Prostate cancer in male BRCA1 and BRCA2 mutation carriers has a more aggressive phenotype

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There is a high and rising prevalence of prostate cancer (PRCA) within the male population of the United Kingdom. Although the relative risk of PRCA is higher in male BRCA2 and BRCA1 mutation carriers, the histological characteristics of this malignancy in these groups have not been clearly defined. We present the histopathological findings in the first UK series of BRCA1 and BRCA2 mutation carriers with PRCA. The archived histopathological tissue sections of 20 BRCA1/2 mutation carriers with PRCA were collected from histopathology laboratories in England, Ireland and Scotland. The cases were matched to a control group by age, stage and serum PSA level of PRCA cases diagnosed in the general population. Following histopathological evaluation and re-grading according to current conventional criteria, Gleason scores of PRCA developed by BRCA1/2 mutation carriers were identified to be significantly higher (Gleason scores 8, 9 or 10, P = 0.012) than those in the control group. Since BRCA1/2 mutation carrier status is associated with more aggressive disease, it is a prognostic factor for PRCA outcome. Targeting screening to this population may detect disease at an earlier clinical stage which may therefore be beneficial.

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Prostate cancer (PRCA) is the most commonly diagnosed malignancy in men in the United Kingdom. It is thought to be composed of aggressive and indolent varieties. Indolent PRCA may exist for many years without causing symptoms or shortening life expectancy. Aggressive PRCA may cause symptoms difficult to palliate with conventional treatments and is likely to shorten life expectancy. Distinguishing which men are at risk of which types of disease could have far-reaching consequences not only in the treatment and follow-up of patients but also in the surveillance of groups at risk of aggressive PRCA.

The morphology of breast cancer found in female BRCA1 and BRCA2 germline mutation carriers has been studied extensively. The histopathological features of breast tumours from patients with BRCA1 and BRCA2 mutations differ from each other and from sporadic breast cancers (Lakhani et al, 1998). BRCA1 and BRCA2 breast cancers are of higher grade (Lakhani, 2001). BRCA1-associated tumours are more likely to be oestrogen, progesterone receptor and Her2 receptor negative, express TP53 protein, and demonstrate medullary/atypical medullary morphology. Lakhani (2001) predicts that a woman diagnosed with high-grade, oestrogen receptor-negative breast cancer before the age of 30 years has a 40–45% chance of harbouring a BRCA1 mutation, compared with a 4–5% chance if these parameters are not met (Lakhani, 2001). Many of the features identified in breast cancer in women who are BRCA1 mutation carriers are associated with a poor prognosis. If similar data were available for men with PRCA who are carriers of these mutations, weighing up the options for radical treatment or active surveillance could be simplified with this added information.

Despite studies on the incidence of PRCA in male BRCA1 and BRCA2 mutation carriers, there are sparse data recording the histopathology of the disease they develop. The largest and most recent study reports a series of 30 male BRCA2 (999del5) Icelandic founder mutation carriers. The mutation carriers had PRCA with a significantly higher Gleason score, lower mean age of diagnosis, more advanced stage and shorter median survival than a control group (Tryggvadóttir et al, 2007). Before this, the largest series was reported by Giusti et al (2003). Twenty-nine carriers of Ashkenazi Jewish (AI) founder BRCA1/2 mutations who had developed PRCA were compared with non-carriers with PRCA. No difference was seen in Gleason pattern, incidence of prostatic intraepithelial neoplasia (PIN) or atypical adenomatous hyperplasia (Giusti et al, 2003). In another study, Hubert et al (1999) compared two groups each of 87 Israeli men: one group diagnosed with PRCA and the other a control group. The number of AJ founder mutations was not found to be the same in each group. The three mutation carriers in the PRCA group were found to have an average Gleason score
above 8, compared with a Gleason score of 5.9 for non-carriers with PRCA (Hubert et al., 1999). The serum PSA level was also higher than that in non-carriers. Gröndberg et al. (2001) reported a family of five male 999delS BRCA2 mutation carriers from Sweden, who developed poorly differentiated PRCA at an early age of onset with a shortened life expectancy (Gröndberg et al., 2001). A recent PRCA screening study enrolled 19 male BRCA1/2 mutation carriers (12 BRCA1 and 7 BRCA2) and an age-matched control group of men with at least one first-degree relative with PRCA. Annual serum PSA (threshold for prostate biopsy 4 ng ml\(^{-1}\)) and digital rectal examination were undertaken. The two mutation carriers with PRCA were noted to have Gleason scores of 6 and 9 compared with the single subject from the control group who had a Gleason score of 6 (Horsburgh et al., 2005).

