Chapter 7
Risk Assessment and Prevention Strategies for Hereditary Gynecological Cancers

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Abstract A variety of hereditary cancer syndromes contribute to the development of gynecological cancers. These syndromes are caused due to germline pathogenic variants (GPVs) in tumor supressor genes or DNA repair genes. With the increasing use of genomic sequencing in clinical practice, the number of individuals diagnosed with GPVs in genes associated with hereditary cancer syndromes is increasing. Hereditary cancer syndromes differ in the types of cancer susceptible to develop, the risk of developing certain cancer, cancer treatment strategies, and possible cancer preventive strategies, depending on the gene responsible for the syndrome. Thus, physicians involved in the management of gynecological cancers perform accurate genetic risk assessments based on accurate knowledge about each syndrome and provide proper medical intervention to prevent developing cancer or to detect cancers in their early stage. Genetic risk assessments also helps in the selection of appropriate fertility preservation methods and treatment strategies for hormonal imbalances in women. Knowledge about significance and accuracy of various genetic tests may be helpful in interpreting the results of the test and in determining the appropriate medical interventions. Here, we reviewed mechanisms of cancer development and clinical features of hereditary gynecological cancers, as well as genetic risk assessment and cancer prevention strategies for those syndromes.

Keywords Hereditary gynecological cancers · Tumor suppressor genes · Loss of heterozygosity · Autosomal dominant inheritance · Genetic risk assessment · Genetic testing · Surveillance for cancer · Risk-reducing surgery

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7.1 Introduction

All cancers develop as a result of mutations in certain genes, such as those involved in the regulation of cell growth and/or DNA repair [1, 2]. Mutations can be classified into two types: germline mutations (recently described as germline variants) and somatic mutations. Germline variants can be passed on to the next generation and may be shared among relatives. Variants associated with certain diseases are defined as germline pathogenic variants. Some germline variants are the causes of hereditary cancer syndrome, which is defined as "a type of inherited disorder in which there is a higher-than-normal risk of certain types of cancer" according to the National Cancer Institute. Most hereditary cancer syndromes exhibit autosomal dominant inheritance, and the responsible genes are mostly tumor suppressor genes. By contrast, somatic mutations are acquired in somatic cells during their lifespan and are restricted to the individual in whom they occur.

RB1 is the first human tumor suppressor gene to be described; it plays an integral role in the development of retinoblastoma. In 1993, the 180-kb genomic region encoding the RB1 transcript was sequenced; at the time, this was the longest stretch of human DNA sequence [3]. In the early 1990s, a number of tumor suppressor genes responsible for hereditary gynecological cancers were identified including *BRCA1*, *BRCA2*, *MLH1*, *MSH2*, *MSH6*, and *PMS2* [4–9]. *BRCA1/2* are most common causes of hereditary breast and ovarian cancers; *MLH1*, *MSH2*, *MSH6*, and *PMS2*, which are generally referred to as mismatch repair (MMR) genes, are responsible for Lynch syndrome. To date, more than 50 hereditary cancer syndromes have been described, and the responsible genes have been cloned.

Germline pathogenic/likely pathogenic variants (GPVs) were found in 8% of 10,389 adult cancer patients across 33 cancer types in the TCGA cohort [10]. The frequency of GPVs varied greatly among cancer types. In gynecological cancer, the prevalence rates of GPVs were 19.9% in ovarian serous cystadenocarcinoma, and 6.8% in uterine endometrial cancer (EC), and 6.6% in cervical cancer. The highest rate was observed in pheochromocytoma and paraganglioma (22.9%) followed by ovarian serous cystadenocarcinoma. Although not all of the GPVs identified were associated with the development of cancer that each individual was currently suffering from, the associations between *BRCA1/2* GPVs and ovarian cancer, *MSH6* and *PTEN* GPVs and EC were identified in this study.

This chapter summarizes the molecular mechanisms, clinical features, genetic risk assessment, and prevention strategies for hereditary gynecological cancers presented in Table 7.1.

Table 7.1 Molecular and clinical features of hereditary gynecological cancers

Syndrome	Responsible genes	Related gynecological cancers	Common histological subtypes	Other nongynecological tumors
BRCA-related breast/ovarian cancer syndrome	*BRCA1*, *BRCA2*	Ovarian cancer	Serous non-mutinous	Breast cancer, prostate cancer, pancreatic cancer
Lynch syndrome	*MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM*	Endometrial cancer	Endometrioid non-serous	Colorectal cancer, gastric cancer, small bowel cancer, urothelial cancer, pancreatic cancer
		Ovarian cancer	Endometrioid	
PTEN hamartoma tumor syndrome (Cowden syndrome)	*PTEN*	Endometrial cancer		Breast cancer, pancreatic cancer, colorectal cancer, gastric cancer, small bowel cancer, thyroid cancer
Peutz-Jeghers syndrome	*STK11*	Non-epithelial ovarian tumor	Sex cord tumor with annular tubules	Breast cancer, pancreatic cancer, colorectal cancer, gastric cancer, small bowel cancer
		Cervical cancer	Gastric type mucinous carcinoma, LEGH	
DICER1 syndrome	*DICER1*	Non-epithelial ovarian tumor	Sertoli-Leydig cell tumor	Pleuropulmonary blastoma, pulmonary cysts, thyroid gland neoplasia, cystic nephroma
		Cervical tumor	Embryonal rhabdomyosarcoma of the cervix	
Rhabdoid tumor predisposition syndrome	*SMARCA4*	Non-epithelial ovarian tumor	Hypercalcemic type of small cell carcinomas	Rhabdoid tumors of central nervous system, renal rhabdoid tumors
Other cancer-susceptible genes	*RAD51C*, *RAD51D*	Ovarian cancer		Breast cancer
	BRIP1			Unknown
	ATM			Breast cancer, pancreatic cancer
	PALB2			Breast cancer, pancreatic cancer

