J Breast Cancer. 2026 Feb;29(1):1-16
https://doi.org/10.4048/jbc.2025.0279
pISSN 1738-6756·eISSN 2092-9900

Journal of Breast Cancer JBC

Review Article

Check for updates

# Risk-Reducing Mastectomy in *BRCA1/2* and Other High-Risk Gene Carriers: Current Evidence and Practical Guidance

**Jun-Hee Lee** [1], **Jai Min Ryu** [2], **Ji Soo Park** [3], **Joo Heung Kim** [4], **Chihwan David Cha** [5], **Kyung Jin Eoh** [6], **Yaewon Yang** [7], **Bom-Yi Lee** [8], **Sang-Ah Han** [9], **Sung-Won Kim** [10]

[1]Department of Surgery, Soonchunhyang University Seoul Hospital, Soonchunhyang University College of Medicine, Seoul, Korea
[2]Division of Breast Surgery, Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea
[3]Hereditary Cancer Clinic of Cancer Prevention Center, Yonsei Cancer Center, Severance Hospital, Yonsei University College of Medicine, Seoul, Korea
[4]Department of Surgery, Yongin Severance Hospital, Yonsei University College of Medicine, Yongin, Korea
[5]Department of Surgery, Hanyang University Hospital, Hanyang University College of Medicine, Seoul, Korea
[6]Department of Obstetrics and Gynecology, Yongin Severance Hospital, Yonsei University College of Medicine, Yongin, Korea
[7]Department of Internal Medicine, Chungbuk University Hospital, Chungbuk University College of Medicine, Cheongju, Korea
[8]Breast Care Center, Breast Cancer Hospital, Daerim St. Mary's Hospital, Seoul, Korea
[9]Department of Surgery, Kyung Hee University Hospital at Gangdong, Kyung Hee University College of Medicine, Seoul, Korea
[10]Department of Surgery, Breast Care Center, Breast Cancer Hospital, Daerim St. Mary's Hospital, Seoul, Korea

OPEN ACCESS

**Received:** Nov 9, 2025
**Revised:** Nov 26, 2025
**Accepted:** Dec 2, 2025
**Published online:** Dec 18, 2025

**Correspondence to**
**Sang-Ah Han**
Department of Surgery, Kyung Hee University Hospital at Gangdong, Kyung Hee University College of Medicine, 892 Dongnam-ro, Gangdong-gu, Seoul 05278, Korea.
Email: hansa@khu.ac.kr



**ORCID iDs**
Jun-Hee Lee
https://orcid.org/0000-0002-3080-4240
Jai Min Ryu
https://orcid.org/0000-0001-5405-7385
Ji Soo Park
https://orcid.org/0000-0002-0023-7740
Joo Heung Kim
https://orcid.org/0000-0002-0417-8434
Chihwan David Cha
https://orcid.org/0000-0003-4522-9565
Kyung Jin Eoh
https://orcid.org/0000-0002-1684-2267
Yaewon Yang
https://orcid.org/0000-0002-1773-134X

## ABSTRACT

Women carrying pathogenic/likely pathogenic variants of high- or moderate-penetrance genes, such as *BRCA1/2*, *TP53*, *PTEN*, *PALB2*, *CDH1*, *STK11*, *CHEK2*, and *ATM*, face markedly elevated lifetime risks of breast cancer. Risk-reducing mastectomy (RRM) reduces incidence by approximately 90% as shown in large observational cohort studies and meta-analyses. However, the survival advantage of RRM remains uncertain given the observational design, heterogeneous population, and the lack of randomized controlled trials. For moderate-penetrance genes, guidance relies more on absolute risk modeling and expert consensus than on direct outcome data. Hence, RRM is recognized as an option for women at high-risk, while emphasizing individualized, multidisciplinary decision-making that incorporates oncological, genetic, reconstructive, and psychosocial perspectives. In addition, choices are shaped by many factors, such as age, family plans, culture, and healthcare systems in real practice. This review integrates the current evidence and evolving guidelines to clarify the benefits, limitations, and controversies surrounding RRM. By addressing existing knowledge gaps and decision-making challenges, it aims to facilitate informed patient-centered counseling for the management of hereditary breast cancer.

**Keywords:** Breast Neoplasms; Genes, Tumor Suppressor; Genetic Predisposition to Disease; Practice Guidelines as Topic; Prophylactic Mastectomy

Journal of Breast Cancer JBC

Bom-Yi Lee
https://orcid.org/0000-0001-9543-5127
Sang-Ah Han
https://orcid.org/0000-0001-6629-955X
Sung-Won Kim
https://orcid.org/0000-0001-5687-1380

**Conflict of Interest**
All authors have served as members of the Hereditary Breast Cancer Subcommittee for the Korean Breast Cancer Society Guidelines (2023–2025). The authors declare that they have no competing interests.

**Data Availability**
In accordance with the ICMJE data sharing policy, the authors have agreed to make the data available upon request.

**Author Contributions**
Conceptualization: Ryu JM, Kim SW, Han SA; Data curation: Cha CD; Investigation: Kim JH, Cha CD; Resources: Eoh KJ, Yang Y; Supervision: Kim JH, Eoh KJ, Yang Y; Validation: Cha CD, Yang Y; Visualization: Eoh KJ; Writing - original draft: Lee JH, Han SA; Writing - review & editing: Ryu JM, Park JS, Lee BY, Kim SW, Han SA.

## INTRODUCTION

According to recent large-scale reports, women carrying pathogenic or likely pathogenic variants of *BRCA1* have a cumulative risk of developing breast cancer of 72% (95% confidence interval [CI], 65–79) by age 80, while the corresponding risk for *BRCA2* carriers is 69% (95% CI, 61–77) [1]. In the Korean Hereditary Breast Cancer study, the estimated cumulative risk of breast cancer by age 70 was 49% (95% CI, 11–98) for *BRCA1* and 35% (95% CI, 16–65) for *BRCA2* carriers, showing results comparable to those observed in Western populations [2]. For comparison, the lifetime risk in the general population was 13.1% in 2021 and 7.2% up to age 74 among Korean women [3,4]. In addition to *BRCA1* and *BRCA2*, other high-to-moderate penetrance variants, such as *TP53*, *PTEN*, *PALB2*, *CDH1*, *STK11*, *CHEK2*, and *ATM*, are linked to an increased risk of breast cancer, although research on them remains limited. People with high-penetrance genes face approximately a 40%–60% lifetime risk, whereas those with moderate-penetrance genes have a 20%–30% lifetime risk [5,6]. Given this elevated risk, guidelines advise magnetic resonance imaging (MRI) surveillance for most [7-10]. More proactive risk-reduction strategies such as risk-reducing mastectomy (RRM) and salpingo-oophorectomy constitute an integral component of *BRCA1/2*-related hereditary breast cancer management. For non-*BRCA1/2* variants, risk-reduction strategies are based on the known phenotype, degree of increased risk for breast and other associated cancers, and available evidence on the efficacy of preventive surgeries [7-10].

RRM—bilateral for unaffected (BRRM) and contralateral for affected carriers (CRRM)—reduces new breast cancer incidence by approximately 90%, although consistent survival benefits remain inconclusive [11-15]. This uncertainty maintains discussions on the benefits, uses, and ethics of RRM.

As randomized trials are not feasible, existing evidence is based on observational and registry studies, necessitating cautious interpretation [13]. This review presents recent findings, examines differences in guidelines, and suggests an evidence-based approach for managing hereditary breast cancer risk.

## METHODS

This is a narrative review of published studies and expert opinions. We examined studies from 1999 to 2025 on the incidence, survival, and outcomes of breast cancer in women with high- or moderate-risk gene variants. Observational studies (prospective, registry-based, or retrospective), matched or pseudo-randomized cohort analyses, and meta-analyses were included. Randomized controlled trials were not included because none exist in this context. We assessed the available evidence regarding breast cancer–specific mortality and survival outcomes, taking into account the study populations and methods employed in previous studies. Additionally, we reviewed current international and national guidelines—Korean Breast Cancer Society (KBCS) 2025, National Comprehensive Cancer Network (NCCN) v3.2025, European Society for Medical Oncology (ESMO) 2023, and Society of Surgical Oncology (SSO) 2025 [7-10]—to compare recommendations according to gene penetrance, clinical setting, and healthcare context.

