Mutations in **BRCA1** and **BRCA2** account for hereditary breast and ovarian cancer syndrome in a majority of families and 14% of epithelial ovarian cancer cases. Despite next-generation sequencing, other identified genes (Lynch Syndrome, **RAD51C**, **RAD51D**, and **BRIP1**) account for only a small proportion of cases. The risk of ovarian cancer by age 70 is approximately 40% for **BRCA1** and 18% for **BRCA2**. Most of these cancers are high-grade serous cancers that predominantly arise in the fimbriae of the fallopian tube. Ovarian screening does not improve outcomes, so women at high risk are recommended to undergo risk-reducing salpingo-oophorectomy around the age of 40, followed by hormone replacement therapy (HRT). Specimens should be carefully examined for occult malignancy. Mutation carriers may benefit from newly developed poly ADP ribose polymerase inhibitors. Genetic testing should only be performed after careful counseling, particularly if testing involves the testing of panels of genes that may identify unsuspected disease predisposition or confusing variants of uncertain significance.

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**Introduction**

In the early 1990s, the molecular etiology of several hereditary cancers became established. The identification of specific genes associated with some cancers has allowed clinicians to more accurately assess cancer risk and establish preventive interventions. One of the best examples of such a scientific discovery and increased awareness in gynecologic cancer has been the discovery of the **BRCA1** and **BRCA2** genes and identification of the molecular basis of Lynch syndrome (LS).
Although the risk of ovarian cancer is associated with a number of reproductive, demographic, and lifestyle factors, the strongest risk factor is family history. A woman with a single first-degree relative diagnosed with ovarian cancer has a threefold increase in risk of ovarian cancer [1,2]. A small proportion of familial cases is associated with a recognized cancer disposition syndrome, whereas for others, despite two decades of research, less than half the excess familial risk is explained by identified high-penetrance genes, rare moderate risk alleles, and common low-risk variants (Figure 1).

As the role of targeted therapies becomes clearer, understanding the hereditary basis of cancers, especially those such as ovarian cancers that typically have a poor outcome from conventional therapy, assumes greater importance. In addition, the behavior of ovarian cancers associated with inherited mutations has provided opportunities for the management of sporadic cancers with somatic mutations in the same genetic pathways.

**Genetic causes of hereditary ovarian cancer**

Germline mutations in BRCA1 and BRCA2 account for hereditary breast and ovarian cancer syndrome in a majority of families and 14% of all epithelial ovarian cancer (EOC) cases overall and 17% of those with high-grade serous ovarian cancer (HGSOC) [3]. Evidence of LS is less common, being found in only 0.5–2% of unselected ovarian cancer cases [4,5].

A 2011 study of 360 women with primary ovarian, peritoneal, or fallopian tube carcinoma unselected for age or family history reported that 24% carried germline loss of function mutations in 12 different genes including BRCA1, BRCA2, BARD1, BRIP1, CHEK2, MRE11A, MSH6, NBN, PALB2, RAD50, RAD51C, and TP53 (Figure 2). The majority (18% of all cancers) were attributed to mutations in BRCA1 or BRCA2. Less than 1% were due to LS [4]. However, there was no control cohort in this series, and the causality of the genetic alterations in a number of these genes has been questioned as mutations are

**Figure 1.** Genetic architecture of cancer risk. This graph depicts the general finding of a low relative risk associated with common, low-penetrance genetic variants, such as single-nucleotide polymorphisms identified in genome-wide association studies, and a higher relative risk associated with rare, high-penetrance genetic variants, such as mutations in the BRCA1/BRCA2 genes associated with hereditary breast and ovarian cancer and the mismatch repair genes associated with Lynch syndrome.
rare and in some studies not significantly more frequent in ovarian cancer patients than in control populations, so the data continue to emerge.

**Epithelial ovarian cancer—A histologically diverse disease**

EOC can be broadly divided into mucinous and nonmucinous cancers. True invasive mucinous ovarian cancers are believed to be rare once metastatic tumors from colon and pancreas and tumors of low malignant potential have been eliminated [6]. They may arise from preinvasive disease, including the cystadenoma—borderline—invasive pathway, with CDKN2A (P16) loss and RAS pathway alterations occurring early in their development [7]. There is a marked prognostic difference between early and advanced disease, with the latter having a poor response to platinum-based chemotherapy [8]. Mucinous ovarian cancers may rarely herald LS but are not associated with BRCA mutation status [9,10].

Invasive nonmucinous EOC types include serous, endometrioid, and clear cell, with high-grade serous accounting for two-thirds of the mortality from EOC. There are clear differences between high- and low-grade serous cancers, both clinically and pathologically. The somatic profile of these subtypes varies, resulting in differences in typical stage at presentation, prognosis, and response to chemotherapeutic targets.

Low-grade serous ovarian cancers and serous borderline tumors are associated with somatic BRAF V600E and KRAS mutations. They have a much lower frequency of somatic TP53 and BRCA1 and BRCA2 mutations. Low-grade EOCs are often ER+ and PR+ and are not associated with germline BRCA1 and BRCA2 mutations [11]. Therefore, women with invasive cancer arising from borderline tumors are less likely to benefit from therapies targeting the BRCA pathway.

