NCCN Guidelines® Insights  
Genetic/Familial High-Risk Assessment: Breast and Ovarian, Version 2.2017

Featured Updates to the NCCN Guidelines

Mary B. Daly, MD, PhD1,*; Robert Pilarski, MS, CGC2,*; Michael Berry, MD3; Saundra S. Buys, MD4,*; Meagan Farmer, MS, CGC5; Susan Friedman, DVM6; Judy E. Garber, MD, MPH7; Noah D. Kauff, MD8; Seema Khan, MD9; Catherine Klein, MD10,*; Wendy Kohlmann, MS, CGC11; Allison Kurian, MD, MSc12,*; Jennifer K. Litton, MD13; Catherine Klein, MD14,*; Wendy Kohlmann, MS, CGC15; Allison Kurian, MD, MSc16,*; Lisa Madlensky, PhD, CGC17; Allison Kurian, MD, MSc18; Seema Khan, MD19,*; Robert Pilarski, MS, CGC20; Mary B. Daly, MD, PhD21,*; Georgia L. Wiesner, MD, MS22; Elizabeth Swisher, MD23,*; Sofia D. Merajver, MD, PhD24,*; Georgia L. Wiesner, MD, MS25,*; and Susan Darlow, PhD26,*

Abstract

The NCCN Clinical Practice Guidelines in Oncology for Genetic/Familial High-Risk Assessment: Breast and Ovarian provide recommendations for genetic testing and counseling for hereditary cancer syndromes and risk management recommendations for patients who are diagnosed with a syndrome. Guidelines focus on syndromes associated with an increased risk of breast and/or ovarian cancer. The NCCN Genetic/Familial High-Risk Assessment: Breast and Ovarian panel meets at least annually to review comments from reviewers within their institutions, examine relevant new data from publications and abstracts, and reevaluate and update their recommendations. The NCCN Guidelines Insights summarize the panel's discussion and most recent recommendations regarding risk management for carriers of moderately penetrant genetic mutations associated with breast and/or ovarian cancer.

From 1Fox Chase Cancer Center; 2The Ohio State University Comprehensive Cancer Center - James Cancer Hospital and Solove Research Institute; 3St. Jude Children's Research Hospital/ The University of Tennessee Health Science Center; 4Huntsman Cancer Institute at the University of Utah; 5University of Alabama at Birmingham Comprehensive Cancer Center; 6FORCE: Facing Our Risk of Cancer Empowered; 7Dana-Farber/Brigham and Women's Cancer Center; 8Duke Cancer Institute; 9Robert H. Lurie Comprehensive Cancer Center of Northwestern University; 10University of Colorado Cancer Center; 11Stanford Cancer Institute; 12The University of Texas MD Anderson Cancer Center; 13UC San Diego Moores Cancer Center; 14University of Michigan Comprehensive Cancer Center; 15Memorial Sloan Kettering Cancer Center; 16Moffitt Cancer Center; 17Fred & Pamela Buffett Cancer Center; 18Massachusetts General Hospital Cancer Center; 19University of Washington Medical Center/Seattle Cancer Care Alliance; 20Case Comprehensive Cancer Center/University Hospitals Seidman Cancer Center and Cleveland Clinic Taussig Cancer Institute; 21Roswell Park Cancer Institute; 22City of Hope Comprehensive Cancer Center; 23Mayo Clinic Cancer Center; 24Vanderbilt-Ingram Cancer Center; and 25National Comprehensive Cancer Network.

*Provided content development and/or authorship assistance.

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Kimberly Callan, MS, Senior Director, Professional and Patient Publications, NCCN, has disclosed that she has no relevant financial relationships.
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Deborah J. Moonan, RN, BSN, Director, Continuing Education, NCCN, has disclosed that she has no relevant financial relationships.
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Rashmi Kumar, PhD, Senior Manager, Clinical Content, NCCN, has disclosed that she has no relevant financial relationships.

