



The American College of
Obstetricians and Gynecologists
WOMEN'S HEALTH CARE PHYSICIANS



Society of Gynecologic Oncology

ACOG PRACTICE BULLETIN

Clinical Management Guidelines for Obstetrician–Gynecologists

NUMBER 182, SEPTEMBER 2017

(Replaces Practice Bulletin Number 103, April 2009)

Committee on Practice Bulletins–Gynecology, Committee on Genetics, Society of Gynecologic Oncology. This Practice Bulletin was developed by the American College of Obstetrician and Gynecologists' Committee on Practice Bulletins–Gynecology and Committee on Genetics in collaboration with Susan C. Modesitt, MD, and Karen Lu, MD, and by the Society of Gynecologic Oncology in collaboration with Lee-may Chen, MD, and C. Bethan Powell, MD.

Hereditary Breast and Ovarian Cancer Syndrome

Hereditary breast and ovarian cancer syndrome is an inherited cancer-susceptibility syndrome characterized by multiple family members with breast cancer, ovarian cancer, or both. Based on the contemporary understanding of the origins and management of ovarian cancer and for simplicity in this document, ovarian cancer also refers to fallopian tube cancer and primary peritoneal cancer. Clinical genetic testing for gene mutations allows more precise identification of those women who are at an increased risk of inherited breast cancer and ovarian cancer. For these individuals, screening and prevention strategies can be instituted to reduce their risks. Obstetrician–gynecologists play an important role in the identification and management of women with hereditary breast and ovarian cancer syndrome. If an obstetrician–gynecologist or other gynecologic care provider does not have the necessary knowledge or expertise in cancer genetics to counsel a patient appropriately, referral to a genetic counselor, gynecologic or medical oncologist, or other genetics specialist should be considered (1). More genes are being discovered that impart varying risks of breast cancer, ovarian cancer, and other types of cancer, and new technologies are being developed for genetic testing. This Practice Bulletin focuses on the primary genetic mutations associated with hereditary breast and ovarian cancer syndrome, BRCA1 and BRCA2, but also will briefly discuss some of the other genes that have been implicated.

Background

BRCA1 and BRCA2

Germline mutations in the *BRCA1* and *BRCA2* (*BRCA*) genes account for most cases of hereditary breast and ovarian cancer syndrome. Approximately 9–24% of cases of epithelial ovarian cancer (2–5) and approximately 4.5% of cases of breast cancer (6) are due to germline mutations in *BRCA1* and *BRCA2*. *BRCA1* is found on chromosome 17 and *BRCA2* is on chromosome 13 (7, 8). Both *BRCA* genes are tumor suppressor genes that encode proteins that function in the DNA repair process (9, 10). Individuals with hereditary breast and ovarian cancer syndrome inherit one defective allele in *BRCA1* or *BRCA2* from their father or mother, but they

have a second, functional allele. If the second allele becomes nonfunctional as a result of a somatic mutation, cancer can develop. This is called the “two-hit hypothesis” (11).

Founder BRCA Mutations

In the general population, it is estimated that approximately 1 in 300 to 1 in 800 individuals carry a mutation in *BRCA1* or *BRCA2* (12). In certain populations founded by a small ancestral group, a specific mutation in *BRCA1* or *BRCA2* may occur more frequently, and is often referred to as a founder mutation. These founder mutations in *BRCA1* and *BRCA2* have been identified in Ashkenazi (Central and Eastern European) Jews, French Canadians, and Icelanders, among other groups.



Particularly relevant to clinical practice in the United States, an estimated 1 in 40 Ashkenazi Jews carries one of three founder mutations in *BRCA1* or *BRCA2* (13, 14). *BRCA1* and *BRCA2* mutations also have been found in individuals of diverse ethnic backgrounds, including Hispanic, African American, and Asian (15, 16).

Other Hereditary Breast and Ovarian Cancer Syndrome Mutations

In addition to *BRCA1* and *BRCA2*, other genes are implicated in hereditary breast and ovarian cancer syndrome. These other genes may account for up to 25% of hereditary ovarian cancer risk (4). Although a comprehensive review of each individual gene is outside the scope of this Practice Bulletin, patients found to have pathogenic variants in other implicated genes (Table 1) may benefit from risk-reduction management strategies for breast cancer, ovarian cancer, or both. The National Comprehensive Cancer Network guidelines are updated annually and may serve as a contemporary reference (17).

Risk of Breast Cancer

The estimated risk of breast cancer in individuals with a *BRCA1* or *BRCA2* mutation is 45–85% by age 70 years (18–20). A meta-analysis of 10 studies that included a

total of 1,641 carriers from multiple countries calculated a mean cumulative risk of breast cancer of 57% for *BRCA1* mutation carriers and 49% for *BRCA2* carriers (21). For *BRCA* mutation carriers with breast cancer, the 10-year actuarial risk of developing subsequent ovarian cancer is 12.7% for *BRCA1* and 6.8% for *BRCA2* (22).

The type of breast cancer also may vary based on *BRCA* mutation type. For example, a woman with triple-negative breast cancer (ie, estrogen-receptor negative, progesterone negative, and *ERBB2*-negative [also known as *HER2/neu* negative]) has a 10–39% chance of having a *BRCA1* or *BRCA2* mutation, with *BRCA1* being more likely (23). This is in contrast to the types of breast cancer diagnosed in women with *BRCA2* mutations, which are more commonly estrogen-receptor and progesterone-receptor positive (24, 25).

