Prostate cancer in BRCA2 germline mutation carriers is associated with poorer prognosis

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BACKGROUND: The germline BRCA2 mutation is associated with increased prostate cancer (PrCa) risk. We have assessed survival in young PrCa cases with a germline mutation in BRCA2 and investigated loss of heterozygosity at BRCA2 in their tumours.

METHODS: Two cohorts were compared: one was a group with young-onset PrCa, tested for germline BRCA2 mutations (6 of 263 cases had a germline BRCA2 mutation), and the second was a validation set consisting of a clinical set from Manchester of known BRCA2 mutation carriers (15 cases) with PrCa. Survival data were compared with a control series of patients in a single clinic as determined by Kaplan–Meier estimates. Loss of heterozygosity was tested for in the DNA of tumour tissue of the young-onset group by typing four microsatellite markers that flanked the BRCA2 gene, followed by sequencing.

RESULTS: Median survival of all PrCa cases with a germline BRCA2 mutation was shorter at 4.8 years than was survival in controls at 8.5 years (P = 0.002). Loss of heterozygosity was found in the majority of tumours of BRCA2 mutation carriers. Multivariate analysis confirmed that the poorer survival of PrCa in BRCA2 mutation carriers is associated with the germline BRCA2 mutation per se.

CONCLUSION: BRCA2 germline mutation is an independent prognostic factor for survival in PrCa. Such patients should not be managed with active surveillance as they have more aggressive disease.

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DNA extraction and LOH studies
Germline DNA was obtained from peripheral blood samples and extracted as reported in previous articles (Edwards et al, 1997). Tumour DNA was obtained from microdissected formalin-fixed paraffin-embedded (FFPE) blocks and extracted as reported in previous articles (Edwards et al, 1998). Normal tissue DNA was also obtained in the same way.

Four microsatellite markers, D13S260, D13S171, D13S267 and D13S1493 within and flanking the BRCA2 gene, were typed on five tumours from those men in group 1 using an ABI (Applied Biosystems, Life Technologies Corporation, Carlsbad, CA, USA) 377 Genetic Analyser. The ‘peak height’ of the alleles was used to determine the ratio of allelic loss compared with either genomic DNA or adjacent normal tissue from paraffin blocks. Percentage allele loss for informative markers (minimum of two) was averaged for each patient.

To determine which allele was lost in the microsatellite LOH results, a sequencing method was used as described in Boettger et al (2003). We used Applied Biosystems dRhodamine chemistry on a 377 Genetic Analyser (Edwards et al, 2003). An average value for the loss was estimated by examining a number of electropherogram peak height signals in the area of the mutation.

RESULTS
Survival analysis
The median overall survival of all BRCA2 mutation carriers was significantly shorter at 4.8 years compared with that of non-carriers at 8.5 years; log rank \( P = 0.003 \) (hazard ratio 2.14 (95% CI: 1.28–3.56); see Figure 1). When analysed by method of ascertainment (see methods), the median survival of the six BRCA2 carriers in group 1 was significantly shorter at 3.6 years \( (P = 0.002; \text{hazard ratio 3.36 (95% CI: 1.50–7.50)}) \), when compared with that of non-carriers. In group 2, the 15 men with germline BRCA2 mutations and PrCa had a median survival of only 5.0 years.

The mutations in BRCA2 in the men with PrCa are listed in Table 1.

Table 2 shows the univariate results. This shows that the following factors are associated with a poorer overall survival: germline BRCA2 mutation status, tumour (T), nodal (N) and metastasis (M) stage, tumour detected clinically rather than by PSA screening, higher Gleason score, treatment that did not involve prostatectomy, PSA at diagnosis of \( \geq 25 \text{ ng ml}^{-1} \) and age \( \geq 55 \) years at diagnosis. In a multivariate analysis, which is shown in Table 3, germline BRCA2 mutation status, T and nodal (N) tumour stage, higher grade, treatment that did not involve

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**MATERIALS AND METHODS**

**Patient recruitment and survival analyses**

Two groups of men with PrCa were studied.

1. A series of men with PrCa from the UK Genetic Prostate Cancer Study (UKGPCS):

   Patient recruitment was conducted as reported in a previous article (Eeles et al, 1997). The coding region of BRCA2 was analysed from blood DNA from 263 PrCa patients diagnosed at \( \leq 55 \) years (2.3%) (Edwards et al, 2003). In this study we report clinical follow-up data and the results of loss of heterozygosity (LOH) analyses on PrCa tumours from the mutation carriers in this report.

