Prostate-specific antigen velocity in a prospective prostate cancer screening study of men with genetic predisposition

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Prostate-specific antigen velocity in a prospective prostate cancer screening study of men with genetic predisposition

Christos Mikropoulos¹ et al.

Background: Prostate-specific antigen (PSA) and PSA-velocity (PSAV) have been used to identify men at risk of prostate cancer (PrCa). The IMPACT study is evaluating PSA screening in men with a known genetic predisposition to PrCa due to BRCA1/2 mutations. This analysis evaluates the utility of PSA and PSAV for identifying PrCa and high-grade disease in this cohort.

Methods: PSAV was calculated using logistic regression to determine if PSA or PSAV predicted the result of prostate biopsy (PB) in men with elevated PSA values. Cox regression was used to determine whether PSA or PSAV predicted PSA elevation in men with low PSAs. Interaction terms were included in the models to determine whether BRCA status influenced the predictiveness of PSA or PSAV.

Results: 1634 participants had ³3 PSA readings of whom 174 underwent PB and 45 PrCas diagnosed. In men with PSA >3.0 ng ml⁻¹, PSAV was not significantly associated with presence of cancer or high-grade disease. PSAV did not add to PSA for predicting time to an elevated PSA. When comparing BRCA1/2 carriers to non-carriers, we found a significant interaction between BRCA status and last PSA before biopsy (P = 0.031) and BRCA2 status and PSAV (P = 0.024). However, PSAV was not predictive of biopsy outcome in BRCA2 carriers.

Conclusions: PSA is more strongly predictive of PrCa in BRCA carriers than non-carriers. We did not find evidence that PSAV aids decision-making for BRCA carriers over absolute PSA value alone.

Men with germline mutations in BRCA2 have an increased risk of prostate cancer (PrCa), estimated at 2.5–8.6 fold increased risk for BRCA2 mutation carriers (Breast Cancer Linkage Consortium, 1999; van Asperen et al, 2005; Kote-Jarai et al, 2011). There remains debate about whether there is an increased risk of PrCa associated with BRCA1 mutations, with some studies reporting no increased risk to those reporting a 1.8–3.75 fold increased risk (Thompson et al, 2002; Leongamornlert et al, 2012; Moran et al, 2012). A number of studies have reported that BRCA2 mutation carriers have more aggressive disease, suggested by their younger age at diagnosis, higher rates of lymph node involvement and distant metastasis at diagnosis, and higher mortality rates compared with non-carriers (Tryggvadottir et al, 2007; Mitra et al, 2008; Edwards et al, 2010; Gallagher et al, 2010; Thorne et al, 2011; Castro et al, 2013). There is increasing evidence that BRCA1 mutation carriers may also harbour more aggressive disease (Giusti et al, 2003; Gallagher et al, 2010; Castro et al, 2013). Furthermore, BRCA2-mutant localised prostate cancer demonstrates increased genomic instability and a mutational profile that more closely resembles metastatic than localised disease, therefore supporting early detection in this at risk patient population (Taylor et al, 2017).

General population prostate specific antigen (PSA) screening remains controversial due to an unclear balance of benefits, in terms of mortality reduction when compared to harms such as overdiagnosis and overtreatment. However, many expert groups continue to recommend PrCa screening with particular attention towards men with risk factors based on family history, genetics and/or race (Roobol et al, 2013; Eeles et al, 2014; Mikropoulos et al, 2014; Murphy et al, 2014).

It has previously been suggested that the rate of PSA change over time, or PSA velocity (PSAV), can be used to assist in differentiating between men with cancer from those with benign disease (Carter et al, 1992; Berger et al, 2005). Monitoring PSA...
over time could also improve the sensitivity of screening. It is also possible that PSAV could distinguish between men who might have advanced or aggressive disease that would require definitive treatment thus avoiding overdiagnosis and overtreatment (Carter et al, 2006; Carter et al, 2007).