## GENE-SPECIFIC EVIDENCE AND STRATEGIES FOR RISK REDUCTION

### Overview of genes considered for RRM

RRM is primarily discussed for carriers of *high-penetrance* breast cancer susceptibility genes, such as *BRCA1/2* [1,5,6], *TP53* [16-18], *PALB2* [5,6,19], *PTEN* [20-22], *CDH1* [6,23-25], and *STK11* [26,27], which confer lifetime risks of approximately 40%–85%. For moderate-penetrance genes, including *CHEK2* [28-30], *ATM* [5,6,31,32], MRI-based surveillance is usually preferred over prophylactic surgery, with RRM reserved for additional modifiers (e.g., a strong family history and prior chest irradiation). Lower-penetrance genes (*BARD1*, *RAD51C*, and *RAD51D*) are included in multigene panels [5,6], but current evidence for clinically actionable breast cancer risk is limited; routine RRM is not recommended [5-10], and these genes are not discussed further. **Table 1** [1,5,6,14-28,30-32] summarizes the lifetime risk, associated syndromes, prevalence of hereditary breast cancer syndromes, and RRM considerations according to gene category.

### Evidence from modern cohorts: bilateral and CRRM in *BRCA* carriers

*BRRM for BRCA1/2*

BRRM is a preventive surgical strategy that is primarily offered to individuals carrying germline pathogenic or likely pathogenic variants of *BRCA1* or *BRCA2*. The purpose of BRRM is to dramatically decrease the lifetime risk of breast cancer in high-risk populations. Multiple studies have consistently demonstrated the preventive efficacy of BRRM, with most finding that it reduces the incidence of breast cancer by more than 90%. However, the impact

**Table 1.** Significant genes: lifetime breast cancer risk, syndrome, and key evidence

| Gene | Syndrome (other cancer risk) | % in HBC (susceptibility) | BC risk (cumulative) | Effect size (OR/HR for BC) | Representative reference |
|---|---|---|---|---|---|
| *BRCA1* | Hereditary breast and ovarian cancer (ovary, pancreas, prostate) | ~25% (high) | 72% by 80 yr [1,15] | OR, 7.62 (5.33–11.27) [14] | Kuchenbaecker et al. [1]; Hu et al. [6]; Breast Cancer Association Consortium [5] |
| *BRCA2* | Hereditary breast and ovarian cancer (ovary, pancreas, prostate) | ~25% (high) | 69% by 80 yr [1,15] | OR, 5.23 (4.09–6.77) [14] | Kuchenbaecker et al. [1]; Hu et al. [6]; Breast Cancer Association Consortium [5] |
| *TP53* | LFS (adrenocortical gland, CNS, bone, soft tissue) | ~5% (high–moderate) | ~85% by 60 yr (female) [16-18] | NA | Bougeard et al. [16]; Mai et al. [17]; Frebourg et al. [18] |
| *PALB2* | Hereditary predisposition (ovary, pancreas, prostate*) | ~5% (intermediate–high) | 33%–58% (by 70 yr) [15,19] | OR, 3.83 (2.68–5.63) [14] | Antoniou et al. [19]; Hu et al. [6]; Breast Cancer Association Consortium [5] |
| *PTEN* | Cowden/PTEN hamartoma tumor syndrome (thyroid, kidney, endometrium, colon) | < 1% (rare) | 25%–85% (lifetime) [20-22] | NA | Orloff and Eng [20]; Tan et al. [21]; Bubien et al. [22] |
| *CDH1* | Hereditary diffuse gastric cancer (stomach, lobular BC) | < 1% (rare) | 37%–55% (lobular type) [23-25] | OR, 2.50 (1.01–7.07) [14] | Pharoah et al. [23]; Kaurah et al. [24]; Roberts et al. [25]; Hu et al. [6] |
| *STK11* | Peutz–Jeghers syndrome (GI tract, pancreas, gynecologic tumors) | < 1% (rare) | 32%–54% (lifetime) [26,27] | NA | Schumacher et al. [26]; Hearle et al. [27] |
| *CHEK2* | Moderate-penetrance gene (colon, prostate, thyroid) | 5–10% (moderate) | 20%–30% (lifetime) [15] | OR, 2.47 (2.22–3.05) [14] | Weischer et al. [28]; Schmidt et al. [30]; Hu et al. [6]; Breast Cancer Association Consortium [5] |
| *ATM* | Moderate-penetrance gene (ovary, pancreas, prostate, stomach, colorectal) | 5–8% (moderate) | 20%–28% (lifetime) [15] | OR, 1.82 (1.46–2.27) [14] | Hu et al. [6]; Breast Cancer Association Consortium [5]; Easton et al. [32]; Southey et al. [31] |
| *BARD1* | Moderate–low penetrance (limited evidence) | 1%–2% (low) | ~20% (estimated) [15] | OR, 1.37 (0.87–2.16) [14] | Hu et al. [6]; Breast Cancer Association Consortium [5] |
| *RAD51C* | Hereditary predisposition (ovary) | ~1% (moderate–low) | 15%–20% [15] | OR, 1.20 (0.75–1.93) [14] | Hu et al. [6]; Breast Cancer Association Consortium [5] |
| *RAD51D* | Hereditary predisposition (ovary) | ~1% (moderate–low) | 15%–20% [15] | OR, 1.72 (0.88–3.51) [14] | Hu et al. [6], Breast Cancer Association Consortium [5] |

Percentages and ranges indicate approximate lifetime risk estimates based on major cohort and meta-analysis data.
HBC = hereditary breast cancer; BC = breast cancer; OR = odds ratio; HR = hazard ratio; LFS = Li–Fraumeni syndrome; CNS = central nervous system; NA = not available; PTEN = phosphatase and tensin homolog; GI = gastrointestinal; NCCN = National Comprehensive Cancer Network.
*Based on NCCN guidelines v1.2026, *PALB2* was newly included among prostate cancer susceptibility genes; all other cancer sites were referenced from NCCN v3.2025.


https://doi.org/10.4048/jbc.2025.0279

of BRRM on survival outcomes, specifically breast cancer–specific survival (BCSS) and overall survival (OS), remains a subject of ongoing debate and uncertainty [11-15].

Hartmann et al. [11] conducted an early influential study on the Mayo Clinic high-risk cohort. In this study, 639 high-risk women, including a subset of women with *BRCA* mutations, were followed for a median of 14 years. Results showed that breast cancer incidence was reduced by 89.5% and mortality by 100% among 425 women defined as having a moderate-risk family history. Among 214 women with a strong family history or *BRCA1/2* mutation, breast cancer incidence was reduced by 90%–94.3%, and mortality decreased by 89.7%. This study provided foundational evidence that RRM markedly reduces breast cancer incidence. However, it had a retrospective design; therefore, selection bias could not be excluded. In addition, the proportion of genetically confirmed *BRCA* carriers in the study was unclear because genetic testing was not available at the time. Methodologically, the expected numbers of breast cancer cases and deaths were predicted using statistical models—the Gail model for the moderate-risk group and the incidence and mortality rates observed among sisters in the high-risk group—while the observed numbers were obtained from medical records and follow-up questionnaires. An overestimation of the apparent risk-reduction effect of prophylactic mastectomy could have resulted from the indirect nature of the incidence and mortality estimations.

Further evidence comes from a prospective multicenter cohort study by Domchek et al. [13]. This study included 2,482 *BRCA1/2* carriers recruited from 22 centers in North America and Europe between 1974 and 2008. Among the 247 women who underwent BRRM, no cases of breast cancer were diagnosed during follow-up compared with 98 of the 1,372 women who did not undergo BRRM. Although BRRM was highly effective in reducing the incidence of breast cancer, the study did not observe any improvement in all-cause mortality. In contrast, risk-reducing salpingo-oophorectomy (RRSO) was associated with reduced cancer-specific and overall mortality.

Li et al. [33] conducted a meta-analysis of 15 studies conducted between 2001 and 2014 to assess the impact of RRSO, BRRM, and CRRM on *BRCA1/2* carriers. Six prospective cohort studies were evaluated to address the impact of BRRM on breast cancer incidence and mortality. As a result, BRRM reduced the risk of breast cancer by approximately 89% (relative risk [RR], 0.11; 95% CI, 0.04–0.32). Notably, BRRM does not completely eliminate the risk of breast cancer, nor does it provide a significant advantage in terms of OS, in contrast to the effect of RRSO, which provides reduced breast cancer risk and improved survival benefit.

