

Medical Policy



Title: Risk-Reducing Mastectomy

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Populations	Interventions	Comparators	Outcomes
Individuals: • With high risk of breast cancer or extensive mammographic abnormalities precluding excision or biopsy	Interventions of interest are: • Risk-reducing mastectomy	Comparators of interest are: • Active surveillance • Standard of care	Relevant outcomes include: • Overall survival • Disease-specific survival • Functional outcomes • Treatment-related morbidity
Individuals: • With unilateral breast cancer but are not otherwise at high risk	Interventions of interest are: • Contralateral risk-reducing mastectomy	Comparators of interest are: • Active surveillance • Standard of care	Relevant outcomes include: • Overall survival • Disease-specific survival • Functional outcomes • Treatment-related morbidity

DESCRIPTION

Risk-reducing mastectomy is defined as the removal of the breast in the absence of malignant disease to reduce the risk of breast cancer occurrence.

OBJECTIVE

The objective of this evidence review is to determine whether risk-reducing mastectomy and/or contralateral risk-reducing mastectomy improves the net health outcome in individuals at risk for breast cancer.

BACKGROUND

Risk-reducing mastectomy may be considered in women thought to be at high-risk of developing breast cancer, either due to family history, presence of genetic variants (e.g., *BRCA1*, *BRCA2*), having received radiotherapy to the chest, or the presence of lesions associated with an increased cancer risk such as lobular carcinoma in situ. Therefore, bilateral risk-reducing mastectomy may be performed to eliminate the risk of cancer arising elsewhere; chemoprevention and close surveillance are alternative risk-reduction strategies. Risk-reducing mastectomies are typically bilateral but can also describe a unilateral mastectomy in a patient who has previously undergone or is currently undergoing a mastectomy in the opposite breast for invasive cancer (i.e., contralateral risk-reducing mastectomy). Use of contralateral risk-reducing mastectomy has increased in the U. S. An analysis of data from the National Cancer Database found that the rate of contralateral risk-reducing mastectomy in women diagnosed with unilateral stage I, II, or III breast cancer increased from approximately 4% in 1998 to 9.4% in 2002.¹

The appropriateness of a risk-reducing mastectomy is a complicated risk-benefit analysis that requires estimates of a patient's risk of breast cancer, typically based on the patient's family history of breast cancer and other factors. Several models are available to assess risk of breast cancer.² The specific risk factors included in the models vary, but all incorporate characteristics related to age, reproductive history and family history. In addition to the patient's risk assessment, the choice of a risk-reducing mastectomy is based on patient tolerance for risk, consideration of changes to appearance and need for additional cosmetic surgery, and the risk-reduction offered by mastectomy vs other options.

REGULATORY STATUS

Mastectomy is a surgical procedure and, as such, is not subject to regulation by the U.S. Food and Drug Administration.

Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

POLICY

Unilateral or bilateral risk-reducing mastectomy may be considered **medically necessary** in patients at high risk of breast cancer with one of the following:

1. A known BRCA1 or BRCA2 variant, **OR**
 2. Received radiotherapy to the chest between the ages of 10 and 30 years, **OR**
 3. Presence of lobular carcinoma in situ, **OR**
 4. Lifetime risk of developing breast cancer of 20% or greater as identified by models that are largely defined by family history, **OR**
 5. Another gene variant associated with increased risk (e.g., *TP53* [Li-Fraumeni syndrome], *PTEN* [Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome], *CDH1*, and *STK11*).
- A. Risk-reducing mastectomy is considered **experimental / investigational** in individuals who do not meet high risk criteria.

Policy Guidelines

1. It is strongly recommended that all candidates for risk-reducing mastectomy undergo counseling regarding cancer risks from a health professional skilled in assessing cancer risk other than the operating surgeon and discussion of the various treatment options, including increased surveillance or chemoprevention with tamoxifen or raloxifene.
2. There is no standardized method for determining a woman's risk of breast cancer that incorporates all possible risk factors. There are validated risk prediction models, but they are based primarily on family history.
3. A number of other factors may increase the risk of breast cancer but do not by themselves indicate high risk (generally considered to be a lifetime risk of $\geq 20\%$). It is possible that combinations of these factors may be indicative of high risk, but it is not possible to give quantitative estimates of risk. As a result, it may be necessary to individualize the estimate of risk taking into account numerous risk factors. A number of risk factors, not individually indicating high risk, are included in the National Cancer Institute Breast Cancer Risk Assessment Tool, also called the Gail model.
4. Another breast cancer risk assessment tool, used in the Women Informed to Screen Depending on Measures of Risk trial, is the Breast Cancer Surveillance Consortium (BCSC) Risk Calculator (<https://tools.bcsc-scc.org/bc5yearrisk/calculator.htm>). The following information is used in that assessment tool:
 - a) History of breast cancer, ductal carcinoma in situ, breast augmentation, or mastectomy
 - b) Age
 - c) Race/ethnicity
 - d) Number of first-degree relatives (mother, sister, or daughter) diagnosed with breast cancer
 - e) Prior breast biopsies (positive or negative)
 - f) BI-RADS breast density (radiologic assessment of breast tissue density by radiologists who interpret mammograms).

RATIONALE

This evidence review has been updated regularly with searches of the PubMed database. The most recent literature update was performed through May 21, 2021.

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life, and ability to function—including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, 2 domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent 1 or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. Randomized controlled trials are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

RISK-REDUCING MASTECTOMY

Clinical Context and Therapy Purpose

The purpose of risk-reducing mastectomy is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with a high-risk of breast cancer or extensive mammographic abnormalities precluding excision or biopsy.

The question addressed in this evidence review is: Does risk-reducing mastectomy improve the net health outcome in individuals at high-risk for breast cancer?

