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Original Article

The psychosocial impact of prostate cancer screening for *BRCA1* and *BRCA2* carriers

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Objectives

To report the long-term outcomes from a longitudinal psychosocial study that forms part of the 'Identification of Men with a genetic predisposition to ProstAte Cancer: Targeted Screening in men at higher genetic risk and controls' (IMPACT) study. The IMPACT study is a multi-national study of targeted prostate cancer (PrCa) screening in individuals with a known germline pathogenic variant (GPV) in either the BReast CAncer gene 1 (*BRCA1*) or the BReast CAncer gene 2 (*BRCA2*).

Subjects and Methods

Participants enrolled in the IMPACT study were invited to complete a psychosocial questionnaire prior to each annual screening visit for a minimum of 5 years. The questionnaire included questions on sociodemographics and the following measures: Hospital Anxiety and Depression Scale, Impact of Event Scale, 36-item Short-Form Health Survey, Memorial Anxiety Scale for PrCa, Cancer Worry Scale, risk perception and knowledge.

Results

A total of 760 participants completed questionnaires: 207 participants with GPV in *BRCA1*, 265 with GPV in *BRCA2* and 288 controls (non-carriers from families with a known GPV). We found no evidence of clinically concerning levels of general or cancer-specific distress or poor health-related quality of life in the cohort as a whole. Individuals in the control group had significantly less worry about PrCa compared with the carriers; however, all mean scores were low and within reported general population norms, where available. *BRCA2* carriers with previously high prostate-specific antigen (PSA) levels experience a small but significant increase in PrCa anxiety ($P = 0.01$) and PSA-specific anxiety ($P < 0.001$). Cancer

risk perceptions reflected information provided during genetic counselling and participants had good levels of knowledge, although this declined over time.

Conclusion

This is the first study to report the longitudinal psychosocial impact of a targeted PrCa screening programme for *BRCA1* and *BRCA2* carriers. The results reassure that an annual PSA-based screening programme does not have an adverse impact on psychosocial health or health-related quality of life in these higher-risk individuals. These results are important as more PrCa screening is targeted to higher-risk groups.

Keywords

prostate cancer, *BRCA1*, *BRCA2*, genetic screening, psychosocial, quality of life

Introduction

Prostate cancer (PrCa) is the most common cancer in men worldwide, with 1.4 million new cases and the cause of 375 000 deaths in 2020 [1]. Incidence is rising, with factors such as family history, ethnicity, and an inherited genetic predisposition to PrCa contributing to a person's risk. Individuals with germline pathogenic variants (GPV) in the BReast CAncer gene 2 (*BRCA2*) gene have a moderately increased risk of PrCa, estimated at a 2.5–8.6-fold relative risk by the age of 65 years. There may also be an increased relative risk associated with *BRCA1*, estimated to be 1.8–3.75-fold by the age of 65 years [2,3]. In addition to being at higher risk, there is strong evidence that having a GPV in *BRCA2* predisposes to younger onset, aggressive disease [4,5]. Therefore, there is a strong case for targeting PrCa screening to these individuals living at higher risk to enable early detection of PrCa, thus reducing disease burden [5].

Currently, general population, age-based PrCa screening programmes based on PSA testing are not supported due to concerns about potential harms of over-detection and over-treatment, despite studies showing a benefit in terms of reduced mortality [6,7]. Treatments for PrCa have significant long-term side-effects that impact sexual function and continence, with some risk of poor long-term psychosocial health and health-related quality of life (HRQoL) [8].

For individuals diagnosed with an early stage, low-grade PrCa, the 5-year survival rate is close to 100%, but this declines to <50% for those with metastatic disease at diagnosis [1]. In an attempt to reduce PrCa mortality and improve health outcomes for people with PrCa, there is a need for different screening approaches to improve the benefit-to-harm ratio of screening. Alongside a screening protocol, it is important to consider the psychosocial impact of the screening programme itself. Previous reports of individuals undergoing PrCa screening have found that a small proportion experience some anxiety, usually whilst waiting for results [9,10]. Risk factors for anxiety include having symptoms, having a family history of PrCa, and having a heightened perceived risk of developing PrCa [9,10].

The 'Identification of Men with a genetic predisposition to ProstAte Cancer: Targeted Screening in men at higher genetic risk and controls' (IMPACT) study, an international, multicentre study, commenced in 2005 to evaluate the utility of targeted PSA screening in individuals with GPVs in *BRCA1/BRCA2* [5]. The evidence from this study has shown a clear clinical benefit of using PSA screening for *BRCA2* carriers in terms of diagnosing clinically important PrCa at an early stage [5], and annual PSA screening for *BRCA2* carriers is now recommended in Europe and the USA [11,12].

Alongside the screening protocol, the IMPACT study also included a longitudinal psychosocial/HRQoL sub-study. The baseline results (an evaluation of psychosocial measures at screening study enrolment) did not find any clinically concerning levels of general or cancer-specific distress, or poor HRQoL in the study cohort as a whole [13]. In participants reporting higher distress levels, risk perceptions were more strongly associated with distress levels than genetic status [13]. Whilst this provided important insight into HRQoL at the start of screening, it is important to consider the longer-term impact on psychosocial health over time for individuals undergoing regular screening.

In this paper, we report the longitudinal results of this sub-study. The aims of this study are to: (i) evaluate the longitudinal psychosocial impact of PrCa screening on individuals at higher genetic risk in terms of cancer worry, screening-related distress and HRQoL; and (ii) inform the counselling and clinical management of this population.

