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REVIEW

The role of *BRCA1* and *BRCA2* in prostate cancer

Elena Castro[1,2] and Rosalind Eeles[1,2]

One of the strongest risk factors for prostate cancer is a family history of the disease. Germline mutations in the breast cancer predisposition gene 2 (*BRCA2*) are the genetic events known to date that confer the highest risk of prostate cancer (8.6-fold in men ⩽65 years). Although the role of *BRCA2* and *BRCA1* in prostate tumorigenesis remains unrevealed, deleterious mutations in both genes have been associated with more aggressive disease and poor clinical outcomes. The increasing incidence of prostate cancer worldwide supports the need for new methods to predict outcome and identify patients with potentially lethal forms of the disease. As we present here, *BRCA* germline mutations, mainly in the *BRCA2* gene, are one of those predictive factors. We will also discuss the implications of these mutations in the management of prostate cancer and hypothesize on the potential for the development of strategies for sporadic cases with similar characteristics.
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INTRODUCTION

Prostate cancer (PCa) is the second commonest tumour in men worldwide, with about 900 000 new cases diagnosed annually, although there is substantial variation in disease incidence across regions. Australia/New Zealand and the countries from North America and Western and Northern Europe have the highest rates of PCa, partially because PCa screening with prostate specific antigen (PSA) and subsequent biopsy has become common practice (although this is not the sole reason), while countries in South-Central Asia have the lowest incidence.[1] Studies of incidence rates in migrant populations from Asia to America[2] suggest that lifestyle risk factors are important determinants of PCa risk. To date, however, these lifestyle risk factors have not been identified. PCa accounts for the second commonest cause of male cancer-related deaths in the United States[3] and the sixth worldwide, with more than 250 000 deaths a year.[1] Thus, it is essential to identify those patients with potentially lethal forms of PCa at their presentation.

PCa is rarely diagnosed in men younger than 50 years, but its incidence rises rapidly thereafter. Excluding advanced age and African-American ancestries, the strongest risk factor for the disease is a family history of PCa.[4–6] PCa is one of the common cancers with a large genetic component, as up to 42% of the risk could be explained by inheritance from studies about twins.[7] Genome-wide association studies (GWAs) have identified 46 susceptibility loci associated with PCa[8–20] that individually contribute to a small increase in PCa risk, but which taken together, could explain more than 25% of the excess of PCa familial risk.[13]

Although present in only 1%–2% of sporadic PCa cases[21–23] germline mutations in the breast cancer predisposition gene 2 (*BRCA2*) are the genetic events known to date that confer the highest risk of PCa (8.6-fold in men ⩽65 years).[23] *BRCA1* has also been associated with an increased risk of sporadic PCa (3.5-fold), even though germline mutations in this gene have only been observed in 0.44% of PCa cases (Leongamonlert *et al.*, in press). Lifetime risk of PCa in *BRCA2* mutation carriers has been estimated to be 20%,[24] while for *BRCA1*, the risk is 9.5% by age 65 years (Leongamonlert *et al.*, in press), similar to that in non-carriers.

The genetic aetiology of PCa is complex and poorly understood, with multiple predisposing factors which may also affect presentation, progression and outcome.[25–27] While the clinical implications of common genetic variants associated with PCa risk remain unclear,[28–34] deleterious germline mutations in both genes, *BRCA1* and *BRCA2*, have been associated with more aggressive disease and poor clinical outcomes.

The increasing incidence of PCa supports the need for new methods to predict outcome, because the factors currently used (TNM stage, tumour grade and PSA at diagnosis) have been proven to be insufficient to identify which men are at risk of developing lethal PCa. As we present here, *BRCA* germline mutations, mainly those mutations in the *BRCA2* gene, are one of those predictive factors. We will also discuss the implications of *BRCA* mutations in the management of PCa and hypothesize on the potential for the development of strategies for sporadic PCa tumours with similar characteristics.

BRCA1 AND *BRCA2* GENES AND THE RISK OF PROSTATE CANCER

Although multiple aetiologies have been proposed to predispose to the development of PCa, the only well-established risk factors are age, ethnic background (men of African descendent have an increased risk of the disease) and a family history of the disease.[35]

PCa exhibits a significant familial aggregation in some men, particularly when affected at young age. High-risk PCa familes have been described as those that present with: (i) three or more first-degree relatives affected with PCa; (ii) PCa in three or more generations, or (iii) an early age of PCa diagnosis among at least two first-degree relatives, usually siblings.[36] The risk of the disease in first-degree

