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Hereditary ovarian cancer

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Abstract

At least 10% of ovarian tumors are hereditary and associated with highly penetrant, autosomal, dominant genetic predisposition. Three clinical manifestations of hereditary ovarian cancer have been identified: site-specific ovarian cancer, hereditary breast and/or ovarian cancer (HBOC) and hereditary non-polyposis colorectal cancer (HNPCC) syndromes. BRCA germline mutations account for more than 90% of all hereditary epithelial ovarian tumors whereas most of the remaining 10% are caused by MLH1 and MSH2 mutations, which are susceptibility genes of HNPCC. Genetic testing is available for each of the three hereditary syndromes above mentioned. The recommendations for OC surveillance in high-risk women having a strong family history or BRCA mutation carriers include transvaginal pelvic ultrasound with color Doppler and serum CA125 every 6 months. Bilateral salpingo-oophorectomy appears to be effective to reduce the risk of ovarian cancer in BRCA mutation carriers. Hysterosalpingo-oophorectomy should be considered in HNPCC women who undergo surgery for colorectal carcinoma.

Keywords: Hereditary ovarian cancer; BRCA; HNPCC; Genetic testing; Prophylactic surgery

1. Introduction

In the Western Countries, ovarian cancer (OC) is the leading cause of death from gynecological malignancy and is the fourth cancer-related cause of death among women with an estimated worldwide prevalence of 192,000 per year [1].

Due to absence of early symptoms and to the inadequacy of available screening methods, OC are often diagnosed at an advanced stage resulting in a low survival rate.

Although no particular environmental risk factors have been associated with ovarian carcinogenesis, the sex hormones exposure and patient's reproductive history are particularly important. In the general population, the birth of one live child reduces the risk of OC; after their first pregnancy women have a risk 45% lower as compared to nulliparous subjects. Every further pregnancy reduces the risk by another 15% [2]. Differently from what happens with sporadic cancer, the risk of OC in BRCA1 mutation carriers has been found to grow significantly with the number of born children; after the fifth child, subsequent pregnancies have a protective effect [3]. Moreover, the risk of OC decreases as the age at the last pregnancy increases and each 5 years interval is associated with a risk reduction of 18%. Women who have all their children after the age of 30 as well as nulliparous women, belong to the lowest risk group. A case–control study has reported that late pregnancies are protective against OC, but this has been proved only for patients with a family history of OC [4].

Among the general population, women who have breast fed at least one child present a reduced risk of developing OC but no data are available in women with an inherited predisposition.

Beside the hormonal exposure, the only relevant risk factor is a family history of OC; in fact, the risk of developing the disease rises from 1.6% in the general population to 4% in women with a first-degree relative with OC and to 7% when two relatives are affected [5,6].

In women with strong familiarity, OC is generally diagnosed at an earlier age as compared with the age of those who develop the disease without a family history.

Moreover in families with a high aggregation of cases diagnosed with OC, the risk is related to the first-degree relative's age at diagnosis. It has been established that the relative risk of OC before the age of 55 is 5.2 and it decreases to 3.4 after 55 years [7].

Anyway a first-degree relationship with an OC patient is itself the major risk factor, while the age at which a relative is diagnosed with cancer seems to have a minor effect with regard to the OC risk.

The purpose of the present review is to give the primary care clinician a useful tool to recognize and manage hereditary ovarian cancers due to mutations in either the *BRCA* or the *MMR* genes. The paper is based on current literature and on our field experience with oncogenetic counseling for hereditary breast/ovarian cancer and for Lynch II syndrome. Given the huge extension of the subject we decided to provide a state of the art review and to avoid offering our critical point of view.

2. Hereditary ovarian cancer syndromes

Up to 5–10% of all OCs are hereditary and associated with a dominant autosomic genetic predisposition at high penetrance. The detection of alterations in *susceptibility genes* is at the basis of genetic counseling, that allows to individuate germline mutation carriers among subjects at high risk of tumor [8–10].

Although serous OC is the most common histological type, other specific subtypes can be found according to the syndrome presenting the risk of an ovarian tumor [11].

OC seems to be the result of a multistep process due to the accumulation of genetic alterations, which, in women with familiarity for ovarian tumors, could be inherited. Beyond mutations in high penetrance major susceptibility genes, other low risk alleles or polymorphisms in different loci take part in the ovarian carcinogenesis and the complexity of the entire process is to date far to be completely understood [12,13].

In families with OC history, members affected by other neoplasms, like breast and colon cancer, can have a greater risk of developing OC too. A strong family history of OC and correlated tumors could suggest three main syndromes:

Table 1
Clinical manifestation of hereditary ovarian cancer

	Susceptibility genes
Hereditary ovarian cancer syndrome (HOC or site-specific ovarian cancer)	*BRCA1*, *BRCA2*
Hereditary breast and ovarian cancer syndrome (HBOC)	*BRCA1*, *BRCA2*
Hereditary non-polyposis colorectal cancer syndrome (HNPCC or Lynch II syndrome)	*MMR genes* (*hMLH1*, *hMSH2*)
Other hereditary ovarian syndromes (<2%)	
Gorlin	*Patch*
Peutz-Jeghers syndrome	*STK11*
Osteochondromatosis (Ollier's syndrome)	*EXTs*

site-specific OC (hereditary ovarian cancer, HOC), hereditary breast and ovarian cancer (HBOC) and hereditary non-polyposis colorectal cancer (HNPCC or Lynch II syndrome) which is characterized by colorectal cancer and an increased risk of endometrial, ovarian, gastric, pancreatic and biliary tract cancers [14,15].

The main contribution comes from breast cancer (*BRCA*) *genes* mutations, which are susceptibility genes of the first two syndromes; 90% of hereditary OCs are linked to such mutations, while the remaining proportion is caused by *MLH1* and *MSH2* mutations, which are susceptibility genes of the Lynch II syndrome [16–19].

There is also another group of minor familial syndromes predisposing to OC, accounting for less than 1% of the total, such as the Gorlin's syndrome, osteochondromatosis or Ollier's syndrome and the Peutz-Jeghers syndrome [15,20–22] (Table 1).

2.1. Site-specific ovarian cancer

This syndrome is generally recognized in families in which two or more first- or first- and second-degree relatives are affected by epithelial-type OC (Fig. 1). The lifetime risk for OC in such family members is of about 5%, three-fold higher than in the general population (1.6%) [5].

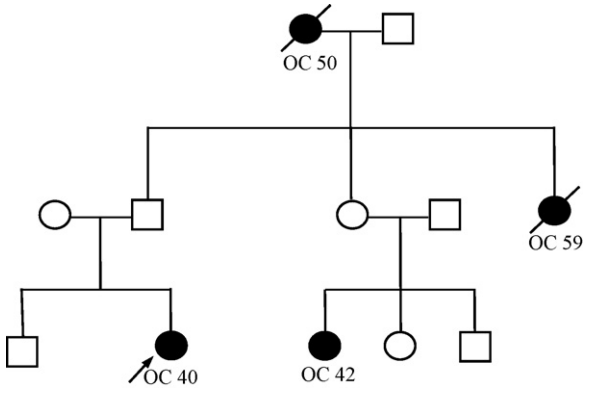

Fig. 1. A pedigree of a real family with hereditary ovarian cancer syndrome (HOC). OC: ovarian cancer.

