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ORIGINAL ARTICLE

Inherited cancer syndromes in 220 Italian ovarian cancer patients

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Abstract

Background: A subsets of ovarian carcinomas (OCs) are related to inherited conditions including Hereditary Breast and Ovarian Cancers (HBOC) and Lynch Syndrome (LS). The identification of inherited conditions using genetic testing might be a strategic model for cancer prevention that include benefits for the ovarian cancer patients and for their family members.

Methods: We describe a retrospective Italian experience for the identification of inherited conditions in 232 patients affected by OCs using both somatic and germline analyses.

Results: Immunohistochemical and microsatellite analyses performed on OCs identified 20 out of 101 MMR defective cancers and 15 of these were from patients carriers of the MMR germline pathogenetic variants.

BRCA1 and BRCA2 testing offered to 198 OC patients revealed 67 (34%) pathogenetic variant carriers of BRCA1/2 genes. Interestingly LS patients revealed a mean age of OC onset of 45.4 years, which was significantly lower than the mean age of OCs onset of HBOC patients.

Conclusions: Somatic and germline analyses offered to OC patients has proved to be an efficient strategy for the identification of inherited conditions involving OC also in absence of suggestive family histories. The identification of LS and HBOC syndromes through OC patients is an effective tool for OC prevention.

Keywords Ovarian cancer, HBOC, Lynch syndrome, MMR, Genetic counselling.

Introduction

Ovarian cancer (OC) is the third most common gynaecological malignancy in Europe. Owing to its unfavorable anatomy and lack of effective screening strategies, it is often diagnosed as advanced stage disease and it has the highest mortality rate of all gynaecological malignancies [1].

Data from the literature reported that approximately 20–25% of all ovarian carcinomas are related to inherited conditions [2–4]. The most common hereditary gynaecological tumor syndromes are Hereditary Breast and Ovarian Cancer Syndrome (HBOC; ORPHA 145) and Lynch Syndrome (LS; ORPHA 144). The genetic risk assessment using molecular testing has been described as a cost-effective method when used in the routine care of women [4–6]. This approach favored the development of evidence-based practices and guidelines towards cancer prevention employing surgical prophylaxis, intensive screening and chemoprevention.

Identification of inherited conditions involving OCs has been traditionally performed through detailed pedigree analysis and germline molecular testing, and more recently through universal screening on colorectal and endometrial cancer samples for LS [7,8]. Considering the epidemiological, clinical and prognostic characteristic of OCs, the identification of an inherited condition might represent an useful strategic model

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of prevention, which includes benefits not only for the actual patients, but also for the potentially affected family members, who can be detected by cascade testing [5,9]. The aim of this retrospective study was to describe germline and somatic genetic strategies in a series of consecutive patients affected by OCs, who were tested to identify inherited conditions.

Methods

We evaluated consecutive patients with histologically-proven ovarian cancer who were referred to the Cancer Genetic Counselling Service of ASST Settelaghi Hospital in Varese (Italy) from 2008 to 2017. All patients were counseled to investigate genetic predispositions to cancer using NCCN criteria [10], Amsterdam [11] and Bethesda criteria [12].

In all cases familial history of three generations was recorded, and specific somatic and/or germline genetic tests were suggested based on pedigree and histological features. Written informed consent was obtained prior to analysis for all women who decided to have genetic testing.

Tumor histology was stratified into high-grade OC, low-grade OC and borderline ovarian tumor.

This series of 218 OCs was from 218 patients and the mean age at diagnosis was 52.6 years (range 26–83 y). OCs showed different histological types including 32 low grade carcinomas,156 high grade carcinomas and 11 borderline ovarian tumours.

Somatic analysis

OCs were screened with IHC staining for four MMR proteins (MLH1, MSH2, MSH6 and PMS2) using previously described methods [13,14].

The normal staining pattern for all proteins was nuclear and a case was considered MMR proficient (P-MMR) in the presence of nuclear staining in neoplastic cells. A patient was considered MMR defective (D-MMR) for the expression of one protein in case of complete absence of nuclear staining in all neoplastic cells, or in a very well-defined clone of tumor cells in the presence of an unquestionable internal positive control represented by normal epithelial cells, stromal cells, muscle cells, or lymphocytes.

MSI analysis was carried out on DNA extracted from manually microdissected tumour areas using a pentaplex panel of monomorphic mononucleotide repeats (BAT25, BAT26, NR-21, NR-22 and NR-24) as previously reported [15]. MSI was scored as high frequency when at least two out of five of the analysed microsatellites were unstable.

