Interim Results from the IMPACT Study

IMPACT Study Collaborators; Page, Elizabeth C; Bancroft, Elizabeth K; Brook, Mark N; Assel, Melissa; Hassan Al Battat, Mona; Thomas, Sarah; Taylor, Natalie; Chamberlain, Anthony; Pope, Jennifer

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

[Link to publication in University of Groningen/UMCG research database](#)

Prostate Cancer

Interim Results from the IMPACT Study: Evidence for Prostate-specific Antigen Screening in *BRCA2* Mutation Carriers

Elizabeth C. Page [a,†], Elizabeth K. Bancroft [a,b,†], Mark N. Brook [a], Melissa Assel [c], Mona Hassan Al Battat [d], Sarah Thomas [b], Natalie Taylor [b], Anthony Chamberlain [a], Jennifer Pope [a], Holly Ni Raghallaigh [a], D. Gareth Evans [e], Jeanette Rothwell [e], Lovise Maehle [f], Eli Marie Grindedal [f], Paul James [g,h,i], Lyon Mascarenhas [g], Joanne McKinley [g], Lucy Side [j], Tessy Thomas [j], Christi van Asperen [k], Hans Vasen [l], Lambertus A. Kiemeney [m], Janneke Ringelberg [l], Thomas Dyrsø Jensen [n], Palle J.S. Osther [o], Brian T. Helfand [p], Elena Genova [p], Rogier A. Oldenburg [q], Cezary Cybulski [r], Dominika Wokolorczyk [r], Kai-Ren Ong [s], Camilla Huber [s], Jimmy Lam [t], Louise Taylor [u], Monica Salinas [v], Lidia Feliubadaló [v], Jan C. Oosterwijk [w], Wendy van Zelst-Stams [m], Jackie Cook [x], Derek J. Rosario [y], Susan Domchek [z], Jacquelyn Powers [z], Saundra Buys [A], Karen O'Toole [A], Margreet G.E.M. Ausems [B], Rita K. Schmutzler [C], Kerstin Rhiem [C], Louise Izatt [D], Vishakha Tripathi [D], Manuel R. Teixeira [E,F], Marta Cardoso [E], William D. Foulkes [G,H], Armen Aprikian [G], Heleen van Randeraad [I], Rosemarie Davidson [I], Mark Longmuir [I], Mariëlle W.G. Ruijs [J], Apollonia T.J.M. Helderman van den Enden [K], Muriel Adank [L], Rachel Williams [M,N], Lesley Andrews [M,N], Declan G. Murphy [h,O], Dorothy Halliday [P], Lisa Walker [P], Annelie Liljegren [Q], Stefan Carlsson [Q], Ashraf Azzabi [R], Irene Jobson [R], Catherine Morton [S], Kylie Shackleton [S], Katie Snape [T], Helen Hanson [T], Marion Harris [U], Marc Tischkowitz [V,W], Amy Taylor [V], Judy Kirk [X,Y], Rachel Susman [Z], Rakefet Chen-Shtoyerman [aa], Allan Spigelman [ab,ac,ad], Nicholas Pachter [ae,af], Munaza Ahmed [ag], Teresa Ramon y Cajal [ah], Janez Zgajnar [ai], Carole Brewer [aj,ak], Neus Gadea [al], Angela F. Brady [am], Theo van Os [an], David Gallagher [ao], Oskar Johannsson [ap], Alan Donaldson [aq], Julian Barwell [ar,as], Nicola Nicolai [at], Eitan Friedman [au], Elias Obeid [av], Lynn Greenhalgh [aw], Vedang Murthy [ax], Lucia Copakova [ay], Sibel Saya [a], John McGrath [ak,az], Peter Cooke [Aa], Karina Rønlund [n], Kate Richardson [g], Alex Henderson [R,Ab], Soo H. Teo [Ac], Banu Arun [Ad], Karin Kast [Ae], Alexander Dias [a,Af], Neil K. Aaronson [J], Audrey Ardern-Jones [b], Chris H. Bangma [Ag], Elena Castro [Ah], David Dearnaley [Ai], Diana M. Eccles [Aj,j], Karen Tricker [e], Jorunn Eyfjord [Ak], Alison Falconer [Al], Christopher Foster [Am], Henrik Gronberg [An], Freddie C. Hamdy [Ao,Ap], Vigdis Stefansdottir [ap], Vincent Khoo [b,T,Ai,Aq], Geoffrey J. Lindeman [S,Aq,Ar], Jan Lubinski [r],

† These authors are joint first authors.
‡ See Appendix 1.
* 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).

Karol Axcrona [As], *Christos Mikropoulos* [At], *Anita Mitra* [Au], *Clare Moynihan* [a], *Gadi Rennert* [Av], *Mohnish Suri* [Aw], *Penny Wilson* [Ax], *Tim Dudderidge* [Ay],

The IMPACT Study Collaborators [‡], *Judith Offman* [Az], *Zsofia Kote-Jarai* [a], *Andrew Vickers* [c], *Hans Lilja* [d,Ap,ba], *Rosalind A. Eeles* [a,b,*]

