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Original Research

BRCA-Mutated Prostatic Adenocarcinoma: A Distinct Clinicopathological Subset With Frequent Cribriform Morphology Associated With Domain-Specific Alterations in Putative Protein Properties

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Abstract

Background: Several studies have demonstrated a worse prognosis in BRCA1 (BRCA1 DNA repair associated)- and BRCA2 (BRCA2 DNA repair associated)-mutated prostatic adenocarcinomas, including shorter disease-free survival, an increased risk of disease progression, and inferior overall survival. This study presents a comparative clinicopathologic analysis of grade-matched BRCA1/2-mutant and wild-type prostatic adenocarcinomas. **Materials and Methods:** Cases of prostatic adenocarcinoma that underwent broad-panel next-generation sequencing (NGS) and were found to harbor *BRCA1* and/or *BRCA2* mutations were retrieved from the pathology archives. The control group consisted of age, Gleason grade group, and stage-matched prostatic adenocarcinomas negative for *BRCA1* and/or *BRCA2* mutations. The hematoxylin and eosin (H&E) slides from both cohorts were retrieved and reviewed. The presence and location of metastasis were also recorded. The NGS data were reviewed, and the reported *BRCA1* and *BRCA2* variants were analyzed. Statistical analysis was performed using IBM SPSS 26 software for Windows, version 26.0 (IBM Corp., Armonk, NY, USA). **Results:** Histological review of the two groups showed a similar distribution of intraductal carcinoma, neuroendocrine differentiation, perineural invasion, necrosis, extraprostatic extension, and metastatic disease. Cribriform pattern was present in all BRCA-mutated cases in the study cohort, but was completely absent in the control group ($p = 0.022$). The *BRCA1* variants were identified in three cases (30%) and included one splice-site variant, one frameshift variant, one nonsense variant, and one missense variant. The nonsense mutation was predicted to disrupt molecular recognition features, amidation, calcium binding, catalytic sites, and carboxylation ($p < 0.01$). In contrast, *BRCA2* variants were identified in nine cases, including three cases with *BRCA2* loss, one case with a large genomic rearrangement involving introns 16 and 18, three cases with missense variants and two cases with frameshift variants. The two frameshift variants showed similar predicted disruption of protein function with significant impact on protein–protein interaction hotspots, catalytic sites, iron binding, and sulfation ($p = 0.01$). **Conclusion:** The current study found that prostatic adenocarcinoma with cribriform morphology may be enriched for BRCA alterations and could be used to prioritize BRCA mutation testing, pending validation in larger cohorts. Mutation Prediction for Loss-of-Function (MutPred-LOF) algorithmic prediction of molecular mechanisms of pathogenicity identified variants that may impact catalytic sites, ion binding, and post-translational chemical modifications in this subgroup of BRCA-mutated prostatic adenocarcinomas; however, further functional studies are required to confirm these findings.

Keywords: prostate; carcinoma; next-generation sequencing; mutations; pathogenicity; *BRCA1*; *BRCA2*

1. Introduction

The incidence of prostate adenocarcinoma, the leading male genitourinary malignancy, is rising. This increase is attributed to lifestyle changes and more stringent screening protocols [1]. Similar to most malignancies, prostate adenocarcinomas are molecularly heterogeneous. However, based on an analysis of 333 primary prostate cancers, The Cancer Genome Atlas (TCGA) reported an enrichment of inactivating alterations in DNA damage repair genes, with 19% of cases showing inactivation of homologous recombination repair pathways, including *BRCA1* (1%), *BRCA2* (3%), *RAD51C (RAD51 paralog C)* (3%), and/or inactivation of kinases such as *CDK12 (cyclin dependent kinase 12)* (2%), *ATM (ATM serine/threonine kinase)* (4%), and *FANCD2 (FA complementation group D2)* (7%) [2]. Based on an analysis of 20 DNA repair genes across 692 metastatic castration-resistant prostate cancers, Pritchard et al. [3] reported DNA repair gene mutations in 11.8% of cases, with *BRCA2* mutations being predominant. Grasso et al. [4] reported similar findings, with *BRCA2* being the most frequently mutated gene (13%), followed by *ATM* (7.3%), *MSH2 (mutS homolog 2)* (2%), and *BRCA1*, as well as *FANCA (FA complementation group A)*, *MLH1 (mutL homolog 1)*, *RAD51B (RAD51 paralog B)*, and *RAD51C* (0.3% each).

