EUROPEAN UROLOGY 66 (2014) 489–499

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Platinum Priority – Prostate Cancer

Editorial by Ola Bratt on pp. 500–501 of this issue

Targeted Prostate Cancer Screening in *BRCA1* and *BRCA2* Mutation Carriers: Results from the Initial Screening Round of the IMPACT Study

Elizabeth K. Bancroft[a,b], *Elizabeth C. Page*[b], *Elena Castro*[b,c], *Hans Lilja*[d,e,f,g], *Andrew Vickers*[h], *Daniel Sjoberg*[h], *Melissa Assel*[h], *Christopher S. Foster*[i], *Gillian Mitchell*[j,k], *Kate Drew*[j], *Lovise Mæhle*[l], *Karol Axcrona*[l], *D. Gareth Evans*[m], *Barbara Bulman*[m], *Diana Eccles*[n], *Donna McBride*[n], *Christi van Asperen*[o], *Hans Vasen*[p], *Lambertus A. Kiemeney*[q], *Janneke Ringelberg*[p], *Cezary Cybulski*[r], *Dominika Wokolorczyk*[r], *Christina Selkirk*[s], *Peter J. Hulick*[s,t], *Anders Bojesen*[u], *Anne-Bine Skytte*[u], *Jimmy Lam*[v], *Louise Taylor*[v], *Rogier Oldenburg*[w], *Ruben Cremers*[q], *Gerald Verhaegh*[q], *Wendy A. van Zelst-Stams*[q], *Jan C. Oosterwijk*[x], *Ignacio Blanco*[y], *Monica Salinas*[y], *Jackie Cook*[z], *Derek J. Rosario*[aa], *Saundra Buys*[bb], *Tom Conner*[bb], *Margreet G. Ausems*[cc], *Kai-ren Ong*[dd], *Jonathan Hoffman*[dd], *Susan Domchek*[ee], *Jacquelyn Powers*[ee], *Manuel R. Teixeira*[ff,gg], *Sofia Maia*[ff], *William D. Foulkes*[hh], *Nassim Taherian*[hh], *Marielle Ruijs*[ii], *Apollonia T. Helderman-van den Enden*[jj], *Louise Izatt*[kk], *Rosemarie Davidson*[ll], *Muriel A. Adank*[mm], *Lisa Walker*[nn], *Rita Schmutzler*[oo], *Kathy Tucker*[pp,qq], *Judy Kirk*[rr,ss], *Shirley Hodgson*[tt], *Marion Harris*[uu], *Fiona Douglas*[vv], *Geoffrey J. Lindeman*[ww,xx,yy], *Janez Zgajnar*[zz], *Marc Tischkowitz*[aaa,bbb], *Virginia E. Clowes*[aaa,bbb], *Rachel Susman*[ccc], *Teresa Ramón y Cajal*[ddd], *Nicholas Patcher*[eee,fff], *Neus Gadea*[ggg], *Allan Spigelman*[hhh,iii,jjj], *Theo van Os*[kkk], *Annelie Liljegren*[lll], *Lucy Side*[mmm], *Carole Brewer*[nnn,ooo], *Angela F. Brady*[ppp], *Alan Donaldson*[qqq], *Vigdis Stefansdottir*[rrr], *Eitan Friedman*[sss], *Rakefet Chen-Shtoyerman*[ttt], *David J. Amor*[uuu], *Lucia Copakova*[vvv], *Julian Barwell*[www,xxx], *Veda N. Giri*[yyy], *Vedang Murthy*[zzz], *Nicola Nicolai*[aaaa], *Soo-Hwang Teo*[bbbb], *Lynn Greenhalgh*[cccc], *Sara Strom*[dddd], *Alex Henderson*[vv], *John McGrath*[ooo], *David Gallagher*[eeee], *Neil Aaronson*[ii], *Audrey Ardern-Jones*[a], *Chris Bangma*[w], *David Dearnaley*[a,b], *Philandra Costello*[n], *Jorunn Eyfjord*[ffff], *Jeanette Rothwell*[m], *Alison Falconer*[gggg], *Henrik Gronberg*[hhhh], *Freddie C. Hamdy*[e,nn], *Oskar Johannsson*[rrr], *Vincent Khoo*[a], *Zsofia Kote-Jarai*[b], *Jan Lubinski*[r], *Ulrika Axcrona*[l], *Jane Melia*[bbb], *Joanne McKinley*[j], *Anita V. Mitra*[b,iiii], *Clare Moynihan*[b], *Gad Rennert*[jjjj], *Mohnish Suri*[kkkk], *Penny Wilson*[llll], *Emma Killick*[a,b], *The IMPACT Collaborators*[†], *Sue Moss*[mmmm], *Rosalind A. Eeles*[b,a,*]

[†] See online Supplement.
[*] Corresponding author. The Institute of Cancer Research and Royal Marsden NHS Foundation Trust, 15 Cotswold Road, Sutton SM2 5NG, UK. Tel. +44 208 722 4094; Fax: +44 208 722 4110.
E-mail address: rosalind.eeles@icr.ac.uk (R.A. Eeles).

0302-2838/$ – see back matter
http://dx.doi.org/10.1016/j.eururo.2014.01.003

Article info

Article history:
Accepted January 2, 2014
Published online ahead of print on January 15, 2014

Keywords:
BRCA1
BRCA2
Prostate cancer
Prostate-specific antigen
Targeted screening

Abstract

Background: Men with germline breast cancer 1, early onset (*BRCA1*) or breast cancer 2, early onset (*BRCA2*) gene mutations have a higher risk of developing prostate cancer (PCa) than noncarriers. IMPACT (Identification of Men with a genetic predisposition to ProstAte Cancer: Targeted screening in *BRCA1/2* mutation carriers and controls) is an international consortium of 62 centres in 20 countries evaluating the use of targeted PCa screening in men with *BRCA1/2* mutations.
Objective: To report the first year's screening results for all men at enrolment in the study.
Design, setting and participants: We recruited men aged 40–69 yr with germline *BRCA1/2* mutations and a control group of men who have tested negative for a pathogenic *BRCA1* or *BRCA2* mutation known to be present in their families. All men underwent prostate-specific antigen (PSA) testing at enrolment, and those men with PSA >3 ng/ml were offered prostate biopsy.
Outcome measurements and statistical analysis: PSA levels, PCa incidence, and tumour characteristics were evaluated. The Fisher exact test was used to compare the number of PCa cases among groups and the differences among disease types.
Results and limitations: We recruited 2481 men (791 *BRCA1* carriers, 531 *BRCA1* controls; 731 *BRCA2* carriers, 428 *BRCA2* controls). A total of 199 men (8%) presented with PSA >3.0 ng/ml, 162 biopsies were performed, and 59 PCas were diagnosed (18 *BRCA1* carriers, 10 *BRCA1* controls; 24 *BRCA2* carriers, 7 *BRCA2* controls); 66% of the tumours were classified as intermediate- or high-risk disease. The positive predictive value (PPV) for biopsy using a PSA threshold of 3.0 ng/ml in *BRCA2* mutation carriers was 48%—double the PPV reported in population screening studies. A significant difference in detecting intermediate- or high-risk disease was observed in *BRCA2* carriers. Ninety-five percent of the men were white, thus the results cannot be generalised to all ethnic groups.
Conclusions: The IMPACT screening network will be useful for targeted PCa screening studies in men with germline genetic risk variants as they are discovered. These preliminary results support the use of targeted PSA screening based on *BRCA* genotype and show that this screening yields a high proportion of aggressive disease.
Patient summary: In this report, we demonstrate that germline genetic markers can be used to identify men at higher risk of prostate cancer. Targeting screening at these men resulted in the identification of tumours that were more likely to require treatment.