However, the utility of PSAV in PrCa decision-making has been called into question. In particular, while PSAV may be predictive of biopsy outcome in univariate analyses, it has not been shown to improve the predictiveness of biopsy outcome over the absolute value of PSA (Roobol et al, 2004; Vickers et al, 2011; Loughlin, 2014). Although some studies have suggested that PSAV can be used to identify men with aggressive disease, these did not investigate whether calculation of PSAV provided additional information than the most recent PSA value (Carter et al, 1992; D’Amico et al, 2004; D’Amico et al, 2005). PSA and PSAV are highly correlated, and this may explain why PSAV does not add predictive value (Vickers et al, 2011). As a result of these considerations, PSAV has been removed from all major guidelines concerning the detection of prostate cancer.

It is currently unknown whether PSAV provides more information, beyond PSA absolute value, among a cohort of men considered to be at increased genetic risk of PrCa and aggressive disease. The IMPACT study (Identification of Men with a genetic predisposition to Prostate Cancer: Targeted screening in men at higher genetic risk and controls; www.impact-study.co.uk) is an international multi-centre study evaluating the role of targeted PSA screening in men with a BRCA1 or BRCA2 mutation and was established in 2005 (Bancroft et al, 2014). To date, ~3000 men have been recruited from 20 countries across the world. Men are followed up with annual (or biannual in the Dutch cohort) PSA screening for a minimum of 5 years within the study and this has produced a wealth of PSA results and follow-up data over time. The primary end-point of the IMPACT study is to determine the incidence, stage and pathology of screen-detected prostate cancer in the study population; a secondary end-point is to determine a profile of PSA level and its predictive value for the development of prostate cancer in the study population. The objective of the present study was to determine whether PSA values and/or PSAV were associated with PrCa and aggressive tumours among men at increased risk enrolled in the IMPACT trial.

MATERIALS AND METHODS

Patient selection. The design and eligibility criteria for the IMPACT study have been described elsewhere (Mitra et al, 2008; Bancroft et al, 2014). 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. Briefly, men aged between 40 and 69 were recruited from families with a known pathogenic germline BRCA1 or BRCA2 mutation. Men were invited to enrol if they had tested positive (carriers) or negative for the familial mutation (BRCA1/2 non-carriers), or if they were at 50% risk of inheriting a mutation but had not yet undergone predictive genetic testing. All participants provide written consent. Men with PrCa or with a prior diagnosis of another cancer with a prognosis of < 5 years were excluded. In the Dutch centres, men were also excluded if they had PSA screening prior to study entry.

According to the IMPACT study design, men underwent annual PSA screening and those with a PSA > 3.0 ng ml\(^{-1}\) were referred for a 10- or 12-core transrectal ultrasound guided (TRUS) biopsy based on institutional clinic practices. Men with a PSA > 3.0 ng/ml and a negative biopsy continue annual screening, with a repeat biopsy recommended when PSA increased by > 50%. Men were also referred for biopsy if they had a PSA ≤ 3.0 ng ml\(^{-1}\) but clinical suspicion (e.g., abnormal digital rectal examination or clinical symptoms). After 5 years in the study, men at a subset of centres were also offered an elective biopsy.

PSA readings in the study are validated in a central laboratory to exclude inter-site variations. The results found a Spearman’s agreement of 0.95 between study sites (Bancroft et al, 2014).

Statistical considerations. PSA velocity (PSAV) has been used as a marker to inform decisions about biopsy or about the timing of the next PSA screen. With respect to the former, we considered that a physician had the most recent PSA measurements available. Our study question was therefore whether adding PSAV to this data point improves prediction of presence of PrCa at biopsy. As elevated PSA is the primary indication in routine clinical practice, our main analysis was restricted to men who had any PSA ≥ 3.0 ng ml\(^{-1}\) prior to biopsy. A sensitivity analysis was conducted including all men who underwent biopsy. We created logistic regression models, adjusted for last PSA measurement and age, for the outcomes of any grade and high-grade cancer. PSAV was calculated using three methods: arithmetic equation of change in PSA over time; linear regression; rate of PSA change using first and last values only. We also used cubic splines with knots at the terciles to test for non-linearity in PSA and in PSAV.

