# Hereditary Ovarian Cancer

# 2

Masayuki Sekine and Takayuki Enomoto

**Abstract**

Hereditary ovarian cancer, approximately 20% of epithelial ovarian cancers, occurs as part of several genetically distinct syndromes, hereditary breast and ovarian cancer (HBOC), Lynch syndrome (hereditary nonpolyposis colorectal cancer, HNPCC), and so on. HBOC are caused by mutations in the *BRCA1/2* genes, and the penetrance of the genes for ovarian cancer was estimated to be 8–62% in different populations. A high-grade serous carcinoma is a major histological subtype, although endometrioid and clear cell carcinomas also have been reported in the *BRCA*-related ovarian cancers. Germline mutations in *BRCA1/2* are responsible for approximately 15% of epithelial ovarian cancers. *BRCA1/2* mutation-positive women with ovarian cancer showed more favorable survival outcomes compared with mutation-negative women due to higher response rates to platinum regimens.

Ovarian cancer screening with transvaginal ultrasound and CA-125 has not been shown to be sufficiently sensitive or specific, so risk-reducing salpingo-oophorectomy (RRSO) after completion of childbearing has been recommended for *BRCA1/2* mutation carriers. RRSO for ovarian and breast cancer was associated with 80% and 50% risk reduction in *BRCA1/2* mutation carriers, respectively. An oral contraceptive significantly reduced the risk for ovarian cancer by approximately 50% for the mutation carriers. So far, more than 20 genes are known to be involved in pathogenesis of hereditary ovarian cancer. The NCCN Guidelines recommend RRSO in *BRCA1/2*, MMR genes, *BRIP1*, *and RAD51C/D* mutation carriers.

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Poly (ADP-ribose) polymerase (PARP) inhibitors cause cancer cell death in *BRCA*-mutated cancers by synthetic lethality. Olaparib was the first PARP inhibitor approved in the EU and USA for the treatment of advanced ovarian cancer patients with a germline *BRCA* mutation. Several trials are ongoing for the inhibitors in other populations such as patients with homologous recombination deficiency.

**Keywords**
*BRCA1* • *BRCA2* • Hereditary breast and ovarian cancer (HBOC) • Risk-reducing salpingo-oophorectomy (RRSO) • Homologous recombination deficiency (HRD) • Poly (ADP-ribose) polymerase (PARP) inhibitors

## 2.1 Introduction

Ovarian cancer is the most lethal disease in gynecological malignancy. A positive family history of ovarian cancer is one of the strongest and most consistent of the risk factors for the development of the disease. It has been reported that first-degree relatives of ovarian cancer patients were found to be at a two- to fourfold increased risk for developing the disease [1, 2].

Now, approximately 20% of ovarian cancers have been related to hereditary conditions [3]. Hereditary ovarian cancer occurs as part of several genetically distinct syndromes, hereditary breast and ovarian cancer (HBOC), hereditary nonpolyposis colorectal cancer (HNPCC), and so on. HBOC caused by inherited mutations of *BRCA1/2* and HNPCC caused by the mismatch repair genes are predicted to be responsible for about 65–75% and 10–15% of hereditary ovarian cancer, respectively. Furthermore, other suppressor genes and oncogenes have been related with hereditary ovarian cancer [4–7]. So far, more than 20 genes are known to be involved in pathogenesis of hereditary ovarian cancer; however, unknown susceptibility genes and their mutations appear to exist [8].

We reviewed the available published data regarding clinical and molecular features and management (i.e., surveillance, chemoprevention, risk-reducing surgery, and molecular targeting agents) of hereditary ovarian cancer, especially *BRCA*-related hereditary breast and ovarian cancer.

## 2.2 Hereditary Breast and Ovarian Cancer (HBOC): *BRCA*-Related Breast and Ovarian Cancer

### 2.2.1 Clinical and Molecular Features of HBOC

Hereditary breast and ovarian cancer (HBOC) is caused by mutations in the *BRCA1/2* genes [9, 10]. *BRCA1/2* genes are tumor suppresser genes and involved in DNA repair of double-strand DNA breaks and the regulation of cell-cycle checkpoints in response to DNA damage [11, 12]. The *BRCA1* gene is located on short arm of chromosome 17, and the *BRCA2* gene on long arm of chromosome 13. The frequency of

pathogenic mutations in *BRCA1/2* genes has been estimated to be 1/300 and 1/800, respectively [13–15].

It has been estimated that more than 90% of hereditary breast and ovarian cancer families are related to germline mutation of *BRCA1/2* genes in Western countries [16]; on the other hand, approximately 80% of breast and ovarian cancer families in Japan are based on the mutation [17]. In analysis of hereditary ovarian cancer families, *BRCA1/2* mutations were detected in 41.9% of families in which there were at least two ovarian cancer cases [18]. In Japanese population, among the 55 ovarian cancer families without breast cancer patients, 24 families were carrying germline mutations in *BRCA1/2* (24/55, 43.6%); however, in 27 breast-ovarian cancer families, 21 families were positive with the mutation (21/27, 77.8%) [17]. About half of families showing a genetic predisposition to ovarian cancer did not have identifiable BRCA1/2 mutations, so other gene mutations predisposing a patient to ovarian cancer are likely to exist [19, 20].

