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Characteristics and outcome of BRCA mutated epithelial ovarian cancer patients in Italy: A retrospective multicenter study (MITO 21)

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HIGHLIGHTS

- This is the largest Italian BRCAmut Epithelial Ovarian Cancer (EOC) cohort, with 331 women diagnosed between 1995 and 2017.
- The most frequent diagnosis was FIGO stage III/IV high grade serous EOC.
- Expected percentage of patients alive at 5 years was 72.5% (CI 60.2–80.8%).
- R = 0 at surgery was correlated with a longer OS.
- EOC patients that developed a subsequent BC were long-term survivors.

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ABSTRACT

Objective. Around 15% of epithelial ovarian cancer (EOC) patients (pts) harbor a germline BRCA1 or 2 mutation, showing different features than BRCA wild-type pts. The clinical and pathological features of an Italian BRCA mutated EOC cohort were described.

Methods. We retrospectively analyzed clinical, pathological and mutational data from a cohort of Italian BRCA mutated EOC pts. treated in 15 MITO centers between 1995 and 2017.

Results. Three-hundred thirty-one pts. were recorded. Two-hundred forty (72%) and 91 (27.5%) pts. harbored a BRCA1 and BRCA2 mutation, respectively. Median age at diagnosis was 52 years. The most frequent diagnosis was a high grade serous FIGO III or IV EOC and platinum doublet in first-line was administered to almost all pts. Fifty-three % of them had no residual disease ($R = 0$) at surgery. Median progression-free-survival (mPFS) after

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first-line chemotherapy was 29 months. Expected percentage of pts. alive at 5 years was 72.5% (CI 60.2–80.8%) and R = 0 predicted a significantly longer overall survival (OS). Sixty-six pts. (19,9%) had both an EOC and a breast cancer (BC) diagnosis. The first diagnosis was BC in 81,8% of cases with a mean interval between the two diagnoses (IBTDs) of 132.4 months. Mutational data show that the founder mutation c.5266dupC in BRCA1 was the most frequently recorded.

Conclusions. This is the largest Italian BRCA mutEOC cohort. The only predictor of longer OS was $R = 0$. EOC pts. that developed subsequently a BC are long-term survivors.

1. Introduction

Ovarian cancer (OC) is the fifth most common and the most lethal among gynecological malignancy worldwide [1]. In Italy, 5200 estimated new cases occurred in 2018 and OC is responsible for 5% of death for tumor in women [2].

It is considered a heterogeneous group of malignancies with a wide variety of histological and molecular features, distinct clinical and biologic behaviors [3]. Malignant epithelial tumors are the most common type of ovarian cancer and account for almost 90% of cases, being high grade serous OC the most frequent histology. Overall, around one fifth of OCs are hereditary and 90% of these are associated with germline mutations in Breast cancer 1 and 2 (gBRCA1 and 2) genes [3,4].

The proteins encoded by BRCA1 and BRCA2, are involved in DNA repair pathways, above all in homologous recombination (HR), a high fidelity mechanism that repairs double strand breaks. The loss of these genes contributes to cancer initiation and progression [5].

BRCA1 and 2 mutations are therefore responsible for genetic predisposition to OC and Breast cancer (BC). The cumulative BC risk to age 80 years is 72% (95% CI, 65%–79%) for BRCA1 and 69% (95% CI, 61%–77%) for BRCA2 carriers while the cumulative OC risk is 44% (95% CI, 36%–53%) for BRCA1 and 17% (95% CI, 11%–25%) for BRCA2 carriers [6–8].

Moreover, BRCA mutated patients have a higher risk to develop both a OC and BC during their lifetime although few reports describe this populations with a second primary cancer [9,10].

Patients with BRCA related OC are usually diagnosed at a younger age, with an advanced disease and an high grade serous histology but they are also are more sensitive to platinum-based chemotherapy and to PoliADP ribose inhibitors (PARPis), showing a longer survival compared to their sporadic counterpart [11–13].

Several studies analyzed features and outcomes of OC and BC patients according to the presence of a BRCA1 or a BRCA2 mutation or between BRCA mutated an BRCA wild type (wt) cohorts but data on the Italian population are scarce and a nationwide multicenter cohort study about BRCA OC patients has not been run in our Country so far [11,14–16].

