

TOPICS IN OBSTETRICS & GYNECOLOGY

Practical CE Newsletter for Clinicians

Hereditary Breast and Ovarian Cancer: A Review of Genetic Testing and Management of High-Risk Patients

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Learning Objectives: After participating in this continuing professional development activity, the provider should be better able to:

1. Identify risk of cancer in *BRCA1* and *BRCA2* mutation carriers.
2. Describe appropriate screening and prevention options for breast and ovarian cancer in *BRCA* carriers.
3. Plan appropriate genetic testing for patients with ovarian cancer.

Key Words: Breast cancer, Genetic testing

Breast cancer is the second most common cause of cancer-related death in women; ovarian cancer ranks fifth in cancer-related deaths and is the deadliest gynecologic malignancy.¹ Although the majority of breast and ovarian cancers are sporadic, approximately 5% to 10% of breast cancer and 10% to 15% of ovarian cancer are hereditary. Two well-established genes implicated in breast and ovar-

ian cancer are *BRCA1* and *BRCA2*. The lifetime risk of breast cancer in *BRCA1* mutation carriers ranges from 40% to 85%, and the lifetime risk of developing ovarian cancer is approximately 39% to 46%.² In *BRCA2* mutation carriers, the lifetime risk of breast cancer is similarly 40% to 85%, and approximately 10% to 27% for ovarian cancer.² The discovery of the *BRCA* genes led to improved screening protocols for breast cancer in mutation carriers and their family members, allowing for earlier cancer detection and risk-reducing treatments. Improved genetic sequencing technology has allowed for the identification of numerous additional susceptibility genes for hereditary breast and ovarian cancer. In this review, we discuss the current screening and prevention guidelines for both *BRCA* and non-*BRCA* homologous recombination deficiency (*HRD*) mutations in breast and ovarian cancer.

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Discovery of *BRCA1* and *BRCA2*

The discovery of *BRCA1* and *BRCA2* revolutionized the understanding of the genetic contributions to breast cancer.

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BRCA1 and *BRCA2* are tumor suppressor genes; their main role is to aid in the repair of double-stranded DNA breaks via homologous recombination.³ Homologous recombination is the primary mechanism in which double-strand breaks are repaired, and typically, is an error-free mechanism in healthy cells. Without homologous recombination, DNA repair is erroneous and leads to genomic instability. Mutations and rearrangements within *BRCA1* and *BRCA2* reduce the ability for DNA damage repair, causing genetic instability and increased risk of malignancy.³

Risk of Cancer in *BRCA1* and *BRCA2* Carriers

Although *BRCA1* and *BRCA2* mutations are known for increasing the risk of breast and ovarian cancer, there are additional risks that must be acknowledged, including an increased risk of certain cancers in genotypically male patients. *BRCA1* and *BRCA2* mutations have been found to increase the risk of pancreatic cancer.⁴ (ANSWER TO QUESTION #1) *BRCA1* is associated with a slightly increased risk of endometrial cancer; *BRCA2* has been associated with an increased incidence of gastric cancer, whereas *BRCA1* has not.⁴ In genotypically male patients, *BRCA1* is associated with a 1% to 5% increased risk of male breast cancer, whereas *BRCA2* is associated with a 5% to 10% increased risk of male breast cancer.⁵ A recent meta-analysis reported that *BRCA* mutations did not increase the incidence of prostate cancer, brain cancer, colorectal cancer, melanoma, bladder and kidney cancer, or cervical cancer.⁴

The NIH Surveillance, Epidemiology, and End Results (SEER) Program 2014-

2018 report noted that the median age of both breast and ovarian cancer diagnosis is 63 years in the general population. The incidence of breast cancer in *BRCA1* and *BRCA2* mutation carriers peaks in women ages 41 to 50 and 51 to 60 years, respectively. For ovarian cancer, *BRCA1* mutation carriers are at increased risk at an earlier age when compared with the general population. The mean age of ovarian cancer diagnosis in *BRCA1* carriers is approximately 51 years, whereas the average age of ovarian cancer in *BRCA2* carriers is approximately 61 years.⁶

BRCA mutations vary given the population of individuals studied. Certain ethnic groups have specific mutations that occur at a higher frequency due to the founder effect. The founder effect occurs when there is a loss of genetic variation that results when a new population is formed by a small number of individuals, causing certain genetic variants to be more prevalent in the population.⁷ Identifying populations with founder mutations can help physicians and genetic counselors recognize high-risk individuals who would benefit from genetic testing. One of the most well-documented examples of the founder effect is in the Ashkenazi Jewish population, where 3 founder mutations have been identified (*BRCA1*-185delAG, *BRCA1*-5382insC, and *BRCA2*-6174delT). There have been other European and non-European populations with evidence of founder mutations in the *BRCA* genes as well.⁷