1. Introduction

Prostate cancer (PCa) is the second most common cancer in men worldwide and the sixth most common cause of death [1]. There is a large degree of variation worldwide in both incidence and mortality because of differences in genetic background, lifestyle, the availability of screening programmes, and treatments.

Men with germline mutations in breast cancer 1, early onset (*BRCA1*) or breast cancer 2, early onset (*BRCA2*) genes have an increased risk of PCa. The relative risk of PCa by ≤65 yr is estimated at 1.8-fold to 4.5-fold for *BRCA1* carriers [2,3] and at 2.5-fold to 8.6-fold for *BRCA2* carriers [4–6]. A number of retrospective studies consistently report that *BRCA2* carriers present at a younger age with aggressive disease, higher rates of lymph node involvement, distant metastasis at diagnosis, and a higher mortality rate compared with noncarriers [7–12]. While there is debate about whether there is an increased risk of PCa for *BRCA1* carriers, there is increasing evidence that these men also present with more aggressive disease [7,9,13]. In addition, *BRCA2* mutation status has been confirmed as an independent prognostic factor for poorer outcome [7]. Therefore, targeted screening of *BRCA1/2* carriers for earlier detection may be beneficial.

The prostate-specific antigen (PSA) test is the most effective PCa biomarker currently available; however, its limitations are well documented. Expert groups have concluded that data from existing clinical trials—notably the Prostate, Lung, Colorectal and Ovary screening study (PLCO) [14] and the European Randomised Study of Screening for Prostate Cancer (ERSPC) [15]—are insufficient to recommend routine general population PSA screening. The main scientific challenge is to differentiate between men who will benefit from screening and men who will not, reducing overdiagnosis and overtreatment while maintaining benefits (ie, lower mortality).

There is no international consensus on targeting screening at men at higher risk. There have been a limited number of studies of screening in men with a family history of PCa [16–18]. Most of the studies support the use of targeted screening; however, methodological differences make it difficult to draw conclusions from these data [16,17,19–26]. The IMPACT study (Identification of Men with a genetic predisposition to ProstAte Cancer: Targeted screening in *BRCA1/2* mutation carriers and controls; www.impact-study.co.uk) is an international, multicentre study evaluating the role of targeted PSA screening in men with *BRCA1/2* mutations. The aims of IMPACT are to evaluate the utility of PSA screening, to determine PCa

incidence, to assess the positive predictive value (PPV) of biopsy using a PSA threshold of 3.0 ng/ml, to determine biopsy rates, and to evaluate the characteristics of the tumours to establish whether PSA screening detects clinically significant disease in this population compared with the control group. This analysis reports the results of the first screening round for all men enrolled in IMPACT from October 2005 to February 2013.

2. Materials and methods

The IMPACT study design and methods have previously been reported elsewhere [27,28] and are summarised below (Fig. 1). The protocol was approved by the West-Midlands Research and Ethics Committee in the United Kingdom (reference 05/MRE07/25) and subsequently by each participating institution's local committee. All participants provide written consent, and interim analyses are presented to the Independent Data and Safety Monitoring Committee biannually.

The target sample is 500 *BRCA1* mutation carriers and 350 *BRCA2* mutation carriers and a control group of 850 men who tested negative for a pathogenic *BRCA* mutation in their family. IMPACT has been powered to detect a twofold increased risk over 5 yr of screening, with 80% power at $p < 0.01$.

We recruited men aged 40–69 from families with a *BRCA* mutation between October 2005 and February 2013. Men were recruited from cancer genetics clinics from families with known pathogenic *BRCA1* or *BRCA2* mutations. Men from these families could enter the study if they had tested positive or negative for the mutation, or if they were at 50% risk of inheriting a mutation but had not yet undergone testing. Men in the latter group were tested within the study to be allocated to the appropriate group for analysis, but this result was not fed back to participants. Men were excluded if they were known to have PCa or if they had a prior cancer diagnosis with a prognosis of <5 yr. In the Dutch cohort, men were also excluded if they had prior PSA screening.

Participants underwent PSA testing at enrolment, and if their PSA value was >3.0 ng/ml, a 10-core transrectal ultrasound–guided prostate biopsy was recommended. PSA quality assurance was measured on a concurrent serum sample. All available samples were tested using the ProStatus PSA Free/Total DELFIA assay at SUS (Malmö, Sweden). In addition, in men undergoing biopsy, serum samples were tested for microseminoprotein (MSP) and four kallikrein markers (free PSA, intact PSA, total PSA, and human kallikrein-related peptidase 2 [hK2]). The methods have been described previously [29,30]. The results from the four kallikrein markers were combined to create a risk score (Rotterdam score) using a previously described model [30].

Participants with PSA ≤3.0 ng/ml will undergo annual PSA screening for ≥5 yr, except participants in the Dutch cohort, who are screened biennially (because of the constraints of the ministerial approval). Participants with PSA >3.0 ng/ml and a negative biopsy will undergo annual PSA testing, repeating the biopsy if PSA increases by >50%. All participants will be followed up for ≥5 yr to evaluate the cancer incidence and PCa-specific mortality and morbidity [27,28].

The local histopathologist at each centre reported the biopsy results to guide treatment in accordance with local guidelines. The Gleason score, clinical stage, and classification of disease into low, intermediate, or high risk of metastasis [31] were reported for each case. Central pathology review was performed by the study pathologist (C.S.F.) to ensure consistency and standardisation. Prostate core biopsies were assessed in accordance with International Society of Urological Pathology guidelines [32] (described previously [10,33]). Whenever high-grade prostate intraepithelial neoplasia (HG PIN) or atypical small acinar proliferation (ASAP) was detected, the biopsy was repeated within 3–6 mo.

2.1. Statistical analysis

Statistical analysis was undertaken using SPSS v.21 and Stata 12.0. The Fisher exact test was used to compare the number of PCa cases detected among groups and differences among disease types. The PPV of the biopsy using PSA >3.0 ng/ml in the different groups was compared using the chi-square test for independence. To compare the mean ages of men with high PSA levels, *t* tests were used; $p < 0.05$ was considered statistically significant. The Wald test was used to test the association

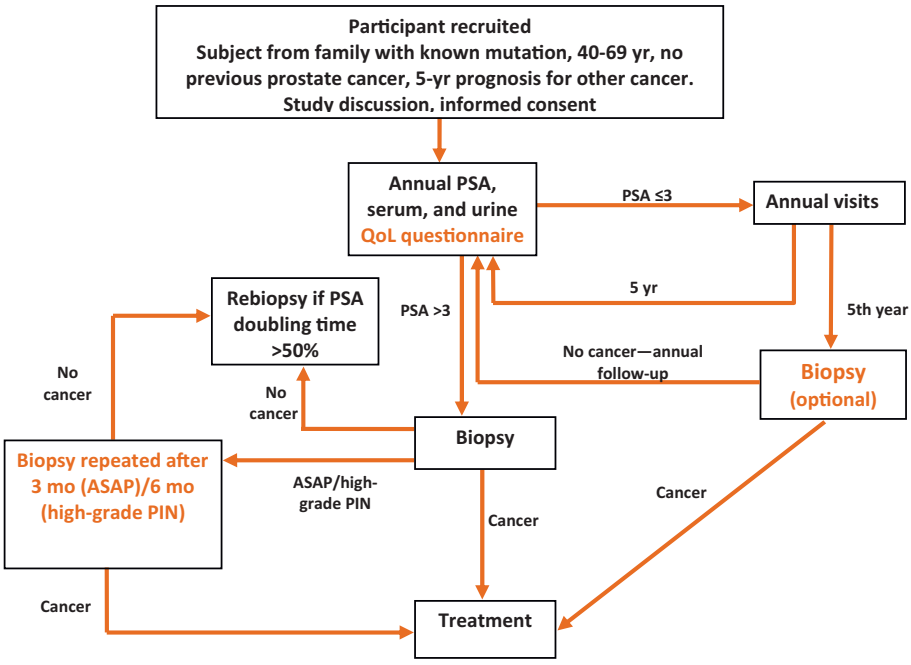

Fig. 1 – Study design.
ASAP = atypical small acinar proliferation; PIN = prostate intraepithelial neoplasia; PSA = prostate-specific antigen; QoL = quality-of-life.

