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


1The Institute of Cancer Research, Sutton, Surrey, UK, 2Royal Marsden Hospital NHS Foundation Trust, Sutton, Surrey, UK, 3Royal Liverpool University Hospital, Liverpool, UK, 4Peter MacCallum Cancer Center, Victoria, Australia, 5Royal Melbourne Hospital, Parkville, Victoria, Australia, 6Repatriation General Hospital, Daw Park, Adelaide, SA, Australia, 7Department of Paediatrics, University of Adelaide, SA, Australia, 8St Mary's Hospital, CMFT, Manchester, UK, 9Department of Clinical Genetics, Vår Frelsers Hospital, Oslo, Norway, 10St George's Hospital, Tooting, London, UK, 11Churchill Hospital, Headington, Oxford, UK, 12Guy's Hospital, London, UK, 13Institute of Human Genetics, Newcastle, UK, 14Prince of Wales Hospital, Sydney, NSW, Australia, 15North West Thames Regional Genetics Service, Kennedy Galton Centre, North West London Hospitals NHS Trust, Harrow, UK, 16Addenbrooke's Hospital, Cambridge, UK, 17NE Thames Regional Genetics Service, Institute of Child Health, London, UK, 18St Michael's Hospital, Bristol, UK, 19Royal Devon & Exeter Hospital, Exeter, UK, 20Department of Urology, Fredericia and Kolding Hospital, Fredericia, Denmark, 21International Hereditary Cancer Center, Pomeranian Medical University, Szczecin, Poland, 22Center for Medical Genetics, NorthShore University HealthSystem, Evanston, IL, USA, 23Huntsman Cancer Institute, University of Utah, Salt Lake City, UT, USA, 24King Edward Memorial Hospital, Perth, WA, Australia, 25Chaim Sheba Medical Center, Tel-Hashomer, Israel, 26Abramson Cancer Center, Philadelphia, PA, USA, 27Hospital de Sant Pau, Barcelona, Spain, 28Hunter Genetics, Newcastle, NSW, Australia, 29University of New South Wales, St Vincent's Clinical School, Sydney, Australia, 30Cancer Research Initiatives Foundation, Subang Jaya Medical Centre, Selangor Darul Ehsan, Malaysia, 31University of Malaya, Kuala Lumpur, Malaysia, 32Istituto Nazionale dei Tumori, Milano, Italy, 33The Netherlands Cancer Institute, Amsterdam, The Netherlands, 34Erasmus University Medical Center, Rotterdam, The Netherlands, 35Faculty of Medicine, School of Health Sciences, University of Iceland, Reykjavik, Iceland, 36Imperial College Healthcare NHS Trust, London, London, UK, 37University Hospital, Umeå, Sweden, 38University of Oxford, John Radcliffe Hospital, Oxford, UK, 39University Hospital of Iceland, Reykjavik, Iceland, 40Memorial Sloan-Kettering Cancer Center, New York, NY, USA, 41Cancer Research UK Genetic Epidemiology Unit, Department of Public Health
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.

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 Ovarian screening study (PLCO) in the Netherlands for males aged ≥65 years [2]. 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].

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 \( \text{BRCA1} \) or \( \text{BRCA2} \) 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 \( \text{BRCA1} \) or \( \text{BRCA2} \) mutations. Men with \( \text{BRCA2} \) 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 \( \text{BRCA1} \) 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 \( \text{BRCA1} \) and \( \text{BRCA2} \) mutation carriers were combined; separately, there was no difference [30]. Consequently, the exact prostate cancer risk for \( \text{BRCA1}/\text{BRCA2} \) mutation carriers remains unclear. The IMPACT study aims to evaluate the utility of PSA screening in men with \( \text{BRCA1} \) and \( \text{BRCA2} \) 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 \( \text{BRCA1} \) and \( \text{BRCA2} \) 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 \( \text{BRCA1} \) or \( \text{BRCA2} \). Men who had received a negative result for a \( \text{BRCA1} \) or \( \text{BRCA2} \) 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 \( \text{BRCA1}/\text{BRCA2} \) 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 \( \text{BRCA1} \) or \( \text{BRCA2} \) 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 ≤6, and a PSA level ≤</p>
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.
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, $P = 0.513$).