Screening Guidelines for Breast Cancer in *BRCA1/2* Carriers

Since the discovery of *BRCA1* and *BRCA2*, significant effort has been made to determine best practices for breast cancer screening and prevention. The American College of

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Obstetricians and Gynecologists (ACOG) recommends that *BRCA1* and *BRCA2* carriers have an annual MRI between ages 25 and 29 years, and alternate MRI and mammography every 6 months beginning at age 30 years.⁸ Mammography is less sensitive in detecting *BRCA1* or *BRCA2* tumors in younger patients with denser breast tissue, and MRI allows for higher detection of early-stage breast cancer (DCIS and stage I) compared with traditional screening methods alone (breast examination and mammography).⁹

Prevention and Risk-Reducing Strategies for Breast Cancer in *BRCA1/2* Carriers

BRCA1 and *BRCA2* carriers have options to pursue both surgical and pharmacologic preventative strategies. Chemoprevention includes the use of tamoxifen, a selective estrogen receptor modulator (SERM), in premenopausal patients. Tamoxifen works by binding to the estrogen-receptor cells in tumors, blocking estrogen, and thus halting progression of tumor growth. For postmenopausal patients, either tamoxifen, raloxifene (another SERM), or aromatase inhibitors (which block the conversion of androgens into estrogen) may be used.³ The National Surgical Adjuvant Breast and Bowel Project demonstrated a 50% risk reduction with 5 years of tamoxifen use in high-risk women without prophylactic mastectomies.¹⁰ The use of tamoxifen is associated with hot flashes, increased risk of thromboembolism, and endometrial cancer; thus, alternative agents have been studied. The STAR trial demonstrated that, in postmenopausal patients, raloxifene reduced the risk of estrogen receptor-positive (ER+) breast cancer by 76% to 84% and had a lower risk of uterine cancer and venous thromboembolic events.¹¹ Aromatase inhibitors (AIs) also decrease the risk of breast cancer by 16 events per 1000 women over 5 years in high-risk women who have not undergone preventive surgery.¹² The National Comprehensive Cancer Network (NCCN) 2020 guidelines state that premenopausal women should be treated with tamoxifen and postmenopausal women should be treated with either raloxifene or AIs.¹³ To date, however, there are no prospective studies designed to evaluate the use of chemoprevention in *BRCA* carriers for primary breast cancer.

Risk-reducing mastectomy (RRM) offers significant reduction in cancer risk in *BRCA1/2* carriers. Rebbeck et al¹⁴ reported a 95% risk reduction of breast cancer in *BRCA1/2* carriers after RRM who also had prior or concurrent prophylactic oophorectomy, and a 90% reduction in women with ovaries intact. The choice of nipple-sparing mastectomy (NSM) versus simple mastectomy is an individualized decision that requires shared decision-making between the surgeon and the patient. A recent review of NSM in *BRCA1/2* mutation carriers reported that NSM is a safe option for RRM, with low rates of new breast cancer on the side of prophylactic surgery and postoperative complications.¹⁵ There is no benefit to adjunctive chemoprevention after risk-reducing surgery and no compelling evidence exists to support continued surveillance with mammography

or MRI after RRM. In this population, physical examinations are sufficient for detection of cancer in the skin or chest wall.¹⁶

Screening Guidelines for Ovarian Cancer in *BRCA1/2* Carriers

Although evidence-based guidelines exist regarding effective cancer screening and prevention strategies for breast cancer in *BRCA1* and *BRCA2* carriers, similar guidelines for hereditary ovarian cancer are less robust. Currently, the NCCN recommends initiation of screening in patients with *BRCA1* and *BRCA2* mutation carriers at age 30 years with a transvaginal ultrasound (TVUS) and CA-125 every 6 months. CA-125 monitoring may be considered at the clinician's discretion in patients between ages 30 and 35 years who have not yet undergone a prophylactic bilateral salpingo-oophorectomy.¹⁷ There have been various methods evaluated as screening tests for ovarian cancer, including imaging and biologic markers. CA-125 is a protein produced by most advanced epithelial ovarian cancers and is often used to monitor cancer response to chemotherapy. However, when evaluated as a screening marker in average-risk women, there was no difference in the number of deaths due to ovarian cancer in the group of women screened with CA-125 as compared with the group of women who had routine gynecologic care. Additionally, CA-125 is often not elevated in early-stage ovarian cancer and can be elevated due to nonmalignant processes, such as cysts, endometriosis, and infection.¹ TVUS is used in the work-up of ovarian cancer and has been evaluated as a screening tool in the general population. Limitations of TVUS include decreased reliability at determining benign from malignant ovarian tumors, and the frequency of benign pathology, such as ovarian cysts, that may be identified on screening TVUS, leading to anxiety, unnecessary follow-up tests, and interventions.¹⁸

