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Epidemiology and Genetic Susceptibility of Breast and Ovarian Cancer in Sardinian Population

Grazia Palomba, Giuseppe Palmieri, Antonio Cossu, Panagiotis Paliogiannis and Maria Cristina Sini

Abstract

The objective of this population-based study is to describe epidemiological and genetic features of breast and ovarian cancer in North Sardinia, Italy. Patients who carry a high-risk mutation in one or both of the BRCA genes (BRCA1 or BRCA2) have a significantly increased risk of developing breast/ovarian cancer (BOC) and other cancers (e.g., prostate cancer in male). Epidemiological data on incidence distribution of breast/ovarian cancer from 2016 to 2019 in North Sardinia are obtained from the local tumor registry and from the cumulative results of 209 genetic testing for BRCA gene mutations performed in all young breast cancer patients and all women (over 50 years) with family history of BOC (total of 164 cases); further, 45 genetic testing is performed, on ovarian cancer patients, at any age. The results provide a different distribution of fraction mutations carried by women and a higher prevalence of the BRCA2 mutation in the north of Sardinia than the entire population and highlight the presence of specific germline mutation associated with the “founder effect” in distinct genetic subgroups reflecting genetic drift. Advances in next-generation sequencing technology, data analysis, and clinical investigation have revolutionized efforts to identify potential targets for BRCA molecular-based therapeutic agents.

Keywords: BRCA1, BRCA2, genetic epidemiology, genetic testing, founder mutations, breast cancer (BC), ovarian cancer (OC), breast and ovarian cancer syndrome (BOC)

1. Introduction

Breast cancer (BC) is the second most common cancer in the female world population, with more than 1.3 million new cases every year [1]. Systemic treatment of breast cancer is based on accurate knowledge of the clinical and molecular characteristics of the tumor and includes cytotoxic, hormonal, or biological agents. Therapies are used in the adjuvant, neo-adjuvant, and metastatic settings of BC patients. In general, systemic agents are active at the beginning of therapy in 90% of primary breast cancers and 50% of metastases. However, disease progression and
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resistance to therapy are expected to occur in a variable period of time, though they are becoming a less common event.

Ovarian cancer (OC) is the seventh most common cancer in women from Western countries (about 5% of all cancers) [2]; its frequency however varies widely among different geographic regions and ethnic groups, with a high incidence in Northern Europe and the United States and low rates in Africa and Asia. In Europe, about 61,000 new cases are estimated to be diagnosed per year. The age-adjusted world incidence is around 11 new cases per 100,000 inhabitants per year.

The majority of OC cases are sporadic, and only 5–10% of them are familial. Ovarian cancer is usually diagnosed at an advanced stage and etiology remains poorly understood. Nevertheless, about 30% of patients present with early-stage disease (FIGO stage I–IIA). Surgery plays a main role in the treatment of epithelial ovarian cancer, and an extensive surgical staging is crucial in selecting the most appropriate systemic therapy. Several factors are associated with the onset of the epithelial ovarian cancer, including age (it is a disease of older age), genetic features (approximately, 5–10% of them result from a hereditary predisposition), site-specific ovarian cancer syndrome (10–15% of all cases), and a positive family history with an affected first-degree relative (mother, daughter, or sister).

In the presence of the breast-ovarian cancer syndrome (BOC), families present with multiple cases (two or more) affected by ovarian and breast cancer in successive generations, tumors with earlier age of onset (usually in the premenopausal age), and evidence of both maternal and paternal transmission [3]. This hereditary syndrome has been linked to the BRCA1 gene at chromosome 17q12–21 (81% of cases) and, less frequently, to the BRCA2 gene at chromosome 13q.

Cumulative breast cancer risks by age 70 are estimated to be 65% for BRCA1 and 45% for BRCA2 mutation carriers. In addition, women with BRCA mutations are at significant risk of developing ovarian cancer and other malignancies [4].

Both BRCA1 and BRCA2 encode proteins that are involved in maintenance of genome stability and in the repair of double-stranded DNA breaks (DSBs) by homologous recombination (HR).