The results of two recently published large-scale cohort studies should be examined. The first comes from the Dutch HEBON registry, as reported by Heemskerk-Gerritsen et al. [34]. This study analyzed 1,712 *BRCA1* and 1,145 *BRCA2* carriers over a mean follow-up of 10.3 years. Among them, 42% (*BRCA1*) and 35% (*BRCA2*) underwent BRRM. In *BRCA1* carriers, breast cancer–specific mortality was 2.0% (20 deaths) in the surveillance group versus 0.1% (1 death) after RRM (hazard ratio [HR], 0.06; 95% CI, 0.01–0.46). In *BRCA2* carriers, no breast cancer deaths occurred among those who underwent RRM (BCSS, 100% vs. 98%), and overall mortality was not significantly different (HR, 0.45; 95% CI, 0.15–1.36). OS was significantly improved in *BRCA1* carriers (HR, 0.40; 95% CI, 0.20–0.90). These findings suggest that BRRM improves long-term survival in *BRCA1* carriers, although the potential selection bias and the inclusion of occult cancers in the surveillance cohort may have overestimated the benefits [34].


https://doi.org/10.4048/jbc.2025.0279

The second, an international prospective study by Metcalfe et al. [35], included 1,654 participants (827 RRM vs. 827 non-RRM) across nine countries using a pseudo-randomized matched design. Over 6.3 years of follow-up, breast cancer incidence was 2.4% (20 cases) after RRM versus 12.1% (100 cases) without surgery (HR, 0.20; $p < 0.0001$). Breast cancer–specific mortality showed a non-significant decrease (2 vs. 7 deaths; HR, 0.26; $p = 0.11$), with a 15-year probability of breast cancer death < 1%. Notably, 15 of 20 cancers (75%) detected in the RRM group were occult malignancies found during surgery, and none resulted in death. This study incorporated occult cancers into the surgical cohort to better reflect clinical practice and applied an emulated randomized design to evaluate the true preventive and survival impact of RRM. Despite methodological progress, limited follow-up and few deaths preclude firm conclusions regarding the long-term survival benefits.

When combining the findings of these two large studies, the long-term survival benefits of RRM have been observed among *BRCA1* carriers, whereas statistically significant evidence remains limited for *BRCA2* carriers. Nevertheless, the reduction in breast cancer incidence following RRM is consistent and well established. Further long-term follow-ups and additional research are required to confirm this survival advantage.

*CRRM for BRCA1/2*

CRRM aims to prevent the development of a second primary breast cancer in mutation carriers previously treated for unilateral breast cancer. The annual incidence of contralateral breast cancer among *BRCA1/2* carriers is estimated to be 2%–3%, corresponding to a 10-year cumulative risk of up to 30%–40%, which is significantly higher than that in sporadic cases [1].

A comprehensive meta-analysis by Li et al. [33] evaluated 15 studies on *BRCA1/2*-associated breast cancer. Four studies examined the effect of CRRM, and authors found that CRRM reduced the risk of developing contralateral breast cancer by approximately 93% (RR, 0.07; 95% CI, 0.03–0.16) and was associated with improved OS (HR, 0.51; 95% CI, 0.37–0.71) compared with unilateral surgery [33]. However, heterogeneity among the included studies was substantial, and the survival benefit diminished when adjustments were made for factors such as age, tumor biology, systemic therapy, and concurrent RRSO [33].

Similarly, a Cochrane systematic review evaluated 26 observational studies on women with unilateral breast cancer who underwent CRRM [15]. The review concluded that CRRM consistently reduces the incidence of contralateral breast cancer. However, no clear improvement was observed in disease-specific or OS after controlling for confounding variables. All available studies had an observational design. The considerable heterogeneity across studies further limited formal meta-analysis after adjusting for multiple confounding factors. Seven independent cohort studies failed to demonstrate significant survival advantages. When analyses accounted for bilateral RRSO, the survival advantage of CRRM disappeared, suggesting that a selection bias, in which younger or healthier women are more likely to undergo CRRM, may have contributed to earlier reports of improved outcomes. The authors concluded that CRRM should be offered selectively owing to the risk of overtreatment if decisions are based solely on perceived risk rather than individualized estimates [15].

More recently, Blondeaux et al. [36] conducted an international registry-based study of 5,290 young (≤ 40 years) *BRCA1/2* mutation carriers diagnosed with breast cancer. In multivariable analyses, RRM (including contralateral procedures in the affected setting) and RRSO were independently associated with improved OS, with adjusted HRs of 0.65 (95%


https://doi.org/10.4048/jbc.2025.0279

CI, 0.53–0.78) for RRM and 0.58 (95% CI, 0.48–0.70) for RRSO. The survival advantage was most pronounced among *BRCA1* carriers and persisted after adjusting for tumor biology, treatment, and menopausal status. Although retrospective, the consistent and robust findings across subgroups support the consideration of CRRM, particularly in young *BRCA1* carriers who have completed systemic therapy and fertility planning. The survival advantage observed in this study was the strongest for *BRCA1* carriers; however, this should be interpreted with caution. Such benefits may not apply uniformly across all genotypes, especially given the potential for selection and immortal-time bias in observational data. However, fertility and reproductive counseling issues are equally important for women with *BRCA2* mutations. In both groups, the timing of childbearing, RRSO, and adjuvant therapy requires careful coordination through personalized multidisciplinary plans.

Collectively, the current evidence shows that CRRM markedly reduces the risk of contralateral breast cancer and may improve survival rates in carefully selected patients, particularly younger patients carrying *BRCA1* mutations. These findings emphasize the need for personalized counseling and selective use of CRRM in hereditary breast cancer care.

*Interpreting RRM benefit: evidence and guideline alignment*

Taken together, the question is no longer whether RRM reduces incidence—it clearly does. The unanswered question is whether this reduction in incidence translates into meaningful survival benefit, and if so, in which genetic and clinical contexts. Current evidence suggests a stronger signal in *BRCA1* carriers and in younger patients, whereas *BRCA2* carriers show inconsistent survival outcomes. This gene-specific difference should reshape counseling from a uniform preventive recommendation to a precision-risk discussion that incorporates variant penetrance, age, family history, reproductive plans, and patient preference.

This evidence-based nuance is reflected across contemporary guidelines. **Table 2** [7-10] summarizes the most recent international guidelines for RRM in *BRCA1/2* mutation carriers.

**Table 2.** Guideline recommendations for risk-reducing mastectomy in *BRCA1/2* mutation carriers

| Object | Guideline | Recommendation | Strength/level of evidence | Key comments |
|---|---|---|---|---|
| Unaffected carrier (BRRM) | NCCN v3.2025 [7] | Discuss as an option for high-risk carriers; consider age, fertility, psychosocial factors, and surgical morbidity. | Category 2A (lower-level evidence but *uniform consensus*) | Clear reduction in incidence (> 90%); OS benefit unproven. MRI surveillance/chemoprevention remain alternatives. |
| | ESMO 2023 [8] | Offer BRRM after multidisciplinary counseling; base on age, family history, and patient preference. | Grade B (strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended) | Individualized approach; not mandatory. |
| | SSO 2025 [9] | Consider BRRM for young carriers or those unable/unwilling to maintain long-term surveillance. | Consensus | Aligns with NCCN; emphasize shared decision-making. |
| | KBCS 2025 [10] | Selective option under Korean clinical and insurance context. | Grade B (level 3 evidence) moderate evidence (prospective or observational) | Requires counseling on irreversibility, cosmetic and psychological impact. |
| Affected carrier (CRRM) | NCCN v3.2025 [7] | May be considered in unilateral BC, especially young *BRCA1* patients. | Category 2B (lower-level evidence + *non-uniform consensus*) | Reduces contralateral BC risk; OS benefit uncertain; assess tumor biology/RRSO status. |
| | ESMO 2023 [8] | Individualized decision; potential advantage in young *BRCA1* with early-stage disease. | Grade B (strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended) | OS advantage inconsistent; consider systemic therapy response. |
| | SSO 2025 [9] | Consider only after full discussion of benefits, risks, and reconstruction plan. | Consensus | Avoid routine CRRM in older *BRCA2* patients. |
| | KBCS 2025 [10] | Optional after counseling; not routinely recommended. | Grade C (expert consensus/low-quality data) | Recognizes psychosocial reassurance but limited survival gain. |

