Hereditary Ovarian and Endometrial Cancers: Current Management

8

Akira Hirasawa and Daisuke Aoki

Abstract

Hereditary breast and ovarian cancer (HBOC), Lynch syndrome, and Peutz-Jeghers syndrome (PJS) are including hereditary gynecological tumors. While such tumors share common phenotypes with non-hereditary (sporadic) tumors, they are autosomal dominant diseases; therefore, knowledge of a family's disease history is the first step towards identifying hereditary tumors.

Keywords

Hereditary tumor • Hereditary breast and ovarian cancer • Lynch syndrome • Genetic testing • Risk-reducing salpingo-oophorectomy

8.1 Introduction

The endpoint of clinical research on hereditary tumors is ***to reduce mortality for cancer***. However, effective screening systems have not been established for detecting ovarian cancer; therefore, risk-reducing salpingo-oophorectomy (RRSO) remains the most effective ovarian cancer prevention strategy for mutation carriers. Furthermore, genetic testing for hereditary tumors is used alongside companion diagnostics to select the appropriate chemotherapy regimens, such as poly (ADP-ribose) polymerase (PARP) inhibitors for carriers of the *BRCA1* and/or *BRCA2* (*BRCA1/2*) mutations.

In this chapter, hereditary tumors, genetic testing, cancer prevention for unaffected mutation carriers, and companion diagnostics for ovarian cancer patients with *BRCA1/2* mutations are described.

A. Hirasawa, M.D., Ph.D. • D. Aoki, M.D., Ph.D. (✉)
Department of Obstetrics & Gynecology, Keio University School of Medicine, Shinjyuku-ku, Tokyo, Japan
e-mail: aoki@z7.keio.jp

I. Konishi (ed.), *Precision Medicine in Gynecology and Obstetrics*, Comprehensive Gynecology and Obstetrics, DOI 10.1007/978-981-10-2489-4_8

8.2 Carcinogenesis of Hereditary Tumors

Both genetic and environmental factors can cause cancers (Fig. 8.1). Germ-line mutations are the underlying cause of hereditary tumors, many of which are autosomal dominant diseases. If a parent harbors a mutant allele, 50% of the mutation carrier's children are likely to be mutation carriers (Fig. 8.2). The two-hit

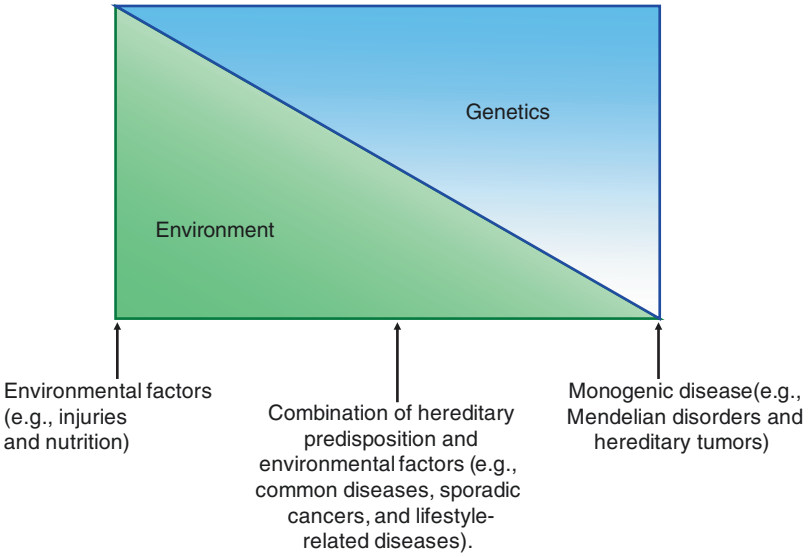

Fig. 8.1 Environmental and genetic factors in diseases. Many diseases, including cancer, are influenced by both environmental and genetic factors. Hereditary tumors are mainly caused by genetic factors. Examples of environmental factors for carcinogenesis are chemicals, smoking, ultraviolet light exposure, diet, viruses, and hormones