HR is a potentially error-free mechanism of DNA damage repair that requires RAD51 localization to DSBs. BRCA2 interacts directly with RAD51 and is required for the formation of RAD51 complex, as is a BRCA2-associated protein called DSS1. The BRCA2 protein contains several copies of a 70 aa motif called the BRC motif, and these motifs mediate binding to the RAD51 recombinase, which functions in DNA repair. BRCA2 is considered a tumor suppressor gene, as tumors with BRCA2 mutations generally exhibit loss of heterozygosity (LOH) of the wild-type allele. BRCA1 is also required for the formation of RAD51 foci, perhaps through direct or indirect interaction with RAD51 or BRCA2 [5]. BRCA2 has also been identified as the FANCD1 gene, a member of the Fanconi anemia complex of proteins, and cells deficient in this protein have a similar phenotype to those deficient in BRCA [6]. Chromosomal instability as a result of BRCA1 or BRCA2 deficiency may be the pathogenic basis for breast tumor formation. In women who inherit an inactivating mutation, BRCA deficiency is critical to the development of disease and is the result of both the inherited inactivating allele and somatic genomic loss of the wild-type allele in breast or ovarian epithelial cells. The risk of developing BRCA-associated ovarian cancer is modified by several factors such as the reproductive history and hormonal exposure of an affected individual, and the coinheritance of modifying genes [6].
2. Breast ovarian cancer family selection

The overall criteria to reconstruct the possible family history of patients with breast cancer can be established by identifying three risk levels: profile 1, level of cancer risk equivalent to general population; profile 2, level of cancer risk two-fold higher than that of general population; and profile 3, level of cancer risk three or more times higher than that of general population.

Six main criteria are taken into consideration to address women diagnosed with breast cancer into the general population to BRCA mutation testing: (a) younger women with breast cancer diagnosed at age less than 36 years; (b) affected male individuals (at any age of onset); (c) women with occurrence of both breast and ovarian cancer (at any age); (d) women with bilateral carcinoma diagnosed before 50 years; (e) women with triple-negative breast cancer who are younger than 50 years; and (f) all women with ovarian (and fallopian tube) carcinoma before 50 years or with high-grade serous ovarian cancer at any age.

Current guidelines recommend genetic testing for women diagnosed with breast cancer and at least one affected family member; a personal history of breast cancer and one or more relatives with breast cancer diagnosed before age 50; two or more relatives diagnosed with breast cancer at any age; one or more relatives with ovarian cancer; one or more relatives with male breast cancer, or two or more relatives with prostate cancer or pancreatic cancer.

In this sense, the American Society of Clinical Oncology, the American College of Obstetrics and Gynecology, and the National Comprehensive Cancer Network do not recommend BRCA mutation testing for women younger than 50 years with breast cancer unless there is a family history of breast/ovarian cancer [7, 8]. Therefore, many young women with breast cancer and lack of a family history of disease will not have the opportunity to undergo BRCA mutation testing. As a result of this, a significant proportion of newly diagnosed women with breast cancer who are younger than 50 years may not be identified as BRCA mutation carriers, and they remain at high risk for subsequent breast and ovarian cancer. Positive BRCA mutation testing in women with ovarian carcinoma allows relatives access to oncological genetic counseling and preventive testing, aimed at verifying the presence or absence in family members, of pathogenic sequence variants. Genetic results are essential to carry out specific recommendations for clinical management of at-risk relatives. In the case of a positive result, the programs are aimed at promoting screening strategies for early diagnosis as well as favoring primary prevention interventions for the reduction in the risk of breast/ovarian cancer. The BRCA test is recommended for all patients with nonmucinous and nonborderline ovarian cancer, carcinoma of the fallopian tubes, or peritoneal primitive carcinoma. It is important to offer the BRCA test since cancer diagnosis. The identification of a pathogenic variant in BRCA genes also allows patients to plan an adequate therapeutic pathway. The identification of pathogenic variant in BRCA genes at germinal level in a patient with ovarian cancer allows to undertake a path of oncogenetic counseling in family members in order to identify high-risk carriers and to propose targeted programs for early diagnosis of syndrome-associated tumors with BRCA-related and to carry out strategies aimed at reducing the risk.