[a] *Oncogenetics Team, Institute of Cancer Research, London, UK;* [b] *Cancer Genetics Unit and Academic Urology Unit, Royal Marsden NHS Foundation Trust, London, UK;* [c] *Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, NY, USA;* [d] *Department of Translational Medicine, Lund University, Malmö, Sweden;* [e] *Genetic Medicine, Manchester Academic Health Sciences Centre, Central Manchester University Hospitals NHS Foundation Trust, Manchester, UK;* [f] *Department of medical genetics, Oslo University Hospital, 0424 Oslo, Norway;* [g] *Parkville Familial Cancer Centre, Peter MacCallum Cancer Centre, Melbourne, VIC, Australia;* [h] *The Sir Peter MacCallum Department of Oncology, University of Melbourne, VIC, Australia;* [i] *Genetic Medicine, The Royal Melbourne Hospital, Parkville, VIC, Australia;* [j] *Wessex Clinical Genetics Service, Princess Anne Hospital, Southampton, UK;* [k] *Leiden University Medical Center, Leiden, The Netherlands;* [l] *The Foundation for the Detection of Hereditary Cancer, Leiden, The Netherlands;* [m] *Radboud University Medical Center, Nijmegen, The Netherlands;* [n] *Department of Clinical Genetics, Vejle Hospital, Vejle, Denmark;* [o] *Department of Urology, Vejle Hospital, Vejle, Denmark;* [p] *John and Carol Walter Center for Urological Health, Division of Urology, NorthShore University HealthSystem, Evanston, IL, USA;* [q] *Department of clinical genetics, Erasmus University Medical Center, Rotterdam, The Netherlands;* [r] *International Hereditary Cancer Center, Department of Genetics and Pathology, Pomeranian Medical University in Szczecin, Szczecin, Poland;* [s] *Clinical Genetics Unit, Birmingham Women's Hospital, Birmingham, UK;* [t] *Department of Urology, Flinders Medical Centre, Bedford Park, SA, Australia;* [u] *Department of Urology, Repatriation General Hospital, Daw Park, SA, Australia;* [v] *Hereditary Cancer Program, ICO-IDIBELL (Bellvitge Biomedical Research Institute, Catalan Institute of Oncology), CIBERONC, Barcelona, Spain;* [w] *University of Groningen, University Medical Center Groningen, Groningen, The Netherlands;* [x] *Sheffield Clinical Genetics Service, Sheffield Children's Hospital, Sheffield, UK;* [y] *Royal Hallamshire Hospital, Sheffield, UK;* [z] *Basser Research Center, University of Pennsylvania, Philadelphia, PA, USA;* [A] *Huntsman Cancer Institute, University of Utah, Salt Lake City, UT, USA;* [B] *Division of Laboratories, Pharmacy and Biomedical Genetics, Department of Genetics, University Medical Centre, Utrecht, The Netherlands;* [C] *Center for Familial Breast and Ovarian Cancer, Center for Integrated Oncology (CIO), University of Cologne, Faculty of Medicine and University Hospital Cologne, Cologne, Germany;* [D] *Clinical Genetics Service, Guy's and St Thomas' NHS Foundation Trust, London, UK;* [E] *Genetics Department and Research Center, Portuguese Oncology Institute (IPO Porto), Porto, Portugal;* [F] *Biomedical Sciences Institute (ICBAS), Porto University, Porto, Portugal;* [G] *Cancer Research Program, Research Institute of McGill University Health Centre, Montreal, Quebec, Canada;* [H] *Lady Davis Institute, Jewish General Hospital, McGill University, Montreal, QC, Canada;* [I] *West of Scotland Genetic Service, Queen Elizabeth University Hospital, Glasgow, UK;* [J] *Netherlands Cancer Institute, Amsterdam, The Netherlands;* [K] *Department of Clinical Genetics, Maastricht University Medical Center, Maastricht, The Netherlands;* [L] *VU University Medical Center, Amsterdam, The Netherlands;* [M] *Prince of Wales Clinical School, Faculty of Medicine, University of New South Wales, Sydney, NSW, Australia;* [N] *Hereditary Cancer Centre, Prince of Wales Hospital, Randwick, NSW, Australia;* [O] *Division of Cancer Surgery, Peter MacCallum Cancer Centre, Melbourne, VIC, Australia;* [P] *Oxford Centre for Genomic Medicine, Oxford University Hospitals NHS Trust, Oxford, UK;* [Q] *Karolinska University Hospital and Karolinska Institutet, Stockholm, Sweden;* [R] *Northern Genetics Service, Newcastle upon Tyne Hospitals, UK;* [S] *Familial Cancer Centre, The Royal Melbourne Hospital, Grattan St, Parkville, VIC, Australia;* [T] *St George's Hospital, Tooting, London, UK;* [U] *Familial Cancer Centre, Monash Health, Clayton, VIC, Australia;* [V] *East Anglian Medical Genetics Service, Cambridge University Hospitals NHS Trust, Cambridge, UK;* [W] *Academic Department of Medical Genetics, NIHR Cambridge Biomedical Research Centre, Level 6 Addenbrooke's Treatment Centre, Cambridge Biomedical Campus, University of Cambridge, Cambridge, UK;* [X] *Familial Cancer Service, Crown Princess Mary Cancer Centre, Westmead Hospital, Westmead, Sydney, NSW, Australia;* [Y] *Sydney Medical School, University of Sydney, Centre for Cancer Research, The Westmead Institute for Medical Research, Westmead, Sydney, NSW, Australia;* [Z] *Genetic Health Queensland, Royal Brisbane & Women's Hospital, Herston, QLD, Australia;* [aa] *The Genetic Institute, Kaplan Medical Center, Rehovot, Israel;* [ab] *Hunter Family Cancer Service, Waratah, NSW, Australia;* [ac] *University of New South Wales, St Vincent's Clinical School, NSW, Australia;* [ad] *Cancer Genetics Clinic, The Kinghorn Cancer Centre, St Vincent's Hospital, Sydney, NSW, Australia;* [ae] *Genetic Services of WA, King Edward Memorial Hospital, Subiaco, WA, Australia;* [af] *Department of Paediatrics, University of Western Australia, Perth, WA, Australia;* [ag] *NE Thames Regional Genetics Service, Institute of Child Health, London, UK;* [ah] *Hospital de Sant Pau, Barcelona, Spain;* [ai] *Institute of Oncology, Ljubljana, Slovenia;* [aj] *Peninsular Genetics, Derriford Hospital, Plymouth, UK;* [ak] *Royal Devon and Exeter Hospital, Exeter, UK;* [al] *Hospital Vall d'Hebron, Barcelona, Spain;* [am] *North West Thames Regional Genetics Service, Kennedy-Galton Centre, London North West University Healthcare NHS Trust, Harrow, UK;* [an] *Academic Medical Center, Amsterdam, The Netherlands;* [ao] *St James's Hospital, Dublin, Ireland;* [ap] *Landspitali—the National University Hospital of Iceland, Reykjavik, Iceland;* [aq] *St Michael's Hospital, Bristol, UK;* [ar] *University of Leicester, Leicester, UK;* [as] *University Hospitals Leicester, Leicester, UK;* [at] *Istituto Nazionale dei Tumori, Milano, Italy;* [au] *Chaim Shema Medical Center, Tel-Hashomer, Israel;* [av] *Fox Chase Cancer Center, Philadelphia, PA, USA;* [aw] *Clinical Genetics Service, Liverpool Women's Hospital, Liverpool, UK;* [ax] *Tata Memorial Centre, Mumbai, India;* [ay] *National Cancer Institute, Bratislava, Slovak Republic;* [az] *University of Exeter Medical School, St Luke's Campus, Exeter, UK;* [Aa] *New Cross Hospital, Wolverhampton, UK;* [Ab] *West Cumberland Infirmary, Whitehaven, UK;* [Ac] *Cancer Research Initiatives Foundation, Subang Jaya Medical Centre, Selangor, Darul Ehsan, Malaysia;* [Ad] *The University of Texas, MD Anderson Cancer Center, Houston, TX, USA;* [Ae] *Department of Gynecology and Obstetrics, Medical Faculty and University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany;* [Af] *Instituto Nacional de Cancer Jose de Alencar Gomes da Silva (INCA), Rio de Janeiro, Brazil;* [Ag] *Department of urology, Erasmus University Medical Center, Rotterdam, The Netherlands;* [Ah] *Spanish National Cancer Research Center, Madrid, Spain;* [Ai] *Division of Radiotherapy and Imaging, The Institute of Cancer Research, Sutton, UK;* [Aj] *The University of Southampton Medical School, Southampton, UK;* [Ak] *Faculty of Medicine, School of Health Sciences, University of Iceland, Reykjavik, Iceland;* [Al] *Imperial College Healthcare NHS Trust, London, UK;* [Am] *HCA Pathology Laboratories, London, UK;* [An] *University Hospital, Umea, Sweden;* [Ao] *Churchill Hospital, Headington, Oxford, UK;* [Ap] *Nuffield Department of Surgical Sciences, University of Oxford, Oxford, UK;* [Aq] *Department of Medicine, The University of Melbourne, Parkville, VIC, Australia;* [Ar] *Cancer Biology and Stem Cells Division, The Walter and Eliza Hall Institute of Medical Research, Parkville, VIC, Australia;* [As] *Department of Urology, Akershus University Hospital, Lørenskog, Norway;* [At] *Medway Hospital, Kent, UK;* [Au] *University College London Hospitals NHS Foundation Trust, London, UK;* [Av] *CHS National Cancer Control Center, Carmel Medical Center, Haifa, Israel;* [Aw] *Nottingham City Hospital, Nottingham, UK;* [Ax] *Innovate UK, Polaris House, Swindon, UK;* [Ay] *University Hospital Southampton, Southampton, UK;* [Az] *School of Cancer and Pharmaceutical Sciences, Faculty of Life Sciences & Medicine, King's College London, Guy's Cancer Centre, Guy's Hospital, London, UK;* [ba] *Departments of Laboratory Medicine, Surgery, and Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY, USA*