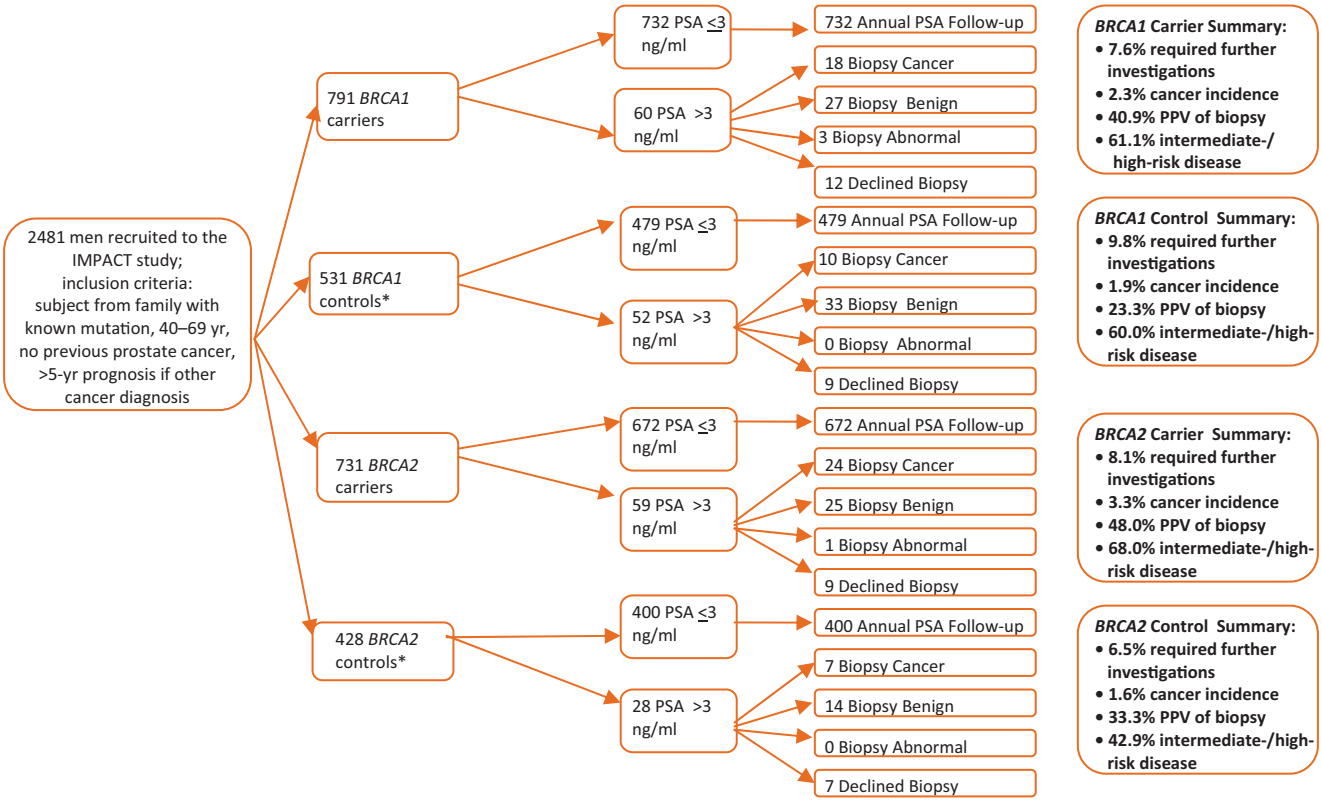

Fig. 2 – Consort diagram for the first round of screening.
BRCA1 **= breast cancer 1, early onset;** ***BRCA2*** **= breast cancer 2, early onset; PSA = prostate-specific antigen; PPV = positive predictive value.**
* **Controls were men who had a negative predictive genetic test for the** ***BRCA*** **mutation in their family.**

between evidence of PCa at biopsy and the Rotterdam score, and the Spearman correlation was used to determine the relationship between PSA measurements taken in the clinical and laboratory settings.

3. Results

3.1. Study population

A total of 2481 participants from 62 centres in 20 countries were recruited over 90 mo (Supplemental Table 1); there were 791 *BRCA1* carriers and 531 *BRCA1* controls, as well as 731 *BRCA2* carriers and 428 *BRCA2* controls) (Fig. 2).

The majority of participants were white (95%) and highly educated (measured using self-reported qualifications), and the mean age at enrolment was 54 yr (Table 1). Twenty-one percent of the men reported urinary symptoms, and 37% had previously had at least one PSA test. No statistically significant differences were observed among groups; 27% reported a family history of PCa in at least one blood relative.

3.2. Prostate cancer detection rates at initial screening and positive predictive value of biopsy

Of the 2481 men, 199 (8.0%) had PSA >3.0 ng/ml (range: 3.0–27.0; median: 4.3) and were referred to a urologist to discuss prostate biopsy (Fig. 2). Of these men, 162 (81.4%) underwent biopsy. Biopsies were declined because of concurrent health conditions ($n = 7$), the urologist's choosing to repeat the PSA test prior to biopsy resulting in a reading ≤3.0 ng/ml ($n = 17$), men changing their minds ($n = 8$), or reason missing ($n = 5$). Fifty-nine of 162 biopsies (36.4%) contained cancer. There was no significant difference in cancer detection rates between men who had or had not undergone PSA screening prior to study entry. No significant differences were seen with the Dutch cohort, in which men with prior PSA screening were excluded. Other than in the Dutch cohort, the prior screening levels were similar in all countries.

The PCa detection rate was 2.4% (59 of 2481 men) (Table 2). The detection rate for *BRCA1* carriers was 2.3% (18 of 791); it was 1.9% (10 of 531) for *BRCA1* controls, 3.3% (24 of 731) for *BRCA2* carriers, and 1.6% (7 of 428) for *BRCA2* controls, with no significant difference among groups. The number of cores taken at biopsy ranged from 6 to 20; however, there were no differences in the median or mean number of cores taken among groups (Table 2). Four men had either ASAP or HG PIN (all mutation carriers) (Table 2). Two men underwent repeat biopsy with no cancers detected. Taking potential geographical variation in cancer incidence into consideration, the data were analysed by region (North America; Australia; Asia; and Western,