When applied correctly, the Gleason scoring system is the most robust and reproducible method currently available for grading the morphological appearances of PRCA (Gleason et al., 1966). The criteria and their application are well documented, but often require adjustment and standardisation if these criteria have not been applied by an expert urological pathologist (Foster, 1991; Deshmukh and Foster, 1998; Epstein et al., 2005; Berney et al., 2007a,b). Currently, the Gleason score is used as a prognostic indicator for individual PRCA in the general population. But the features of PRCA developing in men who harbour a BRCA1 or BRCA2 mutation are not well established. This paper reports the histopathological features of the first UK series of male BRCA1 and BRCA2 mutation carriers with PRCA.

**MATERIALS AND METHODS**

Prostate cancer tissue was collected from cases and controls. A total of 20 cases with BRCA1 or BRCA2 mutations was collected from throughout the United Kingdom and Ireland. These were identified from four sources described below: the EMBRACE (Epidemiological Study of Familial Breast Cancer) study, the IMPACT (Identification of Men with a Genetic Predisposition to Prostate Cancer: Targeted Screening in BRCA1/2 Mutation Carriers and Controls) study, a Cancer Genetics outpatient clinic and a series of young onset PRCA.

Men with PRCA enrolled in the EMBRACE study had consented to the use of their prostate tissue samples for further research. The hospitals where these men had undergone prostate biopsy, prostatectomy or transurethral resection of the prostate (TURP) sent blocks/slides containing prostate tissue to AM. This material was coded anonymously with a unique study number. Where original haematoxylin and eosin slides were not sent, new ones were cut at The Institute of Cancer Research from the blocks provided. Twelve slides were obtained in this manner from England, Ireland and Scotland.

IMPACT is an international screening study for men unaffected by cancer with a known BRCA1 or BRCA2 mutation (and therefore believed to be at increased risk of developing PRCA). One man who was diagnosed with PRCA was recruited from the IMPACT study.

One individual was recruited from the Cancer Genetics outpatient clinic in the Royal Marsden NHS Foundation Trust (RMH).

Six further slides were obtained from The Institute of Cancer Research. A series of 263 men who had PRCA diagnosed under the age of 55 years had previously undergone retrospective BRCA2 mutation analysis using conformational sensitive capillary electrophoresis, which was then confirmed by sequencing. Prostate tissues from the six men found to have deleterious BRCA2 mutations were incorporated into the current study (Edwards et al., 2003).

Controls were obtained from a data set of 4893 men with a diagnosis of PRCA who had been treated at the RMH between 1985 and 2006. One control was obtained from the Royal Liverpool University Hospital. Men were matched for age (± 5 years) wherever possible. The age range was greater than this in four cases (with differences of 7, 9, 9 and 10 years), where it proved difficult to obtain better-matched controls. PSA and disease stage were matched as closely as possible when this information was available from the medical notes. Where PSA or stage was not available, the controls were chosen to have a higher PSA and/or a more advanced stage (Tables 2 and 4). The controls comprised 17 needle biopsies, 2 TURPs and 1 wedge biopsy. Two men from the control group had been tested for and did not harbour any BRCA2 mutations.

Histopathological slides were reviewed by specialist urological pathologists. Seventeen of the control group PRCA slides and all 20 of the BRCA1 and BRCA2 mutation carriers’ PRCA slides were reviewed by a single specialist histopathologist from a tertiary referral centre (CSP). Three of the remaining control group slides were reviewed by one other single, specialist histopathologist, CJ from RMH, a specialist tertiary referral centre. The histopathologists each cross-checked the reporting of a subset of the other’s tissue sections to ensure consistency.

