FULL PAPER

BJC

British Journal of Cancer (2014) 111, 1238–1240 | doi: 10.1038/bjc.2014.428

Keywords: prostate cancer; BRCA2; PSA

The impact of a BRCA2 mutation on mortality from screen-detected prostate cancer

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Background: Men with a BRCA2 mutation face an increased risk of prostate cancer. These cancers tend to have an aggressive nature and it has not yet been demonstrated that regular screening of BRCA2 carriers is associated with improved survival.

Methods: We identified 4187 men who underwent a prostate cancer biopsy for an elevated PSA or an abnormal digital rectal examination between 1998 and 2010. We screened the BRCA2 gene in its entirety for mutations and we followed the men for death from prostate cancer until December 2012.

Results: The 12-year prostate cancer-specific survival rate was 94.3% for men without a BRCA2 mutation and was 61.8% for men with a mutation ($P<10^{-4}$; log-rank test).

Conclusions: The survival of men with screen-detected prostate cancer and a BRCA2 mutation is much poorer than expected.

Men with a BRCA2 mutation are at increased risk of developing prostate cancer (Breast Cancer Linkage Consortium, 1999; Van Asperen *et al*, 2005). Clinical observational studies have shown that the prognosis of men with prostate cancer and a BRCA2 mutation is worse than expected (Tryggvadottir *et al*, 2007; Mitra *et al*, 2008; Narod *et al*, 2008; Castro *et al*, 2013). In a study from the UK (Castro *et al*, 2013), the mortality ratio for men with prostate cancer associated with carrying a BRCA1 mutation was 1.9 (95% CI 1.1–3.1). It has been proposed, based on the elevated risk of aggressive cancer, that men with a mutation be screened annually with a PSA test. In the context of the IMPACT screening study among 731 men with a BRCA2 mutation, 59 had a PSA above 3.0 ng ml^{-1} and of these 24 had cancer detected at biopsy (Bancroft *et al*, 2014). Of the 24 BRCA2-positive cases, 17 had an intermediate or high-risk cancer. The mortality experience of these 24 men has not yet been determined. It is hoped that through regular screening from age 45, death from prostate cancer can be prevented in men with a BRCA2 mutation. In the present study, we have genotyped a large cohort of 4187 men who underwent a prostate biopsy because of an abnormal screening test and we estimated the 12-year survival for men with and without a BRCA2 mutation.

MATERIALS AND METHODS

To evaluate the importance of a BRCA2 mutation on mortality from prostate cancer detected in a screening setting, we sequenced the entire 26 coding exons of BRCA2 gene in the germline DNA of 4187 men from two tertiary care centres in Canada (Sunnybrook Health Sciences Centre and Princess Margaret Hospital) who underwent a prostate biopsy because of an elevated prostate-specific antigen (PSA) blood test (>4.0 ng ml^{-1}) or an abnormal digital rectal examination, between June 1998 and February 2010. Among these men, 1904 (45.5%) were diagnosed with prostate cancer at biopsy (case subjects), and for 2283 men (54.5%) prostate cancer was not found (control subjects). The study was approved by the ethics review board at each centre. All study subjects provided signed informed consent before participation.

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Received 12 March 2014; revised 29 June 2014; accepted 8 July 2014; published online 7 August 2014

The isolated DNA samples from peripheral leukocytes were sequenced using conventional Sanger sequencing method for all 26 coding exons of BRCA2 (NM_000059.3). We determined the crude (unadjusted) odds ratio for prostate cancer, given a BRCA2 mutation, based on 2×2 table analysis of case subjects and control subjects and used Fisher's exact test to test for statistical significance. We estimated the 12-year survival from diagnosis using the Kaplan–Meier method, and adjusted hazard ratios were calculated using the Cox proportional hazards model. Hazard ratios were adjusted for age of diagnosis, PSA level at diagnosis and Gleason grade (<7; $\geqslant 7$). All two-sided P-values of 0.05 or less were considered statistically significant. All analyses were conducted using the SAS System Version 9.3 (Cary, NC, USA).

RESULTS

A BRCA2 mutation was found in 26 of 1904 cases (1.4%) *vs* 9 of 2283 controls (0.4%), and was associated with a significantly increased risk of prostate cancer detected (OR = 3.50; 95% CI = 1.63–7.48, $P = 0.0006$). Among the case subjects with prostate cancer, those who carried a mutation were diagnosed on average at 67 years (range 49–90 years) compared with 65 years for the case subjects without a mutation. The PSA concentration at diagnosis was higher among the case subjects who carried a mutation than among those who did not carry a mutation (56.3 *vs* 13.3 ng ml^{-1}; $P < 0.0001$). The age of the mutation carriers when they had PSA tests was on average 66 years (range 49–89). Of the BRCA2 carriers, 96% had high-grade disease, compared with 54% of the non-carriers ($P < 10^{-4}$). Stage was available for 24 BRCA2-associated cases; of these, 13 men had stage I/II disease, five men had stage III disease and six men had stage IV (metastatic) disease.