The content of this table is based on the Clinical Practice Guidelines published by NCCN v3.2025 [7], ESMO 2023 [8], SSO 2025 [9], and KBCS 2025 [10].
BRRM = bilateral risk-reducing mastectomy; NCCN = National Comprehensive Cancer Network; OS = overall survival; MRI = magnetic resonance imaging; ESMO = European Society for Medical Oncology; SSO = Society of Surgical Oncology; KBCS = Korean Breast Cancer Society; CRRM = contralateral risk-reducing mastectomy; BC = breast cancer; RRSO = risk-reducing salpingo-oophorectomy.


https://doi.org/10.4048/jbc.2025.0279

The NCCN v3.2025 advises discussions on BRRM for high-risk carriers, balancing fertility, psychosocial factors, and surgical morbidity [7]; ESMO 2023 recommends offering it after thorough counseling based on age and family history [8]; the SSO 2025 statement aligns with the NCCN but highlights shared decision-making for younger or surveillance-averse carriers [9]; and the KBCS 2025 guidelines contextualize it within Korean clinical and insurance frameworks, stressing counseling on irreversibility and psychological impact [10]. For affected carriers, all guidelines allow CRRM selectively, mainly in young patients with *BRCA1* mutations, while acknowledging the uncertain survival benefit [7-10]. Collectively, the evidence and guidelines converge on the same message: RRM is a powerful preventive tool, but its survival value is gene-specific, age-dependent, and patient-specific, necessitating individualized, multidisciplinary counseling rather than a universal recommendation.

## Alternative risk-reduction strategies for *BRCA1/2* carriers

### *RRSO*

RRSO remains the only intervention proven to improve breast cancer–specific and OS in *BRCA1/2* carriers. When performed after childbearing—typically between ages 35–40 for *BRCA1* and 40–45 for *BRCA2*—it reduces ovarian cancer risk by 80%–90% and breast cancer mortality by up to 50% [13]. Current guidelines recommend discussing RRSO before or alongside RRM, with thorough counseling on menopausal and fertility considerations [1,7-10].

### *Chemoprevention*

Selective estrogen receptor modulators and aromatase inhibitors have demonstrated a significant reduction in the incidence of breast cancer among high-risk women, including those carrying *BRCA1/2* pathogenic variants. Tamoxifen, approved by the U.S. Food and Drug Administration in 1998 for breast cancer risk reduction, was shown in the NSABP-P1 trial to lower breast cancer incidence by approximately 50% in high-risk populations. In the subset analysis of BRCA carriers, prophylactic tamoxifen use was associated with a 62% risk reduction among healthy *BRCA2* carriers, whereas no significant benefit was observed for *BRCA1* carriers, likely reflecting the predominance of estrogen-receptor–negative tumors in this group. However, this result was based on only 19 mutation carriers and thus remains limited in terms of statistical power [37].

In a matched case–control study of 593 *BRCA1/2* carriers with unilateral or bilateral breast cancer, tamoxifen use reduced contralateral breast cancer risk by 62% for *BRCA1* and 37% for *BRCA2* carriers, with a 75% reduction observed when administered for 2–4 years. The protective effects of oophorectomy (58%) and chemotherapy (60%) were independent of tamoxifen [38]. Nevertheless, tamoxifen has been associated with an increased incidence of endometrial cancer in BRCA mutation carriers, warranting individualized discussion, particularly for women who may also undergo RRSO [39].

Raloxifene is used as an alternative in postmenopausal women. The NSABP-P2 (Study of Tamoxifen and Raloxifene) trial demonstrated that raloxifene (60 mg/day) provided a preventive benefit comparable to that of tamoxifen (20 mg/day) but with lower rates of endometrial hyperplasia, endometrial cancer, and thromboembolic events [40,41]. However, its efficacy in *BRCA1/2* mutation carriers has not yet been established.

Aromatase inhibitors such as exemestane and anastrozole decrease breast cancer recurrence and de novo incidence among postmenopausal high-risk women [42]. While emerging

data suggest preventive potential, current evidence is insufficient to define their benefits, specifically in *BRCA* mutation carriers.

These guidelines support the use of chemoprevention in women who decline or defer prophylactic surgery [7-10]. Most evidence comes from high-risk population trials, not *BRCA*-specific studies, and uptake in Asia is low. Participation increases when chemoprevention is part of structured genetic counseling and risk management.

*MRI-based surveillance*

MRI surveillance has become a cornerstone of breast cancer screening for *BRCA1/2* mutation carriers based on strong evidence supporting its sensitivity and clinical impact. Compared with mammography, breast MRI has demonstrated a significantly higher sensitivity for early-stage cancer detection, especially in younger women with dense breasts. In a pivotal prospective study, Warner et al. [43] reported MRI sensitivity of 77%, markedly outperforming that of mammography (36%) in BRCA carriers. Passaperuma et al. [44] confirmed that MRI screening maintains low rates of advanced-stage cancer over extended follow-up, reinforcing its sustained clinical benefits.

Lubinski et al. [45] reported that annual MRI surveillance significantly reduced breast cancer–specific mortality in *BRCA1/2* carriers, providing real-world survival benefit. Moreover, van Zelst et al. [46] suggested that biannual MRI or combined imaging strategies enhance early detection, particularly in *BRCA1* carriers. Current NCCN guidelines recommend annual breast MRI starting at age 25, adding mammography after age 30, and emphasize the central role of MRI surveillance, a recommendation that closely aligns with those of the ESMO, SSO, and KBCS [7-10]. Specifically, the SSO notes that for patients with hereditary breast cancer syndromes or pathogenic variants (e.g., *BRCA1/2*, *TP53*, *PALB2*, *PTEN*), high-risk surveillance, including breast MRI, is recommended, particularly when surgery is deferred or contraindicated [9].

## Management of non-*BRCA* high- and moderate-penetrance gene carriers and guideline comparison

Multigene panel testing, including *BRCA1/2*, *TP53*, *PALB2*, *PTEN*, *CDH1*, *STK11*, *ATM*, and *CHEK2*, is now recommended for individuals with high or moderate hereditary risk as it frequently identifies clinically actionable variants beyond *BRCA* [7,8]. In Korean multicenter studies, non-BRCA pathogenic variants—most commonly *TP53*, *PALB2*, *ATM*, *CHEK2*, and *CDH1*—were detected in 3.3%–10.9% of high-risk, BRCA-negative women, underscoring the clinical relevance of these genes in Asian populations [47-49].

High-penetrance genes, such as *TP53*, *PALB2*, *CDH1*, *PTEN*, and *STK11*, confer lifetime breast cancer risks exceeding 40%–80%. Because direct studies evaluating the effectiveness of RRM for these genes are lacking—largely due to the rarity of each variant—RRM is considered an option in proportion to the elevated lifetime breast cancer risk associated with them (**Table 3**) [6-8,10,16-19,21,22,25-28]. Among them, *TP53* carriers require mastectomy rather than lumpectomy because of radiosensitivity, *PALB2* shows *BRCA2*-like risk warranting MRI surveillance and optional RRM, and *CDH1* mutation carriers face a lobular cancer predominance with additional gastric cancer risk requiring syndrome-specific counseling [19,20,23,24,50].