Germline mutations in *BRCA1/2* are responsible for more than 10% of epithelial ovarian cancers [21, 22]. Among 1915 patients with ovarian cancer, 280 (15%) had mutations in *BRCA1* ($n = 182$) or *BRCA2* ($n = 98$) [22]. Histological characteristics by BRCA1/2 mutation status in this large mutational analysis were summarized in Table 2.1 [22]. The *BRCA1/2* mutation prevalence was 11–16% in high-grade serous carcinoma [22, 23]. In analysis of invasive ovarian cancer, 13–20% of the patients have a germline mutation of *BRCA1/2* [24–27]. In Japan, Sakamoto et al. reported that 12 of the 95 unselected women with ovarian cancer (12.6%), including 5 in the *BRCA1* (5.3%) and 7 in the *BRCA2* (7.4%), had deleterious mutations and all cases with *BRCA* mutation were diagnosed at advanced stage and had high-grade serous carcinoma [28]. Table 2.2 demonstrates histological and molecular subtypes of epithelial ovarian cancer [29].

**Table 2.1** Histological characteristics by BRCA1/2 mutation status

| | High-grade serous | Low-grade serous | High-grade endometrioid | Low-grade endometrioid | Clear cell | Mucinous | Unspecified carcinoma |
|---|---|---|---|---|---|---|---|
| No. | 1501 | 70 | 64 | 14 | 58 | 16 | 166 |
| BRCA1 (%) | 10.3 | 4.3 | 6.3 | 0 | 6.9 | 0 | 8.4 |
| BRCA2 (%) | 5.7 | 1.4 | 4.7 | 0 | 0 | 0 | 5.4 |
| BRCA1/2 (%) | 16.0 | 5.7 | 10.9 | 0 | 6.9 | 0 | 13.9 |

**Table 2.2** Histological and molecular subtypes of epithelial ovarian cancer

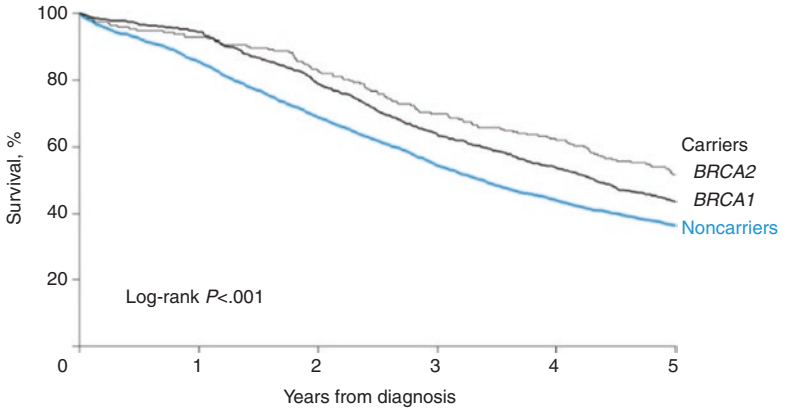
| | High-grade serous | Low-grade serous | High-grade endometrioid | Low-grade endometrioid | Clear cell | Mucinous |
|---|---|---|---|---|---|---|
| Genomic alterations | *TP53*<br>*BRCA1/2*<br>Other HRR genes | *BRAF*<br>*KRAS*<br>*PTEN*<br>*PIK3CA* | *BRCA1/2* | *PTEN*<br>*PIK3CA*<br>*CTNNB1*<br>*ARID1A*<br>*BRAF* | *ARID1A*<br>*PIK3CA* | *KRAS*<br>*CDKN2A*<br>*PIK3CA*<br>*BRAF*<br>*TP53* |
| Copy number alterations | – | – | – | – | *ERBB2* | *ERBB2* |

*HRR* homologous recombination repair

Several founder mutations have been observed in the specific population, for example, the 187delAG and 5385insC mutations in *BRCA1* and the 6174delT mutation in *BRCA2* have been identified in the Ashkenazi Jewish population [30, 31]. In Japanese population, it was reported that the L63X and Q934X mutations in *BRCA1* were the founder mutations with high frequency in hereditary ovarian cancer families [17], and it has been reported that the L63X is a founder mutation with the highest frequency in Japanese breast cancer families [32, 33].