Table 1 – Sociodemographic characteristics

	BRCA1+ (*n* = 791)	*BRCA1*− (*n* = 531)	*BRCA2*+ (*n* = 731)	*BRCA2*− (*n* = 428)	Total cohort
Age group, yr, no. (%)					
40–49	264 (33)	148 (28)	298 (41)	118 (28)	828 (33)
50–59	294 (37)	224 (42)	254 (35)	169 (40)	941 (38)
60–69	233 (30)	159 (30)	179 (25)	141 (33)	712 (29)
Qualifications, no. (%)					
No qualifications	33 (4)	13 (2)	39 (5)	24 (6)	109 (4)
School to 16	105 (13)	59 (11)	116 (16)	43 (10)	323 (13)
School to 18/college degree	133 (17)	117 (22)	89 (12)	86 (20)	425 (17)
Technical/vocational qualifications	191 (24)	134 (25)	143 (20)	81 (19)	549 (22)
University graduate	273 (35)	179 (34)	267 (37)	145 (34)	864 (35)
Other	15 (2)	16 (3)	26 (4)	17 (4)	74 (3)
Unknown	41 (5)	13 (2)	51 (7)	32 (7)	137 (6)
Family history of prostate cancer, no. (%)					
Yes	177 (22)	142 (27)	234 (32)	129 (30)	682 (27)
No	528 (67)	307 (58)	453 (62)	249 (58)	1537 (62)
Unknown	86 (11)	82 (15)	44 (6)	50 (12)	262 (11)
Ethnicity, no. (%)					
Caucasian	750 (95)	514 (97)	695 (95)	410 (96)	2369 (95.5)
East Asian	3 (0.4)	1 (0.2)	3 (0.4)	1 (0.2)	8 (0.3)
North Asian	8 (1,0)	6 (1.1)	0	2 (0.5)	16 (0.6)
Caribbean	1 (0.1)	0	0	0	1 (0.0)
Aboriginal/Torres Strait Islander	1 (0.1)	0	1 (0.1)	0	2 (0.1)
Mixed white and Caribbean	5 (0.6)	2 (0.4)	2 (0.3)	1 (0.2)	10 (0.4)
Mixed white and Asian	3 (0.4)	0	0	0	3 (0.1)
Any other Asian background	0	0	1 (0.1)	0	1 (0.04)
Any other mixed background	3 (0.4)	1 (0.2)	1 (0.1)	0	5 (0.2)
Any other	15 (2)	7 (1)	22 (3)	5 (1)	49 (2)
Not given	2 (0.3)	0	6 (0.8)	9 (2)	17 (0.7)

BRCA1 = breast cancer 1, early onset; *BRCA2* = breast cancer 2, early onset.

Central, and Southern Europe), and no statistically significant differences were observed.

The PPV of biopsy using a PSA threshold of 3.0 ng/ml (ie, the number of cancers detected divided by the number of biopsies performed) was 36% (59 of 162) (Table 2). Broken down by genetic status, the PPV in *BRCA1* carriers was 37.5% (18 of 48); in *BRCA1* controls, 23.3% (10 of 43); in *BRCA2* carriers, 48.0% (24 of 50); and in *BRCA2* controls, 33.3% (7 of 21). There was no statistically significant difference among groups (Pearson chi-square test for *BRCA1*, $p = 0.14$; for *BRCA*2, $p = 0.26$).

There was no significant difference between either mean age at PCa diagnosis or PSA level among groups. Twelve men (20%) reported urinary symptoms prior to diagnosis, and 20 men (34%) had a PSA test prior to study entry (29% *BRCA2* carriers, 50% *BRCA2* controls; 44% *BRCA1* carriers, 33% *BRCA1* controls). There was no difference observed in levels of PSA screening prior to study entry among groups.

Using the NICE classification [31,34], intermediate- or high-risk tumours were diagnosed in 11 of 18 *BRCA1* carriers (61%) compared with 8 of 10 *BRCA1* controls (80%) and in 17 of 24 *BRCA2* carriers (71%) compared with 3 of 7 *BRCA2* controls (43%) (Table 3). There was no significant difference observed between genetic status and disease risk status. The PPV of biopsy using a PSA threshold of 3.0 ng/ml

Table 2 – Summary of outcomes for men with prostate-specific antigen level >3.0 ng/ml

	BRCA1+ (*n* = 791)	*BRCA1*− (*n* = 531)	*BRCA2*+ (*n* = 731)	*BRCA2*− (*n* = 428)	Total cohort (*n* = 2481)
Men PSA >3.0 ng/ml, no.	60	52	59	28	199
Mean age, yr	60.1	59.8	58.1	62.2	59.7
Biopsy rate, %	7.6	9.8	8.1	6.5	8.0
Biopsies performed, no.	48	43	50	21	162
Biopsy–benign, no.	27	33	25	14	99
Biopsy–cancer, no.	18	10	24	7	59
Biopsy–ASAP/HG PIN, no.	3	0	1	0	4
No biopsy, no.	12	9	9	7	37
PPV of biopsy, %	37.5	23.3	48.0	33.3	36.4
Biopsy cores, no., median; mean (range)	10; 9.4 (6–13)	11; 10.3 (6–20)	10; 10.1 (5–12)	10; 10.1 (6–13)	10; 9.9 (5–20)

BRCA1 = breast cancer 1, early onset; *BRCA2* = breast cancer 2, early onset; PSA = prostate-specific antigen; ASAP/HG PIN = atypical small acinar proliferation/high-grade prostate intraepithelial neoplasia; PPV = positive predictive value.