Throughout this study, we have employed only the original grading system, as described by Gleason (1966) and explained by Professor Deshmukh and Foster (1998) (Gleason, 1966; Deshmukh and Foster, 1998). A poorly differentiated tumour was defined as a Gleason pattern greater than 7, that is, combined Gleason score of 8, 9 or 10. Perineural invasion (PNI) and lymphovascular invasion (LVI) were also recorded in each case. The handling of tertiary grades is of practical importance only with respect to grade 7 cancers. The convention defined in the consensus meeting of the International Society of Urological Pathologists and CSF, 2005, in which CSP participated, was followed. In this recommendation, PRCA with a Gleason score of 3 + 4 or 4 + 3 together with a tertiary pattern 5 have their PRCA classified as Gleason score 8 or 9, respectively.

**Statistical methods**

BRCA1/2 mutation carriers were matched with controls for age, PSA and stage of disease to minimise the effect of these factors on the Gleason score comparison. McNemar’s test was used to compare the Gleason score (≤ 7 vs > 7) and presence or absence of PNI and LVI between cases and controls (see Tables 6 – 11). This test looks for differences between the row and column marginal frequencies. It is based on the idea that if there are really no differences in the Gleason scores of BRCA1/2 mutation carriers and non-carriers, then any differences in our sample must have arisen by chance, and are equally likely to occur in favour of the cases than of the controls. Therefore, if there were really no differences, we would expect the number of cases with a low Gleason score who are matched to a control with a low Gleason score (n = 1 in Table 6) to be roughly equal to the number of cases with a high Gleason score who are matched to a control with a low Gleason score (n = 10 in Table 6).

**RESULTS**

Tables 1 – 5 show the characteristics of the patients. The staging of the disease has been corrected to the TNM classification of 2002.

**Patients’ characteristics**

There was a total of 20 cases and 20 controls (4 BRCA1 and 16 BRCA2) (Tables 1 and 3). For the majority of matched cases and controls, where the cases presented with symptomatic or asymptomatic (screen-detected) disease, the controls were matched in the same way. If it was not possible to match for presentation (screen-detected or asymptomatic), the controls were matched to present with symptoms for comparison with cases that presented as a result of screening. This was not possible for three BRCA2 cases and one BRCA1 case; however, where a control either
had unknown cancer or screen-detected disease, the cases that were matched presented with symptomatic disease (Tables 2 and 4).

Of the BRCA2 mutation carriers, nine presented with symptoms, which preceded the diagnosis of PRCA, four men had screen-detected disease and this information was missing for three men. Nine of the control group presented with symptoms, four were screened and three had an unknown presentation.

Three BRCA1 mutation carriers had screen-detected disease.

**Comparison of BRCA1 and BRCA2 mutation carriers with PRCA and controls**

There was a significant difference in the Gleason score between patients with BRCA1 and BRCA2 mutations who had developed PRCA and the controls (Table 6, McNemar’s test, \( P = 0.012 \)). There was no difference in PNI or LVI between the two groups (Tables 7 and 8, McNemar’s test, \( P = 1.00 \) in both cases).

**Table 1**  
**BRCA2 carrier mutation status**

| IM1  | 6819delTG |
| IM4  | 6174delE |
| IM5  | 5910G>G (Y1894X) |
| IM6  | 7771insA |
| IM7  | 6503delTT |
| IM9  | 3386T>G |
| IM11 | 6503delTT |
| IM12 | 3386T>G |
| IM13 | 7084delAAAAG* |
| IM14 | 2558insA |
| IM15 | 7772insA* |
| IM16 | 6710delACAA |
| IM18 | Nucleotide variation 2, intron G>C 1 BP BEF splice site |
| IM19 | 5531delTT |
| IM21 | 83955G>C (D2723H) |
| IM22 | 8205-1G>C |

These mutations are described as pathogenic in the Breast Cancer Mutation Database (BIC; http://research.nhgri.nih.gov/bic/) with the exception of those marked * that are described as pathogenic by Edwards et al (2003).

