# Chapter 12
# Hereditary Gynecological Malignancy and Molecular Features

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**Abstract**  Hereditary gynecological malignancy constitutes a group of women's cancer syndromes caused by constitutional genetic variants, which carry inherited susceptibility to certain pelvic epithelial malignancies, such as endometrial and ovarian cancers, including primary peritoneum and fallopian tube cancers of synchronous or metachronous onset. The most common inherited gynecological malignancy is Hereditary Breast and Ovarian Cancer syndrome (HBOC), which carries increased lifetime risks of breast and ovarian cancers, including other types of malignancies, such as pancreas, male breast, and prostate cancers. The next leading cause of inherited gynecological malignancy is Lynch syndrome (LS), a hereditary cancer syndrome predisposing individuals to various organ malignancies, including gynecological (endometrium is the most common) and non-gynecological (colonic or extracolonic) cancers, including stomach, urinary tract, brain, small intestine, hepatobiliary, and pancreatic cancers, which harbor impaired DNA mismatch repair due to germline disorders of *MLH1*, *MSH2*, *MSH6*, or *PMS2*, or the deletion of *EPCAM*, a gene epithelial cell adhesion molecule. HBOC and LS have communal aspects, which provide effective information for the treatment of symptomatic patients (probands), as well as for at-risk family members or relatives in surveillance and the prevention of malignancies. Cowden syndrome (CS) and Peutz–Jeghers syndrome (PJS), which are inherited hamartoma tumors, or polyposis syndrome are also associated with gynecological malignancies. As CS and PJS are much rarer and have lower malignancy risks, HBOC and LS are discussed as representatives of the hereditary gynecological cancer predisposition syndromes in this chapter.

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## 12.1 Epidemiology and Risks of Hereditary Susceptibility to Ovarian Cancers; Hereditary Breast and Ovarian Cancer Syndrome (HBOC)

It is conventionally known that ovarian cancer is associated with inherited factors [1, 2]. The strongest risk factor for ovarian cancer is a family history of breast or ovarian cancer, and a quarter of all ovarian cancers are caused by heritable conditions [3]. *BRCA1/2* germline pathogenic variants are representative of these heritable factors, leading to an increased lifetime risk of ovarian cancer ranging from 39 to 63% with *BRCA1* variants and 16.5–27% with *BRCA2* variants, both of which are significantly higher risks of ovarian cancer than that in the general population. The accumulated risk of breast cancer is 38% or more, which is estimated to be over 80% by 70 years of age [4–8] (Table 12.1). The overall prevalence of *BRCA1/2* variants is estimated to be 1 out of 400–800, which varies depending on ethnicity; a higher prevalence of 1 in 40 is observed in the Ashkenazi Jewish [7]. A multicentric cohort study showed that the cumulative ovarian cancer risk by 80 years was 44% for *BRCA1* and 17% for *BRCA2* variant carriers, of which the corresponding relative risks are 35–40 times that of women in the general population [9] (Fig. 12.1). Hirasawa et al. demonstrated that *BRCA1/2* is the most frequent germline pathogenic variant in Japanese ovarian cancer patients, with prevalence rates of 8.3% for *BRCA1* and 3.5% for *BRCA2* [10]. A multicenter study also showed that the overall prevalence of germline *BRCA1/2* variants was almost 15%, with germline *BRCA1* variants (9.9%) and *BRCA2* variants (4.7%) in ovarian cancer patients in Japan [11].

## 12.2 Epidemiology and Risks for Hereditary Susceptibility to Endometrial Cancer; Lynch Syndrome (LS)

Lynch syndrome (LS), alternatively termed as hereditary nonpolyposis colorectal cancer (HNPCC), is an autosomal dominant inherited multiple organ malignancy due to a germline variant in one of four DNA mismatch repair (MMR) genes, *MSH2*, *MLH1*, *MSH6*, or *PMS2*, or the deletion of *EPCAM*. The estimated prevalence in the population ranges from 1 in 250 to 1 in 3000, depending on the country and ethnicity, or whether the individual carries founder variants or not [13]. Colorectal carcinoma is generally the most common, followed by endometrial carcinoma in women with LS. Three percent of all new cases of colorectal cancer are attributable to LS in the USA [14]. According to various studies, women with LS are estimated to carry higher risks of endometrial cancer than colorectal cancer [15–17]. Two to four

**Table 12.1** Lifetime risks of gynecological and other malignancies

|  | BRCA1 variant (%) | BRCA2 variant (%) | LS (%) | General population (%) |
|---|---|---|---|---|
| Breast cancer | 46–87 | 38–84 | – | >12 |
| Ovarian cancer | 39–63 | 16.5–27 | 4–12 | 1–2 |
| Endometrial cancer | – | – | 25–60 | 2.7 |
| Male breast cancer | 1.2 | Maximally 8.9 | – | 0.1 |
| Prostate cancer | 8.6 (up to 65 years), 20 (whole lifetime) | 15 (up to 65 years) | – | 6 (up to 69 years) |
| Pancreatic cancer | 1–3 | 2–7 | – | 0.5 |

