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ORIGINAL PAPER

BRCA mutations and prostate cancer: Should urologist improve daily clinical practice?

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Summary ***Introduction: To evaluate BRCA1-2 (breast cancer) detection in men with high risk PCa, including the oncological consequences for the patient and family members.***

Materials and methods: From January 2023 to December 2024, 52 men (median age 73 years;) with confirmed PCa diagnosis underwent somatic and germline BRCA1 and BRCA2 assessment; 11/52 (21%) patients documented a family history of cancer. Patients were at different clinical stages: high-grade (71% had a Gleason score ≥ 8), locally advanced (54% of cases) and/or metastatic PCa (46% of cases) at initial diagnosis, hormone-sensitive and/or castration-resistant PCa (38.2% of cases) at clinical progression. Formalin-fixed paraffin-embedded (FFPE) tissues and next generation sequencing (NGS) analyses of BRCA genes were evaluated on 52 samples (prostate biopsies or definitive samples) collected at Gravina Hospital (Caltagirone, Italy) from different Sicilian pathology departments. The therapeutic and clinical impact of genetic testing for BRCA somatic and germline mutations were evaluated for patients and their families.

Results: All FFPE cases were successfully genotyped, with a good library and sequencing CQ metrics for all genes of interest; 10/52 (19.2%) patients had somatic or germline BRCA mutations, specifically, 3/52 (5.7%) had somatic and 7/52 (13.5%) had germline mutations. In the seven cases with germline variants, 4/7 (57%) had a family history of PCa or other diseases, while the remaining 3/7 (43%) patients had no hereditary predisposition. All identified genetic variants were related to the BRCA2 gene; after genetic screening of the corresponding relatives, various members of the analysed families carried the mutation identified in the proband, so that cancer prevention and/or active surveillance was possible.

Conclusions: NGS analysis for BRCA genetic testing using FFPE tissue in the clinical setting of patients with high-grade and/or metastatic PCa appears to be a valuable tool, not only for therapeutic purposes, but also to identify families with genetic predisposition who may be underdiagnosed according to canonical criteria.

KEY WORDS: Prostate cancer; BRCA and high grade PCa; BRCA mutations and PCa: Somatic and germline BRCA.

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INTRODUCTION

Breast cancer (BRCA) gene mutations are known to be associated with earlier-onset and clinically significant prostate cancer (caPCa) (1). BRCA1 and BRCA2 are tumour suppressor genes: BRCA1 wild-type controls cell cycle checkpoints and repairs DNA in a normal cell (2); BRCA2 is a large protein consisting of 27 exons and may play a role in regulating transcription and is involved in DNA repair to maintain genome integrity during replication (3).

Many retrospective studies have reported higher rates of lymph node involvement, distant metastases at diagnosis and a higher mortality rate in PCa mutation carriers. Germline BRCA2 mutation status is considered an independent prognostic factor for poorer outcome (4). In addition, BRCA2 mutation in men with organ-confined PCa exhibits genomic instability typically seen in metastatic castration-resistant cancer (5), suggesting a poor long-term prognosis. In clinical practice, screening protocols for the early diagnosis of PCa are based on the determination of *prostate specific antigen* (PSA). To improve accuracy, other biological markers (6-8), risk calculators (9), *magnetic resonance imaging* (MRI) (10) and genetic markers (11-13) have recently been introduced. Recently, the IMPACT study (Identification of Men with a genetic predisposition to Prostate Cancer: Targeted screening in men at higher genetic risk and controls) an international and multicentre study, evaluated targeted PCa screening in men with germline BRCA1/2 mutations (13).

In this study, we report on BRCA1/2 evaluation in men with high risk PCa, including the oncological consequences for the patient and family members.

MATERIALS AND METHODS

From January 2023 to December 2024, 52 men (median age 73 years; range: 52-84) with confirmed PCa diagnosis underwent somatic and germline BRCA1 and BRCA2 assessment; 11/52 (21%) patients documented a family history of cancer. Patients were at different clinical stages: high-grade (71% had a Gleason score > 8) (14,15), locally advanced (54% of cases) (16,17) and/or metastatic PCa (46% of cases) at initial diagnosis (18), hormone-sensitive

Table 1.
Clinical findings in the 52 men submitted to NGS BRCA evaluation.

