



1-MINUTE CONSULT

BRIEF
ANSWERS
TO SPECIFIC
CLINICAL
QUESTIONS

Holly J. Pederson, MD

Director, Medical Breast Services, Cleveland Clinic Breast Center, Cleveland Clinic, Cleveland, OH; Department of General Surgery, Digestive Disease and Surgery Institute, Cleveland Clinic, Cleveland, OH; Associate Professor, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH; Former Member of the National Comprehensive Cancer Center Committees for Breast Cancer Risk Reduction and Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic

Allison W. Kurian, MD, MSc

Departments of Medicine and of Epidemiology & Population Health, Stanford University, Stanford, CA

Zahraa Al Hilli, MD

Department of General Surgery, Digestive Disease and Surgery Institute, Cleveland Clinic, Cleveland, OH; Clinical Assistant Professor, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH

Q: What are the considerations in patient selection and timing of risk-reducing mastectomy?

A: In patients with pathogenic or likely pathogenic genetic variants in high-risk genes (*BRCA1*, *BRCA2*, *PALB2*, *PTEN*, *TP53*, and *CDH1*), compelling family history, or a history of thoracic radiation therapy before age 30, risk-reducing mastectomy is an option to be discussed in addition to effective screening and risk-reducing medications. Owing to possible morbidity, impact on body image, psychological distress, and loss of chest-wall sensation, patient selection and shared decision-making are critical to determine optimal patient choices. The option of risk-reducing mastectomy is for those at the highest levels of risk, and multidisciplinary conversations setting patient expectations are critical for optimal patient outcomes.

■ BREAST CANCER RISK AND RISK-REDUCING MASTECTOMY

Breast cancer remains the most common solid tumor in women, making it critical to identify patients with highly penetrant germline genetic variants early, as cancers often begin to develop at age 30.¹ The 3 pillars of risk management for high-risk women include enhanced surveillance (the addition of contrast-enhanced magnetic resonance imaging to mammography, often alternating every 6 months), risk-reducing medication (selective estrogen-receptor modulators such as tamoxifen or raloxifene, or aromatase inhibitors such as anastrozole or exemestane), and risk-reducing mastectomy.

Patients may be over-treated with surgery; it is critical for both clinicians and patients to understand cancer risks and recommendations. That being said, most surgical patients are satisfied with their decision given the reduced risk of breast cancer of at

least 90%.² No randomized studies have compared enhanced surveillance with surgery. Modeling studies have suggested a 6% to 8% mortality reduction for patients with *BRCA1* carriers and 3% for *BRCA2* carriers.^{3,4}

■ HOW TO DISCUSS WITH THE PATIENT?

The decision to undergo risk-reducing mastectomy is highly personal and should not be introduced as a clinician's recommendation. Rather, patients should be presented with the risks and benefits of each option including effective screening for high-risk patients, risk-reducing medications, and risk-reducing mastectomy to make their own informed choice. Further, risk-reducing bilateral salpingo-oophorectomy has been recommended for *BRCA1/2* carriers as screening is neither sensitive nor specific enough to detect early-stage ovarian cancer.²

Guidelines

According to guidelines from the National Comprehensive Cancer Network, the National Cancer Institute, and the American College of Obstetrics and Gynecology, risk-reducing mastectomy should generally be considered only in individuals with a pathogenic or likely pathogenic variant (not a variant of uncertain significance) conferring a high risk for breast cancer, compelling family history, or possibly with a past history of thoracic radiation therapy under age 30 (such as mantle radiation for treatment of Hodgkin lymphoma).⁵ The value of risk-reducing mastectomy in individuals with pathogenic or likely pathogenic variants in moderate risk genes (such as *CHEK2* or *ATM*) in the absence of a compelling family history of breast cancer is unknown.⁶ While risk-reducing mastectomy has been previously considered for lobular carcinoma in situ, the preferred