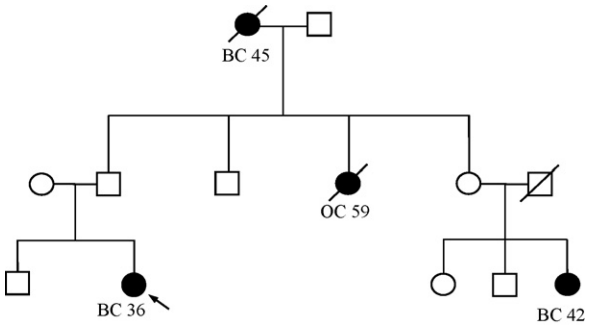

Fig. 2. A pedigree of a real family with hereditary breast and ovarian cancer syndrome (HBOC). BC: breast Cancer; OC: ovarian Cancer.

It has been hypothesized that this disease could represent a variant of HBOC instead of a specific syndrome. A recent report confirms the former hypothesis and, since no susceptibility gene has been identified specifically for OC, this syndrome is still considered as a particular form of HBOC with a prevalence of OC [23].

2.2. Hereditary breast and ovarian cancer

This syndrome is identified in families whose pedigree presents members with both breast and OC (Fig. 2). OC can be associated with many other cancers, but among these the most common is breast cancer. HBOC is characterized by early-onset breast cancer, OC at any age, bilateral breast cancer, breast and ovarian cancer in the same individual or male breast cancer [24–27].

Genetic predisposition to both breast cancer and OC may be maternally and paternally inherited. The aggregation of several cases of breast and ovarian cancer and the early onset of these malignancies have suggested a genetic predisposition in these families. The two susceptibility genes associated with epithelial-type OC are *BRCA1* and *BRCA2*. Both of these genes are autosomal dominant with high penetrance [28,29].

2.2.1. The genetics of susceptibility: BRCA genes

The *BRCA1* gene (OMIM 113705) was the first of the two oncosuppressor genes isolated in 1994 and mapped on chromosome 17q21 [28]; it consists of 24 exons, of which 22 codify for a phosphoprotein of 1863 amino acids with a molecular weight of 220 kDa. Exon 11 of the gene is extremely large and codifies for 60% of the protein.

The *BRCA2* gene (OMIM 600185), discovered about 1 year later, is larger and sited in chromosome 13q12–13; it consists of 27 exons, of which 26 codify for a protein of 3418 amino acids. Both of these genes present a high structural homology while they are different from other known genes [28–30] (Fig. 3).

In the N-terminal region of BRCA1 gene a *ring finger* domain, typical of transcription factors, has been identified. BRCA1 N-terminal region colocalize with BARD 1 (BRCA1-associated ring domain protein 1) and shows an ubiquitin-ligase activity.

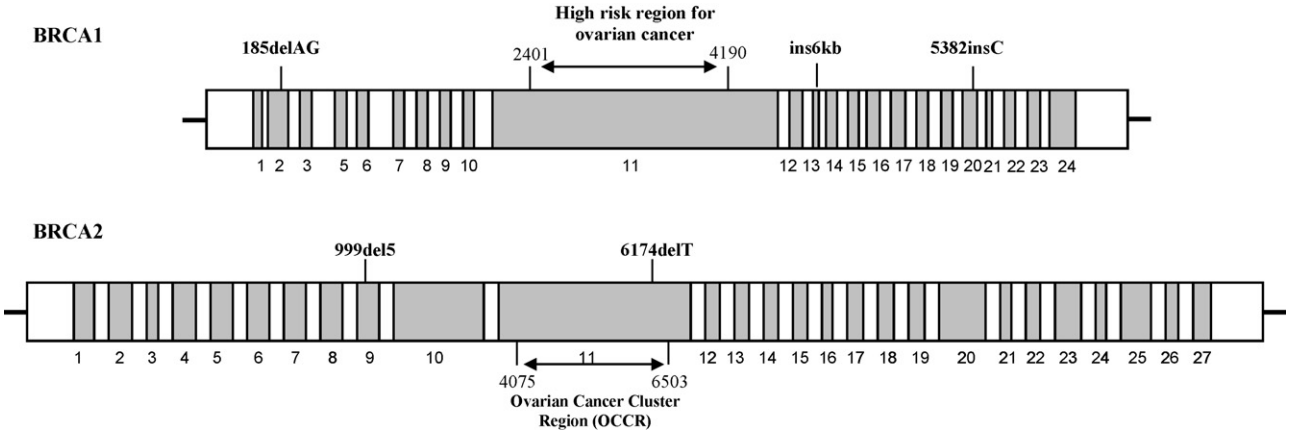

Fig. 3. BRCA1 and BRCA2 genes. Gray boxes indicate the exons with the exon number provided below each box. Location of founder mutations associated with ovarian cancer risk are shown. Moreover, the figure indicates BRCA regions more frequently involved in each gene.

In the C-terminal region of the gene a BRCT domain (BRCA1 C-terminal) with some structural homologies with p53 and p21 and other cell cycle checkpoints proteins, has been sequenced.

Moreover, BRCA1 plays a role in the cromatine remodeling process and interact with Rb and two other proteins of the Histone Deacetylase Complex. Furthermore BRCA1 has been found to colocalize with the CBP (CREB Binding Protein) region of RNA polimerase, and with Rad51, a protein involved in the DNA repair mechanism [31–33].

The BRCA proteins have a nuclear localization, they are expressed in various tissues and play an important role in the DNA repair mechanisms. These proteins are also involved in the control of the cell cycle checkpoints, in protein ubiquitinization and chromatin remodeling [34].

2.2.2. *BRCA genes mutations and OC*

Mutations in the *BRCA* genes have been extensively described in families affected by breast and/or OC. A mutated *BRCA1* has been found in up to 75% of families with hereditary OC [11].

BRCA 1/2 mutations include small deletions, insertions, or puntiform mutations leading to the formation of stop codons with a resulting nonfunctional truncated proteins. There are no hot spots, so that the mutations are distributed throughout the whole gene.

BRCA germline rearrangements have been described in high-risk breast/ovarian cancer families [12,35–37]. With regard to this subject, Mazoyer summarized available data and reported 29 different *BRCA1* germline rearrangements and only 3 for *BRCA2*, probably due to the differences existing between the two genes [38].

The cumulative lifetime risk of epithelial OC associated with mutations of the *BRCA* genes ranges from 40 to 50% for *BRCA1* and from 20 to 30% for *BRCA2*. It has been calculated that these two genes together cause from 3 to 12% of all OCs [25,39].

An international database, known as the Breast Cancer Information Core Database (BIC; http://www.research.nhgri.nih.gov/bic), collects all the known gene variants observed in the two genes and their respective frequencies.