   We then studied a second validation data set of men with germline mutations in the BRCA2 gene from a cancer genetics clinic and assessed their survival to confirm our results in a different UK data set of male BRCA2 mutation carriers with PrCa.

2. Men with PrCa who also harbour a germline BRCA2 mutation from a clinical series:

   Men attending a cancer genetics clinic in Manchester, who were found on clinical genetic testing to harbour BRCA2 mutations, were observed from the Access clinical database and their date of death or last follow-up was ascertained from the cancer registry or from their clinical notes.

   Written informed consent was obtained from individuals in this study (ethics number 06/MRE02/4).

   Overall survival was measured from date of diagnosis to date of death or last follow-up. Kaplan–Meier survival analyses were undertaken with patients censored at date of last follow-up. The overall survival of those with and without germline mutations in BRCA2 in group 1 was compared using the log-rank test. The overall survival for those in group 2 was also calculated separately and in combination with group 1. The effect of other factors that could affect survival was analysed using Cox regression. The factors investigated were stage at diagnosis, incidental PSA detection, Gleason score, grade, whether they had a prostatectomy, PSA at diagnosis and age.

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**Figure 1** Kaplan–Meier survival estimates of 21 BRCA2 mutation carriers.
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**Table 1** List of germline mutations in BRCA2 men with prostate cancer from group 1 (diagnosed at age 55 years or under) and group 2

| Patient ID | Age at diagnosis (Years) | BRCA2 mutation (nt) | BRCA2 mutation (nt) NM_000059.1 | Codon U43746 | Codon NM_000059.1 with HGVS nomenclature |
|------------|--------------------------|---------------------|--------------------------------|--------------|------------------------------------------|
| Group 1    |                          |                     |                                |              |
| patient A  | 44                       | 8205-1g>c (<IVS17-1g>c) | 7977-1g>c                        | ISV17-1g>c (splice site) | Stop 2291 | Arg2287Leu6X4 |
| Group 1    | B                        | 7084delAAAAAG       | 6856delAAAAG                     | Stop 878     | Asp777Glu6X11 |
| Group 1    | C                        | 2558insA or 2558dupA | 2330insA or 2330dupA             | Stop 2778    | Thr276Asn6X11 |
| Group 1    | D                        | 8527delC            | 8297delC                         | Stop 2166    | Lys2162Asn6X5 |
| Group 1    | E                        | 6714delACAA*        | 6486delACAA                       | Stop 2537    | Thr2515Asn6X24 |
| Group 1    | F                        | 7771insA or 7771dupA | 7543insA or 7543dupA             |              |

| Group 2    |                          |                     |                                |              |
| Patient 1  | 66                       | 6174delT            | 5946delE                        | Stop 2003    | Ser1982Arg6X22 |
| Patient 2  | 66                       | 5910C> G            | 5682C> G                        | Y1894X (Tyr to Stop) | Tyr1894X |
| Patient 3  | 79                       | 9610C> T            | 9382C> T                        | R3128X (Arg to Stop) | Arg3128X |
| Patient 4  | 74                       | 860-lg>a            | 632-lg>a                        |              |
| Patient 5  | 46                       | 6503delTT (+) 1020A>T | 6275-6276delTT (+) 9976A>T      | Stop 2098 + K3326X |
| Patient 6  | 77                       | 2157delG            | 1929delG                        | Stop 659     | Arg645GluX15 |
| Patient 7  | 74                       | 6503delTT (+) 1020A>T | 6275-6276delTT (+) 9976A>T      | Stop 2098 + K3326X |
| Patient 8  | 57                       | 6819delTG           | 6591delTG                       | Stop 2201    | Glu2198Asn6X4 |
| Patient 9  | 59                       | 3036delACAA         | 2808delACAA                      | Stop 959     | Ala938Pro6X21 |
| Patient 10 | 72                       | 6137C>G             | 5909C>G                          | S1970X       | Ser1970X |
| Patient 11 | 62                       | 2117delC            | 1889delC                        | Stop 643     | Thr630Asn6X14 |
| Patient 12 | 74                       | del exons 14-16     | 94189-1,97275+1+del             | Del exons 14-16 |
| Patient 13 | 66                       | del exons 14-16     | 94189-1,97275+1+del             | Del exons 14-16 |
| Patient 14 | 56                       | 5950delCT           | 5722delCT                       | Stop 1909    | Leu1908Arg6X2 |
| Patient 15 | 73                       | 2157delG            | 1929delG                        | Stop 659     | Arg645GluX15 |

