Hereditary Ovarian Cancer

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Abstract

The treatment of ovarian cancer has changed significantly over the past few years, particularly in the case of hereditary breast and ovarian cancer (HBOC) syndrome. Genetic testing for *BRCA1* and *BRCA2* is used not only for a diagnosis for HBOC but also a biomarker for PARP inhibitors, which is of great importance in the treatment of ovarian cancer. The characteristics of ovarian cancer in HBOC have been reported of the highest prevalence in high-grade serous carcinoma subtype, high sensitivity to platinum salt chemotherapies and PARP inhibitors, and a better prognosis compared to *BRCA*-negative ovarian cancer. It is important to note that ovarian cancer with a family history is also associated with Lynch syndrome, although less frequently than HBOC. In addition, recent multipanel genetic analysis has led to the identification of genes other than HBOC that are involved in the development of ovarian cancer, which may require further clinical practice.

Keywords

HBOC · Histology · Prevalence · Penetrance · Chemotherapy · Surveillance · Lynch syndrome · Moderate-risk genes

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7.1 Overview of Ovarian Cancer

Ovarian cancer is the most lethal gynecologic malignancy with more than 200,000 cases every year [1]. Due to the lack of effective screening methods, most patients are diagnosed at advanced stages. Less than 40% of women with ovarian cancer can be cured.

7.1.1 Symptoms

Symptoms associated with ovarian cancer were reported as pelvic/abdominal pain, urinary urgency/frequency, increased abdominal size/bloating, and difficulty eating/feeling full when they were frequently present for <1 year [2]. However, the screening by these symptoms, especially in patients with early-stage ovarian cancer, did not show enough sensitivity or specificity [3, 4]. Thus, ovarian cancer is still called as "a silent killer."

7.1.2 Histologic Subtypes

Epithelial ovarian cancer has four main histologic subtypes, including serous, endometrioid, mucinous, and clear cell. High-grade serous carcinoma (HGSC) characterized by *TP53* mutations is the most common and aggressive subtype. This subtype is related to hereditary breast and ovarian cancer (HBOC) syndrome, and its origin is said to be the fallopian tube or ovarian epithelium. Low-grade serous, mucinous, clear cell, and endometrioid tumors are believed to have developed from inclusion cysts or implants in the ovarian surface epithelium. They also have *KRAS, BRAF*, or *PTEN* mutations [5, 6]. Clear cell carcinoma has characteristics of being resistant to anticancer drugs, contrary to its slow growth, and is more common in Japan [7].

7.1.3 Risk Factors

The risk factors of developing ovarian cancer are age, nulliparity, and age (>35 years) at first pregnancy or first birth. Thirty percent to sixty percent decreased risk for cancer, in contrast, is associated with younger age at first pregnancy or first birth (≤25 years), the use of oral contraceptives, and history of breastfeeding [5]. As we will discuss later, having a family cancer syndrome is the most relevant risk of developing ovarian cancer.

7.1.4 Screening

Screening for ovarian cancer did not reduce mortality in two large screening trials. The Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial by

annual screening with serum CA125 and ultrasound showed no reduction in mortality [8]. The other result from the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) based on serum CA125-based screening seemed encouraging, but the mortality reduction was not significant [9].

7.1.5 Treatment

For epithelial ovarian cancer, primary treatment consists of appropriate surgical staging and debulking surgery, followed by systemic chemotherapy in most, but not all, patients. For most patients, initial surgery includes total abdominal hysterectomy and bilateral salpingo-oophorectomy with comprehensive staging with omentectomy, pelvic and para-aortic lymphadenectomy, and peritoneal biopsy [5, 10]. Debulking surgery is recommended for patients at stage II, III, or IV, because the maximal cytoreduction improves survival [11, 12]. Neoadjuvant chemotherapy followed by interval debulking surgery is recommended for patients diagnosed as advanced disease and the optimal surgery is difficult [10]. Regarding systematic lymphadenectomy, one recent RCT has shown that systematic pelvic and paraaortic lymphadenectomy after maximal cytoreduction did not improve survival and might cause postoperative complications when lymph nodes have no suspicious findings [13].