Overall patients' characteristics (tot. n = 52)		
Age (years)	Range	52-97
	Median	73
Cancer family history in a first degree realtive	Range	52-97
	Median	73
Gleason score	≤ 7	15
	≥ 8	37
Metastasis at diagnosis (locally advanced)		28
Metastatic setting		24
BRCA	Mutated	10
	Wild-type	42
Castration resistance	Yes	20
	No	32

and/or castration-resistant PCa (38.2% of cases) at clinical progression (19-21). After institutional review board and ethical committee approval were granted, the informed consent was obtained from all individual participants included in the study. All clinical parameters of the patients are listed in Table 1. *Formalin-fixed paraffin-embedded* (FFPE) tissues and *next generation sequencing* (NGS) analyses of BRCA genes were evaluated (22-24) on 52 samples (prostate biopsies or definitive samples) collected at *Gravina Hospital of Caltagirone* (referral center for genetic analysis) from different Sicilian pathology departments (25, 26). In addition, the therapeutic and clinical impact of genetic testing for BRCA somatic and germline mutations was evaluated for patients and their families. By aligning all sequencing results obtained with NGS analysis of FFPE tissue and peripheral blood, good coverage and uniformity was achieved for all samples with optimal read quality and sequencing metrics for both analyzed genes.

Results

All FFPE cases were successfully genotyped, with a good library and sequencing CQ metrics for all genes of interest. A good sequencing performance was also achieved for old archival samples (i.e. histological samples from 2009). Most of the identified genetic variants had been previously reported in the major mutation databases with clinical impact, being distributed among the different genes and all resulting in a truncated non-functional protein. 10/52 (19.2%) patients had somatic or germline BRCA mutations (Table 2); specifically, 3/52 (5.7%) had somatic and 7/52 (13.5%) had germline mutations. In the seven cases with germline variants, 4/7 (57%) had a family history of PCa or other diseases, while the remaining 3/7 (43%) patients had no hereditary predisposition. All identified genetic variants had been previously described in the major mutation databases, and most of them were related to the BRCA2 gene. In detail, 3/10 (30%) patients without a family history of cancer had germline mutations in the BRCA genes that had predictive significance but also clinical impact on their relatives. After genetic screening of the corresponding relatives, various members of the analyzed families (Figure 1) carried the mutation identified in the proband, so that cancer prevention and/or active surveillance was possible.