For this reason, we carried out a retrospective study recruiting BRCA mutated Epithelial OC (EOC) patients treated in 15 Multicenter Italian Trials in Ovarian Cancer and gynecologic malignancies (MITO) centers all over Italy.

The aim of this study was to describe the clinical and pathological features of an Italian BRCA mutated EOC cohort.

2. Materials and methods

2.1. Study design

This is an observational, retrospective, multicenter clinical study aiming to evaluate the features of BRCA1 and BRCA2 germline mutated EOC patients in Italy.

The main inclusion criteria was a pathologically confirmed EOC (Epithelial Ovarian Carcinoma, carcinoma of the fallopian tube, primitive carcinoma of the peritoneum) with germline BRCA1 or BRCA2 mutation diagnosed between 1995 and 2017 at one of the 15 participant MITO Cancer Centers.

The study protocol was approved by each local Institutional Review Boards. All alive patients signed an informed consent agreeing to use anonymized information for research purposes.

Molecular, pathological and clinical data were obtained from medical records in each center and recorded in a centralized platform. Recorded information included age at diagnosis, place of birth, stage according to International Federation of Gynecology and Obstetrics (FIGO) criteria, histology and grade, type of surgery and residual disease, type of treatments with the first Platinum- Free Interval (PFI), number of lines of therapy.

We performed a subgroup analysis in the Breast and Ovarian Cancer cohort (BOC), i.e. patients in which BC occurred previously, concomitantly or subsequently EOC diagnosis.

2.2. Mutation analysis

Mutation analysis to identify germinal BRCA1 or BRCA2 mutation was performed locally with a variety of previously published techniques. The techniques used in this long period varied from direct sequencing by PCR to DHPLC, MLHP and NGS plus Sanger or direct sequencing. All pathogenetic variants were centrally re-classified using Clinvar and Enigma databases and we included in the final analysis only VUS 4 (being considered clinically pathogenetic for treatment) and VUS 5.

After informed consent signature, both data on mutations and original reports when available were sent to the coordinating center and centrally reviewed by an expert genetic counselor [on the basis of the nomenclature system of Human Genome Variation Society (http://www.hgvs.org/mutnomen) and the conventional nomenclature system from the Breast Cancer Information Core (BIC; http://research.nhgri.nih.gov/bic/)].

Only patients with confirmed deleterious mutations (pathogenic) were analyzed.

We recorded subsequently on the centralized database variant name as reported on Clinvar, the Variant type and the Genomic location, the resulting transcript and protein, the clinical significance according to the interpretation and the evidences submitted to Clinvar and ENIGMA consortium [17,18].

2.3. Statistical analyses

Data were analyzed using IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp. Statistical significance was determined by using an alpha level of 0.05 and two-sided tests. To compare quantitative variables variance analysis (ANOVA) was performed, for qualitative variable we used Chi square test or Fisher exact test. Multivariate analysis was performed using binary logistic regression.

Estimates of survival were calculated by the Kaplan-Meier method and compared using the log- rank test. Multivariate analysis to find predictors of longer OS was performed with the Cox proportional hazard regression.

3. Results

Three hundred and thirty-one patients with a germline BRCA1 or BRCA2 mutation and an EOC diagnosis between 1995 and 2017 were

included, 294 of them were diagnosed before 2015 while only 37 of them received a diagnosis after 2015.

Patients were treated in 15 MITO Cancer Centers all over Italy. For geographical distribution see Fig. 1.

Two-hundred and forty (72.5%) of them were BRCA1 and 91 (27.5%) were BRCA2 mutated.

Median patients' age at diagnosis was 52 years (range 30–84 years, IQR 46–60 years). Patients with BRCA1 seemed to be younger at diagnosis, being median age at diagnosis 51.9 and 57.7 years for BRCA1 and for BRCA2 patients respectively ($p < 0.0001$).

The most frequent histology was high grade serous (87%) followed by endometrioid (8.5%), clear cell or undifferentiated cancer and malignant Brenner tumor (8 patients). Frequently EOC was diagnosed at an advanced stage (FIGO III and IV), with 72.5% women with stage IIIC EOC and 12.4% with stage IV EOC.

EOC patients were candidates to surgery in different MITO Centers in Italy. A primary cytoreductive surgery resulted in a complete resection [Residual disease (R) =0] in 53.2% of patients while 38.3% of patients had residual disease or no surgery.