Subjects and Methods

Study Sample and Procedures

The IMPACT study recruited individuals assigned male at birth from families with GPVs in *BRCA1* or *BRCA2* to participate in annual PrCa screening for a minimum of 5 years. Participants were recruited between 2005 and 2015, with screening rounds completed by December 2019. The full design and methods of the IMPACT study have been reported previously [5,13]. The study was approved by the

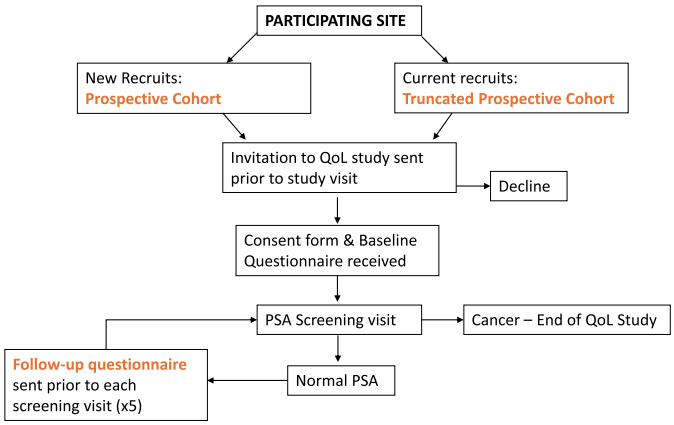
West Midlands Research and Ethics Committee in the UK (reference 05/MRE07/25) and subsequently by each participating institution's local ethics committee.

All individuals eligible for the IMPACT study were eligible for the HRQoL sub-study. Individuals were eligible if they tested either positive or negative for the familial GPV in *BRCA1/BRCA2*, were aged 40–69 years and had not received a diagnosis of PrCa. Individuals testing negative for a familial GPV constituted the control group. Individuals were excluded from the HRQoL sub-study if they were untested and variant status was unknown.

The methods of the HRQoL sub-study, which was added to the IMPACT study protocol in 2009, are summarised in Fig. 1 and in Bancroft et al. 2019 [13]. Sites could opt in or out of participating in this sub-study depending on whether they had the resources to do so. Participants were invited to join the HRQoL sub-study by letter (including the information sheet and consent form, Data S1) ahead of their scheduled IMPACT study visit and this invited them to complete a set of questionnaires annually for 5 years. Participants were sent the questionnaires ~4 weeks prior to their appointment and asked to return them ahead of their appointment. Participants who received a PrCa diagnosis as a result of the screening did not complete questionnaires after diagnosis.

Participants were recruited opportunistically once the HRQoL sub-study opened. Being a largely descriptive study, the sample size was based on expected recruitment numbers across the participating sites, aiming for a minimum of 600 participants, in total. For the purposes of analysis participants were split into two cohorts: (i) Prospective Arm—participants who joined the HRQoL sub-study prior to their first PSA screen within the IMPACT study; and (ii) Truncated-Prospective Arm—participants already enrolled in the IMPACT study before joining the HRQoL sub-study.

Fig. 1 Recruitment methods and participant journey.



For each screening appointment, participants attended a clinic appointment with a member of the IMPACT team (usually a nurse or genetic counsellor) where they had the opportunity to discuss the pros and cons of PrCa screening and have their PSA drawn.

Study Measures

Distress

Psychological distress was measured using four scales:

1. The Hospital Anxiety and Depression Scale (HADS) measures the presence and severity of general anxiety and depression and consists of two seven-item sub-scales [14]. The subscale scores range from 0 to 21, and a score >10 indicates clinically concerning levels of anxiety or depression.
2. The Impact of Event Scale (IES) evaluates PrCa-specific distress by measuring the frequency of intrusive or avoidant thoughts about PrCa in a 15-item scale [15]. The sub-scales scores range from 0 to 35 (intrusion) and 0–40 (avoidance); clinically relevant thresholds are indicated at a score of ≥8.5 (moderate) and ≥19 (high) levels of distress.
3. The Cancer Worry Scale–Revised (CWS-R) is a six-item scale measuring a person's worry about the risk of developing cancer, and the frequency and impact of that worry on mood and daily functioning [16]. The scale gives a total score between 4 and 24. No clinical cut-offs are available.
4. The Memorial Anxiety Scale for Prostate Cancer (MAX-PC) has three sub-scales assessing PrCa anxiety, PSA anxiety, and fear of recurrence. In this study, we used the PrCa anxiety (11 items, score from 0 to 33) and PSA anxiety (three items, score from 0 to 9) sub-scales [17]. A higher score indicates higher anxiety levels. No clinical cut-offs are available.

Health-Related Quality of Life

Health-related quality of life was assessed using the 36-item Short-Form Health Survey (SF-36), version 2.0 [18]. The SF-36 consists of eight subscales. Summary scores are calculated for physical health and mental health. All scales are linearly converted to a 0–100 scale, with a higher score representing better functioning.

Risk Perception

Participants were asked to rate their perceived risk of developing PrCa compared with the average person's risk ('lower', 'the same', 'slightly increased', 'moderately increased', or 'strongly increased'), and to express their perceived lifetime risk of developing PrCa as a percentage.