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|  | Cumulative risk for diagnosis through age 80 years old | | | | Cumulative risk for diagnosis through lifetime |
|---|---|---|---|---|---|
|  | MLH1 (%) | MSH2 (%) | MSH6 (%) | PMS2 (%) | General population (%) |
| Colorectal cancer | 46–61 | 33–52 | 10–44 | 8.7–20 | 4.2 |
| Endometrial cancer | 34–54 | 21–57 | 16–49 | 13–26 | 3.1 |
| Ovarian cancer | 4–20 | 8–38 | ≤1–13 | 3 | 1.3 |
| Prostate cancer | 4.4–11.6 | 3.9–15.9 | 2.5–11.6 | 4.6–11.6 | 11.6 |
| Breast cancer (female) | 10.6–18.6 | 1.5–12.8 | 11.1–12.8 | 8.1–12.8 | 12.8 |

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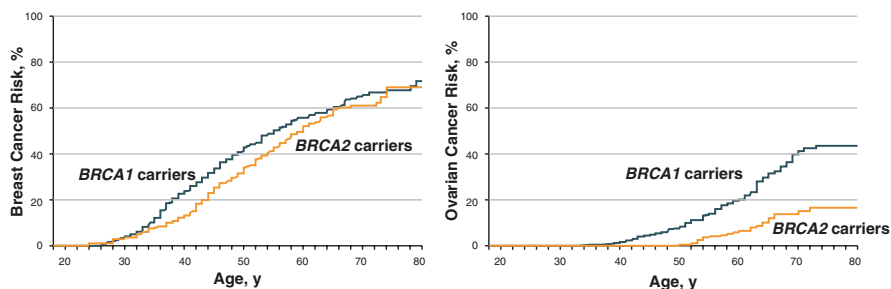


**Fig. 12.1** Estimated cumulative risk of breast cancer (left panel) and ovarian cancer (right panel) among BRCA1 and BRCA2 variant carriers. Adapted from Kuchenbaecker et al., *JAMA*. 2017; 317(23):2402–2416. doi: 10.1001/jama.2017.7112 © 2017, American Medical Association

percent of endometrial cancer before 70 years, and nearly 5% of endometrial cancer onset between 20 and 54 years old, is estimated to be attributed to LS or to those with LS-associated family history [18–20]. Loss of function of any of the *MMR* genes is associated with microsatellite instability, a type of genomic instability, and increased risk of LS-associated cancers. The lifetime risk of endometrial cancer in women with LS is 25–60%, which is comparable to the lifetime risk of colorectal cancer in women with LS [16, 21]. The accumulated penetrance rate of ovarian cancer during the lifetime of women with LS is 6–13%, which is significantly higher than the 1–2% risk of ovarian cancer in the general population [22, 23]. The estimated lifetime endometrial cancer risks in women with LS are dependent on the causative genes. For women with *MLH1* or *MSH2* variants, the lifetime risk of endometrial cancer is reportedly 34–54% with *MLH1* variants and 21–57% with *MSH2* variants. The lifetime risks for ovarian cancer are 4–20% with *MLH1* variants and 8–38% with *MSH2* variants [24–26].

According to the International Society for Gastrointestinal Hereditary Tumors (InSiGHT) database, which records variants identified in over 3000 of LS cases, *MLH1* and *MSH2* are dominantly responsible genes for LS, while the remainder, such as *MSH6* and *PMS2*, are less frequently identified in LS. The proportions of LS attributed to pathogenic variants are 42% in *MLH1* and 33% in *MSH2*, while the smaller population is attributed to *MSH6* (18%) and *PMS2* (7.5%) [27]. *EPCAM* deletion is observed in 1–3% of the population with LS [28, 29]. Although *MSH6* variants are less commonly observed in LS than *MLH1* or *MSH2* variants, *MSH6* is a dominant causative variant gene in LS-associated endometrial cancer and in an older age onset of LS-associated colorectal cancer [17]. The cumulative risk for endometrial cancer by 80 years in women with *MSH6* variants ranges from 17 to 44% [17, 30], while the risks for endometrial carcinoma carrying *PMS2* variants or *EPCAM* deletions are reported to be less than 15 or 12%, respectively [31, 32].

The age of cancer onset in the population with LS is younger than that of the general population; the mean age at the time of diagnosis of endometrial cancer is 48–62 years and the average age for ovarian cancer is 42.5 years in women with LS [8].

According to a cohort study by Win et al., women with a diagnosis of endometrial cancer carrying an *MMR* variant had significantly higher risks in other cancers, such as colorectal cancer, breast cancer, or urological cancers, such as the ureter, urinary bladder, kidney, and renal pelvis cancers, during the 20-year follow-up visits of endometrial cancer patients [33, 34]. Based on this evidence, endometrial cancer can be termed a "sentinel cancer," a preceding cancer which is first detected among a series of primary cancers developed in women with LS.