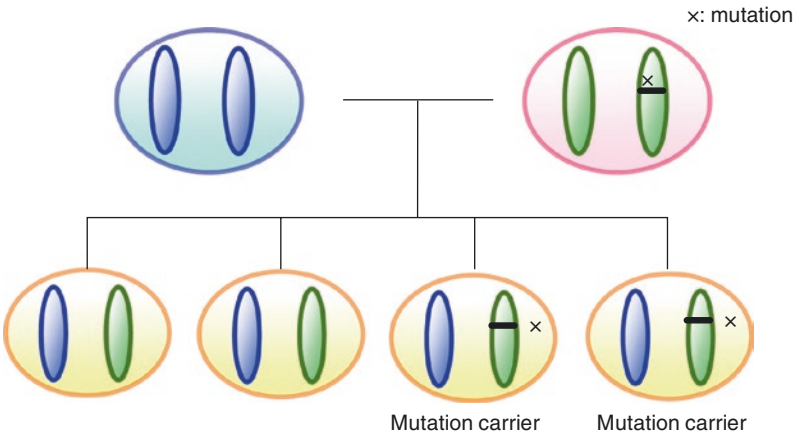

Fig. 8.2 Autosomal dominant inheritance pattern. Many hereditary tumors show an autosomal dominant pattern. Germ-line mutations are represented by (×). Fifty percent of the offspring of a mutantion carriers are also likely to carry mutations

hypothesis formulated by Alfred Knudson [1] stated that multiple hits are necessary to cause cancer (Fig. 8.3); this may explain why hereditary tumors frequently involve onset at a younger age and tend to exhibit multiple lesions and bilateral diseases more frequently (Fig. 8.4) [1].

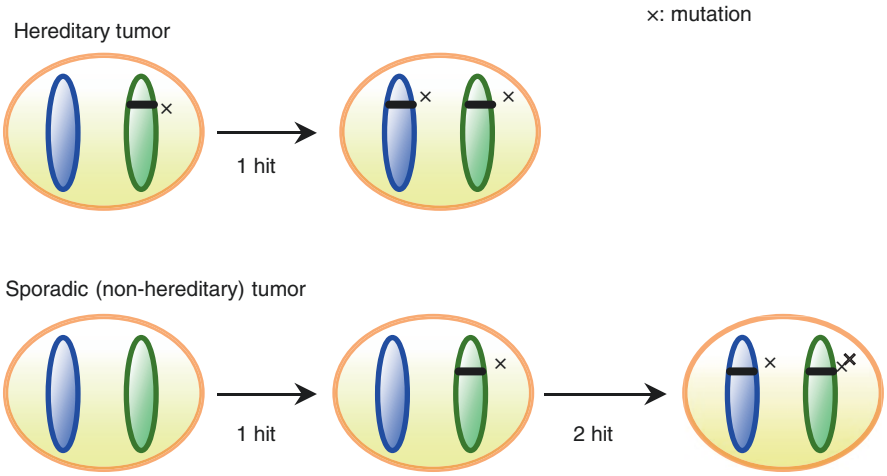

Fig. 8.3 Two-hit theory (Knudson's hypothesis). This hypothesis was based on statistical models from retinoblastoma patients. In this representation, two hits are required for carcinogenesis. Carriers of hereditary germ-line mutations already harbor the first 'hit' and the second hit follows after birth