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is women at high-risk of breast cancer or with extensive mammographic abnormalities precluding excision or biopsy. High-risk is generally considered to be a lifetime risk of 20% or greater. The following list of factors may indicate a high-risk of breast cancer:

- lobular carcinoma in situ which is a precursor to invasive lobular cancer (up to 35% may be bilateral)
- a known *BRCA1* or *BRCA2* variant
- another gene variant associated with high-risk, eg, *TP53* (Li-Fraumeni syndrome), *PTEN* (Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome), *CDH1*, and *STK11*
- received radiotherapy to the chest between 10 and 30 years of age.

Interventions

The therapy being considered is a risk-reducing mastectomy.

Risk-reducing mastectomy is defined as the removal of the breast in the absence of malignant disease to reduce the risk of breast cancer occurrence.

Comparators

The following practice is currently being used to treat women at high-risk of breast cancer or with extensive mammographic abnormalities precluding excision or biopsy: guideline directed active surveillance or use of chemoprevention.

Active surveillance and prescription of chemoprevention are performed by oncologists and primary care providers in an outpatient clinical setting.

Outcomes

The general outcomes of interest are overall survival (OS), disease-specific survival, functional outcomes, and treatment-related morbidity.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought
- Studies with duplicative or overlapping populations were excluded.

REVIEW OF EVIDENCE

Systematic Reviews

This evidence review was informed by a TEC Assessment (1999) that concluded risk-reducing mastectomy met the TEC criteria for patients with a family history of breast cancer.³ The Assessment largely focused on a 1999 retrospective cohort analysis that found approximately 13 moderate-risk women would have to have a risk-reducing mastectomy to prevent 1 cancer. For those at high-risk of breast cancer, reduction in breast cancer incidence ranged from 90% to 94%. Four to 8 high-risk women would need to undergo a risk-reducing mastectomy to prevent a single occurrence of breast cancer.

Several recent systematic reviews have evaluated the impact of a risk-reducing mastectomy on health outcomes in women with *BRCA* variants. Li et al (2016) identified 15 controlled studies evaluating the impact of prophylactic surgeries including a bilateral risk-reducing mastectomy on women with *BRCA1* or *BRCA2* variants.⁴ In a meta-analysis of 6 studies with 2555 *BRCA1* or *BRCA2* variant carriers, compared with controls who did not receive a risk-reducing mastectomy, there was a significantly lower risk of subsequent breast cancer in women who had a bilateral risk-reducing mastectomy (relative risk [RR], 0.11; 95% CI, 0.04 to 0.32). However, in a meta-analysis of 2 studies in *BRCA1* or *BRCA2* variant carriers with no history of breast cancer, there was no significant effect on breast cancer-specific mortality (hazard ratio [HR], 0.29; 95% CI, 0.03 to 2.61) or on all-cause mortality (HR, 0.29; 95% CI, 0.03 to 2.61). Similarly, Ludwig et al (2016) identified 10 studies on the incidence of breast cancer after bilateral risk-reducing

mastectomy in *BRCA1* or *BRCA2* carriers and found a significant reduction in breast cancer risk ranging from 89.5% to 100%.⁵ These reviewers did not conduct pooled analyses of studies on the impact of a risk-reducing mastectomy on mortality.

Honold and Camus (2018) extracted data from systematic reviews and primary studies to determine if risk-reducing mastectomy for women with BRCA genes is more effective than active surveillance (periodic clinical examination plus imaging tests) at preventing breast cancer.⁶ The authors analyzed data from 13 systematic reviews with a total of 50 studies. The results suggest with high certainty of evidence (based on GRADE system) that active surveillance is less effective at preventing breast cancer than risk-reducing mastectomy, with 254 per 1000 patients developing breast cancer with only active surveillance and 12 per 1000 with risk-reducing mastectomy (risk ratio, 0.05; 95% CI, 0.02 to 0.1). Mortality from any cause was also higher for active surveillance than for risk-reducing mastectomy (risk ratio, 0.12; 95% CI, 0.04 to 0.36). The authors also concluded with moderate evidence that up to 64% of women who received the surgery experienced adverse effects (eg, lower sensitivity, pain, infection, edema, contracture). In addition, they found low certainty of evidence that those who underwent risk-reducing mastectomy had a decrease in anxiety and depressive symptoms, did not regret having the surgery, and were satisfied with the cosmetic results. The results of this meta-analysis do not apply to women with low to moderate risk of breast cancer.

A Cochrane review by Carbine et al (2018) examined the impact of risk-reducing mastectomy on mortality and other health outcomes.⁷ Reviewers did not identify any RCTs. Sixty-one observational studies with some methodologic limitations were identified. The studies presented data on 15077 women with a wide range of risk factors for breast cancer who underwent a risk-reducing mastectomy. Studies on the incidence of breast cancer and/or disease-specific mortality (n=21) reported reductions in both after a bilateral risk-reducing mastectomy, particularly for those with *BRCA1* or *BRCA2* variants.

Section Summary: Risk-Reducing Mastectomy

Evidence from systematic reviews has found that risk-reducing mastectomy reduces the incidence of breast cancer in women at high-risk of breast cancer, especially those with *BRCA1*, *BRCA2*, and other pathogenic variants, and those with a formal high-risk familial risk assessment. In addition, 1 study reported that risk-reducing mastectomy could be associated with high satisfaction levels. Fewer studies have examined the impact of a risk-reducing mastectomy on overall or breast cancer-specific survival.

CONTRALATERAL RISK-REDUCING MASTECTOMY

Clinical Context and Therapy Purpose

The purpose of contralateral risk-reducing mastectomy is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with unilateral breast cancer who are not otherwise at high-risk.

