

A review of targeted screening for prostate cancer: introducing the IMPACT Study

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INTRODUCTION

Changing public attitudes towards screening for prostate cancer are evident by the increase in *ad hoc* PSA testing. This is occurring despite the inability to reliably distinguish aggressive from indolent prostate cancer. The mean age of the onset of prostate cancer in the general population is in the eighth decade, when comorbidity is significant. This has to be considered when balancing reductions in life-expectancy from aggressive vs indolent prostate cancer.

Treating early-onset aggressive disease would intuitively be thought to reduce mortality and morbidity. There have been various measures assessed to attempt to differentiate aggressive from indolent disease. These include Gleason score, volume of disease, PSA density, velocity and free : total PSA ratio. Although these are promising methods, further research is needed to define optimum levels and some of these measures do not lend themselves easily to a national screening programme.

A different approach to aim to reduce mortality and morbidity from the disease in men with prostate cancer might lie in targeted screening. There are subsets of men who have a greater incidence of prostate cancer and perhaps more aggressive disease than that found in the general population. They include men of Afro-Caribbean ancestry and in some (but not all reports), those with a family history of prostate cancer. This has been noted over many years. More recently, it appears that men with *BRCA1* and 2 mutations are also at greater risk of prostate cancer. These men might also develop disease when younger, and when curative treatment

is more likely to be recommended, as comorbidity is less relevant.

The scope of this review does not cover those men with Afro-Caribbean ancestry; it focuses instead on studies primarily of men with a positive family history. We aim to give a brief overview of current screening practices and highlight the genetic evidence for prostate cancer. A review of targeted screening practices leads to an introduction of our study, the *Identification of Men with a genetic predisposition to Prostate Cancer: Targeted screening for BRCA1 and BRCA2 carriers and controls*; the IMPACT study. This is the first international study to target PSA screening based upon *known* genotype.

A pilot study to lead into the main IMPACT study is now recruiting at the Royal Marsden Hospital NHS Foundation Trust, St Mary's Hospital, Manchester, The Princess Anne Hospital, Southampton and Addenbrooke's Hospital, Cambridge. Recruitment will be extended into international centres in the coming months if the pilot continues to accrue men at its current rapid rate. If the model of this study proves to be beneficial over the coming years, it will enable the study of targeted prostate cancer screening in carriers of mutations in other candidate prostate cancer genes. Genetic heterogeneity is known to occur in genetic predisposition to prostate cancer and it is likely that several prostate cancer predisposition genes will be identified in the next few years.

SCREENING IN THE GENERAL POPULATION

There are no formal screening recommendations for the early detection of prostate cancer in the UK. Men can ask their GP for a PSA test after reading the Department of Health PSA screening leaflet, which describes the pros and cons of the PSA test. The Cancer Genetics Unit of the Royal Marsden NHS Foundation Trust screens men

with a serum PSA test if they have a strong family history of prostate cancer, are men of Afro-Caribbean descent and those with *BRCA1* or 2 mutations, from the age of 40 years. In the USA, the American Cancer Society and AUA currently recommend offering screening for men beginning at age 50 years. Both organizations recommend offering earlier screening for men considered at high-risk, i.e. of African-American heritage or who have a family history of prostate cancer.

Three international screening trials of the general population are underway. The Prostate, Lung, Colorectal and Ovary Screening Trial in the USA (PLCO), the European Randomised Screening for Prostate Cancer (ERSPC) study and the UK study, ProtecT [1–3]. Whether mortality is reduced will take many years to establish, but it is clear from these studies that asymptomatic prostate cancer is detected at an earlier stage, when curative treatment is more likely to be successful [4].

Several issues have yet to be resolved in this area. The frequency of PSA screening is unclear. Catalona *et al.* [5] argued for annual PSA testing, as the PSA velocity can then be established and used as a surrogate marker for disease aggression. However, Crawford *et al.* [6], using results from the PLCO study, suggested screening every 5 years for those who had a baseline PSA of <1 ng/mL and every 2 years for a baseline PSA of 1–2 ng/mL. This, they argued, could result in halving the number of PSA tests and in <1.5% of men missing earlier positive screens. The ERSPC is currently using a screening interval of 4 years, with the first PSA test in the first year and the second at 4 years [2].