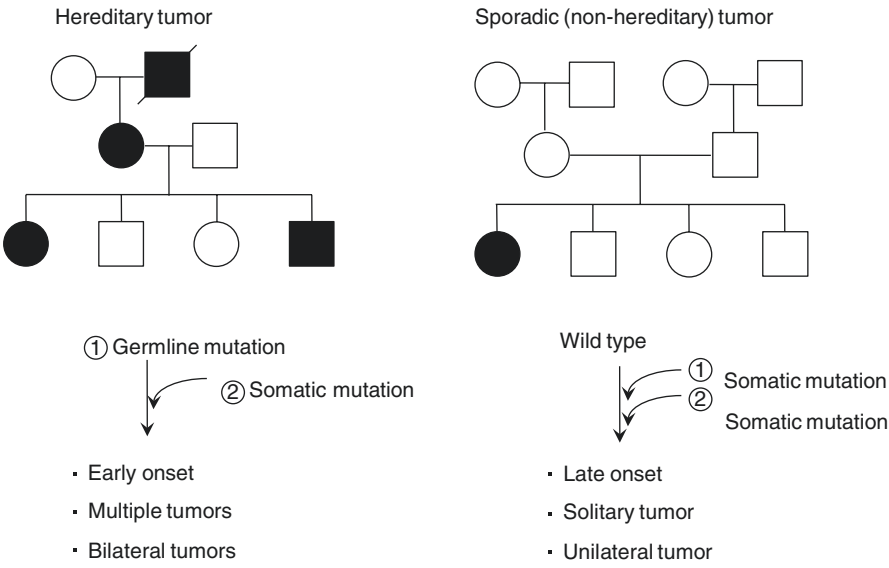

Fig. 8.4 Hereditary and non-hereditary tumors. A comparison of hereditary vs. sporadic (non-hereditary) tumors. Hereditary tumors have different characteristics than sporadic tumors; multiple affected persons can be found in the pedigree. Moreover, onset at a younger age, multiple tumors, and bilateral tumors can occur. This phenomenon can be explained by the two-hit theory

Table 8.1 Hereditary gynecologic cancers

Syndrome	Related tumors and typical phenotype	Associated gene
Hereditary breast and ovarian cancer syndrome	Breast cancer (including male breast cancer)	*BRCA1*
	Ovarian cancer, fallopian tube cancer, peritoneal cancer	*BRCA2*
	Prostate cancer	
	Pancreatic cancer	
Lynch syndrome	Colorectal cancer	*MSH2*
	Endometrial cancer	*MLH1*
	Ovarian cancer	*PMS2*
	Small intestinal cancer	*MSH6*
	Renal pelvic, or ureteral cancer	
	Gastric cancer	
	Hepatobiliary cancer	
	Sebaceous neoplasms of the skin in Muir-Torre syndrome	
Peutz-Jeghers syndrome	Gastrointestinal polyposis	*STK11*
	Mucocutaneous pigmentation	
	Colorectal, stomach and small bowel cancers	
	Adenoma malignum of the cervix	
	Sertoli cell tumors of the testes	
	Sex cord tumors with annular tubules	
	Ovarian tumor	
	Breast cancer	
	Pancreatic cancer	
Cowden syndrome	Breast cancer	*PTEN*
	Thyroid cancer	
	Macrocephaly	
	Endometrial carcinoma	

8.3 Hereditary Gynecologic Cancers

Hereditary gynecologic cancers involve HBOC, Lynch syndrome, PJS, Cowden syndrome and Li–Fraumeni syndrome. Table 8.1 presents a list of hereditary gynecologic cancers with related tumors and associated genes.

8.4 Hereditary Breast and Ovarian Cancer

Pathogenic germ-line variants in *BRCA1/2* produce an increased risk of cancer in the breasts, ovaries, fallopian tubes, peritoneum, prostate, and pancreas. Individuals with male breast cancer are more commonly associated with families in which mutations in *BRCA2* are more prevalent compared with *BRCA1*. Mutations in *BRCA1/2* should be suspected in individuals with a personal or family history (i.e.,

Table 8.2 Factors in the clinical diagnosis of hereditary breast and ovarian cancer [2]

Breast cancer diagnosed at the age of 50 years or younger
Ovarian cancer
Multiple primary breast cancers in either the same or contralateral breast
Comorbid breast and ovarian cancers
Male breast cancer
Triple-negative (estrogen receptor negative, progesterone receptor negative, and HER2 negative) breast cancer
Pancreatic cancer with breast or ovarian cancer in the same individual or on the same side of the family
Ashkenazi Jewish ancestry
Two or more relatives with breast cancer, one under the age of 50
Three or more relatives with breast cancer at any age
A previously identified *BRCA1* or *BRCA2* pathogenic variant in the family

"Breast cancer" includes both invasive cancer and ductal carcinoma in situ (DCIS). "Ovarian cancer" includes epithelial ovarian cancer, fallopian tube cancer, and primary peritoneal cancer

Table 8.3 The lifetime risk for hereditary breast and ovarian-related cancers in individuals carrying pathogenic variants of *BRCA1/2* [2]

Cancer type	Risk (%)
Breast cancer	40–80
Ovarian cancer	11–40
Male breast cancer	1–10
Prostate cancer	Up to 39
Pancreatic cancer	1–7

in a first-, second-, or third-degree relative in either lineage) on the basis of any of the criteria listed in Table 8.2 [2].