Low-grade endometrioid and clear cell cancers are believed to arise from precursor endometriosis [12]. Lu et al. postulated that the epidemiological association between endometriosis and ovarian cancer.
adenocarcinoma is attributable to shared genetic susceptibility loci [13]. However, high-grade endometrioid ovarian cancers seem to have a similar genetic profile to HGSOC [14].

HGSOC accounts for most deaths from EOC, with little improvement in response to standard chemotherapeutic management in recent years. A number of collaborative studies have assessed the inherited basis of EOC, with single genes of major effect accounting for 15–18% of HGSOCs and half the carriers lacking a significant family history [3,15] (Figure 3).

Despite BRCA1 and BRCA2 accounting for the majority of inherited ovarian cancers, spontaneous mutations in these genes are an uncommon cause of ovarian cancer. Methylation of BRCA1, whereby a normal copy of the gene is silenced, accounts for approximately 11% of all HGSOC. Half of all HGSOCs have a disrupted homologous recombination repair (HRR) pathway through mutation, methylation, or amplification of genes such as EMSY, FANC family, RAD51C, and PTEN [16]. This has important implications for treatment as HRR loss further inactivates DNA repair in already compromised tumors and determines platinum sensitivity and response to the newly developed poly ADP ribose polymerase (PARP) inhibitors.

The secretory epithelial cells of the fallopian tube fimbriae are believed to be the cells of origin for the majority of HGSOCs [17], particularly those due to germline mutations [18]; however, some arise without fallopian tube involvement. It is postulated that earlier seeding of the ovaries with fallopian tube cells is the source of these cancers (endosalpingiosis), or dual pathways may exist for the origin of serous tubo-ovarian cancers.

The earliest genetic events in fallopian carcinogenesis are missense or nonsense mutations in TP53, which are a consistent feature of intraepithelial neoplasia and high-grade serous cancer, with 96% of high-grade serous cancers showing TP53 loss [19,20]. Preinvasive changes can be identified as clonal expansion of cells staining for p53 without morphological changes, followed by piling up of cells and loss of epithelial architecture, which indicates serous tubal intraepithelial carcinoma (STIC) with TP53 mutations and finally leads to invasive cancer [21]. Genomic instability occurs in early precancerous lesions, with STIC typically having a high proliferative index indicated by Ki67 staining and overexpression of markers of double-stranded DNA breaks [22]. Subsequent genetic events are primarily genomic structural variations with chromosomal instability, resulting in the inactivation of tumor suppressors.

![Molecular Profiling of Serous Ovarian Cancer](image)

**Figure 3.** Genes identified in serous ovarian tumors. 
The genetic basis of hereditary ovarian cancer—BRCA1 and BRCA2

Hereditary breast and ovarian cancer syndrome is the best-known and most well characterized of the hereditary cancer syndromes. BRCA1 and BRCA2 were identified in the early 1990s, with genetic testing becoming clinically available in 1996. BRCA1 and BRCA2 genes are located on chromosomes 17q and 13q, respectively. Both these genes are quite large and contain at least 20 exons (coding regions) and cover approximately 80,000 base pairs.

International databases now list hundreds of different disease-causing (pathogenic) mutations. Most pathogenic mutations alter the reading frame, with downstream premature stop codons resulting in a shortened protein. Other mutations may affect splice sites at the exon boundaries or involve larger genomic alterations. Simple missense mutations, where there is a single base substitution, are less common than disease-causing mutations in BRCA1 and BRCA2. Many mutations have been reported in single families only, whereas others are found repeatedly, either because of a single ancestral origin or independent identical spontaneous mutations in vulnerable segments of the gene.

In the general population, it is estimated that approximately 1 in 300—800 individuals carry a mutation in BRCA1 or BRCA2 [23]; however, the prevalence varies between populations. Founder mutations are those that are more common in, or even unique to, a specific patient population. They occur in populations that have been genetically isolated because of geography or religious practice for many generations. The population may have shrunk as a result of a disaster, but the mutation was preserved in a few individuals. When the population re-expands, the frequency of that specific mutation can increase within the population (Figure 4).

One example of founder mutations occurs in BRCA1 and BRCA2. Approximately 2% of individuals of Ashkenazi (Eastern European) Jewish ancestry have one of three founder BRCA mutations: 187delAG (BRCA1), 5382insC (BRCA1), and 6174delT (BRCA2) [24,25]. Historically, targeted testing for the specific founder mutations was initiated in Ashkenazi women with a personal and/or family history of breast and/or ovarian cancer, with reflex testing to full BRCA1 and BRCA2 gene testing when none of the three founder mutations were identified, if they are indicated on personal and family history. More recently, the high prevalence and ease of testing has prompted unselected population-based testing for these BRCA founder mutations amongst Jewish communities in Israel, Canada, and the UK. Such programs have been shown to double the number of mutation carriers identified, with improved cost benefit and community acceptance [26,27].

