Longitudinal Examination of Metastatic Prostate Cancer Utilizing Linked Health Insurance Claims and Germline Genetic Testing Data

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Large linked datasets of genetic and real-world data enable identification of associated inequities in healthcare outcomes

Background

Pathogenic germline variants (PGV) in *BRCA1* or *BRCA2*, two homologous recombination repair (HRR) genes, are identified in approximately <1% and 5% of patients with metastatic prostate cancer (mPC), respectively[1]. Approximately 10-20% of patients will progress to metastatic castration-resistant prostate cancer (mCRPC) within 5 years of PC diagnosis[2]. This study utilized a linked dataset to characterize mPC and identify statistically significant differences in disease progression. Comparative analyses were restricted to Black and White patients, castration-resistant/sensitive disease status, and BRCA PGV status.

Methods

A linked dataset of germline genetic testing data (Invitae®) and health insurance claims data (Komodo Health) was assembled for 20,036 patients (**Table 1**). All selected patients received germline genetic testing at Invitae, and had ICD9 or ICD10 codes in their claims data indicating mPC (i.e. both PC and metastasis indicated). Within the mPC cohort, patients with ICD codes indicating mCRPC in their claims data were identified, while patients with ICD codes indicating metastatic castration-sensitive prostate cancer (mCSPC) were similarly identified so long as they did not also have an indication of mCRPC at any time (i.e., mCRPC and mCSPC are mutually exclusive categories of individual herein). Clinician-reported race/ethnicity was extracted from claims. Germline genetic testing data was used to investigate PGV frequency for nine HRR genes: *ATM*, *BRCA1*, *BRCA2*, *BRIP1*, *CDK12*, *CHEK2*, *FANCA*, *HDAC2* and *PALB2*[3], however not every patient requested testing for every HRR gene. Chi-squared tests were used to determine statistical significance (p<=0.05 with Bonferroni correction for 11 comparisons).

To avoid imperfect ICD9/10 translations, longitudinal analyses focused on ICD10 codes, i.e. >95% of the overall mPC study cohort (**Table 2**). An enrichment analysis was performed to identify the forms of metastasis most overrepresented in the claims data for the mPC cohort, with respect to a random background population of Invitae genetic testing patients. Longitudinal analysis involved comparing patient age at first PC diagnosis, and time since PC diagnosis at the first occurrence of each claim code. Mann-Whitney U tests were used to determine statistical significance (p<=0.05 with Bonferroni correction for 10 comparisons).

Results

Table 1: descriptive characteristics

By clinician-reported race/ethnicity, 10.4% of the 20,036 mPC individuals were Black, and 69.7% White*. An HRR+ molecular diagnosis (PGV in any of the nine selected HRR genes) was reported in 9.1% of cases; a 7.0% rate among Black patients versus a 9.4% rate among White patients was a statistically significant difference (corrected p=4.8x10^{-3}). *BRCA1*+ and *BRCA2*+ frequencies of 0.6% and 3.5% were approximately concordant with previously reported values of 0.9% and 5.3% respectively over a cohort of 692 mPC individuals[4]. There were no statistically significant differences in frequency of BRCA PGVs between Black and White patients. 11.0% of the cohort had codes indicating mCRPC and 5.9% mCSPC, with a higher reported frequency of mCRPC for Black versus White patients (13.0% vs. 11.0%, corrected p=8.7x10^{-2}) statistically significant only without Bonferroni correction.

			Black		White		Overall
mPC			2076 (10.4%)		13966 (69.7%)		20036
of which:	HRR+		145 (7.0%)		1307 (9.4%)		1825 (9.1%)
	BRCA1+		12 (0.6%)		85 (0.6%)		126 (0.6%)
	BRCA2+		75 (3.6%)		468 (3.4%)		703 (3.5%)
	mCRPC		269 (13.0%)		1534 (11.0%)		2202 (11.0%)
	of which:	HRR+	20 (7.4%)	129 (8.4%)		184 (8.4%)	
		BRCA1+	2 (0.7%)	7 (0.5%)		9 (0.4%)	
		BRCA2+	8 (3.0%)	53 (3.5%)		81 (3.7%)	
	mCSPC		114 (5.5%)	840 (6.0%)		1180 (5.9%)	
	of which:	HRR+	9 (7.9%)	79 (9.4%)		104 (8.8%)	
		BRCA1+	2 (1.8%)	5 (0.6%)		8 (0.7%)	
		BRCA2+	3 (2.6%)	22 (2.6%)		33 (2.8%)	

Table 1: Clinician-reported race/ethnicity, molecular diagnosis and disease progression across the overall mPC study cohort. Within each race/ethnicity category, mPC is first delineated by molecular diagnosis. mPC is then delineated into mCRPC or mCSPC status, each of which is further delineated by molecular diagnosis. Cell highlighting indicates a statistically significant difference with or without Bonferroni correction.

