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Targeted prostate cancer screening in men with mutations in *BRCA1* and *BRCA2* detects aggressive prostate cancer: preliminary analysis of the results of the IMPACT study

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OBJECTIVES

To evaluate the role of targeted prostate cancer screening in men with *BRCA1* or *BRCA2* mutations, an international study, IMPACT (Identification of Men with a genetic predisposition to ProstAte Cancer: Targeted screening in *BRCA1/2* mutation carriers and controls), was established. This is the first multicentre screening study targeted at men with a known genetic predisposition to prostate cancer. A preliminary analysis of the data is reported.

MATERIALS AND METHODS

Men aged 40–69 years from families with *BRCA1* or *BRCA2* mutations were offered annual prostate specific antigen (PSA) testing, and those with PSA >3 ng/mL, were offered a prostate biopsy. Controls were men age-matched (± 5 years) who were negative for the familial mutation.

RESULTS

In total, 300 men were recruited (205 mutation carriers; 89 *BRCA1*, 116 *BRCA2* and 95 controls) over 33 months. At the baseline screen (year 1), 7.0% (21/300) underwent a prostate biopsy. Prostate cancer was diagnosed in ten individuals, a prevalence of 3.3%. The positive predictive value of PSA screening in this cohort was 47·6% (10/21). One prostate cancer was diagnosed at year 2. Of the 11 prostate cancers diagnosed, nine were in mutation carriers, two in controls, and eight were clinically significant.

CONCLUSIONS

The present study shows that the positive predictive value of PSA screening in *BRCA* mutation carriers is high and that screening detects clinically significant prostate cancer. These results support the rationale for continued screening in such men.

KEYWORDS

prostate cancer, BRCA1, BRCA2, PSA, genetic predisposition

INTRODUCTION

Men with a *BRCA2* mutation are known to be at a higher risk of prostate cancer of approximately five- to sevenfold, whereas the risk of prostate cancer in men with a *BRCA1* mutation is less clear [1,2]. However, there is an indication that *BRCA1* carriers may have approximately double the risk of prostate cancer than that observed in the general population for males aged <65 years [2]. The role of serum PSA screening in both *BRCA1* and *BRCA2* mutation carriers is being evaluated in a large international research study called IMPACT (Identification of Men with a genetic predisposition to ProstAte Cancer: Targeted screening in *BRCA1/2* mutation carriers and controls; http://www.impact-study.co.uk). This is the first multicentre prostate cancer screening study targeted at men with a known genetic predisposition to the disease. This report presents a preliminary analysis of the data from the study.

The utility of PSA screening is a contentious issue because of concerns about overdiagnosis and the benefit in terms of a reduction in mortality remains unclear. Three large population screening studies are evaluating the role of population screening: The European Randomised Study for Prostate Cancer (ERSPC), The Prostate, Lung, Colorectal and Ovarian screening study (PLCO) in the USA and Prostate Testing for Cancer and Treatment in the UK (ProtecT) [3–5]. The PLCO and ERSPC studies have recently reported preliminary data from 7 to 10 years of follow-up and a median of 9 years of follow-up, respectively. The initial results from the PLCO study report a higher prostate cancer mortality rate in a screened compared to an unscreened cohort (screening consisted of an annual PSA test together with DRE). Mortality in both groups was very low (50 vs 44 deaths per 100 000) [6]. Conversely, the ERSPC study observed a higher mortality rate in the unscreened cohort, and reported a 20% reduction in risk of dying from prostate cancer in the PSA-screened cohort [7]. Longer-term follow-up is ongoing. The American Cancer Society currently recommends a discussion about PSA and DRE screening with men aged ≥50 years, or aged ≥45 years for African-American men or those with a family history of prostate cancer [8].

The potential for the overdiagnosis of prostate cancer remains a key concern. It has been estimated that 84% of screen detected cancers may not result in death by the age of 85 years [9]. The ERSPC reported a high risk of overdiagnosis of prostate cancer within their screened cohort [7,10]. This potential for overdiagnosis, with both social and economical cost implications and treatment-

related morbidity, is an important issue for policy-makers when determining screening recommendations. However, men with *BRCA1* or *BRCA2* germline mutations may potentially be at risk of developing highly aggressive prostate cancers that are lethal at an earlier age than that of sporadic cancers in the general population [11,12].

There have been a limited number of studies evaluating the role of prostate cancer screening in men at higher risk of the disease based on a family history of prostate cancer [13–23]. Most published research supports the use of targeted screening in this group [13–15,17,18,21]. However, it is difficult to draw comparisons between studies given that the PSA thresholds used to determine prostate biopsy vary, as do the screening methods (PSA testing alone or used in combination with DRE and/or TRUS), the PSA assay types and the numbers of cores taken at biopsy. The positive predictive values (PPV) of PSA and DRE have been reported to be greater in high-risk groups compared to general population samples [18]. However, the data are often limited by methodological flaws (e.g. a lack of control groups, exposure to recall bias or small sample sizes) [13–15,17,21].