7.2 Biological Impacts of the Germline Variants in Hereditary Cancer

Cancer driver genes are classified as oncogenes or tumor suppressor genes, depending on whether their activation or inactivation contributes to cancer development. Although a single mutation in an oncogene can be sufficient for tumorigenesis, inactivation of both alleles of a tumor suppressor gene is often required.

In 1971, Alfred Knudson proposed the “two-mutation hypothesis” (now known as the two-hit theory), which states that in familial retinoblastoma cases, individuals

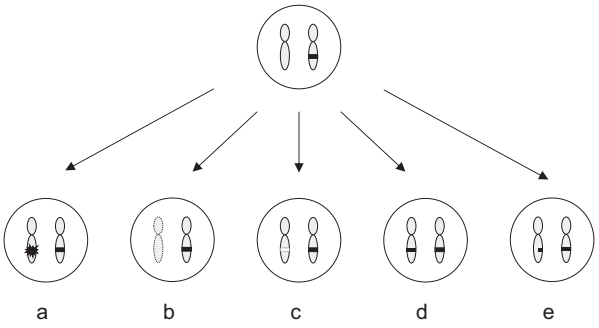

Fig. 7.1 Various events account for the second hit in a cell with a pathogenic germline variant. (**a**) De novo mutation of the wild-type allele. (**b–d**) Three mechanisms of LOH: chromosomal loss, gene deletion, and somatic recombination (copy neutral LOH). Copy neutral LOH is a special case of LOH in which the wild-type allele is replaced with a mutant allele. (**e**) Promoter methylation of the wild-type allele. *LOH* loss of heterozygosity

possess one mutant RB allele due to an inherited or de novo germline mutation in the RB gene (first hit), and when a retina cell acquires a somatic mutation in the remaining wild-type allele (second hit), the cell will be transformed into a retinoblastoma cell [11]. The second hit described by Knudson could be accounted for via alternative molecular events, such as deletion of the wild-type allele, which is referred to as loss of heterozygosity (LOH), or DNA methylation changes in the wild-type allele (Fig. 7.1).

Although the patterns of somatic second-hit events differ depending on the tissue and genes, LOH is thought to be the most common second-hit event. LOH for the wild-type allele was reported in 92–100% and 70–76% of patients with germline *BRCA1* and *BRCA2* truncating variants in ovarian cancer [12, 13]. LOH events occurred more rarely in patients with germline missense variants of *BRCA1* and *BRCA2* than those with truncating variants, with a rate of 11% [13]. Cooperation between germline variants and somatically acquired alterations within not only the same gene but also different genes has been recently described in several tumor localizations [13]. In MMR gene-related cancer, LOH occurred in almost half of the patients with GPVs in MMR genes [14, 15]. Somatic single nucleotide variants were reported as the second most common mechanism of two-hit inactivation of MMR genes [14]. Another second-hit event, promoter methylation in *MLH1*, has been reported in colorectal cancer and ECs with *MLH1* GPVs [15, 16].

Although the two-hit theory is a clear model for explaining the contribution of tumor suppressor genes in tumorigenesis, even partial inactivation of tumor suppressor genes can also critically contribute to tumorigenesis [17]. In some tumor suppressor genes, a single copy of the wild-type allele is not enough to provide sufficient gene function, and thus called haploinsufficiency. Tumors in patients with Li-Fraumeni syndrome, which is caused by *TP53* GPVs, do not always exhibit loss of the wild-type *TP53* allele, suggesting that haploinsufficiency of *TP53* may be sufficient for tumor initiation [18]. *BRCA1/2* also show haploinsufficiency. Microscopically normal tissues in carriers of *BRCA1/2* GPVs have altered mRNA profiles compared with *BRCA* wild-type cells, suggesting an impact of one-hit

events on tumorigenesis [19]. In addition, single-copy mutation of a tumor suppressor gene sometimes interferes with the function of the wild-type gene product, which is described as a dominant negative mutation. Certain missense variants in *ATM* have been reported to act in a dominant-negative manner to increase breast cancer risk, relative to truncating mutations [20–23].

7.3 Hereditary Gynecological Cancers

Gynecological cancers often overlap with hereditary cancer syndromes, therefore, gynecologists need to have a proper insight into hereditary cancer syndromes. The prevalence of GPVs in gynecological cancers and breast cancer is shown in Fig. 7.2. The frequency of GPVs in breast cancer patients was 9.9% [10]. About 10–20% of epithelial ovarian cancer patients are estimated to have GPVs in ovarian cancer susceptibility genes [24–26]. Some genes are associated with the development of non-epithelial ovarian cancer. About 5–10% of EC patients are estimated to have GPVs in EC-related genes [27–29]. Cervical cancer is in most cases caused by the human papillomavirus, and is thus very unlikely to be hereditary. To date, two types