Individuals Who Provided Content Development and/or Authorship Assistance:
Mary B. Daly, MD, PhD, Panel Chair, has disclosed that she has no relevant financial relationships.
Robert Pilarski, MS, CGC, Panel Vice-Chair, has disclosed that he receives consulting fees/honoraria from Invitae.
Saundra S. Buys, MD, Panel Member, has disclosed that she has no relevant financial relationships.
Catherine Klein, MD, Panel Member, has disclosed that she has no relevant financial relationships.
Allison Kurian, MD, MSc, Panel Member, has disclosed that she receives grant/research support from Ambry Genetics, Invitae, and Myriad Genetic Laboratories, Inc.
Jennifer K. Litton, MD, Panel Member, has disclosed that he receives grant/research support from Novartis Pharmaceuticals Corporation, Medivation, Pfizer, and Genentech, Inc.
Tuya Pal, MD, Panel Member, has disclosed that she has no relevant financial relationships.
Elizabeth Swisher, MD, Panel Member, has disclosed that she has no relevant financial relationships.
Myra J. Wick, MD, PhD, Panel Member, has disclosed that she has no relevant financial relationships.
Mary Dwyer, MS, Senior Manager, Guidelines, NCCN, has disclosed that she has no relevant financial relationships.
Susan Darlow, PhD, Oncology Scientist/Medical Writer, NCCN, has disclosed that she has no relevant financial relationships.

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### Genetic/Familial High-Risk Assessment: Breast and Ovarian, Version 2.2017

#### BREAST AND OVARIAN MANAGEMENT BASED ON GENETIC TEST RESULTS

The inclusion of a gene on this table below does not imply the endorsement either for or against multi-gene testing for moderate-penetrance genes.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Breast Cancer Risk and Management</th>
<th>Ovarian Cancer Risk and Management</th>
<th>Other Cancer Risks and Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATM</td>
<td>Increased risk of BC</td>
<td>No increased risk of OC</td>
<td>Unknown or insufficient evidence for pancreas or prostate cancer</td>
</tr>
<tr>
<td></td>
<td>• Screening; Annual mammogram and</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>consider breast MRI with contrast at</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>age 40 y²</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• RRM: Consider based on family history</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRCA1</td>
<td>Increased risk of BC</td>
<td>Increased risk of OC</td>
<td>Prostate cancer</td>
</tr>
<tr>
<td></td>
<td>• See BRCA Mutation-Positive Management</td>
<td>• See BRCA Mutation-Positive Management</td>
<td></td>
</tr>
<tr>
<td>BRCA2</td>
<td>Increased risk of BC</td>
<td>Increased risk of OC</td>
<td>Pancreas, Prostate, Melanoma</td>
</tr>
<tr>
<td></td>
<td>• See BRCA Mutation-Positive Management</td>
<td>• See BRCA Mutation-Positive Management</td>
<td></td>
</tr>
<tr>
<td>BRIP1</td>
<td>No increased risk of BC</td>
<td>Increased risk of OC</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>• See BRCA Mutation-Positive Management</td>
<td>• See BRCA Mutation-Positive Management</td>
<td></td>
</tr>
<tr>
<td>CDH1</td>
<td>Increased risk of lobular BC</td>
<td>No increased risk of OC</td>
<td>Diffuse gastric cancer</td>
</tr>
<tr>
<td></td>
<td>• Screening; Annual mammogram and</td>
<td></td>
<td>• See NCCN Guidelines for Gastric Cancer</td>
</tr>
<tr>
<td></td>
<td>consider breast MRI with contrast at</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>age 30 y²</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• RRM: Consider based on family history</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### NCCN Categories of Evidence and Consensus

**Category 1:** Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

**Category 2A:** Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

**Category 2B:** Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

**Category 3:** Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

**All recommendations are category 2A unless otherwise noted.**

**Clinical trials:** NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

### Overview

Hereditary cancers are often characterized by mutations associated with increased risk for certain cancers (ie, a high penetrance phenotype) and transmission to offspring through the mother and/or father. An individual suspected of being at risk for hereditary cancer should be offered genetic counseling. The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Genetic/Familial High-Risk Assessment: Breast and Ovarian were developed with the intent to (1) serve as a resource for healthcare providers to identify individuals who may benefit from cancer risk assessment and genetic counseling; (2) provide genetic counselors with an updated tool for the assessment of individual breast and ovarian cancer risk and to guide decisions related to genetic testing; and (3) facilitate a multidisciplinary approach in the management of individuals at increased risk for hereditary breast and/or ovarian cancer.