For moderate-penetrance genes, such as *CHEK2* and *ATM*, lifetime risk is approximately 20%–30%, mainly for estrogen receptor-positive tumors [6,51]. Guidelines summarized

**Table 3.** Guideline recommendations and supporting evidence for other high- and moderate-penetrance genes

| Gene/ syndrome | Clinical context | Strength; level of evidence | Key comments | Representative references |
|---|---|---|---|---|
| *TP53* (Li-Fraumeni) | Affected carrier (therapeutic setting) | Consensus/low–moderate evidence | Mastectomy preferred over breast-conserving surgery to avoid RT; consider early-onset profile and radiosensitivity. | Mai et al. [17]; Frebourg et al. [18]; National Comprehensive Cancer Network [7]; Korean Breast Cancer Society [10] |
| | Unaffected carrier (preventive setting) | Consensus/low–moderate evidence | Annual MRI ≥ 20 yr; discuss BRRM case-by-case after genetic and psychological counseling; consider family history, age, and radiation sensitivity. | Bougeard et al. [16]; Frebourg et al. [18]; National Comprehensive Cancer Network [7]; Korean Breast Cancer Society [10] |
| *PALB2* | Unaffected carrier | Moderate evidence (NCCN panel/meta-analysis) | Lifetime BC risk ≥ 50% or strong FHx; risk similar to BRCA2; annual MRI from 30 yr; consider BRRM after counseling. | Antoniou et al. [19]; Hu et al. [6]; National Comprehensive Cancer Network [7]; Sessa et al. [8] |
| *PTEN* (Cowden) | Unaffected carrier | Consensus/low–moderate evidence | Consider BRRM only if overall risk very high; annual MRI ± MMG from 30 yr; coordinate thyroid and endometrial screening. | Tan et al. [21]; Bubien et al. [22]; National Comprehensive Cancer Network [7]; Korean Breast Cancer Society [10] |
| *CDH1* (HDGC) | Affected carrier | Moderate evidence/ syndrome-specific management | CRRM may be offered after unilateral mastectomy in lobular-type disease; coordinate gastric surveillance and genetic counseling. | Roberts et al. [25]; Hu et al. [6]; National Comprehensive Cancer Network [7]; Korean Breast Cancer Society [10] |
| | Unaffected carrier | Moderate evidence/ syndrome-specific management | MRI ± MMG from 30 yr; Discuss BRRM as part of HDGC care; not routinely recommended; parallel gastric risk counseling essential. | Roberts et al. [25]; Sessa et al. [8]; National Comprehensive Cancer Network [7] |
| *STK11* (Peutz-Jeghers) | Unaffected carrier | Consensus/low–moderate evidence | BRRM not routinely recommended; MRI ± MMG from 30 yr; integrate GI and gynecologic screening. | Schumacher et al. [26]; Hearle et al. [27]; National Comprehensive Cancer Network [7]; Sessa et al. [8] |
| *CHEK2* | Unaffected carrier | Consensus/insufficient–low evidence | BRRM not routinely recommended; MRI ± MMG from 40 yr preferred; consider only with multiple modifiers (FHx, prior chest RT, biallelic variants). | Weischer et al. [28]; Hu et al. [6]; National Comprehensive Cancer Network [7]; Sessa et al. [8] |
| *ATM* | Unaffected carrier | Consensus/insufficient–low evidence | MRI + MMG from 40 yr; Consider BRRM only with strong FHx or truncating variant | Hu et al. [6]; National Comprehensive Cancer Network [7] |

All recommendations were synthesized according to the KBCS 2025 [10], NCCN v3.2025 [7], and ESMO 2023 [8] Clinical Practice Guidelines.
RT = radiotherapy; MRI = magnetic resonance imaging; BRRM = bilateral risk-reducing mastectomy; NCCN = National Comprehensive Cancer Network; BC = breast cancer; FHx = family history; MMG = mammography; CRRM = contralateral risk-reducing mastectomy; HDGC = hereditary diffuse gastric cancer; GI = gastrointestinal; KBCS = Korean Breast Cancer Society; ESMO = European Society for Medical Oncology.

in **Table 3** [6-8,10,16-19,21,22,25-28] uniformly recommend annual MRI ± mammography starting at age 30–40 and discourage routine RRM, except in women with additional modifiers such as strong family history, prior chest irradiation, or concurrent atypia.

Although *RAD51C*, *RAD51D*, and *BARD1* are also included in multigene panel testing according to the NCCN guidelines [7], these genes are generally regarded as lower-penetrance susceptibility genes with limited evidence for clinically actionable breast cancer risk. Therefore, they are not discussed in detail in this section.

Overall, the management of non-*BRCA* carriers should follow a multidisciplinary, individualized framework that integrates genetic counseling, risk modeling, and patient preference to balance oncological benefits with quality-of-life considerations.

## PRACTICAL CONSIDERATIONS AND DECISION-MAKING IN RRM

### Surgical morbidity and real-world burden

RRM substantially lowers breast cancer incidence but entails meaningful surgical and psychosocial burdens. A major Cochrane review including > 15,000 high-risk women confirmed that while RRM markedly reduces the incidence, the survival benefit remains uncertain, and complications are common [15]. Reoperation rates range from 4% to 64%, which is the highest after immediate reconstruction. Major complications include infection,

necrosis, seroma, and implant loss; cumulative reoperation occurs in approximately 20%–30% of implant-based and 10%–15% of autologous procedures. Recent data from Kim et al. [52] comparing minimal access (endoscopic or robotic) and conventional nipple-sparing mastectomy demonstrated similar short- and long-term complication rates with no significant differences in seroma, flap necrosis, or implant loss, indicating that minimally invasive approaches are oncologically and surgically comparable. Persistent numbness of the nipple–areolar complex is common. Although most women experience relief from cancer-related anxiety, approximately one-third report poorer body image and sexual satisfaction within 2 years [53].

## Clinical determinants and oncologic implications of RRM

The timing of genetic diagnosis relative to surgery strongly influences RRM decisions. When *BRCA* results are available preoperatively, women are far more likely to undergo immediate bilateral surgery. In U.S. cohorts, 70%–80% of newly diagnosed *BRCA1/2* carriers chose bilateral mastectomy when genetic information was known before surgery [54,55]. A recent prospective cohort study from McGill University confirmed this trend, showing an approximately eight-fold higher likelihood of bilateral mastectomy among those informed preoperatively [56]. Similarly, in a Korean single-institution cohort, CRRM was performed in 45.0% (63/140) of carriers aware of their mutations before surgery, compared with only 2.0% (4/204) of those who learned their results after surgery ($p < 0.001$), representing more than a 20-fold difference [57]. During a median follow-up of 41 months, 10.8% of patients who underwent unilateral surgery developed contralateral breast cancer, whereas no events occurred in the RRM group [57]. Occult malignancy was identified in 2.2% of CRRM specimens [57], a rate consistently reproduced in a subsequent cohort from the same institution (2.2%, 7/320) [58]. Although the incidence was low, these findings indicate a definite yet clinically relevant oncological burden that can be addressed through CRRM. Collectively, these data point to the value of timely *BRCA* testing and counseling as integral to surgical planning and provide a reasonable reference for clinical discussion until stronger prospective evidence emerges. Taken together, preoperative disclosure consistently increases RRM uptake and reveals a small but definite occult disease burden (approximately 2%), informing counseling.

## Global and sociocultural determinants of uptake

International evidence has highlighted substantial regional variations in the uptake of cancer risk–reduction strategies among *BRCA1/2* carriers. In a multinational cohort of 6,223 carriers from ten countries, 27.8% of unaffected women underwent BRRM and 64.7% underwent risk-reducing bilateral salpingo-oophorectomy, with uptake ranging from nearly 50% in the United States and the Netherlands to below 10% in France and Poland and under 5% in Asian centers such as China [59]. While MRI surveillance rates increased to 81% after 2009, the uptake of preventive surgery remained low. This gap between countries reflects differences in healthcare access, reconstruction skills, and attitudes of doctors. Cultural factors also play a role. Western women often perceive BRRM as a proactive and empowering choice. In contrast, women in France, Poland, China, and Korea value body integrity and family agreements, leading to lower acceptance of surgery.

In a U.S. study of 1,613 patients with breast cancer who received panel testing, 26% underwent CRRM, including 37% of non-*BRCA* mutation carriers and 21% of those with variants of uncertain significance [60]. Women aged < 50 years were most likely to undergo CRRM (odds ratio [OR], 3.8). Black and Asian women were approximately half (50%–60%) as likely as


https://doi.org/10.4048/jbc.2025.0279

Caucasian women to choose CRRM (OR, 0.5 and 0.4, respectively), independent of genetic and clinical factors. This finding demonstrates that insurance, health understanding, and cultural views about risk affect surgical decisions more than the mutation itself.

