Contralateral prophylactic mastectomy for patients with unilateral breast cancer

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Patients with unilateral breast cancer are at increased risk of developing a second cancer in the contralateral breast. Some women choose contralateral prophylactic mastectomy (CPM) to prevent cancer in the contralateral breast. Several studies have demonstrated that CPM significantly decreases the occurrence of contralateral breast cancer. However, the effectiveness of CPM at reducing breast cancer mortality is not as clear. Moreover, CPM is not risk free and patients may need to undergo additional surgical procedures, especially if reconstruction is performed. Nevertheless, most patients are satisfied with their decision to undergo CPM. Alternatives to CPM include close surveillance with clinical breast examination, mammography and possibly breast magnetic resonance imaging. Endocrine therapy with tamoxifen or aromatase inhibitors significantly reduces the risk of contralateral breast cancer and may be more acceptable than CPM for some patients. The decision to undergo CPM is complex and many factors likely contribute to its use. Future prospective studies are critically needed to evaluate the decision-making processes leading to CPM.

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Patients with unilateral breast cancer have a significantly increased risk of developing a cancer in the contralateral breast [1–4]. Some women choose contralateral prophylactic mastectomy (CPM) to treat an occult synchronous cancer or to prevent a metachronous cancer in the opposite breast. CPM significantly reduces the risk of contralateral breast cancer, but the procedure is aggressive and irreversible; it is also unnecessary for preventing contralateral breast cancer in most patients [5–8]. Moreover, since the risk of systemic metastases often exceeds the risk of contralateral breast cancer, most patients will not experience any survival benefit. This review will discuss the following issues related to CPM:

- Risk of contralateral breast cancer in patients with unilateral breast cancer
- Outcomes of CPM
- Alternatives to CPM

Risk of contralateral breast cancer

Today, bilateral breast cancer represents approximately 2–5% of all breast cancer cases [9]. A second primary cancer in the contralateral breast may be either synchronous (simultaneous) or metachronous (sequential). Most authors consider a tumor to be synchronous if it is diagnosed within 6 months after the first tumor. Metachronous contralateral breast cancer is more common than synchronous.

The incidence of contralateral breast cancer varies by the method of diagnosis. For instance, Nielsen *et al.* reported that 68% of breast cancer patients had evidence of contralateral breast cancer at autopsy [10]. Using random biopsies of the normal contralateral breast, Wanebo *et al.* found that 18% of patients with unilateral breast cancer harbored unsuspected malignancies in the contralateral breast [11]. In a series of 239 patients with unilateral breast cancer who underwent CPM, Goldflam *et al.* reported that occult cancer

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(infiltrating lobular, infiltrating ductal or ductal carcinoma *in situ*) was identified in 4.6% of CPM specimens, and moderate-to-high risk pathology (lobular carcinoma *in situ*, atypical lobular hyperplasia or atypical ductal hyperplasia) was identified in 18.4% of CPM specimens [12].

Breast MRI is increasingly used in clinical practice for breast cancer staging (FIGURE 1). Breast MRI evaluates both breasts and may identify contralateral cancers not detected by physical examination or mammography. In fact, several studies have reported that breast MRI can detect occult synchronous cancers in the contralateral breast [13–15]. In the American College of Radiology Imaging Network (ACRIN) study of 969 women with breast cancer, MRI detected occult cancer in the contralateral breast in 3.1% of women [14]. In a recent review, Liberman reported that MRI identifies occult contralateral breast cancer in 6% of patients (range: 3–24%) [15]. Pathological confirmation of MRI findings is necessary to prevent unnecessary contralateral mastectomies. Second-look, ultrasound-guided biopsy and MRI-guided needle biopsy may be helpful in this setting.

The annual risk of clinically detected metachronous contralateral breast cancer is approximately 0.7% [1–4,16]. This risk is constant and demonstrates no trend either to increase or decrease with follow-up. By contrast, the peak hazard of systemic recurrence of unilateral breast cancer is 1–2 years after treatment; the risk decreases consistently after 2–5 years [17]. Thus, occurrence of contralateral breast cancer is clinically more significant in patients who are likely to survive for a long time.