The IMPACT study is the first prospective multicentre study of targeted prostate cancer screening in men with *BRCA1* and *BRCA2* mutations. Men with *BRCA2* mutations have been reported to have a relative risk of prostate cancer of 4.65 (95% CI, 3.48–6.22), more aggressive disease and a high mortality rate [1,11,24,25]. Men with *BRCA1* mutations are reported to have a relative risk of prostate cancer of 1.82 (95% CI, 1.01–3.29) at age <65 years [2]. Data from the Ashkenazi Jewish population do not show a greater risk of prostate cancer [26–29]; however, a large study conducted in Israel showed a greater risk of prostate cancer when both *BRCA1* and *BRCA2* mutation carriers were combined; separately, there was no difference [30]. Consequently, the exact prostate cancer risk for *BRCA1/2* mutation carriers remains unclear. The IMPACT study aims to evaluate the utility of PSA screening in men with *BRCA1* and *BRCA2* mutations and to determine the prostate cancer incidence in this population.

The aim of the present study was to conduct a preliminary evaluation of the first 300 men who have taken part in IMPACT to assess the feasibility of conducting targeted screening in this group, the PPV of PSA, biopsy rates and to establish whether screening detects clinically significant disease.

MATERIALS AND METHODS

STUDY DESIGN

IMPACT is a multicentre observational study of screening for prostate cancer and the design of the study has been described elsewhere [31]. The main aim is to determine the incidence, stage and pathology of screen-detected prostate cancer in *BRCA1* and *BRCA2* mutation carriers compared to a control population. An independent ethical committee reviewed and approved the study protocol in the UK (reference 05/MRE07/25). Local ethical approval was subsequently sought in each participating national and international centre. Interim analyses were presented to an independent data and safety monitoring committee biannually.

SUBJECTS

The eligibility criteria included men aged 40–69 years, who had not received a diagnosis of prostate cancer and who had a known pathogenic mutation in *BRCA1* or *BRCA2*. Men who had received a negative result for a *BRCA1* or *BRCA2* mutation known to be present in their family formed the control group. Men were excluded if they had a history of prostate cancer, had previously undergone a prostate biopsy or had received a cancer diagnosis with a terminal prognosis of less than 5 years. Men with variants of uncertain significance alone in *BRCA1/2* were not eligible.

Eligible men were identified and approached through twenty collaborating cancer genetics clinics in five countries between October 2005 and June 2008. All subjects were from families known to harbour a mutation in *BRCA1* or *BRCA2* and had undergone genetic testing through a clinical genetics unit before study enrollment. Subjects were recruited using two methods: first, by sending postal invitations to men who had previously undergone genetic testing and, second, by approaching men currently undergoing testing in the clinic. A patient information sheet outlining the study rationale was provided and subjects who were interested in taking part were asked to complete a reply slip with their contact details. A member of the research team at each site would then contact the gentlemen to arrange a face-to-face appointment. At study entry, all subjects provided their written consent to take part in the study and completed a baseline questionnaire to record demographic characteristics, medical history, screening history and family history of cancer.

SCREENING METHODS

Total PSA was measured annually in subjects at each centre's local laboratory and this value was used to determine referral for biopsy. Men with a PSA level ≤3 ng/mL were screened annually. Men with a PSA of >3.0 ng/mL were referred for a prostate biopsy. A ten core diagnostic biopsy was recommended using a standardized protocol. If the biopsy was benign, the subject's PSA was measured again after 12 months. Re-biopsy was undertaken if the PSA had increased by more than 50%. If a subject received a diagnosis of high-grade prostate intraepithelial neoplasia or the result was inconclusive, the biopsy was repeated within 6 weeks. Figure 1 gives an overview of the study design.

A biorepository for the collection and storage of blood, urine and tissue was an integral component of the study (analyses of these will be reported elsewhere).

PATHOLOGICAL EVALUATION

Biopsy specimens were evaluated by local pathologists, the results of which guided treatment. Central review of the pathology was then performed by a specialist urological histopathologist at the Royal Marsden NHS Foundation Trust (C.J.), A sample was secondarily reviewed by the senior study pathologist (C.S.F.) to ensure consistency and standardization of morphological assessment [32].