Risk of Ovarian Cancer

For a woman with a *BRCA1* mutation, the risk of ovarian cancer (including fallopian tube cancer and primary peritoneal cancer) is approximately 39–46% by age 70 years (18–21). For a woman with a *BRCA2* mutation, the risk of ovarian cancer by age 70 years is 10–27% (18–21). Ovarian cancer that is associated with *BRCA1* and *BRCA2* mutations usually is high grade and has a

Table 1. Genetic Mutations Associated With Hereditary Breast and Ovarian Cancer Syndrome

Gene	Breast Cancer Risk	Ovarian Cancer Risk*	Other Cancer Risk
<i>ATM</i>	Increased	No increased risk	Insufficient evidence
<i>BRCA1</i>	Increased	Increased	Prostate
<i>BRCA2</i>	Increased	Increased	Melanoma, pancreas, prostate
<i>BRIP1</i>	No increased risk	Increased	Insufficient evidence
<i>CDH1</i>	Increased	No increased risk	Stomach
<i>CHEK2</i>	Increased	No increased risk	Colon
Lynch Syndrome Genes: <i>MSH2</i> , <i>MLH1</i> , <i>MSH6</i> , <i>PMS2</i> , and <i>EPCAM</i>	Insufficient evidence	Increased	Colon, uterine, renal pelvis, small bowel, and others
<i>PALB2</i>	Increased	No increased risk	Unknown
<i>PTEN</i>	Increased	No increased risk	Cowden Syndrome
<i>RAD51C</i>	No increased risk	Increased	Unknown
<i>RAD51D</i>	No increased risk	Increased	Unknown
<i>STK11</i>	Increased risk	Increased risk of sex cord stromal tumors	Peutz-Jehger Syndrome
<i>TP53</i>	Increased	No increased risk	Li-Fraumeni Syndrome

*Includes fallopian tube cancer and primary peritoneal cancer.

Data from National Comprehensive Cancer Network. Genetic/familial high risk assessment: breast and ovarian. Version 2.2017. NCCN Clinical Practice Guidelines in Oncology. Fort Washington (PA): NCCN; 2016. Available at: https://www.nccn.org/professionals/physician_gls/pdf/genetics_screening.pdf.



distinct histologic phenotype that is predominantly serous or endometrioid. A woman with high-grade ovarian cancer has a 9–24% chance of carrying a germline *BRCA1* or *BRCA2* mutation. (2–5). Mucinous cancer and borderline ovarian tumors do not appear to be part of the *BRCA*-related tumor spectrum (26–28).

There are growing data to support the fallopian tube as the site of origin for a large percentage of cases of *BRCA*-associated, high-grade serous cancer (29, 30). Multiple pathologic studies of the fallopian tubes and ovaries of women with *BRCA1* and *BRCA2* mutations who underwent risk-reducing salpingo-oophorectomy have identified cases of early microscopic high-grade cancer that were located predominantly in the fallopian tube as well as cases of serous tubal intraepithelial carcinoma (31, 32). Findings of these occult lesions are seen more frequently when risk-reducing salpingo-oophorectomy is delayed until a later age, and women with these findings have a higher risk of subsequent peritoneal carcinoma (33, 34).

Risk of Other Types of Cancer

Patients with *BRCA* mutations also carry other cancer risks (albeit smaller than their risk of breast and ovarian cancer), including prostate cancer, pancreatic cancer, melanoma, and potentially uterine cancer (35, 36). *BRCA2* mutation carriers have a threefold increased risk and up to a 7% lifetime risk of pancreatic cancer. Additionally, *BRCA2* mutation carriers have an increased risk of melanoma, and male carriers have an increased prostate cancer risk (17). There is ongoing investigation regarding the potential significant (but small) increased risk of uterine cancer. Some studies to date have not shown increased risk, whereas others have shown increased risk, specifically of high-grade histology in *BRCA1* mutation carriers (eg, uterine papillary serous cancer) (37, 38).

Clinical Considerations and Recommendations

► ***Who are candidates for genetic counseling for hereditary breast and ovarian cancer syndrome?***

Genetic counseling is recommended for all women with ovarian epithelial cancer (this includes fallopian tube cancer or primary peritoneal cancer) and for individuals who have a personal or family history of breast cancer or ovarian cancer. Evaluating a patient's risk of hereditary breast and ovarian cancer syndrome should be a routine part of obstetric and gynecologic practice. Initial risk

evaluation should include a personal medical history and family history. At minimum, this evaluation should include a personal cancer history and a family cancer history that includes first-degree and second-degree relatives from the paternal and maternal lineages, a description of the type of primary cancer, the age of onset, and the lineage (paternal versus maternal) of the family member. In addition, a patient's ethnic background can influence her genetic risk; thus, understanding this background is relevant in assessing a patient's predisposition to a hereditary breast and ovarian cancer syndrome (39).

The American College of Obstetricians and Gynecologists (39) and the American Society of Clinical Oncologists (40) have published guidance on the elements to be included as part of a cancer family history. When evaluating a family history, it is important to remember that predisposing genes for breast cancer and ovarian cancer, fallopian tube cancer, and primary peritoneal cancer can be transmitted through the father as well as the mother. Therefore, paternal family history should be obtained. Adoption can limit interpretation of a pedigree, and hysterectomy and oophorectomy at a young age in multiple family members can mask a hereditary gynecologic cancer predisposition. Also, the ability to assess breast cancer risk is limited in families with few female members. Women from high-risk groups with a higher rate of *BRCA* mutations (eg, Ashkenazi Jews, French Canadians, and Icelanders) should have a low threshold for referral for genetic counseling.

Guidelines from the American College of Medical Genetics and Genomics (41), the National Society of Genetic Counselors (41), the National Comprehensive Care Network (17), and the Society of Gynecologic Oncology (42) provide specific clinical criteria to assist health care providers in determining which patients would benefit from genetic counseling. The main criteria are similar across the guidelines and are listed in Box 1. Familial risk stratification models also may be used in initial risk screening for *BRCA*-related cancer. These brief risk tools are primarily intended for use by nongenetic specialists to guide patient referrals for more extensive genetic risk assessment and evaluation (43). Several models have been evaluated by the U.S. Preventive Services Task Force and the Agency for Healthcare Research and Quality, although there is insufficient evidence to recommend any particular risk model or a specific risk threshold for referral (43).