Age also affects the choice of surgery. In a Canadian multicenter study of 814 carriers of *BRCA1/2* or *PALB2*, Melanson et al. [61] found that 52.7% chose RRM. This rate declined sharply among older women tested after the age of 60 years. Only 15% of unaffected older carriers chose RRM compared with 40% of younger carriers, whereas nearly half of older affected carriers underwent surgery when genetic results were available preoperatively. These findings suggest that reproductive history, perceived life expectancy, and timing of genetic disclosure influence decision-making more strongly than objective oncological risk alone.

In Korea, real-world and population-based data consistently show a low utilization of preventive surgeries. In a multicenter registry of *BRCA* carriers, only one-third of women underwent or planned RRM, mainly because of cosmetic concerns, family resistance, and limited insurance reimbursements [62]. A recent population-based nationwide survey of Korean women showed that the intention to undergo RRM was closely linked to perceived lifetime cancer risk, reproductive status, and family communication attitudes [63]. Women were more likely to choose RRM if they felt their risk was over 60% when they had completed childbearing and planned to tell family members about their *BRCA* results. Women who felt healthy or were unmarried tended to experience a decline in their RRM. These findings suggest that decisions in Korea are shaped not only by risk numbers but also by relationships, familial roles, and cultural values about the body and caregiving.

## PRACTICAL CLINICAL GUIDELINE FOR DISCUSSING RRM

In practice, RRM should be discussed as an option within a comprehensive prevention plan that considers the genetic risk, life stage, psychological readiness, and healthcare environment of each woman. The clinician's task is to help patients make informed, value-consistent decisions; they should not promote or dissuade surgery (**Table 4**).

**Table 4.** Clinical and psychosocial determinants favoring risk-reducing mastectomy vs. surveillance

| Decision factor | Favors RRM (preventive surgery) | Favors surveillance (non-surgical management) |
|---|---|---|
| Genetic risk level | High-penetrance variant (*BRCA1/2*, *PALB2*, *TP53*, *PTEN*, *CDH1*, *STK11*) with lifetime risk ≥ 50%–60% | Moderate-penetrance variant (*CHEK2*, *ATM*, *NF1*) or absolute risk < 40% |
| Age and life expectancy | Younger (< 45 yr), long life expectancy → greater benefit | Older (> 60 yr) or limited life expectancy → favor surveillance |
| Personal cancer history | Early-onset (< 40 yr) breast cancer or multiple first-degree relatives affected | No personal cancer history and weak family aggregation |
| Tumor biology (if affected) | ER-negative or triple-negative phenotype (aggressive) | ER-positive disease with good prognosis and chemoprevention potential |
| Reproductive context | Completed childbearing, no future fertility plans | Fertility plans pending or pregnancy anticipated |
| Psychological profile | High cancer-related anxiety, low tolerance for uncertainty | Low anxiety, comfortable with MRI surveillance and follow-up |
| Health status & comorbidity | Medically fit for major surgery | Significant comorbidities or anesthesia risk |
| System & feasibility factors | MRI surveillance not feasible due to cost, availability, or claustrophobia; reconstructive expertise accessible; insurance covers RRM | MRI surveillance available and affordable; patient tolerates MRI; health system supports screening; limited access to reconstructive expertise or insurance for RRM |
| Patient preference & culture | Strong desire for maximal risk reduction; family supportive | Prefers non-invasive approach; cultural or family hesitation toward surgery |

RRM = risk-reducing mastectomy; ER = estrogen receptor; MRI = magnetic resonance imaging.


https://doi.org/10.4048/jbc.2025.0279

### Step 1. Confirm genetic and clinical eligibility

RRM may be discussed in carriers of *BRCA1/2* and *PALB2*, particularly when the lifetime risk exceeds 50% or the family history is strong. For *TP53*, *CDH1*, *PTEN*, and *STK11*, guidelines recommend individualized discussion rather than routine prophylactic surgery, considering syndrome-specific features (e.g., radiation sensitivity in *TP53*). Moderate-penetrance variants (*CHEK2*, *ATM*, and *NF1*) are generally managed using MRI-based surveillance rather than RRM. For affected carriers, CRRM may be considered if the contralateral risk is high or anxiety is severe.

### Step 2. Review alternatives and system factors

Before proceeding with surgery, patients should review validated nonsurgical options such as MRI surveillance, chemoprevention, and RRSO, which may delay or replace RRM. RRSO remains the only intervention with a proven survival benefit for *BRCA* carriers, whereas MRI and chemoprevention provide effective but less definitive prevention. Insurance reimbursement, surgeon availability, and prevailing cultural beliefs regarding body integrity substantially affect patient choices. In many Asian settings, the relatively low rate of uptake is largely explained by limited reimbursement policies and cultural reluctance. Therefore, early empathetic counseling that acknowledges these constraints is essential.

### Step 3. Determine timing and life context

When considering the RRM, the timing should align with fertility and family plans. The potential benefit is greatest in younger carriers (< 40 years); however, surgery should be deferred until reproductive goals are achieved. Coordination with gynecological oncologists for concurrent or staged RRSO is encouraged, and interim MRI surveillance or chemoprevention can bridge delays.

### Step 4. Assess psychological readiness and motivation

Before surgical planning, clinicians should evaluate anxiety, risk perceptions, and expectations regarding body image and sexuality. If fear or ambivalence dominates, a referral for psychological counseling is recommended to support decision clarity. A brief cooling-off period may also help patients reflect and ensure that the choice arises from informed understanding rather than short-term anxiety [64].

### Step 5. Review surgical options and complications

If a patient selects RRM after thorough discussion, the available techniques include skin-sparing, nipple-sparing, and minimally invasive (endoscopic or robotic) mastectomy with implant-based or autologous reconstruction. Complications, such as infection, necrosis, seroma, and reconstructive failure (approximately 20%–30% in implant cases), and sensory loss of the nipple–areolar complex are common and often persistent. Recent data indicate that minimal-access nipple-sparing mastectomy has complication rates comparable to conventional methods [52]. All expected outcomes and irreversible physical changes should be reviewed before obtaining informed consent.

## CONCLUSION

RRM reduces breast cancer incidence by approximately 90% in carriers of high-penetrance variants; however, a consistent survival benefit remains uncertain across genes with stronger signals in *BRCA1*. Current guidelines agree that RRM should be discussed as an


https://doi.org/10.4048/jbc.2025.0279

individualized option within comprehensive risk management alongside MRI surveillance, chemoprevention, and RRSO. Decisions must balance objective oncological benefits with surgical morbidity, psychosocial readiness, and system feasibility. Structured multidisciplinary counseling is essential to ensure consistent, equitable, and patient-centered care. Future registry-based research is warranted to refine gene-specific absolute risk thresholds for RRM and evaluate decision quality and psychosocial outcomes of modern reconstruction.