[1]Oncogenetics Team, The Institute of Cancer Research, Sutton SM2 5NG, UK and [2]Academic Urology Unit, The Royal Marsden NH Foundation Trust, London SW3 6JJ, UK
Correspondence: Professor R Eeles, (Rosalind.eeles@icr.ac.uk)
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relatives of cases is approximately twice that in the general population. This familial risk is greater among young cases, being more than four-fold for close relatives of cases diagnosed below age 60. Higher risks have been shown for men with two or more affected relatives.[4–7,37–40] This increase is too great to be explained by non-genetic factors alone. Analyses based on the Nordic twin registries have found higher risks in monozygotic than dizygotic twins, supporting the hypothesis that much of this familial aggregation is due to genetic factors (42%), rather than shared lifestyle factors.[7] Several linkage studies for PCa have been completed, often with conflicting results,[26,41–43] therefore, attempts to identify high-prevalence genes with a dominant mode of inheritance, such as *APC* for colon cancer[44] or *BRCA* for breast and ovarian cancer[45,46] have failed in PCa.

There is a recognized association of breast cancer with PCa in families.[47–49] The contribution of the *BRCA1* and *BRCA2* to male cancer has been extensively studied, since families with these mutations show clustering of cancer in men. These genes have not only been associated with an increased risk of developing breast, ovarian, fallopian tube and peritoneal cancer[50] in women, but also with male breast cancer and PCa.[24,51] For *BRCA1* mutation carriers, the Breast Cancer Linkage Consortium (BCLC) reported an increase in PCa risk in men aged <65 years with a relative risk of 1.82, but no risk increase was seen for men aged $\geqslant 65$ years.[52] For *BRCA2* mutation carriers, the BCLC estimated the relative risk for developing PCa as 4.65, rising to 7.33 for men aged <65 years.[24] We have recently concluded two large studies reporting an 3.5-fold and 8.6-fold increase in the risk of PCa for *BRCA1* and *BRCA2* mutation carriers by age 65, respectively (Leongmonrlert *et al*., in press).[23]

BRCA1 and *BRCA2* are tumour suppressor genes and both are inherited in an autosomal dominant fashion with incomplete penetrance. Tumorigenesis in individuals with germline mutations in the *BRCA* genes requires somatic inactivation of the remaining wild-type allele. Both genes encode large proteins that function in multiple cellular pathways. BRCA1 is a key player in cellular control systems, having been linked to a range of cellular processes, such as DNA damage response and repair, transcriptional regulation and chromatin modelling.[53,54] By contrast, BRCA2 function seems to be limited to DNA recombination and repair processes, being of particular importance in the regulation of RAD51 activity.[53–55] BRCA1 or BRCA2 function loss is associated with a deficiency in repairing DNA double-strand breaks (DSBs) by the conservative mechanism of homologous recombination (HR). Therefore, cells have to repair these lesions through other non-conservative and potentially mutagenic mechanisms. This genomic instability may underlie the cancer predisposition caused by deleterious mutations in the *BRCA* genes, although the reason why these mutations are particularly associated with some specific types of cancer, such as breast, ovarian and PCa, remains unknown.[56]

Although some studies have started to elucidate the role of these genes in PCa, the specific role of *BRCA1* and *BRCA2* in the development and progression of PCa has not been yet elucidated. *BRCA1* has not only been identified as one of the coregulators of the androgen receptor (AR)[57,58] which mediates a signalling pathway essential in the development and progression of PCa, but has also been suggested to modulate another important pathway in PCa through the regulation of IGF-1R in an AR-dependent manner.[59] Using animal models, Francis *et al*.[60] have proposed that BRCA2 may act as a tumour suppressor in epithelial prostate tissue and its functional loss predisposes to premalignant prostatic lesions. They observed that deletion of *Brca2* in murine prostatic epithelia results in focal hyperplasia and low-grade prostate epithelial neoplasia (PIN) in animals over 12 months of age and that the simultaneous deletion of *Brca2* and the tumour suppressor *tp53* lead to focal hyperplasia and atypical cells at 6 months, and to high-grade PIN in animals at 12 months. Moro *et al*.[61] have proposed that a functional *BRCA2* gene may limit the metastatic potential of neoplastic cells by downregulating matrix metalloproteinase 9 (MMP-9) through inhibition of PI3-kinase/AKT and activation of MAP/ERK, effectively preventing cancer cell migration and invasion. In a cohort of sporadic PCas treated with prostatectomy, Bednarz *et al*.[62] found that those tumours with somatic *BRCA1* loss in at last one tumour focus, due to a deletion or hypermethylation of the promotor, had a higher probability of advanced tumour stage and a shorter disease-free survival than *BRCA* wild-type tumours. These results may help to explain the fact that patients with germline deleterious *BRCA1* and *BRCA2* mutations frequently present with nodal involvement and distant metastasis at diagnosis[63,64] and those with local disease, have a shorter disease-free survival than those patients *BRCA* wild type.[63–65]