In BRCA-mutated women, with ascertained diagnosis of ovarian cancer, a psychosocial approach must be envisaged, which takes into account the impact of the diagnosis and treatment on the physical and psycho-emotional sphere, as well as the psychological implications of the hereditary problem and the involvement of healthy family members at risk in the decision-making process [9].
2.1 BRCA molecular profiling and epidemiology in Sardinia population

In Sardinia, breast cancer represents the principal death-causing malignancy, with an incidence similar to that observed in western countries [10]. Familial aggregation is thought to account for 5–10% of all breast cancer cases, and germline mutations in different genes involved in pathways critical to maintain the genomic integrity have accounted for less than 25% of the inherited breast cancer. Prevalence of mutation carriers with breast or ovarian cancer depends on the population studied and displays considerable variation based on ethnic and geographical diversity [11]. In Italy, 4–27% of the identified mutations occurred among apparently unrelated families, while a regional founder effect has been demonstrated for few mutations; contribution of BRCA1–2 mutations to breast cancer predisposition has been reported for populations from the Northern part of Sardinia as well as strong founder effects for several genetic diseases were founded with some geographical differences within the island [12]. BRCA2 mutations are notably more recurrent than BRCA1 mutations in breast cancer families from North Sardinia [13]. Moreover, allelic transmission is identical in males and females as the entire population should comply with the Hardy–Weinberg law [14].

In southern Italy, including Sardinia, standardized mortality rate in ovarian cancer patients is 8.5/100,000 lower than in Italy; also, the cumulative risk of death from the disease is extremely low (0.4%) [4, 15].

Germline mutations in either BRCA1 or BRCA2 genes occur in approximately 10% of unselected women with ovarian cancer, and women with inherited BRCA1/2 mutations are at significant risk of developing ovarian cancer [16].

The lifetime risk of developing ovarian cancer in women who carry a germline BRCA mutation has been estimated to be of 40–60% for BRCA1 and 11–27% for BRCA2 [17]. A meta-analysis of 22 studies with over 8000 disease probands has defined the incidence for ovarian cancer to be approximately 39% for BRCA1 and 11% for BRCA2 [18]. In North Sardinia, less than 10% of breast cancer families presented an association with ovarian cancer (at least one affected family member) [12]. Nevertheless, the presence of ovarian cancer was demonstrated to significantly increase the occurrence of BRCA1/2 germline mutations in Sardinian breast cancer families [12, 19].

2.2 Next-generation sequencing approaches for mutation analyses in Sardinian population

In recent past years, epidemiological data have become available from the Cancer Registry of the Province of Sassari. This registry was created in 1992 by the Local Health Agency (Azienda Sanitaria Locale, ASL) of Sassari for the epidemiological surveillance of tumors in the province. In 1999, it became part of wider web tumor registries, coordinated today by the Italian Association for Tumor Registries (Associazione Italiana Registri Tumori) [20]. Crude incidence and mortality rates for 100,000 inhabitants per year were calculated and standardized rates adjusted for European age population standards. The age-class distribution of cases was analyzed; relative incidence and mortality date was compared between Sardinia and the rest of Italy (Table 1).

Numerous studies by our group have assessed the BRCA1/2 mutation prevalence in various cohorts, although few have evaluated the predictors for the occurrence of both BRCA1 and BRCA2 mutations among younger patients in a hospital-based population. Breast/ovarian cancer patients, originating from North Sardinia, were recruited from clinics at the University of Sassari and Local Health Agencies accounting for cancer patients from the Central and Northern part of the island (Sassari, Olbia,
Sardinian origin was ascertained in all cases through genealogical studies. Patients with a histologically-proven diagnosis of breast/ovarian cancer diagnosed before 50 years were consecutively-collected during a period of 4 years; no additional selection criteria were used for their inclusion into the study.

In such a population-based series of early-onset breast/ovarian cancer, family history of breast and ovarian cancers were assessed according to the above-described standardized criteria. Patients were informed of the aims of the study and blood samples were obtained with their written consent. Genomic DNA was isolated and next-generation sequencing (NGS) investigations were performed using a specific BRCA1/2 gene. Research assay panel allows to detect simultaneously point mutations and CNVs. Samples were sequenced on the Ion Torrent S5 System (Life Technologies, Waltham, MA, USA), and data were processed with the Ion Torrent platform.

Between 2016 and 2019, 209 patients originating from North Sardinia underwent the NGS-based mutation analyzed in BRCA1/2 genes; among them, 164 were diagnosed with primary breast cancer and 45 with primary ovarian cancer, with median age at onset of 51 years (range 27±84), any age for ovarian cancer. Patients with first diagnosis of breast cancer were evaluated for familial occurrence of malignancy using a questionnaire to interview probands about their first- and second-degree relatives. In our series of Sardinian cases, we analyzed sporadic young patients with a breast cancer diagnosis before 50 years (59/164; 36%) and any familiar history; a number of probands with a positive family history for breast cancer (33/164; 20%) and age of onset before 50 years; and patients (72/164; 44%) with breast/ovarian cancer familiar history at any age. Moreover, the analysis was performed on 45 (45/209; 21.5%) ovarian cases at any age.