► ***What issues should be addressed during genetic counseling?***

Genetic counseling is recommended before initiation of genetic testing and can be performed by an



Box 1. Criteria for Further Genetic Evaluation for Hereditary Breast and Ovarian Cancer ◀

- Women affected with one or more of the following have an increased likelihood of having an inherited predisposition to breast* and ovarian, tubal, or peritoneal cancer and should receive genetic counseling and be offered genetic testing:
 - Epithelial ovarian, tubal, or peritoneal cancer
 - Breast cancer at age 45 years or less
 - Breast cancer and have a close relative† with breast cancer at age 50 years or less or close relative† with epithelial ovarian, tubal, or peritoneal cancer at any age
 - Breast cancer at age 50 years or less with a limited or unknown family history‡
 - Breast cancer and have two or more close relatives† with breast cancer at any age
 - Breast cancer and have two or more close relatives† with pancreatic cancer or aggressive prostate cancer (Gleason score equal to or greater than 7)
 - Two breast cancer primaries, with the first diagnosed before age 50 years
 - Triple-negative breast cancer at age 60 years or less
 - Breast cancer and Ashkenazi Jewish ancestry at any age
 - Pancreatic cancer and have two or more close relatives† with breast cancer; ovarian, tubal, or peritoneal cancer; pancreatic cancer; or aggressive prostate cancer (Gleason score equal to or greater than 7)
- Women unaffected with cancer, but with one or more of the following have an increased likelihood of having an inherited predisposition to breast and ovarian, tubal, or peritoneal cancer and should receive genetic counseling and be offered genetic testing:
 - A first-degree or several close relatives† that meet one or more of the aforementioned criteria
 - A close relative† carrying a known *BRCA1* or *BRCA2* mutation§
 - A close relative† with male breast cancer

*Invasive and ductal carcinoma in situ breast cancer.

†Close relative is defined as first degree (parent, sibling, offspring), second degree (grandparent, grandchild, uncle, aunt, nephew, niece, half-sibling), or third degree (first cousin, great-grandparent or great-grandchild).

‡Limited family history includes fewer than two first-degree or second-degree female relatives surviving beyond age 45 years.

§Or carrying another known actionable deleterious mutation associated with hereditary breast and ovarian cancer syndrome.

Adapted with permission from Lancaster JM, Powell CB, Chen LM, Richardson DL. Society of Gynecologic Oncology statement on risk assessment for inherited gynecologic cancer predispositions. *SGO Clinical Practice Committee* [published erratum appears in *Gynecol Oncol* 2015;138:765]. *Gynecol Oncol* 2015;136:3–7.

obstetrician–gynecologist (or other gynecologic care provider) who has expertise in cancer genetics or by a genetic counselor. Pretest genetic counseling includes the following:

- Detailed pedigree (or kindred analysis)
- Risk assessment to determine eligibility for genetic testing and identification of candidates in the family to proceed with genetic testing
- An informed consent process, including patient education about the benefits, harms, limitations, and possible outcomes of genetic testing, as well as the practical and ethical issues associated with disclosure or nondisclosure of test results to family members.

Posttest counseling includes reporting and interpretation of the results and discussion of management options such as intensive screening and risk-reduction interventions.

Several online risk models are available to estimate a woman's risk of developing breast cancer, gynecologic cancer, or both, and to help identify women who are candidates for genetic testing, intensive cancer screening, and risk-reduction measures. These models include *BRCAPRO* (available at www4.utsouthwestern.edu/breasthealth/cagene/), Tyrer–Cuzick or *IBIS* (available at www.ems-trials.org/riskevaluator/), and *BOADICEA* (available at www.srl.cam.ac.uk/genepi/boadicea/boadicea_home.html) (44–46). Two other risk prediction models have been developed for ovarian cancer. They include inherited and noninherited risk factors such as family history of breast and ovarian cancer, age at menarche, oral contraceptive pill use, history of tubal ligation, age at menopause, and menopausal hormonal therapy use (47, 48).

The possible outcomes of any genetic testing should be discussed as part of pretest genetic counseling (Box 2). This includes the possibility of variants of uncertain significance, which are genetic abnormalities for which the clinical significance to the individual and family remain unclear. If providing genetic testing, practitioners should have a process to inform patients if a variant of uncertain significance is reclassified. Genetic counseling also may include discussion of possible psychologic, reproductive, and familial implications of test results. Potential adverse psychologic effects of genetic testing include increased breast cancer-related worry and anxiety for women with positive or uninformative test results (49). Patients may feel burdened and distressed about disclosure of test results to family members. Written materials may help individuals share information with relatives about their potential genetic risks. Because a positive test result may affect family



Box 2. Possible Outcomes of *BRCA* Mutation* Testing ⇐

- True positive—Indicates detection of a pathogenic *BRCA* variant in the individual.
- True negative—Indicates the absence of a pathogenic variant in an individual who has relatives with cancer and a known pathogenic *BRCA* variant in the family.
- Uninformative negative—Indicates the absence of a pathogenic variant in an individual; however, this negative test result is inconclusive because it can occur for several reasons:
 - Other family members have not been tested
 - The family carries a pathogenic *BRCA* variant, but it was not detected because of limitations of the test
 - The family carries a high-risk mutation in another gene
 - There is no high-risk mutation in the family
- Variant of uncertain clinical significance—Indicates the presence of an abnormality of the *BRCA* gene, but it is unknown whether the variant is associated with an increased risk of cancer.

*Or other known actionable deleterious mutation associated with hereditary breast and ovarian cancer syndrome.

Data from Nelson HD, Fu R, Goddard K, Mitchell JP, Okinaka-Hu L, Pappas M, et al. Risk assessment, genetic counseling, and genetic testing for *BRCA*-related cancer: systematic review to update the U.S. Preventive Services Task Force recommendation. Evidence Synthesis No. 101. AHRQ Publication No. 12-05164-EF-1. Rockville (MD): Agency for Healthcare Research and Quality; 2013.

members, all gynecologic care providers can have a role in advocating the education, referral, and testing of family members of affected individuals—otherwise known as “cascade” testing.

Genetic counseling also may include discussion of other potential implications of genetic testing, such as cost, privacy, and insurance coverage. Medicare and other insurance companies have written guidelines for covering the cost of genetic testing, and anyone ordering genetic testing will need to understand the various tests that are available as well as insurance coverage requirements. Another important aspect of genetic counseling is discussion of current legislation regarding genetic discrimination and the privacy of genetic information. The federal Genetic Information Nondiscrimination Act of 2008 protects individuals against health and employment discrimination based on genetic information (50). Many states also have laws that provide similar protection. These laws do not apply to other forms of insurance, which may include life or disability insurance.

