Laboratory-Prostate cancer

Ethnic disparities among men with prostate cancer undergoing germline testing

Daniel Hyuck-Min Kwon, MD\textsuperscript{a,b,1,*}, Hala T. Borno, MD\textsuperscript{a,b,1}, Heather H. Cheng, MD, PhD\textsuperscript{c,d,e}, Alicia Yiran Zhou, PhD\textsuperscript{f}, Eric Jay Small, MD\textsuperscript{a,b}

\textsuperscript{a}Department of Medicine, Division of Hematology and Oncology, University of California San Francisco, San Francisco, CA
\textsuperscript{b}Helen Diller Family Comprehensive Cancer Center, University of California San Francisco, San Francisco, CA
\textsuperscript{c}University of Washington School of Medicine, Seattle, WA
\textsuperscript{d}Fred Hutchinson Cancer Research Center, Seattle, WA
\textsuperscript{e}Seattle Cancer Care Alliance Prostate Cancer Genetics Clinic, Seattle, WA
\textsuperscript{f}Color Genomics, Burlingame, CA

Received 19 June 2019; received in revised form 3 August 2019; accepted 16 September 2019

Abstract

\textbf{Background:} Prostate cancer is among the most heritable cancers, and clinical testing for germline genetic variants based on ethnicity, disease features, and family history has recently become standard of care for men with advanced disease. It is not established whether prevalence of germline variants varies based on ethnicity or race.

\textbf{Methods:} We retrospectively examined germline genetic and clinical data of men reporting a diagnosis of prostate cancer referred to Color Genomics by a healthcare provider for testing of 30 genes associated with hereditary cancer risk. Variants were classified as pathogenic (P), likely pathogenic (LP), variant of uncertain significance (VUS), likely benign, or benign. P/LP and VUS prevalence was compared among subgroups classified by age at diagnosis, self-reported ethnicity, family history, and history of other cancer.

\textbf{Results:} We identified 1,351 men reporting a diagnosis of prostate cancer of any stage who underwent germline testing. Overall, 78\% of men were Caucasian, 11\% Ashkenazi Jewish, 3\% African-American/Canadian (AAC), 2\% Hispanic, 2\% Asian/Pacific Islander (API), and 4\% Other (multiple, unknown, Native-American). One-hundred eighty-seven men (13.8\%) carried a P/LP variant, and the most prevalent P/LP variants were in \textit{BRCA2} (3.4\%), \textit{CHEK2} (2.8\%), \textit{MUTYH} (1.8\%), and \textit{ATM} (1.7\%). Age at diagnosis, ethnicity, type of family member with prostate cancer, and type of second cancer were not associated with risk of carrying any P/LP variant. Ashkenazi Jewish men (6.7\%) were more likely to carry P/LP \textit{BRCA2} variants than Caucasian men (2.8\%) ($P <$ 0.05). Two-hundred eighty-four men (21.0\%) carried a VUS, and AAC (36.6\%) and API (33.3\%) men were most likely to carry a VUS ($P <$ 0.01).

\textbf{Conclusions:} P/LP germline variants are prevalent in men with prostate cancer. AAC, Hispanic, and API men with prostate cancer are under-represented in studies of germline testing, potentially contributing to higher rates of VUS relative to Caucasian and Ashkenazi Jewish men. Further studies in these groups will facilitate reclassification of VUS, increasing opportunities for early detection, cancer risk modification, and targeted therapeutics. Published by Elsevier Inc.

Keywords: Disparities; Germline mutation; Prostate cancer

https://doi.org/10.1016/j.urolonc.2019.09.010
1078-1439/Published by Elsevier Inc.
1. Introduction

Prostate cancer is the most frequently diagnosed cancer among men in the United States. In 2019, there will be an estimated 174,650 new cases accounting for 20% of all cancers, and an estimated 31,620 prostate cancer-related deaths [1]. Prostate cancer is also one of the most heritable cancers, with an estimated 57% of incident cases deemed heritable [2].

Familial susceptibility is thought to be due to a spectrum of rare to common variants with inversely associated effect sizes [3]. Genome-wide association studies have identified over 140 common variants of loci that confer a slightly increased risk of prostate cancer, generally in a polygenic risk model, and explain 28% of excess familial prostate cancer risk [3,4], some of which may have an active role in tumorigenesis [5]. Conversely, variants of genes such as BRCA1/2, CHEK2, ATM, PALB2, and HOXB13, though less common, may confer a substantially greater risk of prostate cancer than common variants [6–10].