Most patients with epithelial ovarian cancer receive postoperative systemic chemotherapy. The combination of platinum and taxane agents is typically administered as a first-line chemotherapy for ovarian cancer. The effect of bevacizumab, anti-angiogenesis agent, was assessed by two RCTs, ICON7 and GOG218. These trials showed that the addition of bevacizumab to upfront chemotherapy with carboplatin/paclitaxel followed by bevacizumab as maintenance therapy improved PFS (hazard ratio[HR] 0.72, 0.81) and is recommended for patients at stage III or IV [14, 15].

The effect of poly(ADP-ribose) polymerase (PARP) inhibitors as maintenance therapy was assessed by several RCTs. The SOLO1 study demonstrated that PFS was prolonged substantially by using olaparib as a maintenance therapy in patients with a germline or somatic *BRCA1/BRCA*2 variant (HR 0.30) [16]. In Japan, olaparib is currently available for advanced ovarian cancer patients with *BRCA1/BRCA2* variants as maintenance therapy. Furthermore, the three RCTs of PARP inhibitors—veliparib, niraparib, and olaparib plus bevacizumab—have recently been shown to improve PFS [HR 0.68, 0.62, 0.59] when used after primary treatment regardless of *BRCA1/BRCA2* variant, but the better outcome was seen in homologous recombination deficiency (HRD)-positive patients [17–19].

The recurrent disease is categorized by platinum-sensitive disease (if the patients have the disease ≥6 months after completion prior platinum-based therapy) or platinum-resistant disease (if the patients have the disease <6 months after completion prior platinum-based therapy). For platinum-sensitive disease, six cycles of platinum-based chemotherapy are preferred. The addition of bevacizumab to standard chemotherapy and maintenance therapy until progression improved PFS for

platinum-sensitive recurrent ovarian cancer. OS was also improved in GOG213 [20, 21]. PARP inhibitors as maintenance therapy improved PFS of platinum-sensitive disease with germline *BRCA1/BRCA*2 variant, platinum-sensitive recurrent HGSC, and HRD positive [22–25]. For platinum-resistant disease, non-platinum-based agents or regimens are preferred. The prognosis is poor, but adding bevacizumab to chemotherapy improved PFS [26].

7.2 Hereditary Ovarian Cancer

It is now known that at least 10% of epithelial ovarian cancer have germline pathogenic variant in ovarian cancer-susceptibility genes, commonly *BRCA1/BRCA2* and DNA mismatch repair (MMR) genes. Of 1915 ovarian cancer patients, 347 (18%) carried a germline mutation in a gene associated with ovarian cancer risk [27]. In Japan, of 230 unselected women with ovarian cancer, 17.8% women had pathogenic germline variant. The variants include genes associated with *BRCA1* (prevalence; 8.3%), *BRCA2* (3.5%), and mismatch repair genes (2.6%) [28]. Patients with HGSC may have germline variants in other genes involved in HR, including *BRIP1*, *BARD1*, *RAD51C*, and *RAD51D*, but the frequency is less compared to *BRCA1* and *BRCA*2 [29]. In addition, some large studies using multiple-gene, next-generation sequencing panels and whole-exome sequencing were conducted, and gene-phenotype associations were examined. Table 7.1 shows the list of genes related to hereditary ovarian cancer and their risks of ovarian cancer reported in NCCN guidelines, and these studies [30, 31, 37]. Detailed personal and family history of cancer is important for cancer risk assessment and choice of gene testing. Comprehensive testing with multigene panel for *BRCA1-/BRCA2*-negative patients and individuals without a known familial pathogenic variant should be considered. In gynecological clinics, a self-administered questionnaire would be a useful tool for screening patient's medical history and familial cancer history [38].