The question addressed in this evidence review is: Does contralateral risk-reducing mastectomy improve the net health outcome in individuals with unilateral breast cancer who are otherwise not at high-risk for breast cancer recurrence?

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with unilateral breast cancer who are not otherwise at high-risk.

Interventions

The therapy being considered is a contralateral risk-reducing mastectomy.

Comparators

The following practice is currently being used to treat women with unilateral breast cancer who are not otherwise at high risk: active surveillance with clinical examination, imaging studies, and guideline-based treatment of primary breast cancer.

Outcomes

The general outcomes of interest are OS, disease-specific survival, functional outcomes, and treatment-related morbidity.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought
- Studies with duplicative or overlapping populations were excluded.

REVIEW OF EVIDENCE**Incidence of a Second Primary Breast Cancer**

The potential for a contralateral risk-reducing mastectomy to impact survival is related to its association with a reduced risk of subsequent primary breast cancer in the other breast (ie, contralateral breast cancer [CBC]). In general, according to data from the U.S. Surveillance, Epidemiology and End Results (SEER) database, annual rates of CBC were stable between 1975 and 1985, after which rates declined about 3% per year (95% CI, 2.7% to 3.5%).⁸ Beginning in 1990, the annual decline in CBC rates was only in women with estrogen receptor-positive cancer, with no decrease in women with estrogen receptor-negative cancer. The investigators suggested that the decrease in CBC rates after estrogen receptor-positive cancer might be attributed at least in part to the increased availability of adjuvant hormone therapies.

Studies were sought to assess the risk of CBC in women who met high-risk and average-risk criteria. Molina-Montes et al (2014) published a systematic review of studies on the risk of second primary breast cancer in women with and without *BRCA1* or *BRCA2* variants.⁹ Twenty studies were included (12 retrospective cohort studies, 2 prospective cohort studies, 6 case-control studies). Most studies included only women who had undergone genetic testing; it is likely that even those who tested negative had other risk factors that motivated testing. A meta-analysis found that the cumulative risk of second primary breast cancer at 5 years after the initial diagnosis was 14% (95% CI, 9% to 19%) in *BRCA1* or *BRCA2* variant carriers and 3% (95% CI, 2% to 5%) in noncarriers. The cumulative risk of a second primary cancer at 10 years after the

initial diagnosis was 22% (95% CI, 18% to 27%) in *BRCA1* or *BRCA2* variants and 5% (95% CI, 3% to 7%) in noncarriers.

Survival After Contralateral Risk-Reducing Mastectomy

As is the case for bilateral risk-reducing mastectomy, no RCTs evaluating the effect of contralateral risk-reducing mastectomy on health outcomes have been published. There are a number of observational studies, including some with large sample sizes, and systematic reviews of those observational studies. Observational studies have attempted to control for potential confounders, but not all relevant factors were measured, and the possibility of selection bias remains.

Systematic Reviews

The previously summarized Cochrane review by Carbine et al (2018) also assessed various outcomes, including mortality and disease-free survival, among women who received a contralateral risk-reducing mastectomy.⁷ Twenty-six observational studies assessed outcomes in women who received contralateral risk-reducing mastectomy. While results showed a reduced incidence of CBC among women who received a contralateral risk-reducing mastectomy, results on disease-specific mortality were inconsistent. Seven of the included studies showed no survival advantage. One additional study showed an improvement in all-cause mortality associated with contralateral risk-reducing mastectomy; however, significance was lost after adjustment for bilateral risk-reducing salpingo-oophorectomy. The authors attributed the variability in mortality findings, in part, to selection bias, since younger, healthier women may be more likely to opt for contralateral risk-reducing mastectomy.

A systematic review and meta-analysis of studies on contralateral risk-reducing mastectomy were published by Fayanju et al (2014).¹⁰ The authors conducted a literature search through March 2012 and identified 17 observational studies that compared the incidence of CBC in women with unilateral disease who did and did not undergo a contralateral risk-reducing mastectomy. Fourteen of the 17 studies were included in various meta-analyses. In a meta-analysis of 4 studies, mortality from breast cancer was lower in the group that had a contralateral risk-reducing mastectomy (RR, 0.69; 95% CI, 0.56 to 0.85). Moreover, in a meta-analysis of data from 6 studies, OS was significantly higher in patients who underwent a contralateral risk-reducing mastectomy (n=10666) than those who did not (n=145490; RR, 1.09; 95% CI, 1.06 to 1.11). Reviewers also conducted a subgroup analysis by risk level. A meta-analysis of patients considered high-risk, which included *BRCA* variant carriers and/or those with a family history of breast cancer (4 studies, 616 undergoing contralateral risk-reducing mastectomy, 1318 not undergoing contralateral risk-reducing mastectomy) found that neither OS nor mortality from breast cancer differed significantly among women who had or did not have a contralateral risk-reducing mastectomy. The RR of breast cancer mortality with and without a contralateral risk-reducing mastectomy was 0.66 (95% CI, 0.27 to 1.64). For OS with and without a contralateral risk-reducing mastectomy, the RR was 1.09 (95% CI, 0.97 to 1.24). The absolute risk-reduction for metachronous breast cancer did not differ between women with and without a contralateral risk-reducing mastectomy when data from all 8 studies were analyzed (risk difference, -18.0%; 95% CI, -42.0% to 5.9%), but was significantly lower in women with a contralateral risk-reducing mastectomy in the 4 studies exclusively enrolling women at increased familial/genetic risk (risk difference, -24.0%; 95% CI, -35.6% to -12.4%). Commenting on the totality of findings, reviewers stated that the improvement in survival after a contralateral risk-reducing mastectomy in the general breast cancer population was likely not due to a decreased incidence

of CBC, but rather was secondary to selection bias (eg, contralateral risk-reducing mastectomy recipients may be otherwise healthier and have better access to health care).