Approximately 10–15% of patients with ovarian cancers harbor *BRCA1/2* germline mutations [3, 4]. Table 8.3 shows the lifetime risk for HBOC-related cancers in patients who carry *BRCA1/2* mutations [2]. Hence, gynecologists are likely to frequently encounter patients who are *BRCA1/2* germ-line mutation carriers. Therefore, gynecologists who work in primary care are required to evaluate the genetic risks of HBOC in their patients and families.

Ovarian serous carcinoma is frequently observed in *BRCA1/2* mutation carriers, and ovarian cancers with *BRCA1/2* mutations have been reported to exhibit unique chemosensitivity and prognosis [5–7]. For example, recently developed PARP inhibitors are more effective against *BRCA1/2*-mutated ovarian cancer [8]. Therefore, *BRCA1/2* genetic testing is increasingly being performed in conjunction with companion diagnostics.

8.5 Lynch Syndrome

Lynch syndrome is caused by germ-line mutations in the mismatch repair (MMR) genes; *MLH1*, *MSH2*, *MSH6*, or *PMS2*. These mutations increase the risk of colon cancer as well as cancers of the endometrium, ovary, stomach, small intestine,

Table 8.4 Cancer risks in individuals ≤70 years with Lynch syndrome compared to the general population [2]

Cancer type	General population risk (%)	Lynch syndrome (*MLH1* and *MSH2* heterozygotes)	
		Risk (%)	Mean age of onset (years)
Colon	4.80	52–82	44–61
Endometrium	2.70	25–60	48–62 years
Stomach	<1	6–13	56 years
Ovary	1.40	4–12	42.5 years
Hepatobiliary tract	<1	1.4–4	Not reported
Urinary tract	<1	1–4	~55 years
Small bowel	<1	3–6	49 years
Brain/central nervous system	<1	1–3	~50 years
Sebaceous neoplasms	<1	1–9	Not reported

hepatobiliary tract, urinary tract, brain, and skin. Table 8.4 lists the characteristics of individuals with Lynch syndrome [2]. Colorectal and endometrial cancers are frequently found among carriers of MMR genes mutations, followed by gastric and ovarian cancers. While the risks of other Lynch syndrome-related cancers are lower, they remain elevated compared to the general population. Microsatellite instability (MSI) within tumor tissues and lower or absent expression of proteins encoded by MMR genes increase the probability of developing Lynch syndrome. Therefore, MSI or protein expression with immunohistochemistry (IHC) of MMR genes are frequently employed to screen Lynch syndrome before genetic testing of MMR genes.

8.6 Detecting Hereditary Tumors in Clinical Practice and Introducing Genetic Counseling

It is important for a primary care physician to determine the family histories of individuals with hereditary tumors; therefore, thorough interviews are necessary. If the primary physician suspects that a patient's tumor is hereditary in nature, screening of the patient's family should be considered, at least up to second-degree relatives (i.e., grandparents, uncles, aunts, nephews, nieces, and grandchildren). Moreover, genetic counseling is recommended in such cases [9, 10].

The American Congress of Obstetricians and Gynecologists has released criteria for identifying patients who are predisposed to HBOC, and for whom genetic risk assessment is recommended [11]; Table 8.5 lists these criteria. Furthermore, the Amsterdam II Criteria are applied for the clinical screening of Lynch syndrome (Table 8.6) [12]. MSI and/or IHC tests can be performed in patients suspected of

Table 8.5 Criteria for genetic risk assessment by the American Congress of Obstetricians and Gynecologists [11]

Patients with an approximate chance greater than 20–25% of having an inherited predisposition to breast and ovarian cancer, and for whom genetic risk assessment is recommended:
• Women with a personal history of both breast and ovarian cancers[a]
• Women with ovarian cancer[a] who has a close relative[b] with ovarian cancer, premenopausal breast cancer, or both
• Women with ovarian cancer[a] who are of Ashkenazi Jewish ancestry
• Women with breast cancer at age 50 years or younger who have a close relative[b] with ovarian cancer[a] or male breast cancer at any age
• Women of Ashkenazi Jewish ancestry in whom breast cancer was diagnosed at age 40 years or younger
• Women with a close relative[b] known to have a *BRCA1* or *BRCA2* mutation