7.2.1 Ovarian Cancer in HBOC

7.2.1.1 Frequency of HBOC in Ovarian Cancer

The frequency of germline *BRCA1/BRCA2* variants in ovarian cancer patients was reported to be 13–15% in some large studies [39, 40]. In Japan, one multicenter analysis reported that the overall prevalence of germline *BRCA1/BRCA2* variants was 14.7% (93/634), where germline *BRCA1* mutations (9.9%) were more common than germline *BRCA2* mutations (4.7%) [41]. In another report, of 230 unselected Japanese women with ovarian cancer, 11.7% women had pathogenic germline variants of *BRCA1/BRCA2* [28].

7.2.1.2 Germline Testing for Ovarian Cancer Patients

Based on personal and familial cancer history, germline *BRCA1/BRCA2* testing should be considered for individuals from a family without a known *BRCA1/BRCA2*

Table 7.1 The list of genes related to hereditary ovarian cancer and their risks of ovarian cancer. In NCCN guidelines, the risk is categorized as increase, potential increase, no increase, or unknown. The risk ratio of ovarian cancer for women with pathogenic variant of each gene is shown here according to each literature

Gene	Ovarian cancer risk (NCCN guidelines)	Odds Ratio (95% CI) [30]	Standardized risk ratio (95% CI) [31]	Relative Risk (95% CI) [32–36]	Odds Ratio (95% CI) [37]
BRCA1	increase	11.8 (9.99–14.0)	11.78 (10.42–13.28)		
BRCA2	increase	5.26 (4.38–6.31)	7.96 (7.00–9.01)		
RAD51C	increase	4.98 (3.09–8.04)	5.12 (3.72–6.88)	5.88 (2.91–11.88) 5.2 (1.1–24)	
RAD51D	increase	4.78 (3.09–8.04)	6.34 (3.16-11.34)	6.30 (2.86–13.85) 12.0 (1.5–90)	ND
BRIP1	increase	2.62 (1.72–3.98)	4.99 (3.79–6.45)	11.22 (3.22–34.10) 8.13 (4.74–13.95)	
NBN	potential increase	1.85 (1.05–3.24)	2.03 (1.27–3.08)		
ATM	potential increase	1.69 (1.19–2.40)	2.25 (1.69–2.94)	0.88 (0.02–5.84)	
PALB2	potential increase	1.60 (0.98–2.60)	3.08 (1.93–4.67)		
CHEK2	no increase	0.86 (0.56–1.33)	0.98 (0.75–1.27)		
TP53	no increase	0.66 (0.05–8.68)			28.96 (2.32–1506.64)
BARD1	unknown	0.59 (0.21–1.68)	1.28 (0.55–2.51)		
MMR genes	increase				
MLH1		3.11 (1.47–6.59)	2.20 (0.81–4.78)		
MSH2		2.04 (1.08–3.84)	13.91 (8.82–20.87)		
MSH6		1.92 (1.19–3.10)	5.04 (3.70–6.70)		6.73 (2.34–18.43)
PMS2		1.57 (0.94–2.60)	1.48 (0.81–2.48)		
STK11	increase of non-epithelial ovarian tumors	41.9 (5.55–315) (No of patients = 5)			

variant. NCCN guidelines recommend testing should be considered for patients at any age with a personal history of ovarian cancer (including fallopian tube cancer or peritoneal cancer) and those with a first- or second-degree blood relative of ovarian cancer [42]. Since 2020, Japanese public health insurance has covered 70% of germline *BRCA1/BRCA2* testing costs for cancer patients suspected of HBOC, and this includes ovarian cancer patients, too.

Detailed personal and family history of cancer is important for cancer risk assessment and choice of gene testing. For those without a known familial pathogenic variant or *BRCA1-/BRCA2*-negative patients, comprehensive testing with multigene panel should be considered. BRCA-related ovarian cancers are associated with epithelial, non-mucinous histology as discussed below; however, bear in mind that Lynch syndrome or other syndromes could be associated with both non-mucinous and mucinous histology.