Knowledge

A 'knowledge questionnaire' was designed in-house using nine true/false questions [13]. The items assessed knowledge of inheritance, the cancer risks associated with carrying a GPV in *BRCA1/2* and prevalence of *BRCA1/2* GPVs in the general population. Scores were calculated by taking the sum of the correct responses, with a higher score indicating a higher level of knowledge.

The internal consistency reliability, as assessed by Cronbach's coefficient alpha, was high for all scales used, ranging between 0.88 and 0.92.

Statistical Analysis

Stata 17 (2021; Stata Corp., College Station, TX, USA) statistical computer package was used to manage and analyse the data. Scores for each questionnaire were calculated in accordance with each scales scoring system.

For missing data, for all scales except for the SF-36, where ≥75% of a sub-scale was complete a total score (corrected for total number of questions) was calculated. Where <75% was completed, data were excluded. For the SF-36 score, scales were excluded when there was <50% of a sub-scale completed, as per the recommendation of the scale's authors [19]. In all, 10% of the data entered were double-checked for coding accuracy and completeness and no errors identified.

BRCA1/BRCA2 genetic status was defined as a three-level categorical variable based on a patient's genetic test result (*BRCA2+*, *BRCA1+*, *BRCA1/BRCA2−*).

We collected information on the following sociodemographic characteristics: country; self-identified ethnicity; employment status; highest educational qualification; age at consent; and date of study entry (baseline, truncated). For the truncated cohort, because baseline questionnaires were missing, date of consent to the HRQoL sub-study was used as a proxy for 'time zero'.

For each of the variables of interest, we used a mixed-effects model with random intercept and slope, with an exponential covariance structure (to allow for unequally spaced and non-integer time values), and a restricted maximum likelihood solution, with *BRCA1/BRCA2−* as the control group. We used time since baseline questionnaire (years) as the temporal variable of interest, with an interaction term between time and *BRCA1/BRCA2* status, allowing the rate of change to vary by *BRCA1/BRCA2* status. This model assumes a linear relationship over time within each person. The variables of interest were: 'Anxiety', 'Depression', 'Intrusion', 'Avoidance', 'PCMAXPC', 'PSAMAXPC', 'Cancer Worry', 'Knowledge', 'Risk' (Likert), and 'Risk' (%). Each variable of interest was modelled independently, with the model adjusted for the following variables, with some variables re-categorised because of low numbers in some categories: country; self-identified ethnicity; highest educational qualification; age at consent; and date of study entry (baseline, truncated). For categorical independent variables, strength of association was calculated with Cohen's *d* for any significant relationship.

Results

Sample Characteristics and Response Rate

Of the 65 centres contributing to the IMPACT study, 16 (12 in the UK, two in Spain and two in the USA) consented participants and submitted data for the HRQoL sub-study. There was no specific funding to support this sub-study at collaborating sites outside of the UK, and therefore, the decision to opt-in or not was based on local resources.

Uptake into the HRQoL sub-study was 85–100% at participating sites, with a total of 804 participants enrolled. In all, 44 were excluded from the analysis (35 returned their questionnaire >1 month after their initial screening visit or did not complete the consent form, and nine participants were untested for their familial variant). Thus, the data presented are from 760 participants, 424 who enrolled prior to their first IMPACT screening visit, the 'prospective cohort', and 336 participants who were already enrolled in IMPACT, the 'truncated prospective cohort'. For participants of the truncated cohort, data were collected between their second and their 12th year of screening. In total, 537 participants were recruited in the UK, 141 from the USA, and 82 from Spain. Over 50% of participants completed the full five annual questionnaires (Fig. 2).

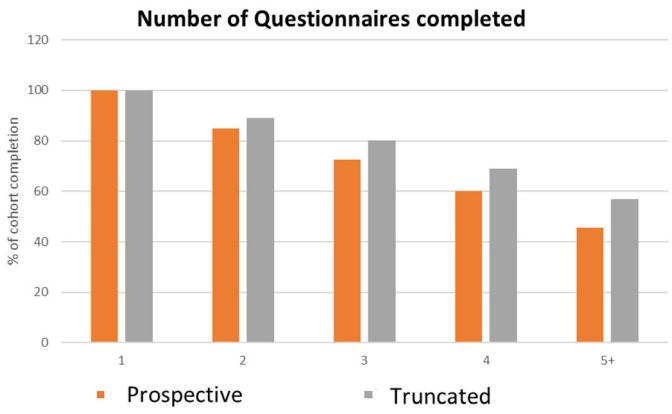
The study sample consisted of 98.6% people of White European ancestry, 77.5% were employed and 75.3% had been educated to university level or equivalent or completed high school (Table S1). There were no significant differences in sociodemographics or genetic status between those who completed the full 5 years of questionnaires vs those who did not.

Distress Levels—General and PrCa Specific

Tables 1 and 2, and Figure S1 summarise the results for the measures of distress at baseline (completion of first questionnaire) and change over time. There was very little variation in mean anxiety and depression scores reported between genetic risk groups for either sub-scale of the HADS (Table 1) and all mean scores were below clinically relevant thresholds.

A low percentage of participants had distress levels above clinical thresholds (HADS, IES) and there was little variation over time (Table 2). A reduction in both anxiety and

Fig. 2 Percentage of participants completing questionnaires at each time point (years).



depression was seen across all groups over time, with no significant differences detected between groups (Table 1 and Fig. S1A,B).