Cancer risks associated with BRCA1 and BRCA2 mutations

From the findings of two meta-analyses, a woman with a BRCA1 mutation has approximately 40% risk of developing an ovarian cancer on average, and a woman with a BRCA2 mutation has 11–18% risk of developing ovarian cancer [28,29]. The risk of ovarian cancer for BRCA1 or BRCA2 mutation carriers by age 40 is less than 3% but increases up to 10% by age 50 (Figure 5). Individual studies have estimated higher and lower risks depending on whether the data were obtained from multiple case families.
recruited for research or from a broader population-based sample. Variations in the penetrance of mutations have been attributed to the specific mutation, the effect of other modifying risk alleles carried by the individual or the family, and the impact of both exogenous and endogenous risk factors. For women with breast cancer, the 10-year risk of developing a subsequent ovarian cancer is 12.7% for BRCA1 mutation carriers and 6.8% for BRCA2 mutation carriers [30].

Clinicopathological features of BRCA1- and BRCA2-related ovarian cancer

Studies have consistently shown that ovarian cancer in women with BRCA1 or BRCA2 mutations is more likely to be high-grade serous adenocarcinoma than other subtypes [9]. Although both BRCA1 and BRCA2 encode proteins integral to DNA repair, BRCA1 has additional functions including cell cycle regulation, which may be the basis of BRCA1 being associated with a higher risk of EOC and earlier age of onset by up to a decade than BRCA2 or sporadic cancers. Women with either BRCA1 or BRCA2 germline mutations are more likely to be diagnosed at an advanced stage but have better response to therapy and longer overall survival than that of noncarriers [3,31,32]. However, acquired resistance to treatment is typical of both inherited and sporadic HGSOC. Multiple mechanisms of resistance have been postulated; however, in patients with germline BRCA1 or BRCA2 mutations, reversions of the germline mutation in tumor cells through subsequent somatic events have been shown to be the basis of chemoresistance [32].

Four molecular subtypes of HGSOC have been identified, namely C1/mesenchymal, C2/immunoreactive, C3/4 differentiated, and C5/proliferative [19,33], with BRCA1-associated cancers more likely to be the C2 (immunoreactive) subtype; however, BRCA2 tumors cannot be distinguished from tumors without BRCA mutations. The finding of a strong association between BRCA1-associated cancers and T-cell infiltration has opened up possibilities for immunotherapy research in these cancers. Genetic profiling of ovarian cancers to predict response to chemotherapeutic options is advancing. The CLOVAR model incorporates BRCA status to predict prognosis and response to platinum therapy [34], but further work needs to be done before this can be incorporated into standard care.

The determinants of metastasis of HGSOC are still unclear; however, there is evidence that the propensity for omental spread may be both vascular and through direct contact, utilizing omental fat as an energy source [35]. Other elements in the HGSOC environment may also influence progression and treatment response, including fibroblasts, endothelial cells, and the extracellular matrix. More research

Figure 5. Cumulative risk of ovarian cancer for unaffected 20 year old carriers of mutation in BRCA and BRCA2. Chen and Parmigiani. JCO.2007.
is needed to understand the multiple mechanisms of acquired resistance and the role of immuno-suppressive factors, with potential therapeutic targets.

**Lynch syndrome (hereditary nonpolyposis colon cancer)**

LS is an autosomal dominant cancer predisposition syndrome caused by inherited mutations in one of four mismatch repair genes: MLH1, MSH2, MSH6, and PMS2. Mutations are believed to be carried by approximately 1 in 660 people [36] and account for 1–3% of all colorectal cancers [37], although there is evidence of considerable under diagnosis. After colon cancer, endometrial cancer is the most common cancer in LS, occurring in 15–30% of carriers, with carriers of mutations in MSH2 and MSH6 being at highest risk. Gynecological cancer, usually endometrial, is the sentinel cancer in more than half the women with LS [38].

LS is also associated with an increased risk of ovarian cancer, occurring in 8–15% of female MLH1 or MSH2 mutation carriers and uncommonly in carriers of MSH6 or PMS2 mutations [39,40]. In a recent review, the mean age at diagnosis of ovarian cancer in LS was 45 years (range 19–82). Most cancers had mixed histology (mucinous, endometrioid, and clear cell), and 23% were endometrioid, 21% serous, and 11% clear cell. Two-thirds were FIGO stage I or II. As many as 22% of gynecological cancers in LS are synchronous endometrial and ovarian cancer. The overall survival in ovarian cancer is better in women with LS than those with BRCA1 or BRCA2 mutations because of the non-serous histological subtype, earlier stage at diagnosis, and younger age of onset; however, the overall survival in women with LS is similar to those with sporadic ovarian cancer [41].

Recommended evaluation of colorectal cancers for the evidence of LS uses tumor microsatellite instability or immunohistochemistry to detect the expression of the mismatch repair proteins. Although these methods are used in the evaluation of ovarian cancer, data on the optimal methods and their sensitivity are limited.

**Rare hereditary syndromes that include ovarian cancer**

Mutations in the STK11 gene, a tumor suppressor gene, result in Peutz–Jeghers syndrome (PJS), a rare (1:20,000) autosomal dominant disease manifesting with mucocutaneous pigmentation; gastrointestinal hamartomas; and an increased risk of breast, ovarian, and cervical neoplasms. Ovarian tumors in PJS include benign sex cord tumors with annular tubules (SCTATs); dysgerminomas; and granulosa, Brenner, and Sertoli cell tumors. SCTATs differ in patients with PJS where they are often multifocal, bilateral, and small [42].