### 2.3 Deleterious variants in BRCA1 and BRCA2 genes

Overall, prevalence of deleterious BRCA1/2 variants was 10 times higher in patients with a positive family history (19/105; 18.09%) as compared with those with sporadic tumors (2/104; 1.92%). Interestingly, all uncertain variants—that is, those with unknown functional significance—were nearly completely prevalent in...
familiar tumor cases. Deleterious variants were found in 68% (15/22) of breast cancer cases and 31.8% (7/22) of ovarian cancer cases; variants with unknown significance (VUS) were observed in 81.2% of breast cancer patients and in 18.7% of ovarian cancer patients. Deleterious germline variants in BRCA2 5.74% (12/209) were featured, followed by BRCA1 4.78% (10/209) patients according to our previous study that explained a different geographical distribution of BRCA1–2 mutations with a higher prevalence of the BRCA2 mutation in the north of Sardinia than the entire population [19].

Among families with high recurrence of breast cancer (≥ 3 cases in first-degree relatives), almost all ones from northern Sardinia were previously demonstrated by our group to share the same haplotype and carry a single mutation in BRCA2 gene (BRCA2-8765delAG), which thus acts as a pathogenic variant with founder effect in the population of this part of the island (due to the occurrence and propagation of a common ancestral deleterious alteration) [21]. The BRCA2-8765delAG mutation was firstly described in breast cancer families from French-Canadian and Jewish-Yemenite populations; however, the families from French Canadian and Jewish-Yemenite populations were demonstrated to present with distinct genetic assets at the BRCA2 locus, arguing thus against a common origin of this mutation among such different populations (it seems to be conducted to the high propensity to deletion error in this part of the BRCA2 gene, within a so-called hot-spot mutational region) [22] (Table 2).

Few BRCA functional mutations account for BRCA-associated cancers among homogenous populations such as Sardinia (a single BRCA2 founder mutation), French-Canadian population (French colonization of the province of Quebec, five recurrent mutations of which one is common with Sardinia BOC family), and Jewish-Yemenite Ashkenazi Jewish families of eastern European ancestry (specific subpopulations; three recurrent founder mutations are known), while more heterogeneous populations tend to display a broad mutation spectrum; founder mutations are specific mutations that appear repeatedly in ethnically defined groups because of a shared common ancestry [23].

The presence of a single BRCA2 mutation that is extremely rare (in less than 1% of breast cancer cases) is characterized in another isolated population such as Iceland, which explains a substantial proportion of the familial risk of breast cancer in Iceland and accounts for most of the prostate and ovarian cancer observed in families of breast cancer patients [24].

The epidemiological and clinical impact of the BRCA2 founder mutation on cancer in isolated population has been extensively studied, particularly with regard to significantly higher risk of BOC. The mutations fall into cluster region of BRCA-gene and can be associated with significantly higher risk of breast and ovarian cancer in female population and prostate cancer in males.

Women carrying ascertained pathogenic mutations have a higher lifetime risk of the disease. It's estimated that 55–65% of women with a germinal mutation in BRCA1 will develop breast cancer before age 70. In our series, median age of first diagnosis of breast cancer was 42.5 years (range 27 ± 50); the median value increases significantly up to 57 years (range 39 ± 83) in ovarian cancer cases. Approximately 45% of women with a BRCA2 mutation will develop breast cancer by age 70.

BRCA2 mutation carrier patients with a family history of breast cancer have early median onset of 44 years (range 27 ± 54). The increase of median value is even more significant in ovarian cancer patients selected at any age: 59 years (range 48 ± 77).

Cancers related to a BRCA1 mutation are also more likely to be triple-negative breast cancer, which can be more aggressive and difficult to treat. Triple-negative
<table>
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<th>Transcript</th>
<th>Coding</th>
<th>Protein</th>
<th>Function</th>
<th>dbSNP</th>
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<th>Enigma</th>
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</tbody>
</table>

*Indicates a variant classified as pathogenic by only ClinVar database and not provided by Enigma.