In 2016, a study of men with metastatic prostate cancer demonstrated a high prevalence (11.8%) of germline mutations in DNA repair genes independent of age at diagnosis or family history [11], stimulating a new era of multigene germline testing, and prompting professional societies to develop guidelines on screening for germline mutations. The National Comprehensive Cancer Network Prostate Cancer Version 2.2019 guidelines recommend cancer predisposition next-generation sequencing for the homologous recombination genes BRCA1, BRCA2, ATM, PALB2, and CHEK2; and MLH1, MSH2, MSH6, and PMS2 for Lynch syndrome in the following situations: family history of high-risk germline mutations (e.g., BRCA1/2, Lynch mutation), suspicious family history, and presence of intraductal carcinoma on biopsy. Germline testing can also be considered for high- or very-high risk prostate cancer, and additional genes such as HOXB13 can be tested depending on clinical context [12]. The Philadelphia Prostate Cancer Consensus and Germline Genetics Working Group of the Prostate Cancer Clinical Trials Consortium presented similar recommendations, though with minor differences in which genes to test (e.g., HOXB13), and age cutoffs for testing [13,14]. While expanded use of multigene testing has created great opportunities to widen the understanding of germline mutations in men with prostate cancer, it has also proven challenging to identify all men at high risk of carrying germline mutations while minimizing unnecessary testing in men at low risk [13,15].

Multiple cohort studies subsequent to Pritchard et al. have described germline variants among men with prostate cancer [11,15,16]. However, few ethnic/racial minority men have been studied (e.g., only 5.8% of men in Pritchard et al. were non-Hispanic black) [11], and whether prevalence of germline variants varies based on race or ethnicity has not been reported. Herein, we aim to determine whether prevalence of germline variants varies by ethnicity. We hypothesize that men with prostate cancer of African-American/Canadian (AAC), Hispanic, or Asian/Pacific Islander (API) descent are under-represented, and carry higher rates of variants of unknown significance than men of Caucasian or Ashkenazi Jewish descent.

2. Materials and methods

A retrospective cohort study of men with a personal history of prostate cancer was undertaken. A publicly available database from Color Data comprising 50,000 individuals from the United States of America and Canada with and without cancer who underwent germline testing ordered by a physician between 2015 and 2018 was queried [17]. Color is considered a “hybrid laboratory,” neither following the physician-centric paradigm of clinical laboratory ordering nor direct-to-consumer in that testing requires either the individual’s primary physician or a consulting physician in the Color network to order the testing [18].

Demographic and clinical information was self-reported by the individual through an online health history tool, including age at testing, age at diagnosis, ethnicity, personal history of cancer, and family history of cancer. These data were deidentified prior to acquisition, and were available only in aggregate. Disease-related variables such as Gleason grade and stage, and outcome data were not available.

Genes in the panel were previously selected based on published evidence of association with hereditary cancer risk and technical feasibility, and included APC, ATM, BAP1, BARD1, BMPR1A, BRCA1, BRCA2, BRI1P, CDH1, CDK4, CDKN2A (p14ARF and p16INK4a), CHEK2, EPCAM, GREM1, MITF, MLH1, MSH2, MSH6, MUTYH, NBN, PALB2, PMS2, POLD1, POLE, PSEN, RAD51C, RAD51D, SMAD4, STK11, and TP53. HOXB13 was not tested. A description of DNA extraction, sequencing, and variant identification has been previously published [17]. Germline variants were classified as pathogenic (P), likely pathogenic (LP), variant of uncertain significance (VUS), likely benign, or benign according to American College of Medical Genetics and Genomics guidelines [19], and classifications were confirmed by a medical geneticist or pathologist.

The overall and individual frequency of P/LP variants and VUS was calculated, stratified into subgroups including ethnicity, and analyzed using chi-squared tests. The 2-sample t test with unequal variance was used to compare the mean age at diagnosis among different ethnic groups. P values less than 0.05 were considered significant and were calculated using STATA (Stata Statistical Software: College Station, TX: Stata Corp LP). Multivariate analyses were unable to be performed since data were structured in aggregate.