Observational Studies

Studies in the Fayanju et al (2014) systematic review were published between 1997 and 2005. More recent large observational studies, described below, reported mixed results for OS and disease-specific survival.

An analysis of 17 years of SEER data from 245,418 women in California with unilateral breast cancer assessed secondary contralateral cancer incidence and mortality in women who had bilateral mastectomy or breast conserving therapy.¹¹ The study adjusted for numerous potential confounders, including demographic and socioeconomic characteristics, clinical characteristics and disease state, and year of diagnosis. After a median 7 years follow-up, the study found that when compared with breast conserving therapy that included radiotherapy, bilateral mastectomy was associated with a reduced risk of secondary breast cancer (HR, 0.11; 95% CI, 0.07 to 0.14) while unilateral mastectomy was associated with increased risk (HR, 1.07; 95% CI, 1.02 to 1.13). However, the study also found bilateral mastectomy was not associated with a significant reduction in breast cancer-related mortality relative to breast-conserving therapy (HR, 1.03; 95% CI, 0.96 to 1.11).

Wong et al (2017) evaluated 496488 women diagnosed with unilateral invasive breast disease.¹² Within this cohort, 58.6% (n=295860) underwent breast-conserving surgery, 33.4% (n=165888) had a unilateral mastectomy, and 7% (n=34740) had a contralateral risk-reducing mastectomy. The median age was 50 years in the contralateral risk-reducing mastectomy group and 60 years in the breast conservation group (p<.001). Patients were followed for a median of 8.25 years. In an analysis adjusting for age and other factors including the stage of the disease, OS was significantly higher after breast conservation than after a contralateral risk-reducing mastectomy (HR, 1.08; 95% CI, 1.03 to 1.14). Similarly, breast cancer-specific survival was significantly higher in the breast conservation group than in the contralateral risk-reducing mastectomy group (HR, 1.08; 95% CI, 1.01 to 1.16).

An analysis of SEER data by Kruper et al (2014) suggested the association between contralateral risk-reducing mastectomy and reduced mortality identified in some data analyses could be attributed at least in part to the selection of a healthier cohort of women for contralateral risk-reducing mastectomy.¹³ In the case-control analysis including 28015 contralateral risk-reducing mastectomy patients and 28015 unilateral mastectomy patients in the SEER database, patients were matched by age group, race/ethnicity, extent of surgery, tumor grade, tumor classification, node classification, estrogen receptor status, and propensity score. The investigators were unable to match for *BRCA* or another genetic variant status. When all matched patients were included, disease-specific survival and OS were significantly lower in women who underwent unilateral mastectomy compared with contralateral risk-reducing mastectomy. For disease-specific survival, the HR was 0.83 (95% CI, 0.77 to 0.90); for OS, it was 0.77 (95% CI, 0.73 to 0.82). Presumably, a contralateral risk-reducing mastectomy would increase survival by lowering the risk of CBC. The authors conducted another analysis excluding women diagnosed with CBC; the remaining sample was still large (25924 women with unilateral mastectomy, 26299 women with contralateral risk-reducing mastectomy). In the analysis excluding women with CBC, disease-specific survival, and OS remained significantly lower in women who had unilateral versus contralateral risk-reducing mastectomy. For disease-specific survival, the HR was 0.87 (95% CI, 0.80 to 0.94); for OS, it was 0.76 (95% CI, 0.71 to 0.81). The investigators suggested that the survival benefits found in

CBC patients were not due to prevention of CBC but to selection bias (eg, healthier women choosing CBC). A limitation of the analysis was the inability to control for risk factors including gene variant status, family history, and a history of radiotherapy to the chest between ages 10 and 30 years.

Yao et al (2013) evaluated OS after contralateral risk-reducing mastectomy using data from the National Cancer Data Base.¹⁷ The database collects information from 1450 Commission on Cancer-accredited cancer programs. The analysis included 219983 women who had a mastectomy for unilateral breast cancer; 14994 (7%) of these women underwent a contralateral risk-reducing mastectomy at the time of their mastectomy surgery. The investigators did not report risk factors such as known genetic variants. The 5-year OS rate was 80%. In an analysis adjusting for confounding factors, the risk of death was significantly lower in women who had a contralateral risk-reducing mastectomy than in women who did not. The adjusted HR for OS was 0.88 (95% CI, 0.83 to 0.93). The absolute risk of death over 5 years with contralateral risk-reducing mastectomy was 2.0% lower than without. In subgroup analyses, there was a survival benefit after contralateral risk-reducing mastectomy for individuals 18 to 49 years and 50 to 69 years but not for those 70 years or older. There was also a survival benefit for women with stage I and II tumors but not stage III tumors.

In a subsequent study, Pesce et al (2014) focused on a subgroup of patients who were young (<45 years old) with stage I or II breast cancer.¹⁴ A total of 4338 (29.7%) of 14627 women in this subgroup had a contralateral risk-reducing mastectomy. Median follow-up was 6.1 years. In a multivariate analysis controlling for potentially confounding factors, OS did not differ significantly between patients who underwent a unilateral mastectomy and those who also had a contralateral mastectomy (HR, 0.93; 95% CI, 0.79 to 1.09). Moreover, among women younger than 45 years with estrogen receptor-negative cancer, there was no significant improvement in OS in those who had a contralateral risk-reducing mastectomy or a unilateral mastectomy (HR, 1.13; 95% CI, 0.90 to 1.42).

Adverse Events

There are risks and benefits associated with contralateral risk-reducing mastectomy. In particular, several analyses have found higher rates of surgical complications in women undergoing contralateral risk-reducing mastectomy (bilateral mastectomy) compared with women undergoing unilateral mastectomy. Besides morbidity associated with these complications, surgical complications may delay receiving adjuvant therapy.

