Prostate Cancer Screening in BRCA and Lynch Syndrome Mutation Carriers

Elena Castro, MD, MSc, PhD, Chee L. Goh, MRCP, and Rosalind A. Eeles, MA, PhD

OVERVIEW

Prostate cancer (PrCa) remains a major public health burden worldwide. Screening programs have been established using the most efficient biomarker to date—prostate-specific antigen (PSA)—with the goal of earlier detection of this disease, which is thought to translate to a reduction in PrCa mortality. However, these screening programs have proved to be controversial following the publication of the two large, randomized, population-based studies in the United States and Europe. There is a recognized need for more refined screening strategies to address some of the deficiencies highlighted in these trials, which include the overdiagnosis and overtreatment of clinically indolent disease. One such strategy could be to include inherited genetic variants in population risk stratification to identify those at higher risk who might benefit more from screening. The genetic component for PrCa risk has been documented from case control and twin studies. The genetic variants include common variants discovered by genome-wide association studies (GWAS). However, their clinical application—including their utility in screening programs—is as yet undefined. There are, however, moderate to rare genetic variants, which confer a much higher risk of PrCa (e.g., BRCA1/2 and mismatch repair [MMR] repair genes). There is more research evidence on the clinical effect of germ-line mutations in these genes; mutation carriers are more likely to develop aggressive PrCa with worse survival. A targeted screening approach might be beneficial if earlier diagnosis, and hence treatment, was to translate into improved outcomes. Clinical trials are currently underway to investigate this further.

PrCa is the second most common tumor in men worldwide.1 However, there exists a substantial worldwide variation in disease incidence and mortality because of genetic background, lifestyle factors, screening programs, and available treatments.2 PrCa accounts for the second most common cause of male cancer-related deaths in the United States and the sixth worldwide, with more than 250,000 deaths a year.3 During the past few decades, significant improvements have been achieved in PrCa treatments that have helped to decrease PrCa mortality, especially in early-stage disease. In the United States, more than 90% of PrCa is diagnosed in early stages (i.e., at local or regional stages) for which the 5-year relative survival rate approaches 100%. Over the past 25 years, the 5-year relative survival rate for all stages combined has increased from 68.3% to 99%.3 Most PrCa in the United States and other developed countries is diagnosed by PSA screening.3 The rationale for PSA screening in the general population is the potential to reduce mortality rates through early detection of the disease. However, many expert groups have concluded that data from existing clinical trials on screening are insufficient to recommend the routine use of this test, and screening for PrCa in the general population is very controversial.4–6 But despite all the arguments against screening, PSA is still widely used as a diagnostic tool for PrCa, and the scientific challenge is to differentiate which men will or will not benefit from screening with its related consequences.

Patients with a PSA above the cutoff value of 3–4 ng/mL are suspected to have PrCa and are usually recommended for transrectal prostatic biopsies. However, it is known that the predictive value of PSA is poor, as less than 25% of patients with PSA higher than 3 ng/mL are diagnosed with PrCa at biopsy, and the use of other indices, such as PSA velocity or free/total PSA ratio, adds little to the accuracy of PSA.7,8 Moreover, it is estimated that almost 50% of patients diagnosed with PrCa through PSA screening are overdiaognosed, and a high percentage of them will also be overtreated as they have indolent tumors that will derive little or no benefit from PrCa treatment.7 Overdiagnosis and overtreatment are probably the most important adverse effects of PrCa screening and occur more frequently compared with screening programs for other common cancers, such as breast or colorectal. Therefore, there is an urgent need for novel biomarkers that can better stratify patients according to their risk of developing clinically significant PrCa to help us decide who should be recommended for screening. Genetic variants such...
as BRCA germ-line mutations are examples of such predictive factors that we could potentially use to identify patients for targeted screening. This paper will discuss the screening controversy as well as the clinical implications of germ-line mutations in BRCA1/2 and the mismatch repair (MMR) genes in targeted PrCa screening strategies.