Near all patients received a platinum-based regimen as first line chemotherapy; only 11.5% received bevacizumab. Less than 10% of our cohort (24 patients) received a PARPi, almost all of them as maintenance therapy in the recurrence setting with only 1 patient receiving a PARPi after first line. The majority of them received PARPi maintenance therapy in the setting of clinical trials.

Data on platinum sensitivity at first relapse were available for 81.9% of patients. Almost all of them (258 patients, 77.9%) were platinum sensitive after first line (PFI ≥ 6 months), while only 13 patients were platinum resistant (PFI < 6 months) at first relapse (see Table 2). The clinical features of our cohort are described in Table 1.

There were no differences in histological characteristics, stage, resection margin, type of first line treatment or PFI according to BRCA status (data not shown).

With a median follow up of 51 months (SD 49.2) months, median progression free survival (PFS) after first line was 29 months (95%CI 24.1–33.9 months). At the moment of data cut off, 30.5% of patients were deceased with an expected percentage of patients alive at 5 years of 72.5% (CI 60.2–80.8%).

At a multivariate analysis, there was no difference in OS according to BRCA mutation, stage at diagnosis (FIGO I/II vs FIGO III/IV) and histology

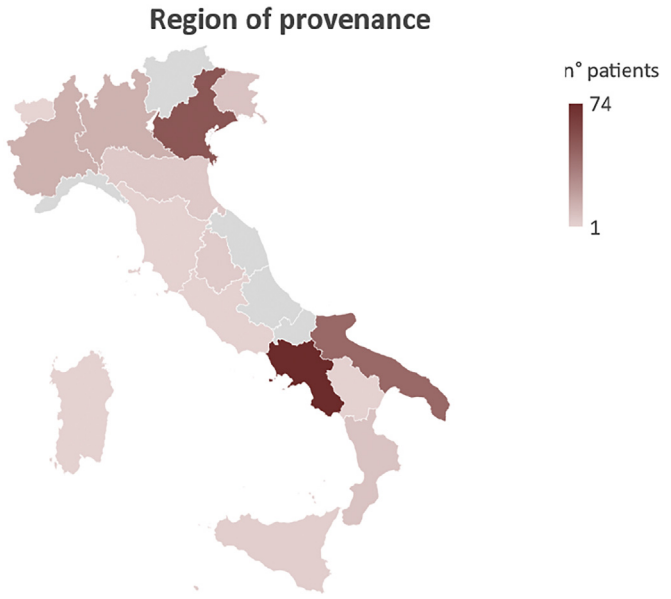

Fig. 1. Geographic location of patients.

Table 1
Patients characteristics.

		N.pts. (%)
BRCA mutation	BRCA1	240 (72.5%)
	BRCA2	91 (27.5%)
Histology	Serous	288 (87%)
	Endometrioid	28 (8.5%)
	Clear cell	1 (0.3%)
	Brenner	8 (2.4%)
	Undifferentiated	2(0.6%)
	Not available	4 (1.2%)
Site	Ovary	305 (92%)
	Primary peritoneal cancer	7 (2%)
	Serous tubal cancer	19 (6%)
FIGO stage	I	30 (9.1%)
	II	20 (6%)
	III	240 (72.5%)
	IV	41 (12.4%)
Grading	G1	8 (2.4%)
	G2	27 (8.2%)
	G3	293 (88.5%)
	Not available	3 (0.9%)
Resection margins	R0	176 (53.2%)
	R1	68 (20.5%)
	R2	59 (17.8%)
	Not available	28 (8.5%)
First line chemotherapy	Carboplatin/Cisplatin	24 (7.3%)
	Carboplatin/Cisplatin-Paclitaxel 3w	222 (67.1%)
	Carboplatin-Paclitaxelweekly	10 (3%)
	Carboplatin-Paclitaxel-Bevacizumab	38 (11.5%)
	Carboplatin-PLD 3w	7 (2.1%)
	Other	21 (6.3%)
	Not available	9 (2.7%)
PFI1	Platinum resistant (PFI < 6 months)	13 (3.9%)
	Platinum sensitive (≥6 months)	258 (77.9%)
	Not available	60 (18.1%)
Treatment with PARPis	Yes	24 (7.2%)
	No	163 (49.2%)
	Unknown	144 (43.5%)

Legend: G: Grade; PARPis: PARP inhibitors; PFI1: Platinum free interval after 1° line; PLD: pegylated liposomal doxorubicin, R: residual disease after primary cytoreduction.