## REFERENCES

1. Kuchenbaecker KB, Hopper JL, Barnes DR, Phillips KA, Mooij TM, Roos-Blom MJ, et al. Risks of breast, ovarian, and contralateral breast cancer for BRCA1 and BRCA2 mutation carriers. JAMA 2017;317:2402-16. PUBMED | CROSSREF
2. Park B, Dowty JG, Ahn C, Win AK, Kim SW, Lee MH, et al. Breast cancer risk for Korean women with germline mutations in BRCA1 and BRCA2. Breast Cancer Res Treat 2015;152:659-65. PUBMED | CROSSREF
3. National Cancer Institute. 2025. Population Risk (per SEER Registry Data) Based on 2017–2021 Data. https://seer.cancer.gov/statfacts/html. Accessed November 6th, 2024.
4. Ministry of Health and Welfare, Korea Central Cancer Registry. 2021 National Cancer Registry Annual Report. Sejong: Ministry of Health and Welfare; 2024.
5. Breast Cancer Association Consortium, Dorling L, Carvalho S, Allen J, González-Neira A, Luccarini C, et al. Breast cancer risk genes - association analysis in more than 113,000 women. N Engl J Med 2021;384:428-39. PUBMED | CROSSREF
6. Hu C, Hart SN, Gnanaolivu R, Huang H, Lee KY, Na J, et al. A population-based study of genes previously implicated in breast cancer. N Engl J Med 2021;384:440-51. PUBMED | CROSSREF
7. National Comprehensive Cancer Network. 2025. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®), Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate Version Ver. 3. 2025. https://www.nccn.org. Accessed March 6th, 2025.
8. Sessa C, Balmaña J, Bober SL, Cardoso MJ, Colombo N, Curigliano G, et al. Risk reduction and screening of cancer in hereditary breast-ovarian cancer syndromes: ESMO Clinical Practice Guideline. Ann Oncol 2023;34:33-47. PUBMED | CROSSREF
9. Showalter SL, Laronga C; Society of Surgical Oncology Breast Disease Site Work Group. Highlights and perspectives from the Society of Surgical Oncology's statements on bilateral and contralateral risk-reducing mastectomy. Ann Surg Oncol 2025;32:3857-60. PUBMED | CROSSREF
10. Korean Breast Cancer Society. Clinical Practice Guideline for Breast Cancer, 11th edition. Seoul: Korean Breast Cancer Society; 2025.
11. Hartmann LC, Schaid DJ, Woods JE, Crotty TP, Myers JL, Arnold PG, et al. Efficacy of bilateral prophylactic mastectomy in women with a family history of breast cancer. N Engl J Med 1999;340:77-84. PUBMED | CROSSREF
12. Meijers-Heijboer H, van Geel B, van Putten WL, Henzen-Logmans SC, Seynaeve C, Menke-Pluymers MB, et al. Breast cancer after prophylactic bilateral mastectomy in women with a BRCA1 or BRCA2 mutation. N Engl J Med 2001;345:159-64. PUBMED | CROSSREF
13. Domchek SM, Friebel TM, Singer CF, Evans DG, Lynch HT, Isaacs C, et al. Association of risk-reducing surgery in BRCA1 or BRCA2 mutation carriers with cancer risk and mortality. JAMA 2010;304:967-75. PUBMED | CROSSREF
14. Rebbeck TR, Kauff ND, Domchek SM. Meta-analysis of risk reduction estimates associated with risk-reducing salpingo-oophorectomy in BRCA1 or BRCA2 mutation carriers. J Natl Cancer Inst 2009;101:80-7. PUBMED | CROSSREF
15. Carbine NE, Lostumbo L, Wallace J, Ko H. Risk-reducing mastectomy for the prevention of primary breast cancer. Cochrane Database Syst Rev 2018;4:CD002748. PUBMED | CROSSREF
16. Bougeard G, Renaux-Petel M, Flaman JM, Charbonnier C, Fermey P, Belotti M, et al. Revisiting Li-fraumeni syndrome from TP53 mutation carriers. J Clin Oncol 2015;33:2345-52. PUBMED | CROSSREF
17. Mai PL, Best AF, Peters JA, DeCastro RM, Khincha PP, Loud JT, et al. Risks of first and subsequent cancers among TP53 mutation carriers in the National Cancer Institute Li-Fraumeni syndrome cohort. Cancer 2016;122:3673-81. PUBMED | CROSSREF

18. Frebourg T, Bajalica Lagercrantz S, Oliveira C, Magenheim R, Evans DG; European Reference Network GENTURIS. Guidelines for the Li-Fraumeni and heritable TP53-related cancer syndromes. Eur J Hum Genet 2020;28:1379-86. PUBMED | CROSSREF

19. Antoniou AC, Casadei S, Heikkinen T, Barrowdale D, Pylkäs K, Roberts J, et al. Breast-cancer risk in families with mutations in PALB2. N Engl J Med 2014;371:497-506. PUBMED | CROSSREF

20. Orloff MS, Eng C. Genetic and phenotypic heterogeneity in the PTEN hamartoma tumour syndrome. Oncogene 2008;27:5387-97. PUBMED | CROSSREF

21. Tan MH, Mester JL, Ngeow J, Rybicki LA, Orloff MS, Eng C. Lifetime cancer risks in individuals with germline PTEN mutations. Clin Cancer Res 2012;18:400-7. PUBMED | CROSSREF

22. Bubien V, Bonnet F, Brouste V, Hoppe S, Barouk-Simonet E, David A, et al. High cumulative risks of cancer in patients with PTEN hamartoma tumour syndrome. J Med Genet 2013;50:255-63. PUBMED | CROSSREF

23. Pharoah PD, Guilford P, Caldas C; International Gastric Cancer Linkage Consortium. Incidence of gastric cancer and breast cancer in CDH1 (E-cadherin) mutation carriers from hereditary diffuse gastric cancer families. Gastroenterology 2001;121:1348-53. PUBMED | CROSSREF

24. Kaurah P, MacMillan A, Boyd N, Senz J, De Luca A, Chun N, et al. Founder and recurrent CDH1 mutations in families with hereditary diffuse gastric cancer. JAMA 2007;297:2360-72. PUBMED | CROSSREF

25. Roberts ME, Ranola JMO, Marshall ML, Susswein LR, Graceffo S, Bohnert K, et al. Comparison of CDH1 penetrance estimates in clinically ascertained families vs families ascertained for multiple gastric cancers. JAMA Oncol 2019;5:1325-31. PUBMED | CROSSREF

26. Schumacher V, Vogel T, Leube B, Driemel C, Goecke T, Möslein G, et al. STK11 genotyping and cancer risk in Peutz-Jeghers syndrome. J Med Genet 2005;42:428-35. PUBMED | CROSSREF

27. Hearle N, Schumacher V, Menko FH, Olschwang S, Boardman LA, Gille JJ, et al. Frequency and spectrum of cancers in the Peutz-Jeghers syndrome. Clin Cancer Res 2006;12:3209-15. PUBMED | CROSSREF

28. Weischer M, Bojesen SE, Ellervik C, Tybjaerg-Hansen A, Nordestgaard BG. CHEK2*1100delC genotyping for clinical assessment of breast cancer risk: meta-analyses of 26,000 patient cases and 27,000 controls. J Clin Oncol 2008;26:542-8. PUBMED | CROSSREF

29. CHEK2 Breast Cancer Case-Control Consortium. CHEK2*1100delC and susceptibility to breast cancer: a collaborative analysis involving 10,860 breast cancer cases and 9,065 controls from 10 studies. Am J Hum Genet 2004;74:1175-82. PUBMED | CROSSREF

30. Schmidt MK, Hogervorst F, van Hien R, Cornelissen S, Broeks A, Adank MA, et al. Age- and tumor subtype-specific breast cancer risk estimates for CHEK2*1100delC carriers. J Clin Oncol 2016;34:2750-60. PUBMED | CROSSREF

31. Southey MC, Goldgar DE, Winqvist R, Pylkäs K, Couch F, Tischkowitz M, et al. PALB2, CHEK2 and ATM rare variants and cancer risk: data from COGS. J Med Genet 2016;53:800-11. PUBMED | CROSSREF

32. Easton DF, Pharoah PD, Antoniou AC, Tischkowitz M, Tavtigian SV, Nathanson KL, et al. Gene-panel sequencing and the prediction of breast-cancer risk. N Engl J Med 2015;372:2243-57. PUBMED | CROSSREF

33. Li X, You R, Wang X, Liu C, Xu Z, Zhou J, et al. Effectiveness of prophylactic surgeries in BRCA1 or BRCA2 mutation carriers: a meta-analysis and systematic review. Clin Cancer Res 2016;22:3971-81. PUBMED | CROSSREF

34. Heemskerk-Gerritsen BAM, Jager A, Koppert LB, Obdeijn AI, Collée M, Meijers-Heijboer HEJ, et al. Survival after bilateral risk-reducing mastectomy in healthy BRCA1 and BRCA2 mutation carriers. Breast Cancer Res Treat 2019;177:723-33. PUBMED | CROSSREF

35. Metcalfe K, Huzarski T, Gronwald J, Kotsopoulos J, Kim R, Moller P, et al. Risk-reducing mastectomy and breast cancer mortality in women with a BRCA1 or BRCA2 pathogenic variant: an international analysis. Br J Cancer 2024;130:269-74. PUBMED | CROSSREF

36. Blondeaux E, Sonnenblick A, Agostinetto E, Bas R, Kim HJ, Franzoi MA, et al. Association between risk-reducing surgeries and survival in young BRCA carriers with breast cancer: an international cohort study. Lancet Oncol 2025;26:759-70. PUBMED | CROSSREF