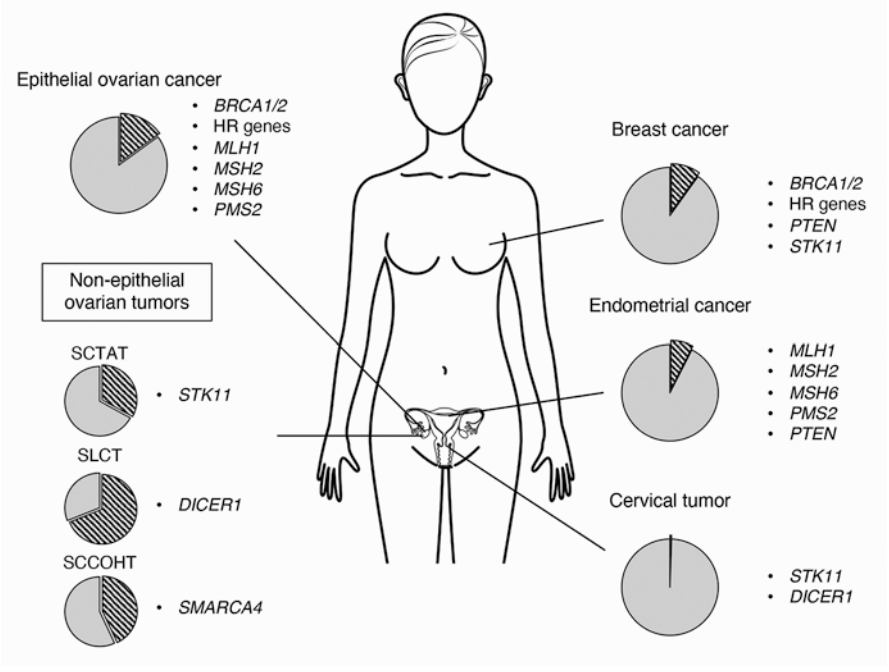

Fig. 7.2 Prevalence of GPVs in breast, ovarian, endometrial and cervical cancers/tumors. The shaded area in the pie chart represents the probability of detecting GPVs in cancer susceptibility genes. Genes in which GPVs are commonly detected are listed on the right side of the pie chart. *GPV* germline pathogenic/likely pathogenic variants, *HR genes* genes involved in homologous recombination repair pathway; *ATM*, *BRIP1*, *PALB2*, *RAD51C*, *RAD51D*, etc.

of cervical cancer have been reported to be associated with hereditary tumors. This section outlines the typical gynecological hereditary cancers shown in Table 7.1.

7.3.1 BRCA-*Related Breast/Ovarian Cancer Syndrome (Hereditary Breast and Ovarian Cancer: HBOC)*

GPVs in *BRCA1/2* are associated with susceptibility to breast, ovarian, prostate, and pancreatic cancers. *BRCA1* and *BRCA2* are located on chromosome 17q21 and 13q12, respectively, and both genes encode proteins involved in DNA repair damage via the homologous recombination repair pathway and serve as tumor suppressors. The cumulative risks of developing breast and ovarian cancers by the age of 80 years are 72% and 44% for women with GPVs in *BRCA1*, 69% and 17% for those with GPVs in *BRCA2*, respectively [30].

GPVs in *BRCA1/2* are responsible for at least 10% of epithelial ovarian cancers [24, 31, 32]. Ovarian cancer in the context of *BRCA1/2* GPVs is characterized by a high proportion of serous carcinoma, advanced disease stage, and younger disease onset [24, 31–34].

It remains unknown whether *BRCA1/2* GPVs are associated with an increased risk of EC or not. A precious prospective cohort study showed a slightly increased risk of EC in a median follow-up of 5.7 years, with a standardized incidence ratio (SIR) of 1.91 (95% confidence interval [CI]: 1.06–3.19) for *BRCA1* carriers and 1.75 (95% CI: 0.55–4.23) for *BRCA2* carriers, which was not statistically significant [35]. In this study, tamoxifen use was identified as the most relevant risk factor for EC. Tamoxifen use significantly increased the SIR in *BRCA1* carriers from 1.91 to 4.43 (95% CI: 1.94–8.76), whereas in *BRCA2* carriers the association was not statistically significant (SIR = 2.29, 95% CI: 0.38–7.59). In another study including 1083 *BRCA1/2* carriers who underwent risk-reducing salpingo-oophorectomy (RRSO) without hysterectomy, the risk of developing EC did not increase within a median follow-up of 5.1 years [36]. However, of the eight incident uterine cancers observed, five were serous/serous-like and four of the five occurred in *BRCA1* carriers, indicating increased risk for serous/serous-like EC in *BRCA1* carriers.

7.3.2 *Lynch Syndrome*

Lynch syndrome (LS) is a hereditary cancer syndrome caused by GPVs in DNA mismatch repair (MMR) genes such as *MLH1*, *MSH2*, *MSH6*, and *PMS2* [37]. Additionally, deletion of the last exon of *EPCAM*, which is located upstream of *MSH2*, also causes LS through hypermethylation of the *MSH2* promoter and subsequent MSH2 silencing [38].

Individuals with LS are at a heightened risk of developing several types of cancers, which vary based on the affected MMR genes and age. An international, multicenter prospective observational study including 6350 participants with GPVs in

MMR genes showed that the cumulative risks of developing ECs by the age of 75 years were 37.0% for *MLH1*, 48.9% for *MSH2*, 41.1% for *MSH6*, and 12.8% for *PMS2* carriers [39]. For ovarian cancer, the cumulative risks were 11.0% for *MLH1*, 17.4% for *MSH2*, 10.8% for *MSH6*, and 3.0% for *PMS2* carriers.