THE PROSTATE CANCER SCREENING CONTROVERSY

The updated results of two large PrCa screening studies—The Prostate, Lung, Colorectal, and Ovarian screening study (PLCO) and The European Randomized Study for Prostate Cancer (ERSPC) have recently been reported.4,5 The PLCO study, conducted in the United States from 1993 to 2006, enrolled a total of 76,685 men age 55 to 74 who were randomly assigned to the intervention (organized screening of annual PSA testing for 6 years and annual digital rectal exam for 4 years) and control (usual care, which sometimes included opportunistic screening) arms.4 A positive test was defined as a PSA value higher than 4 ng/mL. After 13 years’ follow-up, the authors observed a significant 12% relative increase in the incidence of PrCa (relative risk [RR] 1.12, 95% CI 1.07-1.17) and a nonstatistically significant decrease in the incidence of high-grade PrCa in the intervention arm (RR 0.89, 95% CI 0.77-1.01). However, there was no evidence of a mortality benefit for organized annual screening compared with opportunistic screening (RR 1.09, 95% CI 0.87-1.36). In contrast, the ERSPC study involved a total of 162,388 men age 55 to 69 with a median follow-up of 11 years and showed a 21% reduction in PrCa-specific mortality in the screening group.5 In this study, men in the intervention arm had a PSA test every 4 years, and biopsy was recommended with a PSA 3 ng/mL or higher. It is noteworthy that the PLCO study was conducted in the United States where PSA screening is already widespread, and up to 56% of men in the control arm underwent PSA screening compared with 15% in the European study. The ERSPC study also showed that 1,055 men would need to be invited for screening, with two to three PSA tests over 11 years of follow-up (and 37 cancers detected) to prevent one death from PrCa.5

The most common side effects associated with prostatic biopsies reported by these two studies were hematospermia (50%), hematuria (22.6%), fever (3.5%), hospitalization for prostatitis or urosepsis (0.5%), and urinary retention (0.4%; Table 1). We have to bear in mind that a large proportion of these screened men will actually be diagnosed with low-risk PrCa, which may not have presented clinically in their lifetime. Whether the harms of screening are justified by the benefits in terms of the reported reduction of PrCa mortality remains a very controversial issue. It has become even more controversial since the Prostate Cancer Intervention Versus Observation Trial (PIVOT) recently published that for men with localized PrCa detected through PSA testing, radical prostatectomy did not significantly reduce PrCa mortality (p = 0.09).9 Recently, the U.S. Preventive Service Task Force published a review of the evidence for screening for PrCa and made a clear recommendation against it.10 In contrast, the American Society of Clinical Oncology’s provisional clinical opinion is that despite the limitations to the existing data, there is evidence to suggest that men with longer life expectancy may benefit from PSA testing.11 Screening with PSA may identify PrCa earlier, but better screening approaches are needed, such as improved risk stratification for screening and a better assessment of individualized PrCa risk. There are also efforts to evaluate new biomarkers to replace or enhance PSA testing for PrCa. The spectrum of biomarkers evaluated has ranged from genetic-based markers (e.g., single nucleotide polymorphisms) to serologic protein markers (e.g., kallikreins), but until now, none have been found sensitive and specific enough to replace PSA.11 The screening controversy therefore continues.

TABLE 1. Summary of Adverse Events Reported from Current Screening Strategies

<table>
<thead>
<tr>
<th>Event</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overdiagnosis of clinically indolent tumors</td>
<td>8%</td>
</tr>
<tr>
<td>Overtreatment of clinically indolent tumors</td>
<td>7%</td>
</tr>
<tr>
<td>Biopsy related complications:</td>
<td></td>
</tr>
<tr>
<td>Hematospermia</td>
<td>50%</td>
</tr>
<tr>
<td>Hematuria</td>
<td>22.6%</td>
</tr>
<tr>
<td>Fever</td>
<td>3.5%</td>
</tr>
<tr>
<td>Prostatitis</td>
<td>0.5%</td>
</tr>
<tr>
<td>Hospitalization for prostatitis or urosepsis</td>
<td>0.4%</td>
</tr>
</tbody>
</table>

CLINICAL IMPLICATIONS OF BRCA AND MISMATCH REPAIR GENES IN PROSTATE CANCER

PrCa is rarely diagnosed in men younger than 50, but its incidence rises rapidly thereafter. Excluding advanced age and...
black ancestry, the strongest risk factor for the disease is a family history of PrCa.\textsuperscript{12} Twin studies have shown that up to 42% of the risk could be explained by inheritance.\textsuperscript{13} The genetic etiology of PrCa is complex and poorly understood, with multiple predisposing factors that may also affect presentation, progression, and outcome. The risk of PrCa in first-degree relatives of cases is approximately twice that of the general population. This familial risk is greater in families where the PrCa cases are younger, being more than fourfold for close relatives of cases diagnosed before age 60. Higher risks have also been shown for men with two or more affected relatives. This observed increased risk is too great to be explained by nongenetic factors alone. Analyses based on the Nordic twin registries have found higher risks in monozygotic twins than in dizygotic twins, supporting the hypothesis that much of this familial aggregation is caused by genetic factors (42%) rather than shared lifestyle factors.\textsuperscript{13} In an effort to identify these variants, GWAS were performed, which have now identified over 70 susceptibility loci associated with PrCa. Individually, these loci contribute at most a modest increase in PrCa risk, but when combined, they could explain more than 30% of the PrCa familial risk.\textsuperscript{14} These loci could play an important role in the management of PrCa, for example, in refining risk profiling and population stratification with potential screening implications. However, as yet, their clinical utility remains undefined.\textsuperscript{15} Further evaluation is needed.