**Table 2**  
**Age (years), PSA (ng ml\(^{-1}\)), TNM stage, method of detection and year of presentation for BRCA2 mutation carriers**

| Age (years) | PSA (ng ml\(^{-1}\)) | TNM stage | Case | Control | Detection | Year of presentation |
|-------------|----------------------|-----------|------|---------|-----------|---------------------|
| 57          | 59                   | 16.6      | 7.05 | M1      | T3aN1M1c  | Symptomatic         | 1998 |
| 58          | 61                   | 16.6      | 3.4  | M1      | T2ANX1M1 | Symptomatic         | 1999 |
| 67          | 67                   | 107      | 400  | Unknown | T3NX1M1  | Unknown             | 2004 |
| 54          | 52                   | 4.6      | 6.0  | Clinical T1c, pT2c | Clinical T3N1 | Screened            | 2004 |
| 46          | 47                   | 151      | 127  | Negative bone scan, clinically localised | Clinical T3N1 | Screened            | 2004 |
| 46          | 53                   | 4.5      | 15   | m1–ext. iliac LN | Clinical T3N1Mx | Screened            | 2004 |
| 57          | 56                   | 4.7      | 3.5  | pT2cN0  | Clinical T2a | Symptomatic         | 2004 |
| 47          | 52                   | 32       | 49.5 | M1 bone metastases | Clinical T3N1M1 | Screened            | 2004 |
| 48          | 57                   | <1       | 4.6  | T2N0M0  | T1c      | Screened            | 2004 |
| 53          | 58                   | 227      | 200  | T3N0M1  | T3N1M1   | Screened            | 2004 |
| 52          | 49                   | Unknown  | 141  | T2N0M0  | T1c      | Screened            | 2004 |
| 44          | 39                   | 139      | 48.5 | T2N0M0  | T1c      | Screened            | 2004 |
| 56          | 53                   | Unknown  | >100 | T3N0M0  | T3N1M1   | Screened            | 2004 |
| 45          | 50                   | 4.1      | 5.6  | Organ confined | T2, organ confined | Screened            | 2004 |
| 57          | 67                   | 685      | 666  | Unstaged | Unstaged | Screened            | 2004 |

**BRCA2 patients alone**

When the group of BRCA1/2 mutation carriers was divided, the statistically significant difference in Gleason scores between BRCA2 mutation carriers and controls was maintained (Table 9, \( P = 0.0016 \) using McNemar’s test). There was again no difference in PNI or LVI in the two groups (Tables 10 and 11, McNemar’s test, \( P = 1.00 \) in both cases). The BRCA1 mutation carrier group was too small to show statistically significant results.

**DISCUSSION**

We have reported the histopathology found in the first UK series of male BRCA2 and BRCA1 mutation carriers with PRCA. The men who carry the mutations have a diverse heritage (consistent with our population); as such our series is not confined to a few founder mutations. The number of PRCA carriers with Gleason score 8, 9 or 10 is significantly greater in the BRCA1/2 mutation carrier group than that in the control group (\( P = 0.012 \)). This difference is also seen between the BRCA2 mutation carriers alone and the matched control group (\( P = 0.016 \)). These findings would support studies that suggest that male BRCA2 mutation carriers who develop PRCA may have a shorter disease-specific life expectancy than men with PRCA in the general population (Sigurdsson et al, 1997; Edwards et al, 1998, 2005; Tryggvadóttir et al, 2007).

The Breast Cancer Linkage Consortium has conducted a large prospective cohort study. It demonstrated that BRCA2 mutation carriers have a relative risk (RR) of PRCA of 4.65 rising to 7.33 below the age of 65 years and BRCA1 mutation carriers have an RR of PRCA of 1.82 under the age of 65 years (BCLC, 1999; Thompson et al, 2002). Similar data have been recorded in the AJ population.