Methylation of the *MLH1* promoter was analysed by MS-MLPA using the ME011-B3 MMR SALSA MS-MLPA® kit (MRC-Holland, Amsterdam, The Netherlands) as previously described [16]. A sample was classified as methylated when CpG sites in the Deng-C region exhibited methylation.

Germline analysis

Screening for MMR gene variations including *MSH2, MSH6, MLH1, PMS2* and *EPCAM* was carried out on blood DNA by standard procedures including Sanger sequencing and Multiplex ligation-dependent probe amplification (MLPA), as previously reported [17]. MMR variations were classified using Insight classification (InSiGHT Variant Interpretation Committee: Mismatch Repair Gene Variant Classification Criteria, 2018; www.insight-group.org)

BRCA1 and *BRCA2* germline screening was performed using Sanger or NGS sequencing and MLPA analyses using MRC-Holland kits (P002-D1-BRCA1 SALSA MLPA® KIT (CE-IVD) and P045-C1-BRCA2 SALSA® MLPA KIT (CE-IVD) MRC Holland, Amsterdam, The Netherlands). Identified genetic variants were classified according to the IARC 5-tier scheme [18], following the guidelines of the Evidence-based Network for the Interpretation of Germline Mutant Alleles (ENIGMA; http://enigmaconsortium.org). The classification of variants initially considered as variants of uncertain significance (VUS, Class 3) were subjected to regular updates, by reviewing the literature and publicly available databases to the best of our knowledge, and modified accordingly [19].

Statistical analysis

A standard descriptive analysis has been performed. Data has been reported as absolute number and percentage for dichotomous variables. Median (range) or mean (+/− standard deviation) were used to describe continuous variables according with distribution.

A student *t*-test was used to compare age at diagnosis between the groups; box-plot charts were used to indicate median and 5%−95% range of distribution. (GraphPad Prism Software, version 5.0).

A *p-value* < 0.05 two-tailed was considered statistically significant.

Results

A total of 232 patients from different families were referred to the Genetic Counselling Service for suspected cancer syndromes during the study period. Out of these, 218 (94%) underwent genetic investigations, and represented our study population (flow chart shown in Fig. 1). On the base of pedigree analyses 19 patients (8.7%%) were suspected for LS and 117 (53.7%) for HBOC syndrome. In addiction 82 OC patients did not revealed a suggestive cancer family histories and were classified as single OC cases.

Specifically, somatic tests for microsatellite instability (MSI) and immunohistochemistry (IHC) for MMR (MisMatch Repair) proteins were performed on 19 OCs. with family history fulfilled Amsterdam [11] and Bethesda [12] criteria. Somatic analyses were also performed on 82 OCs without cancer family histories .

On the contrary when the family history was suggestive of HBOC syndrome, germline analyses of BRCA1/2 genes were offered. In summary, BRCA1 and BRCA2 germline analyses were performed to 198 (90.8%) patients including 117 (53.7%) patients suspected of HBOC syndrome and 81 (37.2%) patients with MMR-proficient single OC

High microsatellite instability was observed in 18 out of 101 OCs (17.8%); of these eleven OCs (61%) were MSH2 and MSH6 deficient, 4 (22%) were MLH1 and PMS2 deficient, 2 (11%) were MSH6 deficient only and 1 (5%) was discordant