At the other end of the spectrum, there are a few rare to moderate genetic variants for which more data are known with regard to their clinical application. Germ-line mutations in \textit{BRCA2} are the genetic events known to date that confer the highest risk of PrCa (8.6-fold in men age 65 or younger).\textsuperscript{16} The effect of \textit{BRCA1} is more modest (4.5-fold in men age 65 and younger), and patients carrying germ-line mutations in the \textit{MSH2} gene have up to an estimated 10-fold increased risk by age 60, although data are emerging to suggest the risk may be nearer two- to threefold.\textsuperscript{17–19} Targeted screening for carriers of these genetic variants could have potential clinical implications.

Deleterious germ-line mutations in both the \textit{BRCA1} and \textit{BRCA2} genes have been associated with more aggressive disease and poor clinical outcomes. Tryggvadottir et al were the first to analyze the clinical implications of a germ-line \textit{BRCA2} mutation, after observing that the Icelandic \textit{BRCA2 999del5} mutation was present in 2.7% of unselected Icelandic patients diagnosed with PrCa at age 65 or younger.\textsuperscript{20,21} Compared with noncarriers, the mutation carriers were younger at diagnosis, (age 69 vs. 74); presented with more advanced tumor stage (T3–4: 79% vs. 36%); and poorly differentiated tumors (84% vs. 52.7%). Median cause-specific survival (CSS) for carriers was 2.1 years compared with 12.4 years for noncarriers. Edwards et al compared overall survival (OS) after PrCa diagnosis in a series of 21 \textit{BRCA2} mutation carriers and 1,587 controls.\textsuperscript{22} Carriers had a median OS of only 4.8 years compared with 8.5 years for the noncarriers. Thorne et al reported the analysis of the outcome of PrCa in 40 \textit{BRCA2} mutation carriers compared with 97 patients with wild-type \textit{BRCA}.\textsuperscript{23} No difference in age or PSA at diagnosis between carriers and noncarriers was seen, but \textit{BRCA2} carriers presented with less differentiated (65.8% vs. 33%) and larger (T \textsuperscript{\geq} 3) tumors (39.5% vs. 22.6%) than noncarriers; 79% of patients in both groups received similar local treatment with curative intent. However, despite the similarity, those with \textit{BRCA2} mutations had worse CSS, and \textit{BRCA2} mutation status was shown to be an independent predictor of CSS (HR 4.97, 95% CI 2.19–11.25). Gallagher et al also reported a series that included 26 PrCa cases carrying the Ashkenazi founder mutations \textit{BRCA2 6174delT} (20 patients), \textit{BRCA1 185delAG} (6 patients), and 806 noncarriers.\textsuperscript{24} All patients presented with early-stage PrCa and were screened for the two mutations. Those carrying \textit{BRCA2 6174delT} presented with a higher frequency of poorly differentiated tumors compared with noncarriers (85% vs. 57%), although no association with the tumor phenotype was observed for \textit{BRCA1 185delAG}. Both mutations conferred a higher risk of biochemical relapse and metastasis. CSS was 19.1 years for noncarriers compared with 13 years and 12.5 years for \textit{BRCA1 185delAG} and \textit{BRCA2 6174delT}, respectively. Although all these results should be interpreted with caution because of the sample size, both mutations were found to be predictors of poorer CSS (HR 5.16, 95% CI 1.09–24.53 and HR 5.48, 95% CI 2.03–14.79, for \textit{BRCA1} and \textit{BRCA2} mutation carriers, respectively).

In an attempt to better understand the implications of \textit{BRCA1} and \textit{BRCA2} germ-line mutations, our team has recently reported the analysis of 2,019 patients with PrCa; 18 and 61 of them had \textit{BRCA1} and \textit{BRCA2} germ-line mutations, respectively.\textsuperscript{25} Our results showed that a wide spectrum of pathogenic mutations in the \textit{BRCA1/2} genes confers a more aggressive PrCa phenotype, and these tumors are more frequently associated with lymph node involvement and distant metastasis at diagnosis than PrCa in noncarriers. CSS was significantly longer in noncarriers than in carriers (15.7 vs. 8.6 years, p = 0.015, HR 1.8). For localized PrCa, 5-year CSS was significantly higher in noncarriers (96% vs. 82%, p = 0.01, HR 2.6). We have also demonstrated that \textit{BRCA2} status is a prognostic factor in PrCa, which is independent of other established prognostic factors, including stage, Gleason score, and PSA. The role of \textit{BRCA1} was not well defined because of the small patient numbers and short follow-up in this subgroup. Groups have therefore consistently showed worse outcomes for \textit{BRCA} mutation carriers, and screening of this cohort for earlier detection might be warranted.