3. Results

There were 1,351 men with a personal history of prostate cancer who underwent germline testing in this cohort. One-thousand and fifty-three men (78%) reported Caucasian ancestry.
ethnicity, 150 (11%) Ashkenazi Jewish, 41 (3%) AAC, 25 (2%) Hispanic, 24 (2%) API, and 58 (4%) “Other” (Table 1). “Other” ethnicity included 45 men reporting multiple ethnicities, 9 unknown, and 4 Native-American.

Overall, 187 (13.8%) men carried a P/LP variant (Table 1). The most prevalent P/LP variants were BRCA2 (3.4%), CHEK2 (2.8%), MUTYH (1.8%), and ATM (1.7%) (Table 1). Ethnicity was not associated with risk of carrying any P/LP variant (Table 2). Ashkenazi Jewish men (6.7%) were more likely than Caucasian men (2.8%) to carry a P/LP BRCA2 variant (Table 1). Otherwise, there was no significant difference in frequency of individual P/LP variants by ethnicity (Table 1). A detailed description of prevalence of individual P/LP variants by ethnicity can be found in Table 1 and Fig. 1.

VUS was present in 21.0% of all men, and was more prevalent among AAC (37%), API (33%), and Other (34%) men with prostate cancer compared to Caucasian (21%) and Ashkenazi Jewish (12%) men (P < 0.01, Table 2). Frequencies of individual VUS can be found in Supplementary Table 2.

The overall mean age at prostate cancer diagnosis was 61.0 years (interquartile range 55–66), and the mean age at time of genetic testing was 68.6 years (interquartile range 63–74). Age at time of diagnosis was not associated with risk of P/LP variant or VUS (Table 2).

Ashkenazi Jewish men were diagnosed at an older age than Caucasian men (mean age 66.1 years vs. 66.6 years respectively, P < 0.01, Fig. 2). Other, AAC, and Hispanic men were diagnosed at a younger age than Caucasian men (57.9, 55.2, 54.8, and 66.1 years respectively, P < 0.01, Fig. 2). There was no significant difference in age at diagnosis between API and Caucasian men (61.6 vs. 66.6 years respectively, P = 0.79, Fig. 2). When restricting the sample to men with P/LP variants, Ashkenazi Jewish men were diagnosed at an older age than Caucasian men (66.6 vs. 60.5 years, P < 0.01, Fig. 2). Compared to Caucasian men (60.5 years), AAC (59.4 years) and Other (61.4 years) men were diagnosed at a similar age (P = 0.79 and 0.82 respectively, Fig. 2). There were too few Hispanic and API men with P/LP variants to compare age at diagnosis.
Two-hundred forty-one (17.8%) men had a father with a history of prostate cancer, 143 (10.6%) brother, 71 (5.3%) grandfather, and 10 (0.7%) son. Among men with a P/LP variant, there were similar rates of prostate cancer in the father, brother, and grandfather (Table 2). Type of second cancer was not associated with risk of a P/LP variant, but frequency of VUS was highest among men with an additional history of pancreatic cancer (64%) or colorectal cancer (46%) (\( P < 0.01 \), Table 2).

### 4. Discussion

The 13.8% germline P/LP variant prevalence found in this study was slightly higher than the 11.8% prevalence of pathogenic germline mutations found in 692 men with metastatic prostate cancer described by Pritchard et al. who used a 20-gene panel [11]. The higher prevalence observed in this series may be due to the inclusion of variants for genes such as \( APC \) and \( MUTYH \), which have not been shown to increase prostate cancer risk in particular [21]. The frequencies of germline P/LP variants when restricting genes to those tested in both Pritchard et al. and this study were similar (11.1% vs. 11.3% in Pritchard et al.). In contrast, Nicolosi et al., who obtained a cross-sectional sample of 3,607 men with prostate cancer unselected for stage, found a much higher 17.2% prevalence of pathogenic germline mutations [15]. This difference may be due to the inclusion of additional genes in Nicolosi et al. (80 vs. 30), as well as potential selection bias resulting from the ordering clinician’s ability to decide which genes should tested. When comparing only genes tested in both Nicolosi et al. and this study, the difference in frequency of positive variant per requisition remained (18.8% vs. 13.2%, respectively). Lastly, Giri et al., who also obtained a cross-sectional sample of 1,328 men with prostate cancer unselected for stage, reported a similar frequency of pathogenic variants (15.6%) based on a 25-gene panel [16]. A comparison of P/LP variant frequencies among these studies is described in Supplemental Table 1. Of note, the distribution of individual P/LP variants in this cohort was similar to these studies, with the highest prevalence of variants in genes involved in DNA repair [11,15,16].