Median baseline scores for the IES (Table 2, Fig. S1C,D) identified a significant difference between both *BRCA1* carriers and controls ($P < 0.001$) and between *BRCA2* carriers and controls ($P < 0.001$), with higher scores on both the intrusive and avoidant thoughts sub-scales in the carrier groups than in the control group. All mean scores were well below clinically relevant thresholds. Over time a significant difference was detected between *BRCA1* carriers and controls ($P < 0.001$), with *BRCA1* carriers scores declining over time on both scales.

Mean baseline scores for the CWS-R scale showed overall low levels of cancer worry, with a significant difference between *BRCA2* carriers and controls, with *BRCA2* carriers reporting higher levels of cancer worry. All groups exhibited a trend toward a reduction in cancer worry over time, with no significant differences observed between groups (Table 1, Fig. S1G).

Similarly, for the baseline MAX-PC scale, low levels of PrCa- and PSA-related anxiety were observed, but with significant differences in mean scores between both *BRCA1* carriers and controls, and *BRCA2* carriers and controls for the PrCa anxiety scale. Again, there was a trend over time for mean anxiety levels to decline across all groups (Fig. S1E,F).

We evaluated whether having a high PSA level investigated in a prior screening round had an impact on subsequent distress levels within each cohort (Table 3).

Table 1 Distress levels at baseline and change over time.

Variable	Baseline status		Cohen's *d*	Change per year	
	Mean (95% CI)	*P*		Mean (95% CI)	*P*
HADS Anxiety (score range 0–21)					
BRCA1+	6.7 (4.9 to 8.5)	0.7		−0.13 (−0.23 to −0.03)	0.8
BRCA2+	6.8 (5.1 to 8.6)	1.0		−0.13 (−0.21 to −0.05)	0.8
Control	6.9 (5.0 to 8.7)	Ref.		−0.15 (−0.23 to −0.06)	Ref.
HADS Depression (score range 0–21)					
BRCA1+	2.6 (1.1 to 4.1)	0.5		−0.01 (−0.10 to 0.07)	0.7
BRCA2+	2.6 (1.2 to 4.1)	0.5		−0.04 (−0.11 to 0.03)	1.0
Control	2.5 (0.9 to 4.0)	Ref.		−0.04 (−0.11 to 0.03)	Ref.
IES Intrusion (score range 0–35)					
BRCA1+	3.9 (1.7 to 6.1)	**<0.001***	0.31	−0.04 (−0.17 to 0.10)	**<0.001***
BRCA2+	4.0 (1.8 to 6.1)	**<0.001***	0.42	0.20 (0.09 to 0.31)	0.5
Control	2.3 (0.1 to 4.5)	Ref.		0.26 (0.14 to 0.38)	Ref.
IES Avoidance (score range 0–40)					
BRCA1+	5.9 (2.8 to 9.0)	**<0.001**	0.29	−0.16 (−0.36 to 0.04)	**<0.001***
BRCA2+	5.4 (2.3 to 8.4)	**<0.001**	0.27	0.17 (0.01 to 0.34)	0.2
Control	3.3 (0.2 to 6.4)	Ref.		0.34 (0.17 to 0.52)	Ref.
MAX-PC PrCa Anxiety (score range 0–33)					
BRCA1+	5.1 (2.5 to 7.6)	**0.013***	0.21	−0.22 (−0.35 to −0.08)	0.1
BRCA2+	5.2 (2.7 to 7.7)	**0.003***	0.27	−0.04 (−0.15 to 0.08)	0.7
Control	3.8 (1.2 to 6.4)	Ref.		−0.08 (−0.20 to 0.05)	Ref.
MAX-PC PSA Anxiety (score range 0–9)					
BRCA1+	0.3 (0.0 to 0.6)	0.6		0.00 (−0.02 to 0.02)	0.8
BRCA2+	0.4 (0.1 to 0.6)	0.06		−0.01 (−0.03 to 0.01)	0.8
Control	0.3 (0.0 to 0.5)	Ref.		−0.01 (−0.03 to 0.01)	Ref.
CWS-R (score range 4–24)					
BRCA1+	10.6 (9.4 to 11.9)	0.1		−0.08 (−0.14 to −0.02)	0.7
BRCA2+	10.8 (9.6 to 12.0)	**0.005***	0.30	−0.10 (−0.16 to −0.03)	0.9
Control	10.2 (9.0 to 11.5)	Ref.		−0.08 (−0.13 to −0.02)	Ref.

*P, P value for the test of difference in mean score between carrier group and control (BRCA–) group. *Bolded values signify statistically significant (P or P-int < 0.05).*

Table 2 Percentage of participants with scores above clinical thresholds (HADS and IES) at each time point.