## 12.3 Molecular Features and Diagnosis of *BRCA*-Associated Hereditary Gynecologic Malignancy

The germline pathogenic variants of *BRCA1/2* account for the majority of hereditary breast and ovarian cancers showing an autosomal dominant predisposition to those diseases [7]. Both *BRCA1* and *BRCA2* were identified by positional cloning in the early 1990s as genes responsible for susceptibility to breast and ovarian cancers

[35, 36]. The locus of *BRCA1*, which encodes a predicted protein consisting of 1863 amino acids, is at 17q21.31 in the long arm of chromosome 17 (OMIN#113705). *BRCA1* is expressed in numerous tissues, including the testis, thymus, breast, and ovary [35]. *BRCA2* is located at 13q13.1 in the long arm of chromosome 13 (OMIN#600185) and encodes 3418 amino acids [36]. Although there is no structural homology in *BRCA1* and *BRCA2*, these two genes share communal functions as caretakers in the maintenance of genomic integrity and homologous recombination (HR) during DNA damage repair of double-strand breaks [37]. The loss of function of either *BRCA1* or *BRCA2* causes serious disruption in the open reading frame of the transcription unit. BRCA1 protein functions by interacting with several proteins. BRCA1-associated RING domain 1 (BARD1) binds to the RING-finger domain near the N-terminus of BRCA1, both of which carry nuclear exporting signal (NES). BRCA1 creates three different types of complexes exclusively with phosphorylated Abraxas (ABRA1), BRCA1-associated C-terminal helicase (BACH1), or CtBP-interacting protein (CtIP) through the BRCT domain near the C-terminus of BRCA1 [38, 39]. As a consequence of interacting with these different proteins, BRCA1 plays distinct roles in DNA damage resistance, ubiquitination, gene transcription, and cell cycle progression, such as G(2)-M checkpoint control [40]. *BRCA2* plays a role in genomic integrity maintenance through the DNA repair process and facilitates HR. BRCA2 protein functions to prevent nascent DNA degradation and promote HR-mediated prevention in replication fork stalling by loading RAD51 on DNA breaks and gaps [41, 42]. BRCA2 can form a complex with BRCA1 through PALB2 mediation (Fig. 12.2).
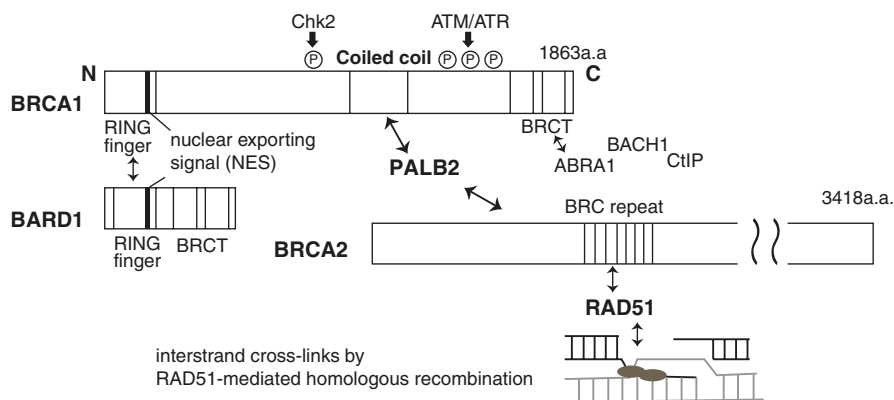


**Fig. 12.2** Structures and Functions of BRCA1 and BRCA2 on DNA double-strand breaks. BRCA1 (1863a.a.) contains several recognizable protein motifs, such as a RING-finger domain near the N-terminus for binding with BRAD1 to function as a nuclear exporting signal (NES), coiled-coil domain on exon 11 for interaction with PALB2, and a BRCT domain at the C-terminus. BRCA2 (3418a.a.) contains eight BRC repeats of 30–40 residue motifs found in exon 11, which mediate the binding of BRCA2 to RAD51. RAD51 functions in homologous recombination through interstrand cross-links. Referenced from Sedukhina A et al. Seikagaku 84(7), 529–538, 2012. ©2012, The Japanese Biochemical Society

More than 1600 or 1800 variants have been identified in *BRCA1* and *BRCA2*, which leads to loss of function due to frameshift deletions, insertions, or premature truncation of transcripts, suggesting the significant functions of *BRCA1* and *BRCA2* as tumor suppressor genes [7, 43, 44]. The loss of function of *BRCA1* or *BRCA2* increases the sensitivity to poly(ADP-ribose) polymerase (PARP), which is referred to as synthetic lethality, resulting in vulnerability to PARP inhibitors [45, 46]. The locus of variants in *BRCA1* and *BRCA2* is also known to affect cancer risk. In the analyses of over 400 families carrying a *BRCA2* variant with the presence of ovarian cancer and other malignancies, families with ovarian carcinoma or breast cancer were more likely to harbor variants in the ovarian cancer cluster region of exon 11 of *BRCA2* than families with variants elsewhere in *BRCA2* [47].