The penetrance of *BRCA1/2* gene mutation in ovarian cancer is lower than that in breast cancer. A lifetime risk for ovarian cancer in *BRCA* mutation carriers was estimated to be 8–62% in different populations; however, that for breast cancer was 41–90%. A meta-analysis of these published data showed the average cumulative risks for breast and ovarian cancer by age 70 years for *BRCA1* mutation carriers were 57% and 40%, respectively. For *BRCA2* mutation carriers, they were 49% and 18%, respectively, in the meta-analysis [5, 24, 34–42]. In a recent prospective study, the estimated average cumulative risks for breast and ovarian cancer by age 70 years for *BRCA1* mutation carriers were 60% and 59%, respectively. In addition, for BRCA2 mutation carriers, they were 55% and 16.5%, respectively [39]. A subsequent alteration or silencing in the second copy of the gene without the hereditary mutation is believed to be necessary for the initiation of cancer development, so the risk of breast and ovarian cancer with *BRCA1/2* mutations is various, even within families with the same mutation. In an international observational study of 19,581 carriers of *BRCA1* mutations and 11,900 carriers of *BRCA2* mutations in 33 countries on 6 continents, 12% of the *BRCA1* mutation carriers and 6% of the *BRCA2* mutation carriers were diagnosed with ovarian cancer, and 46% of the *BRCA1* mutation carriers and 52% of the *BRCA2* mutation carriers were diagnosed with breast cancer [43]. As described above, *BRCA1/2* mutation carriers have a high risk for both breast cancer and an ovarian cancer, so there was a need to consider more intensive screening and prevention strategies such as chemoprevention and prophylactic surgery.

It has been reported that some pathological features are observed more frequently in breast and ovarian cancer patients with *BRCA1/2* mutation. For example, breast cancers with *BRCA1/2* mutation are characterized as ER/PR and HER2 negative: triple negative [44–49]. In ovarian cancers with *BRCA1/2* mutation, high-grade serous carcinoma is a major histological subtype, although endometrioid and clear cell carcinomas also have been reported in the *BRCA*-related ovarian cancers [21, 25–27, 50–53]. Mucinous type is very rare in the population [25, 27]. In Japanese hereditary breast and ovarian cancer families, the major histological type of *BRCA*-associated ovarian cancers was serous carcinoma in 81% of tumors, and only one case was clearcell carcinoma. No tumor with mucinous carcinoma occurred in these families [17]. Mucinous carcinomas appear to be related to other gene mutations; *KRAS* and *TP53* [54]. Borderline epithelial ovarian tumors are not associated with a *BRCA1/2* mutation [21]. Although non-epithelial ovarian carcinomas are not significantly associated with a *BRCA1/2* mutation, sex cord tumors may be associated with Peutz-Jeghers syndrome, and Sertoli-Leydig cell tumors are caused by germline mutations in the *DICER1* gene [55–61].




| No. at risk | | | | | | |
|---|---|---|---|---|---|---|
| Noncarriers | 1047 | 1687 | 1540 | 1395 | 1225 | 1044 |
| Carriers | | | | | | |
| *BRCA1* | 327 | 593 | 569 | 490 | 408 | 342 |
| *BRCA2* | 117 | 199 | 192 | 179 | 164 | 125 |

**Fig. 2.1** Association between *BRCA1/2* mutations and survival in women with invasive epithelial ovarian cancer. *BRCA1* and *BRCA2* mutation carriers showed a more favorable survival than noncarriers (for *BRCA1*, HR = 0.78 [95% CI, 0.68–0.89], $P < 0.001$, and for *BRCA2*, HR = 0.61 [95% CI, 0.50–0.76], $P < 0.001$) in a pooled analysis from 26 observational studies that included invasive epithelial ovarian cancer cases from *BRCA1/2* mutation carriers ($n = 1213$) and noncarriers ($n = 2666$). Kaplan-Meier analysis was adjusted for year of diagnosis and study [63]

Several studies have reported that *BRCA* mutation-positive women with ovarian cancer showed more favorable survival outcomes compared with mutation-negative women [62–67]. Figure 2.1 indicates that *BRCA1/2* mutation carriers showed a more favorable survival than noncarriers (for BRCA1, HR = 0.78 [95% CI, 0.68–0.89], $P < 0.001$, and for BRCA2, HR = 0.61 [95% CI, 0.50–0.76], $P < 0.001$) in a pooled analysis from 26 observational studies that included invasive epithelial ovarian cancer cases from *BRCA1/2* mutation carriers ($n = 1213$) and noncarriers ($n = 2666$) [63]. The 5-year overall survival was 36% for noncarriers, 44% for *BRCA1* carriers, and 52% for *BRCA2* carriers. In a population-based case-control study of women with invasive epithelial (non-mucinous) ovarian cancer ($n = 1001$), patients carrying germline mutations of *BRCA1/2* had improved rates of progression-free survival (median, 20 months vs 16 months; not statistically significant) and overall survival (median, 62 months vs 55.5 months; $P = 0.031$) [62]. Survival outcomes appear to be most favorable for *BRCA2* mutation carriers [63]. An observational study of 1915 women with ovarian cancer from the University of Washington (UW) gynecologic tissue bank and from the Gynecologic Oncology Group (GOG) phase III clinical trials ($n = 1345$) showed that patients with a *BRCA2* mutation from the GOG trials had significantly longer progression-free survival (HR, 0.60; 95% CI, 0.45–0.79; $P < 0.001$) and OS (HR, 0.39; 95% CI, 0.25–0.60; $P < 0.001$), compared with those without mutations [22].