doi:10.3949/cjcm.89a.21114

approach currently is risk-reducing medication given its effectiveness.⁵

Gene carriers and risk

There are 6 gene carriers for which a discussion about risk-reducing mastectomy is indicated due to their absolute estimated risk of developing breast cancer: *BRCA1* (72%),¹ *BRCA2* (69%),¹ *PALB2* (up to 53%),⁷ *PTEN* (up to 85%),⁸ *CDH1* (43%),⁹ and *TP53* (85%).^{8,10} Some patients have clinical features of Cowden syndrome but test negative for a *PTEN* mutation (clinical Cowden syndrome). These patients are felt to be at lower risk for breast cancer,¹¹ and consideration of risk-reducing mastectomy should be based on family history.⁶ Excellent long-term results have been reported for bilateral nipple-sparing mastectomy for breast cancer risk-reduction in appropriate patients.¹²

Genes for which evidence is insufficient for risk-reducing mastectomy and those to be managed based on family history include *CHEK2*, *NF1*, *STK11*, *ATM*, and *BARD1*. Genes for which there is insufficient data, where management (including magnetic resonance imaging screening) is based on family history include *BRIP1*, *RAD51C*, and *RAD51D*.^{6,13}

Treatment determination

The risk associated with many genetic variants decreases with age,¹ and patient selection is critical. Regarding timing, the risk of breast cancer is quite low under the age of 30, and the residual risk decreases after the age of 50.¹ Older women should be advised that their residual risk declines with age, informing decision-making. The benefit of risk-reducing mastectomy may be offset by operative risks and other causes for mortality.^{1,14} There is no absolute age at which risk-reducing mastectomy is no longer recommended. However, it is important to provide age-specific cancer risk estimates to determine appropriate interventions.^{1,14} In a recent study, the cumulative risk of invasive breast cancer in women ages 60 to 80 was 20.1% for *BRCA1* carriers and 17.3% for *BRCA2* carriers.^{1,14}

Chemoprevention is a risk management alternative, although *BRCA1* carriers under age 50 are predisposed to triple-negative breast cancer, and preventive medication is likely to offer little benefit.^{1,5,13,15} Older women with *BRCA1* are more commonly diagnosed with estrogen-receptor-positive disease,¹⁶ and it is reasonable to offer preventive medication to *BRCA1* carriers over age 50.² *RAD51C* and *RAD51D* carriers are predisposed to estrogen-receptor-negative disease and may not benefit from preventive therapy.¹⁷

BRCA, OVARIAN CANCER, AND BREAST CANCER

Women with *BRCA* mutations who have developed ovarian cancer, the most lethal gynecologic malignancy,¹⁸ have an overall 5-year survival rate of 45.6%.¹⁹ Experts suggest that women with stage I ovarian cancer who are disease-free for at least one year, are most likely to benefit from risk-reducing mastectomy.^{7,18,20} In patients with stage II/III disease, *BRCA* mutation carriers have a relatively low risk of breast cancer and their prognosis is largely determined by their ovarian cancer diagnosis. Studies show a 2% to 6% incidence of breast cancer in the first 5 years and an approximate 10% risk in the first 10 years following epithelial ovarian cancer diagnosis.^{7,18,20,21} The risk of breast cancer is lower in ovarian cancer survivors who carry *BRCA* mutations than that reported for *BRCA* carriers who have not developed ovarian cancer (possibly due to oophorectomy or use of chemotherapy that could eliminate microscopic breast cancer at the cellular level).