## 12.4   Genetic Testing of *BRCA1/2*

Genetic testing using blood samples is applicable for clinical diagnosis not only for symptomatic patients (probands) with breast and/or ovarian cancers but also for at-risk relatives as predisposition testing. Distinct testing strategies, for example, targeting analyses, comprehensive analyses, or large genomic rearrangement tests, are provided by Myriad Genetic Laboratories (Salt Lake City, UT, USA). Target analyses may be used for the detection of population-specific founder variants, such as *BRCA1* c.68_69delAG (185delAG), *BRCA1* c.5266dupC (5382insC), or *BRCA2* c.5946delT (6174delT), which are detected at frequencies as high as 1 in 40 individuals of Ashkenazi Jewish heritage [48]. Comprehensive analysis is useful for the evaluation of the predisposition of at-risk individuals through combined methods to detect common *BRCA1/2* variants and five specific large genomic rearrangements in *BRCA1*, which are ethnic-specific or family-specific variants. Further complementary analysis is conducted as a large rearrangement test of the above and beyond the common five rearrangements of *BRCA1*, such as large genomic rearrangements in *BRCA1/2* [7] (Table 12.2).

**Table 12.2**   Genetic testing methods for *BRCA1* and *BRCA2*

| Methods | Population | Mutation detected | Mutation detection frequency (%) |
|---|---|---|---|
| Comprehensive analysis | At-risk individuals | *BRCA1* and *BRCA2* sequence variants and five specific large genomic *BRCA1* rearrangements | ~88 |
| Large rearrangement test | At-risk individuals | Large genomic rearrangements in *BRCA1* and *BRCA2* | 3–4 |
| Targeted mutation analysis | Ashkenazi Jewish heritage | *BRCA1*: 185delAG<br>*BRCA1:* 5382insC<br>*BRCA2*: 6174delT | 90 |

Adapted from Petrucelli et al. *Genet Med* 2010: 12 (5): 245–259. doi: 10.1097/GIM.0b013e3181d38f2f. © 2010, The American College of Medical Genetics

Clinical *BRCA1/2* testing in Japan is covered by the social insurance service as companion diagnostics to determine the indication of PARP inhibitors, as well as for the diagnosis of HBOC only for symptomatic patients (probands) with breast and/or ovarian cancers so far in 2020. Other comprehensive or specific germline cancer panels/analyses including *BRCA1/2* are provided by several diagnostic companies, such as LabCorp (Burlington, NC, USA), Ambry Genetics Corporation (Aliso Viejo, CA, USA), and ACT Genomics (Taipei City, Taiwan). These may be used for the investigation of other related disorders of probands as well as for at-risk relatives and for differential diagnosis.

The analysis of genetic testing is reported in three variant categories: a positive, a negative, or an inconclusive, termed as a variant of uncertain significance (VUS), in clinical pathogenicity. It is estimated that up to 20% of *BRCA1/2* variants are reported as a VUS [49–52]. In the large rearrangement tests and the family-specific variant tests for at-risk relatives, the testing results will be shown in one of two categories: absent (negative) or present (positive). Even if negative results are obtained, careful interpretation is indispensable because negative results do not necessarily eliminate the possibility of a hereditary susceptibility to cancer. There is also a possibility that cancer in the family might be associated with unknown hereditary factors that are undetectable by the genetic test performed. When VUS results are obtained, further analysis using samples from additional family members might be a clue to examine whether the variants co-segregate with cancer in the family [7].

## 12.5   Relationships Between *BRCA1/2* Variants and Histological Properties of Hereditary Gynecological Malignancies

The prevalence of germline *BRCA1/2* variants is known to be associated with frequencies of specific types of histology [11]. The most common histology type of ovarian cancer carrying *BRCA* variants is high-grade serous carcinoma, comprising about 70–80% of women with *BRCA1/2* variants, while it is approximately 50% in sporadic controls or women without *BRCA1/2* variants [53–58]. Endometrioid and mucinous carcinomas of the ovary account for a smaller population, which is a maximum of 6–12% among women carrying *BRCA1/2* variants. In contrast, approximately 10–20% of people in the general population with wild-type germline *BRCA* present with these carcinomas. It is estimated that approximately 10–15% of women with pelvic serous carcinoma have pathogenic germline *BRCA* variants.