Recent studies on these mutations have highlighted the association between the site of the mutation and the risk of OC. In fact, they have found mutations located between nucleotides 2401 and 4190 of the gene *BRCA1* increasing the risk of OC, while they apparently reduce the risk of breast cancer [40] (Fig. 3).

BRCA2 mutations are responsible for 35% of hereditary breast cancer but confer a minor risk (10–20%) of developing OC [41].

Both genes are also involved in the development of male breast cancer (6%) [42].

Reports state that there is a slight increase also, from 6 to 14%, in the risk of developing other types of cancer of the colon, prostate and pancreas [43].

It has been reported that in the gene *BRCA2*, mutations involving the portion 4075–6503 of exon 11, are associated with an increase in the risk of OC. This region has therefore been defined as the "Ovarian Cancer Cluster Region" (OCCR) [44–46].

There are no homozygosis mutations in the gene *BRCA1*, whereas in *BRCA2* such mutations lead to rare diseases, such as Fanconi's anemia and Wilms' tumor [47]. This evidence confirms that, in spite of the considerable homology of the two genes, there are functional differences in their transduction products.

2.2.3. *BRCA founder mutations*

The discovery that specific mutations in both genes could be identified within specific populations and ethnic groups has led to conduct population studies, resulting in the identification of "founder" mutations [48]. The most representative examples are those found in the genes *BRCA1* and *BRCA2* of Ashkenazi Jews. Three founder mutations have been identified to date in this population, *BRCA1*-185delAG, *BRCA1*-5382insC and *BRCA2*-6174delT, respectively in 1%, 0.13% and 1.5% [41,49–58]; the risk of OC in carriers of this

Table 2
Founder mutations of *BRCA* genes in various populations

	BRCA1	*BRCA2*
Europe	1675delA (Norway) 1135insA (Norway) ins6KbEx13 (UK)	999del5 (Iceland)
USA/Israel (Ashkenazi Jewish)	185delAG 5382insC	6174delT

three founder mutations is respectively of 14%, 33% and 20% [49,57].

Two founder mutations have also been identified frequently in cases of OC in the Norwegian population, *BRCA1*-1675delA in 2.1% and *BRCA1*-1135insA in 0.8% [59].

Another founder mutation identified is *BRCA2*-999del5 in 6–7.9% cases of OC in Icelanders [60,61].

Finally, a recent study involving 283 cases of OC in the UK and in the USA seems to confirm the hypothesis that the mutation ins6KbEx13 of the gene *BRCA1* is a British founder mutation, since it has been found only in women of British origin; in the UK this gene has been identified in 6% of inherited OC cases [40] (Table 2).

Moreover, a "founder effect" has been shown for some of the identified BRCA1 germline rearrangements recurring in European populations [38].

2.3. Ovarian cancer in the Lynch II syndrome

Several other tumors beside colon cancer may occur in families affected by the Lynch II syndrome [17,18].

In such families ovarian, endometrial, uro-genital, pancreatic and biliary tract cancers, are not infrequently diagnosed (Fig. 4).

OC could occur three times more in a woman with a Lynch II syndrome compared to the general population, but this risk depends on the frequency of the disease among her first and second-degree relatives [62].

The syndrome involves genes related in the multistep mechanisms of DNA repair, known as the mismatch repair system (*MMR genes*) [63]. For women with

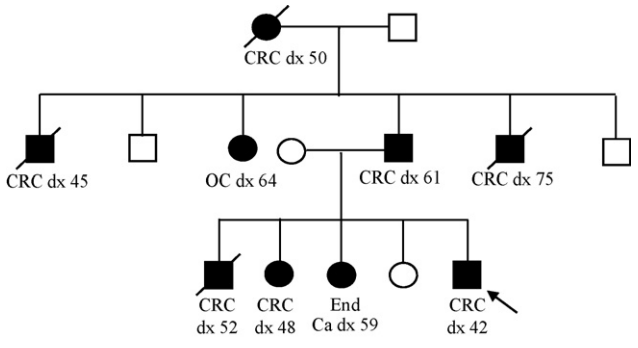

Fig. 4. A pedigree of a real family with hereditary non-polyposis colorectal cancer (HNPCC). OC: ovarian cancer; CRC: colorectal cancer; End: endometrial cancer.

MMR genes mutations OC risk has been estimated to be 9–12% [64].

Until now, very few studies have analyzed cases of OC in HNPCC families; the disease presents with an early onset compared to sporadic OC even if it is not usually observed before the age of 45 [65].

Watson and the other members of the International Collaborative Group on HNPCC have established that most OCs in HNPCC family members are malignant epithelial cases, well or moderately differentiated, FIGO stage I or II at diagnosis. Synchronous endometrial cancer was reported in 21.5% of cases. The more favorable clinical features of these cancers compared to sporadic cases may permit curative surgery [66].

2.3.1. The genetics of susceptibility: MMR genes

Among HNPCC families, germline mutations in *hMSH2* and *hMLH1* genes are found in over 70% of the mutation carriers. Mutations in *hPMS1*, *hPMS2* and *hMSH6* are less common, but also at high penetrance [67–69]. All these genes are involved in the most important DNA repair mechanisms and are responsible for the repair of the nucleotide mismatch during DNA replication [70].

The *MMR* genes are located in five different chromosomes and codify for proteins that, as heterodimers, recognize and repair DNA mismatches. The complex made up of the protein MSH2 with MSH6 or MSH3 recognizes and binds the mismatch during S or G2 phases of cell cycle. MLH1 with PMS1 or PMS2 are involved in the fully resynthesis of the DNA strand [71].

An inactivating germline mutation of *MSH2* blocks the formation of heterodimers which recognize damaged DNA, while MSH6 and MSH3 proteins have overlapping functions, so that an alteration in one of these genes does not impede the normal function of the DNA MMR system [72]. The alteration of this pathway brings about an increased rate of mutations at the DNA microsatellites of growth-regulating genes [73].

2.3.2. MMR genes mutations and OC

MSH2 gene mutations appear to account for most Lynch syndrome diagnosis and confer to women a 12% risk of developing an ovarian tumor during their life [74]. Several studies have attempted to discover possible haplotypes of these genes which, rather than mutations, might contribute to susceptibility to OC [75]. In fact, several common polymorphisms in the MMR genes may be associated with a variable cancer risk. In a study of 1531 cases of OC and 2570 controls, Song et al. have demonstrated that a specific single nucleotide polymorphism (SNP) of the gene *PMS2* determine an increased risk of OC, while two SNPs of *MSH6* and *MSH3* genes seem to have a recessive protective effect, even though the comparisons of genotype frequencies for these variants were not significant [76].

Whereas *BRCA* mutations have been identified mainly in serous OCs, *MMR* genes mutations have been found in various OC histotypes [11]. Furthermore, some cases

of serous, undifferentiated OC present mutations in the *TP53* gene, while endometrioid types have shown 90% overexpression of *BCL2* and microsatellite instability (MSI) and mucinous types present 40–50% of *ki-RAS* mutations [77].