| Table 2 | Univariate analysis of overall survival |
|---------|----------------------------------------|
| Factor Description | Group | Number of patients | Hazard ratio (95% CI) | P-value |
| BRCA2 mutation carrier | No | 1587 | 1.00 | 0.003 |
| Clinical T stage | | | | |
| T1 | 165 | 1.00 | 0.001 |
| T2 | 409 | 1.23 | 0.92 – 1.65 |
| T3 | 510 | 1.88 | 1.43 – 2.49 |
| T4 | 152 | 3.87 | 2.83 – 5.28 |
| TX | 325 | 4.80 | 3.63 – 6.36 |
| N stage | | | | |
| N0 | 882 | 1.00 | | |
| N1-3 | 165 | 3.04 | 2.46 – 3.76 |
| N2X | 514 | 3.32 | 2.88 – 3.84 |
| M stage | | | | |
| M0 | 1008 | 1.00 | | |
| M1 | 456 | 4.38 | 3.80 – 5.05 |
| MX | 86 | 1.61 | 1.21 – 2.15 |
| Incidental PSA detection | Yes | 127 | 1.00 | | |
| Gleason score | ≤7 | 686 | 1.00 | | |
| Grade | 1 | 200 | 1.00 | | |
| 2 | 857 | 1.77 | 1.38 – 2.27 |
| 3 | 330 | 4.02 | 3.09 – 5.23 |
| Prostatectomy | Yes | 82 | 1.00 | | |
| PSA at diagnosis | ≤25 | 498 | 1.00 | | |
| ≥25 | 487 | 2.19 | 1.83 – 2.63 |
| Age group | ≤55 | 119 | 1.00 | 0.02 |
| >55 | 1474 | 1.40 | 1.05 – 1.87 |
| Age | Per year | 1593 | 1.05 | 0.001 |

Abbreviations: CI = confidence interval; M = metastasis; N = nodal; PSA = prostate-specific antigen; T = tumour.

prostatectomy, PSA at diagnosis of ≥25 ng ml⁻¹ and higher age at diagnosis remained independent prognostic factors.

**Loss of heterozygosity (LOH) results**

The DNA from microdissected FFPE tumour tissue was available from 5 of 6 germline BRCA2 carriers. All five showed LOH (see Table 4). A representative microsatellite trace is shown in Figure 2.

To estimate which allele was lost, a sequencing method was adopted. Of the five tumour samples sequenced, it was observed that patient F had lost the mutant allele, whereas patients A, D and E lost the wild-type allele. The tumour from patient B had lost the mutant allele at a low level (approx 10%; Table 4). Representative sequence traces are shown in Figure 3.

**DISCUSSION**

We have shown that men with PrCa, who also harbour a deleterious germline mutation in the BRCA2 gene, have a poorer overall survival. This has been shown in a small sample of men who were diagnosed at ≤55 years with PrCa, compared with those diagnosed at a similarly young age, but who did not harbour a germline mutation as determined by coding sequence analysis from a previous study, and also men from a systematic series of prostate cancer cases in one centre: group 1 (Edwards et al, 2003). We have validated this in a separate data set of men who have had PrCa at any age and who have been found to have a germline mutation in BRCA2 by a clinical genetic testing service, in which genetic testing was offered as part of genetic counselling of families with mutations: group 2. These are usually men within breast cancer families in which women have initially been tested to determine the cause of familial breast cancer clustering within the family. Again, they have a poorer prognosis than men who do not harbour a germline BRCA2 mutation.

It has been shown that local extent or T stage, N stage and presence or not of M stage and higher PSA at presentation are all predictors of poorer survival (Kattan and Scardino, 2002). It was therefore very important to determine whether the poorer survival associated with the presence of a germline BRCA2 mutation was independent. The multivariate analysis confirms that the presence of a germline BRCA2 mutation is a marker of poorer overall survival per se.

This has implications for the detection and management of men with PrCa who are found to harbour germline mutations in the BRCA2 gene, as their poorer survival would be a contraindication for active surveillance. It is not yet known whether these men...
should have a particular modality of treatment (e.g., surgery rather than radiation), as the sample sizes in this paper are too small and treatment data are incomplete in these data sets to be able to determine this.