Schroeder et al (2020) conducted a population-based study of 12959 women who underwent unilateral mastectomy or contralateral risk-reducing mastectomy using data from the New York Statewide Planning and Research Cooperative System.¹⁵ Of these, 1384 underwent a contralateral risk-reducing mastectomy and 11575 underwent a unilateral mastectomy. After controlling for confounding factors (ie, race, ethnicity, year of operation, and type of insurance) and stratifying by breast reconstruction, no difference was found in the likelihood of complications or additional breast-related procedures needed between women who received contralateral risk-reducing mastectomy and those who received unilateral mastectomy (both without breast reconstruction). Addition of breast reconstruction was associated with significant increases in complications and breast-related procedures, both in women with unilateral mastectomy (odds ratio [OR], 3.6; $p < .001$ and OR, 13.7; $p < .001$, respectively) and in those with contralateral risk-reducing mastectomy (OR, 3.3; $p < .001$ and OR, 30.1; $p < .001$, respectively). Patients who underwent contralateral risk-reducing mastectomy were also significantly more

likely to undergo breast reconstruction compared to those who underwent unilateral mastectomy (93.1% vs. 46.3%; $p < .001$).

Silva et al (2015) published a large multicenter study including 20501 women with unilateral breast cancer from the American College of Surgeons National Surgery Quality Improvement Program database.¹⁶ A total of 13268 (64.7%) women underwent a unilateral mastectomy, and 7233 (35.3%) had a bilateral mastectomy. The analysis did not report on high-risk factors such as *BRCA* variant status or family history. All women had breast reconstruction; a higher proportion of women who had a unilateral mastectomy (19.5%) than bilateral mastectomy (8.9%) had autologous reconstruction; the remainder had implant-based reconstruction. The authors conducted analyses controlling for confounding variables (ie, age, race, smoking, diabetes, chronic pulmonary disease, hypertension) and stratifying by type of implant. The rate of overall complications was significantly higher for women who had a bilateral mastectomy, regardless of reconstruction type. Among women with implant reconstructions, overall complication rates were 10.1% after a bilateral mastectomy and 8.8% after a unilateral mastectomy (adjusted OR, 1.20; 95% CI, 1.08 to 1.33). In women with autologous reconstructions, overall complication rates were 21.2% after a bilateral mastectomy and 14.7% after a unilateral mastectomy (adjusted OR, 1.60; 95% CI, 1.28 to 1.99). The most common complication was reoperation within 30 days, followed by surgical site complications. Transfusion rates were also significantly higher ($p < .001$) in women with bilateral mastectomies who had either type of reconstruction. The rates of medical complications were relatively low—approximately 1% of women who had implant reconstructions and 3% of women who had autologous reconstructions experienced a medical complication (ie, pneumonia, renal insufficiency or failure, sepsis, urinary tract infection, venous thromboembolism)—and did not differ significantly between unilateral and bilateral mastectomies.

Several single-center studies have also reported significantly higher surgical complication rates after bilateral compared with unilateral mastectomy. For example, in a study by Miller et al (2013), which included 600 women with unilateral breast cancer, contralateral risk-reducing mastectomy remained associated with a significantly higher risk of any complication (OR, 1.53; 95% CI, 1.04 to 2.25) and a significantly higher risk of major complications (OR, 2.66; 95% CI, 1.37 to 5.19) compared with unilateral mastectomy.¹⁷ Moreover, in a study by Eck et al (2014), which assessed 352 women with unilateral breast cancer, 94 (27%) women had complications, 48 (14%) in the unilateral mastectomy group, and 46 (13%) in the bilateral mastectomy group.¹⁸ The difference between groups was not statistically significant ($p = .11$) but this study might have been underpowered. Eck et al (2014) found a significant delay in adjuvant therapy after surgical complications: women with complications waited longer before receiving adjuvant therapy than those without complications (49 days vs. 40 days, $p < .001$).

Section Summary: Contralateral Risk-Reducing Mastectomy

Large observational studies have reported inconsistent findings on the survival benefit of contralateral risk-reducing mastectomy in women with unilateral breast cancer who do not otherwise meet high-risk criteria. Researchers have suggested that improvements in survival after contralateral risk-reducing mastectomy in the general breast cancer population found in some studies are due at least in part to selection bias. Moreover, there are risks of complications associated with both the surgical and reconstruction procedures.

Summary of Evidence

For individuals who have a high-risk of breast cancer or extensive mammographic abnormalities precluding excision or biopsy who receive a risk-reducing mastectomy, the evidence includes systematic reviews. Relevant outcomes are OS, disease-specific survival, functional outcomes, and treatment-related morbidity. Studies have found that a risk-reducing mastectomy lowers subsequent breast cancer incidence and increases survival in select high-risk patients. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have unilateral breast cancer but are not otherwise at high-risk who receive a contralateral risk-reducing mastectomy, the evidence includes systematic reviews and observational studies. Relevant outcomes are OS, disease-specific survival, functional outcomes, and treatment-related morbidity. Available studies do not demonstrate a consistent survival benefit in women without high-risk criteria. Moreover, there are risks associated with a contralateral risk-reducing mastectomy for both the primary surgical and reconstruction procedures. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Clinical Input From Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests, input was received from 1 specialty society and 6 academic medical centers while this policy was under review in 2016. Input addressed the use of contralateral prophylactic (risk-reducing) mastectomy in women with unilateral breast cancer who are not otherwise at high-risk for developing breast cancer in the contralateral breast. The input was mixed. Clinicians offered suggestions for modifying high-risk criteria but there was no consensus on potential additional risk factors.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American Society for Clinical Oncology, American Society for Radiation Oncology, and Society of Surgical Oncology

In 2020, the American Society for Clinical Oncology, American Society for Radiation Oncology, and Society of Surgical Oncology published joint guidelines on management of hereditary breast cancer.¹⁹The guideline discusses management of patients with breast cancer with germline mutations in breast cancer susceptibility genes (eg, *BRCA1/2*, *ATM*, *TP53*) and makes the following recommendations regarding risk-reducing mastectomy:

"Surgical management of the index malignancy (... contralateral risk-reducing mastectomy [CRRM]) in *BRCA1/2* mutation carriers should be discussed, considering the increased risk of CBC and possible increased risk of an ipsilateral new primary breast cancer compared with noncarriers (Type: formal consensus; Evidence quality: intermediate; Strength of recommendation: strong)."