TREATMENT POLICY

If cancer was diagnosed, treatment was performed according to the local centre's treatment guidelines. The UK National Institute for Health and Clinical Excellence (NICE) guidelines for the treatment of prostate cancer were used to classify prostate cancer into high-, intermediate- or low-risk disease. Low-risk disease is classified as a Gleason score ≤6, and a PSA level <10 ng/mL and TNM stage T1–T2a. Intermediate-risk disease is classified as a Gleason score of 7, or

a PSA of 10–20 ng/mL or TNM stages T2b–T2c. High-risk disease is classified as a Gleason score of 8–10, or a PSA >20 ng/mL or TNM stage T3–T4 [33]. The UK NICE classification is very similar to the AUA classification of disease [34].

STATISTICAL ANALYSIS

The number of prostate cancer cases detected in the mutation carrier and control groups were compared using Fisher's exact test. The median ages of each of the groups were compared using the Mann–Whitney *U*-test. $P < 0.05$ was considered statistically significant.

RESULTS

SUBJECTS

300 subjects from twenty centres were recruited over a period of 33 months. Recruitment uptake rates were in the range 2–84% between centres. The recruitment breakdown for each centre is shown in Table 1. In total, 205 carriers (89 *BRCA1* and 116 *BRCA2*) and 95 controls were enrolled.

The baseline demographic characteristics of the subjects were almost identical in each group (*BRCA1* vs *BRCA2* vs controls; Table 2). The median age at study entry among the mutation carriers was 53 years (*BRCA1* carriers, 52 years; *BRCA2* carriers, 54 years) and 55 years in the control group. No significant difference in age was found between the two groups (Mann–Whitney *U*-test, $P = 0.122$).

Out of the 300 subjects, 138 (46%) had one PSA screen, 127 (42.3%) had two PSA screens and 35 (11.7%) had three PSA screens. Because of the small numbers, data from the third screen are not presented here. Compliance with the screening protocol was 99.7%, with only one recruit withdrawing from the study for medical reasons.

PARTICIPANTS WITH A SERUM PSA ABOVE THE THRESHOLD OF 3 NG/ML

There were 24 men with a PSA level >3 ng/mL (range 3.1–27 ng/mL) and proceeded to biopsy. The number of cores taken for diagnosis ranged from (Table 3) 6–11. There were 13 subjects with a benign biopsy, and eleven prostate cancers were detected. Of the prostate cancers, ten were detected at the baseline PSA screen and one was detected at year 2.

BASELINE YEAR 1

Out of 300 subjects, 22 (7.3%) had a PSA level >3 ng/mL at the first (baseline) PSA screen. Of these, 21 (7·0%) proceeded to biopsy and 81% (17/21) were mutation carriers (11 *BRCA2* and six *BRCA1*) and 19% (4/21) were controls. One subject with a raised PSA level withdrew as a result of a newly-diagnosed heart condition. Figure 2 shows the PSA distribution at the first screen.

Of the 21 biopsies, eleven were benign, whereas 10 were positive for prostate cancer.

FIG. 1. Identification of Men with a genetic predisposition to ProstAte Cancer: Targeted screening in BRCA1/2 mutation carriers and controls (IMPACT) study design.

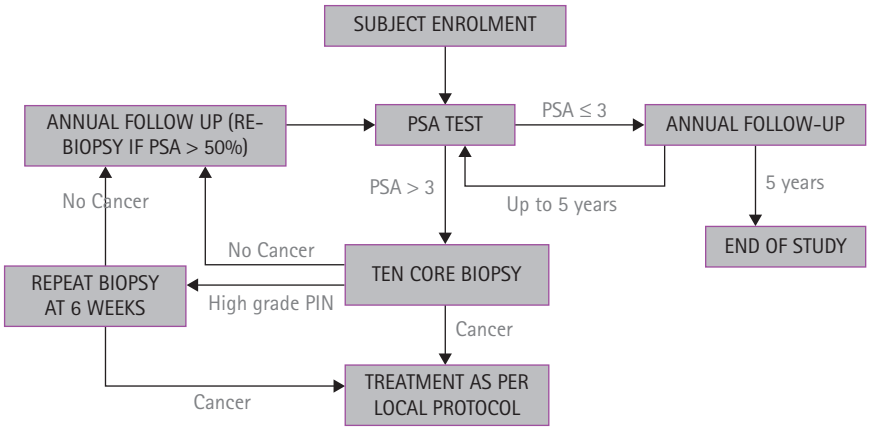

TABLE 1 Breakdown of recruitment per centre

Country/centre	Total recruitment
England	
Royal Marsden NHS Foundation Trust, London	42
St Mary's Hospital, Manchester	34
The Princess Anne Hospital, Southampton	18
St George's Hospital, London	14
Churchill Hospital, Oxford	10
Guy's Hospital, London	9
Northern Centre for Cancer Care, Newcastle	7
Kennedy Galton Cancer Centre, London	5
Addenbrooke's NHS Foundation Trust, Cambridge	4
Great Ormond Street Hospital, London	3
St Michael's Hospital, Bristol	1
Royal Devon and Exeter Hospital, Exeter	1
Australia	
Repatriation General Hospital, Adelaide	41
Peter MacCallum Cancer Centre, Melbourne	25
Westmead Hospital, Sydney	14
Royal Melbourne Hospital, Melbourne	6
Prince of Wales Hospital, Sydney	5
Spain	
Catalonian Institute of Oncology, Barcelona	18
Denmark	
Vejle Hospital, Vejle	31
Norway	
Norwegian Radium Hospital, Oslo	12
Total	**300**