Certain clinical characteristics are associated with higher rates of contralateral breast cancer. Multiple studies have reported that young age at the time of diagnosis of the first breast cancer is associated with a significantly increased risk [2,4,9]. Storm and Jensen estimated that the probability of developing metachronous contralateral breast cancer was 25% for women diagnosed with unilateral cancer at 45 years of age or younger, if they survive to the age of 75 years [2]. Patients with at least one first-degree relative with breast cancer also have an increased risk of contralateral breast cancer [9]. Moreover, patients with unilateral breast cancer who also have *BRCA1* or *BRCA2* genetic mutations have a markedly increased risk of developing contralateral breast cancer [18]. Verhoog *et al.* reported that contralateral breast cancer was four- to five-times more frequent in patients with *BRCA1* mutations compared with a sporadic group of breast cancer patients [19]. Unilateral breast cancer patients with *BRCA* mutations represent one of the highest risk groups for developing contralateral breast cancer.

Specific histological features of the primary tumor are also associated with a higher incidence of contralateral breast cancer. The diagnosis of invasive lobular carcinoma increases the risk of contralateral breast cancer [1,9,20]. Erdreich *et al.* reported that the risk of contralateral breast cancer was 2.6-fold higher in patients with invasive lobular cancer compared with other histologic types [20]. However, Yeatman *et al.* noted that the cumulative incidence of contralateral breast cancer was only slightly higher in patients with invasive lobular cancer (8.1%) compared with invasive ductal cancer (7.8%) [21]. Multicentric unilateral breast cancer also increases the risk of contralateral breast cancer [1].

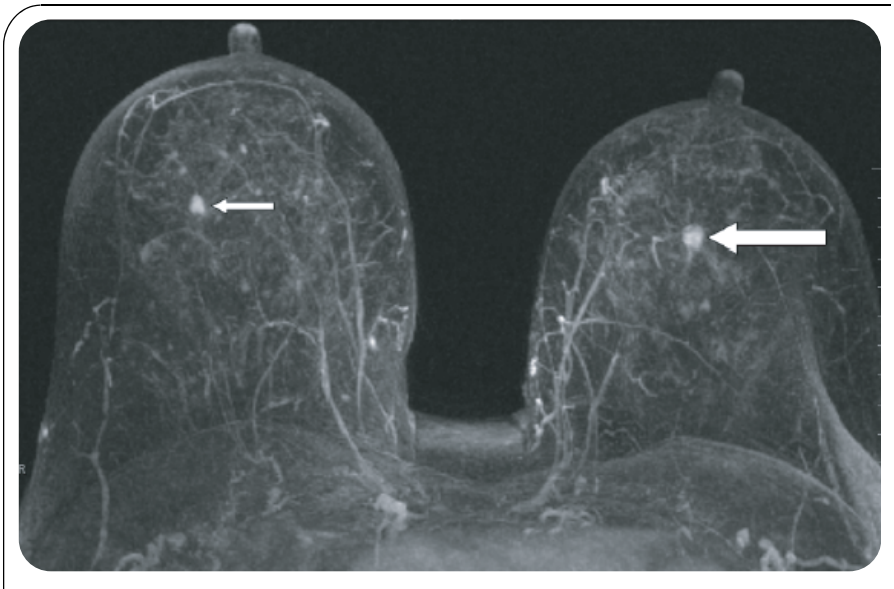

Figure 1. Breast MRI demonstrating the known biopsy-proven cancer (large arrow) and contralateral breast cancer (small arrow) that was not detected on mammography.

Indications for contralateral prophylactic mastectomy

Many women with unilateral breast cancer choose CPM to prevent the occurrence of cancer in the opposite breast. The potential benefit of CPM is greatest for patients who have the highest risk of contralateral breast cancer. Although absolute indications for CPM are not established, the Society of Surgical Oncology has published criteria that physicians should consider for mastectomy of the contralateral, intact breast [101]. Reasons for contralateral mastectomy may include diffuse microcalcifications, lobular carcinoma *in situ*, atypical hyperplasia, multicentric breast cancer, strong family history, the presence of a *BRCA1* or *BRCA2* mutation, dense breast tissue, or a large remaining breast (which complicates symmetric reconstructive techniques).

Surgical procedures

In the past, many CPMs were subcutaneous mastectomies that left behind a substantial amount of breast tissue. Today, total mastectomy, including removal of the nipple–areolar complex, is recommended for prophylactic surgery. Skin-sparing total mastectomies are increasingly performed now to preserve the skin envelope and improve the cosmetic outcomes with reconstructive breast surgery. Some investigators have also performed nipple- and areolar-sparing mastectomies in highly selected patients [22–23]. However, no mastectomy can remove all breast tissue and completely eliminate the risk of breast cancer.