Variable	Range (abnormal threshold)	Time point	*BRCA1* mutation carriers		*BRCA2* mutation carriers		Controls (*BRCA*–)	
			N	Median (IQR) % above threshold	*N*	Median (IQR) % above threshold	*N*	Median (IQR) % above threshold
Total Anxiety (HADS)	0–21 (≥11)	Baseline/Yr 1	97 7	5 (2–7) 7 2	162 11	4 (2–7) 6.8	183 9	5 (2–7) 4.9
		Yr 2	83 9	4 (2–6) 10.8	136 15	4 (2–6) 11	162 11	5 (2–7) 6.8
		Yr 3	99 10	4 (1–7) 10.1	129 11	5 (2–7) 8.5	147 9	4 (2–7) 6.1
		Yr 4	112 8	4 (2–6) 7.1	145 5	4 (2–6) 3.4	151 8	4 (2–7) 5.3
		Yr 5	109 4	4 (2–6) 3.7	138 9	4 (2–7) 6.5	140 5	4 (2–7) 3.6
Total Depression (HADS)	0–21 (≥11)	Baseline/Yr 1	97 3	2 (1–4) 3.1	162 4	2 (1–5) 2.5	183 3	2 (1–4) 1.6
		Yr 2	83 3	2 (0–4) 3.6	136 5	2 (1–4) 3.7	162 5	2 (1–4) 3.1
		Yr 3	99 2	2 (0–5) 2	129 2	2 (1–4) 1.6	147 2	2 (1–4) 1.4
		Yr 4	112 4	2 (0–5) 3.6	145 0	2 (1–4) 0	151 1	2 (1–3) 0.7
		Yr 5	110 1	2 (1–4) 0.9	138 2	2 (1–4) 1.4	139 4	2 (1–4) 2.9
Total Intrusion (IES)	0–35 (≥19)	Baseline/Yr 1	93 12	1 (0–10) 12.9	158 14	1 (0–8) 8.9	178 4	0 (0–3) 2.2
		Yr 2	81 8	3 (0–7) 9.9	134 11	1 (0–6) 8.2	161 9	0 (0–3) 5.6
		Yr 3	99 5	0 (0–6) 5.1	129 12	3 (0–9) 9.3	143 4	0 (0–5) 2.8
		Yr 4	111 5	0 (0–8) 4.5	143 6	1 (0–8) 4.2	150 5	0 (0–5) 3.3
		Yr 5	109 4	0 (0–7) 3.7	139 6	3 (0–8) 4.3	137 7	1 (0–8) 5.1
Total Avoidance (IES)	0–40 (≥19)	Baseline/Yr 1	93 12	1 (0–10) 12.9	158 14	1 (0–8) 8.9	178 4	0 (0–3) 2.2
		Yr 2	81 8	3 (0–7) 9.9	134 11	1 (0–6) 8.2	161 9	0 (0–3) 5.6
		Yr 3	99 5	0 (0–6) 5.1	129 12	3 (0–9) 9.3	143 4	0 (0–5) 2.8
		Yr 4	111 5	0 (0–8) 4.5	143 6	1 (0–8) 4.2	150 5	0 (0–5) 3.3
		Yr 5	109 4	0 (0–7) 3.7	139 6	3 (0–8) 4.3	137 7	1 (0–8) 5.1

IQR, interquartile range; Yr, Year.

We saw a small, but significant increase in intrusive thoughts ($P = 0.018$), PrCa-specific anxiety ($P = 0.01$) and anxiety about PSA testing ($P < 0.001$) in the *BRCA2* carriers only. However, this did not translate into poorer HRQoL with slightly higher mental functioning ($P = 0.002$) reported in *BRCA2* carriers. We observed a significant decrease in general anxiety in *BRCA1* carriers who had a high PSA level in a prior screening round ($P = 0.009$).

We looked at whether there were any differences in psychosocial profile of participants who dropped out of this study compared with those who completed the full 5 years of questionnaires. No significant differences were detected on any measures between the penultimate and final questionnaires completed among those who dropped out, suggesting that dropout was not prompted by a spike in e.g., anxiety levels. Scores on the final questionnaire for those that dropped out were approximately 1 point higher for general anxiety ($P = 0.01$) and depression ($P = 0.005$) measured using the HADS than for those participants that completed the study (Table S2).

Health-Related Quality of Life

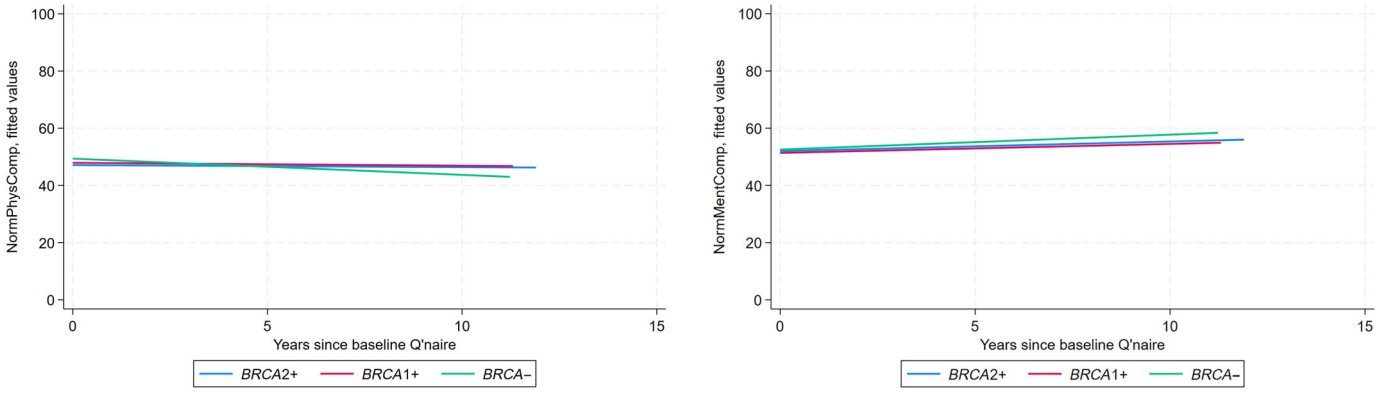
The SF-36 physical and mental functioning summary scores clustered around the standardised mean of 50, demonstrating

Table 3 Change in scores at baseline vs screening rounds after a high PSA result.