Before 2008, the only data available on survival in men with PrCa who harbour germline mutations in BRCA2 were from Iceland, where there is a founder mutation (Thorlacius et al., 1996; Sigurðsson et al., 1997; Tryggvadottir et al., 2007). Tryggvadottir et al. (2007) found that PrCa carriers with the BRCA2 999del5 mutation had a lower mean age at diagnosis, more advanced PrCa as assessed by stage and grade, and a shorter median survival time compared with non-carriers. Their study showed a median survival time for carriers (30) of 2.1 years, which was significantly shorter than the 12.4 years for non-carriers (497). The survival time of the Icelandic carriers is much shorter than that reported for our early-onset group 1 carriers of 4 years. One factor to be noted in the Tryggvadottir et al. (2007) study is that all of the 527 PrCa patients were related to breast cancer patients, 28% of whom were first-degree relatives. Of the 527 patients, 30 were determined to be 999del5 carriers. It is therefore possible that the poorer prognosis that was reported could have pertained only to this specific mutation type. This result, and its potential specificity by virtue of mutation and population, has been discussed further by Boormans and Schröder (2007). In contrast, we have shown that in the UK population, men with a variety of other mutations in BRCA2, are likely to have a similarly poorer survival, and therefore the poorer survival is likely to be related to different deleterious mutations in the BRCA2 gene.

We found LOH in the five available PrCa tumours from men in group 1. Three of the five tumours had lost the wild-type allele. This is consistent with a tumour suppressor model and indicative of a causal relationship between BRCA2 germline mutations and predisposition to PrCa in these individuals. Loss of the mutant allele was also observed. The implication is that for disease causation, maybe a gene dosage effect is important.

Tommaska et al. (2008) have recently proposed a model of 'conditional haploinsufficiency', whereby defects in genes such as BRCA1 or BRCA2 can disrupt the regulation of other important genome integrity monitoring genes such as ATM. In this hypothesis, the local effects of these predisposing genes, by virtue of perhaps increased DNA double-strand breaks, would ultimately cause ATM protein inactivation as the cells progressed to malignancy. Although this haploinsufficiency mechanism has only been investigated in breast cancer, it may have implications for the development of PrCa in the carriers that we studied, and could explain why we saw loss of mutant alleles in comparison with the classical loss of wild type.

There is very scant literature on the 'classical' loss of wild-type alleles from PrCa patients who are BRCA2 carriers. Gudmundsson et al. (1995) and Grönberg et al. (2001) have reported LOH in PrCa patients. Gudmundsson et al. (1995) investigated five high-risk breast cancer families and found seven men with PrCa, six of whom had LOH at the BRCA2 locus. Grönberg et al. (2001) studied a breast/prostate family (three breast cancer, five PrCa) that was found to have a deleterious BRCA2 mutation (6051delA). Of the four brothers with PrCa, two had LOH (loss of WT) and two retained heterozygosity.

Willems et al. (2008) reported on the screening of a large series of kConFab Australian BRCA2 breast cancer families. There were many men with PrCa in these families; however, 20 were confirmed to be BRCA2 carriers, and 14 of them had tumours that were available for analysis by multiplex ligation-dependent probe amplification (MLPA). This technique is able to assay the entire BRCA2 gene for loss of promoter and coding regions. Of the 14 BRCA2 carriers, 10 showed loss of heterozygosity by the MLPA method. The set comprised six men with a known family history of PrCa and all the six showed LOH at BRCA2. The conclusion was that the wild-type allele was most often lost, but for the four cases that showed no LOH, epigenetic and haploinsufficiency models were postulated as possible mechanisms. This allele determination was assessed by a sequencing technique that is similar to the one we used. Willems et al. (2008) reported comprehensive clinical data on their carriers and it is noteworthy that all 10 PrCa cases presented with high Gleason scores of 9. This is a finding that is similar to the high-grade presentation of the men in our study.