"For women with breast cancer who have a *BRCA1/2* mutation and who have been treated or are being treated with unilateral mastectomy, CRRM should be offered. CRRM is associated with a decreased risk of CBC; there is insufficient evidence for improved survival."

"Decisions regarding risk-reducing mastectomy (bilateral or contralateral) are highly personal and must be individualized for every patient. Studies show that women who opt for prophylactic mastectomy report positive outcomes, including decreased concern about developing breast cancer. This benefit must be weighed against possible problems with implants or reconstructive therapy and potential adverse feelings related to body image, femininity, and sexuality. Most patients who opt for prophylactic mastectomy demonstrate satisfaction with their decision."

"For women with breast cancer who have a mutation in a moderate-penetrance breast cancer predisposition gene and who have been treated or are being treated with unilateral mastectomy, the decision regarding [contralateral risk-reducing mastectomy] CRRM should not be based predominantly on mutation status. Additional factors that predict CBC such as age at diagnosis and family history should be considered, as they are in all cases. The impact of CRRM on decreasing risk of CBC is dependent on the risk of CBC for each individual gene. Data regarding the risk of CBC resulting from moderate-penetrance genes are limited (Type: formal consensus; Evidence quality: low; Strength of recommendation: moderate)."

The guideline also provides recommendations for assessing the risk of CBC and role of risk-reducing mastectomy in *BRCA1/2* mutation carriers (Evidence quality: low; Strength of recommendation: moderate) and in women with breast cancer who have a *BRCA1/2* mutation who have been treated or are being treated with unilateral mastectomy when considering contralateral risk-reducing mastectomy (Evidence quality: intermediate; Strength of recommendation: moderate). The guideline recommends consideration of the following:

- Age at diagnosis (the strongest predictor of future CBC)
- Family history of breast cancer
- Overall prognosis from this or other cancers (eg, ovarian)
- Ability of patient to undergo appropriate breast surveillance (magnetic resonance imaging [MRI])
- Comorbidities
- Life expectancy.

Society of Surgical Oncology

In 2017, the Society of Surgical Oncology updated its position statement on risk-reducing mastectomy.²⁰ The position statement concluded the following about risk-reducing mastectomy:

"There is no single-risk threshold above which risk-reducing mastectomy is clearly indicated, and it is important for treating physicians and surgeons to explain to individuals not only the risk assessment but also all available treatment strategies to facilitate a shared decision-making process."

"The available data suggest that BMP [bilateral prophylactic mastectomy] confers a survival advantage in women with the highest risk who undergo the procedure at a relatively early age ...

the impact of CPM [contralateral prophylactic mastectomy] in women with invasive breast cancer is more difficult to assess ... however, CPM does not appear to confer a survival advantage."

National Cancer Institute

In 2013, the National Cancer Institute updated its fact sheet on risk-reducing surgery for breast cancer.²¹ The fact sheet stated women with the following characteristics may consider bilateral risk-reducing mastectomy:

- Deleterious variant in *BRCA1* or *BRCA2*
- Strong family history of breast cancer
- Lobular carcinoma in situ and family history of breast cancer
- Radiotherapy to the chest before the age of 50 years.

Considering contralateral risk-reducing mastectomy, the Institute stated: "Given that most women with breast cancer have a low risk of developing the disease in their contralateral breast, women who are not known to be at a very high risk but who remain concerned about cancer development in their other breast may want to consider options other than surgery to further reduce their risk of a contralateral breast cancer."

American Society of Breast Surgeons

In 2016, a consensus statement from the American Society of Breast Surgeons made the following recommendations on contralateral risk-reducing mastectomy²²:

"CPM [contralateral prophylactic mastectomy] should be considered for those at significant risk of CBC [contralateral breast cancer]

- Documented *BRCA1/2* carrier
- Strong family history, but patient has not undergone genetic testing
- History of mantle chest radiation before age 30 years.

CPM can be considered for those at lower risk of CBC

- Gene carrier of... *CHEK-2*, *PALB2*, *p53*, *CDH1*
- Strong family history, patient *BRCA* negative, no known *BRCA* family member.

CPM may be considered for other reasons

- To limit contralateral breast surveillance (dense breasts, failed surveillance, recall fatigue)
- To improve reconstructed breast symmetry
- To manage risk aversion ... [or] extreme anxiety." (note: anxiety may be better managed through psychological support strategies.)

CPM should be discouraged

- Average-risk women with unilateral breast cancer
- Women with advanced index cancer
- Women at high risk for surgical complications (e.g.,...comorbidities, obesity, smoker , diabetes)
- *BRCA* negative with a family of *BRCA*-positive carriers
- Male breast cancer, including *BRCA* carriers.