7.2.1.3 Penetrance of *BRCA1/BRCA2* Variant Carriers in Ovarian Cancer

Women with a *BRCA1/BRCA2* pathogenic variant are at increased risk of ovarian cancers (including fallopian tube cancer and primary peritoneal cancer). The reliable prediction of developing ovarian cancer (the penetrance) is critical in genetic counseling and a gynecological practice for *BRCA1/BRCA2* variant carriers. A meta-analysis showed the mean cumulative ovarian cancer risks for *BRCA1/BRCA2* variant carriers at age 70 years were 40% (95% CI, 35% to 46%) for *BRCA1* and 18% (95% CI, 13% to 23%) for *BRCA2* variant carriers [43]. A large prospective cohort study of 6036 *BRCA1* and 3820 *BRCA2* female variant carriers showed that the cumulative ovarian cancer risks to age 80 years were 44% (95% CI, 36%–53%) for *BRCA1* and 17% (95% CI, 11%–25%) for *BRCA2* carriers [44]. The risk of ovarian cancer is not the same for all *BRCA1/BRCA2* mutations. A large observational study from data collected by the Consortium of Investigators of Modifiers of BRCA (CIMBA) initiative revealed that women with a variant in the central part of *BRCA1/BRCA2*, especially in exon11 where ovarian cancer cluster regions (OCCRs) were identified, will have a higher lifetime risk of ovarian cancer [45]. The estimated penetrance of ovarian cancer can be influenced by allelic heterogeneity, modifier genes, and environmental and hormonal cofactors, such as oral-contraceptive use or parity and nationality [46].

7.2.1.4 Histology of Ovarian Cancer in HBOC

There are four main histologic subtypes of epithelial ovarian cancer: serous carcinoma (low-grade and high-grade), mucinous carcinoma, endometrioid carcinoma, and clear cell carcinoma. Germline *BRCA1/BRCA2* variants were reported in all histologic subtypes except mucinous carcinoma (Table 7.2). In several large studies, high-grade serous carcinoma had the highest prevalence of *BRCA1/BRCA2* variant [27, 39]. In Japan, a multicenter analysis reported that 28.5% of high-grade serous carcinoma has germline *BRCA* variants [41]. Another multivariate analysis showed that the high-grade serous carcinoma subtype is an independent predictive factor for pathogenic germline *BRCA1/BRCA2* variants [28]. It should be noted that the

Table 7.2 Prevalence of germline *BRCA1/BRCA2* variants in each histological subtype of ovarian cancer

	Prevalence of germline *BRCA1/2* variants			
	Enomoto et al. [41] (Japan)	Hirasawa et al. [28] (Japan)	Norquist et al. [27]	Alsop et al. [39]
Overall	14.7%(93/634)	11.7%(27/230)	15%(280/1915)	14.1%(141/1001)
HGSC	28.5%(78/274)	29.7%(22/74)	16.1%(241/1498)	22.6%(98/433)
LGSC	20%(1/5)	0%(0/3)	5.7%(4/70)	NA
endometrioid	6.7%(8/120)	3.4%(2/58)	not shown	8.4%(10/119)
clear	2.1%(4/187)	2.8%(2/71)	6.9%(4/58)	6.3%(4/63)
mucinous	0%(0/19)	0%(0/18)	0%(0/16)	NA

prevalence of germline *BRCA1/BRCA2* variants differs between studies, especially in clear cell carcinoma. This is because the frequency of germline *BRCA1/BRCA2* variants has not been clarified, due to the low incidence of clear cell carcinoma in Western countries. Large-scale studies will be necessary in the future.