Table 2: longitudinal analyses

Across the mPC cohort, mean age at initial PC diagnosis was 68.0 years; a younger age of diagnosis for *BRCA2*+ and Black patients of 66.5 (corrected p=1.8x10^{-5}) and 65.5 (corrected p=3.1x10^{-36}) years, respectively, and an older age for White patients of 68.5 years (corrected p=5.9x10^{-5}), were observed to be statistically significant differences. mPC developed on average 1.4 years after PC diagnosis, mCRPC after 3.1 years.

Some observations were statistically significant only without Bonferroni correction. 1.6 years to bone metastasis in White patients versus 1.5 years overall (corrected p=2.0x10^{-1}), as well as <0.1 years longer to any metastases for White patients (corrected p=2.1x10^{-1}) were observed. 2.5 years to intra-abdominal lymph node metastasis in *BRCA2*+ individuals versus 2.0 years overall was also observed (corrected p=3.5x10^{-1}); this may indicate the influence of *BRCA2*-specific precision medicines (e.g. PARP inhibitors) and warrants further investigation.

	Black			White			BRCA1+			BRCA2+			Overall		
	Mean	STD	N	Mean	STD	N	Mean	STD	N	Mean	STD	N	Mean	STD	N
Malignant neoplasm of prostate	65.5	8.9	2036	68.5	9.1	13639	68.9	10.5	123	66.5	8.8	693	68.0	9.2	19584
Elevated PSA	0.1	2.0	1231	0.1	1.9	7841	0.0	1.9	58	0.1	1.9	415	0.0	1.9	11177
Metastasis: any	1.4	1.9	2027	1.4	2.0	13582	1.3	2.1	123	1.3	1.9	691	1.4	2.0	19502
Metastasis: bone	1.5	1.9	1498	1.6	1.9	9501	1.6	2.0	82	1.4	1.8	508	1.5	1.9	13715
Metastasis: intrapelvic lymph nodes	1.8	2.0	409	1.7	2.0	3042	1.9	1.9	25	1.8	2.1	149	1.7	2.0	4199
Metastasis: intra-abdominal lymph nodes	2.2	2.2	311	2.1	2.2	2037	2.5	2.0	19	2.5	2.2	119	2.0	2.2	2917
Metastasis: genital organs	2.2	2.1	291	2.1	2.1	1731	1.5	1.1	12	2.0	2.0	122	2.1	2.1	2536
Metastasis: lymph node, unspecified	2.1	2.0	324	2.1	2.1	1775	2.2	2.3	20	2.4	2.2	101	2.1	2.1	2591
Metastasis: unspecified site	2.3	2.1	441	2.3	2.2	2597	2.5	2.5	23	2.0	2.0	152	2.2	2.1	3856
Hormone resistant malignancy status	3.1	1.9	275	3.1	1.9	1566	3.1	1.8	10	2.8	1.8	85	3.1	1.9	2248

Table 2: Patient age at PC diagnosis, and years since PC diagnosis of elevated PSA, common metastases, and hormone resistance. To avoid imperfect ICD9/10 translations, only ICD10 codes are considered (>95% of overall mPC study cohort). Mean, standard deviation (STD) and sample size (N) provided. Cell highlighting indicates a statistically significant difference with or without Bonferroni correction.

Conclusion

This study demonstrates the utility of large linked datasets of genetic and real-world data for investigating differential disease progression by both genetic variation and race/ethnicity, and for exploring potential associated inequities in healthcare outcomes. Our data is concordant with published mPC literature, highlighting the potential of these data to answer clinically relevant questions, such as the identification of likely disease trajectories for individuals.

The impact of BRCA status and race/ethnicity on the course and presentation of mPC merits further exploration. Future work also includes analysis of therapeutic interventions, in particular for investigating the potential role of precision therapies such as PARP inhibitors in the longer time to intra-abdominal lymph node metastasis in *BRCA2*+ individuals observed herein.

1) Messina C. et al., J Oncol. 2020; 4986365.
2) Shore N. D. et al., Adv Ther 2021; 38:4520-4540.
3) Chi K. N. et al., J Clin Oncol. 2022; 40(6):12-12.
4) Pritchard C. C. et al., N Engl J Med. 2016; 375(5):443–453.

* remaining categories: Ashkenazi Jewish (1.6%), Asian (1.6%), Filipino (0.0%), Hispanic (3.0%), Indian (0.1%), Japanese (0.0%), Middle Eastern (0.2%), Multiple (4.9%), Native American (0.1%), Pacific Islander (0.1%), Unknown (8.4%).

HRR = homologous recombination repair; **PGV** = pathogenic germline variant; **PC** = prostate cancer; **mPC** = metastatic prostate cancer; **mCRPC** = metastatic castration-resistant prostate cancer; **mCSPC** = metastatic castration-sensitive prostate cancer.

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