Variable	Genetic status	Individuals, *n*	Number of measurements		Change between pre/post high PSA		
			Pre, *n*	Post, *n*	Mean (95% CI)	*P*	*P-int*
HADS Anxiety Scale	*BRCA–*	16	34	35	−0.40 (−1.29 to 0.49)	0.4	
	BRCA1+	8	10	17	−1.92 (−3.36 to −0.49)	0.009*	0.1
	BRCA2+	11	26	21	−0.72 (−1.91 to 0.46)	0.2	0.7
HADS Depression Scale	*BRCA–*	16	34	35	0.62 (−0.21 to 1.45)	0.1	
	BRCA1+	8	10	17	−0.45 (−1.80 to 0.91)	0.5	0.2
	BRCA2+	11	26	21	−0.75 (−1.84 to 0.34)	0.2	0.05
IES Intrusion Scale	*BRCA–*	16	35	35	0.95 (−0.37 to 2.27)	0.2	
	BRCA1+	8	10	17	−0.33 (−2.50 to 1.84)	0.8	0.3
	BRCA2+	11	26	21	2.09 (0.36 to 3.81)	0.018*	0.3
IES Avoidance Scale	*BRCA–*	16	33	35	1.06 (−1.12 to 3.24)	0.3	
	BRCA1+	8	10	17	−0.79 (−4.44 to 2.86)	0.7	0.4
	BRCA2+	11	25	21	1.07 (−1.64 to 3.77)	0.4	1.0
MAX-PC – PrCa Anxiety Scale	*BRCA–*	16	34	35	−0.08 (−1.50 to 1.35)	0.9	
	BRCA1+	8	10	17	−0.67 (−2.97 to 1.62)	0.6	0.7
	BRCA2+	11	25	21	2.49 (0.58 to 4.40)	0.010*	0.03*
MAX-PC – PSA Anxiety Scale	*BRCA–*	16	34	35	−0.10 (−0.32 to 0.12)	0.4	
	BRCA1+	8	10	16	−0.01 (−0.40 to 0.37)	1.0	0.7
	BRCA2+	11	24	21	0.55 (0.27 to 0.82)	<0.001*	<0.001*
Cancer Worry Scale	*BRCA–*	16	35	35	−0.38 (−0.91 to 0.14)	0.1	
	BRCA1+	8	10	17	−0.44 (−1.29 to 0.41)	0.3	0.9
	BRCA2+	11	26	20	0.24 (−0.48 to 0.96)	0.5	0.2
Perceived Risk (%)	*BRCA–*	16	33	35	5.16 (−3.35 to 13.67)	0.2	
	BRCA1+	8	10	16	3.05 (−11.00 to 17.11)	0.7	0.8
	BRCA2+	11	24	20	−2.31 (−13.43 to 8.80)	0.7	0.3
SF-36 Physical Component Summary score	*BRCA–*	16	34	32	0.02 (−0.23 to 0.26)	0.9	
	BRCA1+	8	10	16	−0.25 (−0.63 to 0.13)	0.2	0.3
	BRCA2+	11	25	20	−0.21 (−0.55 to 0.13)	0.2	0.3
SF-36 Mental Component Summary score	*BRCA–*	16	34	32	−0.03 (−0.31 to 0.25)	0.8	
	BRCA1+	8	10	16	0.34 (−0.10 to 0.77)	0.1	0.2
	BRCA2+	11	25	20	0.60 (0.22 to 0.98)	0.002*	0.008*

*P, P value for the test of within group difference in score pre and post investigations for a high PSA level; P-int, P value for the test of difference in mean score between carrier group and control (BRCA–) group. *Significant difference (P or P-int <0.05).*

Fig. 3 The SF-36 Health Survey: HRQoL summary physical (NormPhysComp) and mental health (NormMentComp) component scores. Q'naire, questionnaire.



good levels of HRQoL within the sample. No significant differences were observed between the groups based on genetic status, and there was no significant change in scores over time (Fig. 3).

Risk Perception

Perception of lifetime risk of PrCa was influenced significantly by a person's genetic status, with the mean

lifetime risk estimates scored as 41.1/100 for *BRCA1*, 48.0/100 for *BRCA2* and 32.4/100 for controls. The difference between *BRCA2* and controls was significant ($P < 0.001$). No significant changes were detected over time regarding participants' risk perceptions. Participants with a GPV in *BRCA2* were more likely to describe their risk of PrCa as moderately or strongly increased compared with the general population risk, when compared with *BRCA1* carriers and the control group. This continued to be the case throughout the duration of the study follow-up (Table S3).

Knowledge

A good level of knowledge was observed across all groups (mean score at baseline: *BRCA1*, 7.8/9; *BRCA2* 7.9/9 and controls 7.6/9). Knowledge scores declined over time across all groups, but not significantly (Fig. S1H).

Discussion

To our knowledge, this is the first longitudinal evaluation of the psychosocial impact of PrCa screening in individuals from families with GPVs in *BRCA1* or *BRCA2*. Our results indicate that, in individuals at higher-risk of PrCa undergoing PSA screening, there is no evidence of clinically concerning levels of general or cancer-specific distress, or poor HRQoL outcomes over time. This confirms and extends the results of our previous analysis, which provided a snapshot of participants psychosocial health at study enrolment [13]. These results extend our understanding of the psychological impact on individuals from families with *BRCA1* and *BRCA2* undergoing screening for PrCa longitudinally.