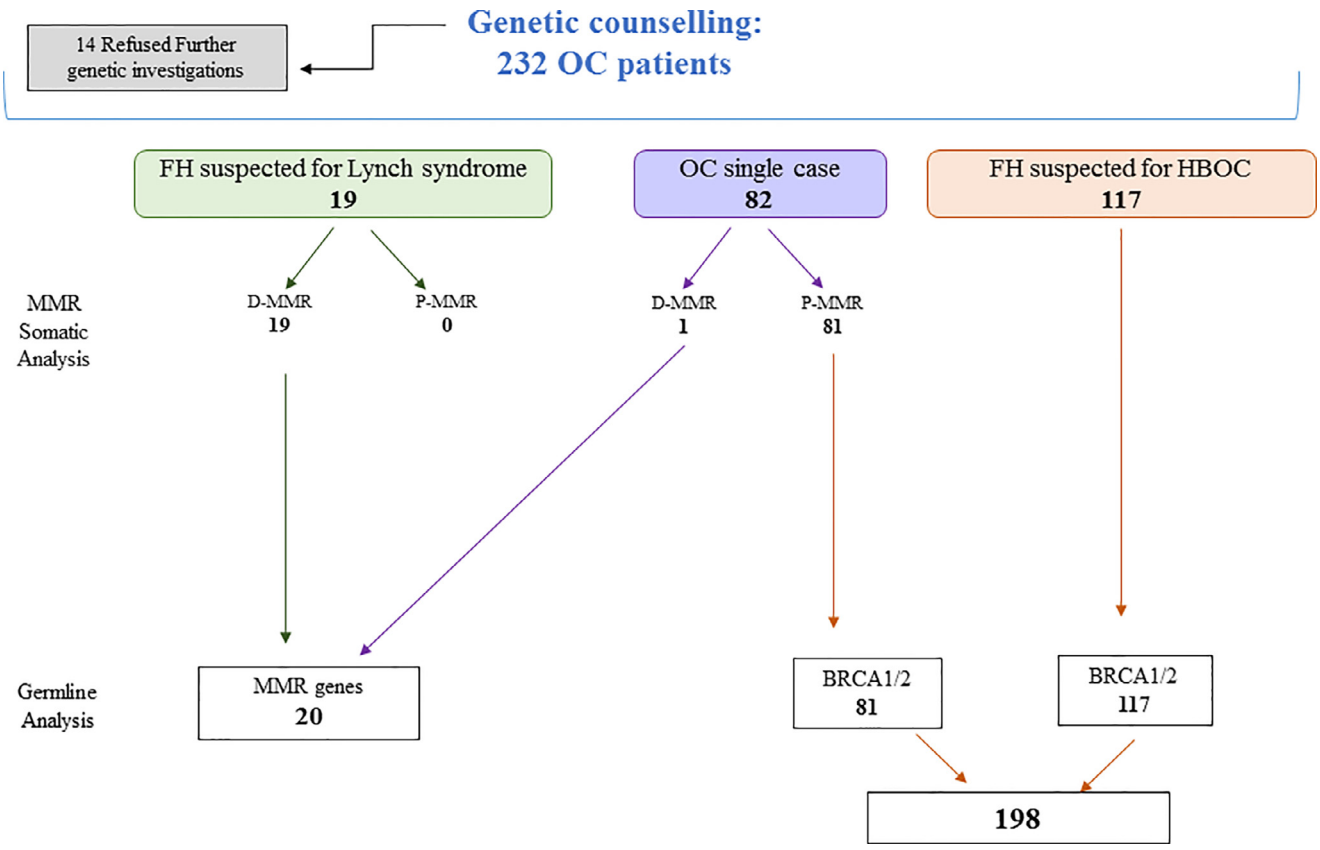

Fig. 1 Flowchart for genetic testing. FH: Family History, D-MMR: defective MisMatch Repair, P-MMR: proficient MisMatch Repair.

showing MSI-H and normal MMR gene expression. Two OCs showed an atypical somatic MMR pattern and the remaining 81 patients had MMR proficient OCs.

All 20 patients with MMR defective or atypical OCs underwent MMR germline testing (Fig. 1) and a gene variant was identified in 15 (75%) patients including 4 (20%) MSH2, 1 (5%) MLH1 and 10 (50%) MSH6. The MMR mutation spectra (Fig. 2 panel A) included 4 truncating, 3 missense, and 2 large rearrangements as well as 6 cases with the 3'UTR variant of the MSH6 gene (c.*23_26dupAGTT), which was attributed to Class 5, based on a multifactorial likelihood model and according to the Insight rules [19]. Interestingly this MSH6 variant was a founder mutation of the Varese/Como geographic area (data not yet published).

The OC IHC pattern was deficient for MSH2 and MSH6 in 4 MSH2 carriers and in 6 carrier of 3'UTR MSH6 variants. One MLH1-PMS2 deficient OC was identified in a MLH1 carrier, the remaining 4 OCs showing MSH6 deficiency were identified in MSH6 variant carriers. Interestingly one single OC patient was carrier of MSH6 pathogenetic variant.

The 3 OCs defective for MLH1 and PMS2 expression without germline MLH1 and PMS2 variants showed somatic MLH1 promoter methylation and were classified as sporadic OCs.

Regarding BRCA investigation, the mutational spectrum of BRCA genes is summarized in Fig. 2 panel B left. 68 out of 198 (34%) OCs patients carried pathogenetic or likely pathogenetic (ENIGMA Classes 4 and 5) variants including 46 (23%) BRCA1 and 22 (11%) BRCA2 (1 patient, carried both BRCA1 and BRCA2 variants). In addition 13 out of 198 (6.5%) OC patients carried variants of unknown significance (ENIGMA Class 3) including 7 (3.5%) BRCA1 and 6 (3.0%) BRCA2.