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN) has made recommendations on several cancers relevant to this evidence review. On breast cancer risk-reduction (v.1.2021), the NCCN recommends:

"Risk-reducing mastectomy should generally be considered only in women with a pathogenic/likely pathogenic genetic mutation (not variants of undetermined significance) conferring a high risk for breast cancer..., compelling family history, or possibly with prior thoracic RT [radiation therapy] at <30 years of age. The value of risk-reducing mastectomy in individuals with pathogenic/likely pathogenic mutations in other genes associated with a 2-fold or greater risk for breast cancer ... in the absence of a compelling family history of breast cancer is unknown."²³,

For invasive breast cancer (v.4.2021) the NCCN has discouraged contralateral risk-reducing mastectomy, except for certain high-risk situations (noted in the risk-reduction guideline previously discussed).²⁴ The guidelines state:

"...risk reduction mastectomy of a breast contralateral to a known unilateral breast cancer treated with mastectomy is discouraged by the panel. The use of a prophylactic mastectomy contralateral to a breast treated with lumpectomy is very strongly discouraged in all patients."

As part of a genetic/familial high-risk assessment for breast, ovarian, and pancreatic cancer (v.1.2021), the NCCN recommends that the option of risk-reduction mastectomy be discussed in women with *BRCA*-related breast and/or ovarian syndrome, Li-Fraumeni syndrome, and Cowden syndrome or *PTEN* hamartoma tumor syndrome.²⁵ In addition, the NCCN guidelines recommend that risk-reducing mastectomy be considered based on family history in women with certain genetic variants including *ATM*, *PALB2*, *CHEK2*, and *CDH1*.

U.S. Preventive Services Task Force Recommendations

No U.S. Preventive Services Task Force recommendations for prophylactic mastectomy have been identified.

Ongoing and Unpublished Clinical Trials

A search of ClinicalTrials.gov in May 2021 did not identify any ongoing or unpublished trials that would likely influence this review.

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. This may not be a comprehensive list of procedure codes applicable to this policy.

Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

The code(s) listed below are medically necessary ONLY if the procedure is performed according to the "Policy" section of this document.

CPT/HCPCS

19303 Mastectomy, simple, complete

ICD-10 Diagnoses

C50.011 Malignant neoplasm of nipple and areola, right female breast
 C50.012 Malignant neoplasm of nipple and areola, left female breast
 C50.111 Malignant neoplasm of central portion of right female breast
 C50.112 Malignant neoplasm of central portion of left female breast
 C50.211 Malignant neoplasm of upper-inner quadrant of right female breast
 C50.212 Malignant neoplasm of upper-inner quadrant of left female breast
 C50.311 Malignant neoplasm of lower-inner quadrant of right female breast
 C50.312 Malignant neoplasm of lower-inner quadrant of left female breast
 C50.411 Malignant neoplasm of upper-outer quadrant of right female breast
 C50.412 Malignant neoplasm of upper-outer quadrant of left female breast
 C50.511 Malignant neoplasm of lower-outer quadrant of right female breast
 C50.512 Malignant neoplasm of lower-outer quadrant of left female breast
 C50.611 Malignant neoplasm of axillary tail of right female breast
 C50.612 Malignant neoplasm of axillary tail of left female breast
 C50.811 Malignant neoplasm of overlapping sites of right female breast
 C50.812 Malignant neoplasm of overlapping sites of left female breast
 C50.911 Malignant neoplasm of unspecified site of right female breast
 C50.912 Malignant neoplasm of unspecified site of left female breast
 C50.021 Malignant neoplasm of nipple and areola, right male breast
 C50.022 Malignant neoplasm of nipple and areola, left male breast
 C50.121 Malignant neoplasm of central portion of right male breast
 C50.122 Malignant neoplasm of central portion of left male breast
 C50.129 Malignant neoplasm of central portion of unspecified male breast
 C50.221 Malignant neoplasm of upper-inner quadrant of right male breast
 C50.222 Malignant neoplasm of upper-inner quadrant of left male breast
 C50.229 Malignant neoplasm of upper-inner quadrant of unspecified male breast
 C50.321 Malignant neoplasm of lower-inner quadrant of right male breast
 C50.322 Malignant neoplasm of lower-inner quadrant of left male breast
 C50.329 Malignant neoplasm of lower-inner quadrant of unspecified male breast
 C50.421 Malignant neoplasm of upper-outer quadrant of right male breast
 C50.422 Malignant neoplasm of upper-outer quadrant of left male breast
 C50.429 Malignant neoplasm of upper-outer quadrant of unspecified male breast
 C50.521 Malignant neoplasm of lower-outer quadrant of right male breast
 C50.522 Malignant neoplasm of lower-outer quadrant of left male breast
 C50.529 Malignant neoplasm of lower-outer quadrant of unspecified male breast
 C50.621 Malignant neoplasm of axillary tail of right male breast
 C50.622 Malignant neoplasm of axillary tail of left male breast
 C50.629 Malignant neoplasm of axillary tail of unspecified male breast
 C50.821 Malignant neoplasm of overlapping sites of right male breast
 C50.822 Malignant neoplasm of overlapping sites of left male breast
 C50.829 Malignant neoplasm of overlapping sites of unspecified male breast
 C50.921 Malignant neoplasm of unspecified site of right male breast
 C50.922 Malignant neoplasm of unspecified site of left male breast
 C50.929 Malignant neoplasm of unspecified site of unspecified male breast
 D05.01 Lobular carcinoma in situ of right breast

D05.02	Lobular carcinoma in situ of left breast
D05.11	Intraductal carcinoma in situ of right breast
D05.12	Intraductal carcinoma in situ of left breast
D05.81	Other specified type of carcinoma in situ of right breast
D05.82	Other specified type of carcinoma in situ of left breast
D05.91	Unspecified type of carcinoma in situ of right breast
D05.92	Unspecified type of carcinoma in situ of left breast
Z15.01	Genetic susceptibility to malignant neoplasm of breast
Z85.3	Personal history of malignant neoplasm of breast
Z40.01	Encounter for prophylactic removal of breast