[a]Cancer of the peritoneum and fallopian tubes should be considered part of the spectrum of hereditary breast and ovarian cancer syndromes
[b]Close relative is defined as a first-degree relative (mother, sister, daughter) or second-degree relative (grandmother, granddaughter, aunt, niece)

Table 8.6 The Amsterdam II criteria for the clinical screening of Lynch syndrome [12]

• Three or more family members (one of whom is a first-degree relative of the other two) with HNPCC-related cancers
• Two successive affected generations
• One or more of the HNPCC-related cancers diagnosed before the age of 50 years
• Exclusion of familial adenomatous polyposis

HNPCC hereditary nonpolyposis colorectal cancer

having Lynch syndrome. Finally, genetic testing for *BRCA1/2* or MMR genes can differentiate the diagnosis of HBOC or Lynch syndrome.

8.7 Cancer Prevention and Risk Reduction Strategies

The endpoint of hereditary tumor research is ***to reduce mortality for cancers in mutation carriers*** who are at risk. RRSO is ***recommend*** for *BRCA1/2* mutation carriers. RRSO reduces the risk of ovarian cancer for unaffected *BRCA1/2* mutation carriers by 71–96% [13–18], and is usually performed after the completion of childbearing and during premenopausal years. However, premenopausal bilateral oophorectomy produces adverse effects; early-stage menopausal symptoms such as hot flashes, fatigue, shoulder stiffness, and palpitations can give rise to coital pain, atrophic vaginitis, urethritis, urinary incontinence, skin atrophy, and obesity. Long-term problems, such as osteoporosis or osteopenia, dyslipidemia, and arteriosclerosis, can also occur. Such adverse effects require monitoring by physicians who work on women health care [19].

Furthermore, according to recent NCCN guidelines, RRSO is also ***recommend*** in mutation carriers of MMR genes (*MSH2*, *MLH1, MSH6, PMS2*, *EPCAM*), and is ***considered*** in mutation carriers of *RAD51C*, *RAD51D* and *BRIP1* [20].

8.8 Current State of HBOC Research

Recently, multi-gene assaying has been introduced that can analyze that status of multiple suspect genes simultaneously. Furthermore, genetic testing for hereditary tumors is applied not only for assisting in cancer diagnosis but also for companion diagnostics. *BRCA1/2* testing is used as a companion diagnostic for PARP inhibitors. Furthermore, MSI screening may be used to predict the sensitivity of PD-1 (anti-programmed death-1) antibody because significant responses of cancers with MSI to anti–PD-1 inhibitors in patients who failed conventional therapy [21].

Conclusion

If clinicians suspect that an unusual number or pattern of cancers within a family may be caused by an inherited cancer predisposition genes, genetic counseling can be provided and genetic testing can be offered to find out inherited cancer genes. Gynecologists can play key roles in identifying women with hereditary cancer syndrome; this may help reduce mortality for mutation carriers.

References

1. Knudson Jr AG. Mutation and cancer: statistical study of retinoblastoma. Proc Natl Acad Sci U S A. 1971;68:820–3.
2. Petrucelli N, Daly MB, Feldman GL. *BRCA1* and *BRCA2* hereditary breast and ovarian cancer. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews. 2013. http://www.ncbi.nlm.nih.gov/books/NBK1247/. Accessed 21 Sept 2016.
3. Pal T, Permuth-Wey J, Betts JA, Krischer JP, Fiorica J, Arango H, et al. BRCA1 and BRCA2 mutations account for a large proportion of ovarian carcinoma cases. Cancer. 2005;104:2807–16.
4. Risch HA, McLaughlin JR, Cole DE, Rosen B, Bradley L, Kwan E, et al. Prevalence and penetrance of germline BRCA1 and BRCA2 mutations in a population series of 649 women with ovarian cancer. Am J Hum Genet. 2001;68:700–10.
5. Bolton KL, Chenevix-Trench G, Goh C, Sadetzki S, Ramus SJ, Karlan BY, et al. Association between BRCA1 and BRCA2 mutations and survival in women with invasive epithelial ovarian cancer. JAMA. 2012;307:382–90.
6. Alsop K, Fereday S, Meldrum C, de Fazio A, Emmanuel C, George J, et al. BRCA mutation frequency and patterns of treatment response in BRCA mutation-positive women with ovarian cancer: a report from the Australian ovarian cancer study group. J Clin Oncol. 2012;30:2654–63.
7. Yang D, Khan S, Sun Y, Hess K, Shmulevich I, Sood AK, et al. Association of BRCA1 and BRCA2 mutations with survival, chemotherapy sensitivity, and gene mutator phenotype in patients with ovarian cancer. JAMA. 2011;306:1557–65.
8. Ledermann J, Harter P, Gourley C, Friedlander M, Vergote I, Rustin G, et al. Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. N Engl J Med. 2012;366:1382–92.