Guidelines for HNPCC families' identification have been referred to as the Amsterdam Criteria [78]. In individuals that meet these criteria, genetic testing is performed using patients' blood samples by a direct sequencing of susceptibility genes, *MLH1* and *MSH2*.

If the family history satisfies less stringent criteria such as the Bethesda Criteria, it could be carried on a pre-screening analysis regarding microsatellite instability and immunohistochemistry (IHC) [79,80]. These analyses require tumor tissue obtained from the youngest family member, without performing DNA mutational analysis. IHC is able to evaluate the presence or not of the proteins MLH1, MSH2, MSH6 and PMS2 by means of specific antibodies but not to predict lack of function due to the formation of truncated proteins [81]. The absence of one of the protein indicates which *MMR* genes is most suitable for mutational analysis. Unfortunately, in the case of missense mutations, IHC does not permit molecular diagnosis; even though the protein may be not functional, its presence could be detected. For this reason, IHC should be used together with MSI analysis as a pre-screening test [79]. The microsatellite markers set used in HNPCC families are the same used for sporadic tumors, which show instability in 10–15% of the cases compared to 85–92% in familial tumors [82,83]. Tumors are defined as having high MSI (H-MSI) when at least 30% of the markers are positive and as low (L-MSI) when positivity is less than 30%. If none of the markers proves to be positive, the tumor is defined as having stable MSI [84]. This method presents a sensitivity of 93% in MMR genes mutation carriers, but with regard to IHC, offers no indication as to which gene might be altered.

2.4. Other hereditary syndromes predisposing to ovarian cancer

An increased risk of ovarian cancer is associated with several hereditary syndromes, such as Gorlin's syndrome, the Peutz-Jeghers syndrome, osteochondromatosis or Ollier's syndrome.

These syndromes are linked to specific susceptibility genes whose mutations may contribute to a particular OC histotype.

Both the Peutz-Jeghers and Ollier's syndrome may determine granulosa cell tumors in affected family members; they involve the *STK11* gene and the *EXT*s genes, respectively. Gorlin's syndrome may cause basal cell carcinomas, odontogenic cheratocysts and nevus diseases in *Patch* gene mutations carriers; it may also cause ovarian fibrosarcomas. For members of families affected by these syndromes, the risk of developing an ovarian tumor during their life is less than 2% [11,20–22].

Table 3
Lifetime risk estimate of developing ovarian cancer

General population	*BRCA1*	*BRCA2*	*MSH2*
1.6	28-44	27	12

The risk is calculated between general population and carriers of *BRCA1*, *BRCA2* and *MSH2* mutations (%).

3. Lifetime risk for familial ovarian cancer

The lifetime risk of members of families with genetic predisposition depends on the susceptibility genes mutations; *BRCA1* mutations seem to confer the highest risk. The risk of OC among HNPCC women is of about 12%, while it may be as high as 50% in *BRCA1* mutation carrier [85]. *BRCA1* mutations are associated with an OC risk ranging from 28% to 44%, compared to 1.6% in the general population. The Breast Cancer Linkage Consortium has established a lower cumulative risk of OC in families whose members are carriers of mutations in *BRCA2*, that is of 0.4% under the age of 50 and 27% at the age of 70. Furthermore, the mean age at diagnosis of OC in *MMR* genes or *BRCA1* mutation carriers is younger than that of patients with sporadic OC (45 and 60 years, respectively), whereas most of the OCs associated with *BRCA2* mutations are diagnosed after the age of 50 [25].

Moreover, mutations in the *BRCA* genes confer an increased risk of OC in women already affected by breast carcinoma, which is apparently 10 times as high as that of non-carrier women (Table 3).

4. Oncogenetic counseling

Oncogenetic counseling is addressed to people with a suspected genetic predisposition to the development of specific neoplasms recurring within their family [86] in order to aware patients about their pathological genetic condition.

Oncogenetic counseling requires a "multidisciplinary approach", involving geneticists, oncologists and psychologists; each of these specialists plays a definite role within the counseling program. Women at high risk of developing an OC must first undergo the analysis of their family history, their genealogical tree must be constructed and their personal risk must be evaluated [87] (Fig. 5).

4.1. Risk evaluation

Risk calculation assesses the probability that the subject will develop the disease and also the woman's personal vulnerability. In this latter context, the psychologist is essential. Oncogenetic counseling and genetic testing can cause a serious psychological stress related to the results and to the subsequent life changes, the loss of privacy and the possible alteration of family dynamics. For these reasons, in the last few years, the importance of psychological support for