PJS is also associated with minimal deviation adenocarcinoma, previously known as adenoma malignum of the cervix, with an estimated 15–30% lifetime risk and an earlier age of onset in PJS vs. non-PJS patients (mean age 33 vs. 55 years, respectively). The risk of any gynecological cancer in women with PJS is 1% at age 30 years, increasing to 18% by age 60 [43,44].

**Other ovarian cancer predisposition genes**

Additional genes in the DNA repair BRCA-FA (Fanconi Anemia) pathway have been reported to confer an increased risk for breast and ovarian cancer, including CHEK2, BRIP1, RAD50, RAD51C, RAD51D, PALB2, BARD1, MRE11, and NBN.

Multiple studies have now demonstrated that RAD51C and RAD51D are inherited ovarian cancer predisposition genes but are not associated with increased risks of breast cancer. They account for less than 1% of all. Mutations in these genes are associated with a relative risk of ovarian cancer of around six for RAD51C and 12 for RAD51D, with mutation carriers more likely to have HGSOCs [45–48].

BRCA1-interacting protein 1 (BRIP1) directly binds to the BRCA1 BRCT domain. A single mutation c.2392C>T is the most common truncating mutation and has been found in patients from diverse populations, suggesting that it has an ancient founder or is recurrent. Mutation carriers have an 8–11-fold relative risk of ovarian cancer, but mutations are not associated with a marked increase in the risk of breast cancer, although it cannot be excluded as a low-risk polymorphic variant [49,50]. Although there is strong evidence justifying the consideration of risk-reducing salpingo-oophorectomy (RRSO),
the lower lifetime risks (5–15%) and later ages of onset (average age at diagnosis ≥60) indicate that postmenopausal surgery, rather than premenopausal surgery, may be appropriate [51].

Conclusive evidence of PALB2, NBN, and BARD1 as ovarian cancer predisposition genes has not been demonstrated; however, their low prevalence implies that a modest risk cannot be excluded [50]. Caution should be exercised in the interpretation of results of cancer panels that include these genes until further data are obtained.

**Lower Risk Alleles and Modifiers**

Genome-wide association studies have identified multiple allele variants conferring a relative risk of ovarian cancer of <1.5. These variants are currently not clinically actionable, but further research is ongoing [52]. Similarly, multiple consortia have identified loci that are likely to be modifiers of risk in BRCA1 and BRCA2 mutation carriers, but these are not yet included in a clinical risk assessment.

**Identifying patients suitable for genetic testing**

Targeted therapy, tailored screening, and prevention strategies can reduce morbidity and mortality in breast and ovarian cancer, making the identification of individuals at inherited risk important. Clinical criteria have been developed to identify patients at risk of having an inherited predisposition to breast or ovarian cancer and those for whom genetic risk assessment is strongly recommended.

The cornerstone of cancer risk assessment remains the review of family history; the appreciation of physical findings and specific pathology related to genetic syndromes; and the construction of a detailed pedigree that includes ages of cancer diagnosis, ages and causes of death, and documentation of complex familial relationships (e.g., consanguinity). Online tools are available to assist patients in the organization of family history. Guidelines to identify patients appropriate for risk assessment and genetic testing are available from a number of professional organizations but vary somewhat from country to country, influenced by funding constraints and insurance issues.

Most guidelines advocate genetic testing for hereditary cancer where there is at least a 10% chance of identifying a mutation. This can be assessed using an office model such as the Manchester scoring system [53] or online models such as the IBIS model (http://www.ems-trials.org/riskevaluator/) or Boadicea (http://ccge.medschl.cam.ac.uk/boadicea/). Testing is typically recommended for any woman diagnosed with HGSOCs or early-onset triple negative breast cancer irrespective of family history. In addition, immunohistochemistry for mismatch repair proteins is indicated for young-onset endometrioid ovarian cancers or endometrial cancer. The upper age limit for these investigations varies by countries and institutions.

**Management guidelines for women with BRCA1 or BRCA2 mutations**

Fundamental to genetic counseling and testing is that the risk of developing disease and its outcomes can be modified by a therapeutic intervention. The three options available for hereditary disease intervention are [1] increased surveillance [2], chemoprevention, and [3] prophylactic surgery.

Multiple organizations have published guidelines for genetic risk assessment and management guidelines for individuals with hereditary breast and ovarian cancer due to BRCA1 and BRCA2, with some local and international variances.

**Surveillance**

The current National Comprehensive Cancer Network recommendations (version 1.2016) http://www.nccn.org/professionals/physicians_gls/PDF/genetics_screening include clinical breast examination every 6–12 months and annual breast MRI beginning at age 25. From age 30–75 years, annual mammogram and annual breast MRI are recommended, often at staggered 6-month intervals. Women with a BRCA mutation and a personal history of breast cancer should continue with annual mammography and breast MRI. A discussion of the option of risk-reducing mastectomy is also recommended.
Screening for ovarian cancer using serial CA125 measurement and/or transvaginal ultrasound (TVUS) remains controversial, with data being compromised by prevalent vs. incident cancers and screening having the potential for harm if unnecessary surgery is performed [54]. The problem with ovarian cancer screening in the general population is that the incidence of the disease is so low that the sensitivity and specificity must be exceedingly high to obtain a positive predictive value reliable enough to be useful for screening. Some authors have proposed the use of a “risk of ovarian cancer algorithm” (ROCA). This suggests that measuring serial CA125 values longitudinally over time and observing velocity increase in the values is a useful screening tool in high-risk populations [55].