The PSA threshold that is used to trigger a prostate biopsy is also much debated. The ERSPC reduced the threshold level from 4 to 3 ng/mL (without using a DRE), resulting in an improvement in the positive predictive value

from 18.2% to 24.3% [7]. The Prostate Cancer Prevention Trial in the USA detected prostate cancer in 15.2% of men who had total PSA levels of <4 ng/mL [8]. This has led some to suggest that a PSA threshold as low as 2.5 ng/mL should be used as the indication for prostatic biopsy in men being screened in the USA [5].

The IMPACT study will use a PSA threshold of 3 ng/mL, offering a prostate biopsy to any man who has a level higher than this, in line with the ERSPC. Annual PSA testing is offered to men with germline mutations in the *BRCA1* or *BRCA2* genes, as we anticipate a higher incidence of young-onset prostate cancer in this targeted group. It also enables the PSA velocity to be assessed in these men, to assess whether it can be used as a surrogate marker for aggressive disease.

GENETIC PREDISPOSITION TO PROSTATE CANCER

Concordance of prostate cancer risk is four times greater between monozygotic than dizygotic twins [9]. Men with a family history (FH) of prostate cancer have a greater risk, which increases the younger the proband, the more cases in the family, the lower the average age of onset, and with any combination of these factors [10]. Bruner *et al.* [11] reported a relative risk of developing prostate cancer of 2.9 with an affected brother, and 1.8–2.1 with an affected father. Segregation analyses suggested the presence of at least one high-risk gene [12–14]. Linkage and other molecular analyses which assess the co-segregation of the disease with genetic markers have implicated that many genes might be involved in the inheritance of prostate cancer. As these genes are identified as 'prostate cancer predisposition' genes, IMPACT will incorporate them into an existing framework which currently assesses men who are carriers of mutations in *BRCA1* and 2.

Within families there is an association of breast with prostate cancer. Male relatives of women with breast cancer in Iceland have a two to three times greater risk of prostate cancer [15]. The results from the Breast Cancer Linkage Consortium show a relative risk of prostate cancer of 4.65 in male *BRCA2* mutation carriers and 1.07 (1.85 if aged <65 years) in *BRCA1* mutation carriers [16,17]. The strength of this group's findings is in the many patients in their study; >3000

BRCA2 mutation carriers and >11 000 *BRCA1* mutation carriers. Despite this, the exact prostate cancer risk from mutations in *BRCA1* and *BRCA2* remains uncertain. There are data from the Ashkenazi Jewish population (whose founder mutations are 185delAG and 5382insC in *BRCA1* and 6174delT in *BRCA2*) that do not show a greater risk of prostate cancer in this cohort [18–21]. One of the largest studies of the Israeli population showed a greater risk of prostate cancer only when both *BRCA1* and *BRCA2* mutations carriers were combined; however, separately there was no difference [22]. The specific penetrance of cancer differs among populations, within populations and among individuals. There are several potential sources of variation. Allelic variation is due to different mutations of a single gene, e.g. the position of *BRCA* within a coding region of the gene can influence the risk of breast and ovarian cancer. It might be that the specific founder mutations of the Ashkenazi Jews do not confer any greater risk of prostate cancer but other *BRCA1* and 2 mutation carriers do.

Our group has found that 2% of men, pooled from the UK population, who were diagnosed with prostate cancer when young (<55 years) had deleterious germline mutations in *BRCA2* (2558insA, 6710del4, 7084del5, 7772insA, 8525delC, IVS17–1G > C). This equates to a relative risk of prostate cancer of up to 23 times by the age of 60 years, which confers an absolute prostate cancer risk of 10% by this age [23]. That these men present with disease of poor prognosis and when young at onset is supported by previous studies [15,24].