Most BRCA1 and BRCA2 pathogenetic variants (52/68 76%) were truncating variants, predominantly nonsense or frameshift (Fig. 2 panel B right). The identified BRCA1/ 2 pathogenetic variants do not cluster in specific gene regions but were distributed spanning all the gene sequences.

As described in Fig. 3 panel A the detection rate of Classes 4 and 5 variants was 33.8%: more than 40% when the selection criteria include OC patients showing a positive family history for OC and/or breast cancer. However when the selection criteria included a single case of OC, the detection rate was 15% (12 out of 81) at any age of OC diagnosis, ranging from 9.7% (>50 years) to 20.5% (<50 years)

With regard to MMR variant detection, MSI and/or IHC analyses allowed a high detection rate to be achieved: 15 out of 20 (75%) MMR defective OCs were due to constitutional MMR pathogenetic variants including one patient with single OC.

In summary, in the present series we identified 67 (33.8%) OC patients affected by HBOC, and 15 (14.8%) OC patients affected by LS.

During genetic counselling of HBOC and LS patients, genetic testing was offered to family members of the index cases. Twenty-seven female family members out of 15 LS detected patients had genetic analysis and 21 of these (77.7%%) carried the familial MMR pathogenetic variant. Conversely, 82

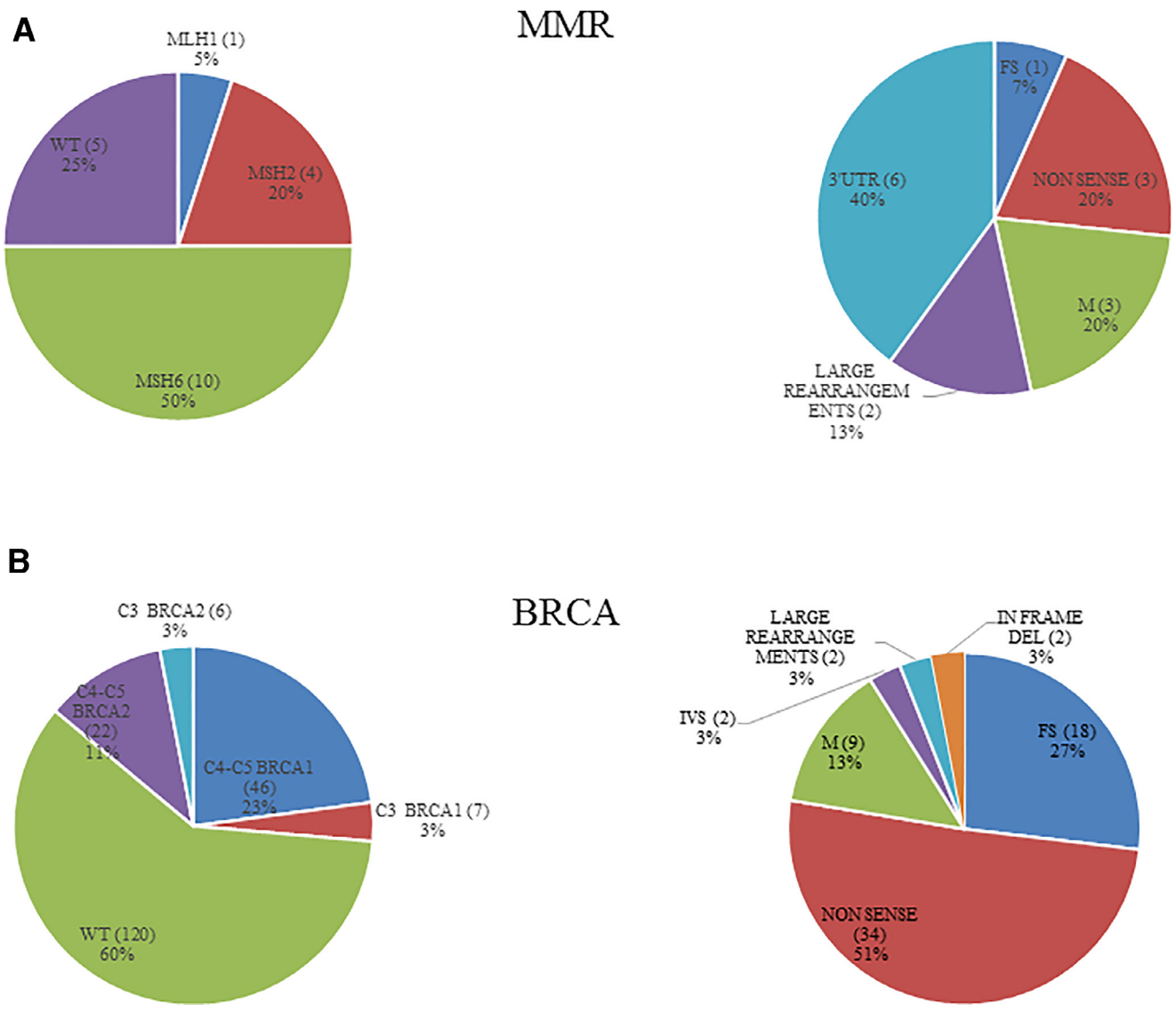

Fig. 2 Panel A describe MMR variant spectra and Panel B describe BRCA1/2 variant spectra.

female family members out of 67 HBOC detected patients had genetic testing, and 39 of these (47.5%) were carrier of BRCA pathogenetic variants.