To investigate whether the effect of PSAV on predicting biopsy outcome differed based on BRCA status, we included an interaction term between PSAV and BRCA status (BRCA1 or BRCA2 carriers vs BRCA non-carrier patients, and BRCA2 carriers vs BRCA1 and BRCA non-carrier patients). Due to a limited number of events, this analysis was performed only for the outcome of any cancer on biopsy. This analysis included 13 cancers diagnosed among 55 BRCA1 carriers and 23 cancers among 65 BRCA2 carriers.

To determine whether PSAV could aid decisions about screening frequency, e.g., whether a man with a high PSAV should receive a subsequent PSA test at a shorter interval than a man with a low PSAV, we assessed whether PSAV was associated with having a future PSA > 3.0 ng ml\(^{-1}\). As a minimum of three PSA measurements are required for accurate estimation of PSAV, we created Cox proportional hazards models for the time from the first PSA measurement to the patient’s third PSA measurement > 3.0 ng ml\(^{-1}\). Four models were then created: one including the third PSA measurement only, and the others including both the third PSA measurement and each of the three methodologies for calculating PSAV. Men who had a PSA > 3.0 ng ml\(^{-1}\) within the first three PSA measurements were excluded from this analysis. A total of 1086 men were included.

We planned to first evaluate the independent statistical significance of PSAV in models that also included absolute PSA level. If significant, we planned to estimate the improvement in concordance index afforded by PSAV after 10-fold cross-validation. All analyses were conducted using Stata 13.0 (Stata Corp., College Station, TX, USA).

RESULTS

Of the 2942 men recruited to the IMPACT study, 1654 men had three or more PSA measurements and appropriate clinical follow-up to be included in the analyses (Figure 1). Table 1 shows the demographic, PSA and biopsy grade characteristics of the analysis cohorts. The cohort of 1654 men consisted of 510 BRCA1 mutation carriers, 584 BRCA2 mutation carriers, 260 BRCA1 non-carriers and 288 BRCA2 non-carriers. Two men carried both a BRCA1 and BRCA2 mutation (included in the BRCA2 group for genetic sub-analysis) and 10 had not yet had a predictive test for the BRCA mutation in their family (excluded from genetic sub-analysis). In
this cohort, 174 men underwent prostate biopsy, with 45 men having any grade cancer of whom 21 having Gleason score 7 or higher (high-grade) cancer. Among men who had any PSA >3.0 ng ml \(^{-1}\), 40 had any grade of whom 20 had high-grade cancer. The median age at the first PSA reading of men diagnosed with cancer was higher than that of men without cancer (60 vs 53 years, respectively, \(P<0.0001\)). Overall, BRCA2 and BRCA1 carriers had significantly lower first PSA values than non-carriers (0.80 vs 0.80 vs 0.89 ng ml \(^{-1}\); \(P=0.022\); however, overall there was no statistically significant difference in the median PSAV between the BRCA2, BRCA1 and non-carrier groups (\(P=0.8\)).

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significant interactions between BRCA2 status and PSAV calculated using the arithmetic equation and linear regression ($P = 0.024$ and $P = 0.049$ respectively, Table 4).

Based on these interactions, we performed subgroup analyses by BRCA2 status. All models were adjusted for age at biopsy and last PSA before biopsy. Due to a limited number of events (26 cancers in BRCA2 non-carriers and 23 in BRCA2 carriers), these models were somewhat overfit. No evidence of an association between PSA and any grade cancer or PSAV and any grade cancer was seen in BRCA2 carriers or non-carriers, likely due to the strong correlation between PSA and PSAV (Table 5).