Advances in molecular genetics have identified a number of genes associated with inherited susceptibility to breast and/or ovarian cancers (eg, BRCA1/2, TP53,
CDH1) and provided a means of characterizing the specific gene mutation or mutations present in certain individuals and families exhibiting an increased risk for cancer. The recent introduction of multigene testing for hereditary forms of cancer has rapidly altered the clinical approach to testing at-risk patients and their families. Multigene testing should focus on identifying a mutation known to be clinically actionable; that is, whether the management of an individual patient is altered based on the presence or absence of a mutation. For some of the genes included as part of multigene testing, especially some low- to moderate-risk genes, there is currently a lack of evidence regarding proper risk management strategies that should follow testing.5

Risk Management Recommendations for Moderate-Penetration Genes Associated With Breast and/or Ovarian Cancer

Penetration, as it applies to genetic mutations, refers to the probability of a clinical condition, such as breast or ovarian cancer, developing in the presence of a specific genotype. In the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian, the panel primarily focuses on assessment of known high-penetration mutations (ie, BRCA1/2, TP53, PTEN) and recommendations for genetic testing, counseling, and management strategies in individuals with these mutations. The following sections include a description of moderate-penetration genes that the panel argues warrant additional screening beyond what is recommended in the general population (ie, those without the specific gene mutation). These include mutations for ATM, BRIP1, CDH1, CHEK2, NBN, PALB2, RAD51C, RAD51D, and STK11. Risk management for genetic mutations associated with Lynch syndrome and neurofibromatosis type 1 are also described. During the 2017 guidelines update meeting, the panel extensively revised their risk management recommendations for these moderate-penetration genes (see GENE-2, GENE-3, GENE-4, pages 11–13).

BREAST AND OVARIAN MANAGEMENT BASED ON GENETIC TEST RESULTS

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<table>
<thead>
<tr>
<th>Gene</th>
<th>Breast Cancer Risk and Management</th>
<th>Ovarian Cancer Risk and Management</th>
<th>Other Cancer Risks and Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHEK2</td>
<td>Increased risk of BC&lt;br&gt;• Screening: Annual mammogram and consider breast MRI with contrast age 40 y&lt;br&gt;• RRM: Evidence insufficient, manage based on family history</td>
<td>No increased risk of OC</td>
<td>Colon&lt;br&gt;• See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal</td>
</tr>
<tr>
<td>MSH2, MLH1, MSH6, PMS2, EPCAM</td>
<td>Unknown or insufficient evidence for BC risk&lt;br&gt;• Manage based on family history</td>
<td>Increased risk of OC&lt;br&gt;• See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal</td>
<td>See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal</td>
</tr>
<tr>
<td>NBN</td>
<td>Increased risk of BC&lt;br&gt;• Screening: Annual mammogram and consider breast MRI with contrast age 40 y&lt;br&gt;• RRM: Evidence insufficient, manage based on family history</td>
<td>Unknown or insufficient evidence for OC risk</td>
<td>Unknown or insufficient evidence</td>
</tr>
<tr>
<td>NF1</td>
<td>Increased risk of BC&lt;br&gt;• Screening: Annual mammogram starting at age 30 y and consider breast MRI with contrast from ages 30–50 y&lt;br&gt;• RRM: Evidence insufficient, manage based on family history</td>
<td>No increased risk of OC</td>
<td>• Malignant peripheral nerve sheath tumors, GIST, others&lt;br&gt;• Recommend referral to NF specialist for evaluation and management.</td>
</tr>
</tbody>
</table>

Comments: Risk data are based only on frameshift mutations. The risks for most missense mutations are unclear.

Comments: Management recommendations are based on data derived from the 657del5 Slavic truncating mutation. Although risks for other mutations have not been established it is prudent to manage patients with other truncating mutations similarly to those with 657del5. Counsel for risk of autosomal recessive condition in children.

Comments: At this time, there are no data to suggest an increased breast cancer risk after age 50 y.


1May be modified based on family history or specific gene mutation.

2There have been suggestions that there is an increased risk for breast cancer in LS patients; however, there is not enough evidence to support increased screening above average-risk breast cancer screening recommendations.

