
African American and Asian males: what do we know about germline predisposition to prostate cancer

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There is a paucity of data related to highly penetrant genes associated with a genetic predisposition to prostate cancer or its virulence among men of diverse ancestral populations including African American and Asian men.

We review the recent published literature to gain insights into whether such genetic alterations previously described among Caucasians are noted among African American and Asian prostate cancer patients

Key Words: African American, Asian, prostate cancer, germline DNA testing

Introduction

African American (AA), Asian, and Caucasian males exhibit both a disparate incidence and mortality from prostate cancer with AA men having a higher incidence and mortality and Asian males a lower incidence and mortality from prostate cancer when compared to Caucasians.¹ Genetic predisposition to prostate cancer is now widely recognized given the discovery of highly penetrant gene mutations associated with several hereditary cancer syndromes (HCS) such as *BRCA1/2* (Hereditary Breast and Ovarian Cancer [HBOC]), *HOXB13* mutations associated with Hereditary Prostate Cancer [HPC] and most recently the mismatch repair gene mutations *MLH1*, *MSH2* associated with Lynch syndrome [LS].²⁻⁴ Among these HCS prostate cancer incidence is increased. Further *BRCA1/2* and other DNA repair gene abnormalities (*ATM*, *CHEK2*) have been detected among patients with lethal and metastatic prostate cancer and can influence subsequent response to therapy.^{5,6} Recently germline-testing recommendations have been incorporated into the National Comprehensive Cancer Network (NCCN) guidelines for the management of prostate cancer.⁷

Given the relevance of detected mutations, it is critical to characterize the incidence and types of genetic mutations predisposing to prostate cancer among diverse populations.

Materials and methods

We performed a PubMed search for articles under the subjects of AA, Asian, and the following terms including: hereditary prostate cancer, *BRCA1/2*, DNA repair genes, and Lynch syndrome from 1995 to the present. Manuscripts that included African or Asian American prostate cancer patients that underwent germline DNA testing and included information related to the incidence and types of mutations found in addition to any associated prostate cancer phenotypic information among affected individuals were included.

In two studies including 293 AA prostate cancer patients tested the incidence of *BRCA1/2* mutations was 0%-4%.^{2,8} In a single recent study with 73 unselected Asian prostate cancer patients tested, *BRCA1/2* mutations were found in 5 (7%) patients.⁸ Among the two AA cohorts with 293 prostate cancer patients *HOXB13* mutations were noted in 3 (1.3%) with no mutations found among 73 Asian subjects.^{3,8} DNA mismatch repair gene abnormalities (*MSH2*, *MLH1*, *MSH6*, *PMS2*) were noted in only one of 227 (0.4%) AA patients and two of 73 (2.7%) Asian patients.⁸

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In a recent multi racial/multiethnic study where 3706 prostate cancer subjects underwent germline multi-gene testing irrespective of family history, cancer stage and grade the cohort consisted of 2594 white men, 234 men identified as Ashkenazi Jewish, 227 Black/AA, 78 Hispanic, 73 Asian, and 401 men categorized as “other” (i.e., not belonging to any of the former groups).⁸ Only mutations classified as pathogenic, likely pathogenic, or increased disease risk were classified as positive. Mutations of unknown significance were recorded but not classified as positive. Among the cohort the overall incidence of genetic alterations was 620 (17.2%) with *BRCA1/2* mutations in 30.7%, *HOXB13* in 4.5% and DNA mismatch repair alterations in 1.74% of the cohort.⁸ Of note the incidence of alterations was not affected by subject age or tumor grade. Family history among this prostate cancer cohort of breast, ovarian, colon, or pancreatic cancer also did not correlate with the incidence of abnormalities. Of note Hispanic and Black patients had a lower incidence of genetic alterations (6.8%-10% respectively) when compared with the white and Ashkenazi Jewish cohorts (17%-22%).⁸ Overall DNA repair gene alterations were less common among non-white/non Jewish cohorts. Among the unselected AA cohort the most frequent mutated genes were *BRCA2* (2.6%), *BRCA1* and *HOXB13*, (1.3% each) and *ATM*, *PALB2*, *MUTYH*, *CHECK2*, *CFTR*, *PMS2*, *RAD51C*, *SMAD4* (all at 1 each [0.8%]).

The Asian population exhibited the following mutations including *BRCA2* (4.1%), *BRCA1* and *ATM* (at 2.7%), with *MSH6*, *PALB2*, *PMS2* and *RET* at 1.3% each.⁸

Another recent study characterizing DNA repair gene alterations among a cohort of men with lethal versus localized prostate cancer found *BRCA2* and *ATM* mutation carriers died at a younger age, and exhibited a decreased time to death when compared to non carriers.⁵ Among this cohort with lethal prostate cancer mutations in either *BRCA2* or *ATM* were noted in 5.36% of European Americans, 3.33% of African Americans, and 18.1% of Chinese patients versus in 0%-1.7% of men with localized cancer.⁵ In the study by Prichard et al specifically characterizing DNA-repair gene mutations among a multiethnic cohort that included Caucasians (n = 912) as well as small numbers of black (n = 98), Hispanic (n = 15) and Asian (n = 24) men the incidence of mutations increased when comparing localized to metastatic patients among each cohort (Caucasian = 4.4 versus 12.1% respectively, Black = 6.8 versus 10% respectively, Hispanic = 14 versus 37.5% respectively, Asian = 0 versus 8.3% respectively).⁶

When evaluating probands with cancers likely related to HCS and a family history of prostate cancer Chandrasekar et al recently found a disparate pattern of germline DNA mutations.⁹

Among AA probands (n = 53) with a HCS and family history linked to prostate cancer germline mutations among the AA cohort involved solely *BRCA1/2* whereas among the Caucasian cohort (n = 292) germline mutations were noted in a spectrum genes.⁹

Conclusion

Accumulating data suggest that men of African and Asian ancestry with prostate cancer and their families may exhibit genetic abnormalities in highly penetrant genes associated with prostate cancer and virulent disease. Given the small cohort sizes of the populations reported thus far, prospective studies with large cohorts of men of diverse ancestry, detailed family history across a spectrum of prostate cancer disease states, with multigene testing panels is needed to define more precisely the optimal patients who should be tested. In addition such data will enable rationale tailoring of gene panels to optimize patient management as well as family counseling.

Disclosure

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