Table 3 – Clinical features of the prostate cancers at diagnosis

Patient	Status	Age, yr	Disease risk classification	PSA test prior to study entry	PSA, ng/ml	Gleason score	Clinical stage	Treatment	Family history of prostate cancer	Urinary symptoms
1	*BRCA1*+	55	High	Yes	5.9	4 + 4	pT2c	Prostatectomy	No	No
2	*BRCA1*+	69	High	Yes	6.3	3 + 3	pT3b	Prostatectomy	No	Yes
3	*BRCA1*+	60	High	Yes	3.3	3 + 3	pT3a	Prostatectomy	Yes	No
4	*BRCA1*+	59	High	No	3.8	3 + 5	T3a	*	Yes	No
5	*BRCA1*+	61	Intermediate	No	9.7	3 + 4	T1c	Prostatectomy	No	No
6	*BRCA1*+	61	Intermediate	Yes	4.5	3 + 4	pT2c	Prostatectomy	Yes	No
7	*BRCA1*+	69	Intermediate	Yes	7.4	3 + 3	T2b	Radiotherapy	Yes	Yes
8	*BRCA1*+	53	Intermediate	No	3.9	3 + 3	T2	Prostatectomy	No	No
9	*BRCA1*+	63	Intermediate	No	4.2	3 + 3	pT2c	Prostatectomy	Yes	No
10	*BRCA1*+	49	Intermediate	Yes	3.8	3 + 3	pT2c	Prostatectomy	No	No
11	*BRCA1*+	45	Intermediate	No	3.2	3 + 4	T2b	Prostatectomy	Yes	No
12	*BRCA1*+	61	Low	Yes	4.1	3 + 3	T1c	Active surveillance	No	No
13	*BRCA1*+	56	Low	No	5.3	3 + 3	pT2a	Prostatectomy	Yes	No
14	*BRCA1*+	63	Low	Yes	3.4	3 + 3	pT2a	Prostatectomy	No	Yes
15	*BRCA1*+	57	Low	No	3.7	3 + 3	T1c	Prostatectomy	No	No
16	*BRCA1*+	64	Low	No	5	3 + 3	T1c	Active surveillance	No	No
17	*BRCA1*+	64	Low	No	6.2	3 + 3	T1c	Active surveillance	No	No
18	*BRCA1*+	48	Low	No	5.3	3 + 3	*	*	No	No
19	*BRCA1*–	61	High	Yes	7.7	4 + 3	pT3a	Prostatectomy	No	No
20	*BRCA1*–	62	High	Yes	3.1	3 + 4	pT3a	Prostatectomy	Yes	Yes
21	*BRCA1*–	62	Intermediate	No	3.3	3 + 3	pT2c	Prostatectomy	No	No
22	*BRCA1*–	61	Intermediate	No	4.8	3 + 3	T2c	Prostatectomy	No	Yes
23	*BRCA1*–	66	Intermediate	Yes	5.5	4 + 3	T1c	Radiotherapy	Yes	No
24	*BRCA1*–	57	Intermediate	No	4.5	3 + 4	T2c	Prostatectomy	Yes	Yes
25	*BRCA1*–	55	Intermediate	No	5.2	3 + 4	pT2	Prostatectomy	No	No
26	*BRCA1*–	65	Intermediate	No	4.7	3 + 3	pT2c	Prostatectomy	No	No
27	*BRCA1*–	59	Low	No	4.3	3 + 3	T1c	Active surveillance	Yes	No
28	*BRCA1*–	62	Low	Unknown	9.9	3 + 3	T1c	Prostatectomy	No	No
29	*BRCA2*+	66	High	Yes	5	3 + 4/4 + 3	pT3a	Prostatectomy	No	No
30	*BRCA2*+	51	High	No	27	4 + 3	pT3a	Prostatectomy	Yes	No
31	*BRCA2*+	66	High	No	24	4 + 4	T4	Radiotherapy	No	No
32	*BRCA2*+	66	High	Yes	11	4 + 5	T3a	Prostatectomy	No	No
33	*BRCA2*+	61	High	No	6.3	4 + 5	T1c	Prostatectomy	No	No
34	*BRCA2*+	67	High	No	12.8	3 + 3	T3a	Brachytherapy	No	No
35	*BRCA2*+	62	High	Yes	8.2	3 + 4	pT3a	Prostatectomy	Yes	Yes
36	*BRCA2*+	49	Intermediate	Unknown	4.9	3 + 4	T2c	Prostatectomy	No	No
37	*BRCA2*+	68	Intermediate	Yes	5.3	3 + 4	T2b	Radiotherapy	No	No
38	*BRCA2*+	54	Intermediate	No	3.1	3 + 3	pT2c	Prostatectomy	No	No
39	*BRCA2*+	56	Intermediate	No	5	3 + 4	pT2c	Prostatectomy	Yes	No
40	*BRCA2*+	59	Intermediate	Yes	3	3 + 4	T2c	Prostatectomy	Yes	No
41	*BRCA2*+	58	Intermediate	No	5.1	4 + 3	pT2c	Prostatectomy	No	No
42	*BRCA2*+	41	Intermediate	No	3.5	3 + 4	pT2c	Prostatectomy	Yes	Yes
43	*BRCA2*+	65	Intermediate	No	4.7	3 + 4	T1c	Radiotherapy	No	No
44	*BRCA2*+	53	Intermediate	No	3.6	3 + 3	T2c	Prostatectomy	No	No
45	*BRCA2*+	63	Intermediate	No	3.5	3 + 3	pT2c	Prostatectomy	Yes	Yes
46	*BRCA2*+	67	Low	No	4.8	3 + 3	T2a	Active surveillance	No	No
47	*BRCA2*+	55	Low	No	4.5	3 + 3	T1c	Active surveillance	Yes	Yes
48	*BRCA2*+	61	Low		3.6	3 + 3	T1c	Brachytherapy	No	Yes
49	*BRCA2*+	57	Low	No	4.9	3 + 3	T1c	Active surveillance	No	Yes
50	*BRCA2*+	45	Low	No	4.7	3 + 3	T1c	Active surveillance	No	No
51	*BRCA2*+	61	Low	No	4.1	3 + 3	T1c	Active surveillance	No	No
52	*BRCA2*+	54	Low	Yes	3.3	3 + 3	T1c	Active surveillance	Yes	No
53	*BRCA2*–	69	High	No	14.3	4 + 3	T3	Radiotherapy	No	No
54	*BRCA2*–	62	Intermediate	No	4.8	3 + 4	pT2c	Prostatectomy	No	No
55	*BRCA2*–	65	Intermediate	Yes	4.2	3 + 3	T1c	Active surveillance	No	No
56	*BRCA2*–	60	Low	No	5.5	3 + 3	T1c	Active surveillance	No	No
57	*BRCA2*–	68	Low	Yes	3.3	3 + 3	T1c	Active surveillance	No	No
58	*BRCA2*–	66	Low	Yes	6.7	3 + 3	T2a	Prostatectomy	No	No
59	*BRCA2*–	53	Low	Unknown	3.4	3 + 3	T2b	Prostatectomy	No	No

BRCA1 = breast cancer 1, early onset; *BRCA2* = breast cancer 2, early onset; PSA = prostate-specific antigen.
* Data pending.

for detecting intermediate- and high-risk PCa for *BRCA2* carriers and controls was 2.38% (17 of 714) and 0.71% (3 of 425), respectively; this difference is significant (Pearson chi-square, $p = 0.04$). No significant difference was observed in *BRCA1* carriers compared with controls (1.41% [11 of 780] compared with 1.33% [8 of 524]; Pearson chi-square test, $p = 0.86$). No cases had nodal involvement or metastatic disease at diagnosis.

Table 4 – Patient characteristics for kallikrein analysis*

Characteristics	No cancer (*n* = 33)	Cancer (*n* = 24)
BRCA1 tested, no. (%)	18 (55)	11 (46)
BRCA1+, no. (%)	10 (56)	10 (91)
BRCA2 tested, no. (%)	15 (45)	13 (54)
BRCA2+, no. (%)	12 (80)	10 (77)
Age at study entry, yr, median (quartiles)	59 (55, 64)	61 (57, 66)
Specific site total PSA, ng/ml, median (quartiles)	4.2 (3.4, 5.0)	4.4 (3.7, 5.2)
Central site total PSA, ng/ml, median (quartiles)	3.9 (3.4, 5.1)	4.2 (3.3, 5.4)
Free PSA, ng/ml, median (quartiles)	0.93 (0.73, 1.19)	0.83 (0.53, 0.96)
Intact PSA, ng/ml, median (quartiles)	0.53 (0.42, 0.69)	0.47 (0.31, 0.67)
hK2, ng/ml, median (quartiles)	0.051 (0.038, 0.076)	0.062 (0.036, 0.083)
MSP, ng/ml, median (quartiles)	19 (11, 26)	18 (11, 24)
Rotterdam score	0.235 (0.162, 0.310)	0.327 (0.243, 0.373)
Gleason total score, no. (%)		
6		17 (71)
7		7 (29)
Clinical T stage, no. (%)		
T1C		8 (33)
T2		2 (8.3)
T2A		1 (4.2)
T2B		2 (8.3)
T2C		3 (13)
T3		1 (4.2)
Unknown		7 (29)

BRCA1 = breast cancer 1, early onset; *BRCA2* = breast cancer 2, early onset; PSA = prostate-specific antigen; hK2 = human kallikrein-related peptidase 2; MSP = microseminoprotein.
* Data are frequency (percentage) or median (quartiles).

Table 5 – Univariate logistic regression for the outcomes of evidence of prostate cancer at biopsy and evidence of high-grade prostate cancer at biopsy*

Predictor	Odds ratio	95% CI	*p* value
Total PSA, ng/ml (*n* = 57)			
Cancer	1.02	0.75–1.37	0.9
High-grade cancer	1.49	1.00–2.23	0.051
Rotterdam score (*n* = 57)**			
Cancer	2.30	1.25–4.22	0.007
High-grade cancer	3.87	1.42–10.60	0.008
MSP, ng/ml (*n* = 57)			
Cancer	1.00	0.95–1.04	0.8
High-grade cancer	0.95	0.86–1.03	0.2
BRCA1 status (*n* = 29)+			
Cancer	8.00	0.76–389.69	0.10
High-grade cancer†			0.5
BRCA2 status (*n* = 28)+			
Cancer	0.83	0.09–7.73	1
High-grade cancer	1.47	0.11–83.27	1
Mutation status (*n* = 57)+			
Cancer	2.50	0.60–12.35	0.2
High-grade cancer	2.33	0.24–114.86	0.7

CI = confidence interval; *BRCA1* = breast cancer 1, early onset; *BRCA2* = breast cancer 2, early onset; MSP = microseminoprotein; PSA = prostate-specific antigen.
* Subset of 57 men biopsied for whom an adequate serum sample was available.
** The odds ratio for the Rotterdam score corresponds to a 0.1-unit increase on a 0–1 probability scale.
+ The 95% CI and *p* values are calculated using the Fisher exact test.
† The odds ratio and 95% CI are not estimable because of zero events in the *BCRA1*-negative group. The *p* value is calculated from the chi-square test.