Table 2
Characteristics of platinum resistant patients (PFI < 6 months) at first relapse.

		N.pts	(%)
Gene involved	BRCA1	8	(61.5)
	BRCA2	5	(38.5)
Name of mutation (clinvar)			
	c.3916_3917del (p.Leu1306fs)	1	(7.7)
	c.4169dupT (p.Leu1390Phefs)	1	(7.7)
	c.4484G>T (p.Arg1495Met)	1	(7.7)
	c.4964_4982del (p.Ser1655fs)	1	(7.7)
	c.5239C>T (p.Gln1747Ter)	1	(7.7)
	c.5410_5411delGT (p.Val1804Lysfs)	1	(7.7)
	c.5718_5719CT[2] (p.Leu1908fs)	1	(7.7)
	c.676delT (p.Cys226Valfs)	1	(7.7)
	c.900A > C (p.Glu300Asp)	1	(7.7)
	NA	4	(30.8)
Variant type	Deletion	5	(38.5)
	Others	4	(30.8)
	NA	4	(30.8)
Molecular output	Missense	2	(15.4)
	Nonsense	1	(7.7)
	Frameshift	6	(46.2)
	NA	4	(30.8)
Location of the mutation	BRCA 1 exon 11	3	(23.1)
	BRCA 1 exon 14	1	(7.7)
	BRCA 1 exon 16	1	(7.7)
	BRCA 1 exon 20	1	(7.7)
	BRCA2 exon 11	3	(23.1)
	NA	4	(30.8)
Resulting protein	Truncated	7	(53.8)
	Other	2	(15.4)
	NA	4	(30.8)

Legend: NA: Not available.

Table 3
Cox regression for overall survival.

Variables	HR	p value
BRCA2 vs BRCA1	1,39	0,238
Hystology (serous vs others)	1,02	0,937
Grading	1,49	0,197
FIGO Stage at diagnosis (III/IV vs I/II)	1,74	0,178
R ≠ 0 vs R = 0	2,57	<0,0001
Platinum based chemotherapy (±beva) vs Carboplatin SA	1,63	0,133

Legend: R: residual disease after primary cytoreduction, SA:single agent.

(serous vs other histologies) or type of first line treatment. Only $R = 0$ after primary cytoreduction ($p < 0.001$) was associated to a longer OS in our cohort of EOC patients (see Table 3).

3.1. Breast and ovarian cancer cohort

Sixty-six (20%) patients had a diagnosis of both BC and EOC (BOC cohort). Among them 44 were BRCA1 mutated and 22 were BRCA2 mutated. The first diagnosis was BC in 81,8% of cases with a mean age at diagnosis of 48,3 years (95%CI 45,4–51,3 years) and a mean interval between the first diagnosis (BC) and the second diagnosis (EOC) of 132.4 months (95%CI 99,2–165,6 months). Twelve patients (8 BRCA1 and 4 BRCA2) were diagnosed first with EOC with a mean age at diagnosis of 55 years (95%CI 42,7–68,5 years) and a mean interval between the diagnosis of EOC and the subsequent diagnosis of BC of 47.9 months (95%CI 21.8–74 months). There was no statistical difference in stage, histology and grade, residual disease at surgery, type of first line treatment and age at diagnosis, according to BRCA status in BOC group.

There was no difference in stage, residual disease at surgery, histology, and platinum sensitivity between BOC cohort and patients with no second primary cancer (EOC only cohort). Patients with BOC were diagnosed at a younger age than the EOC only patients ($p = 0.009$).

Survival analysis suggested that the small group of patients with first diagnosis of EOC and then diagnosis of BC had a longer OS compared to the EOC only cohort [median OS not reached vs 112 months, HR = 0.2 (95%CI 0–1.2) $p = 0.07$].