The BRCA family, a co-regulator of the androgen receptor (AR) and the AR-mediated signaling pathway, plays a pivotal role in the etiopathogenesis of prostate cancers [5]. Several studies have established that BRCA-mutated prostate adenocarcinomas have a worse prognosis, with an increased likelihood of lymph node and/or distant metastases, shorter disease-free survival, a higher risk of disease progression, and inferior overall survival rates [6,7,8,9]. Although BRCA-mutated prostate adenocarcinomas are reported to be histologically aggressive [7], the precise description of these histological features remains vague. Given the sensitivity of BRCA-mutant cancers to poly(ADP-ribose) polymerase (PARP) inhibitors (PARPi), prompt identification of BRCA-mutant-associated histological features can help prioritize mutational analysis, thereby enabling early access to novel therapeutic modalities [10,11].

In addition, elucidating the exact nature and detailed characteristics of these pathogenic BRCA variants may unveil domain-specific information, including precise intron–exon boundaries, thereby supporting the development of superior testing strategies for more accurate risk prognostication and tailored therapy [5].

This study is a comparative clinicopathologic analysis of grade-matched BRCA-mutant and BRCA-wild-type prostate adenocarcinomas to elucidate the histomorphological features associated with the BRCA-mutant subset. Furthermore, the BRCA variants identified in this cohort are scrutinized to identify pertinent genomic domains and explore the associated putative impact on protein function, thereby enhancing our understanding of the pathogenetic mechanisms contributing to disease aggressiveness and poorer prognosis.

2. Materials and Methods

Cases of treatment-naïve, advanced prostatic adenocarcinoma sampled between 2019 and 2024 that underwent broad-panel next-generation sequencing (NGS) testing and were found to have *BRCA1 and/or BRCA2* mutations were retrieved from the pathology archives. Pertinent clinical data, including age, stage, prostate-specific antigen (PSA) levels, and therapy, such as PARPi and current disease status were recorded. The control group consisted of age-, Gleason grade group-, and stage-matched prostatic adenocarcinomas that had undergone similar broad-panel NGS testing but were negative for *BRCA1* and/or *BRCA2* mutations and other DNA damage repair gene alterations. All hematoxylin and eosin (H&E) slides of both cohorts were retrieved and reviewed for grade, presence of cribriform pattern, and/or intraductal carcinoma, presence of necrosis, neuroendocrine features, and perineural invasion by a blinded pathologist using consensus guidelines, and were confirmed by a second pathologist. No additional immunostains were performed for this study; previously performed immunostains, including basal cell and neuroendocrine markers, were reviewed. The presence and location of metastases were also recorded.

The NGS data were retrieved, and the reported *BRCA1* and *BRCA2* variants were identified. Each reported variant was cross-checked using Ensembl Variant Effect Predictor (VEP) [12,13] and, when available, Catalogue of Somatic Mutations in Cancer (COSMIC) [14].

Polyphen 2.0 software (version 2.2.2; Harvard Medical School, Boston, MA, USA) and SIFT software (version 5.2.2; Genome Institute of Singapore, Agency for Science, Technology and Research [A*STAR], Singapore) were used to predict the functional effect of each single-nucleotide polymorphism (SNP) [15,16]. Allele frequencies were derived from the Genome Aggregation Database (gnomAD) [17,18]. MutPred software (version 2.0; Indiana University School of Medicine, Indianapolis, IN, USA) [19] was used to predict the effects of individual SNPs and indels on motifs, structure, dynamics, and protein binding. A p-value < 0.05 was considered significant for predicted protein alterations. Combined Annotation Dependent Depletion (CADD) PHRED scores were calculated for each variant [20,21]. Pathogenic variants identified in other genes were also recorded for both groups.

Statistical analyses were performed using IBM SPSS software for Windows, version 26.0 (IBM Corp., Armonk, NY, USA). Nonparametric data were assessed for statistical significance using Fisher's exact test.