TARGETED SCREENING

Relatively few studies have assessed the value of targeted screening in high-risk populations, but of the 10 published, nine support its use. The first screening study conducted in 1992 recruited 34 men aged 55–80 years and who had two first-degree relatives (FDRs) with prostate cancer [25]. All men had prostate biopsies and 24% had a subsequent diagnosis of prostate cancer. This was a higher incidence of prostate cancer than in the general population. However, population screening studies generally do not take a biopsy from all participants, making it difficult to reliably compare these groups. The lack of an adequate control group and the few patients assessed are significant criticisms of that study.

Narod *et al.* [26] conducted a screening study using PSA levels and a DRE in 6390 men aged 50–80 years, and defined as at high risk by virtue of having one FDR or second DR (SDR) with prostate cancer. If the PSA level was >3 ng/mL or the DRE abnormal, TRUS was offered. Only hypoechoic lesions and areas corresponding to palpable abnormalities were biopsied. This might be considered a weakness of the study, as only half of those men who had TRUS were biopsied. It is not stated how many men had a raised PSA level and were not biopsied, or how many with a PSA level of >3 ng/mL developed prostate cancer. The FH of prostate cancer was reported via questionnaires in 10.3% (FDRs 8.8%; SDRs 1.9%) of men, so these data would have been subject to recall bias. Prostate cancer was detected 2.62 times more often in men with a brother with prostate cancer. The authors also showed that the positive predictive value of the PSA level was higher in men with prostate cancer in a FDR.

Matikainen *et al.* [27] screened 209 unaffected men aged 45–75 years and with two or more FDRs or SDRs affected by prostate cancer; 10% of the screened group had a raised PSA level. Age-specific reference values of PSA were used as thresholds for biopsy. The elevated values were 2.6–28.3 ng/mL; 3.3% had prostate cancer (mean age 65 years), and 1% had prostatic intraepithelial neoplasia. Only one had prostate cancer at an advanced stage, and 43% of cancers were in men aged <60 years. The frequencies of a raised PSA level (28.6%) and sub-clinical cancer (14.3%) were significantly higher in men from families with a mean age of onset of <60 years. That study had no control group and there were few men, but a prostate cancer diagnosis was 21 times higher than expected from age-adjusted rates in the Finnish population.

Makinen *et al.* [28] screened 30 403 men using the serum PSA level and offered biopsy if it was >4 ng/mL. FH questionnaires were given to participants, although there was no verification. A positive FH was defined in that study as one or more FDRs with prostate cancer. In all, 964 men had a positive FH and 11% of these men had a raised PSA level; 3% were diagnosed with prostate cancer. In men with no FH, 8% had a raised PSA level and 2.4% had prostate cancer; this was not a statistically significant difference. The authors therefore concluded that the cause of prostate cancer is not understood sufficiently to enable

identification of a high-risk group. This was the first study to have a control group.

A study by Valeri *et al.* [29] supported the use of targeted PSA screening in men from high-risk families; 691 cases were divided into those with one FDR (sporadic) and those with two or more FDRs (familial) with prostate cancer. FHs were verified and the PSA threshold was 4 ng/mL. There was no difference between the groups overall, but the prostate cancer detection rate was higher in men with a FDR with early-onset prostate cancer (<65 years old). This finding has been echoed in other studies [15,24,28,30]. Of the 10 prostate cancers identified in the study of Valeri *et al.*, most were moderately differentiated and all were clinically localized; again the study was limited by including relatively few cases.

A 10-year longitudinal screening study compared 1224 men of African ancestry, 1227 men with a positive FH and 63 men who had both a positive FH and African ancestry, with 15 964 control men without either African ancestry or FH [31]. In men aged ≥ 50 years, the prostate cancer detection rate was 6.4% for the controls and 10.3%, 10.5% and 17.5%, respectively, for the three high-risk groups. The definition of a positive FH was not provided and PSA threshold for biopsy changed during the study from 4 to 2.5 ng/mL. An abnormal DRE with no raised PSA level was also an indication for biopsy; FHs were verified. The study also screened a group of men aged 40–49 years, but there was no control group and there were few men. The authors concluded that men with both a positive FH and African ancestry had a higher risk of prostate cancer; 75–80% (less than twice) higher than in the general population.

