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Risk-Reducing Mastectomy

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Risk-reducing mastectomy (RRM) refers to surgical removal of the breasts in the absence of malignancy to reduce breast cancer risk in women (**Table**).[1] RRM is synonymous with *prophylactic mastectomy*, and is further specified as either bilateral or contralateral. Bilateral RRM (BRRM) refers to removal of both breasts in asymptomatic women, while contralateral RRM (CRRM) refers to removal of the unaffected breast when bilateral mastectomy is performed for the management of unilateral breast cancer.[1] In high-risk patients, RRM is associated with reduction in breast cancer risk and potential adverse effects on quality of life.[1] Thus, prior to any RRM procedure, patients should be informed of the potential for both benefit and harm.

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Indications for Risk-Reducing Mastectomy

Rare high-risk germline pathogenic variants (ie, mutations) in women are associated with increased breast cancer risk, with lifetime risk exceeding 50% for women with these variants vs 12% for those without.[2] Asymptomatic carriers of these variants may wish to consider BRRM, and carriers diagnosed with unilateral breast cancer may consider CRRM. The most common high-risk variations involve the *BRCA1* and *BRCA2* genes, which are associated with increases in both breast and ovarian cancer risks.[3] Penetrance estimates suggest cumulative breast cancer risk by age 80 years is 72% (95% CI, 65%-79%) for *BRCA1* variant carriers and 69% (95% CI, 61%-77%) for *BRCA2* variant carriers.[3] Cumulative ovarian cancer risk by age 80 years is estimated to be 44% (95% CI, 36%-53%) for *BRCA1* variant carriers and 17% (95% CI, 11%-25%) for *BRCA2* variant carriers.[3] Breast cancer risk increases at an earlier age than ovarian cancer risk for both *BRCA1* and *BRCA2* variant carriers, so BRRM may be undertaken first, with risk-reducing salpingo-oophorectomy deferred until after childbearing years.[3]

Other high-risk patients who may wish to consider RRM are those with germline pathogenic variants in *TP53* (Li-Fraumeni syndrome), *PTEN* (phosphatase and tensin homologue; Cowden syndrome), *STK11* (Peutz-Jeghers syndrome), *CDH1* (hereditary diffuse gastric cancer syndrome), and *PALB2* genes.[2,4] For *STK11*, *CDH1*, and *PALB2* variant carriers, RRM should be considered on the basis of family history.[4]

Besides BRRM, high-risk variant carriers should be informed of 2 other risk-reducing options: screening (with mammography and breast magnetic resonance imaging) and chemoprevention (ie, medications administered for 5 years).[4] For asymptomatic carriers of moderate-risk variants (including pathogenic variants in the *ATM* and *CHECK2* genes, associated with lifetime breast cancer risk ranging between 25% and 50%), BRRM is generally not indicated, and screening and chemoprevention are preferred options for risk reduction.[4] Additionally, CRRM is generally not indicated for carriers of moderate-risk variants with unilateral breast cancer.[4,5]

Genetic testing often identifies variants with uncertain pathogenicity, referred to as *variants of unknown/uncertain significance*.[2] A variant of unknown significance should not influence surgical decision-making and is not an indication for RRM.

RRM may also be considered for women treated before age 30 years with chest wall irradiation for Hodgkin lymphoma or other malignancies.[6] An increase in breast cancer risk emerges approximately 8 years after irradiation, and cumulative risk by age 50 years is comparable to that of *BRCA1* variant carriers. However, breast reconstruction for these patients is often challenging due to postirradiation tissue effects.

Since the late 1990s, increasing numbers of average-risk women with unilateral breast cancer are choosing CRRM, although reliable estimates of the overall number of RRMs performed annually are not available.[1] However, CRRM is not expected to reduce risk of recurrence, and therefore patients contemplating CRRM should understand the distinction between risk of recurrence and risk of a new primary cancer. Women with unilateral breast cancer who carry high-risk germline variants or have received chest wall radiotherapy before age 30 years (ie, patients with a substantially increased risk for