3. Results

A total of 10 cases of prostatic carcinoma that underwent NGS were identified to have *BRCA1* and/or *BRCA2* mutations and were retrieved for this study. The average age of this study cohort was 68.8 ± 5.6 years. The median PSA level at diagnosis was 60.2 ng/mL (range, 15–1000 ng/mL). The prostate adenocarcinomas were grade group 4 in five cases and grade group 5 in four cases. The control group (without *BRCA1* or *BRCA2* mutations) consisted of prostatic adenocarcinomas of grade group 4 (50%) and grade group 5 (50%). The average age of the control group was 63.9 ± 11.7 years. The median serum PSA level at diagnosis was 102.5 ng/mL (range, 9.5–655 ng/mL). The characteristics of the study subjects are summarized in Table 1.

Histological review of the two groups showed similar distributions of intraductal carcinoma (22.2% vs. 0%; $p > 0.05$), neuroendocrine differentiation (11.1% vs. 0%; $p > 0.05$), perineural invasion (55% vs. 50%; $p > 0.05$), necrosis (11.1% vs. 20%; $p > 0.05$), extra-prostatic extension (33.3% vs. 10%; $p > 0.05$), and metastatic disease (90% in both groups). However, a cribriform pattern (Fig. 1) was noted in all BRCA-mutated cases in the study cohort, while this pattern was completely absent in the control group ($p = 0.02$). The distribution of *TP53* (tumor protein p53) and other mutations was similar between the two groups, with no significant differences. The histological features of the two groups are summarized in Table 2.

Table 1. Clinicopathologic characteristics of the subjects.

Characteristics	*BRCA1/2*-mutated cohort (n = 10)	Control cohort (n = 10)
Mean age (years)	68.8 ± 5.6	63.9 ± 11.7
Median serum Prostate-Specific Antigen (PSA) at diagnosis (ng/mL)	60.2 (range, 15–1000)	102.5 (range, 9.5–655)
Grade group 4	5/10 (50%)	5/10 (50%)
Grade group 5	4/10 (40%)	5/10 (50%)
Patient status	1/10 deceased	1/10 deceased