The Fox Chase Cancer Center screened 310 men, aged 35–69 years, who were Caucasian and with at least one FDR with prostate cancer, or African-American with or without a FH of prostate cancer, men with two or more SDRs, and men with *BRCA1* gene mutations (*BRCA2* carriers were not commented upon) [32]. The free : total PSA level was used (if <27%, biopsy was recommended) to detect prostate cancer in men with total PSA levels of 2–4 ng/mL. Twenty-three men met these criteria and agreed to have prostate biopsies; prostate cancer was diagnosed in 52%. The study had no control group; the results were compared with those from other studies, where the cancer detection rate was 19–44%

in unselected men with PSA levels of 2.6–4.0 ng/mL. The authors recommended that high-risk populations should be screened and that those with PSA levels of 2–4 ng/mL should have their free : total PSA measured.

Studies of targeted screening are sparse and limited by variable definitions of a positive FH, variable PSA thresholds at which biopsy is recommended, a variable acceptance rate of biopsy and often no control group. Despite this, there seems to be consistent evidence of cohorts of men at higher risk of prostate cancer and which can be detected at an early stage (when curative treatment is more likely to be successful) using PSA screening.

Germline mutations in *BRCA2* provide the first convincing evidence of a gene predisposing to a high risk of prostate cancer. In the first study of its kind, Horsburgh *et al.* [33] compared 19 men, i.e. 12 with *BRCA1* and seven with *BRCA2*, with a control group with a FH of prostate cancer in at least one FDR. A positive FH of prostate cancer was reported in three *BRCA1* and two *BRCA2* families. The control group was not tested for *BRCA* status. The PSA threshold for biopsy was 4 ng/mL. Mutation carriers were significantly more likely to have an high PSA level at the first visit. Two mutation carriers were found to have prostate cancer, one aged 58 and one aged 65 years. In the control group only one prostate cancer was diagnosed, in a man aged 54 years; the difference was not statistically significant. This study is limited by the very few samples and the control group was not known to be negative for *BRCA* mutations. Most of the carriers had *BRCA1* mutations. *BRCA1* carriers have only a slightly greater relative risk, of 1.07 overall (1.8 for men aged <65 years) of developing prostate cancer than in the general population [17,23]. A FH also confers a greater risk of developing the disease and this might be related to different, as yet undiscovered, genes. On balance, it seems unlikely that there were sufficient samples in the study to detect a meaningful difference in the two groups. However, the median age of cancer diagnosis is much less than that in the general population, and further research on larger cohorts was recommended by the authors. The IMPACT study forms one such cohort.

THE IMPACT STUDY

An international collaboration among 39 worldwide centres aims to investigate the role

of *BRCA1* and *BRCA2* germline mutations in the development of prostate cancer, and the sensitivity and specificity of targeted PSA screening in this group. The largest study of its kind, IMPACT aims to recruit 500 men with identified germline *BRCA1* mutations and 350 with *BRCA2* mutations. They will be unaffected by prostate cancer and aged 40–69 years. The ERSPC and ProtecT studies will provide population-based control groups. In addition, 850 men aged 40–69 years who have tested negative for a known pathogenic familial mutation in *BRCA1/2* will be recruited, to provide a carefully matched control group for the targeted screening and biomarker analysis.

The PSA level will be measured annually in both *BRCA1* and *BRCA2* mutation carriers and in the control group. PSA levels will be measured at the local centre and analysed at a central reference laboratory, to ensure standardization and quality assurance. As PSA level is age-dependent, the results from the male mutation carriers will be compared with age-matched controls from the ERSPC study in Europe and the ProtecT PSA population-screening study in the UK. All men with a PSA level of >3.0 ng/mL will be offered a diagnostic 10-core prostatic biopsy (with a further two cores for research, if consent is given). Those men whose first biopsy detects high-grade prostatic intraepithelial neoplasia will be re-biopsied after 6 weeks (as per the ERSPC protocol). Those men with a negative biopsy will return to annual screening and the biopsy will not be repeated until a the PSA doubling time is >50%. Men with a positive biopsy will be referred to their local urologist for treatment according to local policy.