The randomized prospective Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial found no reduction in mortality with annual CA125 and TVUS in postmenopausal women at average risk of these cancers [56]. The UK Collaborative Trial of Ovarian Cancer Screening randomized over 200,000 unselected postmenopausal women to annual multimodal screening using CA125 interpreted with the use of the ROCA, TVUS, or no screening. The trial reported multimodal screening to have sensitivity and specificity of 89.4% and 99.8% respectively, leading to five surgeries per invasive cancer. Unfortunately, less than half the screen-detected cancers were of early stage (42%), and this included tumors of low malignant potential and low-grade cancers. Multimodal screening indicated a nonsignificant reduction in mortality, but this was significant once prevalent cases were excluded [57]. The study is ongoing using screening every 4 months instead of annually.

The potential fallopian origin of HGSOC, rapid progression, and diverse metastatic pathways imply that early detection of this type of ovarian cancer in BRCA1 or BRCA2 mutation carriers may be even more difficult than in the general population [58]. Hermsen et al. found no difference in stage distribution between incident screen-detected and interval tumors in women with a BRCA mutation having annual CA125 [59]. The UK Familial Ovarian Cancer Screening Study has screened over 4000 women with >10% lifetime risk of ovarian cancer with 4 monthly CA125 using the ROCA. At this early stage of analysis, screening was associated with improved complete cytoreduction at surgery; however, further follow-up is needed to determine if this will translate to better survival [60]. Other trials are trying to affirm the benefits of the ROCA algorithm (GOG 199) [61]. GOG 199 has thus far yielded some preliminary results indicating that there is a multivariate association between ROCA and finding occult cancer at the time of prophylactic BSO.

Despite no firm evidence of benefit, a number of organizations in the USA recommend 6- or 12-month screening with CA125 levels and TVUS for women at inherited risk on the basis of expert opinion only.

There are no data that change the recommendation for RRSO; however, opinions vary regarding whether these preliminary findings at least justify screening in women who defer surgery for childbearing or other reasons.

### Chemoprevention

Oral contraceptives reduce the incidence of ovarian cancer in the general population [62]. A meta-analysis found that OCP halved the risk of ovarian cancer in BRCA1 or BRCA2 mutation carriers. They found no increase in the risk of breast cancer with use of the OCPs formulated after 1975 [63]. These data are reassuring for young women needing contraception but do not replace the recommendation for definitive surgical risk reduction at the appropriate age.

### Risk-reducing surgery

RRSO reduces the risk of ovarian cancer by at least 80% and breast cancer by 50% [64], although there is variation amongst studies suggesting that the risk reduction of ovarian cancer is much greater and the reduction in breast cancer risk may be less. National Comprehensive Cancer Network (NCCN) guidelines include recommendation/consideration of RRSO if there is a pathogenic mutation in BRCA1, BRCA2, BRIP1, RAD51C or RAD51D or any of the LS genes. RRSO is recommended for BRCA1 mutation carriers between the ages of 35 and 40 or when child bearing is complete. The option of delaying RRSO until age 40–45 in women with BRCA2 mutations may be considered because there appears to be a later average age of onset (approximately 8–10 years) than in women with BRCA1 mutation carriers.
and possibly even later in carriers of mutations in **BRIP1**, **RAD51C**, and **RAD51D**. It is important to review a multigeneration family history and note the ages of onset of ovarian cancer in the family and adjust this recommendation if there are women with early-onset disease. NCCN guidelines also review cancer risks and recommendations for men, particularly for those who carry a **BRCA2** mutation and thus are at significantly increased risk of prostate cancer. There are no specific guidelines regarding pancreatic cancer or melanoma, so screening needs to be individualized according to family history and other risk factors. We must also, however, recognize that as family sizes have decreased, extended pedigrees are often more difficult to obtain.

Risk-reducing surgery has demonstrated that between 3% and 8% of RRSO specimens have an occult malignancy [65–68]. The detection of occult cancers is dependent on the stringency of the pathologic assessment of the submitted tubes and ovaries. The sectioning and extensively examining the fimbriated end of the fallopian tube protocol identified many more occult cancers than expected and identified apparent premalignant areas in the fallopian tubes. This led to a new hypothesis regarding the origin of serous cancers of the ovary. Most occult cancers in the BRCA mutation carriers contain a premalignant component within the fimbriated end of the fallopian tube that many believe to be the site of origin of these hereditary cancers. A group from Harvard, led by Crum, characterized these lesions as STICs, and has suggested that most occult cancers have this premalignant component [69–72]. It is therefore critically important for the fallopian tubes and ovaries to be completely submitted as shown in Figure 6. Peritoneal lavage and cytology are also recommended at the time of RRSO.

The recognition of the fallopian origin of serous cancers has raised the question as to whether preventive salpingectomy might be adequate prophylaxis or at least a temporizing measure in women with a known BRCA mutation who wish to preserve ovarian function. There are no data comparing salpingectomy with RRSO with regard to cancer incidence. The GOG 199 study has identified primary cancers within the ovary without apparent tubal involvement; therefore, it is premature to adopt salpingectomy alone as “the” prophylactic procedure, and clearly more data are required to assess the utility of this notion [73].