Table 2.
Variants detected by NGS BRCA panel. Classification criteria were according to the enigma 2015 database.
breast cancer has been classified as a breast cancer subgroup with lack of ER, PR, and HER2 expression and accounts for 15 to 20% of breast cancer cases. Despite a notably favorable rate of response to chemotherapy, triple-negative patients present with a higher risk of relapse and a relatively poor outcome [25].

3. BRCA-related treatments

For breast cancer, treatment options depend on the stage of disease and other factors such as tumor size, results of specific pathology tests (hormone receptors, HER2 receptors, grade of the cells, and proliferation rate of the cells), family history or other risk factors associated with a predisposition for developing breast or ovarian cancer, and age.

Most women with ductal carcinoma in situ (DCIS), a noninvasive breast cancer, have breast-conserving surgery, also known as lumpectomy followed by radiation therapy [26]. Chemotherapy before surgery in women with large stage II or IIA breast tumors is neo-adjuvant therapy to make possible that breast-conserving surgery. Moreover, after surgery, adjuvant therapy and radiation treatment lower the chance of breast cancer returning [27].

The presence of positive hormone receptor tumor cells is called estrogen receptor-positive (ER-positive) breast cancer; standard hormone therapy (tamoxifen) is based on drug administration that blocks the action of estrogen or prevents it from binding to the estrogen receptor [28]. Among women whose tumors do not express the estrogen receptor (ER-negative breast cancer) and are positive for progesterone receptor (PR), tamoxifen has no effect on recurrence [29].

Herceptin (trastuzumab) can be used to treat HER2-positive breast cancer that is either early-stage or advanced stage/metastatic [30]; it is a humanized monoclonal antibody, specifically used in breast carcinomas in which the HER2/neu transmembrane protein is overexpressed [31]. Herceptin is currently approved to treat metastatic HER2-positive breast cancer to stop the cancer from growing; to treat earlier stages of HER2-positive breast cancer, either as part of a regimen with chemotherapy or alone after a chemotherapy regimen that includes an anthracycline; and to reduce the risk of the breast cancer coming back (recurrence) [32], in combination with pertuzumab and docetaxel before surgery to treat HER2-positive, early-stage (the cancer must be larger than 2 cm or cancer must be in the lymph nodes), inflammatory, or locally advanced-stage breast cancer with a high risk of metastasizing or becoming fatal [33]. Moreover, adjuvant treatment (after surgery) with the combination of pertuzumab, trastuzumab, and chemotherapy significantly reduces the risk of recurrence of breast cancer or death in women with early-stage cancer HER2-positive compared to the therapeutic standard consisting of trastuzumab and chemotherapy [34].

Patients with advanced diagnosis of ovarian cancer are expected to relapse within 3 years, after standard treatment with surgery and chemotherapy (carboplatin-Taxol) [35]. Platinum-based therapy continues to be the principal regimen used to treat ovarian tumors that recur at least 6 months after prior therapy [36].

Carboplatin monotherapy is very convenient to administer, is well tolerated, and produces relatively high response rates (RRs). However, the response usually lasts for only a few months, and with each subsequent course of therapy, the treatment-free interval usually becomes shorter until the tumor is declared ‘platinum resistant.’ Several studies have combined platinum-based drugs with other agents. Combinations increase the tumor RR and extend the progression-free survival (PFS) [37, 38].

Targeted therapy of ‘platinum-sensitive’ recurrent OC is conducted in patients at different stages of the treatment pathway. Two classes of drug are being
extensively explored in the ‘platinum-sensitive’ group. These are inhibitors of angiogenesis, an important driver of tumor growth, with a humanized monoclonal antibody, bevacizumab, directed against circulating vascular endothelial growth factor (VEGF) A, an important ligand that binds to the VEGF receptor (VEGFR), stimulating angiogenesis and poly-ADP ribose polymerase (PARP) inhibitors that are active in patients with BRCA gene mutations, and those deficient in the repair of DNA damage through homologous recombination [39, 40].

A germline mutation in one BRCA1 or BRCA2 (gBRCAm) allele is associated with a high risk of the development of a number of cancers, including breast, ovarian, and prostate cancer [41, 42]. Heterozygous BRCA mutations determine loss of function of the remaining wild-type allele, resulting in deficient homologous-recombination DNA repair, which causes genetic aberrations that drive carcinogenesis; the inactivation of the wild-type allele in the tumor is thought to be an obligate step in this process [43, 44].