BC: Breast cancer<br>OC: Ovarian cancer<br>RRM: Risk-reducing mastectomy<br>RRSO: Risk-reducing salpingo-oophorectomy

Gene-3
The question of when to initiate risk management in mutation carriers of moderate-penetrance genes was discussed at length during the panel meeting for the 2017 update. This included consideration and adoption of an absolute-risk approach as proposed by Tung et al. Specifically, these investigators postulated that, for carriers of moderately penetrant genetic mutations (ie, ATM, CHEK2, NBN), screening with mammography should begin when the estimated 5-year risk of developing breast cancer exceeds 1%, consistent with recommendations for the average-risk population. Likewise, breast MRI screening in these carriers should begin when the estimated 5-year risk of developing breast cancer exceeds 2.2%. However, they also noted that, for practical reasons, it is reasonable to begin MRI and mammographic screening at the same time. It is important to note that the age at which breast screening is recommended may be impacted by the presence of risk factors such as family history of breast cancer, especially early-onset breast cancer. There is currently insufficient evidence to recommend risk-reducing mastectomy in carriers of moderately penetrant genetic mutations, although this option may be considered and discussed in the context of a personal or family history of breast cancer.

There is insufficient evidence to recommend a specific age at which risk-reducing salpingo-oophorectomy (RRSO) should be considered in carriers of moderately penetrant genetic mutations associated with ovarian cancer (ie, BRIP1, RAD51C, RAD51D). The decision to perform RRSO should not be made lightly, given the impact of premature menopause. Therefore, Tung et al, who performed an analysis of ovarian cancer risk in carriers of moderately penetrant genetic mutations, argued that RRSO should not be considered until a woman’s expected lifetime risk of developing ovarian cancer exceeds 2.6%, which is the expected lifetime risk of a woman with a BRCA-negative family history of ovarian cancer. A discussion about risk-reducing surgery may be

### Table: BREAST AND OVARIAN MANAGEMENT BASED ON GENETIC TEST RESULTS

<table>
<thead>
<tr>
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<th>Ovarian Cancer Risk and Management</th>
<th>Other Cancer Risks and Management</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PALB2</strong></td>
<td>Increased risk of BC</td>
<td>Unknown or insufficient evidence for OC risk</td>
<td>Unknown or insufficient evidence</td>
</tr>
<tr>
<td></td>
<td>• Screening: Annual mammogram and consider breast MRI with contrast at 30 y</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• RRM: Consider based on family history.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PTEN</strong></td>
<td>Increased risk of BC</td>
<td>No increased risk of OC</td>
<td>See Cowden Syndrome Management</td>
</tr>
<tr>
<td></td>
<td>• See Cowden Syndrome Management</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>RAD51C</strong></td>
<td>Unknown or insufficient evidence for BC risk</td>
<td>Increased risk of OC</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>• Consider RRSO at 45–50 y</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Comments: Counsel for risk of autosomal recessive condition in offspring.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>RAD51D</strong></td>
<td>Unknown or insufficient evidence for BC risk</td>
<td>Increased risk of OC</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>• Consider RRSO at 45–50 y</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Comments: Based on estimates from available studies, the lifetime risk of ovarian cancer in carriers of mutations in RAD51C appears to be sufficient to justify consideration of RRSO. The current evidence is insufficient to make a firm recommendation as to the optimal age for this procedure. Based on the current, limited evidence base, a discussion about surgery should be held around age 45–50 y or earlier based on a specific family history of an earlier onset ovarian cancer.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>STK11</strong></td>
<td>Increased risk of OC</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Consider RRSO at 45–50 y</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Comments: Based on estimates from available studies, the lifetime risk of ovarian cancer in carriers of mutations in RAD51D appears to be sufficient to justify consideration of RRSO. The current evidence is insufficient to make a firm recommendation as to the optimal age for this procedure. Based on the current, limited evidence base, a discussion about surgery should be held around age 45–50 y or earlier based on a specific family history of an earlier onset ovarian cancer.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TP53</strong></td>
<td>Increased risk of BC</td>
<td>No increased risk of OC</td>
<td>See Li-Fraumeni Syndrome Management</td>
</tr>
<tr>
<td></td>
<td>• See Li-Fraumeni Syndrome Management</td>
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</tbody>
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**GENE-4**
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initiated earlier if there is a family history of early-onset ovarian cancer.