TABLE 2 Demographic characteristics

Variable	Total cohort	*BRCA1* (*n* = 89)	*BRCA2* (*n* = 116)	Controls (*n* = 95)
Age (years), *n* (%)				
40–49	99 (33)	34 (38)	37 (32)	28 (29)
50–59	113 (38)	35 (39)	48 (41)	30 (32)
60–69	88 (29)	20 (22)	31 (27)	37 (39)
Ethnicity, *n* (%)				
Caucasian	292 (97)	84 (94)	115 (99)	93 (98)
Mixed Caucasian and Asian	2 (0.7)	2 (2)	0	0
Indian	2 (0.7)	1 (1)	0	1 (1)
Aboriginal	1 (0.3)	1 (1)	0	0
Chinese	1 (0.3)	0	0	1 (1)
Other	2 (0.6)	1 (1)	1 (0.9)	0
Educational level, *n* (%)				
University graduate	85 (28)	25 (28)	35 (30)	25 (26)
Technical/vocational qualifications	76 (25)	26 (29)	33 (28)	17 (18)
Left school at 18 years	25 (8)	8 (9)	6 (5)	11 (12)
Left school at 16 years	57 (19)	18 (20)	23 (20)	16 (17)
No qualifications	19 (6)	6 (7)	7 (6)	6 (6)
Other	6 (2)	1 (1)	1 (0.9)	4 (4)
Missing data	32 (11)	5 (6)	11 (9)	16 (17)
Employment, *n* (%)				
In active paid work	220 (73)	73 (82)	86 (74)	61 (64)
Retired	41 (14)	11 (12)	15 (13)	15 (16)
Unemployed	12 (4)	0	7 (6)	5 (5)
Other	1 (0.3)	1 (1)	0	0
Missing data	26 (9)	4 (4)	8 (7)	14 (15)
Family history of prostate cancer, *n* (%)				
Yes	96 (32)	21 (24)	47 (35)	28 (29)
No	181 (60)	56 (63)	65 (56)	60 (63)
Unknown	23 (8)	12 (13)	4 (3)	7 (7)
Previous PSA test, *n* (%)				
Yes	117 (39)	31 (35)	49 (42)	37 (39)
No	158 (53)	51 (57)	55 (47)	52 (55)
Unknown	25 (8)	7 (8)	12 (10)	6 (6)

Between six and 10 cores were taken for diagnosis. Of the 10 men with cancers, eight were mutation carriers and two were controls. The overall prostate cancer detection rate was 3.3% (10/300) at year 1, with an incidence of 3.9% (8/205) in mutation carriers and 2.1% (2/95) in controls. There was no significant difference between the two groups (Fisher's exact test, $P = 0{\cdot}513$).

The overall PPV of PSA (i.e the number of cancers detected divided by the number of biopsies expressed as a percentage) was 48% (10/21), equating to a false positive rate of 52%. The PPV in the control group was 50% (2/4) (95% CI, 26–74) and, in mutation carriers, the value was 47% (8/17) (95% CI, 23–72). When assessing *BRCA1* and *BRCA2* independently, the PPV in *BRCA1* mutation carriers was 66.7% (4/11) (95% CI, 22–96) and, in *BRCA2* mutation carriers, 36.4% (4/6) (95% CI, 11–69).

YEAR 2

Of the 300 men, 127 (34 *BRCA1*, 51 *BRCA2*, 42 controls) had two PSA screens, 1 year apart. At year 2, six men (4·7%) had a PSA level >3 ng/mL. Of these, three had previously had benign biopsies in year 1, of which two men did not meet the threshold to repeat the biopsy. Four men were referred for biopsy and one *BRCA2* positive subject was diagnosed with prostate cancer. The *BRCA2* carrier's PSA level had risen from 2·7 ng/mL to 4·3 ng/mL in 1 year, representing a doubling time of 17.37 months.