Common clinical and ethical issues regarding genetic counseling and genetic testing in gynecologic care are presented and addressed in a case format in

the *Genetics Toolkit* (www.sgo.org/genetics/genetics-toolkit/), a collaborative effort of the Society of Gynecologic Oncology, the American College of Obstetricians and Gynecologists, the National Society of Genetic Counselors, Bright Pink, and Facing Our Risk of Cancer Empowered (FORCE). The American College of Obstetricians and Gynecologists’ genetics web page (www.acog.org/Genetics) and Committee Opinion No. 693, *Counseling About Genetic Testing and Communication of Genetic Test Results*, include additional guidance and information on the clinical and ethical issues related to genetic testing in gynecologic practice.

► *What genetic testing approach should be offered?*

Genetic testing is recommended when the results of a detailed risk assessment that is performed as part of genetic counseling suggest the presence of an inherited cancer syndrome for which specific genes have been identified and when the results of testing are likely to influence medical management (51). Genetic testing will not be appropriate for every patient referred for genetic counseling and not every patient who is offered genetic testing will choose to act on that recommendation.

The two main genetic testing options for hereditary breast and ovarian cancer syndrome are *BRCA* mutation testing and multigene panel testing that includes *BRCA* and other genetic mutations. The choice of testing strategy will depend on whether or not there is a known mutation in the family (49). If possible, any genetic testing should begin with the cancer-affected individual in the family, who may have early-onset breast cancer, ovarian cancer, or another *BRCA*-associated cancer (eg, pancreatic cancer, melanoma, or early-onset prostate cancer) because this will provide the best answer as to whether the familial cancer is due to a known genetic mutation. If that person cannot be tested, the closest cancer-affected relative to that person may be appropriate for testing, with the understanding that a negative genetic test result in this situation may be uninformative.

***BRCA* Mutation Testing**

BRCA mutation testing comprises single-site testing, targeted multisite mutation testing, comprehensive gene sequencing, and *BRCA* rearrangement testing (49). If a specific *BRCA* mutation is identified in an affected individual, a single-site test can be recommended for family members to look for that specific genetic mutation already identified (ie, “predictive testing”). For members of certain ethnic and geographic groups who are at risk of founder mutations, but who do not have a personal or family history of breast or ovarian cancer,



targeted multisite testing for common mutations can be performed and is less expensive than full sequence testing. Genetic testing has evolved over the years so patients who underwent *BRCA* genetic testing before the routine initiation of *BRCA* Rearrangement Testing, may need repeat testing or evaluation.

Multigene Panel Testing

Technologic advances in genetic sequencing have resulted in the ability to perform parallel sequencing of multiple genes more quickly and cost effectively than in the past. The goal of panel testing is to maximize finding an actionable genetic mutation (ie, findings likely to affect medical management) (Table 1). Multiple companies now offer genetic panel testing for cancer-related genes with combinations of genes that may be associated with specific types of cancer (eg, breast-ovarian, gynecologic, colon, pancreas, and kidney).

Multigene panel testing may be useful when more than one gene may be associated with an inherited cancer syndrome (17, 51) or when a patient has a personal or family history that is consistent with an inherited cancer susceptibility, but single-gene testing has not identified a pathogenic variant (17). Multigene panel tests should be offered by a health care provider with cancer genetics expertise and after genetic counseling and informed consent. Although mutations in *BRCA1* and *BRCA2* account for most cases of hereditary breast and ovarian cancer, other genes have been found to be associated with this hereditary syndrome (Table 1), and results showing mutations in such genes may affect patient counseling regarding screening and risk-reduction measures.

An important consideration for multigene panel testing is the increased complexity and uncertainty of the results and how this affects interpretation, patient counseling, and medical management. Because panel testing involves the simultaneous testing of multiple genes and can include genes that confer moderate or uncertain risk, there is an increased likelihood of finding variants of uncertain significance for which there are limited (or no) data on associated cancer risk to guide appropriate management (17). Health care providers who order these multigene panel tests should be prepared to guide their patients appropriately and contact them if variant classifications change.

► How should women with mutations in *BRCA1* or *BRCA2* be counseled to reduce the risk of ovarian cancer?

Current strategies to reduce the risk of developing ovarian cancer (including fallopian tube cancer) in women at

high risk with known deleterious *BRCA* mutations may include risk-reducing agents and surgery (17).

Screening

In women with *BRCA* mutations or who have a personal or family history of ovarian cancer, routine ovarian cancer screening with measurement of serum CA 125 level or transvaginal ultrasonography generally is not recommended (17). Transvaginal ultrasonography or measurement of serum CA 125 level may be reasonable for short-term surveillance in women at high risk of ovarian cancer starting at age 30–35 years until the time they choose to pursue risk-reducing bilateral salpingo-oophorectomy, which is the only proven intervention to reduce ovarian cancer-specific mortality (17). Available screening procedures (measurement of serum CA 125 level and transvaginal ultrasonography) have not been proved to decrease the mortality rate or increase the survival rate associated with ovarian cancer in high-risk populations (49).

The low prevalence of ovarian cancer and the high likelihood of a positive screening test result that leads to potentially unnecessary invasive surgical evaluation are current obstacles in ovarian cancer screening programs among women at inherited risk (52–54). The largest trial to date in high-risk women (United Kingdom Familial Ovarian Cancer Screening Study-UK-FOCSS, 2017) monitored women with CA 125 level screening (using the risk of ovarian cancer algorithm) every 4 months and annual transvaginal ultrasonography (55). Risk-reducing surgery was encouraged throughout the study. Cases of cancer that were detected during the UK-FOCSS screening trial were more often early stage compared with cases of cancer diagnosed more than 1 year after screening ended. A significant number of cases of cancer were identified at risk-reducing surgery. Survival analysis could not be performed. The authors concluded that screening may be an option for women at high risk of ovarian cancer who defer or decline risk-reducing salpingo-oophorectomy (55). Further investigation is necessary to identify better serum markers and improved screening algorithms to improve the positive and negative predictive value of testing.

Risk-Reducing Agents

A large systematic review and meta-analysis confirmed risk reduction with combined hormonal contraceptive use specifically in *BRCA* carriers. The reported reduction with 1 year of use was estimated at 33–80% for *BRCA1* and 58–63% for *BRCA2* carriers (56). Given the magnitude of the potential benefits (eg, ovarian and endometrial cancer risk reduction, pregnancy



prevention, cycle regulation), it is appropriate for women with mutations in *BRCA1* or *BRCA2* to use oral contraceptives if indicated, and use for cancer prophylaxis is reasonable. Although there have been conflicting reports in the literature on the effect of oral contraceptives on breast cancer risk (17), a recent meta-analysis showed no clear increased risk of breast cancer in *BRCA* mutation carriers who used oral contraceptives (57, 58).