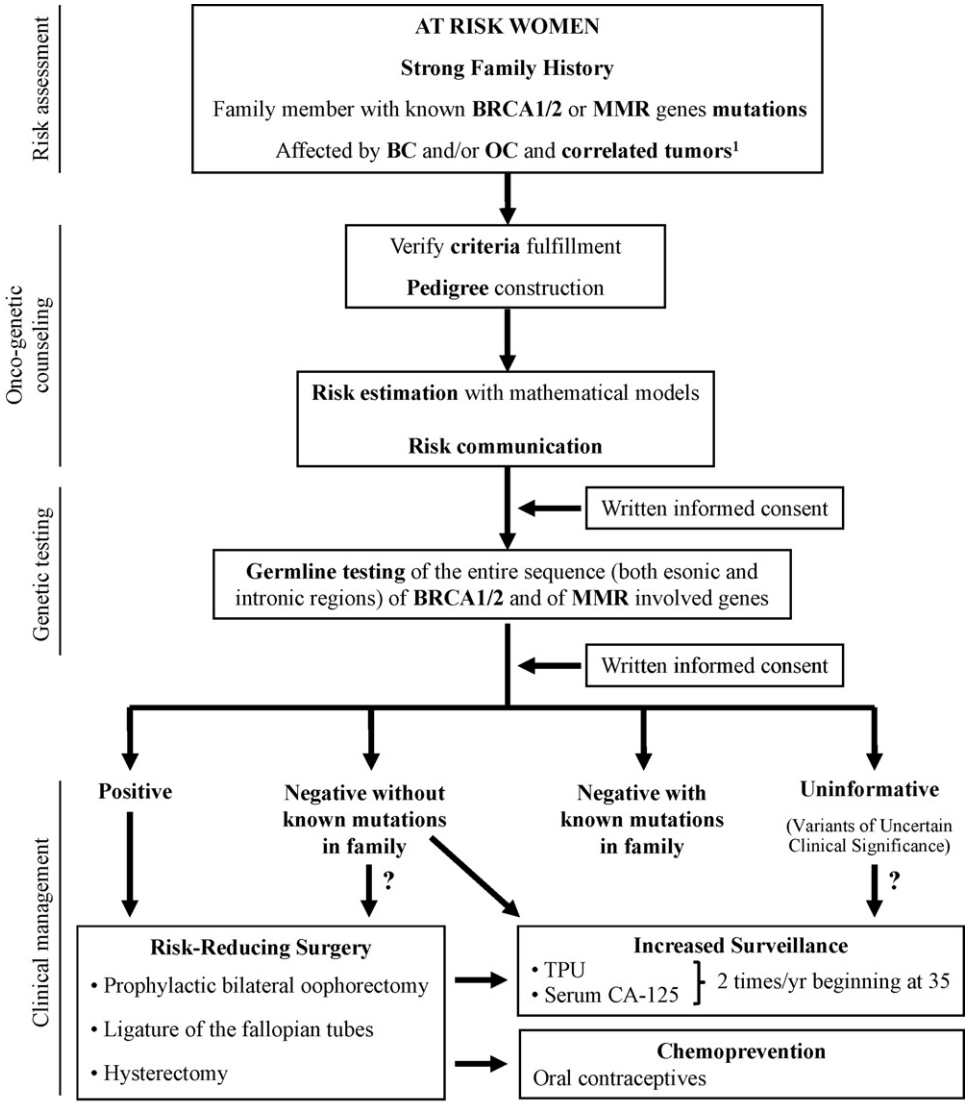

Fig. 5. Management flowchart for women at high risk for ovarian cancer. BRCA genes: breast cancer genes; MMR genes: mismatch repair genes; BC: breast cancer; OC: ovarian cancer; TPU: transvaginal pelvic ultrasound; yr: year. [1]Ovarian, breast, colon, endometrial, pancreatic and biliary tract tumors.

whole family during and after the counseling has been fully recognized [88,89].

Nowadays, risk evaluation regarding OC patients is performed with the use of specific mathematical models, such as *BRCAPro*, the *Couch* and *Myriad* I models.

The risk calculation with *BRCAPro*-Software result is expressed as a percentage value: subjects with a result of more than 10% are considered at high risk of being carriers of a germline mutation and will therefore undergo genetic testing. This includes the molecular analysis of the susceptibility genes. BrcaPro is a computer based Bayesian probability model that uses first and second-degree family history of breast and/or ovarian cancers to determine the probability that a BRCA1 or BRCA2 gene mutation accounts for these cancers.

Another model used (Myriad) allows to estimate the probability of being a BRCA mutation carrier by adopting a table of mutations prevalence available on the Myriad web site.

On the contrary the BRCAPro system uses data from published studies of prevalence, penetrance and mutation frequency.

The Couch model requires data from at least four family members with BC/OC and predicts the risk of BRCA1 mutation only. Moreover it does not fit to families with OC site-specific.

The Myriad system instead may be used in affected individuals with no family history or in patients with OC site-specific.

It is important to underline here that every model system has some weakness and that it is the clinical experience that lead to the choice of the most appropriate model or combination of models to the needs of a specific family [90–94].

4.2. Pedigree analysis and eligibility criteria

The reconstruction of the patient's *family history* is a cornerstone of the genetic counseling process, since a clear understanding of the genealogical tree can enhance correct diagnosis, can allow a more accurate outcome prediction so providing better indications about the following disease management.

The reconstruction of the genealogical tree requires the collection of the clinico-pathological data regarding each member of the family, going back for at least three generations from the "proband".

Furthermore, both paternal and maternal family history should be included, since most of the genes involved in the risk of developing an ovarian tumor derive equally from the mother and the father.

Since a hereditary OC is identified by means of a careful analysis of the family history, the informations leading to the reconstruction of the pedigree must be extremely accurate; informations provided by the patient should be double-checked by means of the evaluation of pathological reports, death certificates or cancer registers.

As soon as the geneticist has explained that there is a possible genetic disorder within the family, the proband must decide whether or not to undergo genetic testing. After being informed about advantages and disadvantages of the procedure, the patient is free to decide and to sign the *informed consent* [95].

Analyzing the family history, the geneticist will decide which of the main hereditary ovarian tumor syndromes is present in the proband's family.

HNPCC families are generally identified by the analysis of a family history of colon carcinoma rather than OC [65]. These families mainly respond to the Amsterdam criteria, which exclude familial adenomatous polyposis, taking into account cancer of the colon and related tumors in three first-degree relatives or else in two successive generations, of which at least one before the age of 50. In certain families, especially when they are not very large, the Bethesda criteria are used; these include the Amsterdam criteria, but also probands affected by carcinoma of the colon diagnosed before the age of 60 and second-degree relatives who have had Lynch syndrome correlated tumors [78,80].

Families with an hereditary syndrome of site-specific OC are recognizable by the large number of OC diagnosed before the age of 50 among the women of the same family, whereas HBOC families present members affected by early-onset breast cancer and OC and members with both malignancies, male breast carcinoma and with two or more first-degree relatives with both breast and OCs diagnosed before the age of 50 [1].

The following criteria identify women at high risk for OC who should undergo genetic testing, taking into account the first grade relatives:

- two or more women with OC at any age;
- one member with OC at any age and with breast cancer under the age of 50;
- one member with OC at any age and two relatives with breast cancer diagnosed before the age of 60;
- one member affected who is a carrier of mutations in genes predisposing to OC;
- three members of the family with cancer of the colon, with at least one of them diagnosed before the age of 50 and one case of OC.

Limitations in these eligibility criteria could exclude fairly small families or families with a large number of male members, since they can transmit germline mutations without manifesting related tumors. In any case, these criteria are the only available instruments which permit the geneticist to identify families at high risk for developing OC [65].

4.3. Genetic testing for BRCA or MMR genes

The result of the genetic testing for the identification of germinal mutations is only able to indicate the probability, but not the certainty, that a cancer will develop; not in all individuals with a positive test for BRCA or MMR gene mutations malignancies will occur. The genetic testing for *BRCA1/2* genes provides automatic sequencing of all codifying exons and of the exon–intron boundaries; recent techniques allow to detect also wide insertions and deletions involving one or more whole exons [96].

In HNPCC families fulfilling the Amsterdam criteria, it is possible to directly sequencing of susceptibility genes from the peripheral blood of the affected patient, whereas in families that correspond to the Bethesda criteria it could be carried on a pre-screening analysis regarding MSI. However, in the case of a strong family history of colon cancer and OC, it is still useful to carry on mutational analysis because HNPCC families selected with the Bethesda criteria could present fewer cases of colon cancer available for MSI analysis than other types of correlated tumors, such as OC [79].

If a particular mutation is identified in an individual who has been diagnosed with cancer, counseling is therefore advised for the other healthy family members who will provide written informed consent. *Pre-test* counseling requires that all the individuals involved in genetic testing are informed about the potential advantages and disadvantages of cancer early detection and prevention strategies, after which they can decide whether or not to give their consent and will be prepared to receive the result [95,97].

4.4. Disclosure of gene test results

The *post-test* counseling concerns the communication of the result of the genetic test and provides another opportunity to meet the at risk family member. This phase is necessary for patients' deeper understanding and/or revision of the information they received [95].

The genetic test may give a positive, negative or non-informative result.

A result is defined as *positive* when a deleterious mutation in the susceptibility genes is detected in the proband. They are considered as deleterious those mutations, such as frameshift mutations due to insertions or deletions, which determine the formation of a truncated protein. A positive result of genetic testing implies the research for the same mutation in all the members of the family and the planning of surveillance program. Testing for a known familial mutation is easier and cheaper than full gene sequencing.