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 2 Demographic characteristics

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

---

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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total subjects</th>
<th>BRCA1 carriers</th>
<th>BRCA2 carriers</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Year 1, N</strong></td>
<td>300</td>
<td>89</td>
<td>116</td>
<td>95</td>
</tr>
<tr>
<td>PSA &gt;3 ng/mL, n (%)</td>
<td>22/300 (73:33)</td>
<td>6 (89:6-74)</td>
<td>11/116 (9:48)</td>
<td>5/95 (5:26)</td>
</tr>
<tr>
<td>Biopsies, n (%)</td>
<td>21/300 (7:00)</td>
<td>6 (89:6-74)</td>
<td>11/116 (9:48)</td>
<td>4/95 (4:21)</td>
</tr>
<tr>
<td>Prostate cancer incidence, n (%)</td>
<td>10/300 (3:33)</td>
<td>4(89:4-49)</td>
<td>4/116 (3:40)</td>
<td>2/95 (2:10)</td>
</tr>
<tr>
<td><strong>Year 2, N</strong></td>
<td>127</td>
<td>34</td>
<td>51</td>
<td>42</td>
</tr>
<tr>
<td>PSA &gt;3 ng/mL, n (%)</td>
<td>6/127 (4:72)</td>
<td>0</td>
<td>5/51 (9:80)</td>
<td>1/42 (2:38)</td>
</tr>
<tr>
<td>Biopsies, n (%)</td>
<td>4/127 (3:15)</td>
<td>0</td>
<td>4/51 (7:84)</td>
<td>0</td>
</tr>
<tr>
<td>Prostate cancer incidence, n (%)</td>
<td>1/127 (0:79)</td>
<td>0</td>
<td>1/51 (1:96)</td>
<td>0</td>
</tr>
<tr>
<td>Positive predictive value of PSA, n (%)</td>
<td>1/4 (2:5)</td>
<td>0</td>
<td>1/4 (2:5)</td>
<td>0</td>
</tr>
</tbody>
</table>

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).
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...
TARGETED PROSTATE CANCER SCREENING

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.

DISCUSSION

RECRUITMENT

The observed recruitment rates were higher than reported in two large population screening procedures carried out in 25 subjects, with two infections reported post-biopsy.

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.
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 difficulties in recruiting controls have been recruited to date, although no specific

**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.

ACKNOWLEDGEMENTS

This research was supported by a grant from The Ronald and Rita McAulay Foundation. We acknowledge support from Cancer Research UK (Grant reference C5047/A8385). The Cancer Councils of Victoria and South Australia, grant number 400048 and the Prostate Cancer Foundation of Australia, grant number PCFA PR04, funded the tissue and urine collections in Australia. We acknowledge funding from Jack and Judy Baker for the study in NorthShore University Health System, Evanston, Illinois. We acknowledge funding from the NIHR to the Biomedical Research Center at The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust, as well as at Central Manchester Foundation Trust. D.F.E., S.P. and M.C. are funded by Cancer Research UK Grants C1287/A10118 and C1287/A8874. We are grateful to the members of the Data and Safety Monitoring Committee: S. Duffy (Chair), P. White and R. Pocock.

CONFLICT OF INTEREST

There are no conflicts of interest to declare.

REFERENCES

3 Schröder FH, Bangma CH. The European Randomized Study of Screening for Prostate Cancer (ERSPC). Br J Urol 1997; 79 (Suppl. 1): 68–71
4 Prorok PC, Andrieu GL, Bresalier RS et al.; Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial Project Team. Design of the the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial. Control Clin Trials 2000; 21 (Suppl.): 273–309
10 Draisma G, De Koning HJ. MISCAN: estimating lead-time and over-detection by simulation. BJU Int 2003; 92 (Suppl. 2): 106–11
15 Matikainen MP, Schleutker J, Morsky P, Kallioniemi OP, Tammela TL. Detection of subclinical cancers by prostate-specific antigen screening in asymptomatic men


28 Hubert A, Peretz T, Manor O et al. The Jewish Ashkenazi founder mutation in the BRCA1/BRCA2 genes are not found at an increased frequency in Ashkenazi patients with prostate cancer. Am J Hum Genet 1999; 65: 921–4


32 Berney DM, Fisher G, Kattan MW et al. Major shifts in the treatment and prognosis of prostate cancer due to changes in pathological diagnosis and grading. BJU Int 2007; 100: 1240–4


38 Roobol MJ, Schröder FH, Krane R. A comparison of first and repeat (four years later) prostate cancer screening in a randomized cohort of a symptomatic men aged 55–75 years using a biopsy indication of 3.0 ng/ml (results of ERSPC, Rotterdam). Prostate 2006; 66: 604–12


46 Khan MA, Partin AW, Rittenhouse HG et al. Evaluation of pro-prostate specific antigen for early detection of prostate cancer in men with a total prostate specific antigen range of 4.0–10.0 ng/mL. J Urol 2003; 170: 723–6


Correspondence: Rosalind Eeles, The Institute of Cancer Research, 15 Cotswold Road, Sutton, Surrey SM2 5NG, UK. e-mail: rosalind.eeles@icr.ac.uk

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.