3.2. Mutation analysis

For 276 patients a full BRCA mutation record was available. Frameshift mutations were the most frequent [174 patients (63%); 126 BRCA1 and 48 BRCA2 mut patients respectively] with 113 (40.9%) patients harboring a deletion (76 BRCA1 and 37 BRCA2 patients). In 228 (82.6%) of the recorded variants, a truncated protein was originated. Since before 2015 molecular panels were not available, among the 177 patients for whom the whole genetic report was available, 121 patients had germline BRCA 1/2 testing only while 56 patients received an NGS analyzing a panel of genes including BRCA1 and 2. Five variants were reported in more than 5 patients (4 located on BRCA1 and 1 located on BRCA2). Specifically, 26 patients with EOC only and 9 patients with BOC had NM_007294.3 (BRCA1) c.5266dupC (p.Gln1756Profs) mutation, being the most frequently recorded variant. It is an Ashkenazi founder duplication on exon 20 of BRCA1. This duplication causes a frameshift, altering the sequence beginning at position 1756 and leading to a truncated non-functional protein. For a list of the most frequent mutations and locations see Fig. 2, for a full description see Table 4.

4. Discussion

Germline BRCA1 and 2 mutations are a risk factor for OC, being responsible for around 15% of high grade serous EOC [4]. Several studies have analyzed BRCA mutated EOC patients worldwide, showing that they have specific characteristics, including a higher sensitivity to platinum compounds and a better clinical outcome than BRCA wildtype patients [12,19]. Moreover, new data on PARPi have highlighted how BRCA testing plays a main role not only to prevent new cases in relatives but also as a prognostic and predictive tool, changing the therapeutic algorithm for BRCA mut patients from the very beginning [20–22].

For this reason, in Italy BRCA1 and 2 mutation screening has been recommended at diagnosis for all EOC patients (with the exception of mucinous and borderline cancers) [23].

During the last years, heterogeneous reports on BRCA mutated Italian BC and/or OC families have shed light on type and frequency of mutations but most of them focused on a specific area of our Country and did not describe clinical features of OC cohorts [15,24,25,26].

MITO 21 study is the largest retrospective cohort of EOC Italian patients harboring BRCA1 or 2 germline mutations. It analyzed clinical and mutational data from 331 EOC patients. These patients were born in different regions both from the South and the North of Italy (Fig. 1). Thus data on mutation status and clinical characteristics can give a realistic picture of BRCA mutated EOC patients treated in Italy during two decades (1995–2017).

In our study High grade serous EOC was the most represented histology. Interestingly 8 patients had a Brenner tumor, being the largest cohort of BRCA mutated Brenner tumors until now.

Most of the patients were diagnosed at an advanced stage and around half of them had no residual disease after primary cytoreduction. The first line treatment was a platinum doublet in approximately all our patients, while bevacizumab was administered only in about 10% of patients (probably due to the fact that most of our patients were treated before its approval). Most of EOC were platinum sensitive at first relapse.

Median PFS and OS in our cohort were comparable, although slightly longer, than other studies describing BRCA mutated patients and outcomes were more favorable than BRCA wildtype cohorts in literature [19].

At multivariate analysis, only having $R = 0$ after surgery correlates with a longer OS. Residual disease has a consolidated role as the main prognostic factor in EOC patients, in all stages and histologies [27,28] and we confirm it also in a BRCA mutated population. Nevertheless, some previous reports suggested that surgery in a BRCA mutated setting might have a lower impact on survival both in first line and in a platinum sensitive setting [29,30]. Thus, our results need to be confirmed in a larger cohort treated with the current standard of care.

Table 4
Features of BRCA pathogenetic variant detected in more than 5 patients.

Name (CLINVAR)	Gene	N° of pt	Varianttype	Molec. conquences	Exon	Truncated protein	N° of pt with OC	N° of pt with BOC
NM_007294.4 (BRCA1):c.1687C>T (p.Gln563Ter)	BRCA1	8	single nucleotide variant	nonsense	11	yes	8	3
NM_007294.3 (BRCA1):c.3752_3755GTCT[1] (p.Ser1253fs)	BRCA1	8	deletion (microsatellite)	frameshift	11	yes	8	1
NM_007294.4 (BRCA1):c.4484G>T (p.Arg1495Met)	BRCA1	6	single nucleotide variant	missense	14	no	6	4
NM_007294.3 (BRCA1):c.5266dupC (p.Gln1756Profs)	BRCA1	35	Duplication	frameshift	20	yes	35	9
NM_000059.4 (BRCA2):c.5796_5797del (p.His1932fs)	BRCA2	6	Deletion	frameshift	11	yes	6	2

Legend: BOC: Breast and Ovarian cancer; N°:number; OC: Ovarian cancer; pt.: patients.