Article info

Abstract

Background: Mutations in *BRCA2* cause a higher risk of early-onset aggressive prostate cancer (PrCa). The IMPACT study is evaluating targeted PrCa screening using prostate-specific-antigen (PSA) in men with germline *BRCA1/2* mutations.
Objective: To report the utility of PSA screening, PrCa incidence, positive predictive value of PSA, biopsy, and tumour characteristics after 3 yr of screening, by BRCA status.
Design, setting, and participants: Men aged 40–69 yr with a germline pathogenic *BRCA1/2* mutation and male controls testing negative for a familial *BRCA1/2* mutation were recruited. Participants underwent PSA screening for 3 yr, and if PSA > 3.0 ng/ml, men were offered prostate biopsy.
Outcome measurements and statistical analysis: PSA levels, PrCa incidence, and tumour characteristics were evaluated. Statistical analyses included Poisson regression offset by person-year follow-up, chi-square tests for proportion t tests for means, and Kruskal-Wallis for medians.
Results and limitations: A total of 3027 patients (2932 unique individuals) were recruited (919 *BRCA1* carriers, 709 *BRCA1* noncarriers, 902 *BRCA2* carriers, and 497 *BRCA2* noncarriers). After 3 yr of screening, 527 men had PSA > 3.0 ng/ml, 357 biopsies were performed, and 112 PrCa cases were diagnosed (31 *BRCA1* carriers, 19 *BRCA1* noncarriers, 47 *BRCA2* carriers, and 15 *BRCA2* noncarriers). Higher compliance with biopsy was observed in *BRCA2* carriers compared with noncarriers (73% vs 60%). Cancer incidence rate per 1000 person years was higher in *BRCA2* carriers than in noncarriers (19.4 vs 12.0; $p = 0.03$); *BRCA2* carriers were diagnosed at a younger age (61 vs 64 yr; $p = 0.04$) and were more likely to have clinically significant disease than *BRCA2* noncarriers (77% vs 40%; $p = 0.01$). No differences in age or tumour characteristics were detected between *BRCA1* carriers and *BRCA1* noncarriers. The 4 kallikrein marker model discriminated better (area under the curve [AUC] = 0.73) for clinically significant cancer at biopsy than PSA alone (AUC = 0.65).
Conclusions: After 3 yr of screening, compared with noncarriers, *BRCA2* mutation carriers were associated with a higher incidence of PrCa, younger age of diagnosis, and clinically significant tumours. Therefore, systematic PSA screening is indicated for men with a *BRCA2* mutation. Further follow-up is required to assess the role of screening in *BRCA1* mutation carriers.
Patient summary: We demonstrate that after 3 yr of prostate-specific antigen (PSA) testing, we detect more serious prostate cancers in men with *BRCA2* mutations than in those without these mutations. We recommend that male *BRCA2* carriers are offered systematic PSA screening.

1. Introduction

It is well established that *BRCA2* gene mutations cause a higher risk of prostate cancer (PrCa), with an estimated relative risk of 2.5–8.6-fold by age 65 yr [1,2], and are associated with earlier-onset, clinically significant disease. A number of retrospective studies report higher rates of lymph node involvement, distant metastasis at diagnosis, and higher mortality rates in mutation carriers [3–6]. Germline *BRCA2* mutation status is reported to be an independent prognostic factor for poorer outcome [3]. Furthermore, tumours of *BRCA2* mutation carriers with localised PrCa have been demonstrated to exhibit genomic instability more typically seen in metastatic castration-resistant PrCa [7].

There is debate about whether there is an increased risk of PrCa for *BRCA1* mutation carriers, with an estimated relative risk of 1.8–3.75-fold by age 65 yr [8] and some evidence of more clinically significant disease [3,9]; however, this warrants further research. It is hypothesised that targeted screening in *BRCA1/2* carriers facilitates early detection.

The controversies of using prostate-specific antigen (PSA) screening in the general population are well

documented, but PSA remains the most effective PrCa biomarker currently available [10–12]. Efforts to improve sensitivity and specificity of PSA by incorporating other biological markers, such as the 4 kallikrein (4 K) marker panel [13,14], PrCa risk calculators [15,16], magnetic resonance imaging (MRI) [17,18], and genetic markers [19,20], into screening algorithms are under evaluation.

The IMPACT study (Identification of Men with a genetic predisposition to ProstAte Cancer: Targeted screening in men at higher genetic risk and controls; http://impact.icr.ac.uk/) is an international, multicentre study evaluating targeted PrCa screening in men with *BRCA1/2* mutations. IMPACT aims to evaluate the utility of PSA screening in detecting clinically significant PrCa (defined as intermediate- or high-risk disease using the National Institute for Health and Care Excellence [NICE] guidelines [21]), PrCa incidence, positive predictive value (PPV) of biopsy using a PSA threshold of 3.0 ng/ml, and tumour characteristics in order to establish whether PSA screening detects clinically significant disease in this population compared with the noncarrier control group.

An analysis of the baseline screen for nearly 2500 men enrolled in IMPACT supported the use of targeted PSA

screening in *BRCA1/2* mutation carriers, suggesting that screening detects a high proportion of clinically significant tumours [22]. Moreover, we have also demonstrated that PSA is more predictive of PrCa in *BRCA1/2* carriers than in noncarriers [23]. It has been reported that men with germline *BRCA1/ BRCA2* mutations, on active surveillance for low-risk PrCa, are at a higher risk of reclassification to higher-grade PrCa than noncarriers [24].

National Comprehensive Cancer Network guidelines advise PrCa screening to begin at 45 yr for male *BRCA2* carriers, consider the same for *BRCA1* carriers, and perform routine *BRCA1/2* testing for men with high-risk PrCa, family history, or metastatic disease [25,26].

The aims of this study were to evaluate the utility of PSA screening, by assessing PrCa prevalence/incidence, PPV of biopsy, and tumour characteristics. A secondary aim was to evaluate the addition of 4 K markers to the algorithm predicting biopsy outcome (full details of this analysis can be found in the Supplementary material).

2. Patients and methods

The IMPACT study design has been reported previously [22,27,28] and is summarised in Fig. 1. The protocol was approved by the West-Midlands Research and Ethics Committee in the UK (reference: 05/MRE07/25) and subsequently by each participating institution's local committee. All participants provided written consent, and interim analyses are presented to the Independent Data and Safety Monitoring Committee biannually.

The target sample is 500 *BRCA1* and 350 *BRCA2* mutation carriers, and a control group of 850 men who have undergone predictive testing and tested negative for a pathogenic *BRCA1/2* mutation known to be present in their family. IMPACT has been powered to detect a two-fold PrCa risk over 5 yr of screening, with 80% power at the $p < 0.01$ level.

Between October 2005 and February 2013, men aged 45–69 yr in The Netherlands and 40–69 yr in all other countries were recruited from families with known pathogenic *BRCA1* or *BRCA2* mutations. Further detail of the inclusion criteria were described previously [22,27,28]. Participants were screened annually in all centres except for those in The Netherlands, which screened biennially in accordance with local regulations. Recruitment was extended to December 2015, and a subset of 95 *BRCA2* noncarriers was sequenced for *BRCA1/2* mutations and used as the control group to cover the loss of numbers that resulted in removing The Netherlands cohort from cumulative analyses and include them as *BRCA1* noncarriers.

All participants underwent annual PSA testing for four screening rounds. If PSA was >3.0 ng/ml, transrectal ultrasound–guided prostate biopsy (PB) was recommended. Decision to biopsy was based on this single PSA level; PSA was not repeated prior to biopsy unless clinically indicated. Centres were requested to follow a standard biopsy protocol, consisting of 10 and 12 biopsy cores taken from specific locations within the prostate gland. Individuals with a benign PB continued annual PSA follow-up. A repeat PB was recommended if PSA was >50% of the pre-PB PSA

[29] (Fig. 1). The local histopathologist at each centre reported the biopsy results to guide treatment in accordance with local guidelines. Cancers were defined using the NICE criteria, and were deemed "clinically significant" if classified as of intermediate or high risk according to these guidelines [21]. Whenever high-grade prostate intraepithelial neoplasia or atypical small acinar proliferation was detected, the biopsy was repeated within 3–6 mo.

The IMPACT results have been compared with the Göteborg cohort of the ERPSC study. This Swedish general population cohort of men aged 50–64 yr was offered biennial PSA screening with further investigations for PSA > 3.0 ng/ml and therefore were the closest general population group available for comparison.

2.1. Statistical analysis

Statistical analyses were undertaken using Stata 14.2 Stata-Corp. 2015. *Stata Statistical Software: Release 14*. College Station, TX: StataCorp LP and GraphPad QuickCalcs Web site: https://www.graphpad.com/quickcalcs (accessed August 2019).

PrCa prevalence for individuals with PSA > 3.0 ng/ml at the first PSA test was calculated. The cumulative incidence was calculated at the fourth screening round, stratified by age group, tumour-node-metastasis stage, and Gleason score, and compared by mutation status using Poisson regression offset by person-year follow-up, adjusted for age, ethnicity, and country. Proportions of screen-detected disease and PPV of PB were compared between groups using the chi-square test. Fisher's exact and Kruskal-Wallis tests were used to compare median age, PSA, and tumour characteristics between groups.