Lower penetrance genes that may be included as part of multigene testing, but for which there is currently insufficient evidence of an association with breast and/or ovarian cancer, include: BARD1, FANCC, MRE11A, MUTYH heterozygotes, RELQ, RAD50, RET1, SLX4, SMARCA4, and XRCC2. Risk management recommendations for these genes should take into account family history and other clinical factors.

**ATM Mutations**

Mutations in the ATM (ataxia-telangiectasia mutated) gene may increase the risk for breast cancer. A meta-analysis of 3 cohort studies of relatives with ataxia-telangiectasia showed an estimated relative risk of 2.8 (90% CI, 2.2–3.7; P < .001). In a sample of 488 women with nonmetastatic breast cancer, 1% had an ATM mutation. An analysis of 82 Dutch patients with early-onset breast cancer showed that 8.5% (n=7) of the patients had a detected ATM mutation.

The association between specific types of ATM genetic variants and breast cancer susceptibility is less clear, with some evidence showing that certain missense mutations may act in a dominant-negative fashion to increase cancer risk, relative to truncating mutations. A meta-analysis including 5 studies showed that ATM mutation carriers have a 38% lifetime risk of developing breast cancer, with carriers of the c.7271T>G missense mutation having a 69% risk of developing breast cancer by age 70 years. An analysis of 27 families in which pathogenic ATM variants were identified showed an association between the c.7271T>G variant and increased risk of breast cancer (hazard ratio [HR], 8.0; 95% CI, 2.3–27.4; P < .001).

Results of the case-control WECARE study suggested that radiation exposure may be associated with increased risk of contralateral breast cancer in women who are carriers of rare ATM missense variants predicted to be deleterious. However, a meta-analysis including 5 studies showed that radiation therapy (with conventional dosing) is not contraindicated in patients with a heterozygous ATM mutation. Therefore, there is currently insufficient evidence to recommend against radiation therapy in women who are carriers diagnosed with cancer.

The panel recommends annual mammogram for women with a mutated ATM gene beginning at age 40 years, with consideration of annual breast MRI. Risk-reducing mastectomy may also be considered based on family history. Given the association between ATM and development of the autosomal recessive condition ataxia telangiectasia, counseling for carriers of ATM mutations should include a discussion of reproductive options.

**BRIP1 Mutations**

In an observational study including 1,915 unselected ovarian cancer cases, 1.4% of patients had a mutation in the BRCA1 interaction protein C-terminal helicase 1 gene (BRIP1), which is a Fanconi anemia gene. An analysis of 3,236 women with epithelial ovarian cancer, 3,431 controls, and 2,000 unaffected high-risk women from an ovarian cancer screening trial (UKFOCSS) showed that BRIP1 is associated with an increased risk for ovarian cancer (P < .001), with the relative risk (RR) for invasive epithelial ovarian cancer being 11.22 (95% CI, 3.22–34.10; P < .001) and 14.09 for high-grade serous disease (95% CI, 4.04–45.02; P < .001).

The cumulative lifetime risk of developing ovarian cancer by age 80 years in BRIP1 mutation carriers is estimated to be 5.8% (95% CI, 3.6–9.1). Tung et al argued that RRSO should not be considered in these mutation carriers until their cumulative risk exceeds that of a woman with a first-degree relative with a non–BRCA-related ovarian cancer (~2.64%). For BRIP1 mutation carriers, this would be around age 50 to 55 years. However, some women may have additive risk factors (eg, multiple family members with ovarian cancer, lack of parity), and delaying the discussion of RRSO until age 50 years may miss some cases of early-onset ovarian cancer. Therefore, the panel recommends that RRSO in BRIP1 mutation carriers be considered beginning at age 45 to 50 years. Ultimately, large prospective trials are needed to make a firm age recommendation regarding when a discussion about RRSO should begin in these mutation carriers.