Serous carcinoma of pelvic malignancies is generally high-grade, a clinically aggressive type, and characterized as a type II tumor, which is frequently bilateral and is often found on the peritoneal surfaces at diagnosis [7, 59]. In *BRCA*-associated ovarian cancers, distinct molecular pathways of carcinogenesis, which are different from sporadic ovarian cancers, are associated with unique histopathologic subtypes [60]. According to the accumulated evidence through careful histopathologic

analyses, such as of the resected fallopian tubes at the risk-reduction salpingo-oophorectomy from patients carrying *BRCA* germline variants, a hypothesis was established that the distal fimbria end may be a potential site for early-stage tubal carcinoma leading to advanced tumorigenesis of pelvic malignancies, including primary peritoneal carcinoma [61–65]. Many studies have clarified that noninvasive carcinoma arising in the fallopian tube is potentially able to metastasize without invading into the substantial stroma of the distal salpinx, and this character is analogous to superficial serous carcinoma of the endometrium [66]. Such early stages of serous carcinoma, termed as serous tubal intraepithelial carcinomas (STICs) in fimbria, are observed with ovarian carcinoma in over 70% of sporadic ovarian and peritoneal malignancies of high-grade serous carcinoma [67]. Therefore, it is hypothesized that STICs, which are detected in fimbria, would be a source of high-grade serous carcinoma in pelvic malignancies, regardless of the status of germline *BRCA1/2*.

Occult malignancy, a small in situ carcinoma, was originally described by Colgan et al. in the study of salpingo-oophorectomy specimens at a prevalence rate of 8.3% in 5 of 60 high-risk women carrying *BRCA1/2* variants [61]. The incidence rate of occult carcinoma varies to some extent in study groups. Leeper et al., for example, reported that the occult carcinoma is observed in 17% (5 patients of 30) of *BRCA1/2*-variant positive women [68]. Paley et al. studied two *BRCA1*-positive patients with occult carcinoma in fallopian tubes and with positive peritoneal cytological malignancy, suggesting the micro-implantation potential of malignant cells in the peritoneum [69]. Another study by Agoff et al. showed that two of four cases of early fallopian tube carcinoma were positive for peritoneal cytology [70]. This leads to the central hypothesis that the inherited *BRCA* status is included as part of the cancer spectrum associated with STICs, which develops into fallopian tube carcinoma with a high potential to metastasize [66]. Depending on the location and the speed of tumor growth, the tumor might be mistakenly presumed as primary carcinomas of the ovary, peritoneum, or fallopian tube [60]. These are significant research outcomes by analyzing salpingo-oophorectomy specimens from pathogenic *BRCA1/2* variant-positive women. These findings are also supported by the finding that almost all STICs showed positive staining for p53, which is similar to that of high-grade serous carcinoma. Small linear p53-positive foci, termed the p53 signature, are commonly detected in the distal fimbria of both *BRCA*-variant positive women and sporadic groups with early tubal cancer [71]. Another study analyzing 29 cases of pelvic serous carcinoma showed that STICs and concordant high-grade serous carcinoma were identical to the *TP53* variant of ovarian carcinoma, which supports a clonal relationship between STICs and *TP53* [72]. Although these data are not necessarily relevant to the germline status of *BRCA1/2*, this suggests that the p53 signature would be an early precursor of high-grade serous carcinoma [66]. The accumulated evidence obtained from analyses of fallopian tubes from *BRCA*-variant-positive women has strengthened the fact that the fimbria end may be an origin of pelvic malignancies. What is more obvious from this evidence is that *BRCA* variants are susceptible factors for a subset of serous carcinomas, which has a strong connection with the distal end of the fallopian tube.

## 12.6 Molecular Features and Diagnosis of Gynecological Malignancies with LS

Microsatellite instability (MSI) and DNA mismatch repair deficiency (MMR-D) are basic tools for screening LS. Latham et al reported that LS was identified in 16.3% of patients with MSI-high (MSI-H). Immunohistochemical staining of LS-positive MSI-H, including MSI-intermediate (MSH-I) tumors, demonstrated MMR-D in 98% of patients [74]. MSI-H status is generally concordant with a high tumor mutational burden (high TMB), but the converse is not always true. According to the study by Chalmers et al., 16% of high TMB (> 20 mutations/Mb) was classified as MSI-H, of which concordance is dependent on malignancy type [73]. High TMB and MSI-H are rarely detected in lung and skin carcinomas, while those two statuses are matched frequently in cases of gynecological malignancies, such as endometrial carcinoma including endometrioid carcinoma of the uterus [73] (Fig. 12.3).

The initial step of clinical screening for gynecological malignancies with LS is the selection of patients and families based on the revised Amsterdam criteria II, a clinical diagnostic criterion of hereditary nonpolyposis colorectal cancer (HNPCC)-associated malignancies, covering colorectal, endometrial, renal pelvic, ureteral, and small intestinal cancers [12] (Table 12.3). Endometrial and ovarian cancers are also listed as LS-associated tumors in the revised Bethesda Guidelines, which is a clinical screening criterion for individuals with HNPCC who should be tested for microsatellite instability (MSI) [75]. MSI is caused by mismatch repair deficiency



**Fig. 12.3** The relationship between tumor mutation burden (TMB) and microsatellite instability (MSI). A majority (83%) of MSI-high (MSI-H) samples also had high TMB (TMB-H), while a smaller population (16%) in TMB-H was classified as MSI-H (panel **a**). Co-occurrence of MSI-H and TMB-H was observed at high incidence in gynecological malignancies, such as endometrial carcinoma of the uterus (panel **b**, *asterisks*). Adapted from Chalmers et al., *Genome Medicine* (2017) 9:34. doi: 10.1186/s13073-017-0424-2 © Zachary R. Chalmers et al.