**Figure 6.** SEE-FIM Protocol – the recommended method for sectioning specimens at risk-reducing salpingo-oophorectomy. Courtesy of Gynaecological Oncology Group.
Hysterectomy at the time of RRSO has been proposed in order to prevent tubal cancers arising in the intramural segment of the fallopian tube, to prevent endometrial cancer in case the woman requires Tamoxifen for breast cancer treatment, and to avoid progestin-containing HRT. However, cancer arising in the proximal tube is believed to be unlikely, and other options for the hormonal management of breast cancer exist. Concern does, however, remain regarding the potential to increase breast cancer risk if progestin-containing HRT is used, and this may prompt the consideration of hysterectomy. At this point, more data are required, particularly regarding the option of progestin-containing intrauterine devices in conjunction with systemic estrogen replacement as an alternative. The decision to add hysterectomy needs to be individualized in the context of gynecological and other issues.

Premature surgical menopause in the general population is associated with significant menopausal symptoms, increase in cardiovascular disease, dementia, osteoporosis, and overall mortality [74]. Rebbeck et al. [75] found that the decreased risk of breast cancer following RRSO was not significantly altered by the use of HRT. Therefore, consideration should be given to short-term hormone replacement, possibly until the age of expected natural menopause unless contraindicated due to cancer or other reasons. Women who have undergone RRSO should also have a regular assessment for modifiable risk factors for cardiovascular and bone diseases.

Management guidelines for the risk of gynecological cancer in Lynch syndrome

As noted previously for hereditary breast and ovarian cancer, multiple organizations published guidelines for genetic risk assessment and management guidelines for individuals with LS, including the NCCN.

The most recent version for LS, version 2.2015, outlines the following: colonoscopy should be initiated between the ages of 20 and 25 years and repeated every 1–2 years. For families with a case of colon cancer diagnosed prior to age 25, screening should begin 2–5 years younger than the youngest diagnosis. Prophylactic colectomy is not routine but may be recommended for individuals with significant repeat adenomatous polyp formation or for those who are unable to undergo regular surveillance. The incidence and mortality of colorectal cancers in this group were shown to be reduced by colonoscopy screening. Chemoprevention using aspirin to reduce the risk of colon cancer has been suggested, but data are still forthcoming and it is presently not the standard of care.

There is no clear evidence to support screening for endometrial cancer by annual pelvic examination and pelvic ultrasound, but annual endometrial sampling is an option. Similarly, screening for ovarian cancer by pelvic ultrasound and serum CA-125 are options. Six studies evaluating the effect of surveillance of ovarian cancer in LS reported that 7 of 22 (32%) ovarian cancers were found during surveillance, and 6 of the 7 (86%) were detected at an early stage. Conclusive benefits of screening for ovarian cancer in women at average and high risk have not been demonstrated; however, ovarian screening of women with LS may improve outcome and needs specific evaluation [76] as results from population-based screening programs or in women with BRCA1 or BRCA2 mutations may not apply in LS because these cancers may be biologically different to either group.

At this time, risk-reducing surgeries include hysterectomy and bilateral salpingo-oophorectomy followed by hormone replacement therapy and remain the recommendation for women with LS aged 40 years or after childbearing is completed, particularly if the patient is undergoing abdominal surgery for another reason.

Data are also limited regarding the efficacy of screening and prevention of other LS-associated cancers such as gastric, small bowel, pancreatic, kidney, and brain tumors and are based on individual risks. Breast cancer is not typically considered a LS-associated cancer, but there are reports of increased risks in some LS families. There are not enough data to presently recommend increased breast cancer screening in women with LS.

Although oral contraceptive pills reduce the incidence of ovarian cancer in the general population and in BRCA1 or BRCA2 mutation carriers, its effectiveness in LS is unknown.
Ovarian cancer treatment implications—Homologous recombination repair defect and its clinical consequences

Patients with BRCA1 or BRCA2 mutation-associated cancers tend to have longer survival than those with no identifiable germline mutations [3]. These cancers are more susceptible to chemotherapeutic agents that cause DNA damage, particularly platinum-based chemotherapy. Identification of germline BRCA mutations, and possibly other BRCA-FA DNA repair genes, is becoming relevant to treatment decisions. Homologous recombination involves the exchange of nucleotide sequences between two similar molecules of DNA. It is used by cells to repair harmful breaks that occur on both strands of DNA known as double-strand DNA breaks. Cancer cells with BRCA mutations have deficiencies in homologous recombination. When BRCA1 or BRCA2 is not functioning properly, other types of DNA repair mechanisms must compensate for the loss of homologous recombination.

Recently, drugs known as PARP inhibitors have been developed that exploit this deficiency by blocking an alternative repair pathway and are part of the armamentarium of growing so-called targeted therapies [77]. The addition of a PARP inhibitor may make these tumors even more sensitive to the traditional chemotherapeutic agents. The PARP inhibitor Olaparib manufactured by Astra Zeneca is now approved for relapsed ovarian cancer in BRCA1 or BRCA2 mutation carriers. Other PARP inhibitors are also undergoing further trials regarding efficacy, optimal dosage regimes, and their role in the treatment of sporadic tumors demonstrating somatic mutations in other genes in the HRR pathway. Other genetic defects that also affect DNA repair may need to be considered in the future when considering PARP inhibitor therapy. These related genes include but are not limited to RAD51C, RAD51D, BRIP1, PALB2, BARD1, and the mismatch repair genes [78]. Research is ongoing on predictors of sensitivity, including DNA-based assays based on the loss of heterozygosity. Because we can more cheaply and easily sequence the human genome with newer technologies, sequencing panels of genes or even the whole genome in either the tumor or the germline to determine optimal treatment is within reach.