Gynecological cancers in the context of LS are mainly EC and characterized by a younger disease onset [40–42]. The prevalence rates of LS have been reported to be 5.8–7.2% in EC patients [28, 29], and 0.4–3% in epithelial ovarian cancer patients [24, 43, 44]. Synchronous endometrial and ovarian cancers were reported in 21.6% of LS-associated EC patients and also in LS-associated ovarian cancer patients [40, 45]. In 81.4% of individuals with LS, EC was first cancer in that individuals. The lower uterine segment was involved in 25% of LS-associated EC patients [40].

7.3.3 PTEN Hamartoma Tumor Syndrome (Cowden Syndrome)

PTEN hamartoma tumor syndrome is a multiple hamartoma syndrome frequently associated with GPVs in *PTEN* [46]. *PTEN*, located on chromosome 10q23, encodes a phosphatase involved in cell signaling pathways that affect cell proliferation and survival.

Hamartomas are benign tumors that result from overgrowth of normal tissues. Multiple hamartomas occurring in various organs are a common manifestation of this syndrome. Individuals with this syndrome often exhibit other characteristic features, such as macrocephaly and multiple mucocutaneous lesions, therefore, most patients would be clinically diagnosed.

This syndrome is also associated with an increased risk of developing several types of cancer, including breast, endometrial, thyroid, and colorectal cancer. Among all, breast cancer is the most common type of cancer in patients with this syndrome, with a lifetime risk of up to 85% [47]. The lifetime risk of developing EC is estimated to be 28%, with the risk beginning to increase at the age of 25 years and rising to 30% by the age of 60 years [28, 47].

7.3.4 Peutz-Jeghers Syndrome

Peutz-Jeghers syndrome (PJS) is characterized by multiple hamartoma polyps in the gastrointestinal tract, pigmentation of the skin mucosa as well as increased susceptibility to cancer in the gastrointestinal tract, uterine cervix, testes, ovary, and breast [48, 49]. Most of the PJS cases are due to GPVs in the *STK11* (*LKB1*) gene [50, 51]. *STK11*, located on chromosome 19p13, encodes a serine-threonine kinase involved in cell polarity, metabolism, and growth.

Gynecological tumors associated with PJS are sex cord tumor with annular tubules (SCTAT) of ovary and cervical gastric type mucinous carcinoma of the endocervix (G-ECA). The lifetime risks of developing SCTAT and G-ECA was

reported to be 21% and 10%, respectively, with the average ages at diagnosis of 28 years for SCTAT and 34–40 years for G-ECA [49, 52]. Among all patients with ovarian SCTAT, approximately one-third have PJS [53]. PJS-related G-ECAs are extremely well-differentiated forms of G-ECA known as adenoma malignum or minimal deviation adenocarcinoma (MDA). Among patients with MDA, 11–17% have PJS [54, 55]. Although lobular endocervical glandular hyperplasia (LEGH) is a basically benign gastric type mucinous lesion of cervix, LEGH with atypia could be a precursor of MDA [56]. The first case of LEGH in a patient with a *STK11* GPV who was diagnosed PJS was reported in 2012 [57]. Since then, a few case reports have shown that LEGH can be associated with PJS [58–60].

7.3.5 DICER1 Syndrome

DICER1 syndrome is characterized by pediatric pleuropulmonary blastoma, nodular hyperplasia of the thyroid, cystic nephroma, Sertoli-Leydig cell tumors of the ovary (SLCT), and other rare types of tumors [61, 62]. This syndrome is caused by GPVs in *DICER1*, located on chromosome 14q32, which encodes an RNase III endonuclease involved in posttranscriptional gene expression by modulating microRNAs [63, 64]. In most cases, biallelic variants in *DICER1* have been detected in tumors: usually a loss-of-function GPV in one allele and a tumor-specific somatic hotspot variant in the second allele [65]. Monoallelic loss of *DICER1* can promote tumorigenesis, indicating its haplo-insufficient function as a tumor suppressor gene [66].

The lifetime risk of developing SLCTs was estimated to be 21.2% with the average age at diagnosis of 16.9 years [67, 68]. In SLCT patients, *DICER1* GPVs were identified in 18 of 26 patients (69%) [69].

Embryonal rhabdomyosarcoma of the cervix (cERMs) is a rare type of tumor that occurs in older children, adolescents and young adults with a median age of 13–14 years [70]. The association between cERMs and SLCT was later reported in a cohort of 14 patients [71]. Although the lifetime risk of developing cERMs in *DICER1* carriers has not been reported, most of the cERMs (18 of 19 patients, 95%) were reported to have *DICER1* mutations, 50% of which were of germline origin (6 of 12 patients tested) [72].

7.3.6 Rhabdoid Tumor Predisposition Syndrome

SMARCA4, located on chromosome 19p13, is a chromatin remodeling gene and encodes BRG1. Recently, biallelic inactivation of *SMARCA4* and the consequent complete loss of BRG1 protein have been identified as molecular event defining small cell carcinoma of the ovary, hypercalcemic type (SCCOHT) [73–75].