9. Moyer VA, U.S. Preventive Services Task Force. Risk assessment, genetic counseling, and genetic testing for BRCA-related cancer in women: U.S. preventive services task force recommendation statement. Ann Intern Med. 2014;160:271–81.
10. Lu KH, Wood ME, Daniels M, Burke C, Ford J, Kauff ND, et al. American Society of Clinical Oncology expert statement: collection and use of a cancer family history for oncology providers. J Clin Oncol. 2014;32:833–40.
11. American College of Obstetricians and Gynecologists, ACOG Committee on Practice Bulletins–Gynecology, ACOG Committee on Genetics, Society of Gynecologic Oncologists. ACOG practice bulletin no. 103: hereditary breast and ovarian cancer syndrome. Obstet Gynecol. 2009;113:957–66.
12. Vasen HF, Watson P, Mecklin JP, Lynch HT. New clinical criteria for hereditary nonpolyposis colorectal cancer (HNPCC, Lynch syndrome) proposed by the international collaborative group on HNPCC. Gastroenterology. 1999;116:1453–6.
13. Finch A, Beiner M, Lubinski J, Lynch HT, Moller P, Rosen B, et al. Salpingo- oophorectomy and the risk of ovarian, fallopian tube, and peritoneal cancers in women with a *BRCA1* or *BRCA2* mutation. JAMA. 2006;296:185–92.
14. Rebbeck TR, Lynch HT, Neuhausen SL, Narod SA, Van't Veer L, Garber JE, et al. Prophylactic oophorectomy in carriers of *BRCA1* or *BRCA2* mutations. N Engl J Med. 2002;346:1616–22.
15. Kauff ND, Satagopan JM, Robson ME, Scheuer L, Hensley M, Hudis CA, et al. Risk-reducing salpingo-oophorectomy in women with a *BRCA1* or *BRCA2* mutation. N Engl J Med. 2002;346:1609–15.
16. Domchek SM, Friebel TM, Neuhausen SL, Wagner T, Evans G, Isaacs C, et al. Mortality after bilateral salpingo-oophorectomy in BRCA1 and BRCA2 mutation carriers: a prospective cohort study. Lancet Oncol. 2006;7:223–9.
17. Kauff ND, Domchek SM, Friebel TM, Robson ME, Lee J, Garber JE, et al. Risk-reducing salpingo-oophorectomy for the prevention of BRCA1- and BRCA2-associated breast and gynecologic cancer: a multicenter, prospective study. J Clin Oncol. 2008;26:1331–7.
18. Rutter JL, Wacholder S, Chetrit A, Lubin F, Menczer J, Ebbers S, et al. Gynecologic surgeries and risk of ovarian cancer in women with BRCA1 and BRCA2 Ashkenazi founder mutations: an Israeli population-based case-control study. J Natl Cancer Inst. 2003;95:1072–8.
19. Hirasawa A, Masuda K, Akahane T, Tsuruta T, Banno K, Makita K, et al. Experience of risk-reducing salpingo-oophorectomy for a BRCA1 mutation carrier and establishment of a system performing a preventive surgery for hereditary breast and ovarian cancer syndrome in Japan: our challenges for the future. Jpn J Clin Oncol. 2013;43:515–9.
20. NCCN. Clinical practice guidelines in oncology, genetic/familial high-risk assessment: breast and ovarian version 1.2017. https://www.nccn.org.
21. Le DT, Uram JN, Wang H, Bartlett BR, Kemberling H, Eyring AD, et al. PD-1 blockade in tumors with mismatch-repair deficiency. N Engl J Med. 2015;372(26):2509–20.