Discussion

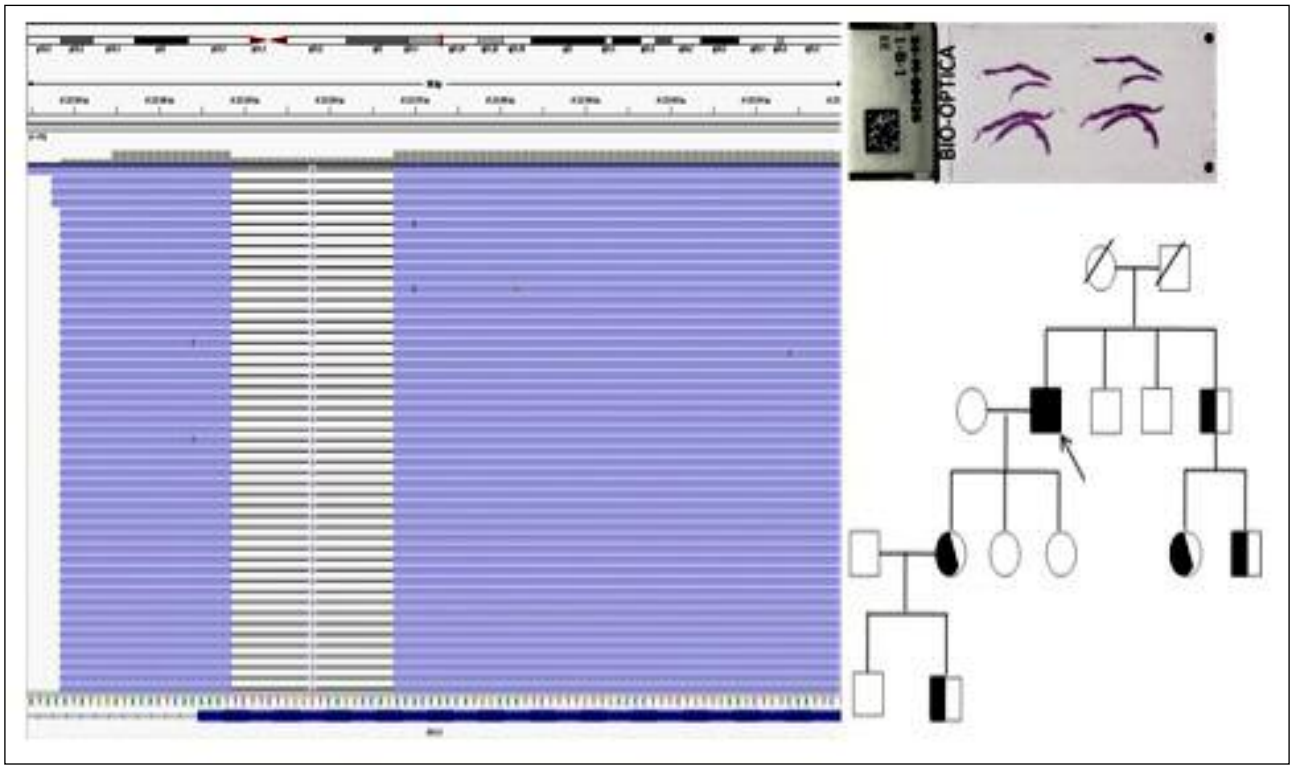
Several sequencing studies have shown that approximately 25% of metastatic castration-resistant PCa patients have genomically aberrant DNA repair pathways, with mutations in the BRCA1 and BRCA2 genes, which have been of important clinical and therapeutic significance since the approval of PARP inhibitors in castration-resistant patients (1). Of all BRCA-mutated metastatic PCa, about half had somatic mutations and the others had germline mutations (27); *Hommerding et al.* (28) reported a prevalence of potentially targetable genetic mutation

BRCA MUTATIONS IDENTIFIED IN ANALYZED PATIENT

Case	BRCA1 (NM_007294.3)	BRCA2 (NM_000059.3)	Mutation' Origin	Annotation	Clinical Significance	Tissue FFPE	Family History
#1	WT	p.(Glu2846GlyfsTer22)	Somatic	rs80359714 ClinVarID9328	Pathogenic ESCAT-IA	Biopsy	No
#2	WT	p.(Lys1691AspfsTer15)	Somatic	rs80359479 ClinVarID51762	Pathogenic ESCAT-IA	Surgical	No
#3	WT	p.(Ile605TyrfsTer9)	Somatic	rs80359306 ClinVarID37763	Pathogenic ESCAT-IA	Surgical	No
#4	WT	p.(Phe1837LeufsTer3)	Germline	rs2137518141 ClinvarID453583	Pathogenic ESCAT-IA	Surgical	Yes
#5	p.(Ser267LysfsTer19)	WT	Germline	rs80357724 ClinVarID37698	Pathogenic ESCAT-IA	Surgical	Yes
#6	p.(Glu23ArgfsTer18)	WT	Germline	rs80357783 ClinVarID37691	Pathogenic ESCAT-IA	Surgical	Yes
#7	WT	p.(Trp1692MetfsTer3)	Germline	rs80359479 ClinVarID37943	Pathogenic ESCAT-IA	Surgical	No
#8	p.(Ser1655TyrfsTer16)	WT	Germline	rs80359876 ClinVarID37616	Pathogenic ESCAT-IA	Surgical	No
#9	p.(Thr1677IlefsTer2)	WT	Germline	rs80359480 ClinVarID37623	Pathogenic ESCAT-IA	Surgical	No
#10	WT	p.(Ile1470LysfsTer10)	Germline	rs397507718 ClinVarID51643	Pathogenic ESCAT-IA	Surgical	Yes

Table 2.
BRCA mutations (somatic and/or germline) in 10/52 (19.2%) patients with aggressiveness prostate cancer.