**Table 12.3** Revised ICG-HNPCC Criteria (Amsterdam Criteria II, 1999) [12]

| There should be at least three relatives with a Lynch syndrome/HNPCC-associated cancer (cancer of the colorectum, endometrium, small bowel, ureter, or renal pelvis); the following criteria should be met: |
| --- |
| 1. One should be a first-degree relative of the other two |
| 2. At least two successive generations should be affected |
| 3. At least one of the relatives with cancers associated with HNPCC should be diagnosed before the age of 50 years |
| 4. Familial adenomatous polyposis should be excluded in the CRC case(s) if any |
| 5. Tumor diagnosis should be confirmed by histopathological examination |

CRC, colorectal cancer

and is characterized by insertion/deletion or alteration in the lengths of repetitive regions within DNA. Polymerase chain reaction (PCR)-based MSI screening is widely conducted using the Bethesda panel, a five-marker panel comprising two mononucleotide repeats, BAT25, BAT26, and three dinucleotide repeats of D2S123, D5S346, and D17S250, of which application is recommended by the National Cancer Institute, USA [76, 77]. If two or more of five markers show instability, for example, variable shifting in the wave patterns in capillary electrophoresis of fluorescent-adjunct and amplified fragments from tumor and unaffected tissue, those MSI statuses are called high-frequency MSI (MSI-H). In contrast, if a single or no marker out of five shows instability, it is termed as low-frequency MSI (MSI-L) or microsatellite status stable (MSS) [76]. In recent years, PCR-based methods using five mononucleotide markers (BAT25, BAT26, MONO27, NR21, and NR24, instead of the Bethesda panel) as well as next-generation sequencing (NGS) techniques have been developed to detect MSI status with high sensitivity and specificity. Quasi-monomorphic variation range (QMVR), in which PCR products from normal DNA are almost confined regardless of ethnicity, is applied to MSI testing using five mononucleotide markers. MSI status can therefore be determined using the mononucleotide marker panel without normal DNA analysis [78]. In the NGS technique by FoundationOne® CDx (Foundation Medicine, Inc., Cambridge, MA, USA), a tumor sequencing used in cancer precision medicine, the MSI status is designated based on the genome-wide analysis of 95 microsatellite loci. Approximately 90% of LS-associated endometrial cancers are estimated to show MSI-H [79], while nearly 30% of sporadic endometrial cancer cases are presumed to show MSI-H [80]. In contrast, in ovarian cancer, the MSI-H population ranges from 3 to 13%, while the prevalence rate of LS in ovarian cancer is estimated to be almost the same or less at 0.9–2.7% [74, 81–83].

Immunohistochemical (IHC) analysis of MMR protein expression has been conventionally and universally performed as the second step in the diagnosis of LS. IHC analysis is advantageous in the direct visual detection of altered MMR. MSH2 functions as a heterodimer with MSH6, forming a major MutSα complex or with MSH3 to form a minor MutSβ complex. MLH1 and PMS2 proteins function as stable

heterodimers by forming a MutLβ complex that detects the short insertion–deletion loop of the mismatch structure. Loss of expression in both MSH2 and MSH6 is typically caused by germline variants. In contrast, loss of expression in both MLH1 and PMS2 indicates a germline alteration of *MLH1* or somatic methylation of *MLH1* promoter in sporadic cancers [14, 84]. To rule out sporadic MSI-H carrying epigenetic methylation of *MLH1*, *BRAF* V600E testing is applied based on the evidence that *BRAF* V600E is positive in approximately 40% of sporadic MSI-H colorectal cancers, while it is rarely observed in LS-associated colorectal cancer [85–87]. It must be noted that this is the case with colorectal cancer but not with endometrial cancer. The *BRAF* V600E test is not applicable to endometrial cancer in clinical practice [88, 89]. It should also be noted that the majority of MSI-H in gynecological malignancy is due to hypermethylation of the *MLH1* promoter rather than germline variants of *MMR* genes.

The majority of LS-associated endometrial cancers are endometrioid carcinomas, most of which are found as Grade 1 of the International Federation of Gynecology and Obstetrics (FIGO). Other non-endometrioid carcinomas including clear cell carcinoma, serous carcinoma, and carcinosarcoma, which is known as malignant mixed Mullerian tumor (MMMT), have also been reported [90]. Mesenchymal tumors, such as leiomyomas, leiomyosarcomas, and other stromal tumors, are not associated with LS. The location of endometrial cancer in patients with LS is likely to be in the lower uterine segment (LUS), which is a rare site for sporadic endometrial carcinoma [91, 92].