Table 1 describe the clinic and pathological features of OCs of HBOC and LS patients: BRCA pathogenetic variants were identified in 59 out of 65 (90.7%) high grade OCs and in 6 out of 65 (9.2%%) low grade OCs. With regard to LS OCs, pathogenetic MMR variants were identified in both low (5) and high (7) grade carcinomas.

Focusing on the histopathologic characteristics, 54 out of 67 (80.5%) BRCA1/2 carriers had serous type OCs (Table 1), but BRCA pathogenetic variants were also identified in patients with endometrioid (7 cases out of 67), clear cells and mixed OCs. Also, in LS patients, MMR variants were identified not only in endometrioid OCs but also in serous, clear cells and mixed OCs (Table 1).

Mutations of either BRCA or MMR genes have also been identified in patients affected by ovarian carcinosarcoma, while no mutations were identified in cases with borderline ovarian tumor. Fig. 4 shows the details of a family in which two sisters were affected by high grade serous OCs both carriers of BRCA1 pathogenetic variant, while the third sister was affected by borderline ovarian tumor, and she was not carrier of the familial BRCA1 variant (Fig. 4).

The distribution of age at OC diagnosis revealed that the mean age of LS and HBOC patients was not significantly different compared to the one observed in patients tested negative (*p-value* 0.099) (Fig. 5 panel A); however, MMR mutated patients were significantly younger than both wild type cases (*p-value* 0.012) (Fig. 5 panel B) and BRCA1-BRCA2 mutated cases (*p-value* 0.006) (Fig. 5 panel D). In addition, age at OC diagnosis of BRCA2 cases was significantly higher than BRCA1 cases (*p-value* 0.037) (Fig. 5 panel C).

Discussion

The identification of high risk OC patients using genetic testing followed by risk reducing bilateral salpingo-oophorectomy has been widely demonstrated as preventive strategy to