On the other hand, BRCA functional loss leads to genomic instability and the accumulation of genetic aberrations in cells. As a consequence, one would expect other recurrent driving molecular events to be present in *BRCA*-mutated tumours. Several translocations have been recently described in sporadic PCa (i.e., *TMPRSS2/ETS* gene fusions, *SLC45A3/BRAF*, *RAF1-ESRP1*), and some of them could have prognostic and therapeutic implications,[66,67] although the frequencies of such events have not yet been characterized in *BRCA*-related PCa.

CLINICAL IMPLICATIONS

Several epidemiological studies that examined the risk of PCa among *BRCA1* and *BRCA2* mutation carriers have suggested that protein-truncating *BRCA2* mutations confer an increased risk of PCa, while the effect of mutations in the *BRCA1* gene seems to be more modest (Leongamonlert *et al*., in press).[23,24,51,68–73] However, one of the challenges of studies analysing the susceptibility of PCa in *BRCA* mutation carriers is the low incidence of germline mutations in those genes in the general population which is estimated to be between 0.07% and 0.24% in different studies,[72,74–76] and therefore, results have often been inconsistent. The ethnic population that has more extensively been studied is the Ashkenazim Jewish, due to the relative high incidence of three founder mutations (*BRCA1* 185delA, *BRCA1* 5382insC and *BRCA2* 6174delT). It has been estimated that ~2% of this population carries at least one of these mutations.[77–80] Even in this population, the results of these epidemiological studies have been contradictory, but many of them were underpowered, due to small sample size or lack of covariate information.[22,81–86]

Another *BRCA2* founder mutation that has been extensively studied is the Icelandic *BRCA2* 999del5 mutation. Johannesdottir *et al*.[87] reported that this mutation was present in 2.7% of unselected Icelandic patients diagnosed with PCa at age $\leqslant 65$ years. This prevalence is double the prevalence of germline *BRCA2* mutations reported by Kote-Jarai *et al*.[23] and Agalliu *et al*.[22] in two cohorts of PCa patients diagnosed at age $\leqslant 65$ years (1.2% and 0.78%, respectively). In these latter two studies, patients were screened for any[22] mutation, not only the founder ones.

To assess whether *BRCA2* 999del5 mutations contribute to PCa phenotype and prognosis, Tryggvadottir *et al*.[64] analysed a group of 89 PCa patients diagnosed in Iceland between 1955 and 2004. The study included 30 men carrying the Icelandic founder mutation, and for each carrier, two control patients without the mutation. Compared with non-carriers, the mutation carriers were younger at diagnosis (69 years *vs*. 74 years); presented with more advanced tumour stage (T) (T3–4: 79% *vs*. 36%) and poorly differentiated tumours (84% *vs*.

52.7%). Median cause-specific survival (CSS) for carriers was 2.1 years compared with 12.4 years for non-carriers.

After Tryggvadottir *et al.*[64] suggested that *BRCA* mutations could have clinical implications beyond increasing the risk of PCa, another two studies analysed the role of a wide spectrum of mutations in *BRCA2*. None of them included patients with the Icelandic founder mutation. Edwards *et al.*[88] compared overall survival (OS) after PCa diagnosis in a series of 21 *BRCA2* mutation carriers and 1587 controls, 263 of which had tested negative for *BRCA2* mutations. Carriers had a median OS of only 4.8 years compared with 8.5 years for the non-carriers. More recently, Thorne *et al.*[89] reported the analysis of the outcome of PCa in 40 *BRCA2* mutation carriers compared with 97 *BRCA* wild-type patients. Non-carriers belonged to families with a history of breast cancer. No difference in age or PSA at diagnosis between carriers and non-carriers was seen. *BRCA2* carriers presented with less differentiated (65.8% *vs.* 33%) and larger ($T \geqslant 3$) tumours (39.5% *vs.* 22.6%) than non-carriers. Despite 79% of patients in both groups (carriers and non-carriers), receiving similar local treatment with curative intent, those with *BRCA2* mutations had a worse CSS. *BRCA2* mutation status was shown to be an independent predictor of CSS (hazard ratio (HR): 4.97; 95% confidence interval (CI): 2.19–11.25). Interestingly, the non-carrier group also had a poorer outcome compared with other series of sporadic PCa, suggesting that a family history of breast cancer might, somehow, affect the prognosis of PCa patients.