A *negative* result indicates that no deleterious mutations have been identified. If a genetic mutation has been found previously within the family, and the patient does not present it, the result is considered a "true negative", meaning that the patient did not inherit the known familial mutation. On the other hand, when a negative result is obtained in a patient with a strong family history without an already known mutation, the negative result cannot exclude the possible presence of other unknown germline mutations [97].

A *non-informative* result means that there has been the identification of an "unknown variant", that is a genetic alteration of unknown biological significance. This group is made up of the missense mutations or mutations found in non-codifying regions of the gene. Biochemical/functional assays are required to determine the clinical significance of these variants [98].

Nevertheless, the genetic counseling program does not end with the communication of the result to the patient; the genetic consultant should always be at the patient's disposal in order to answer any further questions that might occur after disclosure counseling.

5. Clinical and histopathological relationships and prognosis

The histopathological features of OCs associated with germline BRCA mutations have not yet been clarified.

Since BRCA1 germline mutations are found four times more often than BRCA2 mutations in patients with hereditary OC, most publications investigating the correlations between clinical behavior and histopathological features in familial OC include only BRCA1 mutation carriers (Table 4).

Historically, serous carcinoma is the most common histotype occurring in patients with BRCA1 mutations accounting for more than 90% of all cases, while it is found in about 60% of sporadic OCs [99]. Nevertheless, more recent studies reported that serous carcinomas are less frequent and BRCA mutation-associated carcinomas have pathological features similar to those of sporadic cancers (Table 4).

Mucinous tumors are uncommon in BRCA1 mutation carriers; it may be that mutations in BRCA1 gene are less involved in the development of this OC histological type [100]. Even though only occasionally described, invasive and borderline mucinous carcinomas have also been observed in BRCA1 mutation carriers [101,102]. Other histopathological types such as endometrioid and clear-cell carcinomas show almost the same or a slightly lower frequency in BRCA1 mutation carriers versus sporadic cases. Transitional-cell and squamous carcinomas, sarcomas and dysgerminomas are fairly rare.

Table 4
Histopathological features of BRCA mutation carriers

Histopathological type	BRCA1 mutation, carriers no. (%) [1–6]	BRCA2 mutation, carriers no. (%) [2,4]
Serous	296 (55)	43 (53)
Mucinous	12 (2)	3 (4)
Endometrioid	128 (24)	22 (27)
Clear cell	54 (10)	6 (7)
Undifferentiated	13 (2)	–
Other	40 (7)	7 (9)
Total	543 (100)	81 (100)

1. Berchuck A, et al. Clin Cancer Res 1998;4(10):2433–7.
2. Lakhani SR, et al. Clin Cancer Res 2004;10(7):2473–81.
3. Piver MS. Gynecol Oncol 2002;85(1):9–17.
4. Risch HA, et al. Am J Hum Genet 2001;68(3):700–10.
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OCs associated with BRCA1 and BRCA2 germline mutations are high grade, present a larger solid component and are diagnosed at a more advanced stage compared to sporadic ovarian tumors. In addition, they overexpress p53, while HER2 expression is similar to that found in sporadic [101].

Similar morphological and immunophenotype patterns have been found in BRCA1 and 2 related OCs and in sporadic ones, whereas BRCA1/2 associated breast cancer expresses different features when compared to the sporadic form.

High grade and overexpression of p53, usually associated with familial OC, are generally recognized as unfavorable prognostic factors. However one study has reported a better prognosis among BRCA1 mutation carriers with advanced OCs compared with a series of sporadic cases at the same stage and a survival rate of 77 months versus 29 months, respectively [103]. A better clinical outcome of BRCA-associated cancers has also been confirmed by a national research program conducted in Israel [104] and in a Japanese study in patients treated with cisplatin [105]. Nevertheless, two further studies have found no differences in survival rate between patients with hereditary OC and those affected by sporadic ovarian tumors [106,107].

It has been hypothesized that OCs associated with BRCA mutations might achieve longer overall survival and disease-free interval after chemotherapy because of the higher sensibility of BRCA-deficient neoplastic cells to some cytotoxic agents. In fact, BRCA proteins are implicated in the mechanisms of recognition and repair of DNA double-strand breaks produced by agents such as platinum compounds. On the other hand resistance of BRCA-associated tumors to mitotic-spindle drugs, such as taxanes and vinka alkaloids, has been reported in model systems [108].

The main difference between BRCA1 and 2 mutation carriers is that the latter implicate a lower risk for tumor development, which in any case evolves later on in life.

The clinical and histopathological features of HNPCC-linked endometrial and OCs are similar to those observed in the most part of sporadic cases, even if they occur at an earlier age. These cancers are usually well differentiated, identified at an early stage and often synchronous [66,109].

6. Strategies for the primary care clinician

6.1. Gynecologic screening in high-risk groups

The main goal of screening is to identify OC at an earlier and more curable stage. A screening program is now considered conventionally acceptable if it allows to detect an early OC case every ten screening tests performed. Since OC is rare in the general population, a specificity of 99.6% is required. In a high-risk group, such as carriers of mutations in the BRCA1 and BRCA2 genes, 90% specificity is enough to maintain the positive predictive value (PPV) above 10% [110].

6.1.1. Pelvic examination

In the general population, this procedure has neither the specificity nor the sensitivity required for the efficient detection of an OC. Few data are available on its clinical usefulness in high-risk women. A sensitivity of 40%, a specificity of 98% and a PPV of 21% has been achieved using a pelvic examination only [111].

6.1.2. Colpocytological examination

PAP test may occasionally detect malignant cells exfoliating from the ovaries, but it cannot be considered a practical screening method for OC, since it presents a sensitivity of no more than 10–30% [112].

6.1.3. Serum CA125

There is limited evidence to establish whether routine screening with serum CA125 levels for the high-risk population would result in a decrease in mortality from OC. A study regarding 180 high-risk women reported a CA125 increase in four out of eight ovarian epithelial carcinomas, but above all at an advanced stage (25% at stages I–II vs. 75% at stage II) [113].

Bourne et al. conducted a large study on 1502 women with familial history of OC. They found that the CA125 assay could improve the PPV of transvaginal pelvic ultrasound (TPU) from 12.7% to 42.9%, with a detrimental effect on the sensitivity which was reduced from 100% to 43% [85].

In another study on women at high risk for hereditary carcinoma of the breast/ovary or hereditary non-polyposis colorectal cancer (HNPCC), this marker proved to be elevated in 11% of the cases; during the premenopausal period rising values of CA125 were associated with benign pelvic diseases, such as endometriosis, adenomyosis and myomas, whereas during the menopause no suspect in-depth ultrasound images were observed [114].