BRCA mutation carriers appeared to be more responsive to cytotoxic chemotherapy compared with noncarrier patients [68]. Several studies have shown a higher response rate to platinum regimens and longer treatment-free intervals between relapses in *BRCA* mutation carriers compared with noncarriers [62, 63, 66, 69–71]. These clinical features of BRCA-associated ovarian cancer are attributed to homologous recombination repair deficiency in the absence of *BRCA1/2* function, which results in an impaired ability of tumor cells to repair platinum-induced double-strand breaks [66, 70, 72]. Thereby conferring increased chemosensitivity and increased sensitivity to poly (ADP-ribose) polymerase (PARP) enzyme inhibition and other DNA-damaging chemotherapeutic agents such as pegylated liposomal doxorubicin (PLD) [68].

### 2.2.2 Ovarian Cancer Screening for Surveillance

Ovarian cancer screening with transvaginal ultrasound and CA-125 has not been shown to be sufficiently sensitive or specific. So far, there is no evidence that these screening are appropriate methods of substituting for ovarian cancer risk-reducing surgery [73, 74]. In recent large randomized controlled trial, the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS), which assessed multimodality screening with ultrasound and CA-125 versus either ultrasound alone or no screening, showed that a significant mortality reduction was not observed after a median of 11 years of follow-up; however, a prespecified analysis of death from ovarian cancer of multimodality screening versus no screening with exclusion of prevalent cases showed significantly different death rates ($P = 0.021$) [75, 76]. In this trial, the cases with increased risk of familial ovarian cancer were included in exclusion criteria. The NCCN Guidelines recommend that ovarian cancer screening with transvaginal ultrasound and CA-125 may be considered starting at age 30–35 years by the doctor's discretion for women who have not selected the risk-reducing surgery [13]. GOG-0199 is a two-arm, prospective, nonrandomized study for managing the risk of ovarian cancer in high-risk women. One arm is women who elected RRSO, and the other is those who chose the ROCA (risk of ovarian cancer algorithm) surveillance using transvaginal ultrasound and CA-125. This 5-year follow-up period ended in November 2011 and the data has been analyzed [77].

### 2.2.3 Risk-Reducing Salpingo-Oophorectomy (RRSO)

The risk for ovarian cancer in *BRCA1/2* mutation carriers is generally considered to be lower than the risk for breast cancer. However, due to the absence of reliable methods of early detection and the poor prognosis associated with advanced ovarian cancer, RRSO after completion of childbearing has been recommended for *BRCA1/2* mutation carriers. The NCCN Guidelines recommend RRSO for women with

*BRCA1/2* mutation, typically between ages 35 and 40 years for women with a *BRCA1* mutation [13]. For women with a *BRCA2* mutation who have undergone efforts to maximize their breast cancer prevention (i.e., bilateral mastectomy), it is reasonable to delay RRSO until between ages 40 and 45 years since ovarian cancer onset tends to be later in women with a *BRCA2* mutation [78]. RRSO should only be considered upon completion of childbearing.

The effectiveness of RRSO in reducing the risk for ovarian cancer in *BRCA1/2* mutation carriers has been reported in various studies. In a meta-analysis including ten studies, RRSO was associated with a statistically significant reduction in the risk of *BRCA*-associated ovarian or fallopian tube cancer (HR = 0.21; 95% CI = 0.12–0.39) [78]. In an international observational study of 5783 women with a *BRCA1/2* mutation, risk-reducing oophorectomy was associated with an 80% reduction (HR, 0.20; 95% CI, 0.13–0.30) in the risk of ovarian, fallopian tube, or peritoneal cancer in *BRCA1/2* carriers and a 77% reduction in all-cause mortality (HR, 0.23; 95% CI, 0.13–0.39) [78]. RRSO reduces mortality at all ages in *BRCA1* mutation carriers; however, RRSO is not associated with reduced mortality in those at the ages of more than 61 in *BRCA2* mutations carriers [78]. Furthermore, in prospective, multicenter cohort study of 2482 women with *BRCA1/2* mutations, RRSO was associated with lower all-cause mortality (10% vs 3%; HR, 0.40 [95% CI, 0.26–0.61]), breast cancer-specific mortality (6% vs 2%; HR, 0.44 [95% CI, 0.26–0.76]), and ovarian cancer-specific mortality (3% vs 0.4%; HR, 0.21 [95% CI, 0.06–0.80]) [79]. We have to take care that 1–4.3% risk of a primary peritoneal cancer has remained after RRSO [80–84]. The ovarian cancer risk and management were shown in Table 2.3 [13].