This study examined psychological and HRQoL outcomes over a 5-year period in participants enrolled in the IMPACT study, but for participants in the truncated-prospective arm, whose data were collected when they had already been in the study for several years, their 5 years stretched out as far as their 12th screening year. This longitudinal design, capturing both individuals enrolling in the study, and those already undergoing annual screening with data collected over many screening years, provided a robust longitudinal evaluation.

It is known that individuals with PrCa experience some psychological distress related to waiting for PSA results as part of their cancer management [20]. It could be hypothesised that individuals who have a genetic predisposition to developing a future PrCa could experience similar heightened levels of concerns associated with PSA screening. However, there is no evidence of any PSA-related anxiety within this study. We do need to consider that these individuals were taking part in a research study where they were counselled about their personal risk of PrCa and whether this counselling is likely to have contributed to their psychological health. However, the psychological questionnaires were completed each year before undergoing their annual screening appointment, and therefore prior to counselling and knowing their screening result, which would minimise the impact of this on their responses. General population screening studies in the UK and Europe have similarly reported that PrCa screening does not have a detrimental effect on psychological health or measures of HRQoL [21,22].

Mean general anxiety and depression scores, using the HADS, were within previously reported population norms and remained low during study participation. No differences were observed between groups and a slight reduction in both anxiety and depression was seen across all cohorts over time.

Confirming the baseline findings there was a significant difference in PrCa-specific distress observed between groups. *BRCA1* and *BRCA2* carriers had significantly higher levels of distress than controls on both the intrusion and avoidant scales of the IES and the PrCa-specific anxiety scale of the MAX-PC. In terms of general cancer worry, measured using the CWS-R, *BRCA2* carriers scored significantly higher than controls, but no significant difference was observed between *BRCA1* carriers and controls. Whilst these differences were sustained over time, they were small and mean scores remained below clinically relevant levels (where available). In fact, a slight reduction in all distress was seen across all cohorts and all measures over time. Therefore, these results confirm that undergoing regular PSA screening does not increase distress levels in individuals at higher risk of PrCa.

Our results align with those of a study of anxiety in the European Randomised Study of Screening for Prostate Cancer (ERSPC) Gothenberg cohort, which reported a low-to-moderate level of anxiety associated with PrCa screening, even in individuals with increased PSA levels [23]. In the ERSPC study, severe anxiety affected only a small subset of participants, and this was among individuals predisposed to anxiety, which continued throughout their experience of cancer screening [9,21–23]. This anxiety can be heightened whilst waiting for screening results. Risk factors for anxiety include having a family history of PrCa, symptoms, or a genetic predisposition [9,10]. Our data support this finding, with only a small proportion reporting clinically significant levels of distress and experiencing this over the entire duration of the study. This suggests that a short psychological screening questionnaire could be used at entry to a PrCa-screening programme to identify individuals predisposed to higher levels of psychological distress who may require additional support in managing their distress. Heightened anxiety can have an impact on subsequent cancer screening behaviours [24] and strategies, e.g., motivational interviewing techniques have been shown to increase compliance with colorectal cancer screening [25].

Both the European and USA screening studies reported higher levels of anxiety in individuals previously investigated for elevated PSA levels [23,26]. This was also observed in our *BRCA2* carrier cohort, although there was no evidence of such an impact in either *BRCA1* carriers or controls. Indeed, the *BRCA1* carriers with a high PSA level in a prior screening round had a significant decrease in levels of general anxiety. As individuals with GPVs in *BRCA2* specifically are alerted to the higher risk of PrCa during the counselling process, it is not surprising to see a small but significant impact on worry about PrCa and PSA specifically. The higher PrCa cancer risk associated with *BRCA2* would explain the differences observed between the *BRCA1* and *BRCA2* carriers. It is important for clinicians to be mindful of the higher-risk faced by *BRCA2* carriers specifically and further research investigating ways of managing and easing distress during the course of investigations would be helpful. Levels of anxiety and worry experienced are likely to be strongly influenced by the information and counselling provided during the screening process and therefore it would be beneficial to follow-up on these findings using qualitative methods to understand the impact of this on a more personal level.

Health-Related Quality of Life

Confirming our baseline findings, the HRQoL assessments did not detect any clinically significant differences in either physical or mental health between groups, or over time. The IMPACT study baseline results were compared with a matched normative sample and found that the overall physical and mental health functioning was higher in the IMPACT cohort than in the normative sample, but as with the longitudinal data, all scores fell close to the standardised means [13,27]. Similar results were observed in the Finnish ERSPC study cohort in which HRQoL scores (assessed using the SF-36) were slightly, but not significantly higher than those in the general Finnish population [21]. This is likely to be because both the ERSPC and IMPACT cohorts included participants who were generally healthy and with higher socioeconomic status. These results therefore provide further evidence that PrCa screening is not having a negative impact on HRQoL. This is important, as very little research has focussed on the impact of screening on the HRQoL of individuals living with a genetic predisposition to, or those with *BRCA1/BRCA2* variants who have gone on to develop PrCa [28].