Surgical Risk Reduction

Risk-Reducing Bilateral Salpingo-oophorectomy

The most effective ovarian cancer risk-reduction strategy for women with known *BRCA* mutations remains risk-reducing bilateral salpingo-oophorectomy (removal of the ovaries and fallopian tubes in their entirety). Women with *BRCA* mutations or who carry another actionable deleterious mutation predisposing to ovarian cancer should be offered risk-reducing bilateral salpingo-oophorectomy. The current National Comprehensive Cancer Network guidelines recommend that bilateral salpingo-oophorectomy also be considered for carriers of *BRIP1*, *RAD51C*, and *RAD51D* at ages 45–50 years and that hysterectomy along with bilateral salpingo-oophorectomy be considered for those with Lynch syndrome (17).

Meta-analysis results show that risk-reducing bilateral salpingo-oophorectomy reduces the risk of ovarian cancer, fallopian tube cancer, or peritoneal cancer by approximately 80% (hazard ratio, 0.21; 95% CI, 0.12–0.39) in women with known mutations in *BRCA1* or *BRCA2* (59). In addition, risk-reducing bilateral salpingo-oophorectomy has been shown to decrease overall mortality in women with a *BRCA1* or *BRCA2* mutation (60–62). Reported adverse effects of risk-reducing bilateral salpingo-oophorectomy include symptoms of early menopause (eg, vasomotor symptoms and decreased sexual functioning) and surgery complications (eg, wound infection, bladder perforation, small bowel obstruction, and uterine perforation) (49).

The timing of risk-reducing bilateral salpingo-oophorectomy can be individualized based on the particular genetic mutation, the patient's desires for further childbearing, and family history. Typically, risk-reducing salpingo-oophorectomy is recommended at age 35–40 years for *BRCA1* carriers with the highest lifetime risk of ovarian cancer, whereas women with *BRCA2* may consider delaying until age 40–45 years because of later onset of ovarian cancer (17). Ovarian cancer will be diagnosed in less than 2–3% of women with *BRCA1* or *BRCA2* mutations before age 40 years. For women

with *BRCA1* mutations, the risk of ovarian cancer markedly increases during their 40s, with 10–21% of *BRCA1* mutation carriers developing ovarian cancer by age 50 years. The risk of premenopausal ovarian cancer is much lower in *BRCA2* mutation carriers, with no more than 3% of *BRCA2* mutation carriers developing ovarian cancer by age 50 years (20, 63). Given the different timing of ovarian cancer risk, consideration can be given to counseling patients with *BRCA1* mutations differently than patients with *BRCA2* mutations. However, women with *BRCA2* mutations have a 26–34% chance of developing breast cancer by age 50 years (13, 18, 20), and the maximum benefit of removing the ovaries for breast cancer risk reduction is achieved the earlier the ovaries are removed (64, 65). Given these issues, the timing of risk-reducing salpingo-oophorectomy should be based on individual patient needs, taking into consideration the woman's desire to preserve fertility or prevent premature surgical menopause with the age-dependent effect of risk-reducing salpingo-oophorectomy on breast cancer and gynecologic cancer risks.

Bilateral Salpingectomy

Bilateral salpingectomy alone in high-risk women is not currently recommended for ovarian cancer risk reduction, although clinical trials are underway (17). There is increasing interest in risk-reducing bilateral salpingectomy as an option for women with *BRCA* mutations. This option is primarily driven by the desire of high-risk women to reduce the risk of ovarian cancer but also to avoid the adverse effects of early menopause that occur with removal of the ovaries. However, bilateral salpingectomy with oophorectomy may have the added benefit of reducing breast cancer risk, which is an important consideration given that many of these high-risk women are often also at increased risk of breast cancer. Population data for women at average risk confirm a marked ovarian cancer risk reduction of up to 65% for those receiving a bilateral salpingectomy (66, 67), but trials are still ongoing for high-risk women. One study created a theoretical model to quantify the potential risk of a staged bilateral salpingectomy followed by a delayed oophorectomy and estimated that the differences in ovarian cancer risk were very small (68). Thus, in high-risk women who are undergoing tubal sterilization for contraception, bilateral salpingectomy followed by future oophorectomy may be a reasonable option to offer (69). Women at high risk of ovarian cancer should be counseled that the efficacy of bilateral salpingectomy intended solely for ovarian cancer risk reduction remains under evaluation and that bilateral salpingectomy without oophorectomy does not provide added protection against breast cancer.



► **How should women with mutations in BRCA1 or BRCA2 be counseled to reduce the risk of breast cancer?**

Current strategies to reduce the risk of breast cancer in women with known deleterious *BRCA* mutations include increased surveillance with more intensive breast cancer screening, chemoprevention, and surgery.

Screening

For women aged 25–29 years with known *BRCA* mutations, recommended breast cancer surveillance includes clinical breast examination every 6–12 months and annual radiographic screening (preferably, magnetic resonance imaging [MRI] with contrast) (17). Magnetic resonance imaging of the breast with contrast is preferred over annual mammography from ages 25–29 years because of evidence of radiation exposure leading to an increased breast cancer risk in European women with *BRCA* mutations who were exposed to mammography before age 30 years (70), even though this finding was not replicated in a North American cohort (71). For women aged 30 years and older with known *BRCA* mutations or other actionable breast cancer mutations, recommended breast cancer surveillance includes annual mammography and annual breast MRI with contrast, often alternating every 6 months (17). Magnetic resonance imaging is more sensitive for the detection of breast cancer than mammography, and the combination of MRI, mammography, and clinical breast examination has the highest sensitivity for the detection of breast cancer in high-risk *BRCA* mutation carriers (72–74).