Figure 2a

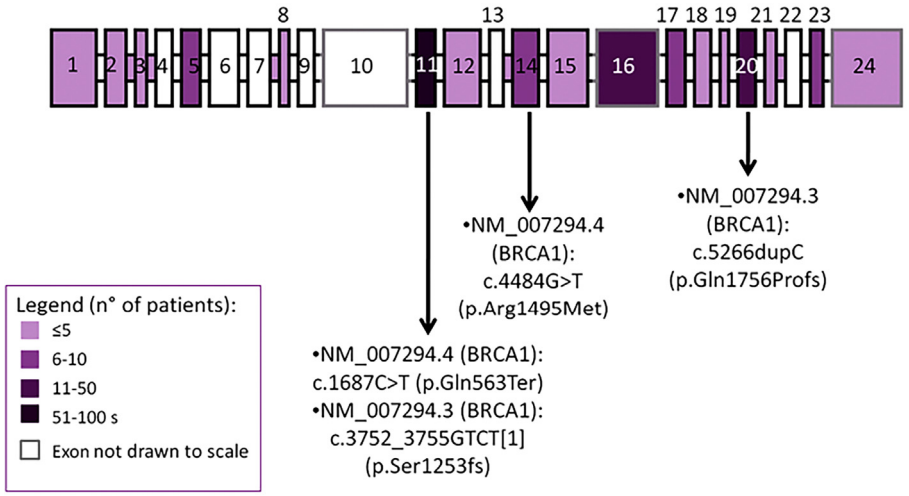

Figure 2b

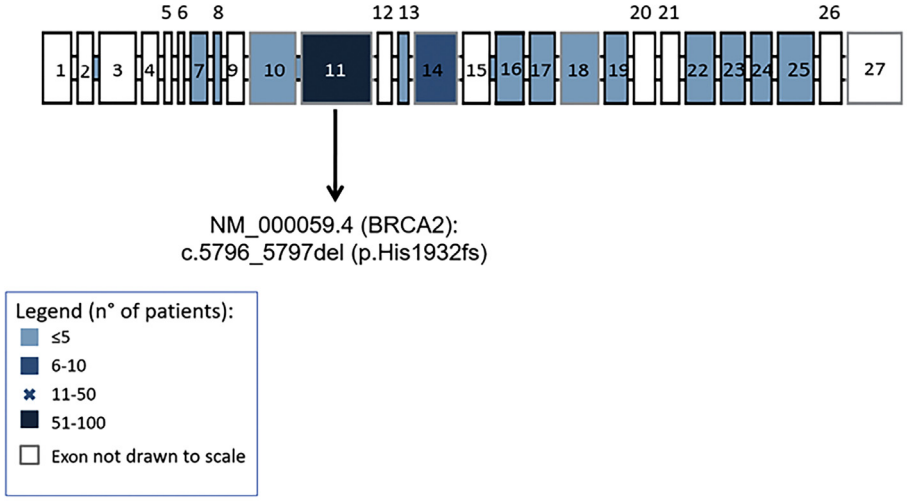

Fig. 2. representation of BRCA1 (a) and BRCA2 (b) genes.

In our study we recorded 66 patients with both BC and EOC, being the largest report of BRCA mutated BOC. Several reports suggested that risk to develop second malignancies is higher after a BC or EOC diagnosis [31–33]. Specifically, the 10-year risk of BC in BRCA mutated EOC patients is less than 10%, conditional on survival [34,35]. In our cohort 3.6% (12/331) EOC patients had a subsequent diagnosis of BC and the mean time between diagnosis of EOC and BC in this small group of patients was around four years. These women seem to have a longer OS than the EOC only cohort highlighting once again that prognosis in patients with a BRCA mutation and an EOC diagnosis is driven by EOC itself and questioning again the role of MRI screening and prophylactic mastectomy in this specific subgroup of patients, being recommended only in long survival EOC patients [34,35]. On the other hand, 54 EOC patients had a history of previous BC. The mean interval between these two diagnosis is around 10 years in concordance with other previous reports [36,37], highlighting the fundamental role of lifelong follow up and of risk-reducing salpingo-oophorectomy [38].

Lastly, the most frequent mutations in our cohort have been yet reported in Italian families [39]. In particular, c.5266dupC mutation in BRCA1 has been recorded as the most frequent mutation in Italian population [39,40]. It is one of the three most recorded founder mutations in the Ashkenazi Jews, originating probably more than 38 generation ago from a single founder and spreading both to North America and Europe. For this mutation the lifetime risk of OC is 33%, being the highest among the Jewish founder mutations [40]. It would be interesting to evaluate if BRCA screening and the prophylactic surgery will modify the types of detected mutations in OC patients in the next decades.