**Table 3**  
**BRCA1 carrier mutation status**

| IM2  | 3875delGTCT |
| IM3  | 1294del40 |
| IM8  | 185delAG |
| IM10 | 185delAG |

These mutations are described as pathogenic in the Breast Cancer Mutation Database (BIC; http://research.nhgri.nih.gov/bic/).
In the current data set, six men were identified from a previous study conducted at The Institute of Cancer Research, as described in the Materials and Methods section. As these men were selected for mutation analysis following the diagnosis of young onset PRCA, this data set is skewed for young age and so the controls have been matched for age. The median age of PRCA diagnosis in the BRCA2 mutation carriers is 52.5 years and in the matched control group it is 55.5 years. The difference between these two age groups is not significant, but the age of onset in these groups is considerably less than the average age of onset of PRCA in the UK general population (75 years) (www.statistics.gov.uk). It is possible that PRCA in a young age group may show a different histopathology to that in an older age group. However, the controls were matched for age and were found to have a significantly lower Gleason score. Prostate cancer incidence has been shown to be higher in BRCA1 and BRCA2 mutation carriers under the age of 65 years (BCLC, 1999; Thompson et al, 2002). If these carriers do develop more aggressive disease at a younger age than the general population, then screening them for PRCA may be a prudent use of resources.

Matching the cases to the control group was not always straightforward. Prostate cancer dedifferentiates over time (Draisma et al, 2006). Therefore, it can be difficult to match men who may

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### Table 4

| Case (years) | PSA (ng ml⁻¹) | TNM stage | Detection | Year of presentation |
|-------------|---------------|-----------|-----------|----------------------|
| Case Control | Case Control | Case Control | Case Control | Case Control |
| 62 | 64 | 11.6 | 13 | P T3N0M0 | Screened | 1998 |
| 69 | 68 | 6.5 | 6.7 | T3aN0M0 | Symptomatic | 1995 |
| 70 | 74 | 13.4 | 8.3 | Clinical T3a | Screened | 2000 |
| 48 | 50 | 3.8 | 0.6 | Clinical T3N0M0 | Symptomatic | 2003 |

### Table 5

| Median age (cases) | BRCA2 series | 52.5 (44–67) | Wilcoxon signed ranks, P = 0.056 |
|-------------------|--------------|--------------|----------------------------------|
| BRCA1 series      | 65.5 (48–70) | Wilcoxon signed ranks, P = 0.141 |

| Median PSA (cases) | BRCA2 series | 24.3 (4.1–685.0) | Wilcoxon signed ranks, P = 0.583 |
|-------------------|--------------|------------------|----------------------------------|
| BRCA1 series      | 9.1 (38–134) | Wilcoxon signed ranks, P = 0.465 |
| Combined BRCA1 +2 | 12.5 (3.8–685.0) | Wilcoxon signed ranks, P = 0.438 |

### Table 6

| Gleason ≤ 7 | Gleason > 7 | Total |
|-------------|-------------|-------|
| BRCA1/2 mutation carriers | | |
| Gleason ≤ 7 | 2 | 1 | 3 |
| Gleason > 7 | 10 | 7 | 17 |
| Total | 12 | 8 | 20 |

### Table 7

| Control PNI | No | Yes | Total |
|-------------|----|-----|-------|
| BRCA1/2 cases PNI | | | |
| No | 5 | 6 | 11 |
| Yes | 6 | 2 | 8 |
| Total | 11 | 8 | 19*

PNI = perineural invasion. *PNI was reliably commented upon in 19 of the cases.

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(Struwing et al, 1997; Warner et al, 1999; Giusti et al, 2003), although smaller clinical studies have generally not demonstrated an increased frequency of founder BRCA1/2 mutations among Jewish men with PRCA (Lehrer et al, 1998; Hubert et al, 1999; Nastiuk et al, 1999; Vazina et al, 2000).
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Table 10 PNI status of BRCA2 mutation carriers and their matched controls

| Control PNI | Case PNI | Total |
|-------------|----------|-------|
| No | Yes | Total |
| No | 4 | 5 | 9 |
| Yes | 5 | 1 | 6 |
| Total | 9 | 6 | 15 * |

PNI = perineural invasion. *PNI was reliably commented upon on 15 of the cases.