Genetic Testing in Patients With Ovarian Cancer

Although there are not well-established screening methods for ovarian cancer, there are established recommendations for genetic testing in patients diagnosed with ovarian cancer. The American Society of Clinical Oncology (ASCO) recommends genetic testing for patients with epithelial ovarian, fallopian tube, or primary peritoneal cancers, regardless of family history.¹⁹ Similarly, updated NCCN guidelines encourage genetic testing for patients diagnosed with invasive epithelial ovarian cancer, regardless of age at diagnosis. The genes tested have evolved over the last decade; patients now have options for multigene panel testing. The NCCN 2019 guidelines recommend using multigene panels when initial genetic testing for a single mutation is indeterminate in a high-risk patient or when more than one gene can explain an inherited cancer syndrome, as is the case in both breast and ovarian cancer.¹⁷ The Society of Gynecologic Oncology (SGO) also recommends genetic counseling to all patients with ovarian,

fallopian tube, and peritoneal carcinoma to determine which genetic testing is appropriate based on family and personal history.¹⁹ The US Preventive Services Task Force recommends that primary care providers assess women with a family or personal history of breast, ovarian, tubal, or peritoneal cancer or who have a family history of *BRCA1/2* gene mutations with a familial risk assessment tool; women with a positive result should go on to receive genetic counseling.²⁰ Despite clear recommendations for genetic counseling and testing, the majority of eligible patients are never referred. Proposed mechanisms to increase genetic testing accessibility include increased public and provider education, an increase in the number of genetic counselors, a greater understanding of the role of insurers in paying for genetic testing, and costs by racial and socioeconomic status.¹⁹

Genetic testing allows for the identification of individuals who would benefit from risk-reducing strategies. One common method is cascade testing, where family members of an individual with an identified genetic mutation are tested for that specific mutation and no other genes. Many providers also now order multigene panel testing for their patients. Although the genetic contribution of high-penetrance genes, such as *BRCA1* and *BRCA2*, is well-known, there is less information about the association between moderate- and low-penetrance genes with breast and ovarian cancer risk. Penetrance refers to the proportion of individuals with a genetic variant who are likely to develop cancer, and is categorized based on lifetime relative risk: high penetrance (relative risk >4), moderate penetrance (relative risk 2-4), and low penetrance (relative risk <2).²¹ A large study by the Breast Cancer Association Consortium evaluated 34 breast cancer susceptibility genes in more than 60,000 patients; the risk of breast cancer was associated with genetic variants in the following 5 genes: *ATM*, *BRCA1*, *BRCA2*, *CHEK2*, and *PALB2*.²² Although the SGO recommends that all women with ovarian cancer receive genetic counseling, they do not provide clear guidelines on the management of patients with moderate- or low-penetrance mutations.

Commercial Testing

Over the past decade, there has been an increase in the use of consumer genetic testing through commercial companies. The challenges of consumer testing include a lack of oversight by genetic specialists and physicians, issues with privacy and confidentiality, and the difficulty of interpreting nuanced results. ACOG advises that genetic tests should be conducted only after counseling has occurred, and if patients do pursue consumer genetic testing, a confirmatory screen should be performed under the supervision of an obstetrician-gynecologist or genetics professional.²³

Prognostic Implications of *BRCA* Mutations in Ovarian Cancer

Although *BRCA* carriers are at an increased risk of developing ovarian cancer in comparison to the general

population, carriers have an overall better survival than noncarriers who develop cancer. Results from a 5-year survival analysis of *BRCA1/2* mutation carriers versus noncarriers with invasive epithelial ovarian cancer showed that the overall survival was 36% for nonmutation carriers, 44% for *BRCA1* carriers, and 52% for *BRCA2* mutation carriers.²⁴ *BRCA1* and *BRCA2* mutation carriers had better survival even when adjusting for multiple variables, including stage, grade, histology, and age at cancer diagnosis. This finding is likely secondary to a heightened response to platinum-based chemotherapy.

