement with respect to scientific quality will be a protocol describing the purpose, methods and analysis of the secondary research.

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Supplementary Table 1: Characteristics of 'other' category to be kept as a supplementary table

					Weighted		
					NI		Total
Stage I/II	High (8 to 10)				248	52	300
	Unknown	157			168	3	171
Unknown	Low (2 to 4)	34		46	32	8	40
	Intermediate (5 to 7)	147	100	247	164	101	265
	High (8 to 10)	36	32	68	41	25	67
	Unknown	65	43	108	76	39	116
Total Patients		664	258	922	730	229	959

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6,7,8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6,7,8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6,7
Bias	9	Describe any efforts to address potential sources of bias	*8*
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6,7,8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	8
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	8
		(*e*) Describe any sensitivity analyses	N/A
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	6
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	At bottom of tables
Outcome data	15*	Report numbers of outcome events or summary measures	Tables
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Tables
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	9,10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	24
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	21,22,23
Generalisability	21	Discuss the generalisability (external validity) of the study results	24
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	25

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Correction

Gavin AT, Donnelly D, Donnelly C, *et al*. Effect of investigation intensity and treatment differences on prostate cancer survivor's physical symptoms, psychological well-being and health-related quality of life: a two country cross-sectional study. *BMJ Open* 2016;6:e012952.

The contributions are incorrect. They should read as follows;

Contributors ATG, LS, CD and FJD were involved in conception of study, funding and ethics. ATG and DD were involved in data analysis. FJD, ATG, LS and GJG were involved in study organisation. All authors were involved in data interpretation and write-up.

BMJ Open 2017;**7**:e012952corr1. doi:10.1136/bmjopen-2016-012952corr1