The low proportion of AAC, Hispanic, or API men in this sample is an important finding. Although the slightly lower representation of these ethnicities in this cohort (7%) than what has been previously reported (9%–11%) [11,15]...
may partially be due to selection biases, all numbers from these studies are significantly lower than the 25% of new cancer cases of prostate cancer in the United States represented by these populations [22]. Giri et al. did not report ethnicity [16]. This finding highlights a critical cancer disparities dilemma, specifically, the need for improved access to and dedicated research in germline testing among racial/ethnic minorities. Men who do not participate in germline testing may have differential access to healthcare for early detection, cancer risk modification, and clinical trial participation [23], which may subsequently amplify disparities in their clinical outcomes. Reasons for such disparities in germline testing are not well understood, but may be related to competing life and health priorities, and a lack of insurance or underinsurance; the reimbursement rate for genetic testing has been reported to be as low as 10% [20].

This study leverages data collected through a hybrid laboratory, an emerging model of genetic testing described above that has only recently been defined [18]. It is thought to improve access to genetic testing by various means, including removing barriers such as lack of insurance/underinsurance, travel and appointment time, and scarcity of genetic counselors. However, it is unknown whether removal of the insurer is leading to higher out-of-pocket costs overall and differential access to testing. The net effect of hybrid laboratories on improving access to genetic testing has not been evaluated and warrants further investigation.

The differences in rates of P/LP variants across ethnicities are difficult to evaluate given the small sample size and low frequency of P/LP variants, but it is unsurprising that Ashkenazi Jewish men have a higher prevalence of P/LP BRCA2 variants than Caucasian men given higher baseline prevalence in the general population [24].

Importantly, this study is the first to describe a higher prevalence of VUS among AAC and API men with prostate cancer than among Caucasian and Ashkenazi Jewish men. Previous studies have found higher rates of VUS among individuals of non-European ancestry [25,26], but these cohorts included few if any men with prostate cancer. For example, in Ricker et al., among 475 patients with or without cancer seen in a genetics practice, 63% Black, 41.8% Asian, and 38.6% White, non-Hispanic individuals carried a VUS [25]. In Susswein et al., among 10,030 patients with or without cancer (none with known prostate cancer) referred for a next-generation sequencing hereditary cancer panel, 39.7% African-American, 37.3% Asian, and 22.7% Caucasian individuals carried a VUS, similar to our cohort of men with prostate cancer [26]. As described above, these differences are likely due to the under-representation of
these groups in studies of germline variants. These results are worth noting in light of the association of VUS disclosure with psychological distress among women with breast cancer [27]. Though the psychological consequences of VUS disclosure have not been studied in men with prostate cancer, these men may similarly experience distress or uncertainty upon receipt of a VUS result.

In addition, the high observed overall prevalence of VUS underscores the need for clear communication to patients. Management should be based on personal and family history, and include recommendations for follow-up since a VUS may be reclassified to a pathogenic or benign variant [28]. Overall VUS prevalence in this cohort is lower than others perhaps due to the lower proportion of AAC and API men and higher proportion of Ashkenazi Jewish men [11,15,16].

This study’s strengths include the large sample size and use of a publicly available online database from a “hybrid laboratory” genomics platform. Limitations include the retrospective design, potential selection bias, absence of clinical data such as Gleason grade and stage, and under-representation of certain ethnic groups. In addition, clinical and demographic data such as prostate cancer diagnosis and ethnicity were self-reported and not verified by medical records or genetic testing.

5. Conclusions

P/LP germline variants are common among men with prostate cancer. AAC, Hispanic, and API men with prostate cancer are under-represented in studies of germline testing, potentially contributing to higher rates of VUS relative to Caucasian and Ashkenazi Jewish men. Further studies in these groups will facilitate reclassification of VUS, which will in turn better define opportunities for early cancer detection, cancer risk modification, and targeted therapeutics.

Acknowledgments

We thank Color Genomics for providing data.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urolonc.2019.09.010.

References