*APPENDIX – LIST OF COLLABORATORS

AUSTRALIA

Peter MacCallum Cancer Center, Melbourne: Gillian Mitchell, Rebecca Doherty, Kate Drew, Jo McKinley, Sarah Pratt, Mary-Anne Young The Walter & Eliza Hall Institute of Medical Research, Melbourne: Geoffrey Lindeman, Michael Bogwitz Adelaide Repatriation General Hospital, Adelaide: Alan Stapleton, Jimmy Lam, Louise Taylor. Women’s and Children’s Hospital, Adelaide: Graeme Suthers, Meryl Aitree. Prince of Wales Hospital, Sydney: Kathy Tucker, Robyn Ward

Westmead Hospital, Sydney: Judy Kirk King Edward Memorial Hospital, Perth: Sharron Townshend Royal Brisbane & Women’s Hospital, Brisbane: Julie McGaughran Royal Hobart Hospital, Tasmania: David Amor Hunter Genetics, Newcastle, New South Wales: Allan Spigelman, Rodney Scott St Vincent’s Hospital, Sydney, Allan Spigelman Monash Medical Center, Melbourne: Marion Harris, Mark Frydenberg

CANADA

Department of Oncology, McGill University, Montreal: Marc Tischkowitz, Nassim Taherian, William Foulkes, Armen Aprikian.

CYPRUS

The Cyprus Institute of Neurology & Genetics: Kyriacos Kyriacou, Andreas Hadjisavvas

DENMARK

Vejle Hospital, Vejle: Dorte Cruger, Anne-Bine Skytte, Marie Luise Soes Bisgaard Fredericia and Kolding Hospital, Fredericia: Palle Osther Odense University Hospital, Odense, Anne-Marie Gerdes

FRANCE

Center Jean Perrin, Clermont-Ferrand: Yves-Jean Bignon

ISRAEL

Chaim Shema Medical Center, Tel-Hashomer: Eitan Friedman

ITALY

Istituto Nazionale dei Tumori, Milan: Nicola Nicolai, Paolo Radice, Riccardo Valdagni

LATVIA

Hereditary Cancer Institute, Riga: Andris Abele, Janis Gardovskis, Arvīds Irmējs

MALAYSIA

Cancer Research Initiatives Foundation, Subang Jaya Medical Center, Selangor Darul Ehsan: Soo Hwang Teo, Hui Meng Tan, Sook-Yee Yoon

University of Malaya, Kuala Lumpur: Soo Hwang Teo, Meow Keong Thong

THE NETHERLANDS

Leiden University Medical Center, Leiden: Christi van Asperen. Radboud University Nijmegen Medical Center: Bart Kiemene

NORWAY

Norwegian Radium Hospital, Oslo: Lovise Maehle, Pål Møller, Bjorn Brennhovd, Eibdyrg Hanslien, Heidi Medvik

POLAND

International Hereditary Cancer Center, Szczecin: Cezary Cybulski, Jan Lubinski, Dominika Wokolorczyk

SLOVAKIA

National Cancer Institute, Bratislava: Denisa Ilencičiková, Lucia Copakova

SLOVENIA

Institute of Oncology, Ljubljana: Janez Zgajnar, Mateja Krajc

SPAIN

Catalonian Institute of Oncology, Barcelona: Ignacio Blanco, Merce Peris, Mónica Salinas Hospital de Sant Pau, Barcelona: Teresa Ramón y Caja

SWEDEN

Karolinska Institute, Stockholm: Annelie Liljegren, Marie Hjälm-Eriksson, Sten Nilsson, Annika Lindblom, Brita Wasteson Arver, Lars Egevad, Stefan Karlsson

TURKEY

Akdeniz University, Antalya: Guven Luleci, Esra Manguoglu

UK

Royal Marsden NHS Foundation Trust: Rosalind Eeles, Elizabeth Bancroft, Yolanda Barbachano, Susan Shanley, Audrey Ardern-Jones, Jennifer Wiggins, Vincent Khoo, Alan Thompson, Cyril Fisher, Charles Jameson, Kelly Kohut, Sarah Thomas, Lisa Robertson