Analyses were performed on the whole cohort and by *BRCA* status. Secondary analyses were conducted excluding prevalent cancers (cancers diagnosed within <12 mo of enrolment). A p value of <0.05 was considered statistically significant.

3. Results

3.1. Study population

A total of 3027 persons (2932 unique individuals) were recruited from 65 centres in 20 countries over 120 mo (Supplementary Table 1): 919 *BRCA1* carriers, 709 *BRCA1* noncarriers, 902 *BRCA2* carriers, and 497 *BRCA2* noncarriers. Ninety-five *BRCA2* noncarriers sequenced for both *BRCA1/*2 mutations were included in both control cohorts. The cohorts were overrecruited, as advised by the study's Independent Data Monitoring Committee. The rationale was that overrecruitment would only strengthen the data and would compensate for any participants who withdrew from the study.

The majority of participants were Caucasian (97%), highly educated, and in work (Supplementary Table 2); median enrolment age was 54 yr; 24% of men reported urinary symptoms and 36% previously had at least one PSA test; and 31% reported a family history of PrCa. No statistically
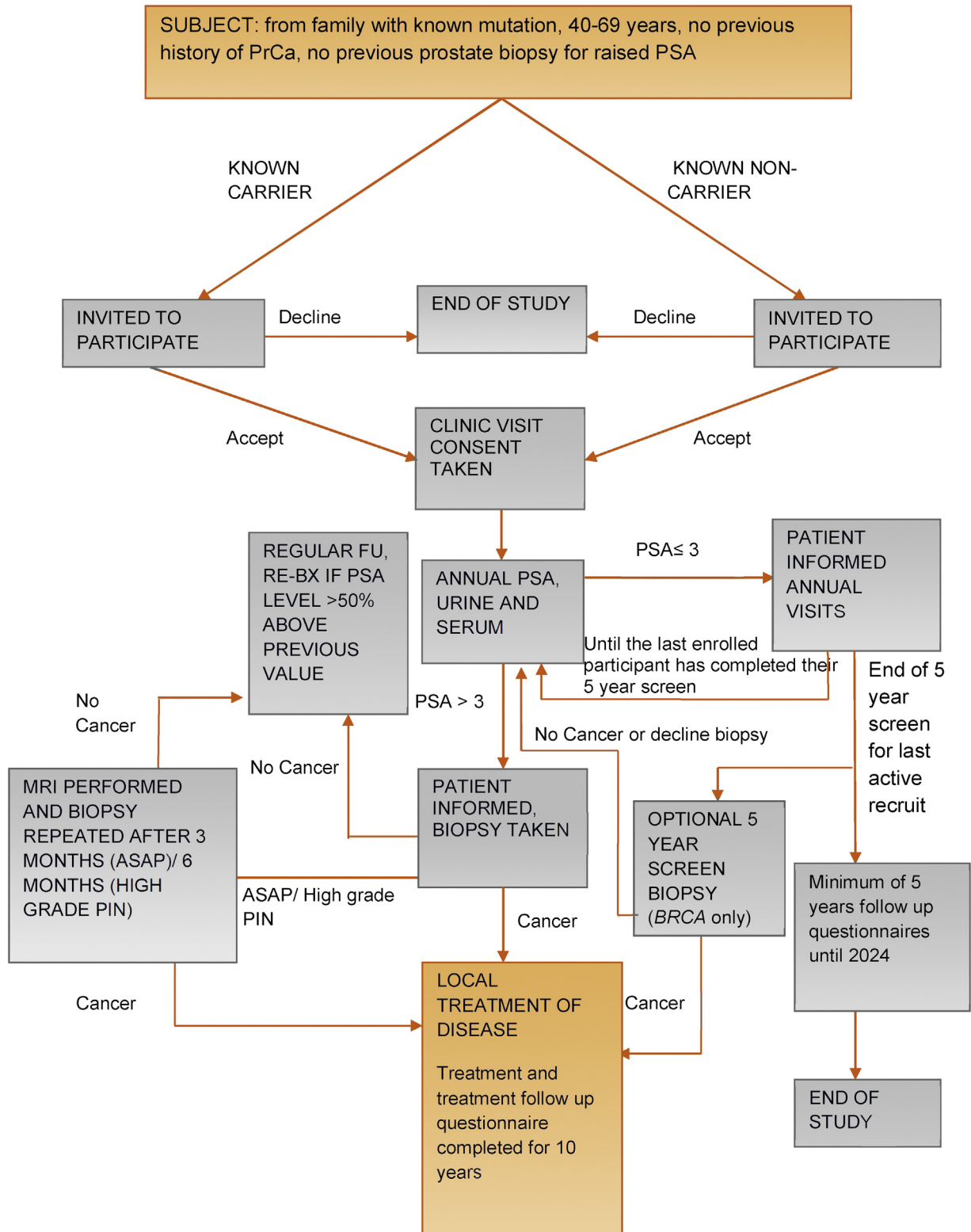
Fig. 1 – Study design algorithm.
ASAP = atypical small acinar proliferation; FU = follow-up; MRI = magnetic resonance imaging; PIN = prostate intraepithelial neoplasia; PrCa = prostate cancer; PSA = prostate-specific-antigen; Re-BX = repeat biopsy.

Table 1 – Prostate cancer detection rates after four rounds of screening.