The aims of IMPACT are as follows: (i) to establish an international targeted prostate cancer-screening study in *BRCA1* and *BRCA2* germline mutation carriers; (ii) to determine the incidence of a raised PSA level and abnormal biopsy as a result of annual PSA screening in this group; (iii) to determine if the incidence of a raised PSA level and pathology differs from screen-detected disease in controls; (iv) to determine the sensitivity, specificity and positive predictive value of PSA screening for prostate cancer in *BRCA1/2* germline mutation carriers; and (v) to evaluate new markers of early prostate cancer (e.g. HK2, new markers from proteomics from prostate cancer cases) in *BRCA1/2* germline mutation carriers.

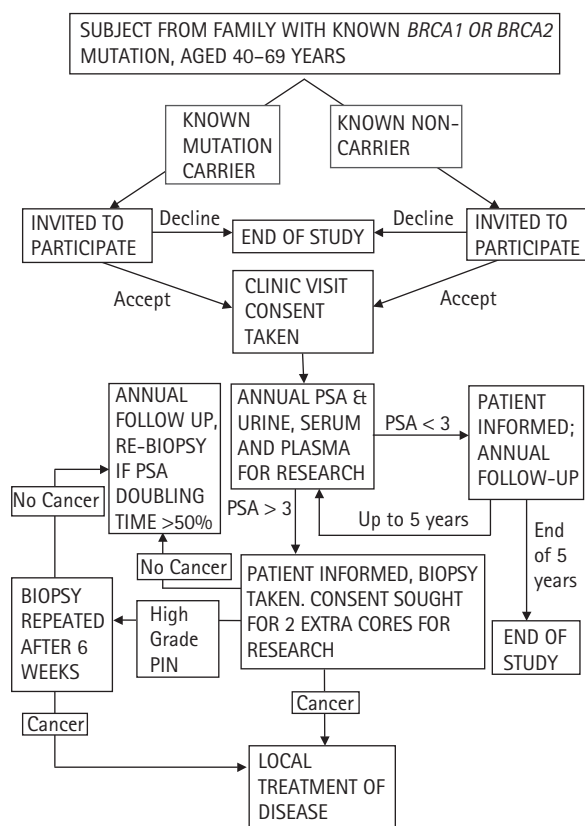


FIG. 1. A flowchart showing the patient pathway during the IMPACT study.

There will be the potential for investigating new prostate cancer predisposition genes or new biomarkers in this population. Whole blood, lymphocytes, serum, plasma, urine and prostate tissue specimens are being collected for further study using proteomic, metabolomic and microarray approaches. The flow of patients through the study is shown in Fig. 1.

CONCLUSION

Screening the general population for prostate cancer has not yet shown a convincing reduction in mortality, but trials are ongoing. Screening can be targeted to a group of men who have a higher incidence of disease, by identifying an at-risk genotype. Such disease occurs when younger at onset and therefore curative treatment is more likely to be offered.

IMPACT is the largest international screening study of men with a known genetic predisposition to prostate cancer. Male mutations carriers of *BRCA1* and *BRCA2* genes are currently being recruited. To date, *BRCA2* and to a lesser extent *BRCA1* mutations are among the genes with the strongest association with a greater risk of

prostate cancer. It is apparent that these are not the only genes implicated in this disease, and as research reveals other prostate cancer predisposition gene mutations, IMPACT will provide an essential framework for targeted screening in these men. For further information about the IMPACT study, please visit www.impact-study.co.uk.

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CONFLICT OF INTEREST

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Abbreviations: PLCO, Prostate, Lung, Colorectal and Ovary Screening Trial; ERSPC, European Randomised Screening for Prostate Cancer; FH, family history; F(S)DR, first (second)-degree relative.

APPENDIX

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