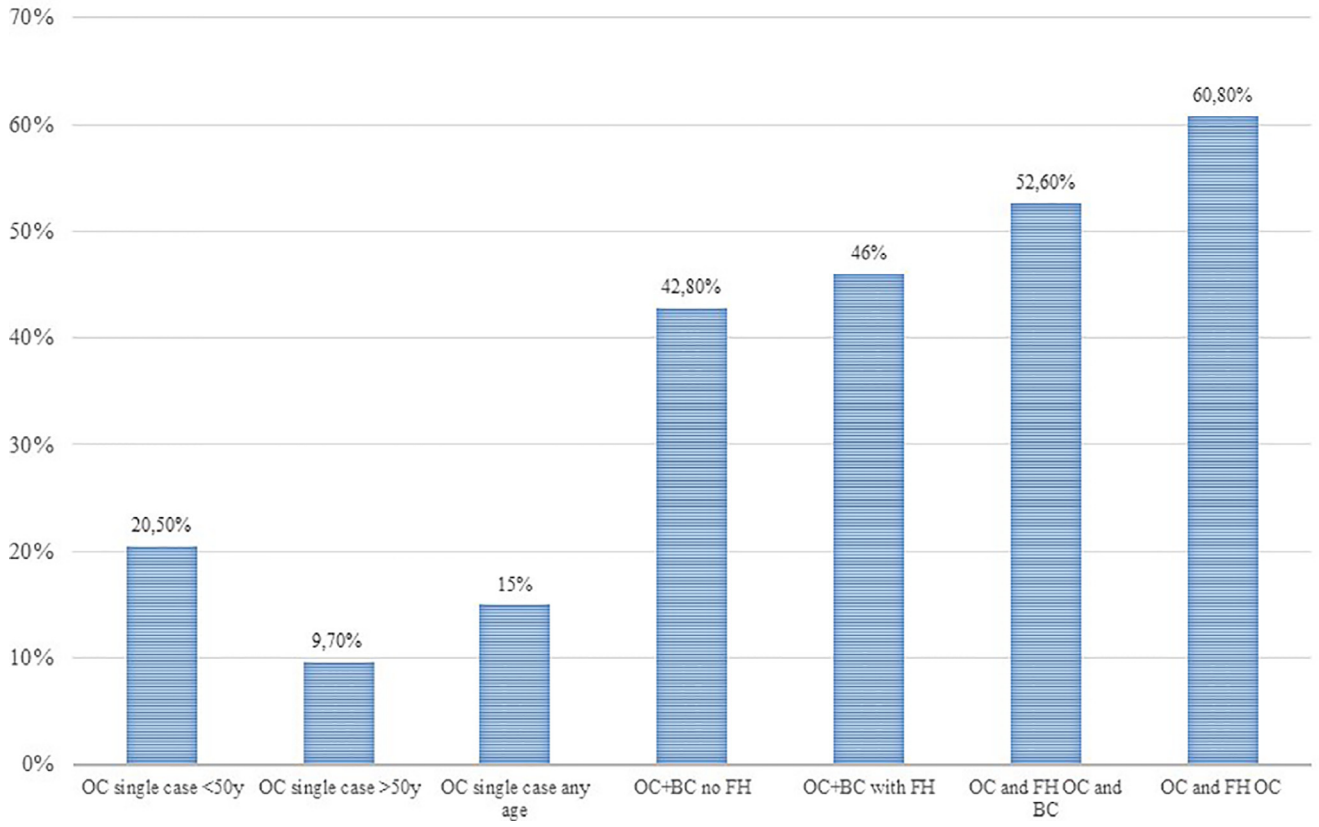

Fig. 3 BRCA1/2 detection rate in relationship to family history. OC: ovarian cancer, BC: breast cancer, FH: Family history.

Table 1 Comparison of OC clinico-pathological features in patients carrier of BRCA1/2 and/or MMR genes pathogenetic variants respect to patients without pathogenetic variants.

	Total cases **218**	BRCA patients **67**	LS patients **15**	No pathogenetic variants patients **136**
No. of tumors	**218**	**67**	**15**	**136**
Mean age at diagnosis	52,6 y	52.1 y	45.4 y	53,5 y
Site of onset (218)				
Tube	8	3	0	5
Ovary	209	64	15	130
Peritoneum	1	0	0	1
Grade of differentiation (199)		**65**	**12**	**122**
Borderline	11	0	0	11
Low grade carcinoma (G1-G2)	32	6	5	21
High grade carcinoma (G3)	156	59	7	90
Histological type (218)				
Serous	144	54	2	88
Endometrioid	39	7	8	24
Clear cells	10	2	3	5
Mixed	9	2	1	6
Mucinous	2	0	0	2
Carcinosarcoma	2	1	1	0
STIC	1	1	0	0
Borderline	11	0	0	11

decrease the risk of ovarian cancer in the last decades [6,20–22]. Therefore, it becomes mandatory the definition of efficient strategies able to identify the target high-risk population to carry out cancer prevention.

We here reported our experience of HBOC and LS characterization using both constitutional BRCA1/2, somatic and constitutional MMR analyses. Eighty-two OC patients out of 218 (37.6%) affected by inherited cancer susceptibility were