Potential adverse effects of intensive breast cancer screening in women with increased familial risk (including *BRCA* mutation carriers) include false-positive test results, unnecessary imaging, unneeded surgeries, discomfort, pain, and anxiety (49). Systematic review evidence shows that compared with mammography, MRI is associated with higher rates of false-positive test results (8.2–14% MRI; 4.6–15% mammography), recall (11% MRI; 3.9% mammography), and unneeded biopsy (25–43% MRI; 27–28% mammography) (49). Reported rates of discomfort, pain, and anxiety do not differ significantly between MRI, mammography, and clinical breast examination (49).

Risk-Reducing Agents

The risk-reduction agents tamoxifen and raloxifene (in postmenopausal women) may be considered for breast cancer risk-reduction in *BRCA* mutation carriers. Studies have suggested that chemoprevention with tamoxifen may reduce breast cancer risk by approximately 62%

in *BRCA2* mutation carriers (75). This is similar to the reduction observed in estrogen-positive breast cancer after tamoxifen use among the general population (76). In contrast, tamoxifen has not been found to reduce the risk of breast cancer among *BRCA1* mutation carriers (75). This likely reflects the lower prevalence (10–24%) of estrogen receptor-positive breast cancer among *BRCA1* mutation carriers; whereas *BRCA2* mutation carriers have tumors that are predominantly (65–79%) estrogen receptor positive (75).

In a systematic review and meta-analysis of published studies of breast cancer risk-reducing medications, raloxifene was found to reduce invasive breast cancer in women at increased risk, including those with a family history of breast cancer, although none of the trials evaluated breast cancer incidence specifically in women who were *BRCA* mutation carriers (77). There was a decreased risk of invasive breast cancer over 5 years in women who received raloxifene (relative risk [RR], 0.44; 95% CI, 0.27–0.71) compared with women randomized to placebo. In the only head-to-head trial in the analysis, tamoxifen was associated with a greater risk reduction than raloxifene (RR of invasive cancer for raloxifene, 1.24; 95% CI, 1.05–1.47). Both medications were associated with a decreased risk of estrogen receptor-positive breast cancer but not estrogen receptor-negative breast cancer (77).

Commonly reported adverse effects of tamoxifen include vasomotor symptoms and vaginal symptoms (discharge, itching, dryness, and dyspareunia) (77). Tamoxifen also is associated with an increased risk of thromboembolic events (RR, 1.93; 95% CI, 1.41–2.64) and endometrial cancer (RR, 2.13; 95% CI, 1.36–3.32) (77). Reported adverse effects of raloxifene include vasomotor symptoms, leg cramps, dyspareunia, and weight gain (77).

Two trials have shown a reduction in breast cancer in postmenopausal high-risk women who use aromatase inhibitors. Neither trial specifically studied women with *BRCA* mutations. Given the protective effects in other at-risk populations, aromatase inhibitors may be an alternative for women who cannot take tamoxifen (78, 79).

Risk-Reducing Surgery

Bilateral Mastectomy

Women with *BRCA* mutations or who carry another actionable deleterious mutation that is predisposing to breast cancer should be offered risk-reducing bilateral mastectomy. Bilateral mastectomy reduces the risk of breast cancer in *BRCA* mutation carriers by 85–100% depending on the type of mastectomy procedure (49, 80, 81). The National Comprehensive Cancer Network



and U.S. Preventive Services Task Force recommend discussion of this option with the patient (17, 43). Total mastectomy removes the entire breast tissue, nipple, and areola, whereas a nipple-sparing mastectomy removes all breast tissue except the nipple and areola. There have been no trials that compared the efficacy of the two methods. Consideration of a contralateral prophylactic mastectomy is strongly recommended for *BRCA*-mutation carriers with breast cancer, given the 30% risk of contralateral recurrence in the 10 years following initial diagnosis (82).

Complete discussion with the patient who is considering prophylactic mastectomy is important and should include the psychosocial effects of mastectomy as well as the short-term and long-term complications (83). A meta-analysis of four descriptive studies of the effects of risk-reducing mastectomy with or without breast reconstruction found that adverse physical events included a 3–59 % risk of surgical complications (eg, postoperative infection, hematoma, flap necrosis, and failed reconstruction) and a 64–87% risk of postsurgical physical symptoms (eg, pain, numbness, tingling, swelling, and breast hardness) (49). In a retrospective cohort study of the psychosocial effects of risk-reducing bilateral mastectomy after a mean follow-up of 14.5 years, 70% of the 572 participants reported being satisfied with their decision to undergo surgery, and 74% reported decreased anxiety and concern about breast cancer (84). Commonly reported adverse psychosocial effects include decreased sexual satisfaction and negative body image (49, 85).

Bilateral Salpingo-Oophorectomy

Risk-reducing bilateral salpingo-oophorectomy for ovarian cancer prevention may have the added benefit of reducing the risk of breast cancer by 37–100% in *BRCA* mutation carriers (49). In addition, risk-reducing bilateral salpingo-oophorectomy may improve breast cancer outcomes and prevent subsequent ovarian cancer in *BRCA*-positive women with breast cancer (86, 87). The protective effect against breast cancer likely occurs only if patients are premenopausal at the time of risk-reducing bilateral salpingo-oophorectomy (87). In a large 2016 prospective study, premenopausal oophorectomy was associated with prevention of premenopausal breast cancer (before age 50 years) in *BRCA2* mutation carriers (age-adjusted hazard ratio, 0.18; 95% CI, 0.05–0.63) but not in *BRCA1* mutation carriers (age-adjusted hazard ratio, 0.79; 95% CI, 0.55–1.13) (88).

However, some researchers have called into question the breast cancer risk reduction from bilateral salpingo-oophorectomy. In one study, by using different analytics and adjusting for cancer at the time of test

and time preceding risk-reducing bilateral salpingo-oophorectomy, the authors found no decrease in breast cancer risk associated with risk-reducing bilateral salpingo-oophorectomy (89).

► *How should risk-reducing salpingo-oophorectomy be technically performed? How should surgical specimens be examined?*

For a risk-reducing bilateral salpingo-oophorectomy, all tissue from the ovaries and fallopian tubes should be removed. Thorough visualization of the peritoneal surfaces with pelvic washings should be performed. Complete, serial sectioning of the ovaries and fallopian tubes is necessary, with microscopic examination for occult cancer. The optimal approach will depend on patient and physician preference and the availability of an experienced health care provider to perform adequate staging. Decisions about the surgical approach should be made as part of an informed decision-making process, combining the patient's values and preferences with the knowledge and capability of the surgeon.