As survival improves for patients with ovarian cancer, identification of a germline mutation can guide screening or prevention recommendations for the early detection or prevention of second primary cancers such as breast or colon cancer.

General guidelines for genetic testing for hereditary cancer risk

Genetic testing should always be initiated in an affected relative, if possible, to determine whether there is an identifiable mutation in one of the hereditary cancer genes. If the relative with cancer does not have a mutation, it may be appropriate to test another affected relative, in the event there is a mutation in the family and the first person tested is a phenocopy (someone who developed the same type of cancer by chance). If no mutation is identified in the affected relative, it is not appropriate to pursue genetic testing in the unaffected relative. The cancer family history should be used to guide recommendations for increased cancer screening and prevention because genetic testing is not informative. If an affected relative has a mutation, targeted mutation-specific testing can be offered to unaffected relatives.

It is important to always obtain both maternal and paternal cancer family history for any patient undergoing genetic testing to determine if there may be additional cancer risk from the other side of the family. It is important to confirm the parental origin of a mutation and not just assume that the mutation explains the family history. It is possible that more than one mutation is traveling in a family. When there is no confirmation of the lineage or presence of the mutation in other affected relatives, a multigene test may be appropriate.

Criteria for referral for hereditary cancer risk assessment and genetic testing continue to evolve. Referral to a genetic counselor for risk counseling and possible testing should not be limited to those with high-risk criteria. Some features may not be apparent at first glance in the patient’s history. Inaccurate histories are common; furthermore, as families become smaller, the accuracy of family history in predicting inherited disease becomes less. Referral to a counselor can occur at any time but immediately after or during treatment seems to be the most practical and common.
Genetic counseling in hereditary ovarian cancer

It is important to emphasize that hereditary cancer risk assessment is a process that

- includes assessment of risk, education, and counseling;
- is conducted by a physician, genetic counselor, or other provider with expertise in cancer genetics;
- may include genetic testing if desired after appropriate counseling and consent has been obtained.

Genetic testing for cancer predisposition requires informed consent that should include pretest education and counseling regarding the risks, benefits, and limitations of testing, including the implications of both positive and negative genetic test results. Pretest counseling should also include education on the limitations of current genetic testing technology including the risks of false negative results and the uncertainties associated with genetic variants of unknown clinical significance. Individuals considering genetic testing should be aware that the potential risks of genetic testing include psychological stress and changes to family dynamics. Risks may also include the potential for discrimination in health insurance or employment in the USA, but there is little evidence that this has occurred to date [79,80]. In addition, although legal protection against discrimination is not absolute, the Health Insurance and Portability and Accountability Act of 1996 did prohibit a genetic test result in the absence of symptoms from being classified as a pre-existing condition. The potential for genetic testing to adversely affect the ability to obtain insurance products will vary according to local regulations.

Genetic counseling should also consider the personal circumstances of the individual, including preexisting psychosocial issues and the cultural and community context. All these factors may influence decision-making and adherence to screening and risk management recommendations.

A distinction should be made between mutation searching in an affected individual based on their family history, phenotypic features, or tumor characteristics and predictive testing of unaffected relatives for a known mutation. Both psychosocial and insurance implications vary between these settings, and counseling should be tailored accordingly. The uptake of genetic testing has been shown to be strongly influenced by psychosocial factors [81]. There is a general tendency for women to overestimate their risk of breast and ovarian cancer, particularly those with a family history. High anxiety regarding cancer risk is associated with both over and under screening; however, genetic counseling improves the accuracy of risk perception [82].

Women identified with a cancer predisposition mutation face the challenge of relaying this information to at-risk relatives, often at a time when they themselves are under stress related to their diagnosis. De novo mutations (new spontaneous mutations) in BRCA1 or BRCA2 or the mismatch repair genes are exceedingly rare, so at-risk relatives may include a parent and their extended relatives, siblings, and offspring. Genetic counselors have a role in facilitating family communication, balancing the rights of the individual to privacy and autonomy against the rights of the relatives to know important health-related information.

Despite initial concerns about the psychological impact of genetic testing results, most studies conducted over many years have shown low levels of distress, particularly in the long term [83]. These reassuring findings and the need for expedited genetic testing results to facilitate treatment decisions such as bilateral mastectomy instead of breast conservation, choices of chemotherapy, or participation in clinical trials have led to a need for more genetic testing soon after diagnosis by nongenetic clinicians [84].

Testing for BRCA1 and BRCA2 mutations is limited to adults over the age of 18 as the results will not alter the health care of a minor but has the potential for harm and denies the child the autonomy of deciding if and when to be tested. Testing for LS is also typically reserved for those over the age of 18; however, in families where there is particularly early onset of disease, testing may influence decisions regarding screening and so may be advised at a younger age.