### Table 3

| Factor                        | Group | Number of patients | Number of events | Hazard ratio (95%CI) | P-value |
|-------------------------------|-------|--------------------|------------------|----------------------|---------|
| BRCA2 mutation carrier        | No    | 506                | 218              | 1                    | 0.002   |
|                               | Yes   | 3                  | 3                | 7.54 (2.11 – 26.98)  |         |
| Clinical T stage              | T1    | 51                 | 16               | 1                    | 0.002   |
|                               | T2    | 158                | 49               | 0.99 (0.56 – 1.75)   |         |
|                               | T3    | 202                | 87               | 1.19 (0.68 – 2.05)   |         |
|                               | T4    | 50                 | 34               | 1.87 (1.00 – 3.48)   |         |
|                               | TX    | 48                 | 35               | 2.34 (1.24 – 4.40)   |         |
| N stage                       | N0    | 344                | 111              | 2.01 (1.36 – 2.98)   | <0.001 |
|                               | N1 – 3| 66                 | 40               | 3.72 (2.65 – 5.23)   |         |
|                               | NX    | 99                 | 70               | 4.04 (2.75 – 5.65)   |         |
| Grade                         | 1     | 33                 | 7                | 2.04 (1.37 – 2.98)   | <0.001 |
|                               | 2     | 376                | 152              | 2.24 (1.03 – 4.88)   |         |
|                               | 3     | 100                | 62               | 3.94 (1.78 – 8.73)   |         |
| Prostatectomy                 | Yes   | 31                 | 4                | 2.84 (1.03 – 7.85)   | 0.044   |
|                               | No    | 478                | 96               | 1.39 (1.04 – 1.86)   | 0.027   |
| PSA at Diagnosis              | <25   | 282                | 125              | 1.02 (1.00 – 1.04)   | 0.026   |
|                               | ≥25   | 227                | 221              | 1.02 (1.00 – 1.04)   |         |

### Table 4

| Patient ID | Number of informative markers | LOH (%) by microsatellite analysis (average) | Allele lost by sequencing |
|------------|-----------------------------|--------------------------------------------|--------------------------|
| A          | 3                           | 77                                         | WT                       |
| B          | 4                           | 87                                         | MUT                      |
| D          | 2                           | 97                                         | WT                       |
| E          | 4                           | 77                                         | WT                       |
| F          | 3                           | 81                                         | MUT                      |

Abbreviations: CI = confidence interval; N = nodal; PSA = prostate-specific antigen; T = tumour.
group 1. The risk estimates of 3.5-fold for PrCa, as reported by Willems et al (2008), are lower than the RR reported by us in 2003 (Edwards et al, 2003).

In 2008, Narod et al (2008) reported data on a panel of PrCa patients with BRCA1 and BRCA2 germline mutations identified from breast cancer families. For the combined group of known and inferred carriers, the median survival for 183 BRCA2 patients was 4.0 years vs 8.0 years for the 119 men in the BRCA1 group. When only known carriers were analysed, the results were 5.0 years (67 BRCA2 known carriers) and 15.0 years (37 BRCA1

Figure 2  Example of LOH seen with D13S1493 in two patients – A and D.

Figure 3  Examples of allele loss in patients A, D and F. Arrows show the position of a representative peak for signal analysis.
known carriers). Although there is a difference in the survival of BRCA1 patients, which is discussed by the authors, the poorer survival of BRCA2-related patients is not in dispute. Use of either survival measure, 4 or 5 years, illustrates that the median survival of the patients studied is very similar to that observed in our study of 4.8 years.

It is not yet known whether earlier detection of PrCa in men with germline mutations in BRCA2 will result in a better outcome and whether PSA screening is suitable for such a population. The IMPACT study (Identification of Men with a genetic predisposition to Prostate Cancer: Targeted screening in BRCA1 and BRCA2 mutation carriers and controls) has been developed to investigate the role of targeted PrCa screening in male BRCA1 and BRCA2 gene mutation carriers using an annual PSA screen (Mitra et al., 2007). Early data have suggested that men will uptake screening and that PrCa was twice as likely in BRCA1/2 mutation carriers (Horsburgh et al., 2005).

Our data have shown that the observation in Iceland, which shows that men who carry the Icelandic founder mutation in the BRCA2 gene who also develop PrCa have a poorer survival, is not restricted to this mutation and we have shown that this is due to the presence of a deleterious mutation within the BRCA2 gene per se. There is some dispute about the precise frequency of germline BRCA2 mutation in men with PrCa. This is reported to be about 1% in men aged ≤55 years in a US series (Agalliu et al., 2007), but this may be equivalent to 65–68 years at clinical diagnosis, as the prevalence of PSA screen-detected disease is higher in the United States. This is likely to be the case, as in this US series, 67.3% of men had a PSA of <10. We have found that 2.3% of men diagnosed with clinically presenting disease (non-PSA detected) have a germline BRCA2 mutation (Edwards et al., 2003). Even if the incidence of a germline mutation in men with young-onset (defined as ≤55 years at diagnosis) PrCa was as low as 2%, the finding of a BRCA2 mutation would be an indication to avoid active surveillance in these patients, as they have a more aggressive disease outcome.

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Conflict of interest

The authors declare no conflict of interest.

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