Table. Breast Cancer Risk-Reducing Strategies According to Category of Risk

Breast cancer risk	Clinical scenario	RRM option for women with unilateral breast cancer diagnosis	RRM option for asymptomatic women	Alternatives to RRM as risk-reducing options for asymptomatic women
High risk	Pathogenic germline variants in *BRCA1*, *BRCA2*, *PTEN*, *STK11*, *CDH1*, and *PALB2* genes	Consider CRRM	Consider BRRM after age 25 years	Screening (mammography and MRI)[a]; chemoprevention[a]
	Chest radiotherapy before age 30 years	Consider CRRM	Consider BRRM if ≥8 years after radiotherapy	Screening (mammography and MRI)[a]; chemoprevention[a]
Moderate risk	Pathogenic germline variants in *ATM* and *CHEK2*	Generally no indication for CRRM	Generally no indication for BRRM	Screening (mammography and MRI)[a]; chemoprevention[a]
Uncertain risk	Variants of uncertain significance	No indication for CRRM	No indication for BRRM	Screening mammography
Average risk	No known variants	No indication for CRRM	No indication for BRRM	Screening mammography

Abbreviations: BRRM, bilateral risk-reducing mastectomy; CRRM, contralateral risk-reducing mastectomy.

[a] On the basis of family history and risk factors, other asymptomatic women with an increased risk for developing breast cancer may also be evaluated for magnetic resonance imaging (MRI) screening and chemoprevention.

developing contralateral breast cancer) may reasonably choose CRRM to reduce risk of a new primary cancer in the opposite breast.[1,5]

Surgical Considerations

No randomized trials have assessed the efficacy of RRM. Observational studies suggest that RRM does not completely eliminate breast cancer risk, and absolute risk reduction associated with BRRM for *BRCA* variant carriers is about 65%.[1] Although some observational studies suggest a survival benefit after CRRM in certain patient subsets, these results are generally attributed to selection bias, and reliable estimates of benefit are lacking.[1]

All RRM procedures are associated with potential risks, including wound complications, unanticipated additional surgical procedures, and adverse effects on quality of life.[1] Numerous studies have examined quality of life and psychological morbidity after RRM with varied results.[1] Although most women who choose to undergo RRM are generally satisfied with their decision, many report adverse effects on body image/femininity and sexual relationships, as well as emotional distress due to a sense of loss and abnormal chest wall sensations.[1]

For carriers of high-risk germline variants, breast cancer risk increases from age 25 years and older compared with average-risk women.[2,3] Thus, BRRM might be considered for high-risk variant carriers older than 25 to 30 years. Moreover, younger high-risk variant carriers seem more likely to benefit from RRM. For example, among *BRCA* variant carriers, the absolute risk of contralateral breast cancer declines with increasing age of first (unilateral) cancer diagnosis, so any potential mortality benefit of CRRM would be expected to decline with age as well.[3] This decline might partly be attributable to the increased risk of non–breast cancer deaths associated with aging.

Three RRM procedures are commonly used, generally with breast reconstruction.[7] Simple (total) mastectomy refers to removal of the nipple-areolar complex, breast, and most overlying skin. Skin-sparing mastectomy is similar, except that most overlying skin is preserved. Nipple-sparing mastectomy refers to removal of only breast tissue, preserving both the nipple-areolar complex and overlying skin, often performed through an inframammary incision. Observational studies suggest that after breast reconstruction, nipple-sparing mastectomy is associated with the best cosmetic results and no increased breast cancer risk compared with the other 2 procedures.[7] Although breast imaging as a screening strategy is not indicated following RRM, periodic clinical examinations of the mastectomy site are appropriate because these patients retain a small risk for developing breast cancer.

Conclusions

Women who carry high-risk germline variants or have received chest wall radiotherapy before age 30 years may wish to consider BRRM to lower breast cancer risk or CRRM to reduce risk of a new primary cancer in the opposite breast if diagnosed with unilateral breast cancer. Asymptomatic carriers of high-risk germline variants should be informed that screening and chemoprevention are potential alternatives to BRRM. For asymptomatic carriers of moderate-risk variants, BRRM is generally not recommended and screening and chemoprevention are preferred means of lowering breast cancer risk. Additionally, CRRM is not generally indicated for carriers of moderate-risk variants who are diagnosed with unilateral breast cancer.

ARTICLE INFORMATION

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