	Total cohort[a]	Mutation status			
		BRCA2+	BRCA2−	BRCA1+	BRCA1−
Baseline ("yr 1")					
Unique individuals, n (%)	2932	902 (30)	497(16)	919 (30)	709 (24)
Total PSAs taken, n	2931	902	497	919	708
Median PSA (IQR)	0.9 (0.6-1.5)	0.9 (0.5-1.5)	0.9 (0.6-1.4)	0.9 (0.5-1.4)	1.0 (0.6-1.7)
PSA > 3 ng/ml, n (%)	228 (7.5)	68 (7.5)	29 (5.8)	73 (7.9)	61 (8.6)
PSA > 3 ng/ml requiring action, n	228	68	29	73	61
Biopsies, n (biopsy rate %)	180 (79)	56 (82)	19 (66)	57 (78)	49 (75)
Including repeats, n	195	61	21	62	52
Benign, n	107	29	12	32	35
ASAP/HG PIN, n	13	5	0	6	2
Malignant (PrCa incidence), n (%, 95 CI)	69 (2.4, 1.8-3.0)	25 (2.8, 1.7-3.8)	7 (1.4, 3.7-2.4)	24 (2.6, 1.6-3.6)	13 (1.8, 0.8-2.8)
Diff. in detection rate: BRCA + vs BRCA− (%, 95 CI)		(1.4, -0.1-2.9)		(0.8, -0.6-2.2)	
p value for detection rate: BRCA + vs BRCA−		0.10		0.3	
Diagnosed within 6 mo of entry, n	65	25	6	22	12
Diagnosed within 12 mo of entry, n	68	25	7	23	13
PPV of biopsy (%, 95 CI)	(35, 29-43)	(41, 29-53)	(33, 13-53)	(39, 27-51)	(25, 13-37)
Diff. in PPV, biopsy: BRCA + vs BRCA− (%, 95 CI)		(8, −16-31)		(14, −3-31)	
p value for PPV, biopsy: BRCA + vs BRCA−		0.5		0.12	
PPV of PSA > 3 ng/ml requiring action (%, 95 CI)	(30, 24-37)	(37, 25-48)	(24, 9-40)	(33, 22-44)	(21, 11-32)
Diff. in PPV, PSA > 3: BRCA + vs BRCA− (%, 95 CI)		(13, −7-32)		(12, −3-26)	
p value for PPV, PSA > 3: BRCA + vs BRCA−		0.2		0.14	
3-yr follow-up ("yr 4")					
Total PSAs taken, n (%)	9363	3108 (32)	1600 (16)	2847 (29)	2183 (22)
Median PSA (IQR)	0.9 (0.6-1.5)	0.9 (0.6-1.5)	0.9 (0.6-1.5)	0.9 (0.5-1.5)	1.0 (0.6-1.7)
PSA > 3 ng/ml, n (%)	695 (7.4)	200 (6.4)	117 (7.3)	218 (7.7)	182 (8.3)
PSA > 3 ng/ml requiring action, n (%)	527 (5.6)	150 (4.8)	84 (5.3)	138 (4.8)	126 (5.8)
Biopsies, n (biopsy rate%)	332 (63)	110 (73)	50 (60)	93 (67)	89 (71)
Including repeats, n	357	122	54	98	95
Benign, n	208	59	32	60	67
ASAP/HG PIN, n	26	10	5	7	6
Malignant (PrCa incidence), n (%, 95 CI)	112 (3.8, 3.2-4.6)	47 (5.2, 3.8-6.7)	15 (3.0, 1.5-4.5)	31 (3.4, 2.2-4.5)	19 (2.7, 1.5-3.9)
Diff. in detection rate: BRCA + vs BRCA− (%, 95 CI)		(2.2, 0.1-4.2)		(0.7, −0.9-2.3)	
p value for detection rate: BRCA + vs BRCA−		0.057		0.4	
PPV of biopsy (%, 95 CI)	(31, 27-36)	(39, 30-47)	(28, 16-40)	(32, 22-41)	(20, 12-28)
Diff. in PPV, biopsy: BRCA + vs BRCA− (%, 95 CI)		(11, −4-25)		(12, −0.6-24)	
p value for PPV, biopsy: BRCA + vs BRCA−		0.17		0.065	
PPV of PSA > 3 ng/ml requiring action (%, 95 CI)	(21, 18-25)	(31, 24-39)	(18, 10-26)	(23, 16-29)	(15, 9-21)
Diff. in PPV, PSA > 3: BRCA + vs BRCA− (%, 95 CI)		(13, 2-25)		(7, −2-17)	
p value for PPV, PSA > 3: BRCA + vs BRCA−		0.025		0.13	
Prevalence of PrCa in all PSAs (%, 95 CI)	(1.2, 1-1.4)	(1.5, 1.1-1.9)	(0.9, 0.5-1.4)	(1.1, 0.7-1.5)	(0.9, 0.5-1.2)
Diff. in prevalence of PrCa: BRCA + vs BRCA− (%, 95 CI)		(0.6, −0.1-1.2)		(0.2, −0.3-0.8)	
p value for prevalence of PrCa: BRCA + vs BRCA−		0.10		0.4	
Follow-up time (yr), median (IQR)					
Noncancers	3.0 (2.18, 3.12)	3.0 (2.91, 3.14)	3.0 (2.17, 3.11)	3.0 (2.09, 3.12)	3.0 (2.12, 3.10)
Cancers	0.3 (0.12, 2.05)	0.4 (0.18, 2.27)	1.0 (0.12, 2.28)	0.2(0.10, 1.12)	0.2 (0.06, 1.43)
Total follow-up time, person yrs					
Noncancers	7185	2371	1227	2206	1674
Cancers	110	57	20	19	14
Cancer incidence rate (per 1000 person yrs)	15	19	12	14	11
Incidence rate ratio (crude), (95 CI)		1.61 (0.90-2.88)		1.24 (0.70-2.19)	
IRR, adjusted for age, ethnicity, country (95 CI) (p value)		1.95 (1.06-3.56) (0.031)		1.36 (0.75-2.45) (0.3)	

ASAP = atypical small acinar proliferation; CI = confidence interval; Diff. = difference; HG PIN = high-grade prostate intraepithelial neoplasia; IQR = interquartile range; IRR = incidence rate ratio; PPV = positive predictive value; PrCa = prostate cancer; PSA = prostate-specific antigen.

[a] A total of 95 individuals contribute to both BRCA1 and BRCA2 controls; therefore, the sum of mutation status will not match the total cohort.

significant differences were observed in sociodemographic variables, symptoms, or previous screening between groups.

3.2. PrCa detection rates after 3 yr of screening and PPV of biopsy

At baseline, 2932 participants had a PSA test, 228 (7.7%) had PSA > 3.0 ng/ml, and 69 (2.4%) had cancers diagnosed from 195 biopsies.

Cumulatively, after four PSA screens, 527 individuals (18%) had PSA > 3.0 ng/ml and 112 cancers diagnosed from 357 biopsies. In the *BRCA2* cohort, 47 (5.2%) cancers were diagnosed in carriers and 15 (3.0%) in noncarriers; 31 cancers (3.4%) were diagnosed in *BRCA1* carriers compared with 19 (2.7%) in noncarriers (Table 1 and Fig. 2).

Overall PrCa detection rate was 3.8% (112/2932), and the cancer incidence rate per 1000 person years was 15. The cancer incidence rates were 19 and 12 in *BRCA2* carriers and
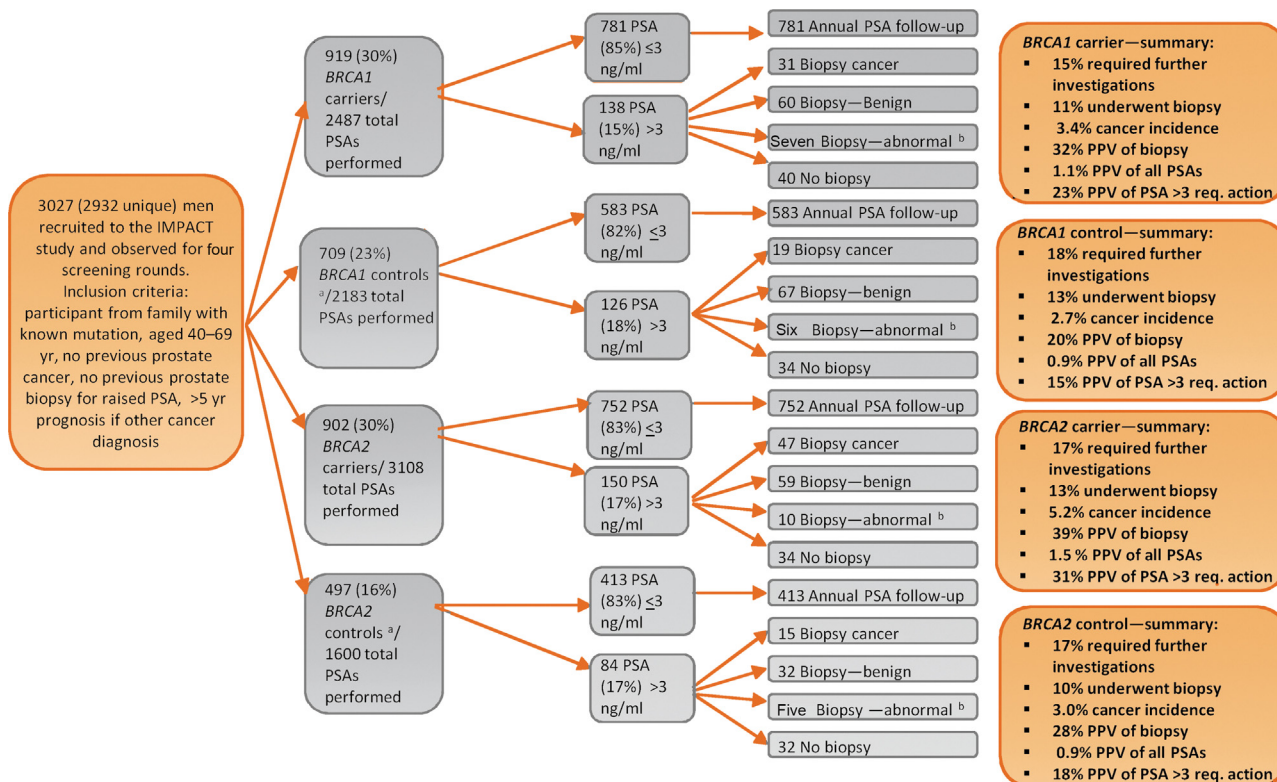
Fig. 2 – A consort diagram of the IMPACT study after four screening rounds. ASAP = atypical small acinar proliferation; PIN = prostate intraepithelial neoplasia; PPV = positive predictive value; PSA = prostate-specific-antigen.
[a]Controls were men who had a negative predictive genetic test for the BRCA mutation in their family.
[b]Biopsy—abnormal refers to high-grade PIN and ASAP.

noncarriers, respectively (incidence rate ratio [IRR] = 1.95, p = 0.031), and 14 and 11 in *BRCA1* carriers and noncarriers, respectively (IRR = 1.36, p = 0.3).