TABLE 3 Summary of the first and second rounds of screening PSA positive predictive values for each year

Variable	Total subjects	*BRCA1* carriers	*BRCA2* carriers	Controls
Year 1, *N*	300	89	116	95
PSA >3 ng/mL, *n* (%)	22/300 (7·33)	6/89 (6·74)	11/116 (9·48)	5/95 (5·26)
Biopsies, *n* (%)	21/300 (7·00)	6/89 (6·74)	11/116 (9·48)	4/95 (4·21)
Prostate cancer incidence, *n* (%)	10/300 (3·33)	4/89 (4·49)	4/116 (3·40)	2/95 (2·10)
	(95% CI, 1·61–6·04)	(95% CI, 1·24–1·10)	(95% CI, 0·95–8·60)	(95% CI, 0·26–7·40)
Positive predictive value of PSA, *n* (%)	10/21 (47·61)	4/6 (66·67)	4/11 (36·36)	2/4 (50·0)
	(95% CI, 24.0–68.0)	(95% CI, 22.0–96.0)	(95% CI, 11.0–69.0)	(95% CI, 6·8–93·0)
Year 2, *N*	127	34	51	42
PSA >3 ng/mL, *n* (%)	6/127 (4·72)	0	5/51 (9·80)	1/42 (2·38)
Biopsies, *n* (%)	4/127 (3.15)	0	4/51 (7·84)	0
Prostate cancer incidence, *n* (%)	1/127 (0.79)	0	1/51 (1·96)	0
Positive predictive value of PSA, *n* (%)	1/4 (25)	0	1/4 (25)	0
	(95% CI, 6·3–80·6)		(95% CI, 6·3–80·6)	

Of the men who had undergone PSA screening before study entry, 10 out of 117 (8.5%) had a raised PSA level, and five out of 10 (50%) of those with a raised PSA level had a cancer diagnosis. Of the men who had not previously undergone PSA screening, eight out of 158 (5.1%) had a raised PSA level, and five out of eight (62.5%) had a cancer diagnosis. Twenty-five men were unsure of whether they had undergone PSA screening before study entry.

COMPARISON WITH ERSPC DATA

The threshold for prostate biopsy in the IMPACT study is PSA >3 ng/mL. The PSA threshold used in the ERSPC is ≥3 ng/mL. To compare the prevalence of prostate cancer at the initial screening round in the two studies, the number of men with PSA ≥3 ng/mL in IMPACT were examined (Table 4). In year 1, 25 men had PSA ≥3 ng/mL (i.e. three participants had a PSA equal to 3 ng/mL). One man had a negative biopsy (off study).

Overall (mutation carriers and controls combined), the PPV at a threshold of ≥3.0 ng/mL is 45·5% compared to 24·1% in the ERSPC [7]. If the analysis is limited to those men aged ≥55 years, in direct comparison with the ERSPC, the PPV is 35.0%.

DIAGNOSIS AND TREATMENT

The characteristics of the eleven prostate cancers detected are shown in Table 5 [35]. Using the UK NICE classification [33], two of the cancers were high grade, six were intermediate grade and three were low grade. All cancers were adenocarcinomas.

Of the nine cancers detected in the mutation carriers, five were in *BRCA2* and four were in *BRCA1* mutation carriers. Of these nine cancers, one was high risk, six were intermediate risk and two were low risk. Of the two cancers detected in the control group, one was high-risk and one low-risk disease.

All three men with low-risk disease were treated with active surveillance. Of the nine clinically significant cancers (high or intermediate risk), eight were treated with radical prostatectomy and one with

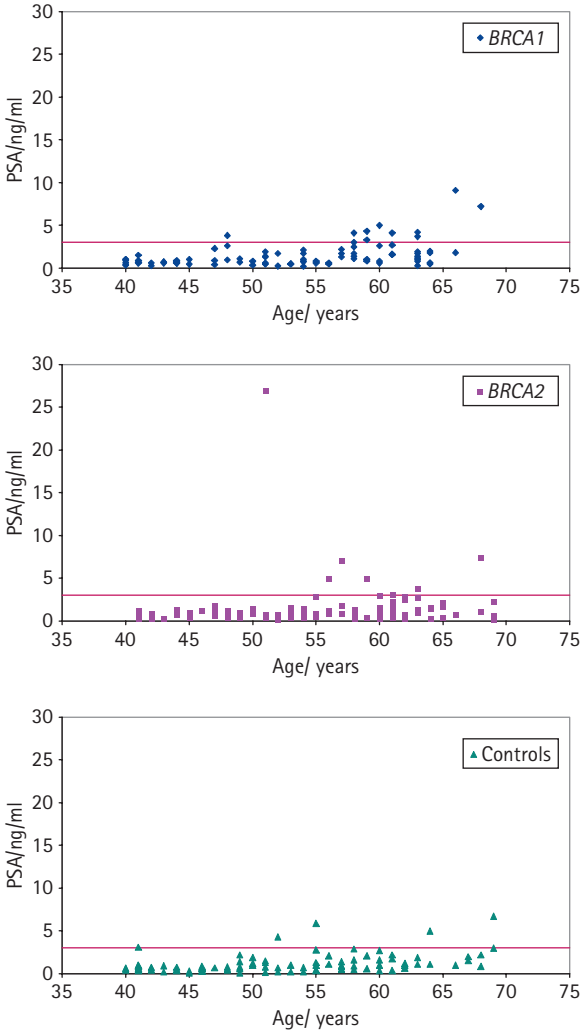

FIG. 2.
Year 1 PSA distribution (red line indicates a PSA of 3 ng/mL).