Consideration of risk-reducing mastectomy after ovarian cancer diagnosis

In a modelling study by Gamble et al,²⁰ the added gain in survival benefit in months following risk-reducing mastectomy, if performed in the first several years after an ovarian cancer diagnosis, was small and greatest in women under 50.²⁰ The study also noted that risk-reducing mastectomy is not indicated within 5 years of an ovarian cancer diagnosis due to a high rate of ovarian cancer relapse.²⁰ It has been suggested that consideration of risk-reducing mastectomy for *BRCA* carriers be reserved for those who remain in remission for 5 years,⁷ and possibly for women age 50 or younger at ovarian cancer diagnosis.^{18,22} Furthermore, a study of 1,455 women who developed primary breast cancer after ovarian cancer showed mean time from ovarian cancer diagnosis to breast cancer diagnosis of 7.3 years.²³

TAKE-HOME POINTS

- Discuss the option of risk-reducing mastectomy in patients with pathogenic or likely pathogenic variants in *BRCA1*, *BRCA2*, *PALB2*, *PTEN*, *TP53* and *CDH1*.
- Consider risk-reducing mastectomy in patients with compelling family history or with a past history of thoracic radiation therapy under the age of 30.
- Discuss the option of risk-reducing mastectomy in *BRCA* carriers following an ovarian cancer diagnosis only after 5 years of remission.

THE BOTTOM LINE

Although most women who choose to undergo risk-reducing mastectomy are generally satisfied with their decision, many report adverse impact on body image and sexual relationships, and emotional distress due to a sense of loss and abnormal chest-wall sensation. Despite constant improvements in reconstructive cosmetic outcomes, there is considerable morbidity related to the procedure, and patient selection is

critical for optimal results. Shared decision-making is key. Risk-reducing mastectomy is for patients with the highest levels of risk, and multidisciplinary conversations setting patient expectations are critical for optimal patient outcomes.

REFERENCES

- Kuchenbaecker KB, Hopper JL, Barnes DR, et al. Risks of breast, ovarian, and contralateral breast cancer for BRCA1 and BRCA2 mutation carriers. *JAMA* 2017; 317(23):2402–2416. doi:10.1001/jama.2017.7112
- Li X, You R, Wang X, et al. Effectiveness of prophylactic surgeries in BRCA1 or BRCA2 mutation carriers: a meta-analysis and systematic review. *Clin Cancer Res* 2016; 22(15):3971–3981. doi:10.1158/1078-0432.CCR-15-1465
- Kurian AW, Sigal BM, Plevritis SK. Survival analysis of cancer risk reduction strategies for BRCA1/2 mutation carriers. *J Clin Oncol* 2010; 28(2):222–231. doi:10.1200/JCO.2009.22.7991
- Giannakeas V, Narod SA. The expected benefit of preventive mastectomy on breast cancer incidence and mortality in BRCA mutation carriers, by age at mastectomy. *Breast Cancer Res Treat* 2018; 167(1):263–267. doi:10.1007/s10549-017-4476-1
- National Comprehensive Cancer Network. NCCN guidelines: detection, prevention, and risk reduction. Breast cancer risk reduction. https://www.nccn.org/guidelines/category_2. Accessed May 13, 2022.
- Daly MB, Pal T, Berry MP, et al. Genetic/familial high-risk assessment: breast, ovarian, and pancreatic, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw* 2021; 19(1):77–102. doi:10.6004/jnccn.2021.0001
- Peters ML, Garber JE, Tung N. Managing hereditary breast cancer risk in women with and without ovarian cancer. *Gynecol Oncol* 2017; 146(1):205–214. doi:10.1016/j.ygyno.2017.04.013
- Tan M-H, Mester JL, Ngeow J, Rybicki LA, Orloff MS, Eng C. Lifetime cancer risks in individuals with germline PTEN mutations. *Clin Cancer Res* 2012; 18(2):400–407. doi:10.1158/1078-0432.CCR-11-2283
- Xicola RM, Li S, Rodriguez N, et al. Clinical features and cancer risk in families with pathogenic CDH1 variants irrespective of clinical criteria. *J Med Genet* 2019;56(12):838–843. doi:10.1136/jmedgenet-2019-105991
- Mai PL, Best AF, Peters JA, et al. Risks of first and subsequent cancers among TP53 mutation carriers in the National Cancer Institute Li-Fraumeni syndrome cohort. *Cancer* 2016; 122:3673–3681. doi:10.1002/cncr.30248
- Tan M-H, Mester J, Peterson C, et al. A clinical scoring system for selection of patients for PTEN mutation testing is proposed on the basis of a prospective study of 3042 probands. *Am J Hum Genet* 2011; 88(1):42–56. doi:10.1016/j.ajhg.2010.11.013
- Grobmyer SR, Pederson HJ, Valente SA, et al. Evolving indications and long-term oncological outcomes of risk-reducing bilateral