## 12.7 Risk Assessment, Surveillance, and Prevention of Hereditary Gynecological Malignancies

While ovarian cancer is a relatively rare type of malignancy, in which the prevalence rate in the general population is as low as 1.3% (1 of 78) according to the statistics in the USA, the lifetime incidence of ovarian cancer increases to 39–58% in women carrying germline pathogenic *BRCA* variants, and it rises to 9–12% in women with germline *MMR* pathogenic variants according to a study in the USA [93]. Population-based, single institutional, or nationwide multicentric studies showed that the positive rates for germline *BRCA* variants are 11–15% in invasive ovarian cancer patients regardless of ethnicity [10, 11, 55, 94]. It is as much as 2% in invasive ovarian cancer cases, which are positive for germline *MMR* variants [83]. The positive rates may be increased in patients with early onset of ovarian cancer (before 40 years of age) [95]. Due to the genes inherited in an autosomal dominant manner, each child of a person with HBOC or LS carrying germline pathogenic mutations in *BRCA1/2* or *MMR* genes has a 50% chance of having inherited causative variants, irrespective of gender. Appropriate surveillance following proper genetic testing at the right time point is important for the prevention of cancer development associated with inherited cancer syndromes.

### 12.7.1 Guideline Overview on BRCA1/2-Associated Gynecological Malignancies

Identifying women at high lifetime risk for ovarian cancer, due to germline variants relevant to the inherited syndromes, provide asymptomatic women with prevention opportunities, such as surveillance, chemoprevention, and risk-reducing surgery, by using a systematic tailored screening strategy [96]. Some medical societies recommend germline genetic testing for all women diagnosed with ovarian cancer. According to the American Society of Clinical Oncology (ASCO) Guidelines, published in 2020, it is strongly recommended that all women diagnosed with epithelial ovarian cancer should have germline genetic testing for *BRCA1/2* and other ovarian cancer susceptibility genes, irrespective of their clinical features or family cancer history [97]. It is moderately recommended that women diagnosed with clear cell, endometrioid, or mucinous ovarian cancer should undergo somatic tumor testing for mismatch repair deficiency (dMMR) [97]. The National Comprehensive Cancer Network® (NCCN®) (NCCN) regularly updates its clinical practice guidelines in oncology (NCCN Clinical Practical Guidelines in Oncology® (NCCN Guidelines®)) which can link to NCCN.org. According to Version 1.2020 of NCCN Guidelines® for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic, focusing on *BRCA1/2* variant-positive management, clinical breast examination should be performed every 6–12 months, starting at the age of 25 years. Genetic counseling on risk-reducing mastectomy should include a discussion regarding the degree of protection, reconstruction options, and risks [98]. Risk-reducing salpingo-oophorectomy (RRSO) is recommended, which is typically performed between 35 and 40 years of age and upon completion of childbearing [98]. There is also a description regarding the management of RRSO, depending on the variant status of *BRCA1/2*. For patients with *BRCA2* pathogenic/likely pathogenic variants, RRSO can be reasonably delayed until the age of 40–45 years, since the onset of ovarian cancer in patients with *BRCA2* pathogenic/likely pathogenic variants is an average of 8–10 years later than in patients with *BRCA1* pathogenic/likely pathogenic variants [98]. Salpingectomy alone, which is based on the detection of precursor lesions, including serous tubal intraepithelial carcinomas (STICs) in fimbria, is not standard of care for risk reduction [98]. Clinical trials of interval salpingectomy and delayed oophorectomy are ongoing. As a discretion option, transvaginal ultrasound (TVUS) combined with serum CA125 level may be considered for ovarian cancer screening for patients who have not elected RRSO [98]. In any case, education regarding signs and symptoms of cancers, especially those associated with *BRCA* pathogenic/likely pathogenic variants, is important for women (ovarian cancer) and men (male breast and prostate cancers) carrying these variants [98]. Symptoms of pelvic or abdominal pain, bloating, and increased abdominal girth are associated with ovarian cancer development. The US Preventive Services Task Force recommends that primary care clinicians assess women with a personal or family history of breast, ovarian, tubal, or peritoneal cancer or who have an ancestry associated with *BRCA* variants with an appropriate brief familial risk assessment tool [99]. Women with a positive result on the risk assessment tool should receive genetic counseling, and genetic testing at the indicated time points thereafter [99].