Prevention and Risk-Reducing Strategies for Ovarian Cancer in *BRCA1/2* Carriers

Risk-reducing strategies for ovarian cancer include oral contraceptive therapy (OCPs) and prophylactic salpingo-oophorectomy. OCPs most likely reduce ovarian cancer via inhibition of ovulation. OCP use has a protective effect on ovarian cancer, with risk reduction up to 50% for individuals who use therapy for at least 5 years.²⁵ Risk-reducing salpingo-oophorectomy (RRSO) is recommended to *BRCA1* carriers between ages 35 and 40 years and to *BRCA2* carriers between ages 40 and 45 years, or when childbearing is complete.²⁶ RRSO is associated with over an 80% reduction in the risk of ovarian, fallopian tube, or peritoneal cancer in *BRCA1/2* carriers.²⁷ Data are mixed regarding the protective effects of RRSO on breast cancer in *BRCA+* individuals. One study showed that a RRSO reduced risk of breast cancer by over 50% in *BRCA+* patients²⁷ whereas a large, prospective analysis reported no statistically significant association between RRSO and *BRCA*-associated breast cancer after accounting for potential bias.²⁸

Importantly, there has been increasing evidence that the fallopian tubes play a key role in the pathogenesis of epithelial ovarian cancer. Thus, it has been proposed that prophylactic salpingectomy with delayed oophorectomy (PSDO) could be an alternative risk-reducing strategy in premenopausal women, especially those who aim to preserve fertility.²⁹ Although studies have shown that tubal ligation and salpingectomy are associated with decreased risk for sporadic and hereditary ovarian cancer, there are no prospective outcome data available to support this conclusion.³⁰ However, many prospective trials regarding PSDO are currently underway.

Hormone Therapy After Oophorectomy

Premenopausal oophorectomy is associated with increased risk of heart disease, which can be reduced by estrogen therapy.³¹ Hormone replacement therapy (HRT) has been shown to mitigate worsening vasomotor symptoms related to early menopause and decrease vaginal dryness and dyspareunia, but did not increase sexual pleasure.³² In determining the association between HRT and breast cancer, a prospective cohort study demonstrated that HRT was not associated with increased risk of breast cancer at 7.6 years of follow-up from primary diagnosis.³³ In summary, research supports using HRT in patients who undergo RRSO until

mean age of natural menopause as long as the patient did not have a personal history of estrogen-receptive breast cancer. Further continuation should be made based on age of the patient, menopausal symptoms, and the molecular/hormonal characteristics of the tumor if applicable.

PARP Inhibitors

The development of poly-adenosine diphosphate ribose polymerase (PARP) inhibitors (PARPis) has changed the landscape of ovarian cancer therapy in patients with *HRD* mutations. PARPis prevent the repair of single-strand breaks, leading to subsequent double-strand breaks. In a homologous recombination deficient cell, such as a *BRCA*-mutated cell, the double-strand break cannot be repaired and cell death ensues. Based on the success of recent clinical trials, the current standard of care is to use PARPis as maintenance therapy after adjuvant chemotherapy in the population of patients with *HRD* mutations. Common adverse events associated with PARPis that patients should be counseled on are hematologic toxicity, specifically anemia and thrombocytopenia, gastrointestinal reactions, fatigue, renal toxicity, hypercholesterolemia, and transient increase in aminotransferases.³⁴

Conclusion

The ability to detect genetic mutations associated with hereditary breast and ovarian cancer increases the opportunity to detect high-risk patients earlier and allows for counseling on the appropriate screening and risk-reducing strategies. *BRCA1* and *BRCA2* significantly increase the

lifetime risk of breast and ovarian cancer. Current screening guidelines for hereditary breast cancer include MRI and mammograms at appropriate ages. Prevention strategies include hormonal therapy, such as tamoxifen and AIs, and prophylactic mastectomy. With regard to ovarian cancer, screening options in *BRCA1* and *BRCA2* mutation carriers include TVUS and CA-125 testing. However, the utility of these tests is less clear, and more physicians are relying on risk-reducing salpingectomy at the conclusion of childbearing for high-risk patients. The discovery of PARPis has also changed the management of hereditary ovarian cancer for patients with homologous recombination-deficient tumors. Further research is needed to better understand the prognostic implications of non-*BRCA* *HRD* mutations. Additionally, better strategies to identify, refer, and follow up with patients who are eligible for genetic testing must be developed to ensure that all patients are referred appropriately.