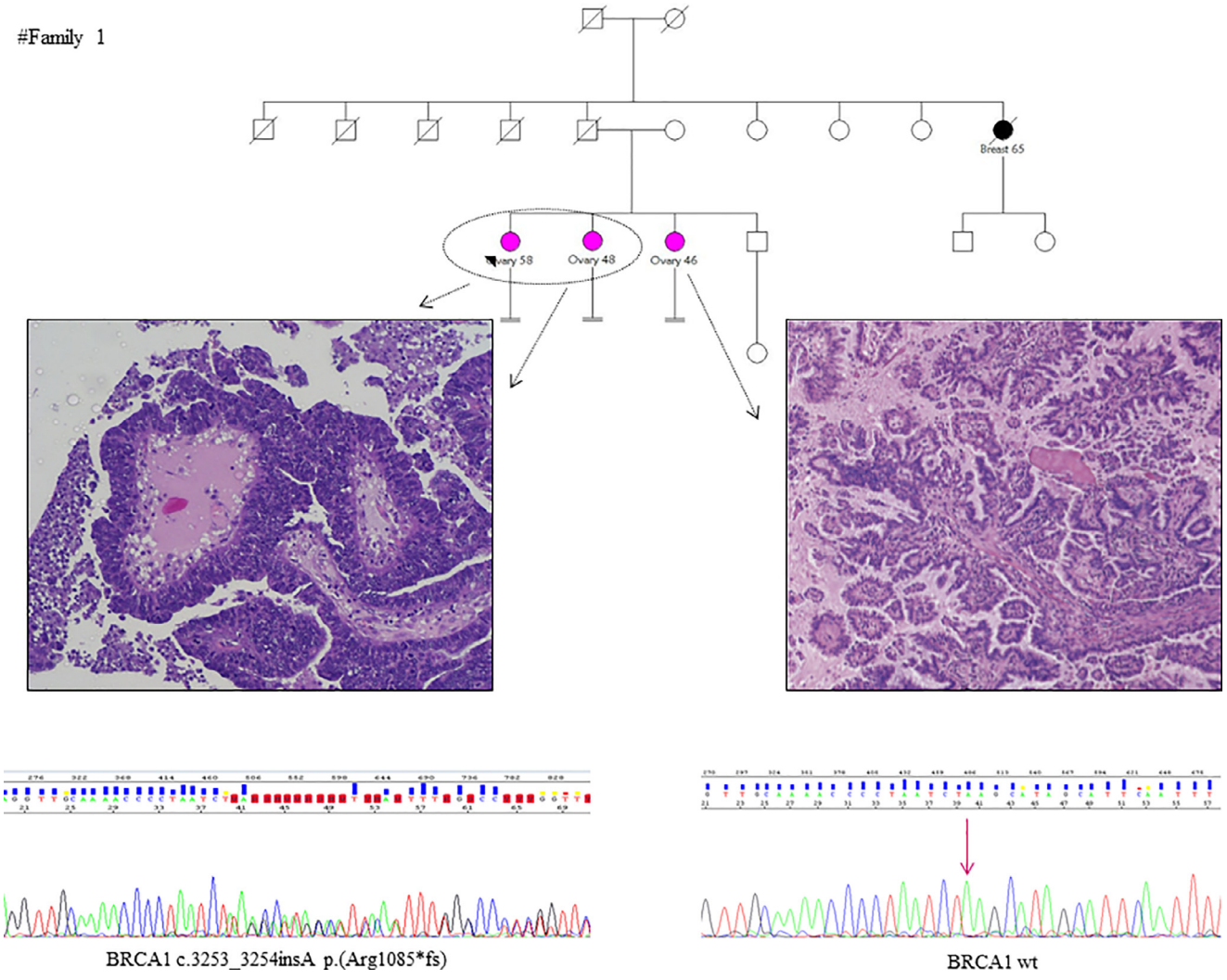

Fig. 4 Pedigree of HBOC showing two sisters affected by high grade OCs carriers of BRCA1 pathogenetic variants and one sister affected by borderline ovarian cancer wild-type for BRCA1 pathogenetic variant.

identified including 67 BRCA1/2 and 15 MMR carriers of pathogenetic variants.

In the present study we found a rate of BRCA1/2 mutations (33.8%) higher than the one reported by other authors in literature showing constitutional BRCA1/2 mutations in 14% to 15% of all OCs [23,24] and in 22.6% of high grade OCs [23,24]. This difference might be due to our sample selection, which included not only single OC cases but also OC patients with suggestive family history of ovarian and/or breast cancer. Our data showed a rate of BRCA1/2 mutations higher when OC patients revealed a strong family history of ovarian (60.8%) or breast and ovarian cancers (52.6%). However, the subset of OC patients without positive family history revealed a non-negligible detection rate (15% at any age in Fig. 4).

Additionally, the findings of our analysis showed LS as responsible for a significant proportion of hereditary ovarian cancers, and the algorithm for OC screening with IHC, and/or MSI analysis has been proven to be an efficient approach to identifying LS. Moreover, the use of this strategy together with the cascade genetic testing might be helpful to identify patient relatives potentially at high risk for LS and related tumors. Also, the use of somatic analyses was useful for tailoring germline testing and crucial for the detection of LS in six carriers of the variant outside the coding sequence of the MSH6 gene not previously classified in InSight database.

In agreement with recent literature [25], BRCA1/2 mutations were common also in non-serous histological OC types, and MMR mutations were interestingly found not only in endometrioid OCs but also in serous and other histological types. These results might suggest that the conventional strategies to direct germline testing using histological features alone could be not accurate enough to identify BRCA1/2 and MMR mutation carriers.