The diaphragm, liver, omentum, bowel, paracolic gutters, and appendix should be inspected in the abdomen. The ovaries, fallopian tubes, uterus, bladder serosa, and cul-de-sac should be inspected in the pelvis. Any abnormal areas should undergo biopsy. The ovarian vessels should be isolated and ligated approximately 2 cm proximal to the end of identifiable ovarian tissue to ensure that all ovarian and tubal tissue is completely removed. If a hysterectomy is not being performed, the fallopian tube should be divided at its insertion into the uterine cornu and the ovary removed at the utero-ovarian ligament as close to the uterus as possible. When performing a laparoscopic procedure, to optimize preservation of the ovarian surface epithelium, the specimens can be placed in an endoscopic bag before removal from the abdomen. If gross unsuspected cancer is identified, surgical staging with lymphadenectomy and omentectomy may be performed at the time of risk-reducing surgery, provided appropriate preoperative consent has been obtained. It also is reasonable, however, to await final pathology test results and proceed with definitive surgery in an expeditious manner if cancer is identified. Routine performance of an intraoperative frozen section procedure is discouraged because most malignancies found at risk-reducing salpingo-oophorectomy are occult (90).

Complete, serial sectioning of the ovaries and fallopian tubes is necessary, with microscopic examination for occult cancer (91). Occult, microscopic cancer of the ovary or fallopian tube has been identified in *BRCA1*



and *BRCA2* mutation carriers undergoing prophylactic risk-reducing salpingo-oophorectomy (92–95). This is more common in women older than 45 years than in younger women.

Thorough pathology review of the ovaries and the fallopian tubes is critical in order to detect microscopic cancer in these high-risk women. Rather than taking only one or two representative sections from each ovary, the complete ovaries and fallopian tubes should be serially sectioned and evaluated (91). In fact, more cases of microscopic fallopian tube cancer have been detected than microscopic ovarian cancer in the prophylactic risk-reducing salpingo-oophorectomy specimens of *BRCA1* and *BRCA2* mutation carriers. Although the tumors identified are microscopic, they are often high grade, and information from the peritoneal lavage may reflect the aggressiveness of the disease (96). Because occult cancer may be found only through serial sectioning and thorough evaluation of the ovaries and tubes, it is possible that some subsequent primary peritoneal carcinoma actually represents the recurrence of a previously unrecognized occult cancer (97).

The decision to perform a concurrent hysterectomy should be individualized. Salpingo-oophorectomy alone confers a significant cancer risk reduction with less surgical risk and shorter postoperative recovery (98, 99). However, benefits of hysterectomy include a more simplified hormone therapy strategy (with estrogen only) and the removal of the cornual fallopian tube, which is associated with a theoretical increased risk of cancer (100). The potentially increased risk of high-grade histology endometrial cancer in *BRCA1* mutations carriers also can be discussed and patient preferences taken into account (38). In addition, hysterectomy may be considered when there are other medical indications for removal of the uterus and cervix. For women taking tamoxifen, hysterectomy may be considered to reduce their endometrial cancer risk (101, 102).

► ***What follow-up should women with mutations in *BRCA1* or *BRCA2* receive after risk-reducing salpingo-oophorectomy?***

Women with mutations in *BRCA1* or *BRCA2* who undergo risk-reducing salpingo-oophorectomy by the recommended age of 35–45 years will experience early menopause and the possibility of associated symptoms, and may have long-term health outcomes of heart disease and bone loss. Women who have undergone risk-reducing salpingo-oophorectomy and who are unaffected by breast cancer should be offered hormone therapy to mitigate the effects of early menopause. Patients should be counseled that limited data suggest that use

of estrogen-only or combination hormone therapy for a few years does not significantly diminish the protective effect of risk-reducing bilateral salpingo-oophorectomy on breast cancer risk reduction (103). However, the effect of long-term hormone therapy on breast cancer risk reduction in the patient who is premenopausal at time of risk-reducing salpingo-oophorectomy is not known. There are only two small studies that have looked at the safety of hormone therapy in this cohort after risk-reducing salpingo-oophorectomy (104, 105).

► ***What surveillance for primary peritoneal cancer should be performed for women after risk-reducing salpingo-oophorectomy?***

No laboratory or imaging surveillance is recommended for primary peritoneal cancer in women who have undergone risk-reducing salpingo-oophorectomy. The benefit of serum CA 125 measurement or imaging surveillance after risk-reducing salpingo-oophorectomy is not known because peritoneal cancer is relatively uncommon (1–6% cumulative risk for all carriers) (105). Patients should be informed that because screening for primary peritoneal cancer is investigational, there is limited information available regarding the relative risks and benefits. Counseling should include information about symptom awareness and a discussion of the need to continue routine well-women screenings and care.

► ***How should women with *BRCA* mutations be counseled regarding fertility and quality of life?***

There have been contradictory reports on whether women with *BRCA* mutations, particularly *BRCA1* mutations, without a history of cancer and who have not undergone risk-reducing surgery have an increased incidence of premature menopause (106–108). Recent evidence suggests that *BRCA1* mutation carriers may have decreased ovarian reserve (as measured by circulating anti-müllerian hormone levels) compared with *BRCA2* carriers and noncarriers (109). Nevertheless, fertility often is affected because many women with *BRCA* mutations will have breast cancer at a young age and undergo chemotherapy. The recommendation for offering a risk-reducing salpingo-oophorectomy by age 35–45 years also limits the fertility window. This warrants a careful discussion with a young *BRCA* carrier to ensure that her fertility needs are met. Those facing a cancer diagnosis or a decision for risk-reducing surgery may be candidates for oocyte or embryo cryopreservation (110).

Menopausal symptoms, including hot flashes, sexual discomfort (resulting from vaginal atrophy), and reduced libido are common in women who have



undergone risk-reducing salpingo-oophorectomy. For women without a history of breast cancer, hormone therapy can mitigate many of these symptoms. Quality-of-life studies of high-risk women who have undergone risk-reducing salpingo-oophorectomy demonstrate no significant change in their quality of life, except for a subset who report decreased sexual satisfaction (49). *BRCA* mutation carriers may benefit from supportive services, including counseling for sexuality and adjustment (111, 112).