This tumor-specific defect can be exploited by using PARP inhibitors (e.g., olaparib) to induce selective tumor cytotoxicity, sparing normal cells. Poly(ADP-ribose) polymerase (PARP) is an enzyme involved in base excision repair mechanisms, enabling the adjustment of DNA single-strand breaks repair [45]. Different PARP inhibitors were approved by US FDA: olaparib was approved for use in women with deleterious germline BRCA mutated advanced ovarian cancer and deleterious gBRCAm HER2-negative metastatic breast cancer, while rucaparib was approved for use in women with germline and/or somatic BRCA mutation in advanced ovarian cancer. Several additional PARP inhibitors are in late-phase clinical trials [46].

PARP inhibition in mutated tumor cells with deficient homologous-recombination repair generates unrepaired DNA single-strand breaks that are likely to cause the accumulation of DNA double-strand breaks and collapsed replication forks [47, 48]. Contrariwise, the normal tissue cells that are heterozygous for BRCA mutations and that therefore retain homologous-recombination function have a sensitivity to PARP inhibitors similar to that of wild-type cells, predicting a high therapeutic effect for PARP inhibition in BRCA carriers [49, 50].

The benefits of olaparib (as inhibitor of poly-adenosine diphosphate ribose polymerase) are already widely known in disease relapses. The SOLO-1 study, a double-blind, randomized, prospective phase 3 trial, went to explore for the first time the effects of olaparib as a maintenance therapy, immediately after surgery and chemotherapy, in the newly diagnosed tumor forms, advanced (phase III-IV), BRCA mutated, with a partial or complete clinical response after chemotherapy. Results of the study are encouraging: after a median follow-up of 41 months, the risk of disease progression and/or mortality was 70% lower in patients treated with olaparib than in the control group [51].

4. Conclusions

Genetic testing for breast and ovarian cancer has clinical importance for identification of potentially affected families and for cancer prevention. Approximately, only 5–10% of breast and ovarian cancer are familiar.

Sardinia population shows genetic peculiarity due to geographical isolation and strong genetic drift. The geographical distribution of BRCA1–2 mutations is related to three specific large areas of Sardinia, reflecting its ancient history: the Northern area, linguistically different from the rest of the island where a BRCA2-8765delAG mutation with founder effect, already displayed in our previously study, is predominant [19]. Considering the incidence of the BRCA2-8765delAG variant among the unselected patients from the Sardinian population, our extensive past screening
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clearly indicated that such a mutation is recurrent in North Sardinia, confirming its role as founder mutation in this part of the island but absent in South Sardinia [52].

Breast cancer families originating from South Sardinia, where BRCA1 mutations are demonstrated to be much more prevalent, present markedly higher rates of association with ovarian cancer [12].

BRCA2 mutations were notably more recurrent than BRCA1 mutations in breast cancer families from North Sardinia and less than 10% of breast cancer families presented an association with ovarian cancer (at least one affected family member) [17]. Nevertheless, the presence of ovarian cancer was demonstrated to significantly increase the occurrence of BRCA1/2 germline mutations in Sardinian breast cancer families [12, 19].

The incidence and mortality trends of ovarian cancer in North Sardinia remained relatively stable in the last decade with cumulative risk of death from the disease being low. Furthermore, survival of patients with ovarian cancer was relatively good in the area, sanctioning the adequacy of the preventive and clinical measures employed in the management of the disease. As for other malignancies, concurrence of different environmental factors and genetic backgrounds may determine the incidence of ovarian cancer.

4.1 Future perspectives

The identification of pathogenic mutations makes it possible to identify, within familial cases, a subpopulation of individuals who present mutations in BRCA-genes. In this classification, however, individuals in whom deleterious mutations could not be identified are excluded, despite having an important family history. Furthermore, the uncertain variants of two major genes do not explain the cancer susceptibility to germ cells.

The future venue of this study is to extend the analysis to possible minor breast cancer susceptibility genes involved in homologous recombination pathways and in repair mechanisms, thanks to the use of increasingly advanced sequencing technologies that involve the use of multigene cancer panels. Functional study and bioinformatics prediction tools provide a putative clinical significance for the identification of somatic variants of interaction between BRCA1 and DNA repair genes and may contribute to identify a role many genes in cancer development.

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Conflict of interest

All authors declare the absence of any conflict of interest.

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