Two studies have analysed the implications of both *BRCA1* and *BRCA2* mutations. Narod *et al.*[90] reported a series of 67 *BRCA2* and 37 *BRCA1* mutation carriers or obligate carriers of different *BRCA* mutations. The study analysed the prognosis of *BRCA1 vs. BRCA2* mutation carriers and did not include a *BRCA* wild-type group for comparison. No information was available on pathology or clinical features of the PCa cases. They observed that the 5-year OS for all causes of death was shorter for *BRCA2* than for *BRCA1* (42% *vs.* 64%, respectively) with a median OS of 15 years for *BRCA1* mutation carriers and 5 years for *BRCA2* mutation carriers. Gallagher *et al.*[65] reported a series that included 26 PCa cases carrying the Ashkenazi founder mutations *BRCA2* 6174delT (20 men) and *BRCA1* 185delAG (6 men), and 806 non-carriers. All patients presented with early-stage PCa were screened for the two mutations. Patients carrying *BRCA2* 6174delT presented with poorly differentiated tumours more frequently than non-carriers (85% *vs.* 57%). No association with the tumour phenotype was observed for *BRCA1* 185delAG. Both mutations conferred a higher risk of biochemical relapse and metastasis. CSS was 19.1 years for non-carriers compared with 13 and 12.5 years for *BRCA1* 185delAG and *BRCA2* 6174delT, respectively. Although these results should be assessed cautiously due to 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 *BRCA1* and *BRCA2* mutation carriers, respectively). In general, these previous series were limited when analysing patient outcomes, due to the small number of *BRCA* mutation carriers with little clinical information, or to the lack of a comprehensive multivariate analysis. Thus, the real independent prognostic contribution of *BRCA* mutations might be overestimated, compared with other classical prognostic factors for PCa outcome. In an attempt to better understand the implications of *BRCA1* and *BRCA2* germline mutations, we have recently reported the analysis of 2019 PCa patients, 18 and 61 of them harbouring *BRCA1* and *BRCA2* germline mutations, respectively.[63] This is the largest study to date investigating the clinical characteristics and outcome of PCa patients with and without *BRCA* mutations. Our results reveal that a wide spectrum of pathogenic mutations in the *BRCA1* and *BRCA2* genes confers a more aggressive PCa phenotype and these tumours are more frequently associated with lymph node involvement and distant metastasis at diagnosis than PCa in non-carriers. We have not seen differences in age at diagnosis as previously reported by others.[65,84,89,91] This contradicts Tryggvadottir's observations,[64] but our study[63] did not include any patients with the Icelandic founder mutation *BRCA2* 999del5, and we cannot exclude that some mutations are associated with younger age at diagnosis. *BRCA1* and *BRCA2* carriers had a higher incidence of poorly differentiated tumours, presented with larger tumours and a higher incidence of node involvement and distant metastasis. We have also demonstrated that *BRCA* germline mutations in PCa, particularly in the *BRCA2* gene, are associated with poor OS and CSS independently of other classical prognostic factors, including stage, Gleason score and PSA.

CURRENT MANAGEMENT OF *BRCA*-MUTATED PROSTATE TUMOURS

While PCa screening in unselected men remains controversial,[92–94] targeting screening to higher-risk groups may have a greater impact in men with a higher risk of aggressive and fatal PCa. *BRCA1* and *BRCA2* mutation carriers may constitute one of such populations. Early diagnosis in these patients may be crucial, and currently, the IMPACT study is evaluating the utility of PSA-based PCa screening in asymptomatic *BRCA1* and *BRCA2* mutation carriers.[95]

At this time, there is no evidence as to which is the most appropriate radical treatment for *BRCA* mutation carriers with local PCa. Although clinical trials to assess the most adequate management of these cases are still needed, radical treatment with either surgery or radiotherapy seems to be preferable to active surveillance, even for low-risk cases. The studies previously presented also support clinical trials evaluating the role of adjuvant treatment in *BRCA* mutation carriers as they have a higher early nodal spread and metastasis rate.

One of the key clinical issues to be addressed in the treatment of BRCA-related tumours is the choice of chemotherapy in both, the adjuvant and the palliative settings. Platinum, taxanes and more recently poly(ADP-ribose) polymerase (PARP) inhibitors have been demonstrated to be active in breast and ovarian tumours harbouring germline mutations in either of the two *BRCA* genes, although their roles in PCa needs further investigation.