6.1.4. Transvaginal pelvic ultrasound (TPU)

TPU is superior to transabdominal ultrasound for the preoperative diagnosis of adnexal masses [115]. Both these techniques are less specific when used in premenopausal women compared to those in the postmenopause due to the ovarian changes occurring during the menstrual cycle. The positive and negative predictive values of TPU in women with familial history for OC are higher than the corresponding values in the general population and can be further improved by the addition of Doppler color techniques, at least in postmenopausal women [116,117]. Two studies by Bourne et al., using these tools, reported a sensitivity of 100% and a specificity of 97% of TPU after screening 776 women with at least one close relative who had developed the disease and an abnormality rate of TPU of 3.8%, that is, 61 out of 1601 women screened, six of whom had primary OC detected at surgery [118,119]. In another paper, all the five OCs found in a group of 180 high-risk women had been correctly diagnosed by TPU, but one only was at stage I, while the other four were at stage IV [113].

6.1.5. Combined screening tests

In the general population, the sensitivity of a screening program based on a CA125 assay and TPU is of about 80–100%, but its predictive value is extremely low. If only the CA125 value is considered, from 0.1 to 0.6% of healthy women will undergo a useless surgical procedure, and the rate further increases to 4.4% when TPU is used alone. A randomized clinical study reported that only 6 out of 10000 women screened with sequential CA125 antigen and ultrasonography had a correctly diagnosed OC, half of which curable, while 24 underwent unnecessary surgery [120]. The same study suggested that the combination of the two methods might produce an earlier diagnosis of ovarian neoplasms, which might result in both a downstaging of cancer and an improved survival rate. At the same time, it is clear that there are consistent problems and costs that must be considered when conceiving a screening program for such a rare disease. The situation might be different with regard to high-risk patients with mutations in the genes BRCA1 and BRCA2, for whom the higher incidence of the disease might have a significant effect on the cost/benefit ratio of the screening program. Moreover most OCs that occur in women at high genetic risk are high-grade serous cancers and these are infrequently screen-detected at an early stage. Hogg and Friedlander reviewed 12 studies reporting on more than 6000 high-risk screened women: of the 38 OCs diagnosed in women at increased risk, 24 (63%) were stage IIC or higher [121].

The National Comprehensive Cancer Network recommends that women with BRCA1 or BRCA2 mutations participate in intensive surveillance programs with twice-yearly concurrent transvaginal ultrasound and serum CA125

(http://www.nccn.org/professionals/physician_gls/PDF/genetics_screening.pdf).

6.2. Oral contraceptives

Chemoprevention is a primary prevention strategy that aims to reduce hereditary cancer risk with drugs: oral contraceptives have been extensively evaluated in ovarian cancer prevention. In the population at large, the use of oral contraceptives is associated with a risk reduction of developing OC ranging from 40 to 50%, which increases during the period of their use and persists for 10–15 years after their suspension [122,123]. The same effect has been observed in women with familial positivity for OC [124] and between BRCA1 and BRCA2 gene mutation carriers [125]. Nevertheless, a retrospective study on a large cohort of patients with OC suggested that the protective effect did not involve the carriers of BRCA1 mutations [126]. Furthermore, caution is required before oral contraceptive use can be routinely recommended since a higher rate of breast carcinoma has been reported in BRCA1/2 mutation carriers who had taken oral contraceptives for at least 48 months (OR 7.8; $p = 0.004$) [127]. A case–control study by Narod et al. showed an increased risk of early-onset breast cancer, among BRCA1 mutation carriers, in women who first used oral contraceptives before 1975, who used them before age 30, or who used them for 5 or more years. Oral contraceptives did not appear to be associated with risk of breast cancer in BRCA2 mutation carriers [128]. These limited data suggest that the administration of an oral contraceptive should not be considered as an option for reducing the risk of OC in BRCA1/2 mutation carriers [23,129].

More recently, McLaughlin et al. published a case–control study on 3223 women with BRCA mutations. The authors reported that oral contraceptive use lead to a highly significant reduction in ovarian cancer risk (BRCA1 odds ratio = 0.56, BRCA2 odds ratio = 0.39) in both univariate and multivariate analyses. The maximum protective effect was seen with 3–5 years of oral contraceptive use [130].

6.3. Prophylactic surgery

6.3.1. Prophylactic salpingo-oophorectomy (PSO)

Women with ascertained BRCA1 and BRCA2 mutations should be counseled that, at the present time, prophylactic salpingo-oophorectomy is considered the most appropriate option to prevent OC and that it is suggested after the 35th year of age or after childbearing is completed (Fig. 5).

There is general agreement regarding the fact that protection is incomplete, since primary peritoneal carcinoma indistinguishable from primary OC could develop in 1.8–10.7% women with a history of familial OC who have undergone PSO, probably due to the common embryonic origin of the peritoneum and the ovaric epithelium [131–133]. However, thorough histological examination of prophylactically removed ovaries could detect foci of malignant tumors which were overlooked at the initial examination and were not be detected on ultrasonograms [134,135]; several of the peritoneal carcinomas found in such cases might therefore be metastases of OCs which were not diagnosed at the first surgical intervention.

Moreover, the risk/benefit ratio of PSO should take account of the potential morbidity and mortality of the surgical procedure [136], of the cardiovascular risks [137], of the possibility of osteoporosis developing [138] and of risks linked to long-term hormone-replacement therapy (HRT) [139].

In 1995, the U.S. National Institute of Health (NIH), after reviewing the available literature on the efficiency of PSO as demonstrated by the follow-up of high-risk women who had not received genetic counseling, concluded that mutation carriers should undergo PSO ideally after the age of 35 or upon completion of child bearing [140].

The Cancer Genetic Studies Consortium concluded adversely that evidence was insufficient to suggest or advise against prophylactic surgery as a measure for reducing OC risk [141].

After the publication of these recommendations, several studies evaluated the impact of prophylactic mastectomy and oophorectomy on the risk for breast and gynecological cancers in BRCA mutation carriers [142–144]. In the most recent of these (Van Roosmalen et al.), PSO performed at the age of 30 brought about an increase of expected survival rate of 5.3–9.5 years depending on the penetrance of the gene; furthermore, a protective effect against breast carcinoma was found when bilateral prophylactic oophorectomy was performed during the premenopause and this had also been confirmed in mutation carriers of the BRCA genes [145].

More recently, four case–control studies have been published concerning BRCA1/2 mutation carriers who underwent either prophylactic oophorectomy or clinico-instrumental follow-up [146–149] (Table 5).

In the first retrospective study (Rebbeck et al.), conducted on 551 BRCA1 and BRCA2 mutation carriers, 259 women underwent oophorectomy and 292 clinico-instrumental follow-up for an average of 8 years. At the time of surgery, six women (2.3%) received a diagnosis of stage I ovarian neoplasms, while two cases of papillary serous peritoneal carcinoma (0.2%) were observed respectively 4 and 9 years after surgery. Among the follow-up group, 58 neoplasms (19.9%) were detected. Excluding those cases found at the time of the procedure, PSO reduced the risk of celomic epithelial cancer by 96% (IC 95% 0.01–0.16). Furthermore, the oophorectomy proved to reduce the risk of breast carcinoma by 47% compared to controls among women who had not undergone prophylactic bilateral mastectomy too (IC 95% 0.29–0.77).