Table 11 LVI status of BRCA2 mutation carriers and their matched controls

| Control LVI | Case LVI | Total |
|-------------|----------|-------|
| No | Yes | Total |
| No | 4 | 5 | 9 |
| Yes | 5 | 1 | 6 |
| Total | 9 | 6 | 15 * |

LVI = lymphovascular invasion. *LVI was reliably commented upon on 15 of the cases.

or may not have had the disease in situ for differing lengths of time. To minimise such lead-time bias, the men in the control group were matched for PSA and stage of disease. This produced complications, as adequate data were not always recorded in the patients’ medical notes. In cases where relevant data were found to be missing, the controls were chosen with advanced stage and with a serum PSA level higher than 100 ng ml⁻¹. This was done in order to bias the control group towards more advanced disease and therefore with potential for dedifferentiation to a more aggressive Gleason pattern. This means that the effect that we have reported in BRCA1/2 mutation carriers is probably greater in reality.

Similarly, it could be argued that men who present with symptomatic disease could have a more advanced natural history than those men who present with screen-detected disease (Draisma et al, 2006). In this series of men, the controls have been carefully chosen so that they have presented with symptoms more often than the BRCA1/2 mutation carrier group. In the BRCA2 series, the control group only presented with screen-detected disease in four men, whereas the BRCA1 mutation carrier cases presented with symptomatic disease once.

A more difficult variable for which to correct is the fact that this series of cases and controls uses data from a variety of sources, including prostate biopsies, TURPs and prostatectomies for comparison. Also, the patients in this series had sextant biopsies (Hodge et al, 1989). Reports have suggested that needle biopsy and radical prostatectomy Gleason scores only match in 45% of cases (Bostwick, 1994; Levine et al, 1998; King et al, 2004). This is likely to result from intraobserver and interobserver variability in Gleason grading and sampling error in taking the biopsy. Ozdamar et al (1996) showed that grading error was greatest with well-differentiated (Gleason scores 2–4) tumours. In these cases, the accuracy was only 15% with needle biopsy (Ozdamar et al, 1996). Of patients with Gleason scores 5–7 on needle biopsy, 97% were graded correctly. All those with Gleason scores 8–10 on needle biopsy were graded correctly. Deshmukh and Foster (1998) argue that some pathologists do not identify milder forms of grade 3 PRCA and label it instead as grade 2. In this study, no PRCA were found to have a Gleason score less than 6.

There is also discordance in the reporting of Gleason scores among pathologists (Allsbrook et al, 2001a). This is, however, significantly less between specialist urological pathologists (Allsbrook et al, 2001b). Both CJ and CSF are specialist urological pathologists. Recently, these criteria have been used to assess a large number of PRCA in the United Kingdom and to resolve discrepancies (Berney et al, 2007a,b). Risk of interobserver variability was further minimised in this study by having CJ review a subset of the cases and controls; there was no discordance between the two histopathologists.

Of the 16 controls for the BRCA2 series, 14 had not been tested for a BRCA2 mutation. Edwards et al (2003) found that the incidence of BRCA2 mutation in early-onset PRCA sufferers (under the age of 55 years) could be as high as 3.0% (Edwards et al, 2003). The average age of our control group was 55.5 years, so we would expect that at most one of these men could have harboured a BRCA2 mutation.

In conclusion, this data set is the first UK series of male BRCA1 and BRCA2 mutation carriers with PRCA. These mutation carriers have a significantly higher Gleason score than the non-carriers with PRCA. It would follow that the BRCA1 and BRCA2 mutations are therefore prognostic markers for aggressive PRCA. If screening for PRCA using serum PSA detects malignant disease at an earlier stage, this may have the potential to reduce mortality from a histologically aggressive disease in this population. These data would support screening male BRCA1 and BRCA2 mutation carriers for PRCA. The IMPACT study is currently recruiting nationally within the United Kingdom and internationally in Australia and Norway. IMPACT will investigate whether targeted PSA screening detects PRCA in this subgroup of high-risk men.

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