### 12.7.2  Surveillance and Prevention Strategy for LS-Associated Gynecologic Malignancies

A majority (e.g., 67% in Cancer Statistics 2017) of endometrial cancer patients show symptoms, such as vaginal bleeding, and are diagnosed at an early stage with disease confined to the uterus [100, 101]. The NCCN Guidelines® for Genetic/ Familial High-Risk Assessment: Colorectal Version1.2020 recommend that women should be educated regarding the importance of prompt reporting and evaluation of any abnormal uterine bleeding or postmenopausal bleeding [26]. Endometrial biopsy is included as an option for the evaluation of these symptoms; a screening via endometrial biopsy every 1–2 years starting at age 30–35 years can be considered [26]. Hysterectomy may be considered as a risk-reducing surgery for endometrial cancer in at-risk women [26]. Schmeler et al. demonstrated that prophylactic hysterectomy with bilateral salpingo-oophorectomy is effective for preventing endometrial and ovarian cancer in women with LS [102]. Consideration and discussion on the risks and benefits of these risk-reduction agents, as well as patient education regarding the early symptoms of endometrial cancer, are important. Genetic counseling, which is a critical component in cancer risk assessment and helping clients make informed decisions, covers those procedures. As for ovarian cancer, there is no effective screening strategy so far. Transvaginal ultrasound for ovarian cancer screening with or without serum CA125 is not a routine recommendation since those modalities have not been shown to be sufficiently sensitive or specific as the screening of ovarian cancer. To conduct the referral to the genetic counseling at the right time point, including genetic testing, information regarding significant family history of the involved disease will be very important, especially for ovarian cancer.

## 12.8  Cancer Susceptibility Gene to Gynecological Malignancies Is Presumed Through Tumor Genomic Sequencing

Somatic genomic testing using next-generation sequencing (NGS) is becoming a common practice in clinical oncology, such as for the care of patients with advanced or metastatic cancer. The analysis of tumor genomes also has the potential to uncover germline variants as the underlying background information, called germline findings [103]. *BRCA1/2* and *MMR* genes are important presumed germline genes among the minimum 59 listed genes whose disclosure is recommended by the statement of the American College of Medical Genetics and Genomics (ACMG) [104, 105]. The goal of the disclosure of those presumed germline pathogenic variants (PGPVs) is to identify and manage risks for selected highly penetrant genetic disorders that can be prevented and of which morbidity and mortality can be reduced through established interventions after confirmation as pathogenic germline variants (PGVs) [105]. Both *BRCA1/2* and *MMR* are high-actionable cancer susceptibility genes (CSGs), which confer a predisposition to specific tumor types, such as

breast, ovarian, or colon cancer. Even though pathogenic CGCs are detected in organs in which elevated risk of cancer is generally not conferred by those genes, the pathogenic variants of *BRCA1/2* or *MMR* genes should be regarded as germline origin [106]. The NCCN Guidelines® for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic Version 1.2021 introduces that *BRCA1/2* germline genetic testing should be considered if a pathogenic or likely pathogenic variant is found through tumor profiling [76, 98]. The homologous recombination deficiency (HRD) status, due to deleterious variants of *BRCA1/2*, can be used for response prediction to poly(ADP-ribose) polymerase (PARP) inhibitor. Detection of somatic variants and subsequent confirmation as PGVs allows for a higher likelihood of responses to PARP inhibitors, as well as the effective chance of surveillance to prevent ovarian cancer, colon cancer, or other associated cancers in patients and relatives.

## 12.9 For Understanding of Hereditary Gynecological Malignancies

Web-based resources and links for HBOC with *BRCA1* and *BRCA2* variants and LS with *MMR* variants:

- GeneReviews®: https://www.ncbi.nlm.nih.gov/books/NBK1116/
- National Comprehensive Cancer Network (NCCN) Guidelines® for Detection, Prevention, & Risk Reduction: https://www.nccn.org
- American Society of Clinical Oncology Guidelines: https://www.asco.org/research-guidelines
- European Society of Medical Oncology (ESMO) Clinical Guidelines: Gynaecological Cancers: https://www.esmo.org/guidelines/gynaecological-cancers
- U.S. Preventive Services Task Force Recommendation Statement: BRCA-Related Cancer: Risk Assessment, Genetic Counseling, and Genetic Testing: https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/brca-related-cancer-risk-assessment-genetic-counseling-and-genetic-testing

**Book**
- Hereditary Gynecologic Cancer: Risk, Prevention and Management edited by Karen H. Lu, published in 2012 by Informa Healthcare, UK.

## 12.10 Conclusion

*BRCA1/2*-associated ovarian cancer and LS-associated endometrial cancer are representatives of hereditary gynecological malignancies. A better understanding of these symptoms as well as attention to significant family history provides women

with opportunities to identify HBOC or LS, leading to the early detection of asymptomatic stages of ovarian cancer and prevention of secondary cancers. Owing to the progress of analytical technologies and risk-reducing modalities, we have unveiled the detailed mechanisms by which ovarian carcinogenesis and development occur. By identifying specific germline variants associated with gynecologic malignancies, unaffected family members, and relatives also have the opportunity to undergo predictive testing and surveillance. Recent advancements in cancer genomic analytical technology using next-generation sequencing are becoming a common modality that provides us with another opportunity to consider pathogenic variants presumed as germline origin, as well as other potential cancer susceptibilities, called germline findings. The utilization of inherited information, which is estimated through somatic genomic testing and germline analysis, is becoming more common and important in the management of gynecological malignancies.

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