We then investigated whether PSAV was associated with time to PSA $\geq 3.0$ ng ml$^{-1}$. Using Cox proportional hazards models, we found no evidence of an association between PSAV and time from the third PSA measurement to PSA $\geq 3.0$ ng ml$^{-1}$. Out of 1533 men who did not have a PSA $\geq 3.0$ ng ml$^{-1}$ within the first three PSA tests, there were 28 who had a PSA $\geq 3.0$ ng ml$^{-1}$ within 1 year, 50 within 2 years and 62 within 3 years.

**DISCUSSION**

This is the first study to show that there are differences in PSA values among men with different genetic backgrounds. These PSA differences could be used to identify those men considered to be at high genetic risk of more aggressive disease. However, when evaluated with absolute PSA values, PSAV did not appear to provide additional information for BRCA1 or BRCA2 carriers.

A major problem of PSA screening is that, in attempting to detect clinically significant disease, it is inevitable that indolent disease will also be detected leading to overdiagnosis. However, early diagnosis and identification of men with high-risk disease is important to prevent mortality from PrCa. This might be particularly essential in light of recent publications indicating that men with a BRCA1 or BRCA2 mutation are at risk of more aggressive disease (Castro et al, 2013; Castro et al, 2015), early identification of those with clinically significant disease will be imperative. In view of the controversy about the role of PSAV in prostate screening in the general population, it was important to assess its role in BRCA1 and BRCA2 carriers and whether it added to the ability to detect clinically significant disease.

In this analysis of the IMPACT study cohort, we found BRCA2 carriers on average to be screened at a relatively young age. This may account for lower overall PSA values for BRCA2 carriers in this analysis compared to non-carrier controls. However, there were no differences in median PSAV between carriers and non-carriers. Given the possibility that higher PSAV may associate with aggressive PrCa (D’Amico et al, 2004; D’Amico et al, 2005), we would expect BRCA2 carriers who are at risk of aggressive disease would exhibit higher PSAVs (Castro et al, 2013; Castro et al, 2015). BRCA2 carriers in this group may be too young to demonstrate this trend at this point of follow up.

A single PSA reading over 3 ng ml$^{-1}$ was applied to guide biopsy decisions according to the IMPACT protocol, as well as if there was clinical suspicion on digital rectal examination or clinical symptoms. PSAV was not a good indicator in this analysis for distinguishing between those with any grade cancer and high-grade cancer when men were biopsied for either indication. It is possible that PSAV could be a good predictor of high-grade disease in men who had PSA values $\leq 2$ ng ml$^{-1}$ (Kitagawa et al, 2014). However, due to the protocol’s 3 ng/ml PSA threshold for prostate biopsy, we were limited in the number of cancers diagnosed when PSA was $\leq 2$ ng ml$^{-1}$. Further follow up will be required to assess when additional cancers are diagnosed. As part of the IMPACT trial, there is an optional end of study biopsy regardless of PSA. This may help delineate PSAV among men diagnosed with PrCa with low PSA values (Carter et al, 1992; Kitagawa et al, 2014).
Table 4. Models for any grade cancer based on BRCA status (BRCA positive carriers vs BRCA negative non-carriers) and BRCA2 status (BRCA2 positive vs BRCA1 positive and BRCA negative)