TABLE 4 Comparison of the (IMPACT) study and the ERSPC first screening rounds

Variable	IMPACT (year 1) total	*BRCA1*	*BRCA2*	Controls	ERSPC
Number of subjects	300	89	116	95	10 191
Mean (range) age of subjects (years)	53 (40–69)	52 (40–69)	54 (40–69)	55 (40–69)	66 (55–75)
PSA ≥3 ng/mL, *n* (%)	25/300 (8·33)	6/89 (6·74)	12/116 (10·34)	7/95 (7·36)	2 048/10 191 (20·09)
Biopsies, *n* (%)	22/300 (7·33)	6/89 (6·7)	11/116 (9·48)	5/95 (5·26)	1 850/10 191 (18·15)
Prostate cancer incidence, *n* (%)	10/300 (3·33)	4/89 (4·.49)	4/116 (3·44)	2/95 (2·10)	541/10 191 (5·30)
Positive predictive value of PSA, *n* (%)	10/22 (45·45)	4/6 (66·66)	4/11 (36·36)	2/5 (40·00)	541/1 850 (29·24)
	(95% CI, 24–68)	(95% CI, 22–96)	(95% CI, 11–69)	(95% CI, 5–85)	(95% CI, 25–31)

TABLE 5 Characteristics of the prostate cancers at diagnosis

Case	Family history of prostate cancer	Biopsy cores	Mutation status	Age	PSA (ng/mL)	Gleason score	Stage*	Symptoms	Disease risk classification	Treatment[8]	Amount of prostate cancer	Year detected
1	Yes	>10	Control	59	4·3	6 (3 + 3)	T1c	None	Low	AS	1/16 cores (<5% of core involved)	1
2	Yes	10	Control	62	3·1	7 (3 + 4)	pT3a	Difficulty passing urine	High	RP	20 mm cancer with a <1 mm extension outside the capsule	1
3	No	10	*BRCA1*	49	3·8	6 (3 + 3)	pT2c	None	Intermediate	RP	40 mm cancer, posterior margin involved. PIN present. Biopsy identified Gl4 in one core	1
4	No	6	*BRCA1*	64	5·0	6 (3 + 3)	T1c	None	Low	AS	1/6 cores (right apex) have cancer	1
5	Yes	6	*BRCA1*	63	4·2	6 (3 + 3)	pT2c	None	Intermediate	RP	Cancer in <5% but in both lobes. Extensive PIN and PNI	1
6	Yes	>10	*BRCA1*	69	7·4	6 (3 + 3)	T2b	Difficulty passing urine	Intermediate	Brachy	3/10 cores, cancer in 31%,28%, 25% of each core	1
7	Yes	7	*BRCA2*	56	5·0	7 (3 + 4)	pT2c	None	Intermediate	RP	Multifocal cancer. Largest tumour diameter 1 cm	1
8	Yes	10	*BRCA2*	51	27·0	7 (4 + 3)	pT3a	None	High	RP	Multifocal disease with a nodule breaching the capsule. Cancer in 18% of the gland	1
9	No	10	*BRCA2*	60	4·3	7 (4 + 3)	pT2c	None	Intermediate	RP	Cancer in 7% of whole gland involved. High grade PIN seen	2
10	Yes	7	*BRCA2*	42	3·5	7 (3 + 4)	pT2c	Long history of frequency	Intermediate	RP	Cancer in 15% of whole gland, one positive margin, PNI invasion present	1
11	No	6	*BRCA2*	61	4·1	6 (3 + 3)	T1c	None	Low	AS	1/6 cores (left apex) have cancer	1

[8]*AS, active surveillance; Brachy, brachytherapy; PIN, prostatic intra-epithelial neoplasia; PNI, perinuclear invasion; RP, radical prostatectomy.*
**Stage classified using TNM stages of prostate cancer [35].*

brachytherapy. There were no deaths from prostate cancer.

ADVERSE EVENTS

No adverse events were reported from PSA screening. Complications from diagnostic procedures occurred in two out of 25 subjects, with two infections reported post-biopsy (8%). No treatment-related complications were reported. One subject died in a non-study-related event.