7.2.1.5 Ovarian Cancer Initiation in HBOC

After risk-reducing salpingo-oophorectomy (RRSO), a precursor lesion called tubal intraepithelial carcinoma (TIC) was detected in 5–10% of cases in women with *BRCA* variants [47–50]. The distal fallopian tube is suspected to be the dominant origin of early malignancies found in RRSO samples [47, 50, 51]. TICs and their associated ovarian carcinomas share identical mutations of *TP53* [52]. Although the idea of fallopian tube to be the origin of many serous carcinomas of ovary for *BRCA1/BRCA2* variant carriers is now generally accepted, there is a subset of HGSC with no apparent precursor lesion in the fallopian tube, so further study is needed to understand how these cancers develop [29]. It is not clear whether surgical staging and/or adjuvant chemotherapy is beneficial for women with STIC.

7.2.1.6 Prognosis of *BRCA1/BRCA2* Variant Carriers with Ovarian Cancer

Recently, meta-analysis of women's survival with ovarian cancer was done. This study was based on 26 reports including data from 1213 epithelial ovarian cancer patients with germline *BRCA1/BRCA2* variants and 2666 noncarriers. Germline variants in *BRCA1* or *BRCA2* are associated with higher 5-year overall survival among patients with ovarian cancer. After adjusting the methods of studies and years of diagnosis, *BRCA1/BRCA2* variant carriers showed better survival than noncarriers (for *BRCA*1, hazard ratio [HR], 0.78; 95% CI, 0.68–0.89, and for *BRCA2*, HR, 0.61; 95% CI, 0.50–0.76) [53]. However, other reports suggested a positive effect of germline *BRCA1/BRCA2* variant, where mortality in patients with ovarian cancer decreased to 10 years [54].

7.2.1.7 Chemosensitivity and HRD of Ovarian Cancer in HBOC

Both *BRCA1* and *BRCA2* take part in DNA repair such as homologous recombination (HR) and the maintenance of genomic integrity. Cells with defective *BRCA1* or

BRCA2 are hypersensitive to agents that crosslink DNA strands. These are also sensitive to agents that produce breaks in double-stranded DNA, such as platinum salt chemotherapies [46]. Multiple case-control studies compared the effect of primary therapy between ovarian cancer patients with and without *BRCA1/BRCA2* variants. These studies revealed that *BRCA*-related ovarian cancer showed better survival outcomes and platinum sensitivity [39, 55, 56]. However, one study showed that, among women with high-grade serous ovarian cancer, *BRCA2* mutation, but not *BRCA1* deficiency, was associated with improved survival and chemotherapy response [57]. Not only germline *BRCA1/BRCA2* variant but also germline variants of other cancer-associated genes such as *BRIP1*, *RAD51C*, *RAD51D*, *PALB*2, and *BARD1* were more frequent in patients with ovarian cancer than in the general population. There wasn't a significant difference in survival rate between women with mutations in *BRCA1* and other ovarian cancer-associated genes [27]. In addition to germline variant, ovarian cancer with somatic *BRCA1/BRCA2* variants or somatic variants in other homologous recombination DNA repair genes, such as *ATM*, *BARD1*, *BRIP1*, *CHEK1*, *CHEK2*, *FAM175A*, *MRE11A*, *NBN*, *PALB2*, *RAD51C*, and *RAD51D*, had higher primary platinum sensitivity and improved overall survival than those without variants [39, 58].