In accordance with the current literature, the mutation spectra revealed that BRCA1 was more involved than BRCA2 while MSH6 was the most frequently mutated MMR gene in this subset of patients [14,26–28].

Interestingly, in our investigation we found LS carriers at OC diagnosis significantly younger than both BRCA1/2 and wild-type, thus probably opening a debate on the most appropriate age for risk reducing surgery in this selected population.

In conclusion, our results outlined that the identification of inherited cancer syndromes using OC patients as index cases

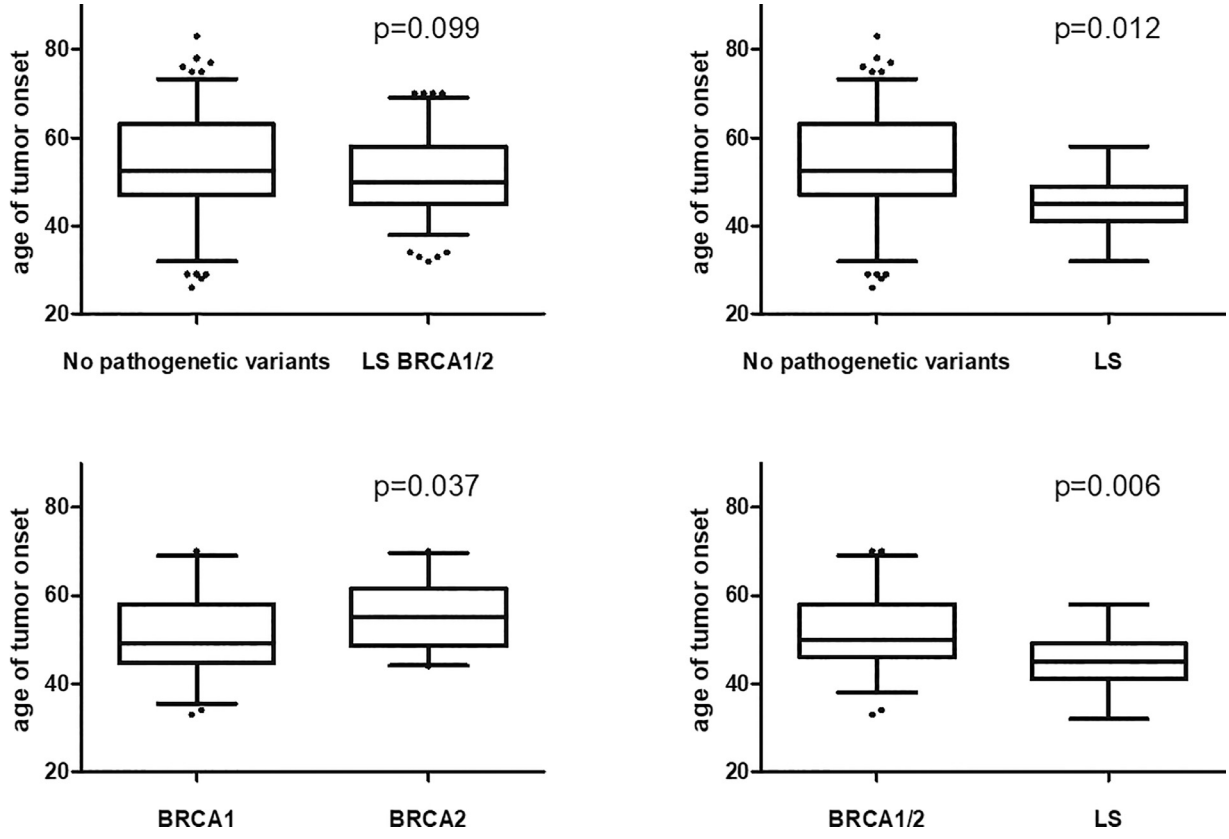

Fig. 5 Correlation of OC age of onset in different inherited syndromes.

for somatic and germline molecular testing might be an efficient strategy for cancer prevention, also in the absence of suggestive family histories. Universal screening using IHC for MMR defect on OCs could be an accurate method to identify LS families. When constitutional gene panel testing is offered to OCs patients for inherited syndromes identification, the inclusion of MMR genes constitutional testing in addition to genes involved in homologous recombination is mandatory. This should be taken into account especially after the introduction of new therapies like PARP-inhibitor and immunotherapy.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cancergen.2019.06.005.

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