Updated December 2019 (NCCN v1.2020)

Hereditary Breast and Ovarian Cancer Syndrome (HBOC): *BRCA1* and *BRCA2* Mutations

Cancer Risks and General Management Recommendations

Cancer Type	*BRCA1/2* Mutation Carrier Cancer Risks	General Population Lifetime Cancer Risks	Surveillance/Management Recommendations[1]

Female Breast[2]	Primary: 49-57%
	
	Second Primary: 40-60%
		12.4%	*Surveillance*
			• Age 18 years: Breast awareness
			  ○ Periodic, consistent breast self-exam may facilitate breast self-awareness
			  ○ Breast changes should be promptly reported to a healthcare provider
			• Age 25 years: Clinical breast exam every 6-12 months
			• Age 25-29 years: Annual breast MRI with contrast (or mammogram with consideration of tomosynthesis, if MRI is unavailable)
			  ○ If there is a breast cancer diagnosis in the family before age 30, screening should be individualized based on family history
			• Age 30-75 years: Annual mammogram with consideration of tomosynthesis, and breast MRI with contrast
			• Age >75 years: Management should be considered on an individual basis
			Surgery
			• Discuss option of risk-reducing mastectomy, including degree of protection, reconstruction options, and procedure-related risks
			  ○ Family history and residual breast cancer risk with age and life expectancy should be considered
			  ○ Prophylactic mastectomy can reduce the risk of breast cancer by up to 90-95%[3-5]
			Chemoprevention
			• Chemoprevention can reduce the risk of breast cancer in the contralateral breast in women with *BRCA1* and *BRCA2* mutations who have been diagnosed with breast cancer[6,7]
			• Use of chemoprevention may reduce the risk of breast cancer by up to 62%. Risks, benefits, and limitations of chemoprevention should be discussed with a clinician
			Treatment
			• Olaparib (Lynparza) was approved by the FDA in January 2018 for patients with germline *BRCA*-positive, HER2-negative metastatic breast cancer who have previously received chemotherapy. For patients with hormone receptor (HR)-positive breast cancer to qualify they should have been treated with a prior endocrine therapy or be considered inappropriate for endocrine treatment. Patients should speak with their treating physician to see if they qualify for Olaparib.

Male Breast Cancer[8,9]	*BRCA1*: 1% *BRCA2*: 6%	0.1%	*Surveillance* • Age 35 years: Breast self-exam training and education and clinical breast exam every 12 months
Ovarian Cancer[2]	*BRCA1*: 40% *BRCA2*: 18%	1.3%	*Surgery* • Age 35-40 years: Risk-reducing salpingo-oophorectomy (RRSO) is recommended upon completion of childbearing • Women with a *BRCA2* mutation may delay until age 40-45 years due to later onset of ovarian cancer (average 8-10 years later) unless age of diagnosis in the family warrants earlier age for consideration of surgery • RRSO reduces breast cancer and ovarian cancer incidence in women with *BRCA1*/2 mutation[3] • Further pathological examination of the ovarian specimen can yield greater detection of ovarian cancer[10], and is recommended *Surveillance* • Age 30-35 years: Although there is uncertain benefit, individuals who have not elected RRSO can consider transvaginal ultrasound combined with serum CA-125 at clinician's discretion *Chemoprevention* • Oral contraceptive use has been shown to reduce the risk of ovarian cancer by approximately 60% in *BRCA* mutation carriers if taken for at least 5 years[11] *Treatment* • Olaparib (Lynparza) approved by the FDA in December 2018 as a maintenance treatment for *BRCA*-positive patients with advanced ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to frontline platinum-based chemotherapy. Patients should speak with their treating physician to see if they qualify for Olaparib.
Prostate Cancer[8,9]	*BRCA1*: Possibly increased *BRCA2*: 20-30%	11.2%	*Surveillance* • Age 40 years: Prostate cancer surveillance (i.e., PSA, digital rectal exam) • Consider annual surveillance intervals (versus every other year) *Treatment* • Olaparib (Lynparza), a PARP inhibitor, is being evaluated for the treatment of metastatic, castration resistant prostate cancer in patients with a *BRCA* mutation. However, the use of Olaparib for this indication is considered investigational at this time. Patients should speak with their treating physician for more information regarding Olaparib.
Pancreas	*BRCA1*: 1-4% *BRCA2*: 6%	1.6%	*Surveillance*[1,12] • Age 50 years: Consider surveillance using annual abdominal MRI/MRCP, EUS, and/or enrollment in research protocols for individuals with pancreatic cancer in ≥1 first- or second-degree relative from the same side of the family as the mutation ○ Age to initiate pancreatic surveillance may be modified based on family history (10 years

			younger than the earliest diagnosis in the family) ○ In absence of a close family history of pancreatic cancer, no pancreatic screening is currently recommended
Melanoma	*BRCA1*: Possible increased risk *BRCA2*: Increased risk	2.3%	*Surveillance* • No specific screening guidelines, but general melanoma risk management (such as annual full-body skin exams and minimizing UV exposure) is appropriate

Other Cancer Risks: Limited data suggest that there may be a slightly increased risk for serous uterine cancer in women with a *BRCA1* mutation.[13] Current NCCN guidelines recommend that women with a *BRCA1* mutation discuss the risks and benefits of concurrent hysterectomy at the time of RRSO with their healthcare provider.[1] There are also data to suggest increased risks for colon cancer among *BRCA1* mutation carriers, and gastric cancer in *BRCA1/2* mutation carriers.[13-15] Currently, there are no consensus management guidelines for these additional cancers. Individuals with a *BRCA1/2* mutation are encouraged to discuss these cancer risks, along with family history and personal risk factors, to establish an appropriate surveillance regimen.

Implications for Family Members/Reproductive Considerations

- First-degree relatives (i.e., parents, siblings, and children) have at 50% chance to have the familial *BRCA* mutation. Second-degree relatives (i.e., nieces/nephews, aunts/uncles, and grandparents) have a 25% chance to have the familial mutation.
- Rarely, individuals inherit two *BRCA2* mutations (one from each parent), and have Fanconi Anemia (FA).
    - FA is characterized by physical abnormalities as well as pediatric leukemia and other cancers.
    - *BRCA2* genetic testing for the partner of an individual with a *BRCA2* mutation may be appropriate to clarify the risk of having a child with FA.
- For carriers of a known mutation, assisted reproduction (with or without egg or sperm donation), pre-implantation genetic testing, and prenatal diagnosis options exist.
- All family members are encouraged to pursue genetic counseling to clarify their risks. Family members can visit www.FindAGeneticCounselor.com to find genetic services near them.

Support Services for HBOC

- FORCE (www.facingourrisk.org) is a national organization that offers resources, support and advocacy for families facing hereditary breast and ovarian cancer syndrome. FORCE offers local support group meetings for these families, as well as online resources and support. Bright Pink (www.brightpink.org) is another hereditary breast and ovarian cancer support group.

References

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