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Original article

The role of the prostate cancer gene 3 urine test in addition to serum prostate-specific antigen level in prostate cancer screening among breast cancer, early-onset gene mutation carriers

Ruben G. Cremers, M.D.[a], Rosalind A. Eeles, M.D., Ph.D.[b,c], Elizabeth K. Bancroft, Ph.D.[b,c], Janneke Ringelberg-Borsboom, M.Sc.[d], Hans F. Vasen, M.D., Ph.D.[d], Christi J. Van Asperen, M.D., Ph.D.[e], The IMPACT Steering Committee[1], Jack A. Schalken, Ph.D.[f], Gerald W. Verhaegh, Ph.D.[f], Lambertus A. Kiemeney, Ph.D.[a,*]

[a] *Radboud Institute for Health Sciences, Radboud University Medical Center, Nijmegen, the Netherlands*
[b] *The Institute of Cancer Research, London, UK*
[c] *Royal Marsden Hospital NHS Foundation Trust, London, UK*
[d] *The Netherlands Foundation for the Detection of Hereditary Tumours, Leiden, the Netherlands*
[e] *Department of Clinical Genetics, Leiden University Medical Centre, Leiden, the Netherlands*
[f] *Radboud Institute for Molecular Life Sciences, Radboud University Medical Center, Nijmegen, the Netherlands*

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Abstract

Objective: To evaluate the additive value of the prostate cancer gene 3 (PCA3) urine test to serum prostate-specific antigen (PSA) in prostate cancer (PC) screening among breast cancer, early-onset gene (*BRCA*) mutation carriers. This study was performed among the Dutch participants of IMPACT, a large international study on the effectiveness of PSA screening among *BRCA* mutation carriers.

Materials and methods: Urinary PCA3 was measured in 191 *BRCA1* mutation carriers, 75 *BRCA2* mutation carriers, and 308 noncarriers. The physicians and participants were blinded for the results. Serum PSA level ≥3.0 ng/ml was used to indicate prostate biopsies. PCA3 was evaluated (1) as an independent indicator for prostate biopsies and (2) as an indicator for prostate biopsies among men with an elevated PSA level. PC detected up to the 2-year screening was used as gold standard as end-of-study biopsies were not performed.

Results: Overall, 23 PCs were diagnosed, 20 of which were in men who had an elevated PSA level in the initial screening round. (1) PCA3, successfully determined in 552 participants, was elevated in 188 (cutoff ≥25; 34%) or 134 (cutoff ≥35; 24%) participants, including 2 of the 3 PCs missed by PSA. PCA3 would have added 157 (≥25; 28%) or 109 (≥35; 20%) biopsy sessions to screening with PSA only. (2) Elevated PCA3 as a requirement for biopsies in addition to PSA would have saved 37 (cutoff ≥25) or 43 (cutoff ≥35) of the 68 biopsy sessions, and 7 or 11 PCs would have been missed, respectively, including multiple high-risk PCs. So far, PCA3 performed best among *BRCA2* mutation carriers, but the numbers are still small. Because PCA3 was not used to indicate prostate biopsies, its true diagnostic value cannot be calculated.

Conclusions: The results do not provide evidence for PCA3 as a useful additional indicator of prostate biopsies in *BRCA* mutation carriers, as many participants had an elevated PCA3 in the absence of PC. This must be interpreted with caution because PCA3 was not used to indicate biopsies. Many participants diagnosed with PC had low PCA3, making it invalid as a restrictive marker for prostate biopsies in

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[1] A complete list of the members of the IMPACT Steering Committee is available in Appendix A.

* Corresponding author. Tel.: +3-124-361-9630; fax: +3-124 -361-3505.
E-mail address: Bart.Kiemeney@radboudumc.nl (L.A. Kiemeney).

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men with elevated PSA levels.