Many studies have reported that RRSO reduced the risk for breast cancer in *BRCA1/2* mutation carriers [80, 81, 83, 85, 86]. In a meta-analysis of all reports of RRSO published between 1999 and 2007, RRSO was associated with a statistically significant reduction in risk of breast cancer in *BRCA1/2* mutation carriers (HR = 0.49; 95% confidence interval [CI] = 0.37–0.65), *BRCA1* mutation carriers (HR = 0.47; 95% CI = 0.35–0.64), and *BRCA2* mutation carriers (HR = 0.47; 95%

**Table 2.3** Ovarian cancer risk and management

| | Ovarian cancer risk | Management |
|---|---|---|
| *BRCA1* | Increased risk of OC | Consider RRSO at 35–40 year |
| *BRCA2* | Increased risk of OC | Consider RRSO at 45–50 year |
| MMR genes | Increased risk of OC | Consider RRSO and hysterectomy at completion of childbearing |
| *BRIP1* | Increased risk of OC | Consider RRSO at 45–50 year |
| ***RAD51C*** | Increased risk of OC | **Consider RRSO at 45–50 year** |
| ***RAD51D*** | Increased risk of OC | **Consider RRSO at 45–50 year** |
| ***PALB2*** | **Insufficient evidence for OC risk** | —— |
| ***TP53*** | **No increased risk of OC** | —— |

*MMR* mismatch repair, *OC* ovarian cancer, *RRSO* risk-reducing salpingo-oophorectomy

CI = 0.26–0.84) [80]. Results of a prospective cohort study suggest that RRSO may be associated with a greater reduction in breast cancer risk for *BRCA2* mutation carriers compared with *BRCA1* mutation carriers [87]. Reductions in breast cancer risk for *BRCA1/2* mutation carriers following RRSO may be associated with decreased hormonal exposure due to resection of the ovaries. In an international case-control study of 1439 patients with breast cancer and 1866 matched controls derived from a registry of *BRCA1/2* mutation carriers, the risk reduction was greater if the oophorectomy was performed before age 40 (OR = 0.36; 95% CI, 0.20–0.64 for *BRCA1* carriers) than after age 40 (OR = 0.53; 95% CI, 0.30–0.91), and no significant reduction was found for women aged 51 years or older in breast cancer risk [86]. However, the hazard ratio for breast cancer-specific mortality in *BRCA1/2* mutation carriers was 0.76 (95% CI, 0.32–1.78; $P = 0.53$) for women with estrogen receptor-positive breast cancer and 0.07 (95% CI, 0.01–0.51; $P = 0.009$) for women with estrogen receptor-negative breast cancer [88].

RRSO is an opportunity for occult gynecologic cancer detection in *BRCA1/2* mutation carriers. In studies of women with a *BRCA1/2* mutation who underwent RRSO, occult gynecologic carcinomas and ovarian, tubal, or peritoneal cancer were identified in 4.5–9% of cases, and tubal intraepithelial carcinoma (TIC) was detected in 5–8% of cases [84, 89–92]. The fimbriae or distal tube was reported to be the predominant site of origin for these early malignancies found in patients with *BRCA1/2* mutations [89, 92, 93].

In a prospective cohort of 462 women with *BRCA1/2* mutation carriers, short-term hormone replacement therapy (HRT) in women undergoing RRSO does not negate the protective effect of bilateral prophylactic oophorectomy on subsequent breast cancer risk in BRCA1/2 mutation carriers [94]. Moreover, results of a case-control study of BRCA1 mutation carriers showed no association between use of HRT and increased breast cancer risk in postmenopausal *BRCA1* mutation carriers [95]. However, there is no randomized study of the issue, so the use of HRT in *BRCA1/2* mutation carriers undergoing RRSO should be carried out carefully [96, 97].

Salpingectomy has been performed in premenopausal women, and there have been some evidence regarding the safety and feasibility of this procedure [98, 99]. However, there is limited data regarding its efficacy in reducing the risk for ovarian cancer [100, 101]. In addition, *BRCA1/2* mutation carriers undergoing salpingectomy alone may not get the 50% reduction in breast cancer risk of *BRCA1/2* carriers following oophorectomy. Hence, the salpingectomy alone has not been recommended as the standard risk-reducing surgery in *BRCA1/2* mutation carriers at this time.

The NCCN Guidelines recommend RRSO protocol [102]: (1) Perform operative laparoscopy. (2) Survey upper abdomen, bowel surfaces, omentum, appendix (if present), and pelvic organs. (3) Biopsy any abnormal peritoneal findings. (4) Obtain pelvic washing for cytology. (5) Perform total BSO, removing 2 cm of proximal ovarian vasculature/IP ligament, all tube up to the cornua, and all peritoneum surrounding the ovaries and tubes, especially peritoneum underlying areas of adhesion between tube and/or ovary and the pelvic sidewall. (6) Engage in minimal

instrument handling of the tubes and ovaries to avoid traumatic exfoliation of cells. (7) Both ovaries and tubes should be placed in an endobag for retrieval from the pelvis. (8) Both ovaries and tubes should be processed according to SEE-FIM protocol [103]. (9) If occult malignancy or STIC is identified, provide referral to gynecologic oncologist. (10) The prevention benefits of salpingectomy alone are not yet proven. If considered, the fallopian tube from the fimbria to its insertion into the uterus should be removed.

Japan Society of Gynecologic Oncology guidelines 2015 for the treatment of ovarian cancer described procedures for the examination and management of HBOC. In the guidelines, it was recommended that RRSO only be performed by a gynecologic oncologist who is a member of the Japan Society of Gynecologic Oncology in cooperation with a clinical geneticist at a medical facility with an established genetic counseling system and cooperative pathologists, after review and approval by the institutional ethics committee [104]. In addition, the Gynecologic Oncology Committee of Japan Society of Obstetrics and Gynecology have proposed the requirement of RRSO for *BRCA1/2* mutation carriers in more detail [105].