DISCUSSION

RECRUITMENT

The observed recruitment rates were higher than reported in two large population prostate screening studies, which described recruitment rates as low as 11%, although this may be a result of it being possible to check eligibility before approaching patients in the present study, whereas this was not always the case in the previous studies [36,37]. In line with the results reported in the present study, the ERSPC reported an uptake rate of 39.5% [38]. It was observed that centres using a face-to-face approach rather than postal invitations yielded a higher uptake rate. One centre reported an uptake rate of 84%; however, this value is probably biased because referrals were received from six regional genetics centres where subjects had given verbal consent to be contacted. Data on subjects declining participation would not have been captured using this method.

A very high level of compliance with both PSA screening and the biopsy recommendations was observed. Thirty-nine percent of men had undergone PSA testing before enrollment in the study and this may have influenced compliance. There was a very low drop-out rate, with only one man withdrawing from the study as a result of confounding medical problems. This compares favourably with the 82–86% compliance rates reported in the ERSPC and PLCO trials [6,7]. However, the short length of follow-up must be taken into consideration, and longer-term follow-up may result in a fall in compliance.

No report to date has looked at screening behaviour in men with *BRCA1/2* mutations, apart from a small study by Liede *et al.* [39]. However, men from families with *BRCA1* or *BRCA2* mutations, especially those that have

opted for presymptomatic testing, may have greater motivation to enter research studies because the results obtained may ultimately benefit their relatives. Indeed, only 10–20% of men opt for testing in most studies [39,40]. Men often cite their primary motivation for seeking genetic testing as being to determine the risk for their family, in particular their daughters, rather than for their own immediate health benefit [41,42]. Their partners may also play an important role in influencing prostate screening behaviour [43].

More mutation carriers than controls have been recruited to date, although no specific difficulties in recruiting controls have been identified. Most genetics centres do not have regular contact with men who have tested negative for *BRCA1/2* mutations, whereas they are more likely to be in contact with mutation positive men. This may explain the recruitment of more mutation carriers than controls in this initial phase of the study.

PSA THRESHOLD

There is much controversy around the PSA level that should be used to determine biopsy. It is reported that the lack of specificity of PSA may expose as many as 80% of men with PSA levels over 4 ng/mL to unnecessary prostate biopsies [7,44]. Although it is too early to identify statistical differences within the cohorts, it is fair to conclude that, despite the wide CIs, the observed PPV of PSA is at least the same, if not greater than reported in the ERSPC. There are several explanations for the higher PPV of PSA observed within this study, and these are discussed below.

The age of the cohort (range, 40-69 years; mean, 54 years) may affect the PPV of PSA. In the ERSPC, the age range is 55–75 years, with a mean age of 66 years [45]. When this analysis was limited to those men aged 55–69 years, the PPV was 35%, which is higher than that reported in the ERSPC. A PSA of >3 ng/mL in a younger age range is less likely to be related to BPH, one of the major factors contributing to the lack of specificity of PSA for prostate cancer detection [46]. BPH is the benign enlargement of the prostate gland that is very common in men over the age of 50 years, and it is accompanied by a moderate rise in PSA. However, this previously simplistic view is being augmented by a realization that other non-malignant conditions are responsible for an appreciable rise in PSA, further confusing the power of PSA to detect prostate cancer [47]. The prevalence of BPH reaches maximum levels for those individuals aged in their seventies, which coincides with the age at which most prostate cancers are diagnosed in Western populations [48]. Lowering the age range of men enrolled in PSA screening reduces the likelihood of detecting BPH and increases the sensitivity and specificity of PSA [44]. The ERSPC report a much higher number of men with raised PSA levels (20%) compared to the data reported in the present study (8%), as well as a higher number of resultant biopsies. The most probable explanation for this difference is the older age of the ERSPC cohort, and may reflect the higher incidence of BPH in the ERSPC cohort.

Oesterling *et al.* [49] recommended age specific PSA thresholds of 2.5 ng/mL for men aged 40–49 years, 3.5 ng/mL for men aged 50–59 years and 4.5 ng/mL in men aged 60–69 years [49]. Therefore, it could be argued that the threshold of 3.0 ng/mL is high for men aged 40–49 years, which could explain the high PPV observed. Schröder *et al.* [50] argue that a PSA threshold of 3.0 ng/mL is adequately low for men aged 55–75 years [50]. Schröder *et al.* [51] estimate that, out of the 2279 cancers that would have been diagnosed if all men in the ERSPC with a PSA of <3.0 ng/mL had been biopsied, only 14 interval cancers would have been avoided [51]. With this very low level of 'missed' prostate cancers, the number of men exposed to potential complications of undergoing prostate biopsy would not be justified.

The higher population incidence of prostate cancer, as observed particularly in *BRCA2* mutation carriers, may affect the PPV. However, when the cohorts are separated, a lower PPV is seen among the *BRCA2* mutation carriers. The numbers presented are too small to allow meaningful conclusions. Once recruitment is complete (the target based on power calculations, assuming a relative risk of prostate cancer of fivefold in *BRCA2* and twofold in *BRCA1* by age 65 years, is 350 *BRCA2* mutation carriers and 500 *BRCA1* mutation carriers with 850 bloodline non-mutation carrier controls), further analyses will determine whether there are any differences in the development of prostate cancer between the mutation carriers and the control group.