3.3. Central analysis of prostate-specific antigen and the kallikrein panel

There was a strong correlation between PSA values measured in the clinical and laboratory settings (Spearman $r = 0.85$). Serum samples of 57 (24 with PCa) of the 162 men who underwent a biopsy were analysed for MSP and four kallikrein markers (Table 4).

We found no association between PCa at biopsy and total PSA or MSP (Table 5). We compared the proportion of PCa in mutation carriers with controls and found no association between PCa at biopsy and mutation status. There was an association of PCa at biopsy and Rotterdam score (Wald test $p = 0.024$). The discrimination of the Rotterdam model was 0.70 (95% confidence interval [CI], 0.56–0.84). For the outcome of high-grade cancer, the Rotterdam score was the

only statistically significant predictor ($p = 0.009$), with a discrimination of 0.86 (95% CI, 0.73–0.99).

For 1202 of 2481 participants with available blood samples, we found a strong correlation of total PSA between measurements taken in the clinical and laboratory settings (Spearman $r = 0.95$).

3.4. Serious adverse events

Six study-related serious adverse events were reported, all occurring after biopsy. Complications occurred in 6 of 158 participants (3.8%), with five infections (3.2%) reported, two requiring hospitalisation. The sixth participant was hospitalised because of fainting after biopsy.

4. Discussion

In this paper we have presented the results of the first screening round of IMPACT, including the number and features of the PCa detected. With germline mutations in *BRCA1* and B*RCA2* being rare, the success of IMPACT has been in the formation of an international consortium of 62 centres with both clinical genetics and urologic collaboration. Enrolment was open until the required number of recruits was obtained in all four cohorts, exceeding the numbers required for statistical power in all groups.

Compliance with the protocol was high, with 162 men with PSA >3.0 ng/ml (>81%) proceeding to biopsy. This number compares favourably with the 86% in the ERSPC [35] and the 31.5% in the PLCO study [35–37]. In the PLCO study, with no strict protocol to guide intervention, 74% of men with an abnormal screening test underwent further diagnostic evaluation, and 64% underwent biopsy within 3 yr [37]. Thus, a similar increase in compliance may be anticipated in IMPACT at subsequent screening rounds. The potential utility of multiparametric magnetic resonance imaging (MRI) as a screening tool before biopsy has been the subject of recent debate [38]; however, the IMPACT protocol was designed prior to the use of MRI in this diagnostic capacity.

In total, 8% of the men had a positive PSA test (>3.0 ng/ml), which is lower than the 16.2% (range: 11.1–22.3% among sites) reported in the ERSPC general population screening study [35]. However, the ERSPC recruited an older cohort of men (55–75 yr), with a mean age of 61 yr compared with 54 yr in IMPACT. It is known that PSA increases with age, so higher PSA levels would be expected. In addition, a number of ERSPC centres used a threshold of 4.0 ng/ml rather than 3.0 ng/ml to determine biopsy, so the two studies are not entirely directly comparable. These results indicate that overbiopsy is not a concern in this younger cohort.

There is controversy about the PSA level used to trigger biopsy, with no clear consensus. The results presented show that while not statistically significant, the PPV of biopsy using a PSA threshold of 3.0 ng/ml is higher for *BRCA2* carriers than for controls (48% vs 33%) and higher for *BRCA1* carriers than controls (41% vs 23%). For *BRCA2* carriers, this percentage is double the 24.1% reported in the ERSPC general population sample. This higher PPV observed in mutation carriers may be explained, at least in part, by the fact that the ERSPC screened older men. Also, given the younger age of the IMPACT cohort, the incidence of benign prostatic hypertrophy (BPH) may have been lower; the incidence of BPH increases with age, and BPH lowers the specificity of PSA screening [27,39,40]. These data suggest that lowering the PSA threshold for biopsy in *BRCA2* carriers could potentially detect early-stage disease, thus reducing the need for more toxic treatments and ultimately reducing PCa mortality. However, this lowering would need to be balanced against the risk of potentially life-threatening side-effects of biopsy [41,42].

In IMPACT, men will be offered a prostate biopsy at the end of the study (at the centres with the capacity), which may provide evidence for the optimal PSA threshold for detecting clinically significant PCa in this cohort of higher-risk men.

The observed differences in PPV may also reflect the higher incidence and grade of PCa previously reported, particularly in *BRCA2* carriers. The higher PPV in *BRCA2* carriers suggests that PSA may have a higher specificity in this high-risk setting. However, as the number of cancers is relatively small, subsequent PSA screening rounds are essential to confirm this hypothesis. Evaluation of the panel of four kallikrein markers in subsequent screening rounds may provide further insights into the panel's potential role in predicting biopsy outcome [30].

The ERSPC reported that 4.2% of men had a cancer diagnosis at the first screening round [43]. In IMPACT, the PCa detection rate was 2.4%, and two-thirds of the men in the cohort were previously unscreened. The younger age of the IMPACT sample is likely to explain this lower detection rate. More than two-thirds of the PCa detected in the *BRCA2* carriers were classified as intermediate – or high – risk, supporting retrospective reports of a more aggressive phenotype and poorer prognosis in this group [7–12]. Sixty-one percent of *BRCA1* carriers were classified as having intermediate- or high-risk disease. By comparison, in the ERSPC, only 27.8% of the PCa diagnosed in the screened cohort were Gleason score ≥7 [35]. Longer-term follow-up will determine whether there is a difference in metastatic events and mortality between carriers and controls. From the PLCO study, after 13 yr of follow-up, there is no evidence to support the idea that organised PSA screening reduces mortality compared with opportunistic screening [14]. In contrast, after a median of 11 yr of follow-up, the ERSPC reported a 21% reduction in PCa-specific mortality in the screened cohort [15]. It is important to note that in the PLCO, 56% of men in the control arm had PSA screening, compared with 15% in the ERSPC.

The higher incidence of clinically significant disease in the *BRCA2* mutation carriers, together with the significantly younger age of *BRCA2* carriers with PSA >3.0 ng/ml, is an important observation in view of the younger age of this cohort compared with the ERSPC study. The only cancers detected in men <50 yr were in *BRCA1* and *BRCA2* carriers. These data add to the increasing evidence that *BRCA1/2* carriers develop more aggressive disease, and at a younger

age. Of note, the control groups also had a higher level of intermediate- or high-risk disease compared with the ERSPC. However, the number of cancers is relatively small, and with 19% of men declining biopsy, these data should be interpreted with caution.

The population incidence of PCa in each of the recruiting countries must be considered. The incidence in the majority of the countries is very similar, except in India and Malaysia [44]. Given the relatively low number of recruits from these regions, geographical variation is unlikely to have a major impact on the results. A limitation of IMPACT is that 95% of the men were white. Thus, the results cannot be generalised to all ethnic groups known to have a higher risk of PCa and a more aggressive phenotype (eg, black). A second limitation is that 37% of the cohort had previously had a PSA test. This fact could potentially bias the study to either having men with a lower PSA or having men with higher PSAs due to noncancerous causes. However, no difference in screening levels was observed among those men with and without cancer. A further limitation is that the control group was recruited from families known to have *BRCA* mutations. It is possible that this group of men has a different PCa risk profile than the general population.