SMARCA4 GPVs were identified in 43% of SCCOHT patients (26/60), with significantly younger age at diagnosis than those without GPVs [76]. *SMARCA4*

carriers also develop rhabdoid tumors involving the central nervous system or kidneys [77]. Since the incidence of GPVs is high, the International SCCOHT Consortium recommends referral of all patients with SCCOHT to a clinical genetics service and offering genetic tests for *SMARCA4* GPVs [78].

7.3.7 Other Cancer-Susceptible Genes

Recently, several genes that are involved in the development of hereditary ovarian cancers have been identified. Compared with *BRCA1/2* and MMR genes, the penetrance of these genes is lower, but not negligible. Among these genes, *ATM*, *BRIP1*, *PALB2*, *RAD51C*, and *RAD51D* are involved in the homologous recombination repair pathway as well as *BRCA1/2*.

ATM GPVs were found in 0.64–0.87% of ovarian cancer patients, which was significantly greater than the 0.1% frequency in healthy controls [79]. *ATM* GPVs were estimated to slightly increase the risk of developing ovarian cancer [80].

BRIP1 GPVs were found in about 1% of ovarian cancer patients [24, 25]. A previous large case control study showed that *BRIP1* is associated with an increased risk of developing ovarian cancer, especially high-grade serous ovarian cancer, with a relative risk of 14.09 (95% CI, 4.04–45.02, $p < 0.001$). In *BRIP1* carriers, the cumulative lifetime risk of developing ovarian cancer by the age of 80 years was estimated to be 5.8% [81].

PALB2 GPVs were found in about 0.38–0.62% of ovarian cancer patients [24, 25]. Whether *PALB2* GPVs increase the risk of developing ovarian cancer remains unknown. Although two previous studies demonstrated an association, three other studies did not show a statistically significant association between *PALB2* GPVs and increased ovarian cancer risk [24, 81–84].

RAD51C and *RAD51D* GPVs were found in about 0.5% of ovarian cancer patients respectively [24, 25]. Previous case control studies identified an association between *RAD51C* and *RAD51D* GPVs and increased ovarian cancer risk, with odds ratios of 3.4–5.2 and 4.78–12.0, respectively [24, 83, 85].

7.4 Genetic Risk Assessment

The typical clinical features of hereditary cancers are as follows: (1) younger age of onset, (2) accumulation of certain types of cancers in the family members, (3) presence of multiple types of cancer in one person, and (4) occurrence of cancer in both paired organs. The purpose of genetic risk assessment is to identify the individuals who may be at risk of hereditary cancer syndromes and may benefit from genetic testing, additional screening, or preventive medical interventions. In many cases, gynecologists will play an important role in the identification and referral of women at risk for these conditions. In this section, we will summarize the clues for evaluating the personal risk of hereditary cancer syndromes.

7.4.1 Personal and Family History of Cancer

Collecting a detailed personal and family history is the first step in genetic risk assessment. Accurate genetic risk assessment requires, at a minimum, family history of first- and second-, and hopefully third-degree relatives of both maternal and paternal sides. Personal and family history will change over time; therefore, clinicians are required to update the data. History of cancer should be collected, including age at diagnosis, subtype, pathology, and laterality of the disease. Surgical history, such as salpingo-oophorectomy for benign ovarian tumors or total hysterectomy for uterine myomas, is an important information since these may serve as risk-reducing surgeries for ovarian or endometrial cancers. Hormonal therapy history, the use of oral contraceptive, carcinogen exposure history, and ethnic background can also influence the results of genetic risk assessment.

To identify candidates for genetic services, clinicians can use published categorical guidelines available through professional organizations [86–90]. In addition, some models are provided to predict the probability that an individual has GPVs in *BRCA1/2* or any of the MMR genes. These include the BRCAPRO and BOADICEA models in *BRCA1/2* and the PREMM5, MMRpredict, and MMRpro for MMR genes [91–95]. Because each model is developed based on a study of a certain population, the use of these models is appropriate only when the patient's characteristics and family history are similar to those of the study population. Ethnicity, the histology of cancer, and laterality of cancer can influence the accuracy of the models [96–100]. In addition, BRCAPRO was insufficient to predict *BRCA1/2* GPVs in ovarian cancer patients [101].

7.4.2 Characteristic Physical Findings Other than Cancer

Some hereditary cancer syndromes are accompanied by distinctive clinical findings other than the development of certain cancers. Detection of trichilemmomas or oral mucosal papillomatosis on dermatologic examination, macrocephaly on measurement of head circumference, and multinodular goiter on thyroid palpation can be helpful in the diagnosis of PTEN hamartoma tumor syndrome (Cowden syndrome). In addition, hamartomas or esophageal glycogenic acanthoses can be detected incidentally during gastrointestinal endoscopy.

Hyperpigmentation of the mouth, lips, nose, eyes, genitalia, or fingers on inspection, or hamartomatous polyps of the gastrointestinal tract on endoscopy can be helpful in the diagnosis of PJS.

7.4.3 Result of Prior Genetic Tests in Family

The results of prior genetic tests of other family members would be helpful for the assessment. If a GPV has already been identified in other family members, searching only for the same location in the gene can be a reasonable and cost-effective

diagnostic approach. However, more than one GPV may be present in a single family; thus, broader testing should be considered if multiple GPVs are suspected.