▶ ***What is the appropriate management for a woman with a strong family history who does not have a documented mutation in BRCA1, BRCA2, or other hereditary breast and ovarian cancer-associated gene?***

Women who have a personal or family history of breast or ovarian cancer but who do not have a documented mutation in *BRCA1*, *BRCA2*, or other hereditary breast or ovarian cancer-associated gene should be managed based on their family history. Preliminary data have suggested that women from families with a history of only breast cancer (but not ovarian cancer) in which no *BRCA* mutation is identified remain at a significantly increased risk of breast cancer, but not ovarian cancer (113, 114). Most cases of inherited predisposition to ovarian cancer are caused by pathogenic variants in *BRCA1*, *BRCA2*, or the other hereditary breast and ovarian cancer-associated genes (Table 1), although there may be other less prevalent genes that have not yet been identified (115). If women were tested before 2009, they may not have had large gene rearrangement testing in the *BRCA* genes (ie, the *BRCA* Rearrangement Test). Furthermore, women tested before 2013 would not have had access to multigene panel testing. For these women, further consultation with a specialist in cancer genetics may help to clarify their residual risk and the need for additional testing. It is important for high-risk individuals to stay in contact with clinicians experienced in the care of women at increased risk of hereditary breast and ovarian cancer, given the continued and rapidly developing research and refinements in testing technology.

Summary of Recommendations

The following recommendations are based on good and consistent scientific evidence (Level B):

- ▶ Genetic counseling is recommended for all women with ovarian epithelial cancer (this includes fallo-

pian tube cancer or primary peritoneal cancer) and for individuals who have a personal or family history of breast cancer or ovarian cancer.

- ▶ Women with *BRCA* mutations or who carry another actionable deleterious mutation that is predisposing to breast cancer should be offered risk-reducing bilateral mastectomy.
- ▶ Women with *BRCA* mutations or who carry another actionable deleterious mutation predisposing to ovarian cancer should be offered risk-reducing bilateral salpingo-oophorectomy. The timing of risk-reducing bilateral salpingo-oophorectomy can be individualized based on the particular genetic mutation, the patient's desires for future childbearing, and family history. Typically, risk-reducing salpingo-oophorectomy is recommended at age 35–40 years for *BRCA1* carriers with the highest lifetime risk of ovarian cancer, whereas women with *BRCA2* may consider delaying until age 40–45 years because of later onset of ovarian cancer.
- ▶ For a risk-reducing bilateral salpingo-oophorectomy, all tissue from the ovaries and fallopian tubes should be removed. Thorough visualization of the peritoneal surfaces with pelvic washings should be performed. Complete, serial sectioning of the ovaries and fallopian tubes is necessary, with microscopic examination for occult cancer.

The following recommendations are based primarily on consensus and expert opinion (Level C):

- ▶ Evaluating a patient's risk of hereditary breast and ovarian cancer syndrome should be a routine part of obstetric and gynecologic practice. Initial risk evaluation should include a personal medical history and family history.
- ▶ Genetic testing is recommended when the results of a detailed risk assessment that is performed as part of genetic counseling suggest the presence of an inherited cancer syndrome for which specific genes have been identified and when the results of testing are likely to influence medical management.
- ▶ The two main genetic testing options for hereditary breast and ovarian cancer syndrome are *BRCA* mutation testing and multigene panel testing that includes both *BRCA* and other genetic mutations. Multigene panel testing may be useful when more than one gene may be associated with an inherited cancer syndrome or when a patient has a personal or family history that is consistent with an inherited cancer susceptibility, but single-gene testing has not identified a pathogenic variant.



- ▶ In women with *BRCA* mutations or who have a personal or family history of ovarian cancer, routine ovarian cancer screening with measurement of serum CA 125 level or transvaginal ultrasonography generally is not recommended. Transvaginal ultrasonography or measurement of serum CA 125 level may be reasonable for short-term surveillance in women at high risk of ovarian cancer starting at age 30–35 years until the time they choose to pursue risk-reducing bilateral salpingo-oophorectomy, which is the only proven intervention to reduce ovarian cancer-specific mortality.
- ▶ For women aged 25–29 years with known *BRCA* mutations, recommended breast cancer surveillance includes clinical breast examination every 6–12 months and annual radiographic screening (preferably, MRI with contrast).
- ▶ For women aged 30 years and older with known *BRCA* mutations or other actionable breast cancer mutations, recommended breast cancer surveillance includes annual mammography and annual breast MRI with contrast, often alternating every 6 months.
- ▶ Women who have a personal or family history of breast or ovarian cancer but who do not have a documented mutation in *BRCA1*, *BRCA2*, or other hereditary breast or ovarian cancer-associated gene should be managed based on their family history.

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The American College of Obstetricians and Gynecologists
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Hereditary breast and ovarian cancer syndrome. Practice Bulletin No. 182. American College of Obstetricians and Gynecologists. *Obstet Gynecol* 2017;130:e110–26.

The MEDLINE database, the Cochrane Library, and ACOG's own internal resources and documents were used to conduct a literature search to locate relevant articles published between January 2000 and May 2017. The search was restricted to articles published in the English language. Priority was given to articles reporting results of original research, although review articles and commentaries also were consulted. Abstracts of research presented at symposia and scientific conferences were not considered adequate for inclusion in this document. Guidelines published by organizations or institutions such as the National Institutes of Health and the American College of Obstetricians and Gynecologists were reviewed, and additional studies were located by reviewing bibliographies of identified articles. When reliable research was not available, expert opinions from obstetrician–gynecologists were used.

Studies were reviewed and evaluated for quality according to the method outlined by the U.S. Preventive Services Task Force:

- I Evidence obtained from at least one properly designed randomized controlled trial.
- II-1 Evidence obtained from well-designed controlled trials without randomization.
- II-2 Evidence obtained from well-designed cohort or case–control analytic studies, preferably from more than one center or research group.
- II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments also could be regarded as this type of evidence.
- III Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Based on the highest level of evidence found in the data, recommendations are provided and graded according to the following categories:

Level A—Recommendations are based on good and consistent scientific evidence.

Level B—Recommendations are based on limited or inconsistent scientific evidence.

Level C—Recommendations are based primarily on consensus and expert opinion.

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