37. King MC, Wieand S, Hale K, Lee M, Walsh T, Owens K, et al. Tamoxifen and breast cancer incidence among women with inherited mutations in BRCA1 and BRCA2: National Surgical Adjuvant Breast and Bowel Project (NSABP-P1) Breast Cancer Prevention Trial. JAMA 2001;286:2251-6. PUBMED | CROSSREF

38. Narod SA, Brunet JS, Ghadirian P, Robson M, Heimdal K, Neuhausen SL, et al. Tamoxifen and risk of contralateral breast cancer in BRCA1 and BRCA2 mutation carriers: a case-control study. Hereditary Breast Cancer Clinical Study Group. Lancet 2000;356:1876-81. PUBMED | CROSSREF

39. Beiner ME, Finch A, Rosen B, Lubinski J, Moller P, Ghadirian P, et al. The risk of endometrial cancer in women with BRCA1 and BRCA2 mutations. A prospective study. Gynecol Oncol 2007;104:7-10. PUBMED | CROSSREF

40. Vogel VG, Costantino JP, Wickerham DL, Cronin WM, Cecchini RS, Atkins JN, et al. Effects of tamoxifen vs raloxifene on the risk of developing invasive breast cancer and other disease outcomes: the NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 trial. JAMA 2006;295:2727-41. PUBMED | CROSSREF

41. Vogel VG, Costantino JP, Wickerham DL, Cronin WM, Cecchini RS, Atkins JN, et al. Update of the National Surgical Adjuvant Breast and Bowel Project Study of Tamoxifen and Raloxifene (STAR) P-2 Trial: preventing breast cancer. Cancer Prev Res (Phila) 2010;3:696-706. PUBMED | CROSSREF

42. Zhang Y, Simondsen K, Kolesar JM. Exemestane for primary prevention of breast cancer in postmenopausal women. Am J Health Syst Pharm 2012;69:1384-8. PUBMED | CROSSREF

43. Warner E, Plewes DB, Hill KA, Causer PA, Zubovits JT, Jong RA, et al. Surveillance of BRCA1 and BRCA2 mutation carriers with magnetic resonance imaging, ultrasound, mammography, and clinical breast examination. JAMA 2004;292:1317-25. PUBMED | CROSSREF

44. Passaperuma K, Warner E, Causer PA, Hill KA, Messner S, Wong JW, et al. Long-term results of screening with magnetic resonance imaging in women with BRCA mutations. Br J Cancer 2012;107:24-30. PUBMED | CROSSREF

45. Lubinski J, Kotsopoulos J, Moller P, Pal T, Eisen A, Peck L, et al. MRI surveillance and breast cancer mortality in women with BRCA1 and BRCA2 sequence variations. JAMA Oncol 2024;10:493-9. PUBMED | CROSSREF

46. van Zelst JCM, Mus RDM, Woldringh G, Rutten MJCM, Bult P, Vreemann S, et al. Surveillance of women with the BRCA1 or BRCA2 mutation by using biannual automated breast US, MR imaging, and mammography. Radiology 2017;285:376-88. PUBMED | CROSSREF

47. Shin HC, Lee HB, Yoo TK, Lee ES, Kim RN, Park B, et al. Detection of germline mutations in breast cancer patients with clinical features of hereditary cancer syndrome using a multi-gene panel test. Cancer Res Treat 2020;52:697-713. PUBMED | CROSSREF

48. Park JS, Shin S, Lee YJ, Lee ST, Nam EJ, Han JW, et al. Implication and influence of multigene panel testing with genetic counseling in Korean patients with BRCA1/2 mutation-negative breast cancer. Cancer Res Treat 2022;54:1099-110. PUBMED | CROSSREF

49. Yoo J, Lee GD, Kim JH, Lee SN, Chae H, Han E, et al. Clinical validity of next-generation sequencing multi-gene panel testing for detecting pathogenic variants in patients with hereditary breast-ovarian cancer syndrome. Ann Lab Med 2020;40:148-54. PUBMED | CROSSREF

50. Corso G, Robson ME, Sacchini V. Points to consider regarding risk-reducing mastectomy in high-, moderate-, and low-penetrance gene carriers. Ann Surg Oncol 2022;29:5821-5. PUBMED | CROSSREF

51. Couch FJ, Shimelis H, Hu C, Hart SN, Polley EC, Na J, et al. Associations between cancer predisposition testing panel genes and breast cancer. JAMA Oncol 2017;3:1190-6. PUBMED | CROSSREF

52. Kim JH, Ryu JM, Bae SJ, Ko BS, Choi JE, Kim KS, et al. Minimal access vs conventional nipple-sparing mastectomy. JAMA Surg 2024;159:1177-86. PUBMED | CROSSREF

53. Metcalfe K, Lynch HT, Foulkes WD, Tung N, Kim-Sing C, Olopade OI, et al. Effect of oophorectomy on survival after breast cancer in BRCA1 and BRCA2 mutation carriers. JAMA Oncol 2015;1:306-13. PUBMED | CROSSREF

54. Chiba A, Hoskin TL, Hallberg EJ, Cogswell JA, Heins CN, Couch FJ, et al. Impact that timing of genetic mutation diagnosis has on surgical decision making and outcome for BRCA1/BRCA2 mutation carriers with breast cancer. Ann Surg Oncol 2016;23:3232-8. PUBMED | CROSSREF

55. Yadav S, Reeves A, Campian S, Sufka A, Zakalik D. Preoperative genetic testing impacts surgical decision making in BRCA mutation carriers with breast cancer: a retrospective cohort analysis. Hered Cancer Clin Pract 2017;15:11. PUBMED | CROSSREF

56. Apostolova C, Ferroum A, Alhassan B, Prakash I, Basik M, Boileau JF, et al. Timing of genetic testing in BRCA1/2 and PALB2-Associated breast cancer: Preoperative result disclosure increases uptake of risk-reducing mastectomy and reduces unnecessary exposure to radiotherapy. Eur J Surg Oncol 2024;50:108324. PUBMED | CROSSREF

57. Woo J, Gwak G, Park I, Bae BN, Lee SK, Chae BJ, et al. Preoperative diagnosis of BRCA1/2 mutation impacts decision-making for risk-reducing mastectomy in breast cancer patients. Sci Rep 2021;11:14747. PUBMED | CROSSREF

58. Lee CE, Shin DS, Kim KJ, Nam SJ, Kim SW, Yu J, et al. The incidence of occult malignancy in contralateral risk reducing mastectomy among affected breast cancer gene mutation carriers in South Korea. J Breast Cancer 2025;28:1-10. PUBMED | CROSSREF

59. Metcalfe K, Eisen A, Senter L, Armel S, Bordeleau L, Meschino WS, et al. International trends in the uptake of cancer risk reduction strategies in women with a BRCA1 or BRCA2 mutation. Br J Cancer 2019;121:15-21. PUBMED | CROSSREF

60. Murphy BL, Yi M, Arun BK, Gutierrez Barrera AM, Bedrosian I. Contralateral risk-reducing mastectomy in breast cancer patients who undergo multigene panel testing. Ann Surg Oncol 2020;27:4613-21. PUBMED | CROSSREF

61. Melanson A, Mashal S, Apostolova C, Ferroum A, Basik M, Boileau JF, et al. Uptake of risk reducing mastectomy in older BRCA1/2 and PALB2 carriers undergoing genetic testing after 60 years of age. Ann Surg Oncol 2026;33:108-17. PUBMED | CROSSREF

62. Jung SM, Ryu JM, Park HS, Park JS, Kang E, Lee S, et al. Trends in risk-reducing mastectomy and risk-reducing salpingo-oophorectomy in Korean carriers of the *BRCA1/2* mutation. J Breast Cancer 2020;23:647-55. PUBMED | CROSSREF

63. Choi YJ, Park Y, Park B, Chae H, Jung SY, Ryu KH, et al. Impact of graphical display on the intention to undergo risk-reducing salpingo-oophorectomy and mastectomy in individuals positive for BRCA pathogenic variant. Sci Rep 2024;14:24281. PUBMED | CROSSREF

64. Basu NN, Ross GL, Evans DG, Barr L. The Manchester guidelines for contralateral risk-reducing mastectomy. World J Surg Oncol 2015;13:237. PUBMED | CROSSREF