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Clinical Management of Prostate Cancer in Men with BRCA Mutations

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Clinical Management of Prostate Cancer in Men with BRCA Mutations

This month's issue of European Urology includes a report on the outcome after local prostate cancer (PCa) treatment in men with mutations in the cancer susceptibility genes "Breast cancer 1, early onset" (*BRCA1*) or "Breast cancer 2, early onset" (*BRCA2*) [1]. Germ-line mutations in these genes confer a much increased risk of breast and ovarian cancers in women and, to a somewhat lesser degree, PCa and other cancers in men [2, 3]. In female *BRCA* carriers, breast cancer screening and risk reducing, prophylactic surgery have documented effects on breast and ovarian cancer morbidity and mortality [2]. In comparison, the scientific basis for the management of male *BRCA* mutation carriers is poor and the present report by Castro and co-workers therefore welcome. They analysed the outcome of 67 *BRCA* mutation carriers and 1,235 non-carriers with PCa treated with either radical prostatectomy or radiotherapy and found that the rates of metastatic disease and death from PCa were significantly higher among the carriers [1]. A *BRCA* mutation was an independent, negative prognostic factor even after adjusting for cancer grade, stage and prostate-specific antigen (PSA) level in multivariable analysis.

What are the clinical implications of the results from this and other studies on germ-line *BRCA* mutations in men with and without PCa? The first step is to always obtain a thorough cancer family history from our PCa patients and in men with increased PSA values. A germ-line *BRCA* mutation should be suspected in families with multiple cases of early onset prostate, breast and/or ovarian cancer. Such families should be offered appropriate oncogenetic counselling, including molecular genetic diagnostics [2, 3].

Second, since male unaffected *BRCA2* mutation carriers clearly have a much increased risk of early onset, aggressive PCa [3-5], they should be recommended PSA testing from the age of 40 years [6]. A remarkably high PCa mortality following standard screening with PSA and digital rectal examination has been reported for men with *BRCA2* mutations [5], indicating that the screening intervals should be shorter and the PSA thresholds lower for them, than for men in the general population. The reports are less consistent regarding the PCa risk and phenotype in *BRCA1* mutation carriers [3]. A reasonable approach is to inform male *BRCA1* mutation carriers that they may have a significantly increased risk of PCa and to offer them PSA-testing from age 40 years. The PCa detection rate following screening of male *BRCA* mutation carriers was recently reported in the *European Urology*, but *BRCA1* and *BRCA2* mutation carriers were not reported separately [6]. Further reports from this important, prospective study are eagerly awaited, not least on the possible different impact of *BRCA1* and *BRCA2* mutations on PCa risk and phenotype.

Third, radical local therapy should be initiated early when PCa is diagnosed in *BRCA* mutation carriers, at least in *BRCA2* mutation carriers. Active surveillance may not be safe even for a “very low risk PCa” in these men. Castro and co-workers report that a *BRCA* mutation is an independent negative prognostic factor after treatment with either radical prostatectomy or radiotherapy [1]. They did not report the outcome of *BRCA1* and *BRCA2* mutation carriers separately, presumably because there were too few men in each group. Their results, together with the poor outcome of PCa screening in *BRCA2* mutation carriers [5], highlight a need for combining the local treatment with adjuvant systemic therapy. However, there is no evidence to support that adjuvant therapy decreases mortality in this group of patients, or indeed in any other group of PCa patients. Since germ-line *BRCA* mutations are found in only ~ 2% of PCa cases [5, 7], it is unlikely that we will see specific studies of adjuvant PCa treatment in *BRCA* mutation carriers. Most likely, future studies of adjuvant treatment of high risk PCa in men with unknown *BRCA* mutation status will have to guide the adjuvant treatment also in men with *BRCA* mutations.

Fourth, *BRCA* mutation carriers with metastatic PCa may benefit from other systemic treatments than those usually offered to men with PCa. Olaparib, an inhibitor of poly-(adenosindiphosphat-ribose) polymerase (PARP) has a specific activity in *BRCA* associated cancers, including PCa [8]. Furthermore, *BRCA2* mutations may be associated with better response to platinum based chemotherapy [9]. This may explain the somewhat less adverse prognosis observed among ovarian cancer patients with a *BRCA* mutation compared with sporadic cases [10].

To conclude, men with a suspected or confirmed germ-line *BRCA* mutation are a small but clinically important patient group. It is important that we identify the potential *BRCA* mutation carriers among the great numbers of men with PCa or increased PSA levels in our daily clinical practice, and that we manage them and their families adequately. An absolute prerequisite for the further advance on the management of men with a *BRCA* mutation is the continued effort by multi-institutional networks, like those represented by Castro and co-workers. We applaud their efforts and hope that they and others will continue to collect prospective data on an increasing number of men with a genetic predisposition to PCa.

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