Pharmacogenetic tests, such as microsatellite instability (MSI) testing of tumor tissue, tumor testing for homologous recombination deficiency (HRD), or tumor clinical sequencing, could reveal the possibility of hereditary cancers. LS was identified in 16.3% of patients with MSI-high tumors [102]. BRCA1/2 play central roles in the homologous recombination pathway; thus, the HRD status indicates the possibility of *BRCA1/2* GPVs. GPVs of other genes involved in the homologous recombination pathway may cause HRD. Mutations found in clinical tumor sequencing could be of germline origin; therefore, offering opportunity to take the confirmation tests should be considered [103].

These results should be obtained from laboratories certificated for genetic testing. Recently, the genetic test results obtained through direct-to-consumer (DTC) services have been increasing. DTC genetic testing can be performed directly by an individual because DNA sampling from oral mucosa or hair is easily performed as it does not require for special equipment and is usually less expensive than clinical genetic testing. Given the limited testing methods and the higher rate of false-positive and false-negative results compared with clinical genetic testing, the results of DTC genetic testing should be re-evaluated by experts in genetics [104].

7.4.4 Clinical use of Multigene Panel Testing

Historically, genetic testing for cancer patients has been conducted by first inferring the most likely hereditary cancer syndromes based on genetic risk assessment, and then testing for the single genes associated with these syndromes.

Genetic risk assessment plays an important role in the identification of individuals at risk of hereditary cancer syndrome, however, multiple factors may influence the accuracy of assessment. These factors include small family size, unknown family history, early deaths, and de novo pathogenic variants. In addition, with the rapid advances in sequencing technology, a number of genes with low to moderate cancer susceptibility have been identified. This variability in the penetrance of pathogenic variants may influence the risk assessment as well as the patterns of inheritance and mosaicism.

Moreover, several studies have reported that GPVs in cancer predisposition genes were identified not only in those who met the previous National Comprehensive Cancer Network (NCCN) testing criteria based on the genetic risk assessment but also in those who did not meet the criteria [105, 106]. Another retrospective analysis showed that only 18.9% of positive results in genetic test were consistent with the suspected syndromes and associated genes [107].

Now, next generation sequencing technology has enabled the simultaneous testing of a set of genes at low cost, that is, a multigene panel testing (MGPT). The

introduction of MGPT should increase the number of individuals diagnosed with GPVs in hereditary cancer-associated genes that cannot be identified by conventional single gene tests. Indeed, in clinical settings, with growing evidence showing that certain genes other than *BRCA1/2* confer an increased risk of cancer predisposition, MGPT replaced the *BRCA1/2*-only tests in 2014 [108]. In 2020, the NCCN guidelines underwent a major paradigm shift by changing the description to consider MGPT first among genetic tests.

As mentioned above, MGPT is a useful and cost-effective tool for diagnosing hereditary cancer syndromes. However, for many of genes with low to moderate cancer susceptibility, only limited data are available on the degree of cancer risk, and no clear guidelines on risk management have been established. Therefore, medical intervention for individuals with GPVs in these genes should be considered based on the results of genetic risk assessment; genetic risk assessment remains important in management of hereditary cancer syndromes.

7.5 Cancer Prevention Strategies for Hereditary Cancer Syndromes

Individuals who are presumed to be at risk of hereditary cancer syndromes or who are concerned about these syndromes should be provided with the opportunity to receive genetic counseling prior to making any decisions regarding genetic testing. Genetic counseling has been defined as "the process of helping people understand and adapt to the medical, psychological, and familial implications of genetic contributions to disease" [109]. Through this process, individuals will be informed about the genes they may be tested, possible results and medical management associated with the results, and the implications of genetic testing for other family members. The benefits, risks, and limitations of genetic testing should also be discussed. This process facilitates informed decision-making and adaptation to the results of genetic testing.

Genetic testing is not always necessary for individuals who have already been diagnosed with certain hereditary cancer syndromes according to the clinical diagnostic criteria, as in most of such cases, the results of the test will not change medical management. Though, if a GPV was identified in the individual diagnosed with the disease, this information can also be used for genetic testing in other family members and can help predicting the inheritance manner. As such, identified genetic information can be information that can be of medical or psychological benefit to family members. The results of genetic testing should be carefully evaluated and disclosed to individuals along with the medical management options that could be offered to them. In this section, the recommended cancer risk management based on the genetic test results are summarized (Table 7.2).

Table 7.2 Prevention strategies for hereditary gynecological tumors

Gene	Gynecological organs	Screening[a]	Risk-reducing surgery	Other options
BRCA1, BRCA2	Ovary	Consider serum CA125 and TVUS	Recommend salpingo-oophorectomy	Oral contraceptives
MLH1, MSH2, MSH6, PMS2, EPCAM	Endometrial	Consider endometrial biopsy and TVUS	Consider hysterectomy	
	Ovary	Consider serum CA125 and TVUS	*MLH1*, *MSH2, EPCAM*: Consider salpingo-oophorectomy *MSH6*, *PMS2*: Insufficient evidence to recommend	
PTEN	Endometrial	Consider endometrial biopsy and TVUS	Discuss option of hysterectomy	
STK11	Cervix/Ovary	Annual pelvic exam with annual pelvic ultrasound and pap smear Endometrial biopsy if abnormal bleeding	Consider hysterectomy	
BRIP1	Ovary	Consider serum CA125 and TVUS	Consider salpingo-oophorectomy	
RAD51C, RAD51D	Ovary	Consider serum CA125 and TVUS	Consider salpingo-oophorectomy	
ATM	Ovary	Consider serum CA125 and TVUS	Consider salpingo-oophorectomy based on family history	
PALB2	Ovary	Consider serum CA125 and TVUS	Consider salpingo-oophorectomy based on family history	

TVUS transvaginal ultrasound

Table was created based on NCCN Guidelines Genetic/Familial High-Risk Assessment: Colorectal Version 1.2022, and Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic Version 2.2022

[a]Screening for ovarian cancer and endometrial cancer is of uncertain benefit

7.5.1 BRCA1/2

BRCA1/2 GPV carriers have an extremely high risk of developing breast and ovarian cancers, as well as an increased risk for pancreatic and prostate cancers.