Platinum agents induce DNA crosslinks that are substrates for HR DNA repair, which is deficient in *BRCA*-mutated cells. Therefore, these tumours show high sensitivity to platinum-based chemotherapy, both *in vitro*[96–98] and *in vivo*.[99–101] Previous studies in ovarian cancer suggested that mutations in both genes were associated with similar responses to platinum-based chemotherapy.[101] Recently, Yang *et al.*[102] have reported a series of 316 ovarian cancer patients treated with surgery and adjuvant platinum-based chemotherapy in which *BRCA2* mutations were associated with improved outcomes, while *BRCA1*-mutated or -hypermethylated tumours were not significantly different from *BRCA* wild-type cases. *BRCA2* mutations were also associated with an increased rate of response to primary platinum chemotherapy. Interestingly, an increase in genomic instability was found in *BRCA2*-related tumours, but not in those with *BRCA1* loss, due to mutation or hypermethylation. This could indicate that *BRCA2* lesions cause more substantial HR defects than *BRCA1*.

Gallagher *et al.*[103] have recently suggested that those patients with metastatic disease and *BRCA* mutations do not respond less to the standard chemotherapy regimen with docetaxel plus prednisolone than PCa which are *BRCA* wild type. We observed that *BRCA2* mutations are associated with worse outcome for all survival endpoints, except for survival from metastasis. No difference was seen between mutation

carriers and non-carriers, which may be due to a more favourable response to chemotherapy treatments.[63]

PARP is an enzyme that produces large chains of poly(ADP-ribose) from NAD^+.[104] PARP is involved in the repair of single-strand DNA breaks and its inhibition produces the accumulation of these lesions which may end in the arrest of the replication fork and the formation of DSBs.[105] These DSB are only proficiently repaired by HR. In the absence of HR, as occurs when *BRCA* mutations are present, these DSBs are repaired by error-prone forms of DSB, such as non-homologous en-joining potentially resulting in accumulation of gene aberrations and loss of cell viability.[106,107] Significant efficacy has been established for PARP inhibitors in *BRCA*-mutated breast and ovarian tumours,[108–110] although the evidence for PCa is still limited. Clinical trials are currently ongoing to assess the role of PARP inhibitors in PCa *BRCA*-related, as well as in sporadic tumours. The most effective scheme is still to be established. At the moment, clinical trials are investigating the efficacy of different combinations of chemotherapy and PARP inhibitors in metastatic patients, but there are no data of its role in the adjuvant setting, either in monotherapy or in concomitance with other agents. There is concern that it may potentiate the effects of some modalities such as radiotherapy.

'BRCANESS' IN PROSTATE CANCER

Several studies in breast and ovarian cancer have identified sporadic cancers with molecular and clinical characteristics similar to *BRCA*-related tumours,[56] defining a group of tumours with *BRCAness* characteristics that benefits from the same therapeutic strategies as those for *BRCA* mutant tumours.[101,108–110]

The aggressive phenotype and poor prognosis associated with PCa in patients with germline *BRCA* mutations is very likely to be associated with a different cancer biology from *BRCA* wild-type PCa. The identification of these differential molecular characteristics could be essential in tailoring treatment for this population, but it may also be of great importance for the management of some sporadic PCa cases which may have similar clinical characteristics and aggressive behaviour.

Gene promoter hypermethylation is a mechanism of *BRCA* function loss in sporadic breast and ovarian cancer that triggers tumours with similar characteristics to those with germline mutations in these genes, although this has still not been analysed in PCa. At this time, the study by Bednarz *et al.*[62] is the only one that has analysed a series of sporadic PCas, finding that those with BRCA1 somatic loss presented more frequently with node involvement and shorter disease-free survival than those with functional BRCA1.

CONCLUSION

Germline mutations in the *BRCA* genes, mainly in *BRCA2*, not only increase the risk of developing PCa, but also have implications in the prognosis and management of the disease. BRCA-related PCa is usually aggressive, and radical treatments are preferred to surveillance, even for low-risk cases. Further studies are needed to design a tailored management for these patients. An ongoing study, IMPACT, will clarify the benefits of PCa screening in this higher-risk population. Promising clinical trials are evaluating the role of PARP inhibitors in the metastatic setting, but more studies are needed to establish the role of adjuvant treatment, with PARP inhibitors and/or conventional chemotherapy. The role of chemoprophylaxis in patients with high risk of aggressive forms of PCa also needs to be addressed. A better characterization of *BRCA*-related prostate tumours would help to identify sporadic cases with potential lethal forms of the disease that might benefit from the therapeutic strategies designed for *BRCA*-mutated tumours.

COMPETING FINANCIAL INTERESTS

The authors declare no competing financial interests.

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