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Practice Pearls

- BRCA1* and *BRCA2* are associated with breast, ovarian, and pancreatic cancer. *BRCA1* is associated with endometrial cancer, whereas *BRCA2* is associated with gastric cancer.
- BRCA1/2* carriers should be screened with breast MRI from ages 25 to 29 years and alternate MRI and mammogram every 6 months beginning at age 30 years.
- BRCA* carriers can use tamoxifen if premenopausal and either raloxifene or AIs if postmenopausal for medical prevention of breast cancer. RRM offers more than 90% risk reduction in breast cancer in *BRCA1/2* carriers and should be offered as a surgical prevention strategy.
- BRCA1/2* carriers should be screened with TVUS and CA-125 starting at age 30 years.
- RRSO should be offered between ages 35 and 40 years for *BRCA1* carriers and 40 and 45 years for *BRCA2* carriers.
- All patients diagnosed with epithelial ovarian, fallopian tube, or primary peritoneal cancers should be sent for genetic testing, regardless of family history.
- PARP inhibitors should be used as maintenance therapy after chemotherapy in patients who have *HRD* mutations.

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The screenshot shows the website interface for 'TOPICS IN OBSTETRICS & GYNECOLOGY', a Practical CME Newsletter for Clinicians, published by Wolters Kluwer. The page includes a search bar with 'All Issues' selected, navigation tabs for Home, Current Issue, Previous Issues, CME, For Authors, and Journal Info. The current issue is 'January 31, 2016 - Volume 36 - Issue 2'. The Editor-in-Chief is listed as William Schlaff, MD, and Lorraine Dugoff, MD. The ISSN is 2380-0216 and the Online ISSN is 2380-0224. The frequency is 24 issues per year. A 'Subscribe to eTOC' checkbox is present. A login section is also visible with fields for Username or Email, Password, and a 'Remember me' checkbox. A message prompts users to activate a new subscription or register a new account.

Current Issue Highlights

Continuing Professional Development Quiz: Volume 42, Number 12

To earn CME credit, you must read the article and complete the quiz and evaluation on the enclosed answer form, answering at least seven of the 10 quiz questions correctly. **Select the best answer and use a blue or black pen to completely fill in the corresponding box on the enclosed answer form.** Please indicate any name and address changes directly on the answer form. If your name and address do not appear on the answer form, please print that information in the blank space at the top left of the page. Make a photocopy of the completed answer form for your own files and mail the original answer form in the enclosed postage-paid business reply envelope. Your answer form must be received by Lippincott CME Institute by **August 30, 2024**. Only two entries will be considered for credit. For more information, call (800) 638-3030.

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- In addition to breast and ovarian cancer, *BRCA1* and *BRCA2* mutations are associated with increased risk of
 - pancreatic cancer.
 - cervical cancer.
 - brain cancer.
 - prostate cancer.
- A 27-year-old woman is diagnosed with a *BRCA1* mutation. Which one of the following breast screening approaches should be recommended to this patient, according to ACOG guidelines?
 - no screening necessary at her age
 - routine breast examinations but no further screening
 - annual MRI
 - MRI and mammography alternating every 6 months
- A woman with a known *BRCA* mutation underwent a risk-reducing bilateral mastectomy. She asks whether she should still have mammograms and MRI in case cancer develops in the remaining tissue or chest wall. Which one of the following statements is *true*?
 - She no longer needs imaging but should be taking tamoxifen as prophylaxis.
 - She only needs annual mammograms.
 - She does not need imaging, and physical examination of the chest wall is appropriate.
 - She should continue with mammograms and MRI alternating every 6 months.
- A 35-year-old woman with a known *BRCA2* mutation is being followed up for ovarian cancer screening. In addition to a TVUS, which one of the following tumor markers should be checked per NCCN guidelines?
 - HE4
 - AFP
 - CA-125
 - CEA
- Tamoxifen use is associated with an increased risk of all the following, *except*
 - blood clots.
 - endometrial cancer.
 - ovarian cancer.
 - hot flashes.
- Prophylactic RRSO is recommended in *BRCA1* mutation carriers at age
 - 30 to 35 years.
 - 35 to 40 years.
 - 40 to 45 years.
 - 45 to 50 years.
- Prophylactic RRSO is recommended in *BRCA2* mutation carriers at age
 - 30 to 35 years.
 - 35 to 40 years.
 - 40 to 45 years.
 - 45 to 50 years.
- Per NCCN and ASCO guidelines, which of the following patients should be referred for genetic counseling?
 - only patients with epithelial ovarian cancer diagnosed before age 40 years
 - only patients with epithelial ovarian cancer who have a history of ovarian cancer in first-degree relative
 - only patients with epithelial ovarian cancer who have a previous cancer diagnosis
 - all patients with epithelial ovarian cancer, regardless of age of diagnosis or family history
- HRT is generally safe to use in patients who undergo RRSO before average age of menopause as long as the patient did not have a personal history of estrogen-receptive breast cancer?
 - true
 - false
- PARP inhibitors can be used as maintenance therapy after chemotherapy for any type of ovarian cancer.
 - true
 - false