DISCLOSURES

Dr. Pederson has disclosed consulting for Myriad Genetics. Dr. Kurian and Dr. Al Hilli report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

nipple-sparing mastectomy. *BJS Open* 2018; 3(2):169–173. doi:10.1002/bjs5.50117

- National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology. Genetic/Familial High Risk Assessment: Breast, Ovarian and Pancreatic. v2.2022. https://www.nccn.org/professionals/physician_gls/pdf/genetics_bop.pdf. Accessed May 13, 2022.
- Stjepanovic N, Lubinski J, Moller P, et al. Breast cancer risk after age 60 among BRCA1 and BRCA2 mutation carriers. *Breast Cancer Res Treat* 2021; 187(2):515–523. doi:10.1007/s10549-020-06072-9
- King MC, Wieand S, Hale K, et al. Tamoxifen and breast cancer incidence among women with inherited mutations in BRCA1 and BRCA2: National Surgical Adjuvant Breast and Bowel Project (NS-ABP-P1) Breast Cancer Prevention Trial. *JAMA* 2001; 286(18):2251–2256. doi:10.1001/jama.286.18.2251
- Hu C, Polley EC, Yadav S, et al. The contribution of germline predisposition gene mutations to clinical subtypes of invasive breast cancer from a clinical genetic testing cohort. *J Natl Cancer Inst* 2020; 112(12):1231–1241. doi:10.1093/jnci/djaa023
- Hu C, Hart SN, Gnanaolivu R, et al. A population-based study of genes previously implicated in breast cancer. *N Engl J Med* 2021; 384(5):440–451. doi:10.1056/NEJMoa2005936
- Wahner Hendrickson AE, Bakkum-Gamez JN, J Couch F, Ghosh K, Boughhey JC. Management of breast cancer risk in women with ovarian cancer and deleterious BRCA1 or BRCA2 mutations. *Ann Surg Oncol* 2017; 24(11):3107–3109. doi:10.1245/s10434-017-5999-8
- Howlander N, Noone AM, Krapcho M, et al; National Cancer Institute. Surveillance, Epidemiology, and End Results Program. SEER cancer statistics review, 1975–2014. Bethesda, MD: April 2017. https://seer.cancer.gov/archive/csr/1975_2014/. Accessed May 13, 2022.
- Gamble C, Havrilesky LJ, Myers ER, et al. Cost effectiveness of risk-reducing mastectomy versus surveillance in BRCA mutation carriers with a history of ovarian cancer. *Ann Surg Oncol* 2017; 24(11):3116–3123. doi:10.1245/s10434-017-5995-z
- Gangi A, Cass I, Paik D, et al. Breast cancer following ovarian cancer in BRCA mutation carriers. *JAMA Surg* 2014; 149(12):1306–1313. doi:10.1001/jamasurg.2014.1081
- Domchek SM, Jhaveri K, Patil S, et al. Risk of metachronous breast cancer after BRCA mutation-associated ovarian cancer. *Cancer* 2013; 119(7):1344–1348. doi:10.1002/cncr.27842
- Zhang W, Zhang W, Lin Z, et al. Survival outcomes of patients with primary breast cancer following primary ovarian cancer. *Med Sci Monit* 2019; 25:3869–3879. doi:10.12659/MSM.914163

Address: Holly J. Pederson, MD, Department of Breast Services, A80, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; pedersh@ccf.org