Risk Perceptions

The participants' perceptions of their PrCa risk were higher across all groups than the risk communicated during genetic counselling, which was also observed in our baseline analysis [13]. A person's perceived risk has been shown not to reflect true risk in individuals both with and without a family history of PrCa [10,29]. It is reassuring to see that the mean estimation of lifetime risk in *BRCA2* carriers was considerably higher than the controls (41.1% compared with 32.1%), confirming that the participants understood how carrier status impacted on PrCa risk. Those with GPVs in *BRCA2* reported the highest perceived risk of PrCa, most frequently classifying risk as 'slightly' or 'moderately' increased, and controls most frequently classifying risk as the 'same' as the general population. The higher perception of risk, and lifetime risk estimates were sustained and do not change over time, demonstrating good recall of risk discussions.

Knowledge

At study entry, levels of knowledge about inheritance of GPVs in *BRCA1/BRCA2* and associated cancer risks were high across all cohorts, irrespective of genetic status, education level, and time since testing [13]. Levels of knowledge declined slightly over time, but not significantly, as would be expected with an increase in time since undergoing genetic counselling, and therefore having an impact on accuracy of recall.

Study Limitations and Strengths

It is important to consider whether individuals who declined participation and those who dropped out during the course of the study may have had a different psychological profile which impacted either their decision to join the study, or compliance with completing the questionnaires. We previously investigated whether there were any differences in sociodemographic characteristics between the participants of the HRQoL sub-study and those in the full IMPACT study and did not find any differences. We also did not identify any differences in sociodemographics between those who dropped out during the course of the psychosocial study and those who completed all questionnaires. However, we did observe a significant difference in general anxiety and depression scores (measured using the HADS), but the difference was very small, with those dropping out scoring only 1 point higher on average compared with those who completed the study. The overall average scores were well within previously reported population norms.

It is also important to note that not all centres were able to take part in this sub-study. There was no additional funding for this part of the study and so ability to participate depended on local site resources, and it was sites with larger recruitment numbers and English speaking who were more likely to participate due to the additional cost of translating the questionnaires. The sample was strengthened by the inclusion of two Spanish sites, and as there were no notable differences between these participants and the English speaking participants, the results are likely to be representative of the wider IMPACT cohort [13].

A limitation of this study is the homogeneity of the study participants, representing a largely White, well-educated, and employed population, who had already engaged with the health care system, being actively involved in an existing research study. Therefore, the generalisability of these results should be approached with caution when considering the impact of PrCa screening on individuals of different ethnic and sociodemographic backgrounds. Future research focussed on how to get more individuals from underserved communities involved in cancer screening is imperative.

The high uptake and compliance levels are a strength of this study. We report a similar level of uptake as that seen in another general population PrCa screening programme, the ERSPC Swedish cohort, with 84–94% of participants with abnormal PSA levels completing a questionnaire measuring anxiety levels [23]. The high participation rate in both studies is likely attributable to the participants being highly motivated to contribute to research, as evidenced by their already being involved in the primary screening study.

A further strength of this study is the number of different, standardised measures of psychological and psychosocial health that were used. This allowed us to carry out a thorough investigation of the impact of PrCa screening on a range of relevant and related outcomes.

Conclusion

To the best of our knowledge, this is the first study to report longitudinal psychosocial and HRQoL outcomes in individuals with GPVs in *BRCA1/BRCA2* undergoing a targeted annual PrCa screening programme. The results reassure us that this high-risk population, in general, does not experience clinically concerning levels of anxiety or distress, or poor HRQoL as a consequence of undergoing PrCa screening. We observed a slightly higher level of PrCa- and PSA-specific distress in *BRCA2* carriers who had previously high PSA levels. It is important for healthcare professionals counselling individuals at higher risk to be aware that this may have a negative impact on participants' mental health at future screening rounds, and to provide psychosocial support. These results are particularly important as we are seeing the implementation of routine PSA screening in Europe and the USA for individuals with GPVs in *BRCA2* from the age of 40 years.

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Disclosure of Interests

Prof. Rosalind Eeles has the following conflicts of interest to declare: Honoraria from GU-ASCO, Janssen, University of Chicago, Dana Farber Cancer Institute USA as a speaker. Educational honorarium from Bayer and Ipsen, member of external expert committee to Astra Zeneca UK and the Active Surveillance committee for Movember. She undertakes private practice as a sole trader at The Royal Marsden NHS Foundation Trust and 90 Sloane Street SW1X 9PQ and 280 Kings Road SW3 4NX, London, UK. Prof. Julian Barwell carries out educational sessions for AstraZeneca and occasional consultancy. Mara Cruellas - Roche: Invited speaker, Lilly: Conference expenses. Prof. Derek Rosario is employed by the UK National Screening Committee (NSC) as prostate advisor. All other authors have no conflicts of interest to declare.

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Abbreviations: *BRCA*(*1*)(*2*), BReast CAncer gene (1)(2); CWS-R, Cancer Worry Scale–Revised; GPV, germline pathogenic variant; HADS, Hospital Anxiety and Depression Scale; HRQoL, health-related quality of life; IES, Impact of Event Scale; IMPACT, Identification of Men with a genetic predisposition to ProstAte Cancer: Targeted Screening in men at higher genetic risk and controls; MAX-PC, Memorial Anxiety Scale for Prostate Cancer; PrCa, prostate cancer; SF-36, 36-item Short-Form Health Survey.

APPENDIX 1
The IMPACT Study Steering Committee and Collaborators

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Fig. S1. Distress levels over time.
Data S1. The IMPACT study: a quality of life study.
Table S1. Sociodemographic characteristics of the cohort.
Table S2. Differences in measures for participants dropping out vs completing all questionnaires.
Table S3. Participants perceptions of their risk of prostate cancer compared with average risk.