BRIP1 is not believed to be significantly associated with increased risk of breast cancer, and no single truncating variant has been found to be associated with increased risk of breast cancer.
CDH1 Mutations
Germline mutations in CDH1 are associated with hereditary diffuse gastric cancer and lobular breast cancer, and studies have reported a cumulative lifetime risk for breast cancer of 39% to 52%. Given the considerable risk for lobular breast cancer in women with a CDH1 mutation, the panel recommends screening with annual mammogram (or consideration of breast MRI) beginning at age 30 years. Screening may be considered earlier in patients with a family history of early-onset breast cancer. The option of risk-reducing mastectomy should be discussed for these carriers.

CHEK2 Mutations
Another breast cancer susceptibility gene that has been identified is CHEK2 (cell cycle checkpoint kinase 2). In a study of BRCA-negative patients with breast cancer who have a strong family history of breast or ovarian cancer, a CHEK2 mutation was detected in 5%. Deleterious CHEK2 mutations have been reported to occur with a higher frequency in Northern and Eastern European countries compared with North America. The cumulative lifetime risk for breast cancer in women with CHEK2 mutations and familial breast cancer has been estimated to range from approximately 28% to 37%, and is higher in women with stronger family histories of breast cancer than those without. The estimated relative risk of breast cancer, based on data from 2 large case-control studies, was 3.0 (90% CI, 2.6–3.5).

Studies investigating the association between breast cancer risk and specific CHEK2 variants have primarily been based on the truncating variant 1100delC. An analysis from the Copenhagen General Population Study (N=86,975) showed that CHEK2 1100delC heterozygotes had an increased risk of breast cancer when analyses were stratified by age and sex (HR, 2.08; 95% CI, 1.51–2.85). A case-control study (10,860 cases and 9,065 controls) performed by the CHEK2 Breast Cancer Case-Control Consortium of Europe and Australia showed that the 1100delC variant is associated with an increased risk of breast cancer, even in women unselected for family history (OR, 2.34; 95% CI, 1.72–3.20; P<.001). Another case-control study (44,777 cases and 42,997 controls) showed that heterozygous 1100delC carriers have a significantly increased risk of developing estrogen receptor (ER)–positive breast cancer (OR, 2.55; 95% CI, 2.10–3.10; P<.001), but not ER-negative breast cancer (OR, 1.32; 95% CI, 0.93–1.88; P=.12). Results from a meta-analysis including 18 case-control studies (26,336 cases and 44,219 controls) showed that the missense variant I157T is associated with increased risk of breast cancer (OR, 1.58; 95% CI, 1.42–1.75; P<.001).

The panel recommends annual mammogram beginning at age 40 years for women with a mutated CHEK2 gene, with consideration of annual breast MRI. Forty years was chosen by the panel as the age at which to begin breast screening, taking into account the average 5-year risk of breast cancer in CHEK2 mutation carriers (see “ATM Mutations,” opposite page), based on risk data that only takes into account frameshift mutations such as 1100delC. There are no data on the benefit of risk-reducing mastectomy for women with CHEK2 mutations, but this procedure may be considered based on family history.

MLH1, MSH2, MSH6, PMS2, and EPCAM Mutations
Women with Lynch syndrome are at increased risk of endometrial and ovarian cancers (up to 60% and 24%, respectively). Total abdominal hysterectomy and/or bilateral salpingo-oophorectomy are options that may be considered for risk reduction in women who have completed childbearing and carry a MLH1, MSH2, MSH6, PMS2, or EPCAM mutation. No clear evidence supports routine screening for gynecologic cancers in these mutation carriers. Annual endometrial sampling may be considered, but the benefit is uncertain. Routine transvaginal ultrasound and serum CA-125 testing are not endorsed because they have not been shown to be sufficiently sensitive or specific, but there may be circumstances in which these tests may be helpful.

Some studies have suggested that female MLH1 mutation carriers may be at increased risk for breast cancer, with one study estimating an 18.6% cumulative risk to age 70 years (95% CI, 11.3–25.9). However, not enough evidence currently exists for...
the panel to recommend breast screening for women with Lynch syndrome beyond that which is recommended for the average-risk population.

More information regarding risk management recommendations for Lynch syndrome can be found in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal (available at www.NCCN.org).