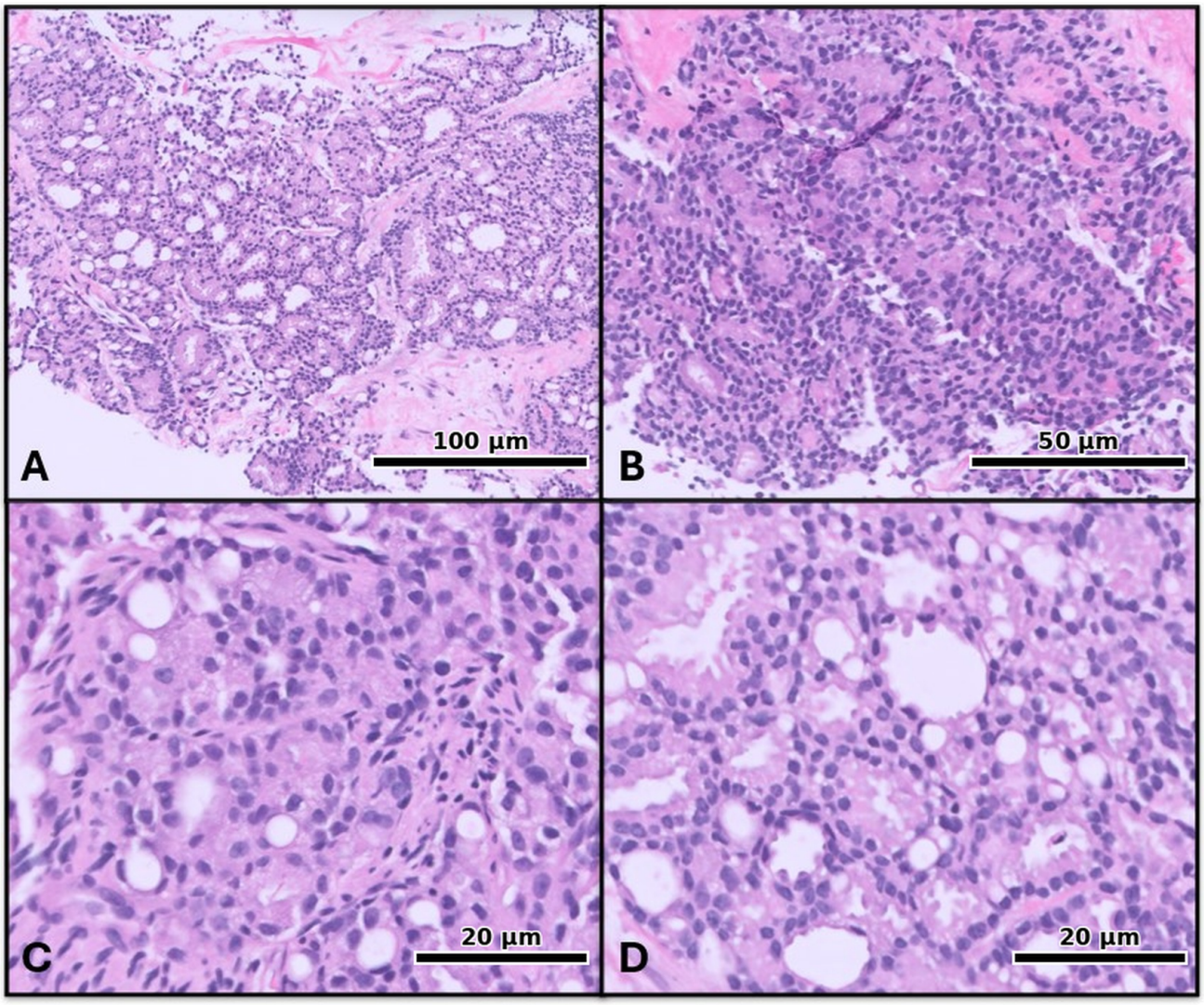

Fig. 1. Representative photomicrographs demonstrating the cribriform pattern in hematoxylin and eosin (H&E)-stained sections. Panels: (A) 10× (100 µm scale bar), (B) 20× (50 µm scale bar), (C) 40× (20 µm scale bar), and (D) 40× (20 µm scale bar).

Of the 10 cases included in the study set, one case showed an isolated *BRCA1* variant, seven cases showed variants in and/or loss of *BRCA2*, and two cases showed mutations in both *BRCA1* and *BRCA2*. The *BRCA1* variants found in three cases (30%) included one splice-site variant, one frameshift variant co-occurring with a nonsense variant, and one missense variant. The splice-site variant c.4357+1G>A is a splice donor variant impacting exon 10, with a CADD PHRED score of 32. The frameshift variant, p.R1726fs*3, affects exon 18, with a MutPred score of 0.65268, was concomitant with the stop–gain variant p.Q491*, which had a CADD PHRED score of 28.2 and a MutPred score of 0.73882. The p.Q491* variant was predicted to significantly disrupt molecular recognition features, amidation, calcium binding, catalytic site integrity, and carboxylation according to the MutPred algorithm ($p < 0.01$). These variants were classified as pathogenic. The single missense variant in *BRCA1* was located in exon 14, resulting in p.D1546N, with a SIFT score of 0.12, PolyPhen-2 score of 0.464, and a CADD PHRED score of

Table 2. Histological features of BRCA-mutated and BRCA-wild-type cohorts.

Histological features	*BRCA1/2*-mutated cohort (n = 10*)	Control cohort (n = 10)	*p*-value
Cribriform pattern	100% *	None	0.022
Intraductal carcinoma	22.2%*	None	0.211
Neuroendocrine differentiation	11.1%*	None	0.474
Perineural invasion	55%*	50%	0.586
Necrosis	11.1%*	20%	0.542
Extra-prostatic extension	33.3%*	10%	0.259
Metastatic disease	90%	90%	0.737
*TP53*** mutations	40%	20%	0.249

*Slides of the primary prostate carcinoma were available for review in only nine cases.

***TP53*, Tumor protein p53.

5.058. The MutPred score for this variant was 0.037, indicating a likely lack of pathogenicity. However, given the very low population allele frequency of 0.00000434 and the absence of homozygotes, this variant was classified as a variant of uncertain significance (VUS).

