Editorial Commentary

The established risk of prostate cancer comorbidity in *BRCA1/2* mutation carriers: where is the clinically relevant hotspot for prostate cancer?

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BRCA2 carriers have a higher risk of prostate cancer (PCa), especially of an aggressive pattern, according to new data from a prospective cohort study published by Nyberg *et al.* in *European Urology* (1). Two prospective reports on PCa risks for *BRCA1/2* carriers have previously been published (2,3). However, these were limited in that the 95% confidence interval (CI) was wide and absolute risk was not represented, owing to small sample sizes. The aim of the current EMBRACE study (Epidemiological Study of Familial Breast Cancer; http://ccge.medschl.cam.ac.uk/embrace/) is to create a register of families carrying *BRCA1/2* mutations and to obtain prospective estimates of cancer incidence for these carriers. This cohort study including *BRCA1* (n=376) and *BRCA2* (n=477) mutation carriers started in 1998 across the UK and Ireland. All participants were male with no PCa diagnosis at recruitment. Their median follow-up times were 5.9 and 5.3 years for UK and Irish patients, respectively.

Nyberg *et al.* examined the relationship between *BRCA2* mutation carriers and PCa risk or clinical grade. Twenty-six *BRCA2* carriers were diagnosed with PCa during follow-up and had a higher risk [standardized incidence rate (SIR), 4.45; 95% CI, 2.99–6.61] compared with population in the UK. Notably, the risk at age <65 years was also high (SIR, 3.99; 95% CI, 1.88–8.49). Moreover, *BRCA2* mutation carriers with a family history of PCa showed a prominently higher risk (SIR, 7.31; 95% CI, 3.40–15.7). *BRCA2* mutation carriers also had a higher Gleason score (≥7). However, *BRCA1* mutation carriers were associated with a more modest incidence risk of PCa. Consistently, a meta-analysis by Oh *et al.* that summarized eight cohort, seven case-control, four case series, 28 frequencies, and 11 survival studies, found that *BRCA2* mutations were associated with a greater risk of PCa [odds ratio (OR), 2.64; 95% CI, 2.03–3.47] than *BRCA1* mutations (OR, 1.35; 95% CI, 1.03–1.76) (4).

Intriguingly, *BRCA1* mutations are more common in ovarian and breast cancer than *BRCA2* mutations. In fact, the percentages of patients with *BRCA1/2* alterations differ in various cancer types (5). BRCA1 and BRCA2 share a common pathway of genome repair. To maintain genomic integrity, DNA damage response (DDR) genes mediate cellular signals against double-strand breaks caused by genotoxic stresses such as ionizing radiation and other genotoxic compounds. The DDR also includes the activation of checkpoints that delay the cell cycle at G1/S or G2/M, enabling sufficient time for DNA repair not to be transmitted to subsequent generations.

Two systems are employed to repair double-strand breaks, homologous recombination (HR) and non-homologous end-joining (NHEJ). BRCA1 and BRCA2 are associated with HR which is mostly error-free in their roles as tumor suppressors. However, *BRCA1/2* genes function differently in terms of DDR (6). BRCA1 has functions in both checkpoint activation and DNA repair, whereas BRCA2 is a mediator of the core mechanism of HR. Mutations in both *BRCA1* and

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BRCA2 lead to HR deficiency (HRD) and compensatory repair of double-strand breaks by NHEJ, which is error-prone repair mechanism compared with HR. Thus, repair-errors caused by HRD by *BRCA1/2* mutations accumulate in the genome and increase the rate of carcinogenesis; thus, *BRCA1/2* mutation carriers have an increased risk of PCa at a younger age. To account for tissue-specific roles of *BRCA1* and *BRCA2* mutations, the interactions of BRCAs and steroid receptors including estrogen receptor and progesterone receptor were suggested (7). However, the mechanism by which *BRCA2* is a higher risk factor for PCa compared with *BRCA1* remains unclear and requires further study.

The increased risk of cancer death not only reflects increased carcinogenesis, but also the onset of a clinically high grade of cancer at an early age. Therefore, *BRCA1/2* mutation carriers have worse outcomes than non-carriers with respect to treatment for locally-advanced PCa. Castro *et al.* reported that *BRCA2* mutations are an independent prognostic factor for cause-specific survival in all stages of PCa including localized disease (8). They also reported that *BRCA1/2* mutation carriers have worse metastatic-free survival and cause-specific survival after radical treatment such as radical prostatectomy or external beam radiation therapy (9). The controversies regarding prognosis following treatment with non-curative therapy (10) indicate that further investigations into *BRCA1/2* mutations and prognosis in PCa are required.

Nyberg *et al.* investigated the association between the ovarian cancer cluster region (OCCR) and PCa risk. OCCR is a well-known region which is strongly associated with ovarian cancer risk (11). This study reported that *BRCA2* mutations located in positions c.2831 and c.6401 of the OCCR were less associated with PCa risk (SIR, 2.46; 95% CI, 1.07–5.64) than other regions (SIR, 5.88; 95% CI, 3.75–9.22), suggesting that mutations outside the OCCR play an important role in the PCa incidence. This is consistent with breast cancer findings, in which BRCA1/2 mutations outside the OCCR were associated with a significantly higher breast cancer risk compared with mutations within the OCCR (12). However, so far, the association between *BRCA2* mutations in the OCCR and PCa risk is controversial. Lubinski *et al.* reported that *BRCA2* carriers of the 6174delT mutation were less likely to have a family member with PCa (OR, 0.62; P=0.04) than those without mutations (13). In contrast, Moran *et al.* showed that a higher risk of PCa (HR, 2.92; 95% CI, 1.54–5.54) was found in males with mutations in the *BRCA2* OCCR region than in other regions (14). To resolve these discrepancies, additional studies into the relationship between the OCCR and PCa risks as well as prognosis are required.

Finally, *BRCA1/2* mutations have an important clinical impact because precision medicine is considered for carriers. Page *et al.* assessed the utility of prostate-specific antigen (PSA) screening in an IMPACT study for mean aged 40–60 years with or without *BRCA1/2* mutations (15). In an interim report 3 years after screening began, *BRCA2* mutation carriers were associated with a higher incidence of PCa, younger age of diagnosis, and more clinically significant tumors compared with men with no *BRCA1/2* mutations. Therefore, they concluded that PSA screening for men with *BRCA2* mutations is recommended. In terms of treatment, Pomerantz *et al.* reported that *BRCA2* mutation carriers responded favorably to platinum-based chemotherapy normally used in the treatment of breast and ovarian cancers (16). Additionally, poly adenosine diphosphate (ADP)-ribose polymerase (PARP) inhibitors are a novel and promising drug for PCa patients carrying *BRCA1/2* mutations. Single strand annealing by PARP is an alternative pathway for DNA repair. PARP is essential for the survival of cells with HRD, and further inhibition of PARP function in such cells renders DDR impossible leading to cell death. Thus, the confirmation of *BRCA1/2* mutations is important for genomic medicine.

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appropriately investigated and resolved.

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