Almost 50% of epithelial ovarian cancers exhibit defects within the homologous recombination DNA repair (HRR) pathway. As cells with double-strand break repair deficiency have synthetic lethality to PARP inhibitors (PARPi), ovarian cancer with homologous recombination repair deficiency (HRD) exhibits a sensitivity to PARPi and platinum salt chemotherapies [58]. HRD is often caused by loss of function mutations in HRR genes, such as *BRCA1*, *BRCA2*, *RAD51C*, *RAD51D*, or *PALB*2, promoter hypermethylation of the *BRCA1* and *RAD51C* gene promoter (leading to reduced expression), or unknown mechanisms. HRD testing is hoped to be a predictive biomarker for PARPi sensitivity. A wide range of assays, referred as "HRD tests," have been developed to define which cancers have HRD. These HRD tests fall into three main categories: (1) HRR pathway, which is related to genes that identify specific causes of HRD, (2) genomic "scars" or mutational signatures which identify the patterns of somatic mutations that accumulate in HRD cancers irrespective of the underlying defect, and (3) functional assays that have the potential to provide a real-time readout of HRD or homologous recombination proficiency (HRP) [59]. A commercially available assay, Myriad MyChoice®, can now be used as a biomarker for PARPi in Japan. This test is the combination of *BRCA1/BRCA2* variant and genomic instability scores (GIS). GIS includes loss of heterozygosity (LOH), telomeric allelic imbalance (TAI), and large-scale state transitions (LST), which is categorized by the genomic scar assay. Although there are several clinical benefits of HRD testing on PARPi response in ovarian cancer, HRD testing is not completely overlapped to PARPi sensitivity, where HRP ovarian cancer has sensitivity to PARPi. Better biomarkers are needed for HGSC management [59] (Fig. 7.1). When analyzing cancer genome by next-generation sequencing like HRD testing, we should bear in mind that mutations in DNA of a tumor may reveal germline variants with clinical significance [60]. Further detail about significance of PARPi for ovarian cancer is described in another section.

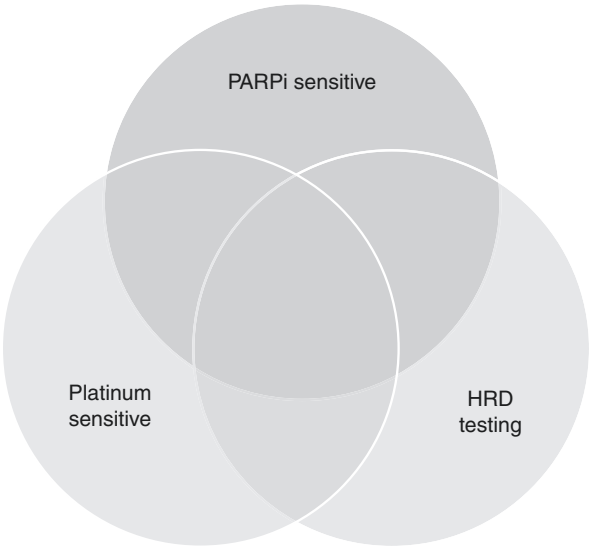

Fig. 7.1 Venn diagram showing the relation between HRD testing, platinum sensitivity, and PARPi sensitivity. Although HRD testing is approved as a clinical biomarker for PARPi sensitivity, patients with positive for HRD testing are not completely overlapped to responses of PARPi

7.2.1.8 Surveillance for Ovarian Cancer

Women with a *BRCA1/BRCA2* pathogenic variant are at increased risk of having ovarian cancers. Several studies on significance of ovarian cancer screening had been conducted. Phase II study of the UK Familial Ovarian Cancer Screening Study (UK FOCSS) included 4348 women with an estimated lifetime ovarian cancer risk of ≥10% and did not choose risk-reducing salpingo-oophorectomy (RRSO). They were assessed by serum CA-125 tests (every 3 months, with using the risk of ovarian cancer algorithm [ROCA]) and TVUS (annually or within 2 months of an abnormal ROCA result). Thirteen ovarian cancer patients were screen-detected, and 5 (38.5%) of the 13 patients were diagnosed at an early stage (stages I to II). Sensitivity, positive predictive value, and negative predictive value for detecting ovarian cancer within 1 year were 94.7%, 10.8%, and 100%, respectively [61].