In contrast, *BRCA2* variants were identified in nine cases in this cohort, including three cases with *BRCA2* loss, one case showing a large genomic rearrangement involving introns 16 and 18, three cases with missense variants, and two cases with frameshift variants. The large genomic losses and rearrangements were not analyzed further, given the known loss of DNA repair function. The two frameshift variants, p.N2135fs*3 (MutPred score 0.43712) and p.L2015fs*23 (MutPred score 0.43876), showed similar predicted disruption of protein function, with significant impact on protein–protein interaction hotspots, catalytic sites, iron binding, and sulfation ($p < 0.01$). Additionally, p.N2135fs*3 was predicted to affect proteolytic cleavage, while p.L2015fs*23 was predicted to affect disulfide linkage ($p < 0.01$). The missense variants p.D1923A, p.R2336C, and p.I505V had SIFT scores of 0.08, 1, and 0.28, respectively, and PolyPhen-2 scores of 0.29. 0 and 0.201, all predicting likely benign effects. The CADD PHRED scores ranged from 0.007 for p.I505V to 7.77 for p.D1923A and 11.75 for p.R2336C. The MutPred scores were all below 0.120, with no significant predicted impact on protein properties according to the MutPred algorithm. The population allele frequencies were 0.000159 or lower.

Variant data along with PolyPhen-2, SIFT, MutPred, and CADD PHRED scores are summarized in Table 3.

The predicted impact of variants on protein properties, as determined by the MutPred algorithm, is summarized in Table 4.

Among the study cases, three patients received PARPi therapy in addition to a gonadotropin-releasing hormone (GnRH) agonist and/or conventional chemotherapy. The control cohort received conventional chemotherapy, with eight patients additionally undergoing radiotherapy. Of the 10 patients in each group, 9 were alive at the time of this report.

4. Discussion

BRCA1 and *BRCA2*, the well-known cancer predisposition genes, play vital roles in double-strand break repair via homologous recombination [22]. *BRCA1*, located on chromosome 17, contains a coding sequence of approximately 5.6 kb, whereas *BRCA2*, located on chromosome 13, contains a coding sequence of approximately 10.2 kb [19]. Pathogenic variants in *BRCA1* and *BRCA2* are well-recognized risk factors for breast, ovarian, pancreatic, and prostate cancers, in addition to other inherited cancer syndromes [22].

Although the association between prostate adenocarcinoma and BRCA, particularly *BRCA2*, has been well established for some time, recent reports have highlighted a greater risk of death using overall survival (OS) data in *BRCA2* carriers compared with non-carriers [23,24]. Clinical studies have shown that BRCA1- and BRCA2-mutant prostatic adenocarcinomas are more likely to present with lymph node involvement or distant metastases and have shorter disease-free survival than wild-type BRCA cases [6].

These findings underscore the high clinical burden, worse prognosis, and poor outcomes in these patients.

The pathobiological elucidation of *BRCA1* and *BRCA2* in tumorigenesis has led to advances in targeted therapeutics, particularly the development of PARP inhibitors, which are approved by the United States Food and Drug Administration (FDA) for multiple *BRCA1/2*-associated cancers [25,26,27]. Clinical trials and large-scale studies have reported sensitivity of metastatic castration-resistant prostate carcinoma with somatic or germline variants in DNA damage repair genes (especially *BRCA1/2*) to PARPi [28,29]. The PROfound phase III clinical study reported longer progression-free survival and improved response endpoints with olaparib in metastatic castration-resistant prostate cancer patients with alterations in homologous recombination repair pathway genes whose disease had progressed on enzalutamide or abiraterone therapy [30].

Table 3. BRCA1/2 variant data with corresponding PolyPhen-2, SIFT, and CADD PHRED scores.

Case ID	*BRCA* variant type	Nucleotide/protein change in sequence	Laboratory classification	Germline/somatic	PolyPhen-2 score	SIFT score	CADD PHRED score##	Population allele frequency
1	*BRCA1* frameshift	p.R1726fs*3	Pathogenic	Germline	NA#	NA	NA	0.000008
	BRCA1 nonsense	p.Q491*	Pathogenic	Germline	NA	NA	28.2	NA
	BRCA2 missense	p.D1923A	VUS#	Somatic	0.29	0.08	7.77	≤0.000159
2	*BRCA1* splice site	c.4357+1G>A	Pathogenic	Germline	NA	NA	32	0.0000082
	BRCA2 large genomic rearrangement			Somatic				
3	*BRCA2* loss			CNL/LOH#				
4	*BRCA2* loss			CNL/LOH#				
5	*BRCA2* frameshift	p.N2135fs*3	Pathogenic	Germline	NA	NA	NA	<0.00001
6	*BRCA2* frameshift	p.L2015fs*23	Pathogenic	Somatic	NA	NA	NA	NA
7	*BRCA2* loss			CNL/LOH#				
8	*BRCA2* missense	p.R2336C	VUS#	Somatic	0	1	11.75	≤0.000159
9	*BRCA2* missense	p.I505V	VUS#	Somatic	0.2	0.28	0.007	≤0.000159
10	*BRCA1* missense	p.D1546N	VUS#	Somatic	0.464	0.12	5.058	0.00000434