Overall, PPV of PB was 31%, with 39% and 28% in *BRCA2* carriers and noncarriers, respectively (p = 0.17), and 32% and 20% in *BRCA1* carriers and noncarriers, respectively (p = 0.065).

The overall PPV of PSA > 3.0 ng/ml was 21%, with 31% and 18% in *BRCA2* carriers and noncarriers, respectively (p = 0.025), and 23% and 15% in *BRCA1* carriers and noncarriers, respectively (p = 0.13).

To compare results with the population-based Göteborg cohort [30], we restricted the IMPACT cohort to entry ages 50–64 yr (Supplementary Table 3). The Göteborg study report 2.5% PrCa incidence (confidence interval [CI]: 2.2%, 2.8%) after 4 yr [30,31] compared with 5.3% (CI: 4.2–6.5) in IMPACT.

PPV for PB is 30% in the Göteborg cohort and is 26% for PSA (above threshold). PPV for PB is 33% in IMPACT, restricted to the Göteborg age range, and 24% for PSA > 3.0 ng/ml. When comparing PPVs in the Göteborg cohort with IMPACT for clinically significant disease, we see a higher incidence in the *BRCA2* carriers for both PSA ($p \leq$ 0.001) and PB ($p \leq$ 0.001).

As a sensitivity analysis, analyses were repeated excluding centres in The Netherlands (Supplementary Table 4) that screened patients biennially. No differences in the distributions of cancer incidence, incidence rate, or PPV of PB were observed. To rule out the *BRCA2* control group being an

outlier, the analyses were repeated combining the control groups, and all significant differences remained.

Analyses were repeated removing cancers diagnosed within <12 mo of study entry (Supplementary Table 5). These analyses show increased PrCa incidence in *BRCA2* carriers; however, these analyses are currently underpowered.

During the first four screening rounds, the biopsy compliance rate for raised PSA (>3) was 73% in *BRCA2* carriers, 60% in *BRCA2* noncarriers, 67% in *BRCA1* carriers, and 71% in *BRCA1* noncarriers. From the 357 biopsies performed including repeat biopsies, the median age at biopsy of *BRCA2* carriers was 60 yr, compared with 64 yr in *BRCA2* noncarriers ($p \leq$ 0.001). No differences were observed in the *BRCA1* cohort (Table 2). When comparing by genetic status, no differences were seen in median PSA, which triggered biopsy, time (in days) between PSA test and biopsy, age at biopsy, and number of diagnostic cores taken at biopsy.

3.3. Cancer characteristics

Table 3 and Supplementary Table 6 show the characteristics of all screen-detected PrCa cases diagnosed in patients with a PSA level of >3.0 ng/ml during the first four screening rounds.

The median age at PrCa diagnosis was 61 yr (interquartile range [IQR]: 56, 64) in *BRCA2* carriers and 64 yr (IQR: 60, 66) in *BRCA2* noncarriers (p = 0.044, Kruskal-Wallis). In the

Table 2 – Summary of characteristics of men who underwent biopsies in the first four screening rounds of the IMPACT study.

	Total	BRCA1+	BRCA1−	p value	BRCA2+	BRCA2−	p value
Total biopsies (n)	357[a]	98	95		122	54	
Biopsy compliance (%)	68	71	75		81	64	
Median PSA (ng/ml) to trigger biopsy (IQR)	4.2 (3.5–5.6)	4.2 (3.7–5.6)	4.0 (3.5–4.8)	0.1	4.5 (3.5–5.9)	4.2 (3.4–6.2)	0.8
Median age (yr) at biopsy (IQR)	61 (56–65)	61 (56–64)	61 (56–65)	0.9	60 (56–64)	64 (60–67)	<0.001
Median time difference (d) PSA to biopsy (IQR)	51 (27–89)	56 (28–72)	42 (22–79)	0.3	57 (28–94)	50 (25–87)	0.1
Median cores taken, n (IQR)	10 (8–12)	10 (9–12)	10 (8–12)	0.5	10 (8–12)	10 (8–12)	1

IQR = interquartile range; PSA = prostate-specific antigen.
[a] Twelve biopsies contribute to both BRCA1 and BRCA2 controls, therefore the sum of mutation status will not match total cohort.

Table 3 – Summary of cancer characteristics of PSA detected cancers using final clinical pathology (ie, if available after prostatectomy)[a].

Genetic status	BRCA2+ (n = 48)	BRCA2− (n = 15)	p value	BRCA1+ (n = 33)	BRCA1− (n = 20)	p value
Median age (yr) at diagnosis	61 (56, 64)	64 (60, 66)	0.044	62 (57, 66)	61 (58, 62)	0.3
Median PSA (ng/ml) at diagnosis (IQR)	4.5 (3.6, 5.5)	4.2 (3.4, 6.1)	0.9	4.4 (3.8, 5.9)	4.4 (3.6, 5.3)	0.7
Gleason score 6	18 (38)	11 (73)	0.019[b]	18 (55)	13 (65)	0.6[a]
Gleason score 7 (3 + 4)	15 (31)	1 (7)		9 (27)	4 (20)	
Gleason score 7 (4 + 3)	9 (19)	2 (13)		4 (12)	3 (15)	
Gleason score 8+	6 (12)	1 (7)		2 (6)	0	
T stage—T1/T2a	16 (35)	8 (57)	0.2[b]	9 (31)	8 (40)	0.6[a]
T Stage—T2b	2 (4)	2 (14)		0	1 (5)	
T Stage—T2c/T3	28 (61)	4 (29)		20 (69)	11 (55)	
Risk category[c]—low	11 (23)	9 (60)	0.011[b]	10 (30)	4 (20)	0.5[a]
Risk category[c]—intermediate	7 (14.5)	1 (7)		3 (9)	6 (30)	
Risk category[c]—high	30 (62.5)	5 (33)		20 (61)	10 (50)	
Screening round diagnosed—1	25 (52)	7 (47)		23 (70)	13 (65)	
Screening round diagnosed—2	7 (14.5)	1 (7)		3 (9)	3 (15)	
Screening round diagnosed—3	9 (19)	5 (33)		6 (18)	2 (10)	
Screening round diagnosed—4	7 (14.5)	2 (13)		1 (3)	2 (10)	
Active surveillance	8 (17)	7 (47)		5 (17)	6 (30)	
Radical prostatectomy	32 (70)	6 (40)		22 (76)	12 (60)	
Nonsurgical treatment	6 (13)	2 (13)		2 (7)	2 (10)	

IQR = interquartile range; NICE = National Institute for Health and Care Excellence; PSA = prostate-specific antigen.
Some pathology information is not available from sites yet.
Values are presented as median (IQR) and n (%).
[a] Note four cancers included in this analysis were diagnosed as a result of additional off-protocol repeat biopsies in men with high PSA.
[b] p values calculated on difference between clinically significant disease and non–clinically significant disease.
[c] Risk category classification system using NICE guidelines [21].

BRCA1 cohort, there was no difference in median age at diagnosis (p = 0.33).

Looking at the overall risk category, 37/48 (77%) BRCA2 carriers had intermediate- or high-risk PrCa (clinically significant disease), compared with six/15 (40%) BRCA2 noncarriers (p = 0.011, Fisher's exact). There were no statistically significant differences between BRCA1 carriers (70%) and noncarriers (80%; Fig. 3).