As *BRCA1/2* GPVs are associated with early-onset breast cancer, breast cancer screening should be initiated earlier than the standard recommendation [110]. For women with *BRCA1/2* GPVs, training in breast awareness starting at the age of 18 years, clinical breast examination every 6–12 months and annual breast MRI screening with contrast starting at the age of 25 years, and additional annual mammography with consideration of tomosynthesis beginning at the age of 30 years are recommended. In a prospective screening trial evaluating the performance of annual MRI and mammography in women with *BRCA1/2* GPVs, the sensitivity of MRI

was significantly higher than that of mammography [111]. Furthermore, the majority or cancers detected by MRI screening are early-stage tumors. Another study reported that breast MRI had sensitivity rates of 79% for all cancers and 88.5% for invasive cancers, and a specificity rate of 86% [112]. Risk-reducing mastectomy (RRM) reduces the risk of developing breast cancer, although there is still no consensus on whether RRM reduces mortality. Therefore, the option of RRM should be carefully discussed during genetic counseling.

In contrast to breast cancer, RRSO is the current standard of care for ovarian cancer risk management in women with *BRCA1/2* GPVs [88, 113, 114]. In patients with *BRCA1/2* GPVs, the effectiveness of RRSO in reducing the risk of ovarian or fallopian cancer was reported to be 80–85%, with reduced mortality [115–117]. RRSO may provide an opportunity to detect clinically occult gynecologic cancers, especially serous tubal intraepithelial carcinoma (STIC), which is considered to be an early precursor lesion for serous ovarian cancers, in approximately 5–8% of patients [118, 119].

As described above, RRSO is an effective approach to reduce the risk of ovarian cancer in patients with *BRCA1/2* GPVs. However, before deciding to undergo RRSO, several topics should be discussed, such as the reproductive impact, residual risk of peritoneal cancer, and premature menopause. Even after RRSO, a 1–4.3% risk of developing peritoneal carcinoma remains, with the older age at RRSO and the presence of STIC in the RRSO specimen as the risk factors [120, 121]. Premenopausal women who undergo RRSO will experience acute climacteric symptoms of hormonal withdrawal.

Hormone replacement treatment (HRT) will not only attenuate these symptoms, but will also prevent the occurrence of osteoporosis and cognitive decline and help maintain cardiovascular health. HRT after RRSO for a short period has no reported effect on the breast cancer risk [122, 123]. Another study showed that short-term HRT use (mean duration: 4.3 years) did not increase breast cancer risk in female *BRCA1* GPV carriers without RRSO [124]. Although there have been no data about association between long-term use of HRT in *BRCA1/2* GPV carriers and breast cancer risk, in general population, the long-term use of HRT (median: 5.6 years) was associated with higher breast cancer incidence [125]. Therefore, information on the benefits and risks of HRT in individuals with *BRCA1/2* GPVs should be provided to them and the choice of whether to use HRT and for how long should be carefully discussed.

Salpingectomy with delayed oophorectomy could be another option for premenopausal women. Although several studies have shown the safety and feasibility of this procedure, more data are needed to determine its efficacy in reducing the risk of ovarian cancer [126, 127]. For those who have not elected RRSO, screening with transvaginal ultrasound and measurement of serum CA-125 levels may be considered in the clinical setting, although the clinical benefits remain uncertain.

The use of oral contraceptives (OCs) was reported to reduce the cumulative incidence of ovarian cancer from 1.2% to a maximum of 0.7% in general population; the incidence became lower the longer the OCs were used [128]. Three meta-analysis studies showed that the use of OCs reduces the risk of developing ovarian cancer by approximately 50% in *BRCA1/2* carriers [129–131].

Previous data showed conflicting data on the effect of OC use on breast cancer risk among *BRCA1/2* carriers [132–135]. Two meta-analyses showed no significant association between OC use and breast cancer risk in *BRCA1/2* carriers [129, 131]. Taken together, OC can be used to prevent ovarian cancer risk; however, physicians should be aware that the preventive effect is smaller than that of RRSO, and the appropriate duration of OC use remains uncertain.

Men with *BRCA1/2* GPVs have an increased risk of developing breast cancer, with the cumulative lifetime risks of 1.2% for those with *BRCA1* GPVs and 7–8% for those with *BRCA2* GPVs, compared with the cumulative lifetime risk of 0.1% in the general population [136–139]. For men with *BRCA1/2* GPVs, training in breast self-examination starting at age of 35 years is recommended, while starting annual mammography should be considered at age 50 or 10 years prior to the earliest known breast cancer in the family for those with gynecomastia.

Men with *BRCA1/2* GPVs also have an increased risk of developing prostate cancer [140–143]. Prostate cancer in male *BRCA1/2* carriers were often at an advanced or metastatic stage. Screening for prostate cancer using serum PSA starting at the age of 40 years should be recommended for those with *BRCA2* GPVs and should be considered for those with *BRCA1* GPVs [142].