CNL/LOH, copy number loss/loss of heterozygosity; VUS, variant of uncertain significance; NA, not applicable.

For CADD scores, higher values indicate variants that are less frequently observed in the general population and are more likely to be deleterious.

* denotes a termination (stop) codon; in frameshift variants, the number following the asterisk indicates the position of the premature termination codon in the new reading frame.

Table 4. MutPred scores and the algorithm predicted impact on protein properties of identified BRCA variants.

Case ID	BRCA Variant Type	Impact	MutPred Score
	BRCA1 R1726fs*3	Exon 18	0.65268
1	*BRCA1* Q491*	Significant disruption in the molecular recognition feature, amidation, calcium binding, catalytic site, and carboxylation ($p < 0.01$)	0.73882
	BRCA2 D1923A	No significant predicted impact on protein properties	0.119
2	*BRCA1* c.4357+1G>A	Exon 10	
5	*BRCA2* N2135fs*3	Significant impact on protein–protein interaction hotspots, catalytic sites, iron binding, sulfation ($p = 0.01$), and proteolytic cleavage ($p < 0.01$)	0.43712
6	*BRCA2* L2015fs*23	Significant impact on protein–protein interaction hotspots, catalytic sites, iron binding, sulfation ($p = 0.01$), and disulfide linkage ($p < 0.01$)	0.43876
8	*BRCA2* I505V	No significant predicted impact on protein properties	0.031
9	*BRCA2* R2336C	No significant predicted impact on protein properties	0.036
10	*BRCA1* D1546N	No significant predicted impact on protein properties	0.037

* If interpreted as a probability, a score threshold of 0.50 would suggest pathogenicity.

In the pre-molecular era, histologic differentiation and grading using the Gleason score and grade groups were the cornerstone of risk prognostication [31,32]. Although several studies have suggested a more aggressive phenotype in BRCA-mutated prostate cancers [8,33,34], large-scale studies have failed to establish any major histopathologic correlations for the BRCA-mutant subset apart from higher Gleason scores [35,36]. Giusti et al. [35] evaluated benign and preneoplastic features, including atrophy, benign prostatic hyperplasia, chronic prostatitis, basal cell hyperplasia, atypical adenomatous hyperplasia, atypical small acinar proliferation, the presence of low-grade and/or high-grade prostatic intraepithelial neoplasia, and adverse pathological features such as perineural invasion, lymphovascular invasion, neuroendocrine features, extra-prostatic extension, and seminal vesicle involvement, and found no significant differences between the BRCA- mutated and non-mutated groups. Similarly, our study did not identify any significant differences in these features between the two groups. Gallagher et al. [7] conducted a study of 832 cases of localized prostate cancer and attempted to establish histological markers for the BRCA-mutated subset of prostate cancers; however, histological assessment was largely limited to Gleason grading. Several studies have reported conflicting data on the association of high-grade morphological features, such as cribriform pattern and intraductal carcinoma, with BRCA mutations [37,38,39,40]. The current study found a significant association between the presence of a cribriform pattern and BRCA mutational status [41]. Lozano et al. [40] similarly reported an association between biallelic somatic loss of *BRCA2* and cribriform and intraductal histology.

However, the current study found this association to be limited to the cribriform pattern, with intraductal carcinoma not showing significant differences between the two subgroups. Cribriform morphology has been reported to exhibit increased genomic instability and a higher burden of copy number alterations compared with other morphological subtypes [42,43]. This finding raises the possibility of prioritizing genetic testing in cases with cribriform morphology to identify novel therapeutic targets and improve outcomes in patients presenting with advanced disease [44]. However, the routine implementation of cribriform morphology as a trigger for BRCA testing in prostate carcinoma would require additional large-scale studies to evaluate testing workflows and potential barriers, including interobserver variability.