Limiting to incident cases, 48 cancers were diagnosed: 23 in BRCA2 carriers, eight in BRCA2 noncarriers, 10 in BRCA1 carriers, and seven in BRCA1 noncarriers; there is no significant difference by carrier status. No significant difference was also seen when limiting to incident cases and excluding men who had had a previous benign biopsy (n = 9).

After four screening rounds, no deaths from PrCa were reported in the IMPACT study participants.

4. Discussion

The IMPACT study is the only international prospective PrCa screening study conducted exclusively in families with BRCA1/2 mutations. IMPACT will screen all but the Dutch patients for a total of five screening rounds, and collect cancer incidence and mortality data for a further 5 yr.

Controversy about PSA level that used to trigger PB continues, and we have demonstrated that using a PSA level of >3.0 ng/ml, after four screening rounds, 13% of the total cohort was recommended to have a PB with a 3.8% cancer detection rate. The IMPACT study continues to collect screening data, and a further component of the protocol is to offer men the option of undergoing PB after the completion of five screening rounds, irrespective of the PSA level. This will provide the opportunity to evaluate the number of clinically significant cancers missed in carriers and noncarriers when using a PSA threshold of 3.0 ng/ml.

We have demonstrated that the trends reported after the baseline screen are strengthened after 3 yr of follow-up. The PPV of PSA > 3.0 ng/ml was significantly higher in BRCA2 mutation carriers (31%) compared with noncarriers (18%; p = 0.025). When compared with the Göteborg cohort, the PPV of PB in BRCA2 carriers was 41% compared with 30%, therefore biopsying fewer men unnecessarily. As previously

A

B
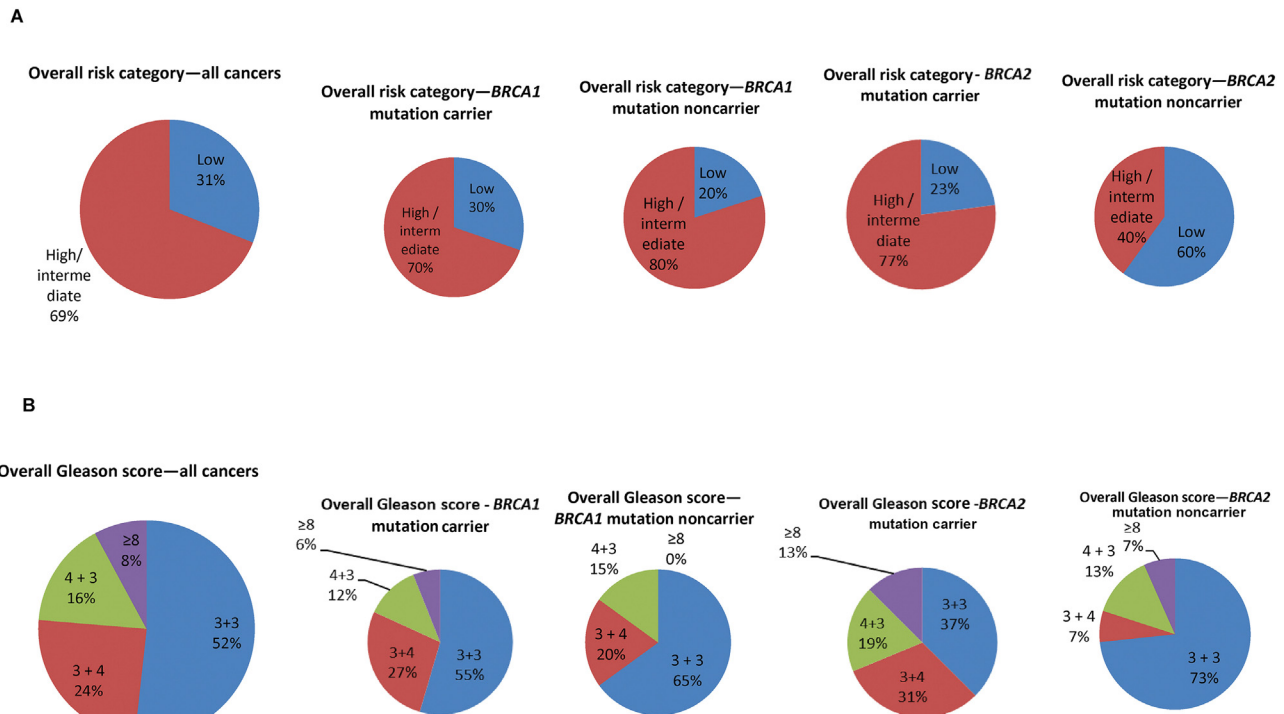
Fig. 3 – (A) Pie charts showing the overall prostate cancer risk category (as defined by the NICE guidelines—www.nice.org.uk: low: PSA < 10 and Gleason ≤6 and T1/T2a; intermediate: PSA 10–20 or Gleason 7 or T2b; and high: PSA > 20 or Gleason 8–10 or ≥ T2c), for all study PSA-detected cancers in screening rounds 1–4 and broken down by genetic status. (B) Pie charts showing the overall Gleason score, for all study PSA-detected cancers in screening rounds 1–4 and broken down by genetic status.
NICE = National Institute for Health and Care Excellence; PSA = prostate-specific-antigen.

reported, no significant differences were detected between *BRCA1* carriers and noncarriers [19].

After four screening rounds, *BRCA2* carriers have a statistically significantly higher cancer incidence rate (19) per 1000 person years compared with noncarriers (12; *p* = 0.03). With a higher number of cancers detected than reported previously [22], we have confirmed that *BRCA*2 carriers are diagnosed at a younger age (*p* = 0.044) than *BRCA*2 noncarriers and that a significantly greater proportion of cancers were intermediate- or high-risk disease (*p* = 0.011). Overall, 77% of cancers diagnosed in *BRCA*2 carriers were clinically significant, compared with 49% in the general population [11]. The youngest age of diagnosis of clinically significant disease was 41 yr for *BRCA*2 carriers and 43 yr for *BRCA*1 carriers, which may suggest screening from an early age. Regarding the number of men needed to screen to detect one clinically significant PrCa after four screening rounds, screening 60 *BRCA*2 carriers aged 40–54 yr and 13 carriers aged 55–69 yr will detect one clinically significant PrCa, respectively. Eventually, long-term follow-up data on the clinical benefit of early detection are needed to determine the best starting age.

Analyses of the cancer detection rates, PPV, and characteristics were repeated excluding prevalent cancers (PrCa diagnosed within 12 mo of baseline PSA). It was found that whilst not statistically significant, there was greater PrCa incidence in *BRCA*2 carriers than in noncarriers (9.1 vs 6.4), and substantially higher numbers of intermediate- and

high-risk cancers were detected in *BRCA*2 carriers than in noncarriers (*p* = 0.074). Owing to the relatively small number of cancers diagnosed in the *BRCA*2 noncarriers, we also re-ran these analyses combining the two noncarrier control groups, and statistically significant differences in tumour characteristics remained. In addition, clinically significant cancers were diagnosed at every screening round, supporting the use of systematic PSA screening. After 3 yr of follow-up, it is possible that disease was present, but not detectable by PSA, at study entry. A further aim of the IMPACT study is to offer PB to all men after five screening rounds, to evaluate the utility of a baseline biopsy irrespective of the PSA level with respect to cancer prevalence and tumour characteristics. However, it is reassuring to see from the data presented that using a cut-off of 3 ng/ml, the majority of the tumours detected were at an early stage.

No statistically significant differences were detected in age of onset or cancer characteristics between *BRCA*1 carriers and noncarriers. Further follow-up is required to conclude the clinical management of *BRCA*1 carriers.

Similar to our report for the IMPACT baseline screen [22], the ProtecT score using the 4 K panel (Supplementary material) was able to predict PB outcome, with a discrimination of 0.73 for high-grade disease. This adds further evidence to support the use of additional biological markers, such as the 4 K panel in improving the detection of clinically significant PrCa.