In another study, 3692 women with a strong family history of breast/ovarian cancer or *BRCA1/BRCA2* variant were assessed by serum CA125 (every 3 months, with using the risk of ovarian cancer algorithm [ROCA]) and transvaginal ultrasound (TVUS) (if ROCA increased above a baseline). Three (50%) of six incidental ovarian cancers were at early stage. ROCA flagged 50% of incidental cases. This method had better early-stage sensitivity at high specificity, but low PPV compared with CA125 every 6 months or annually [62].

Given its high sensitivity and significance in stage shift, these surveillance methods could be an option for *BRCA1/BRCA2* variant carriers who did not choose RRSO. However, significance of these strategies to improve survival rate in screened *BRCA1/BRCA2* variant carriers remains unknown. In NCCN guidelines, RRSO is

the standard method of ovarian cancer risk management in *BRCA1/BRCA2* carriers. For those patients who did not select RRSO, regular checkup by transvaginal ultrasound and serum CA-125 for ovarian cancer screening may be considered from the age of 30 to 35, although its benefit is not certain [42]. Further details about RRSO and chemoprevention for ovarian cancer are described in other sections.

7.2.2 Ovarian Cancer in Lynch Syndrome

Lynch syndrome is a hereditary syndrome associated with familial cancers, including colorectal cancer and Lynch syndrome-related cancers, such as endometrial cancer. The cause of the disease is the germline variant of DNA mismatch repair (MMR) genes, such as *MLH1*, *MSH2*, *MSH6*, and *PMS2*, characterized by autosomal dominant inheritance. Women with Lynch syndrome are also at increased risk of ovarian cancer.

The histological types of ovarian cancer were mixed type (mucinous/endometrioid/clear cell carcinomas) 33%, endometrioid carcinoma 25%, serous carcinoma 22%, clear cell carcinoma 12%, and mucinous carcinoma 4%. Most tumors (65%) were diagnosed at an early stage [63].

Microsatellites are short DNA repeat sequences that increase or decrease in number when MMR is dysfunctional. An MSI test is recommended before examining germline mutation when a patient is suspected of suspected Lynch syndrome. Screening of ovarian cancer specimens by MSI may be an efficient way to diagnose Lynch syndrome [64].

There is no definite evidence to support routine screening for ovarian cancers in Lynch syndrome. Total abdominal hysterectomy and bilateral salpingo-oophorectomy are options that may be considered for risk reduction in women with Lynch syndrome who have completed childbearing [5].

7.2.3 Other Germline Variants Associated with Ovarian Cancer

7.2.3.1 *RAD51C, RAD51D, BRIP1*

DNA recombinase RAD51 protein is a central player in homologous recombination and DNA repair. *BRIP1* encodes the BRCA1-interacting protein C-terminal helicase 1 protein, which is required for the normal double-strand break repair function of *BRCA1*. *RAD51C* and *RAD51D*, genes in the RAD51 protein family, and *BRIP1* have been shown to be associated with increased risk for ovarian cancer [32–36].

The frequency of germline *RAD51C/RAD51D* variants and *BRIP1* variants in ovarian cancer patients was reported to be about 1% [30, 31].

In carriers of a *RAD51D* variant or *BRIP1* variant, the cumulative risk of ovarian cancer approaches 2.6% around 50 to 54 years of age, which is the expected lifetime risk for a woman with a BRCA-negative family history of ovarian cancer [65]. The NCCN guidelines recommend that RRSO in carriers of *RAD51C*, *RAD51D*, or *BRIP1* pathogenic or likely pathogenic variants be considered beginning at 45 to

50 years of age. In women with variants in these genes who also have a family history of ovarian cancer in a first-degree relative, the risk threshold might cross earlier and the timing for RRSO should be considered [42].

7.2.3.2 *NBN, ATM, PALB2*

Some studies suggest that there may be a moderately increased risk for ovarian cancer in carriers of an *NBN*, *ATM*, or *PALB2* variant, but there is currently insufficient evidence to recommend RRSO in these carriers [27, 30, 31].

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