If at least one first- or second-degree relative developed pancreatic cancer, pancreas cancer screening may be considered [144]. Pancreas cancer screening contributes to the earlier detection of pancreatic cancer and the improvement of resection rates, which may decrease the mortality rate [145, 146]. Screening may be performed using contrast-enhanced MRI/MRCP and/or endoscopic ultrasound starting at the age of 50 years or 10 years younger than the earliest pancreatic cancer diagnosis in the family [144].

7.5.2 MMR Genes (Lynch Syndrome)

Individuals with LS have an increased lifetime risk of developing several types of cancers, particularly colorectal and endometrial cancer. Although different genes carry different risks, the lack of large-scale cohort studies on the risks among specific variant carriers has resulted in the application of the same management at present.

Annual or semiannual colonoscopy starting at the age of 20–25 years or 2–5 years younger than the youngest diagnosis age in the family is recommended [147–152].

In women with LS, endometrial cancer is the second most common type of cancer, with a lifetime risk of up to approximately 50%; the risk varies by gene [39]. Due to the lack of sufficient evidence for specific routine screening, uniform guidelines for the surveillance of endometrial cancer in patients with LS are not currently available. However, in the clinical setting, endometrial biopsy in combination with transvaginal ultrasound is often performed with the expectation of improving the rate of endometrial cancer detection [153–155]. Women with LS are also at a higher risk of developing ovarian cancer. However, there has been no data supporting routine screening for ovarian cancer. Total hysterectomy and bilateral salpingo-oophorectomy can be performed as risk-reducing surgery [156].

There is no clear evidence to support the appropriate method for screening other types of cancer, including gastric, small bowel, urothelial, and pancreatic cancer. However, individuals with a familial history of each cancer may benefit from upper endoscopy, urinalysis, or imaging of the pancreas using MRI/MRCP or EUS. Recently, a PSA screening study in those with GPVs in MMR genes was conducted, demonstrating a higher prostate cancer incidence in *MSH2* and *MSH6* GPV carriers than in noncarrier controls and the usefulness of PSA screening in detecting prostate cancer [157].

7.5.3 PTEN *(PTEN Hamartoma Tumor Syndrome/ Cowden Syndrome)*

In PTEN hamartoma tumor syndrome, the cumulative lifetime risk for any types of cancer is estimated to be more than 80%, with a twofold greater cancer risk in women compared with that in men [158, 159]. The recommended screening strategy for breast cancer is similar to that for *BRCA1/2* GPV carriers. Although there has been no data regarding the efficacy of risk reduction surgery for breast cancer, RRM could be an option for women with this syndrome. For endometrial cancer, no study has reported the efficacy of screening; however, endometrial biopsy combined with transvaginal ultrasound could be considered. An annual thyroid ultrasound starting at the age of 7 years should be performed [160]. For risks of other cancers, colonoscopy, renal ultrasound, or upper endoscopy should be considered.

7.5.4 STK11 *(Peutz-Jeghers Syndrome)*

Individuals with this syndrome have increased risks of developing several types of cancers, including colorectal, breast, pancreatic, ovarian and gallbladder cancer. Surveillance for the multiple organs mentioned above is recommended, although there exist limited data regarding the efficacy of the screening modalities in this syndrome. For cervical and ovarian cancer, annual pelvic examination and pap smear should be considered. Pap smear alone reported to have limited diagnostic power for PJS-related cervical neoplasm, therefore, combination of MRI, Pap smears, and testing for gastric mucin may improve the accuracy of diagnosis [161].

7.5.5 BRIP1/RAD51C/RAD51D/ATM/PALB2

These genes are involved in the homologous recombination repair pathway as well as *BRCA1/2*, therefore, the risk prevention strategies for ovarian cancer should be similar to those for *BRCA1/2*.

Among them, *BRIP1*, *RAD51C*, and *RAD51D* are associated with a relatively higher risk of ovarian cancer, with estimated lifetime risk of over 10%. Therefore, RRSO should be considered in individuals with GPVs of these genes, although the optimal age for surgery remains unclear. Since the risk of ovarian cancer in *ATM* and *PALB2* GPV carriers is estimated to be relatively low, RRSO might be an option, depending on the family history.

7.6 Conclusions

Recent advances in DNA sequencing technology and development of molecularly targeted drugs have increased opportunity to identify GPVs in cancer-susceptible genes. Whole exome and genome sequencing, which will be used in clinical practice in near future, will further increase such opportunities. Genetic information will not change over lifetime, can predict the onset of disease, and may be shared with blood relatives. Hence, diagnosing an individual with hereditary cancer syndrome is equivalent to diagnosing an entire family with a hereditary cancer syndrome.

To know the genetic information will be the first step toward preventing cancer in families with hereditary cancer syndromes. The second step will be to understand the exact risk of developing susceptible cancers and preventive strategies for these conditions, and the third will be to share the genetic information with at-risk relatives. As gynecologists will be involved in each of these steps, it is essential to be familiar with gynecological hereditary cancers. Thus, gynecologists are encouraged to perform proper assessment of genetic risk, provide accurate information about the syndromes, and discuss with the patients how to share and effectively use the genetic information obtained for the health management of other family members. Last but not least, to collaborate with specialists in other departments is also important as multiple organs other than gynecological organs are involved in hereditary cancer syndrome.

Conflict of interest The authors declare no competing interests.

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