5. Conclusions

The first screening round of IMPACT demonstrates that targeted screening for PCa in men with a genetic predisposition detects clinically significant disease. Using a PSA threshold of 3 ng/ml results in a low biopsy rate (8.0%) and a high PPV, particularly in *BRCA2* carriers, for the detection of intermediate- and high-risk disease. Although the observed differences in PCa detection rates between carriers and controls was not statistically significant, the trend is clear. With larger numbers of PCa in the follow-up phase (5 yr), these differences, if sustained, are likely to be significant.

Future screening rounds will determine the optimal frequency of PSA testing, determine the utility of PSA screening in *BRCA1* carriers, and provide further data on the value of annual screening in *BRCA2* carriers.

A previously published statistical model based on four kallikrein markers was able to predict biopsy outcome in participants with PSA >3 ng/ml with a discrimination of 0.86 for high-grade disease. Longer-term follow-up will be used to validate the role of the kallikrein panel in this population.

IMPACT is the first prospective study to demonstrate the use of germline genetic markers to identify men at higher risk of PCa, which has the potential to enable better risk stratification to inform targeted screening. These early results indicate that the tumours detected are more likely to need treatment based on national guidelines for management of more aggressive PCa. Therefore, our preliminary results support the use of PSA screening for *BRCA2* carriers.

Author contributions: Rosalind A. Eeles had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Eeles, Bancroft, Page, Castro, Lilja, Vickers, Mitra, Evans, Eccles, Mitchell, Mæhle, Foster, Johannsson, Lubinski, Aaronson, Ardern-Jones, Dearnaley, Gronberg, Hamdy, Khoo, Kote-Jarai, Falconer, Melia, Moynihan, Rennert, Suri, Wilson, Moss, Blanco, Bangma, Eyfjord.

Acquisition of data: Eeles, Bancroft, Page, Castro, Mitra, Drew, Mæhle, Bulman, Costello, McKinley, Ringelberg, Skytte, Taylor, Salinas, Conner, Selkirk, Hoffman, Powers, Maia, Teixeira, Taherian, Stefansdottir, Copakova, Rothwell, Blanco, Cybulski, McBride, Clowes, Giri, Murthy, Teo, Liljegren, Wokolorczyk, Ramon y Cajal, Gadea, Chen-Shtoyerman, Gallagher.

Analysis and interpretation of data: Bancroft, Page, Castro, Lilja, Vickers, Eeles, Moss, Assel, Sjoberg.

Drafting of the manuscript: Bancroft, Page, Moss, Eeles, Castro, Vickers, Lilja.

Critical revision of the manuscript for important intellectual content: Bancroft, Page, Moss, Eeles, Castro, Vickers, Lilja, Kiemeney, Cybulski.

Statistical analysis: Bancroft, Page, Castro, Lilja, Vickers, Eeles, Moss, Assel, Sjoberg.

Obtaining funding: Eeles, Selkirk, Hulick, Kiemeney, Vasen, van Asperen, Mitchell, Domchek, Strom, Lindeman, Zgajnar, Walker, Liljegren, Buys, Evans, Giri, Foulkes, Tischkowitz.

Administrative, technical, or material support: Drew, Bojesen, Ringelberg, McBride, K. Axcrona, Bulman, Powers, Salinas, Walker, Hodgson, Side, Liljegren, Buys, Conner, Giri, Killick, McKinley, Wokolorczyk, Skytte, Cybulski, Lam, Taylor, Oldenburg, Cremers, Verhaegh, van Zelst-Stams, Oosterwijk, Cook, Rosario, Ausems, Ong, Teixeira, Maia, Kirk, Tucker, Davidson, Izatt, Foulkes, Taherian, Ruijs, Adank, Schmutzler, Helderman-van den Enden, Harris, Douglas, Lindeman, Tischkowitz, Clowes, Susman, Ramon y Cajal, Patcher, Gadea, Spigelman, van Os, Brewer, Brady, Donaldson, Stefansdottir, Friedman, Chen-Shtoyerman, Amor, Barwell, Murthy, Nicolai, Teo, Greenhalgh, Henderson, McGrath, Gallagher, Rothwell, U. Axcrona, Selkirk, Hulick, Hoffman, Domchek, Powers, Zgajnar, Copakova, Costello, The IMPACT Study Collaborators.

Supervision: Eeles.

Other (specify): None.

Financial disclosures: Rosalind A. Eeles certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: Hans Lilja holds patents for free PSA, hK2, and intact PSA assays. Rosalind A. Eeles has received educational grants from Janssen Pharmaceuticals, GenProbe (formerly Tepnel), Illumina, and Vista Diagnostics and honoraria from Succinct Communications.

Funding/Support and role of the sponsor: The authors are indebted to the 2481 men who are taking part in this study. This research is coordinated by the Institute of Cancer Research, London, UK, and is supported by grants from the Ronald and Rita McAulay Foundation and Cancer Research UK (grant references C5047/A15007 and C5047/A13232). In Australia, this project was cofunded by Cancer Council Tasmania and Cancer Australia, grant number 1006349 (2011–2013); Prostate Cancer Foundation of Australia, grant number PCFA PR04 (2008); Cancer Councils of Victoria and South Australia, grant number 400048 (2006–2008); the Victorian Cancer Agency Clinical Trial Capacity CTCB08_14; and Translational grants EOI09_50. The Association of International Cancer Research funded data collection in The Netherlands (AICR 10–0596). The authors received funding from the NIHR to the Biomedical Research Center at the Institute of Cancer Research and the Royal Marsden NHS Foundation Trust, and at Central Manchester Foundation Trust; the Basser Research Centre (to Susan Domchek); the National Cancer Institute (R01CA160816, R01 CA175491, and P50-CA92629); the Sidney Kimmel Center for Prostate

and Urologic Cancers; David H. Koch through the Prostate Cancer Foundation, the National Institute for Health Research (NIHR) Oxford Biomedical Research Centre Program, Swedish Cancer Society project no. 11–0624, a FiDIPro-program award from TEKES in Finland, and Fundacion Federico SA; and the Slovenian Research Agency, research programme P3–0352.

Acknowledgment statement: R. Eeles is the chief investigator of the IMPACT study and has overall responsibility for the study. E. Bancroft, E. Page, E. Castro had overall responsibility for the analyses and writing of the article, together with R. Eeles. S. Moss is the study statistician. H. Lilja, A. Vickers, D. Sjoberg, M. Assel performed the analysis of the panel of four kallikrein markers. C.S. Foster performed the central pathology review. 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.

The authors acknowledge Mr. and Mrs. Jack Baker for the study at North Shore University Health System (Evanston, IL, USA) and Myriad Genetics Laboratory (Salt Lake City, UT, USA) for providing research *BRCA* testing rates for North Shore University Health System participants. The authors are grateful to the members of the Data and Safety Monitoring Committee: S. Duffy (chair), P. White (UK NEQAS representative), and R. Pocock (BAUS representative). The authors acknowledge the contribution of past members of the IMPACT steering committee: D. Easton, S. Peock, F. Schroder, R. Sharifi, and P. Sibley.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.eururo.2014.01.003.