Keywords: PSA; prostate cancer gene 3; PCA3; BRCA2; marker; diagnostic value

1. Introduction

Prostate cancer (PC) is the most frequently diagnosed cancer in men in the Western world [1]. Serum prostate-specific antigen (PSA) testing is the only commonly used biomarker for PC, but its low specificity has led to a consensus not to implement population-wide screening [2,3]. Possibly, the advantages of screening may outweigh the disadvantages for groups with an increased risk of PC. It has been suggested that carriers of a pathogenic mutation in one of the "breast cancer, early-onset" genes (*BRCA1* or *BRCA2*) have an increased risk of PC [4,5]. Particularly, *BRCA2* mutation carriers might present with PC at a younger age, more aggressive disease, and shorter survival [6–10]. To evaluate the effectiveness of PSA screening in *BRCA* mutation carriers, an international study was initiated, entitled "IMPACT: Identification of Men with a genetic predisposition to ProstAte Cancer: Targeted screening in BRCA1/2 mutation carriers and controls" (www.impact-study.co.uk). The results of IMPACT's first screening round have already been published. These preliminary results support PSA screening among *BRCA2* mutation carriers [11,12].

The large number of false-positive results on PSA tests, particularly in the range of 3 to 10 ng/ml, has prompted ongoing research into new (bio)markers to improve PC diagnosis. One of the promising biomarkers, prostate cancer gene 3 (*PCA3*), was discovered in 1999 as a gene that is strongly up-regulated in PC [13]. Based on the prostate-specific and cancer-associated expression of PCA3, the PROGENSA urine-based test was developed. Previous multicenter studies suggested that its specificity and sensitivity were significantly higher than those of evaluation of serum PSA levels [14–16]. PCA3 is currently used as a biomarker to determine the need for repeat biopsies when PSA level remains elevated after prostate biopsies with negative results. We aimed to determine the potential role of PCA3 in addition to PSA testing in this high-risk group by performing a substudy among the Dutch participants of IMPACT.

2. Materials and methods

Men who were eligible for IMPACT, i.e., *BRCA* mutation carriers and their relatives who were proven noncarriers, were identified and contacted by the 10 Dutch Clinical Genetic Centres. All eligible men received an invitation by mail, including a detailed patient information leaflet describing IMPACT and the Dutch substudy (IMPACT-NL). The IMPACT protocol has been described in detail elsewhere [17]. Owing to restrictions set by the Dutch Minister of Health (the Dutch "Law on Screening" requires all cancer screening projects to obtain ministerial approval), the IMPACT-NL protocol (Fig. 1) deviated from the IMPACT protocol: (1) the screening interval was once every 2 years instead of annually;

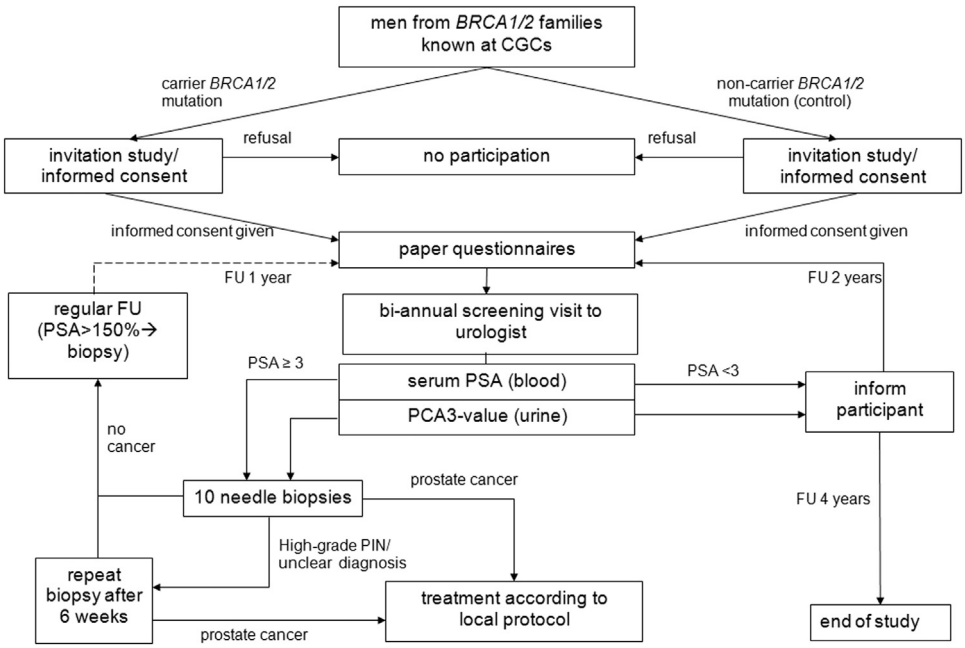

Fig. 1. The IMPACT screening protocol in the Netherlands adapted according to the ministerial approval. CGC = clinical genetic center; PIN = prostate intraepithelial neoplasia.