The distribution of pathogenic *BRCA1/2* variants has been well characterized in several population-based studies worldwide, which consistently demonstrate a predominance of *BRCA2* mutations in prostate carcinoma [45,46]. This study also showed similar findings, with *BRCA2* variants being more frequent in this cohort.

BRCA variants identified in this study included frameshift, missense, splicing variants, and major genomic rearrangements as previously reported [47]. However, in contrast to prior reports [47] in which missense mutations were the most frequent, this study found large genomic rearrangements, frameshift, and nonsense variants to be more common across both *BRCA1* and *BRCA2*. Chen et al. [5] performed a study of 172 BRCA- associated prostate cancers, also reported a higher frequency of frameshift variants. Additionally, the missense variants found in this limited study set were predominantly VUS, with questionable pathogenicity and no definite impact on any of the protein properties included in the MutPred2 algorithm [17].

The localization of BRCA mutations to key domains, particularly specific exons or introns, and the resulting impact of these variants on protein properties will further enhance the understanding of carcinogenesis in these cases and may significantly influence future therapeutic strategies. Similar to prior reports [5], this study did not identify distinct hotspot mutations in *BRCA1/2* variant analysis. However, the MutPred-LOF algorithm [18] pre-

dicted molecular mechanisms of pathogenicity, identifying variants affecting catalytic sites, ion binding, and post-translational chemical modifications as enriched in this subgroup of BRCA-mutated prostate adenocarcinomas. Although BRCA1 and BRCA2 proteins have no intrinsic catalytic roles, these proteins form heterodimers with, and regulate the catalytic activity of, the primary orchestrators of homologous recombination [48]. Although BRCA2, in particular, lacks direct intrinsic catalytic function [49], the findings of the current study suggest that regions annotated as catalytic sites in *BRCA2* may be crucial to the associated tumor-suppressor function. The enrichment of variants impacting ion binding and post-translational modifications is not unexpected given the pivotal role of these proteins in regulating the activity, stability, and localization of BRCA proteins [50]. Functional defects in BRCA1 and BRCA2 lead to defective DNA repair via the homologous recombination pathway results in genomic instability and accumulation of genetic aberrations that drive the development of more aggressive, metastatic, and castration-resistant prostate cancer. This study is limited by a small sample size (n = 10), with a power of 0.475, which is below the conventionally acceptable threshold of 0.80. In addition, NGS testing was performed only in selected/high-risk cases (e.g., metastatic cases), introducing ascertainment bias and limiting the generalizability of the findings. Moreover, the impact of non-BRCA pathogenic variants and variants of uncertain significance, such as those in phosphatase and tensin homolog (*PTEN*), *ATM*, and other potential confounders, was also not assessed in this study. Nevertheless, the identification of impacted protein domains in BRCA-associated prostate adenocarcinoma may facilitate a more comprehensive understanding of tumor biology and behavior and aid in the development of novel therapeutic strategies targeting these domains. Therefore, these findings warrant further evaluation in a larger cohort of BRCA-mutated prostatic adenocarcinomas.

5. Conclusion

The current study found cribriform morphology may be enriched for BRCA alterations and could be used to prioritize BRCA mutational testing pending validation in larger cohorts.

The MutPred-LOF algorithmic prediction of molecular mechanisms of pathogenicity identified variants that may affect catalytic sites, ion binding, and post-translational chemical modifications as potentially enriched in this subgroup of BRCA-mutated prostate adenocarcinomas; however, further functional validation studies are required to confirm these observations.

Availability of Data and Materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

SK and KK designed the research study. SK performed the case retrieval and data collection. SK and KK analyzed the data. Both authors contributed to editorial changes in the manuscript. Both authors read and approved the final manuscript. Both authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by the institutional review board and ethics committee at Montefiore Medical Center, IRB approval number 2024-16225. This retrospective observational study utilized archived human prostate carcinoma specimens and de-identified clinical and genomic data obtained from existing pathology records. The requirement for informed consent was waived by the IRB due to the retrospective nature of the study and the use of de-identified data.

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Conflicts of Interest

The authors declare no conflicts of interest.

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