### 2.2.4 Chemoprevention

As regards the effect of oral contraceptives (OC) in *BRCA1/2* mutation carriers, two meta-analyses showed significant reduction of the risk for ovarian cancer. In analysis of *BRCA1/2* mutation carriers with ($n$ = 1503) and without ($n$ = 6315) ovarian cancer, OC use significantly reduced the risk for ovarian cancer by approximately 50% for both the *BRCA1* mutation carriers (RR, 0.51; 95% CI, 0.40–0.65) and *BRCA2* mutation carriers (RR, 0.52; 95% CI, 0.31–0.87) [106]. The other including one cohort study ($N$ = 3181) and three case-control studies (1096 cases and 2878 controls) also showed an inverse association between OC use and ovarian cancer (OR, 0.58; 95% CI, 0.46–0.73), and the risks appeared to decrease with longer duration of oral contraceptive use [107]. Two meta-analyses showed that OC use is not significantly associated with breast cancer risk in *BRCA1/2* mutation carriers [106, 108]. However, case-control studies in the analyses on the effect of OC use on breast cancer risk in *BRCA1/2* mutation carriers have showed conflicting results.

## 2.3 Genes Other than *BRCA1/2* Involved in Hereditary Ovarian Cancer

### 2.3.1 Mismatch Repair Genes (Lynch Syndrome)

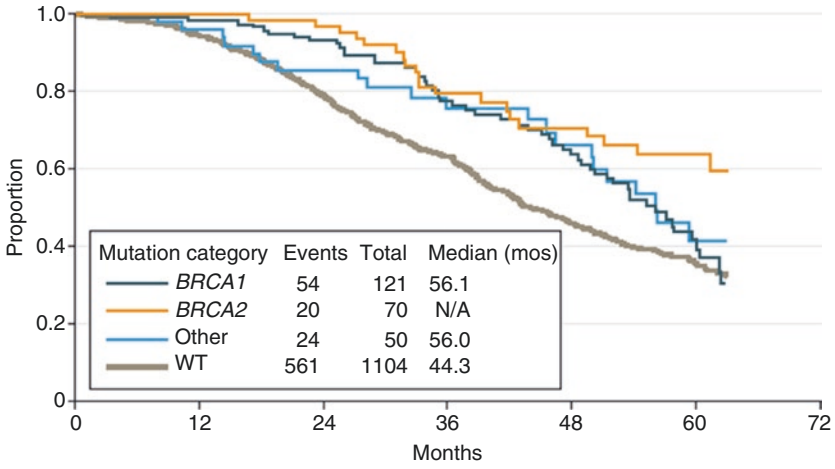
Ovarian cancer is a component tumor of Lynch syndrome that is associated with germline mutations in mismatch repair genes (*MLH1*, *MSH2*, *MSH6*, *MLH3*, and *PMS2*) [109]. Lynch syndrome, also known as hereditary nonpolyposis colon cancer (HNPCC), accounts for 10–15% of all hereditary ovarian cancers [109] and is at increased risk for endometrial and ovarian cancers: up to 60% and 24%, respectively

[110–113]. The loss of function of one of the mismatch repair proteins results in the accumulation of repeated nucleotide sequences phenotypically expressed as microsatellite instability (MSI). Several oncogenes and tumor suppressor genes contain microsatellites; impairment of MMR could cause mutations in many genes implicated in ovarian tumorigenesis [114–118]. *BRCA*-related ovarian cancers are associated with non-mucinous tumors; on the other hand, Lynch syndrome-associated ovarian cancers appear to be associated with both non-mucinous and mucinous tumors. Ovarian cancers in Lynch syndrome are mostly endometrioid or clear cell [119–123]. The cumulative lifetime risk of ovarian cancer is estimated to be 6–10% in *MSH2* and *MLH1* mutation carriers. An average age of diagnosis was 51 years in families associated with *MLH1* mutations and 45 years in families associated with *MSH2* mutations [113, 124, 125]. Lynch syndrome-associated ovarian cancers were more likely at diagnosis to be of low grade and early stage and generally showed a better prognosis [124, 126, 127]. Total abdominal hysterectomy and/or bilateral salpingo-oophorectomy are options that may be considered for risk reduction in women with mutation of mismatch repair genes who have completed childbearing [128–132]. No evidence has been showed to support routine transvaginal ultrasound and CA-125 testing in these mutation carriers because they have not been shown to be sufficiently sensitive or specific [128, 133–137].