Kauff et al. performed a prospective study on 170 BRCA1 and BRCA2 mutation carriers, 98 of whom underwent prophylactic surgery and the rest were fol-

Table 5
Case–control studies in BRCA1/2 mutation carriers undergoing PSO

Study	Year	No. of patients	No. of PSO	Gynecologic cancer at time of surgery	Gynecologic cancer RR (%)	Breast cancer RR (%)
Kauff et al. [134]	2002	170	98	Two stage I ovarian One stage I fallopian tube	85	68
Rebbeck et al. [135]	2002	551	259	Six stage I ovarian	96	47
Scheuer et al. [136]	2002	251	90	One stage I ovarian One stage I fallopian tube	63	
Finch et al. [137]	2006	1828	1045	Seven ovarian Three fallopian tube One malignant cytology	80	

PSO: prophylactic salpingo-oophorectomy; RR: risk reduction.

lowed with surveillance alone. During the 24.2 follow-up months, in the first group three breast carcinomas and one peritoneal celomic carcinoma were found, while in the follow-up group, eight breast carcinomas, four OCs and one carcinoma of the peritoneal celomic epithelium were detected. The hazard ratio for subsequent BRCA-related breast and gynecologic cancer combined in the PSO group was 0.25 (IC 95% 0.08–0.74).

The third study (Scheuer et al.) was a prospective evaluation in a group of 251 mutation carriers of the genes BRCA1 and BRCA2. Among the 90 women who underwent PSO, one stage IC OC and one stage IA fallopian tube neoplasm were found at the time of surgery, while among the women who chose follow-up one peritoneal carcinoma and three OCs at stages I and II were detected during a median follow-up of 24.8 months.

In the largest prospective study on BRCA1 and BRCA2 mutation carriers who had undergone PSO, a 80% risk reduction was calculated including ovarian, fallopian tube and peritoneal cancers. The cumulative incidence of peritoneal cancer in the 20 years following oophorectomy was estimated to be 4.3% [149]. It was retrospectively ascertained that oophorectomy is also an effective means of reducing the risk of breast cancer in BRCA1 mutations carriers [150].

Overall, these data confirm the efficacy of PSO in reducing the risk of carcinoma of the peritoneal celomic epithelium and the possibility of removing stage I ovarian neoplasms which might have overlooked during the clinico-instrumental examinations. This latter fact highlights the importance of performing a detailed histopathological evaluation of the excised tissues in order to detect possible microscopic ovarian and fallopian tube cancers.

As a matter of fact, prophylactic surgery is more effective in decreasing ovarian cancer mortality compared to close surveillance and chemoprevention. However any beneficial intervention in cancer risk reduction should be balanced against concerns about quality of life and adverse effects.

With regard to patient acceptance of the procedure, BRCA mutation carriers of American, Canadian and European nationality tend to accept PSO more readily that prophylactic mastectomy (50% vs. 8–28%) [151,152]. Furthermore, most of the published studies reported greater patient satisfaction and improvement in the quality of life for women who chose prophylactic surgery compared to those who preferred clinico-instrumental follow-up.

Menopausal symptoms are common after PSO. Most BRCA mutation carriers decide to accept HRT after prophylactic adnexectomy [153–155]. Although HRT might increase the incidence of breast cancer, a case/control study seemed not to confirm this hypothesis in high-risk women. In fact, bilateral PSO was associated with a reduced breast cancer risk in women who carry a BRCA1 mutation (RR 0.53 after 5 years and RR 0.33 after 10 years), even in HRT users [145,156]. Nevertheless, premature surgical menopause clearly increases osteoporosis and cardiovascular disease risk [137] that should be properly assessed and managed in each woman who had undergone PSO.

The elective laparoscopic oophorectomy is preferable compared to laparotomic approach, since it involves a complication rate of 9%, of which only 1–2% is serious [157].

Since the fallopian tubes might represent an elective site of malignancy in BRCA mutation carriers, contemporary hysterectomy is often recommended in order to remove the isthmic portion of the salpinges in the cornua of the uterus, although the real incidence in this site is unknown and the large majority of fallopian tube cancers originate in the distal or middle portion [158].

6.3.2. Tubal ligation

A prospective study associated this technique to a reduction of 33% of OC risk in the general population [159]. Another case–control study concerning women with BRCA1 and BRCA2 mutations also reported a significant reduction of the risk (OR 0.39) in those undergoing tubal ligation [160].

6.3.3. PSO during hysterectomy

It has been calculated that in the general population, women older than 40 who undergo hysterectomy, 400 PSO are required in order to prevent one case of OC. The resulting 10% reduction of the incidence of OC would lead to the prevention of 2300 new cases a year in the United States alone [161]. In patients undergoing laparoscopic hysterectomy for

other indications, prophylactic oophorectomy is performed more often than in those where the transvaginal access is used [162].

Since the benefit is proportional to the incidence of the tumor, the removal of the ovaries during hysterectomy in a group of high-risk women would result in a higher prevention rate of OC [136].

Furthermore, with regard to the risks of an early menopause resulting from oophorectomy, it should be considered that within 2 years since hysterectomy performed during the premenopause, 30% of the women presents symptoms of estrogen deficit and a reduction of the bone mass even when the ovaries have been preserved [163].

6.3.4. Prophylactic hysterectomy

Simple hysterectomy is associated with a reduction of the risk of OC in the general population [159]. Women carriers of genetic mutations linked to the HNPCC syndrome should be informed about possible prevention strategies. Among HNPCC families, recommendations for screening and risk reducing surgery are established for colorectal cancer but not for endometrial and ovarian malignancies. Women who completed child-bearing, especially if undergo surgery for colorectal carcinoma, should be counseled about prophylactic hysterectomy and adnexectomy, so as to reduce the risk of the occurrence of gynecological malignancies [164].

7. Practice points

- Major risk factor for the development of OC is a strong familial history.
- Three main familial syndromes are reported: HOC (hereditary ovarian cancer), HBOC (hereditary breast and ovarian cancer), HNPCC (hereditary non-polyposis colorectal cancer or Lynch II syndrome); the first is actually considered a variant of HBOC.
- HOC and HBOC are linked to mutation in BRCA1 and BRCA2 genes.
- HNPCC is associated to mutation in MMR genes.
- Patients with strong family history for OC should be referred for genetic counseling and potential genetic testing.
- Ovarian cancer associated with germline BRCA mutations are mostly advanced stage at diagnosis and high-grade serous carcinomas.
- Recommendations for OC surveillance in women having a strong family history or in BRCA mutation carriers include TPU with color Doppler and serum CA125 every 6 months.
- BRCA mutation carriers should undergo prophylactic salpingo-oophorectomy after the 35th year of age or after childbearing is completed, but it does not protect against primary peritoneal cancer.
- Hysterosalpingo-oophorectomy should be considered in HNPCC women who undergo surgery for colorectal carcinoma.

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