Figure 1.
Family evaluation in a case of BRCA germline mutation.



criteria of 20.8% in 197 cases of primary and metastatic PCa. The inclusion of genomic testing based on FFPE samples for predictive purposes in the management of patients with metastatic PCa has relevant implications for their healthy relatives in the presence of germline mutations. It also offers the real possibility of preventing cancer in BRCA1/2 mutation carriers through screening protocols (29). Men with BRCA1/BRCA2 germline mutations who are on active surveillance for low-risk PCa have been reported to be at higher risk of reclassification than non-carriers (30); in these cases, closer surveillance incorporating other clinical parameters may be recommended (31-33).

The *European Urological Association* (34) recommends starting PCa screening at the age of 40 for male BRCA2 carriers. The *National Comprehensive Cancer Network* (NCCN) guidelines do the same for BRCA1 carriers and routinely perform BRCA1/2 testing for men with high-risk PCa (Gleason score > 8), ductal or cribriform PCa and metastatic disease (35). T-NGS analysis for BRCA genetic testing using FFPE tissue in the clinical setting of patients with metastatic PCa appears to be a valuable tool, not only for therapeutic purposes, but also to identify families with genetic predisposition who may be underdiagnosed by canonical criteria. The IMPACT study (13) investigated targeted PCa screening in men with germline BRCA1/2 mutations; among the 357 men who underwent prostate biopsy, the 112 men with PCa were found to have a higher detection rate in BRCA2 carriers compared to non-carriers (73% *versus* 60%). In addition, BRCA2 carriers were diagnosed at a younger age and were more likely to have csPCa than BRCA2 non-carriers (77 vs 40%). In contrast, no differences were found between BRCA1 carriers and BRCA1 non-carriers in terms of age or tumour characteristics.

The ability to test BRCA1/2 genes from FFPE samples would allow the simultaneous assessment of both somatic and germline mutations using an accessible material that is routinely available in any pathology laboratory (36). Therefore, there is a need for efficient and timely methods to detect both somatic and germline mutations starting from FFPE tissue under expert guidance, considering the high percentage of failures in this tumour setting (37). Recently, a consensus paper was developed and approved by a multidisciplinary expert panel on behalf of the Italian scientific societies (38) to improve accurate patient selection by the use of standardized and harmonized procedures and adherence to homogeneous BRCA testing criteria. *Loeb et al.* (39) reported on a survey of urologists in the USA that examined knowledge of germline testing guidelines and practice patterns. Of a total of 132 respondents from different practices, 12% performed germline testing, 44% refer to a genetic counsellor, 11% do both and 33% do not test/refer, 4% had formal training in genetics, suggesting that there are significant gaps in urologists' knowledge of germline testing and how to align practice with national guidelines. Although somatic and germline BRCA2 testing is only recommended in men with metastatic castration-resistant PCa, the possibility of also performing the test in men with locally advanced and/or aggressive PCa, as suggested in the NCCN guidelines, offers the opportunity to

select patients at high risk of clinical progression and to perform adequate clinical cancer screening in family members with germline mutations to prevent aggressiveness and/or advanced cancer at diagnosis. In addition, early genetic tissue testing could reduce the risk of non-diagnostic tissue patterns that are useful for genetic testing, especially many years after diagnosis of PCa, as well as the difficulty of performing biopsies of metastases (i.e., bone, retroperitoneal nodes) (37). Definitely, the role of the urologist in a multidisciplinary approach is fundamental to adequately inform the patient affected by aggressive PCa at the time of diagnosis about the role of genetic testing (somatic and germline) to improve oncological treatment and prevent cancer through early screening protocols in family members with germline mutations. These data should be analyzed in a larger number of patients and in a multidisciplinary team to assess the best timing for BRCA testing, the cost-effectiveness and the therapeutic impact of early genetic analysis. In our series, 3/7 (43%) patients with BRCA2 germline mutations and negative family history for PCa underwent genetic counselling, including family members, for appropriate oncological screening.

Conclusions

NGS analysis for BRCA genetic testing using FFPE tissue in the clinical setting of patients with high-grade and/or metastatic PC appears to be a valuable tool, not only for therapeutic purposes, but also to identify families with genetic predisposition who may be underdiagnosed according to canonical criteria.

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Declarations

Ethical approval: *Institutional review board and ethical committee approval were granted the informed consent was obtained from all individual partecipants included in the study.*

Availability of data and material: *The data that support the findings of this study are available from the corresponding authors upon reasonable request.*

Competing interests: *The authors declare that there is no conflict of interest.*

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