### 2.3.2 Homologous Recombination Deficiency (HRD)-Related Genes

Homologous recombination (HR) plays in a repair of double-strand breaks (DSBs) [29]. A lot of proteins involved in homologous recombination are recognized to also contribute to hereditary cancer risk, e.g., BRCA1/2, ATM, PALB2, RAD51C, RAD51D, CHEK2, BARD1, Mre11, RAD50, NBS1, BRIP1, and Fanconi anemia proteins [3]. These proteins interact with BRCA1/2 proteins in the DNA repair and the maintenance of genomic stability. It has been hypothesized that genes coding for these proteins would be alternative candidates for ovarian cancer susceptibility. The Cancer Genome Atlas (TCGA) has showed that around half of high-grade serous ovarian cancers have aberrations in homologous recombination repair (See Fig. 7.1) [138, 139]. These patients with mutation of HRD-related gene are at increased risk for both ovarian and breast cancers, similar to *BRCA1/2* mutation carriers. In addition, these tumors present a specific phenotype similar to *BRCA*-related ovarian cancers [7], including sensitivity to platinum agents and improved survival rates [71, 72]. The survival was similar for women with mutations in *BRCA1* and other HRD-related genes (Fig. 2.2) [22].

*RAD51* genes are involved in homologous recombination, and this biallelic mutation can cause a Fanconi anemia-like phenotype [140]. *RAD51C* and *RAD51D* have been shown to be associated with increased risk for ovarian cancer [140]. In 1915 unselected ovarian cancer cases, 1.1% of patients had either a *RAD51C* or *RAD51D* mutation [22]. In cases from 1100 German families with gynecological malignancies, Meindl et al. identified six monoallelic pathogenic mutations in




No. at risk

| | | | | | | |
|---|---|---|---|---|---|---|
| *BRCA1* | 121 | 118 | 104 | 63 | 50 | 19 |
| *BRCA2* | 70 | 69 | 63 | 41 | 32 | 18 |
| Other | 50 | 47 | 41 | 28 | 21 | 9 |
| WT | 1104 | 1039 | 832 | 435 | 293 | 153 |

**Fig. 2.2** Overall survival by mutation category in advanced ovarian cancers. The survival was similar for women with mutations in *BRCA1* and other HRD-related genes in GOG 218 and GOG 262. GOG indicates Gynecologic Oncology Group; NA indicates not applicable; other indicates the genes *BRIP1*, *PALB2*, *RAD51C*, *RAD51D*, and *BARD1*; WT indicates wild type [22]

*RAD51C* that confer an increased risk for breast and ovarian cancer [141]. Loveday et al. reported that 8 inactivating *RAD51D* mutations were identified in unrelated individuals from 911 breast-ovarian cancer families, and the mutations confer a 6.3-fold increased risk of ovarian cancer but cause only a small increase in breast cancer risk (RR = 1.32) [142]. The analyses from the same trial including 1132 probands with a family history of ovarian cancer and 1156 controls also showed that *RAD51C* was associated with an increased risk for ovarian cancer (RR, 5.88; 95% CI, 2.91–11.88; $P < 0.001$) [143]. In a case-control analysis of 3429 ovarian cancer cases and 2772 controls, both *RAD51C* (OR, 5.2; 95% CI, 1.1–24; $P = 0.035$) and *RAD51D* (OR, 12.0; 95% CI, 1.5–90; $P = 0.019$) were associated with an increased risk for ovarian cancer [144]. The NCCN Guidelines recommend that RRSO in *RAD51C* and *RAD51D* mutation carriers is considered beginning at ages 45–50; however, further analyses are needed to confirm recommendation age of RRSO in these mutation carriers [13].

*BRIP1*, *BRCA1*-interacting protein C-terminal helicase 1, is a DNA helicase and defective in Fanconi anemia complementation group J. In 1915 unselected ovarian cancer cases, 1.4% of patients had a mutation in *BRIP1* [22]. In analysis of Icelandic 656 ovarian cancer cases and 3913 controls, *BRIP1* frameshift mutation confers an increase in ovarian cancer risk (OR, 8.13; 95% CI, 4.74–13.95; $P < 0.001$) [145]. In addition, an analysis of 3236 invasive ovarian cancer patients, 3431 controls, and 2000 unaffected high-risk women from a clinical screening trial of ovarian

cancer (UKFOCSS) showed that *BRIP1* is associated with a significant increased risk for ovarian cancer and relative risks associated with *BRIP1* mutations were 11.22 for invasive ovarian cancer (95% CI, 3.22–34.10; $P < 0.001$) and 14.09 for high-grade serous disease (95% CI, 4.04–45.02; $P < 0.001$) [146]. The cumulative lifetime risk of developing ovarian cancer by age 80 in *BRIP1* mutation carriers is estimated to be 5.8% (95% CI, 3.6–9.1) [146]. The NCCN Guidelines recommend that RRSO in *BRIP1* mutation carriers be considered beginning at ages 45–50; however, their cumulative risk exceeds that of a woman with a first-degree relative with a non-*BRCA*-related ovarian cancer in around age 50–55 years. Further prospective trials are needed to confirm recommendation age of RRSO in these mutation carriers [13].

