ADVANCES IN ONCOLOGY

Current Developments in the Management of Solid Tumor Malignancies

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Prostate Cancer in Focus

BRCA Mutations in Prostate Cancer Patients

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H&O What have previous data suggested about BRCA mutations in prostate cancer patients?

DO Previous studies have suggested that some specific *BRCA* mutations are associated with more aggressive prostate cancer histology, as measured by Gleason score. These include studies by Agalliu and colleagues, Mitra and associates, and Gallagher and coauthors.

EC In addition, studies have suggested that the Icelandic founder mutation in the *BRCA2* gene and 2 Askhenazi founder mutations are associated with worse prostate cancer outcomes. Tryggvadottir and colleagues published one of 2 large studies analyzing the effect of founder *BRCA1* and *BRCA2* mutations in specific populations, and a paper by Gallagher and coauthors has the largest and most complete series of patients with Askenazi *BRCA* mutations. Little is known about the impact of other *BRCA* mutations in more extended populations, however. The Gallagher study had suggested that *BRCA* mutations were associated with more dedifferentiated tumors with higher Gleason scores, but this study looked at survival without taking into account other prognostic factors for prostate cancer, such as prostate-specific antigen (PSA) at diagnosis, TNM classification, Gleason score, and age.

H&O How common are BRCA mutations in prostate cancer patients, and are certain patient groups at higher risk of having these mutations?

EC *BRCA2* and *BRCA1* mutations have been indentified in approximately 1.2% and 0.45%, respectively, of all sporadic (nonfamilial) prostate cancers. Currently, there are not any clinical or histologic characteristics that make us suspect germline or tumoral *BRCA* mutations in a specific patient. We should suspect *BRCA* mutations in patients with a strong familiar history of breast and/or ovarian cancer.

H&O How common is BRCA testing in patients with prostate cancer?

DO Because of the low frequency of these mutations in sporadic cancer, routine testing of prostate cancer for *BRCA* mutations is not currently indicated in clinical practice. However, this might change if research that is currently ongoing confirms that these tumors should be treated differently. In addition, new sequencing technologies are making DNA sequencing quicker and more affordable, and therefore I think that screening for *BRCA* and other germline mutations will become common practice in the near future, with implications for patient management.

H&O What prompted your recent study on BRCA mutations in prostate cancer patients?

EC At the Royal Marsden Hospital in London, Dr Eeles—the senior author of our study—runs a clinic for *BRCA* carriers who have prostate cancer. We observed in the clinic that these patients have more aggressive forms of prostate cancer. These observations, together with the aforementioned papers about *BRCA* mutations in prostate cancer, made us question whether *BRCA* mutations could be prognostic factors for prostate cancer, independent of other well-known factors, such as TNM clasification, PSA score, and Gleason score. We also wanted to know whether these mutations led to different clinical outcomes.

H&O Could you please describe the design and findings of your study?

DO Our study was a prospective follow-up of an observational cohort of sporadic and familial prostate cancer patients taking part in the UKGPC (UK Genetic Prostate Cancer Study). In our study, patients were classified as cases or controls according to *BRCA1* and/or *BRCA2* germline mutations. We also enriched the cases (*BRCA* carriers) with prostate cancer patients enrolled in an observational study of *BRCA* carrier families in the United Kingdom, the EMBRACE (Epidemiological Study of Familial Breast Cancer) study.

EC Our study differs from previous studies in the size (more than 2000 patients studied), in the analyses of complete *BRCA1* and *BRCA2* genes (and not just specific founder mutations), in the amount of clinical data collected, and in the duration of follow-up. Our main findings were that prostate cancer patients with *BRCA* mutations had similar age and PSA levels at the time of diagnosis compared with noncarrires, but their tumors trended to be more aggressive—the Gleason scores were higher—and spread outside the prostate more often than those in noncarriers. We also found that these patients had worse survival than noncarriers, even when only patients with localized disease were considered.

H&O How can your study results be applied to clinical care?

EC While waiting for the results of studies that we and others are currently carrying out on how to treat these patients, we should continue to treat *BRCA* mutation carriers following the same protocols used for noncarriers. We did, however, recently present some data at the February 2013 American Society of Clinical Oncology (ASCO) Genitourinary Cancer Symposium, suggesting that *BRCA* carriers respond differently than noncarriers to conventional treatments for localized prostate cancer, as they frequently present with earlier biochemical relapse. Therefore, clinicians may follow these patients more closely after radical treatment.

DO Finally, although prostate cancer screening with PSA remains controversial for the general population, high-risk patients, such as those harboring *BRCA* mutations, may benefit from it. This question will be answered when we get the final results of the IMPACT (Identification of Men With a Genetic Predisposition to Prostate Cancer: Targeted Screening in *BRCA1/2* Mutation Carriers and Controls) study. This is the first prospective multicentric study of targeted prostate cancer screening in men with *BRCA1* and *BRCA2* mutations. A preliminary analysis showed that the positive predictive value of PSA screening is higher in *BRCA1/2* than in noncarriers. We are in the process of having the results of the first round of screening published, with Dr Eeles as the lead author and Dr Bancroft as the first author. The final results are expected in 2017.

H&O Is other research continuing in this area?

DO We and others continue to work in this area. As for the study we presented at the ASCO Genitourinary Cancers Symposium, we found that men who were *BRCA* carriers had worse outcomes than noncarriers when treated with radiotherapy, but not with radical prostatectomy.

More recently, in the *Annals of Oncology,* Sandhu and colleagues reported on a small series of advanced prostate cancer in *BRCA* carriers treated successfully with poly (ADP-ribose) polymerase (PARP) inhibitors. Apart from this, several novel drugs that target the DNA repair pathway are being tested in clinical trials.

Suggested Readings

Agalliu I, Gern R, Leanza S, Burk RD. Associations of high-grade prostate cancer with BRCA1 and BRCA2 founder mutations. *Clin Cancer Res.* 2009;15(3):1112-1120.

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Mitra AV, Jameson C, Barbachano Y, et al. Elevated expression of Ki-67 identifies aggressive prostate cancers but does not distinguish BRCA1 or BRCA2 mutation carriers. *Oncol Rep.* 2010;23(2):299-305.

Sandhu SK, Omlin A, Hylands L, et al. Poly (ADP-ribose) polymerase (PARP) inhibitors for the treatment of advanced germline BRCA2 mutant prostate cancer. *Ann Oncol.* 2013;24(5):1416-1418.

Tryggvadottir L, Vidarsdottir L, Thorgeirsson T, et al. Prostate cancer progression and survival in BRCA2 mutation carriers. *J Natl Cancer Inst.* 2007;99(12):929-935.