References

[1] Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin 2011;61:69–90.
[2] Leongamornlert D, Mahmud N, Tymrakiewicz M, et al. Germline BRCA1 mutations increase prostate cancer risk. Br J Cancer 2012;106:1697–701.
[3] Thompson D, Easton DF. Cancer incidence in BRCA1 mutation carriers. J Natl Cancer Inst 2002;94:1358–65.
[4] Breast Cancer Linkage Consortium. Cancer risks in BRCA2 mutation carriers. J Natl Cancer Inst 1999;91:1310–6.
[5] Kote-Jarai Z, Leongamornlert D, Saunders E, et al. BRCA2 is a moderate penetrance gene contributing to young-onset prostate cancer: implications for genetic testing in prostate cancer patients. Br J Cancer 2011;105:1230–4.
[6] van Asperen CJ, Brohet RM, Meijers-Heijboer EJ, et al. Cancer risks in BRCA2 families: estimates for sites other than breast and ovary. J Med Genet 2005;42:711–9.
[7] Castro E, Goh C, Olmos D, et al. Germline BRCA mutations are associated with higher risk of nodal involvement, distant metastasis, and poor survival outcomes in prostate cancer. J Clin Oncol 2013;31:1748–57.
[8] Edwards SM, Evans DG, Hope Q, et al. Prostate cancer in BRCA2 germline mutation carriers is associated with poorer prognosis. Br J Cancer 2010;103:918–24.
[9] Gallagher DJ, Gaudet MM, Pal P, et al. Germline BRCA mutations denote a clinicopathologic subset of prostate cancer. Clin Cancer Res 2010;16:2115–21.
[10] Mitra A, Fisher C, Foster CS, et al. Prostate cancer in male BRCA1 and BRCA2 mutation carriers has a more aggressive phenotype. Br J Cancer 2008;98:502–7.
[11] Thorne H, Willems AJ, Niedermayr E, et al. Decreased prostate cancer-specific survival of men with BRCA2 mutations from multiple breast cancer families. Cancer Prev Res 2011;4:1002–10.
[12] Tryggvadottir L, Vidarsdottir L, Thorgeirsson T, et al. Prostate cancer progression and survival in BRCA2 mutation carriers. J Natl Cancer Inst 2007;99:929–35.
[13] Giusti RM, Rutter JL, Duray PH, et al. A twofold increase in BRCA mutation related prostate cancer among Ashkenazi Israelis is not associated with distinctive histopathology. J Med Genet 2003;40:787–92.
[14] Andriole GL, Crawford ED, Grubb III RL, et al. Prostate cancer screening in the randomized Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial: mortality results after 13 years of follow-up. J Natl Cancer Inst 2012;104:125–32.
[15] Schroder FH, Hugosson J, Roobol MJ, et al. Prostate-cancer mortality at 11 years of follow-up. N Engl J Med 2012;366:981–90.
[16] Catalona WJ, Antenor JA, Roehl KA, Moul JW. Screening for prostate cancer in high risk populations. J Urol 2002;168:1980–3, discussion 1983–4.
[17] McWhorter WP, Hernandez AD, Meikle AW, et al. A screening study of prostate cancer in high risk families. J Urol 1992;148:826–8.
[18] Neuhausen SL, Skolnick MH, Cannon-Albright L. Familial prostate cancer studies in Utah. Br J Urol 1997;79(Suppl 1):15–20.
[19] Bunker CH, Patrick AL, Konety BR, et al. High prevalence of screening-detected prostate cancer among Afro-Caribbeans: the Tobago Prostate Cancer Survey. Cancer Epidemiol Biomarkers Prev 2002;11:726–9.
[20] Kiemeney LA, Broeders MJ, Pelger M, et al. Screening for prostate cancer in Dutch hereditary prostate cancer families. Int J Cancer 2008;122:871–6.
[21] Makinen T, Tammela TL, Stenman UH, et al. Family history and prostate cancer screening with prostate-specific antigen. J Clin Oncol 2002;20:2658–63.
[22] Matikainen MP, Schleutker J, Morsky P, Kallioniemi OP, Tammela TL. Detection of subclinical cancers by prostate-specific antigen screening in asymptomatic men from high-risk prostate cancer families. Clin Cancer Res 1999;5:1275–9.
[23] Narod SA, Dupont A, Cusan L, et al. The impact of family history on early detection of prostate cancer. Nat Med 1995;1:99–101.
[24] Sartor O. Early detection of prostate cancer in African-American men with an increased familial risk of disease. J La State Med Soc 1996;148:179–85.
[25] Uzzo RG, Pinover WH, Horwitz EM, et al. Free prostate-specific antigen improves prostate cancer detection in a high-risk population of men with a normal total PSA and digitalrectal examination. Urology 2003;61:754–9.
[26] Valeri A, Cormier L, Moineau MP, et al. Targeted screening for prostate cancer in high risk families: early onset is a significant risk factor for disease in first degree relatives. J Urol 2002;168:483–7.
[27] Mitra AV, Bancroft EK, Barbachano Y, et al. 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. BJU Int 2011;107:28–39.
[28] Mitra AV, Bancroft EK, Eeles RA. A review of targeted screening for prostate cancer: introducing the IMPACT study. BJU Int 2007;99:1350–5.
[29] Haiman CA, Stram DO, Vickers AJ, et al. Levels of beta-microseminoprotein in blood and risk of prostate cancer in multiple populations. J Natl Cancer Inst 2013;105:237–43.
[30] Vickers A, Cronin A, Roobol M, et al. Reducing unnecessary biopsy during prostate cancer screening using a four-kallikrein panel: an independent replication. J Clin Oncol 2010;28:2493–8.

[31] D'Amico AV, Whittington R, Malkowicz SB, et al. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. JAMA 1998;280:969–74.
[32] Epstein JI, Allsbrook Jr WC, Amin MB, Egevad LL. The 2005 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma. Am J Surg Pathol 2005;29:1228–42.
[33] 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.
[34] National Institute of Health and Clinical Excellence (NICE). Prostate cancer: diagnosis and treatment. NICE clinical guidelines, no. 58. Cardiff, UK: National Collaborating Centre for Cancer; 2008.
[35] Schroder FH, Hugosson J, Roobol MJ, et al. Screening and prostate-cancer mortality in a randomized European study. N Engl J Med 2009;360:1320–8.
[36] Andriole GL, Crawford ED, Grubb III RL, et al. Mortality results from a randomized prostate-cancer screening trial. N Engl J Med 2009; 360:1310–9.
[37] Pinsky PF, Andriole GL, Kramer BS, Hayes RB, Prorok PC, Gohagan JK. Prostate biopsy following a positive screen in the prostate, lung, colorectal and ovarian cancer screening trial. J Urol 2005;173: 746–50, discussion 750–1.
[38] Dickinson L, Ahmed HU, Allen C, et al. Clinical applications of multiparametric MRI within the prostate cancer diagnostic pathway. Urol Oncol 2013;31:281–4.
[39] Khan MA, Partin AW, Rittenhouse HG, et al. Evaluation of proprostate specific antigen for early detection of prostate cancer in men with a total prostate specific antigen range of 4.0 to 10.0 ng/ml. J Urol 2003;170:723–6.
[40] Verhamme KM, Dieleman JP, Bleumink GS, et al. Incidence and prevalence of lower urinary tract symptoms suggestive of benign prostatic hyperplasia in primary care—the Triumph project. Eur Urol 2002;42:323–8.
[41] Nam RK, Saskin R, Lee Y, et al. Increasing hospital admission rates for urological complications after transrectal ultrasound guided prostate biopsy. J Urol 2013;189:S12–7, discussion S17–8.
[42] Rosario DJ, Lane JA, Metcalfe C, et al. Short term outcomes of prostate biopsy in men tested for cancer by prostate specific antigen: prospective evaluation within ProtecT study. BMJ 2012; 344:d7894.
[43] Hoedemaeker RF, van der Kwast TH, Boer R, et al. Pathologic features of prostate cancer found at population-based screening with a four-year interval. J Natl Cancer Inst 2001;93:1153–8.
[44] Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM, editors. Globocan 2008: cancer incidence and mortality worldwide. IARC CancerBase no. 10. International Agency for Research on Cancer Web site. http://globocan.iarc.fr/factsheets/cancers/prostate.asp. Accessed January 3, 2013.