**NBN Mutations**

The NBN gene is responsible for producing the protein nibrin. Women with heterozygous NBN mutations are at increased risk of developing breast cancer (OR, 3.1, 95% CI, 1.4–6.6; P=.004).49 A meta-analysis including 7 studies showed a significant association between the variant 657del5 and breast cancer risk (OR, 2.42; 95% CI, 1.54–3.80).50 An analysis of women with breast cancer in Poland (N=562) showed that this founder mutation is associated with early-onset breast cancer (OR, 8.36; 95% CI, 2.57–27.27; P<.001).51 The panel recommends annual mammogram for women with a mutated NBN gene beginning at age 40 years, with consideration of annual breast MRI. Forty years was chosen by the panel as the age at which to begin breast screening, taking into account the average 5-year risk of breast cancer in these mutation carriers (see earlier discussion).52 This recommendation is based primarily on data derived from the Slavic truncating mutation 657del5.49–52 There are no data on the benefit of risk-reducing mastectomy for women with NBN mutations. Therefore, risk-reducing mastectomy is not recommended in these mutation carriers, but this procedure may be considered based on family history. The NBN gene is associated with development of the autosomal recessive condition Nijmegen breakage syndrome. Therefore, counselling for carriers of NBN mutations should include a discussion of reproductive options.

**NF1 Mutations**

Neurofibromatosis type 1 (NF1) is an autosomal dominant hereditary cancer syndrome that is caused by an NF1 mutation. NF1 is associated with increased risk of malignant peripheral nerve sheath tumors, other central nervous system tumors, and gastrointestinal stromal tumors.53–56 A population-based study in Finland of 1,404 patients with NF1 showed an estimated lifetime cancer risk of 59.6%.53 This study showed a significant association between NF1 and an increased risk of breast cancer (standardized incidence ratio [SIR], 3.04; 95% CI, 2.06–4.31; P<.001). Among patients with breast cancer, NF1 was associated with poorer survival, with 5-year survival rates of 67.9% compared with 87.8% in patients without NF1. Excess incidence was highest in women younger than age 40 years (SIR, 11.10; 95% CI, 5.56–19.50; P<.001). A population-based study in England of 848 patients with NF1 also showed an increased risk of breast cancer (SIR, 3.5; 95% CI, 1.9–5.9), especially among women younger than 50 years (SIR, 4.9; 95% CI, 2.4–8.8).57 Cumulative lifetime risk of developing breast cancer by age 50 years was 8.4% in this sample.

Given the increased risk of early-onset breast cancer in these mutation carriers, annual breast screening with mammography should begin at age 30 years.58 Screening with breast MRI could also be considered. A prospective study of patients with NF1 from the United Kingdom (N=448) showed that breast cancer risk in these mutation carriers is not significantly increased at age 50 years and beyond.59 Case-control analyses of women with NF1 from England showed that RR estimates for women aged 30 to 39 years was 6.5 (95% CI, 2.6–13.5) and 4.4 for women aged 40 to 49 years (95% CI, 2.5–7.0).59 RR estimates then decrease for women aged 50 to 59 years (RR, 2.6; 95% CI, 1.5–4.2), and continue to decrease as age increases (RR, 1.9; 95% CI, 1.0–3.3 for age 60–69 years, and RR, 0.8; 95% CI, 0.2–2.2 for age 70–79 years). These studies show that, beginning at age 50 years, breast cancer risk in women with NF1 may not significantly differ from that of women in the general population. Therefore, breast MRI screening in patients with NF1 may be discontinued at age 50 years. There are no data regarding the benefit of risk-reducing mastectomy for women with NF1 mutations. Therefore, risk-reducing mastectomy is not recommended in these patients, but this procedure may be considered based on family history. Complications related to NF1 may appear early in life, and these have the potential to be severe.60 Therefore, referral to a neurofibromatosis specialist for management is recommended.

**PALB2 Mutations**

PALB2 (partner and localizer of BRCA2) is a Fanconi anemia gene. Mutations in this gene are associated with increased risk for breast cancer, with studies of women with breast cancer showing that
RAD51D Mutations

Genes in the RAD51 protein family are involved in homologous recombination and DNA repair. RAD51C and RAD51D have been shown to be associated with an increased risk of ovarian cancer. In an observational study including 1,915 unselected ovarian cancer cases, 1.1% of patients had either a RAD51C or RAD51D mutation. In a comparison of 1,132 probands with a family history of ovarian cancer and 1,156 controls, RAD51C was associated with an increased risk of ovarian cancer (RR, 5.88; 95% CI, 2.91–11.88; P < .001).