The underlying population incidence of prostate cancer in each of the recruiting countries needs to be taken into consideration. The incidence of prostate cancer in the UK is reported at one in 10 men by age 80 years, which is very similar to the incidence in the rest of Western Europe and in Australia [52,53]. Therefore, geographical variation is unlikely to affect the observed cancer incidence in this cohort. One limitation of the present study is that there were no subjects of African-American descent included in the analysis. In view of the higher risk of invasive prostate cancer in men of African-American descent, these results cannot be extrapolated for this group. Every effort is being made within the IMPACT study to enroll men from a variety of ethnic groups.

There was no significant difference seen in cancer detection rates between men who had undergone PSA screening before study entry compared to those with no screening history. It could be hypothesized that more cancers would be diagnosed in the unscreened group, although this was not observed.

Howard *et al.* [54] have discussed the use of Markov modelling in groups at varying risk and have reported that not only are more prostate cancer deaths averted in higher risk men, but also more prostate cancers are diagnosed and there may be related harms. This is why longer-term follow-up in IMPACT will be important.

There is much debate around the number of diagnostic cores that should be taken at biopsy, with large international variation in practice. The IMPACT study protocol advised that a ten core biopsy should be undertaken, in line with the ProtecT study and current practice at the time the study was designed. However, achieving standardization across the study, which involves a large numbers of centres, has proven challenging. In all but three of the cases with a negative biopsy result, ten cores were taken for diagnosis.

HISTOLOGY OF THE SCREEN-DETECTED PROSTATE CANCERS

A higher proportion of the *BRCA1* and *BRCA2* mutation carriers were diagnosed with prostate cancer than men in the non-carrier control group. Most of the mutation carriers had clinically significant disease (22% low risk, 67% intermediate risk and 11% high risk). By comparison, data from the first round of the ERSPC showed that 64% of the prostate

cancers diagnosed were of low grade and were in the low-risk group, 27% were of intermediate grade and 8% were high grade (based on Gleason score) [45]. The higher incidence of clinically significant disease in the mutation carriers is an important observation in view of the younger age of this cohort compared to the ERSPC cohort. Younger men would be predicted to have lower risk of disease compared to older men, and this adds to the increasing evidence that mutation carriers, in particular *BRCA2* carriers, develop more aggressive disease.

It is too early to be able to compare the prognosis of disease observed in the mutation carriers with the non-carrier control group. The literature supports the finding that *BRCA2* mutation carriers, and, to a lesser extent, *BRCA1* mutation carriers, tend to have an aggressive tumour histology and that median survival is comparatively short [11,24,25]. The clinical aggressiveness of the tumours and survival will be analyzed in a longer-term follow-up and correlated with objective phenotypic parameters.

TREATMENT

The NICE guidelines for the treatment of prostate cancer recommend prostatectomy, brachytherapy or conformal radiotherapy as the treatment options for intermediate- and high-risk disease [33]. Active surveillance is recommended for low-risk disease. These are similar to the treatment guidelines issued by the AUA [34]. The treatments chosen for men within this study were determined by local protocols but are in line with these recommendations.

Preliminary data from the IMPACT study show that there is a relatively low rate of biopsy (7%) with a PSA threshold of >3 ng/mL but that the PPV is high at 48%. Hence, the present study provides evidence that screening men with genetic predisposition detects clinically significant prostate cancer. These data support the rationale for continued screening in such men.

FUTURE DIRECTIONS

The present study will continue to recruit until the end of December 2012, when it is anticipated the planned target of 1700 subjects will have been recruited. All men enrolled will be screened for at least 5 years. As of January 2010, thirty-two centres in eleven countries were enrolling subjects. A health-related quality of life study is planned to commence in early 2010.

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CONTRIBUTORS

R. Eeles is the Chief Investigator of the IMPACT study and had overall responsibility for the study. A. Mitra and E. Bancroft had overall responsibility for the analyses and writing of the article. All authors contributed to the study design, provided data and contributed to data interpretation, writing and editing of the report, and approved the final version.

CONFLICT OF INTEREST

There are no conflicts of interest to declare.

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Abbreviations: **ERSPC**, European Randomised Study for Prostate Cancer; **IMPACT**, Identification of Men with a genetic predisposition to ProstAte Cancer: Targeted screening in BRCA1/2 mutation carriers and controls; **NICE**, National Institute for Health and Clinical Excellence; **PLCO**, Prostate, Lung, Colorectal and Ovarian screening study; **PPV**, positive predictive value.

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