Carriers of pathogenic mutations who are planning a pregnancy should be made aware of options for prenatal diagnosis and preimplantation genetic diagnosis (PGD) [85]. Although prenatal diagnosis followed by termination of pregnancy for an otherwise healthy embryo is rarely considered for
embryos at risk of carrying a BRCA mutation, PGD is being used where either the mother or father carries a BRCA mutation. The current practice is to test several cells from day 5 blastocysts obtained through IVF for the BRCA mutation. Mutation-negative embryos are frozen and implanted as requested by the couple. Unlike other conditions for which PGD is used, BRCA mutations do not cause serious illness in children but increase the risk of predominantly female adult-onset cancers, which are potentially avoidable through timely surgery. Consequently, the ethics of using this technology for BRCA mutations are debated.

When there is an Ashkenazi Jewish ancestry or a family history of breast and ovarian cancer, cancer family history should be obtained for the individual’s partners and genetic testing should be considered. If both parents carry a BRCA2 mutation, there is risk for a rare autosomal recessive disorder called Fanconi anemia in the offspring.

**Laboratory methods for testing**

Genetic testing for BRCA1 and BRCA2 has significantly changed since 1996; the initial testing only included automated fluorescence-based sequencing using methods first described by Sanger for BRCA1 and BRCA2. This testing was later updated to include the addition of large rearrangement testing for both genes. Individuals who underwent genetic testing for BRCA1 and BRCA2 some time ago may benefit from updated genetic testing if no mutations were identified.

Recently, genetic testing has undergone rapid changes. Massively parallel sequencing, also known as next-generation sequencing (NGS), allows for the rapid testing of large amounts of DNA sequence. NGS is quicker and less expensive than previous genetic testing tools. It is becoming routine to order a single test that simultaneously evaluates panels of multiple genes. The Supreme Court Decision in June 2013, overturning the ruling on allowing gene patents, particularly BRCA1 and BRCA2, brought an immediate change in the availability of multigene panel testing through commercial laboratories. These panels may be specific for a particular tumor type or may cover a broad range of hereditary cancer genes. NGS is also used in research studies and may include whole exome or genome sequencing. Depending on location and insurance, these tests may be part of routine clinical care, performed through research, or be at the patient’s own cost.

Panel testing or exome/genome sequencing requires additional pretest counseling as it has the potential to identify disease-causing mutations, which have been unsuspected on the clinical history. Not all genes covered in such panels have clear risk association and guidelines for clinical care of affected and unaffected carriers of mutations. This creates a clinical conundrum where patients may receive test results of a mutation in a gene for which expert recommendations are limited or nonexistent, placing providers in a challenging position to develop a prevention plan. In addition, the reported associations may be mutation-specific and not applicable to all mutations. Even more difficult, patients may receive an indeterminate result if a variant whose significance is unclear is identified. For patients and providers, this presents a potentially frustrating situation as risks cannot be quantified, leaving patients and relatives with even greater uncertainty than they may have had before testing. Results are further complicated by the fact that more the number of genes that are tested, the greater the possibility of identifying a variant of uncertain significance, causing confusion for clinicians and patients alike. The advantages and disadvantages of panel testing have been extensively reviewed [86]. Conversely, although a provider may be clinically most focused on only one or a few genes, the relative advantage of a panel test is the ability to examine multiple common and rare causes of cancer risk at the time of first presentation for testing rather than requiring patients to return for additional testing and counseling for successive tests. Finally, it is important for patients and providers to recognize that diagnostic genetic testing is constantly evolving as technologies become more powerful and incorporate more clinically relevant genes.

**Summary**

The recognition of a hereditary cancer syndrome has the potential for proven benefits with regard to treatment, early diagnosis, and prevention of future cancers for the patient with ovarian cancer and her relatives. Guidelines are available to assist in determining which patients should be referred for
further assessment, who should undergo genetic testing, and how to manage those individuals with a demonstrated mutation. Advances in technology mean that genetic testing is cheaper, quicker, and covers many more genes. However, caution needs to be exercised in using results to determine care that is not yet supported by robust data.

RRSO remains the mainstay of management for women at increased risk of ovarian cancer, with careful examination of pathology specimens, short-term use of hormone replacement therapy, and long-term follow-up for evidence of bone or cardiovascular disease.

Practice points

- Approximately 14% of EOCs are due to inherited mutations.
- BRCA1, BRCA2, and the mismatch repair genes account for the majority of hereditary ovarian cancer, usually HGSOC, with clinical implications of several other genes being evaluated.
- Mutations in these genes can be either paternally or maternally transmitted, so an extensive family history on both sides is critical for accurate assessment.
- Mutation carriers may benefit from newly developed PARP inhibitors.
- Ovarian screening has not been proven to improve outcome, so RRSO with careful pathological examination of the specimen is the key recommendation.
- Mutation carriers should be counseled regarding screening, chemoprevention, risk-reducing surgery, and implications for children and future childbearing including PGD.
- Although panel testing for multiple genes may have advantages, caution must be exercised as the clinical implications of mutations in many genes available for testing remain unclear, and there is the potential to identify an increased risk of other unrelated conditions or variants of uncertain significance.

Research agenda

- The role and management of other genes in familial ovarian cancer
- Improved early detection for serous ovarian cancer
- The effectiveness of salpingectomy with delayed oophorectomy

Conflict of interest

The authors declare no conflicts of interest.

References