<table>
<thead>
<tr>
<th></th>
<th>BRCA1 and BRCA2 vs BRCA non-carriers</th>
<th>BRCA2 vs BRCA1 and BRCA non-carriers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR  95% CI</td>
<td>P value</td>
</tr>
<tr>
<td>Age at biopsy</td>
<td>1.07 1.01, 1.13</td>
<td>0.017*</td>
</tr>
<tr>
<td>Last PSA measurement before biopsy</td>
<td>0.87 0.65, 1.16</td>
<td>0.79 0.81, 1.20</td>
</tr>
<tr>
<td>BRCA1 or BRCA2 Positive</td>
<td>0.40 0.10, 1.67</td>
<td>0.74 0.21, 2.65</td>
</tr>
<tr>
<td>Interaction between last PSA measurement and BRCA+</td>
<td>1.44 1.03, 2.02</td>
<td>1.28 0.97, 1.69</td>
</tr>
<tr>
<td>Age at biopsy</td>
<td>1.06 1.00, 1.12</td>
<td>0.034*</td>
</tr>
<tr>
<td>Last PSA measurement before biopsy</td>
<td>1.14 0.97, 1.35</td>
<td>1.06 0.89, 1.27</td>
</tr>
<tr>
<td>PSA velocity using all PSAs (arithmetic equation)</td>
<td>0.77 0.51, 1.16</td>
<td>0.72 0.49, 1.08</td>
</tr>
<tr>
<td>BRCA1 or BRCA2 Positive</td>
<td>1.54 0.66, 3.61</td>
<td>1.07 0.43, 2.67</td>
</tr>
<tr>
<td>Interaction between PSAs and BRCA+</td>
<td>1.31 0.74, 2.34</td>
<td>2.63 1.13, 6.12</td>
</tr>
<tr>
<td>Age at biopsy</td>
<td>1.07 1.01, 1.13</td>
<td>0.014*</td>
</tr>
<tr>
<td>Last PSA measurement before biopsy</td>
<td>0.97 0.81, 1.18</td>
<td>0.93 0.75, 1.15</td>
</tr>
<tr>
<td>PSA velocity using all PSAs (linear regression)</td>
<td>1.19 0.49, 2.89</td>
<td>1.46 0.69, 3.11</td>
</tr>
<tr>
<td>BRCA1 or BRCA2 Positive</td>
<td>0.99 0.37, 2.68</td>
<td>&gt;0.9 0.93 0.34, 2.52</td>
</tr>
<tr>
<td>Interaction between PSAs and BRCA+</td>
<td>2.26 0.74, 6.90</td>
<td>3.26 1.01, 10.54</td>
</tr>
<tr>
<td>Age at biopsy</td>
<td>1.07 1.01, 1.13</td>
<td>0.013*</td>
</tr>
<tr>
<td>Last PSA measurement before biopsy</td>
<td>0.97 0.79, 1.18</td>
<td>0.92 0.74, 1.16</td>
</tr>
<tr>
<td>PSA velocity using all PSAs (first and last value)</td>
<td>1.24 0.50, 3.07</td>
<td>1.48 0.68, 3.18</td>
</tr>
<tr>
<td>BRCA1 or BRCA2 Positive</td>
<td>1.01 0.37, 2.74</td>
<td>&gt;0.9 0.92 0.34, 2.51</td>
</tr>
<tr>
<td>Interaction between PSAs and BRCA+</td>
<td>2.08 0.70, 6.20</td>
<td>2.96 0.97, 9.02</td>
</tr>
</tbody>
</table>

Abbreviations: CI = confidence interval; OR = odds ratio; PSA = prostate-specific antigen. All models were adjusted for age at biopsy, last PSA measurement before biopsy, BRCA status and the interaction between PSA or PSA velocity and BRCA status. *Statistically significant.

A strength of this study is the unique patient cohort of men with a genetic predisposition to PrCa, in particular BRCA2 carriers who are predisposed to aggressive PrCas (Mitra et al, 2008; Narod et al, 2008; Castro et al, 2013; Castro et al, 2015). Within the group of BRCA2 carriers, PSAV proved predictive of any grade cancer, however, given the low number of cancers diagnosed overall it was not possible to assess whether PSAV was associated with high grade cancer and BRCA2 status. A high PSAV in an individual with a BRCA2 mutation could be used as an indicator of presence of PrCa and therefore as an indication for prostate biopsy. This model could lead to diagnosis of lower grade cancers in BRCA2 carriers. It may lead to better prognosis for men at risk for more aggressive disease and better disease-free survival when treated early. Although there are no definitive treatment recommendations for men with BRCA2 mutations when found to be diagnosed with low grade cancers, their risk for aggressive disease may spur them to follow a more active treatment plan such as radical prostatectomy vs external-beam radiation therapy or active surveillance (Brett and Loman, 2015; Castro et al, 2015).