All subjects were followed for prostate cancer mortality. The mean length of follow up was 8.7 years (range 0.1–12 years). Of the 26 case subjects with a BRCA2 mutation, 19 are currently alive (73%). Of the 1878 case subjects without a BRCA2 mutation, 1799 are currently alive (96%). The 12-year survival for men with a BRCA2 mutation was inferior to that of men without a BRCA2 mutation (61.8% *vs* 94.3%; $P < 10^{-4}$) (Figure 1). The crude hazard ratio for mortality was 7.8 (95% CI 3.6–17). After adjusting for age at diagnosis, PSA level at diagnosis and grade, the hazard ratio for prostate cancer-specific mortality associated with a BRCA2 mutation was 3.48 (95% CI 1.58–7.72; $P < 0.002$). Among the men with high-grade disease (Gleason 7–9), the presence of a BRCA2 mutation was associated with a hazard ratio of 4.38 (95% CI 1.99–9.62; $P < 0.0001$) after adjusting for age and PSA level.

DISCUSSION

In this study of screen-detected prostate cancers, the long-term survival of the BRCA2 carriers was much worse than that of the non-carriers, in particular for men with advanced stage disease; 25% of patients with a BRCA2 mutation had metastatic cancer at diagnosis and for these the 12-year survival rate was poor (33%). Among the 75% of patients with less advanced disease (stage I–III), the 12-year survival rate was 66% (Figure 2). We did not have a comparison group of mutation carriers diagnosed with prostate cancer as a consequence of clinical symptoms, but in the previous study (Castro *et al*, 2013) of men with (clinically or screen detected) prostate cancer, the 5-year survival was 68% compared with 87% in our study. The difference in 5-year survival could not be attributed to downstaging associated with screening, in our study, 46% of men (11/24) with a mutation presented with stage III/IV disease, compared with 37% of men in the Castro *et al* (2013) study. The superior survival rate observed in our series of screen-detected patients suggests that screening might be associated with improved survival in BRCA2 carriers, but the potential impact of lead-time bias and of relatively small samples must also be considered.

The principal strength of our study was that both the carrier group and the non-carrier comparison group were identified through the genotyping of a single cohort. The risk of aggressive prostate cancer is increased in men with a BRCA2 mutation. In the absence of data from a randomised trial, these observational studies support the recommendation for prostate screening for men with BRCA2 mutation. The earliest age of diagnosis of prostate cancer in a BRCA2 carrier in our study was 49 years, and it is possible that if all the BRCA2 carriers have regular PSA screening from age 45, the survival might be higher. The average PSA in the carriers at diagnosis was 56.3 ng ml^{-1} and it is likely that the PSA level was abnormal for several years prior. We do not have data on previous screening in the cohort but the data suggest a rationale for offering PSA screening to BRCA2 carriers before age 50, as is the recommendation for the general population. PSA screening has not been shown to be clearly of benefit in the general population (Andriole *et al*, 2009). To some extent, this might be due to the very good survival of men with screen-detected prostate cancer and few cancer deaths were documented in the cohorts studied (as seen in our study). This is not the case for BRCA2 carriers; the 12-year mortality rate of 38% for the BRCA2 carriers attests to the aggressive nature of these malignancies. Data from the general population should not be extrapolated to promote screening policies for the BRCA2-positive men. BRCA2 mutations accounted for only 1.4% of all prostate cancers in this series, but for

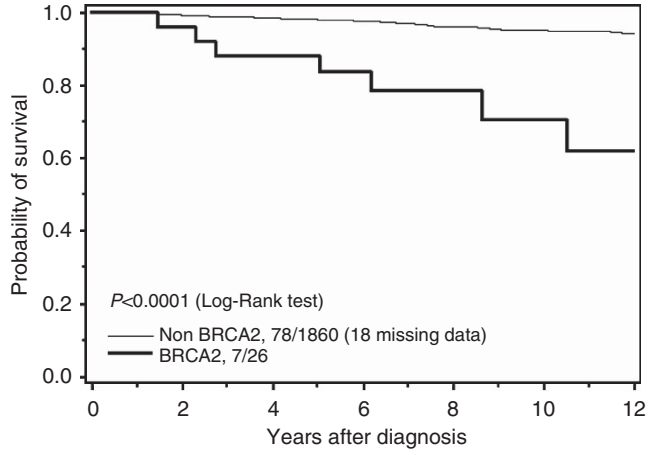

Figure 1. Prostate cancer-specific survival by BRCA2 mutation status.

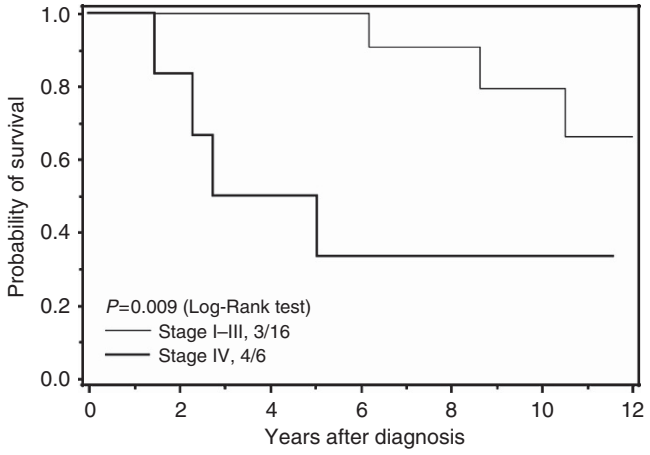

Figure 2. Prostate cancer-specific survival in BRCA2 carriers, by stage.

8.2% of the deaths from prostate cancer. BRCA2 carriers with prostate cancer may benefit from additional therapies, such as with cis-platinum or a PARP inhibitor.

ACKNOWLEDGEMENTS

This work was supported by a grant from the CIHR.

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