4.1. Limitations

A limitation of IMPACT is that not all men comply with the study protocol, and therefore cancers may be missed either in men who refuse PB, or in men who are advised locally to have MRI or repeat PSA instead of a PB. Genetic status may play a role in protocol compliance with fewer noncarriers, particularly *BRCA2* noncarriers, proceeding with a PB (73% vs 60%). This differential biopsy rate is likely to have underestimated the PrCa incidence in both *BRCA2* carriers and noncarriers. Complete data would be expected to strengthen the power to detect the difference in clinically significant disease between these groups. As follow-up will continue for a further 5 yr, these data will become available as part of future analyses. The higher observed biopsy rate within *BRCA2* carriers could represent variation in how health professionals counsel men with high PSA levels, with a bias towards encouraging biopsy in *BRCA2* carriers. Of note, no variation was seen between the number of cores taken at biopsy and mutation status. Variation was observed between sites and across the course of the study as the protocol increased from 10 to 12 biopsy cores as standard practice changed.

Given the rarity of *BRCA1/2* mutations, it was not possible to restrict the protocol to those with no prior urinary symptoms or PSA testing. Those with a prior PB were excluded. There was no difference in cancer incidence rates in those with symptoms or prior PSA testing.

In comparing with the Göteborg cohort, we acknowledge that this general population cohort is not stratified for *BRCA* status; however, the population frequency of *BRCA1/2* mutations is low. This study also used biennial rather than yearly PSA and was restricted to sextant PB, and therefore cancer detection rates at PB may be lower than that in IMPACT.

IMPACT started in 2005, prior to the implementation of multiparametric MRI in PrCa screening [17,18]. Without a systematic evaluation of the use of MRI in men at genetically high risk, it is difficult to extrapolate general population data to this setting and needs further research.

The Dutch protocol, as outlined above, screened men every 2 yr, and also included digital rectal examination and PCA3 in the algorithm of whether to proceed to biopsy or not. Therefore, some men with PSA < 3.0 ng/ml were biopsied, some of whom were diagnosed with cancer. However, despite this differing protocol in this cohort, sensitivity analyses excluding the Dutch data demonstrate that this approach did not affect the overall results.

A challenge of a longitudinal study such as IMPACT is in balancing the standardisation of procedures and changes in practice. For example, there have been changes in PB during the course of this study; the protocol has been updated to increase the number of diagnostic cores from 10 to 12 during the study's duration. Some centres have used the transperineal approach in line with local practice guidelines.

5. Conclusions

We demonstrate that, after four annual PSA screening rounds, *BRCA2* mutation carriers have a higher incidence of PrCa, are diagnosed at a younger age, and present with more clinically significant tumours than *BRCA2* noncarriers. Further follow-up is required to assess the role of screening in *BRCA1* mutation carriers. Therefore, these data support the use of systematic PSA screening in male *BRCA2* carriers.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.eururo.2019.08.019.

References

[1] Breast Cancer Linkage Consortium. Cancer risks in BRCA2 mutation carriers. J Natl Cancer Inst 1999;91:1310–6.

[2] 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.

[3] 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.

[4] 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.

[5] 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 (Phila) 2011;4:1002–10.

[6] 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.

[7] Taylor RA, Fraser M, Livingstone J, et al. Germline BRCA2 mutations drive prostate cancers with distinct evolutionary trajectories. Nat Commun 2017;8:13671.

[8] Leongamornlert D, Mahmud N, Tymrakiewicz M, et al. Germline BRCA1 mutations increase prostate cancer risk. Br J Cancer 2012;106:1697–701.

[9] 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.

[10] Pinsky PF, Yu K, Kramer BS, et al. Extended mortality results for ovarian cancer screening in the PLCO trial with median 15 years follow-up. Gynecol Oncol 2016;143:270–5.

[11] Schroder FH, Hugosson J, Roobol MJ, et al. Screening and prostate cancer mortality: results of the European Randomised Study of Screening for Prostate Cancer (ERSPC) at 13 years of follow-up. Lancet 2014;384:2027–35.

[12] Martin RM, Donovan JL, Turner EL, et al. Effect of a low-intensity PSA-based screening intervention on prostate cancer mortality: the CAP randomized clinical trial. JAMA 2018;319:883–95.

[13] Assel M, Sjoblom L, Murtola TJ, et al. A four-kallikrein panel and beta-microseminoprotein in predicting high-grade prostate cancer on biopsy: an independent replication from the Finnish section of the European Randomized Study of Screening for Prostate Cancer. Eur Urol Focus 2017. http://dx.doi.org/10.1016/j.euf.2017.11.002.

[14] Kim EH, Andriole GL, Crawford ED, et al. Detection of high grade prostate cancer among PLCO participants using a prespecified 4-kallikrein marker panel. J Urol 2017;197:1041–7.

[15] Poyet C, Nieboer D, Bhindi B, et al. Prostate cancer risk prediction using the novel versions of the European Randomised Study for Screening of Prostate Cancer (ERSPC) and Prostate Cancer Prevention Trial (PCPT) risk calculators: independent validation and comparison in a contemporary European cohort. BJU Int 2016;117:401–8.

[16] Verbeek JFM, Bangma CH, Kweldam CF, et al. Reducing unnecessary biopsies while detecting clinically significant prostate cancer including cribriform growth with the ERSPC Rotterdam risk calculator and 4Kscore. Urol Oncol 2019;37:138–44.

[17] Brown LC, Ahmed HU, Faria R, et al. Multiparametric MRI to improve detection of prostate cancer compared with transrectal ultrasound-guided prostate biopsy alone: the PROMIS study. Health Technol Assess 2018;22:1–176.

[18] Johnston E, Pye H, Bonet-Carne E, et al. INNOVATE: a prospective cohort study combining serum and urinary biomarkers with novel diffusion-weighted magnetic resonance imaging for the prediction and characterization of prostate cancer. BMC Cancer 2016;16:816.

[19] Eklund M, Nordstrom T, Aly M, et al. The Stockholm-3 (STHLM3) model can improve prostate cancer diagnostics in men aged 50–69 yr compared with current prostate cancer testing. Eur Urol Focus 2018;4:707–10.

[20] Lecarpentier J, Silvestri V, Kuchenbaecker KB, et al. Prediction of breast and prostate cancer risks in male BRCA1 and BRCA2 mutation carriers using polygenic risk scores. J Clin Oncol 2017;35:2240–50.

[21] National Institute for Health and Care Excellence. Prostate cancer: diagnosis and management, NICE guideline, NG. 131. https://www.nice.org.uk/guidance/ng131.

[22] Bancroft EK, Page EC, Castro E, et al. Targeted prostate cancer screening in BRCA1 and BRCA2 mutation carriers: results from the initial screening round of the IMPACT study. Eur Urol 2014;66:489–99.

[23] Mikropoulos C, Hutten Selkirk CG, Saya S, et al. Prostate-specific antigen velocity in a prospective prostate cancer screening study of men with genetic predisposition. Br J Cancer 2018;118:e17.

[24] Carter HB, Helfand B, Mamawala M, et al. Germline mutations in ATM and BRCA1/2 are associated with grade reclassification in men on active surveillance for prostate cancer. Eur Urol 2019;75:743–9.

[25] Epstein JI, Egevad L, Amin MB, et al. The 2014 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason grading of prostatic carcinoma: definition of grading patterns and proposal for a new grading system. Am J Surg Pathol 2016;40:244–52.

[26] Daly MB, Pilarski R, Berry M, et al. NCCN guidelines insights: genetic/familial high-risk assessment: breast and ovarian, version 2.2017. J Natl Compr Canc Netw 2017;15:9–20.

[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] Ehdaie B, Poon BY, Sjoberg DD, et al. Variation in serum prostate-specific antigen levels in men with prostate cancer managed with active surveillance. BJU Int 2016;118:535–40.

[30] Hugosson J, Godtman RA, Carlsson SV, et al. Eighteen-year follow-up of the Goteborg Randomized Population-based Prostate Cancer Screening Trial: effect of sociodemographic variables on participation, prostate cancer incidence and mortality. Scand J Urol 2018;52:27–37.

[31] Hugosson J, Carlsson S, Aus G, et al. Mortality results from the Goteborg randomised population-based prostate-cancer screening trial. Lancet Oncol 2010;11:725–32.