This study has several limits. The first one is that although it involved MITO Centers all over Italy, it does not cover homogeneously all the Country and data from some regions are missing. Moreover, MITO Centers are referral hospitals for EOC patients, thus data on outcomes might be influenced by above the range surgical outcomes and the inclusion in clinical trials.

Secondly, the retrospective nature of the study itself harbors some limitations like the lack of information about the drugs administered as subsequent therapies after first line and their outcome, data on secondary cytoreduction and the cause of death for patients in the BOC cohort. Nevertheless, the major limit of this study is that a small

percentage of patients received a PARPi or bevacizumab up to last follow up and information on these treatments are scarce in our cohort. This means that data on outcomes can be difficulty translated in the current clinical practice including PARPi maintenance therapy from first line with data suggesting that these drugs might modify the history of BRCA mut disease [20–22]. Nevertheless, the study recruited patients treated both in a "Pre-targeted therapy" and "Post-targeted therapy" era and further update with a longer follow up of MITO21 patients can surely provide interesting data on real life use of biological agents.

In conclusion, taking into account these drawbacks, the study remains a valuable and wide description of the largest Italian BRCA mutated EOC cohort. Data on OS suggest that a complete surgical resection significantly affect prognosis also in BRCA mutated patients.

Contributed to the study

Dr. Artioli: Conceptualization, Methodology, formal analysis, Data curation, writing original draft, writing-Review & editing, Supervision, Funding acquisition, Resoures, Project administration; Dr. Giannone: formal analysis, writing original draft, writing-Review & editing, visualization; Dr. Pignata: writing-Review & editing Dr. Lorusso: writing-Review & editing Dr. De Giorgi: writing-Review & editing; Dr. Orditura: writing-Review & editing; Dr. Maggiorotto: writing-Review & editing, Dr. Genta: writing original draft, writing-Review & editing; dr Valabrega: methodology, writing original draft, writing-Review & editing, Project administration; Dr. Cormio: writing-Review & editing, Dr. Scalone: writing-Review & editing, Dr. Nicoletto: writing-Review & editing, Dr. Greco: writing-Review & editing, Dr. Rossi: writing-Review & editing, Dr. Spagnoletti: writing-Review & editing, Dr. Mosconi: writing-Review & editing; Dr. Kardhashi: writing-Review & editing; Dr. Bogliolo: writing-Review & editing; Dr. Borgato: writing-Review & editing, Conceptualization, formal analysis, writing original draft, Supervision, Resources, Project administration.

Declaration of Competing Interest

Dr. Artioli reports grants from ASTRAZENECA, during the conduct of the study; grants and speaking honoraria from GSK-TESARO, ASTRAZENECA, ROCHE, PHARMAMAR, outside the submitted work; Dr. Giannone reports grants from Roche, outside the submitted work. Dr. Valabrega reports grants and speaking honoraria from Astrazeneca, GSK-Tesaro, Roche, Amgen, and PharmaMar, outside the submitted work. Dr. Pignata was on the Advisory Board for GSK-TESARO, ASTRAZENECA, CLOVIS, ROCHE, PHARMAMAR, MSD, and PFIZER, outside the submitted work;. Dr. Lorusso was on the Advisory Board for Merck AstraZeneca, Roche, Amgen, Clovis, Pharmamar, GSK, Immunogen and Genmab and her Institution received supports from Merck, Clovis, GSK-Tesaro, Dr. De Giorgi reports personal fees and non-financial support from Janssen-Cilag, Astellas, Sanofi, Bayer, Pfizer, BMS, Novartis, Ipsen MSD, Roche, Astrazeneca, Pharmamar, outside the submitted work; Dr. Orditura reports personal fees from GSK-TESARO, outside the submitted work Dr. Borgato reports grants and speaking honoraria from GSK- TESARO, and ASTRAZENECA, outside the submitted work.

Dr. Maggiorotto, Dr. Genta, Dr. Cormio, Dr. Scalone, Dr. Nicoletto, Dr. Greco, Dr. Rossi, Dr. Spagnoletti, Dr. Mosconi, Dr. Kardhashi, Dr. Bogliolo, have no conflicts of interest to disclose.

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