Another group that is known to have a higher PrCa risk is patients with Lynch syndrome. Lynch syndrome is a multi-cancer syndrome caused by germ-line mutations in the MMR genes: \textit{MLH1}, \textit{MSH2} or \textit{MSH6}. Colorectal cancers are the predominant cancer phenotype, and patients with this syndrome have a 70% probability of developing the disease by age 70. In addition, there is an increased risk of extracolonic tumors, including endometrium, stomach, small bowel, ovary, ureter, renal pelvis, biliary tract, brain, and pancreas.\textsuperscript{26} PrCa has been reported in these families, but not until recently has it been shown to be a feature of the Lynch
syndrome. Grindedal et al estimated that the cumulative risk of PrCa by age 70 in MMR carriers is 30%, compared with 9% in the general population. In that study, PrCa cases were diagnosed as a result of regular PSA testing and were asymptomatic at the time of diagnosis. Interestingly, all tumors diagnosed were poorly differentiated, with a Gleason score of 8 or higher. Recently, Engel et al showed that the risk of less common cancers in Lynch syndrome depends on the sex of the patient and the specific mutated MMR gene he or she carries. They found an increased risk of PrCa in MSH2 mutation carriers but not in MLH1 carriers. Similarly, Barrow et al reported a 10-fold increased risk of PrCa by age 60 in MSH2 mutation carriers. Although MMR deficiency is associated with colorectal cancer prognosis, further studies are needed to assess its clinical implications in PrCa.

TARGETED SCREENING IN GENETICALLY HIGHER-RISK POPULATIONS

There have been a limited number of studies evaluating the role of screening in men at high risk of PrCa based on a family history of the disease. Although better evidence is needed regarding the benefits and risks of screening in these high-risk groups, most of the studies support the use of targeted screening, and the positive predictive value of PSA has been reported to be higher in these patients. IMPACT is a multicenter observational study of screening for PrCa in which men age 40 to 69 are offered annual PSA and the threshold for prostatic biopsy is PSA higher than 3 ng/mL (Fig. 1). The target population of the study is 500 BRCA1, 500 BRCA2 carriers, and 850 men who have tested
negative for the BRCA mutation present in their family. In the Lynch syndrome arm of the study, 190 men with a germ-line mutation in either MSH2, MSH6, or MLH1, and 190 noncarriers will be recruited. Patients have a minimum of 5-years of follow-up. The main aim of the study is to determine the incidence, stage, and pathology of screen-detected PrCa in mutation carriers compared with a control population. The preliminary results of the study have recently been reported and showed that the positive predictive value of PSA in BRCA carriers is high and that screening detects clinically significant tumors. The final results of the study are awaited in 2018, and it is expected to inform the clinical management of these high-risk patients as well as potential screening strategies.

CONCLUSION

There is a recognized need to refine the PrCa screening programs currently in place. The use of genetic markers could potentially enable better risk stratification in the general population to identify men who are at a higher risk and who should be selectively targeted for screening. Although the clinical implications of the more common GWAS loci are yet to be determined, evidence exists regarding the poorer outcomes of those who develop PrCa with mutations in BRCA and MMR genes. There is a prospect that earlier detection through screening in these latter genetic cohorts should result in a higher proportion of clinically significant cancer and would be an example of targeted genetic medicine. Efforts are now underway to investigate the clinical benefits of such a targeted screening approach for such populations.

ACKNOWLEDGMENT

Elena Castro is funded by CRIS foundation for cancer research. Chee Leng Goh is funded by the Genetic Associations and Mechanisms in Oncology (GAME-ON) Initiative (NIH ELLIPSE grant U19CA148537). Rosalind Anne Eeles is a Senior Investigator of the National Institutes of Health Research in England. Rosalind Anne Eeles receives funding from Cancer Research United Kingdom C5047/A13232, Prostate Action, the NIH U19 CA 148537–01, The Institute of Cancer Research, and The European Community’s Seventh Framework Program under the grant agreement 223175 (Health-F2–2009-223175-COGS). We acknowledge support from the National Institute for Health Research to the Biomedical Research Centre at The Institute of Cancer Research and Royal Marsden Foundation NHS Trust.

Disclosures of Potential Conflicts of Interest

Relationships are considered self-held and compensated unless otherwise noted. Relationships marked “L” indicate leadership positions. Relationships marked “I” are those held by an immediate family member; those marked “B” are held by the author and an immediate family member. Relationships marked “U” are uncompensated.


References