Analyses from the same trial (911 probands and 1,060 controls) also showed an association between RAD51D and an increased risk of ovarian cancer (RR, 6.30; 95% CI, 2.86–13.85; P < .011). In a case-control analysis of 3,429 women with epithelial ovarian cancer and 2,772 controls, both RAD51C (OR, 5.2; 95% CI, 1.1–24; P = .035) and RAD51D (OR, 12.0; 95% CI, 1.5–90; P = .019) were associated with an increased risk for ovarian cancer.

The cumulative risk of developing ovarian cancer in carriers of a RAD51C mutation does not approach 2.6% (ie, the expected lifetime risk of a woman with a first-degree relative with ovarian cancer) until age 60 to 64 years, with a cumulative risk of 1.5% between the ages of 55 and 59 years. In carriers of a RAD51D mutation, the cumulative risk approaches 2.6% around age 50 to 54 years. As with carriers of a BRIP1 mutation, there may be the presence of additive risk factors that may increase the risk of early-onset ovarian cancer. Therefore, the panel recommends that RRSO in RAD51C and RAD51D mutation carriers begin considering at age 45 to 50 years. As with BRIP1 mutations, large prospective trials are needed to make a firm age recommendation regarding when a discussion about RRSO should begin in RAD51C and RAD51D mutation carriers.

There is currently insufficient evidence that mutations in RAD51C and RAD51D are associated with increased risk of breast cancer. Therefore, carriers of these gene mutations are advised to follow guidelines for women at average risk of developing breast cancer. RAD51C is associated with Fanconi anemia, inherited in an autosomal recessive manner. Therefore, counseling for carriers of RAD51C mutations should include a discussion of reproductive options.

STK11 Mutations

Germline mutations in STK11 are associated with Peutz-Jeghers syndrome, an autosomal dominant disorder characterized by gastrointestinal polyps, mucocutaneous pigmentation, and elevated risk for gastrointestinal cancers as well as breast or nonepithelial ovarian cancers. Breast cancer risk in women with Peutz-Jeghers syndrome is 8% at age 40 years, 13% at age 50 years, 31% at age 60 years, and 45% at age 70 years. There are no data on the benefit of risk-reducing mastectomy for women with STK11 mutations. Therefore, risk-reducing mastectomy is
not recommended in these patients, but this procedure may be considered based on family history. Information regarding screening for patients with Peutz-Jeghers syndrome can be found in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal (available at www.NCCN.org).

Summary and Conclusions

During the panel meeting for the 2017 update, members discussed a number of important updates to the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian, including principles of multigene testing and risk management recommendations for moderately penetrant genetic mutations associated with breast and/or ovarian cancer. In the guidelines, risk management recommendations are described for carriers of the following mutations: ATM, BRIP1, CDH1, CHEK2, NBN, PALB2, RAD51C, RAD51D, and STK11. Recommendations for genetic mutations associated with Lynch syndrome and NF1 are also described. Multigene testing should be offered in the context of professional genetic counseling. Carriers of a genetic mutation should be encouraged to participate in clinical trials or genetic registries. The evidence supporting risk management recommendations for mutations in genes of moderate, low, and uncertain penetrance is continuing to evolve, and it is important for these recommendations to reflect the current evidence base.

References


Genetic/Familial High-Risk Assessment: Breast and Ovarian, Version 2.2017

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Posttest Questions
1. According to the 2017 NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian, the following gene mutations are associated with increased risk of breast cancer:
   a. ATM
   b. CHEK2
   c. PALB2
   d. a and b
   e. a and c
   f. all of the above

2. True or False: A 62-year-old woman with an NF1 mutation and no family history of breast cancer should receive an annual breast MRI with contrast.

3. According to the 2017 NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian, at which age should a woman with a BRIP1 mutation and no family history of ovarian cancer consider RRSO?
   a. 18 years
   b. 30 years
   c. 40 years
   d. 48 years