REVISIONS

10-28-2011	Policy added to the bcbsks.com web site.
07-13-2012	Description section updated.
	In the Policy section: <ul style="list-style-type: none"> ▪ In Item #2, replaced "p" with "TP" to read "Presence of a TP53 or PTEN mutation" (Note—this was a clarification. No policy intent change.)
	Rationale section updated.
	Reference section updated.
11-29-2013	Updated Description section.
	In Policy section: <ul style="list-style-type: none"> ▪ In Item A, removed "or moderately increased risk" to read "unilateral or bilateral prophylactic mastectomy may be considered medically necessary in patients at high risk of breast cancer with one of the following:" ▪ Removed Item A, #2 ▪ Removed Item A, #7-#18 ▪ Added new #6 to Item A, "Li-Fraumeni syndrome or Cowden syndrome or Bannayan-Riley-Ruvalcaba syndrome or a first-degree relative with one of these syndromes." ▪ Added Item B, "Prophylactic mastectomy is considered experimental / investigational in women who do not meet high risk criteria."
	Updated Rationale section.
	In Coding section: <ul style="list-style-type: none"> ▪ Added ICD-10 Diagnosis codes. <i>(Effective October 1, 2014)</i>
	Updated Reference section.
06-23-2015	Updated Description section.
	In Policy section: <ul style="list-style-type: none"> ▪ In Item A 1, removed "Presence of a" and added "or" to read "A known BRCA1 or BRCA2 mutation, OR" ▪ In Item A 2, removed "radiation therapy" and added "radiotherapy" and "or" to read "Received radiotherapy to the chest between the ages of 10 and 30 years, OR" ▪ In Item A 3, added "or" to read "Presence of lobular carcinoma in situ, OR" ▪ In Item A 4, added "or" to read "Extensive mammographic abnormalities (i.e., calcifications), OR" ▪ In Item A 5, removed "the Gail or Claus model (Characteristics of the Gail and Claus models http://www.cancer.gov/cancertopics/pdq/genetics/breast-and-ovarian/HealthProfessional/page1#Section_66)," and added "developing", "models that are largely defined by family history", "or" to read "Lifetime risk of developing breast cancer of 20% or greater as identified by models that are largely defined by family history, OR"

	<ul style="list-style-type: none"> ▪ In Item A 6, added "or" to read "Li-Fraumeni syndrome or Cowden syndrome or Bannayan-Riley-Ruvalcaba syndrome or a first-degree relative with one of these syndromes, OR" ▪ Added Item A 7, "Another gene mutation associated with increased risk (e.g., PTEN, TP53, CDH1, and STK11)." ▪ In Policy Guidelines, removed "Cancer risk assessment should include a complete family history and use of the Gail or Claus model to estimate the risk of cancer." and "should be discussed", and added "other than the operating surgeon and discussion of the", to read "It is strongly recommended that all candidates for prophylactic mastectomy undergo counseling regarding cancer risks from a health professional skilled in assess cancer risk other than the operating surgeon and discussion of the various treatment options, including increased surveillance or chemoprevention with tamoxifen or raloxifene."
	Updated Rationale section.
	Updated References section.
10-01-2015	Policy published 05-25-2016. Retro-effective to 10-01-2015 with ICD-10 coding implementation.
	In Coding section: <ul style="list-style-type: none"> ▪ Added ICD-10 code: Z15.01.
05-25-2016	Updated Description section.
	Updated Rationale section.
	Updated References section.
06-08-2016	In Revision section: <ul style="list-style-type: none"> ▪ Removed "Updated Description, Updated Rationale, Updated References" sections from 10-01-2015 revision and created a 05-25-2016 revision.
11-22-2016	In Policy section: <ul style="list-style-type: none"> ▪ In Item B, removed "women" and added "individuals" to read, "Prophylactic mastectomy is considered experimental / investigational in women who do not meet high risk criteria."
10-28-2017	Updated Description section.
	In Policy section: <ul style="list-style-type: none"> ▪ In Item A 1, removed "mutation" and added "variant" to read, "A known BRCA1 or BRCA2 variant," ▪ Removed Item A 4, "Extensive mammographic abnormalities (i.e., calcifications), OR". ▪ Removed Item A 6, "Li-Fraumeni syndrome or Cowden syndrome or Bannayan-Riley-Ruvalcaba syndrome or a first-degree relative with one of these syndromes, OR". ▪ In new Item A 5, removed "mutation" and added "variant", "(Li-Fraumeni syndrome)," and "(Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome)" to read, "Another gene variant, associated with increased risk (e.g., <i>TI53</i> (Li-Fraumeni syndrome), PTEN (Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome), <i>CDH1</i>, and <i>STK11</i>)."
	Updated Rationale section.
	Updated References section.
09-12-2018	Revised title from "Prophylactic Mastectomy."
	Updated Description section.
	In Policy section: <ul style="list-style-type: none"> ▪ In Item A, removed "prophylactic" and added "risk-reducing" to read, "Unilateral or bilateral risk-reducing mastectomy may be considered medically necessary in patients at high risk of breast cancer with one of the following:" ▪ In Item B, removed "prophylactic" and added "risk-reducing" to read, "Risk-reducing mastectomy is considered experimental / investigational in individuals who do not meet high risk criteria." ▪ In Policy Guidelines, added new Item 4.

	Updated Rationale section.
	In Coding section: ▪ Removed ICD-9 codes.
	Updated References section.
08-28-2019	Updated Description section.
	Updated Rationale section.
	Updated References section.
04-19-2021	Updated Description section.
	Updated Rationale section.
	In the Coding section: • Removed code 19304 (termed 12-31-20)
	Updated References section.
09-17-2021	Updated Rationale section.
	Updated Rationale section.

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