*PALB2*, partner and localizer of *BRCA2*, is a Fanconi anemia gene and an integral component of the *BRCA* complex required for homologous recombination repair [147]. *PALB2* mutations have been detected in 1–4% of families negative for *BRCA* mutations [148]. Norquist et al. reported that 12 patients had germline mutations of *PALB2* in analysis of 1915 ovarian cancer patients [22]. In sequence analysis of genomic DNA of 1144 familial breast cancer patients with wild-type sequences at *BRCA1* and *BRCA2*, *PALB2* heterozygotes were 1.3-fold more likely to have a relative with ovarian cancer ($P = 0.18$) [6]. Overall, significantly less ovarian cancer is seen in *PALB2* families when compared with *BRCA1* and *BRCA2* families; therefore, it remains to be seen whether ovarian cancer risk is truly increased in individuals who are *PALB2* mutation carriers or not [148].

## 2.4 PARP Inhibitors

Poly (ADP-ribose) polymerase (PARP) inhibitors cause cancer cell death in BRCA-mutated cancers by synthetic lethality. Olaparib was the first PARP inhibitor approved in the European Union and the USA for the treatment of advanced ovarian cancer patients with a germline *BRCA* mutation. The FDA approved olaparib for the patients who have received treatment with three or more lines of chemotherapy [149, 150]. Recent data suggest that olaparib is especially active in patients with platinum-sensitive recurrent ovarian cancer; on the other hand, a lower response rate is observed in patients showing resistance or refractory to platinum agent [151–156].

Maintenance monotherapy with olaparib significantly prolonged progression-free survival versus placebo in patients with platinum-sensitive recurrent serous ovarian cancer. In a randomized, double-blind, phase 2 study, median PFS was significantly longer in the olaparib group than in the placebo group of patients with a *BRCA* mutation (11.2 months [95% CI, 8.3 to not calculable] vs 4.3 months [3.0–5.4]; HR 0.18 [0.10–0.31]; $P < 0.0001$); however, overall survival did not significantly differ between two groups (HR 0.88 [95% CI, 0.64–1.21]; $P = 0.44$). Interestingly, in the patients with wild-type *BRCA*, median PFS was also significantly longer in the olaparib group than in the placebo group (7.4 months [5.5–10.3] vs 5.5 months [3.7–5.6]; HR 0.54 [0.34–0.85]; $P = 0.0075$) [157]. A recent trial of

monotherapy with olaparib showed that the overall response rate was 34% in women with recurrent advanced ovarian cancer [149, 158].

A combination of olaparib plus paclitaxel and carboplatin followed by maintenance monotherapy significantly improved progression-free survival versus paclitaxel plus carboplatin alone in patients with platinum-sensitive, recurrent, high-grade serous ovarian cancer in a randomized phase 2 study. Progression-free survival was significantly longer in the olaparib plus chemotherapy group (median 12.2 months [95% CI, 9.7–15.0]) than in the chemotherapy-alone group (median 9.6 months [95% CI, 9.1–9.7]) (HR 0.51 [95% CI, 0.34–0.77]; $P = 0.0012$), especially in patients with *BRCA* mutations (HR 0.21 [0.08–0.55]; $P = 0.0015$) [159].

Multiple PARP inhibitors, olaparib, veliparib, talazoparib, rucaparib, and niraparib, have been evaluated in clinical trials. Current study is extending the use of PARP inhibitors beyond *BRCA* mutations, and several trials are ongoing for the inhibitors in other populations such as patients with HR deficiency [160, 161].

## Conclusions

We reviewed the recent data regarding clinical and molecular features and management of hereditary ovarian cancer. RRSO after completion of childbearing has been recommended for *BRCA1/2* mutation carriers due to the absence of reliable methods of early detection and the poor prognosis associated with advanced ovarian cancer. The effectiveness of RRSO in reducing the risk for breast and ovarian cancer in *BRCA1/2* mutation carriers has been reported in various studies, and RRSO was associated with lower all-cause mortality. Genetic counseling in RRSO for *BRCA1/2* mutation carriers should include discussion of extent of cancer risk reduction, risks associated with surgeries, reconstructive options, and risks associated with premature menopause (e.g., osteoporosis, cardiovascular disease, vasomotor symptoms, and sexual concerns), management of menopausal symptoms, and discussion of reproductive desires.

In Japan, *BRCA1/2* genetic testing has been available as a routine clinical examination for patients with epithelial ovarian cancer; however, there are too few genetic counselors to do the counseling sufficiently. Therefore, genetic testing has not been widely performed in Japan**.** It is important to organize a system which can usually perform a genetic counseling in every cancer treatment centers.

Olaparib was the first PARP inhibitor approved in the EU and USA for the treatment of advanced ovarian cancer patients with a germline *BRCA* mutation. Multiple PARP inhibitors, olaparib, veliparib, talazoparib, rucaparib, and niraparib, have been evaluated in clinical trials. It has been shown that around half of high-grade serous ovarian cancers have aberrations in homologous recombination repair. Current study is extending the use of PARP inhibitors beyond BRCA mutations, and several trials are ongoing for the inhibitors in other populations such as patients with HR deficiency. Further clinical studies are needed to extend the use of PARP inhibitors to non-*BRCA*-mutated ovarian cancers.

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