One major limitation of this analysis is the relatively small number of men in the study who had undergone diagnostic prostate biopsy. End of study biopsies are not mandated and the true incidence of PrCa is unknown in this population. As more men progress through the IMPACT screening study, undergo prostate biopsy and follow-up time increases, the findings from this analysis can be explored and validated. At this point, the results from this analysis did not justify modifying the study algorithm to include a PSAV calculation.

In the general population, PSAV is not part of any major screening guideline. We also did not find PSAV to be an independent prognostic factor in BRCA1 or BRCA2 mutation carriers and therefore for screening an absolute PSA cut-off value should preferably be used.

Table 5. Models for any grade cancer by BRCA2 status (BRCA2 carriers vs BRCA1 carriers and BRCA1/2 non-carriers)

<table>
<thead>
<tr>
<th></th>
<th>BRCA2 Carriers (N = 65)</th>
<th>BRCA2 Non-carriers (N = 109)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR  95% CI</td>
<td>P value</td>
</tr>
<tr>
<td>Age at biopsy</td>
<td>1.02 0.95, 1.10</td>
<td>0.6</td>
</tr>
<tr>
<td>Last PSA measurement before biopsy</td>
<td>1.27 1.05, 1.54</td>
<td>0.013*</td>
</tr>
<tr>
<td>Age at biopsy</td>
<td>1.03 0.95, 1.11</td>
<td>0.5</td>
</tr>
<tr>
<td>Last PSA measurement before biopsy</td>
<td>1.12 0.81, 1.55</td>
<td>0.5</td>
</tr>
<tr>
<td>PSA velocity (arithmetic equation)</td>
<td>1.61 0.57, 4.55</td>
<td>0.4</td>
</tr>
<tr>
<td>Age at biopsy</td>
<td>1.04 0.96, 1.12</td>
<td>0.4</td>
</tr>
<tr>
<td>Last PSA measurement before biopsy</td>
<td>1.01 0.71, 1.44</td>
<td>&gt;0.9</td>
</tr>
<tr>
<td>PSA velocity (linear regression)</td>
<td>3.27 0.65, 16.38</td>
<td>0.15</td>
</tr>
<tr>
<td>Age at biopsy</td>
<td>1.04 0.96, 1.12</td>
<td>0.4</td>
</tr>
<tr>
<td>Last PSA measurement before biopsy</td>
<td>1.00 0.67, 1.49</td>
<td>&gt;0.9</td>
</tr>
<tr>
<td>PSA velocity (first and last value)</td>
<td>3.08 0.58, 16.42</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Abbreviations: CI = confidence interval; OR = odds ratio; PSA = prostate-specific antigen. All models are adjusted for age at biopsy and last PSA measurement before biopsy. *Statistically significant.

CONCLUSION

PSA is more strongly predictive of PrCa in BRCA carriers than BRCA non-carriers. We did not find evidence that PSAV aids to decision making for either indicating biopsy or frequency of follow-up testing in BRCA carriers, but further follow-up is required for more definitive conclusions.
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CONFLICT OF INTEREST

Hans Lilja holds patents for free PSA, hK2, and intact PSA assays, and is named, along with Andrew J. Vickers, on a patent application for a statistical method to detect prostate cancer. The marker assay patents and the patent application for the statistical model has been licensed and commercialised as the 4Kscore by OPKO Diagnostics. Drs Vickers and Lilja receive royalties from sales of this test. Additionally, Dr Lilja owns stock and Dr Vickers owns stock options in OPKO. Professor Rosalind Eeles—Jansen—provided medical education support to GU ASCO Feb 2013. Succinct Communications: received an honorarium and expenses for attending and speaking at UK Cancer Convention Oct 2013. The authors have no other conflict of interest to declare.

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273
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