Several authors have evaluated the utility of performing sentinel lymph node (SLN) biopsy at the time of CPM [24,25]. The major advantage of this approach is avoidance of axillary lymph node dissection if occult cancer is unexpectedly found in the CPM specimen. However, the disadvantages of performing SLN biopsy at the time of CPM are increased cost and time and potential morbidity (pain, parasthesias, seroma and lymphedema) of an unnecessary procedure. In a study of 382 patients undergoing CPM, Boughey *et al.* reported that only seven patients (1.8%) had occult invasive cancers; SLN biopsy was used selectively in these patients [24]. Similarly, in a study of 163 patients undergoing prophylactic mastectomy, King *et al.* reported that four (2.5%) had an occult invasive cancer; breast MRI was only used in four patients [25]. Overall, the utility of SLN staging for CPM, especially if MRI staging is also performed, is very low.

Effectiveness

Several studies have demonstrated the effectiveness of CPM in preventing contralateral breast cancer (TABLE 1) [5–8,12]. In a study of 745 breast cancer patients with a family history of breast cancer, McDonnell *et al.* reported that CPM reduced the incidence of contralateral breast cancer by more than 90% [6]. In a cohort of patients with unilateral breast cancer and BRCA1 or BRCA2 mutations, van Sprundel *et al.* reported that CPM reduced the risk of contralateral breast cancer by 91% [8]. In a retrospective study of 239 patients, Goldflam *et al.* reported that only one (0.4%) contralateral breast cancer developed after CPM [12].

However, the effectiveness of CPM in preventing breast cancer mortality is not as clear. A recent Cochrane review of eight retrospective studies included 1708 patients who underwent CPM; the authors concluded that CPM decreased the incidence of contralateral breast cancer, but was not associated with any survival improvement [26]. However, in a retrospective cohort study of 1072 patients from the Cancer Research Network, Herrinton *et al.* reported that CPM was associated with a significant decrease in the breast cancer mortality rate (hazard ratio [HR]: 0.57; 95% confidence interval [CI]: 0.45–0.72) and overall mortality rate (HR = 0.6; 95% CI: 0.5–0.72) [7]. In this study, women who underwent CPM were less likely to die from nonbreast cancer-related causes, emphasizing the selection bias that healthier patients undergo CPM more frequently. In a retrospective case–control study, Peralta *et al.* reported that CPM significantly increased the disease-free survival rate (CPM: 55%; no CPM: 28%; p = 0.01), but not the overall survival rate (CPM: 64%; no CPM: 49%; p = 0.26) [5]. Finally, using a Markov state transition model, Schrag *et al.* estimated that a 30-year-old patient with early-stage breast cancer and a *BRCA* mutation would gain an additional 0.6–2.1 years in life expectancy after CPM [27].

Despite the potential benefits of CPM, the procedure is not risk free. Severe complications after CPM may potentially delay recommended chemotherapy or radiation therapy after surgery. In a series of 239 patients undergoing CPM (most received immediate reconstruction), Goldflam *et al.* reported a 16.3% complication rate (ipsilateral breast: 8.4%; contralateral breast: 6.3%; both breasts: 1.7%) [12]. Barton *et al.* reported that the most common complications after bilateral prophylactic mastectomy were pain (35%), infection (17%) and seroma (17%) [28].

Patient decision & satisfaction

Despite potential risks and complications, most patients are satisfied with their decision to undergo CPM [29–31]. Frost *et al.* reported that 83% of patients were either satisfied or very satisfied with their decision to undergo CPM at a mean of 10 years after surgery [29]. Montgomery *et al.* reported that the most common reasons for regret after CPM were a poor cosmetic outcome and diminished sense of sexuality [30]. Geiger *et al.* found that patients who underwent CPM were less likely to express breast cancer concern, as compared with patients who did not undergo CPM [31]. In a study of patients with BRCA mutations and unilateral breast cancer, Tercyak *et al.* reported that patients who chose CPM did not exhibit decreased quality of life, compared with those who underwent unilateral mastectomy or breast-conserving surgery [32].

Table 1. Contralateral prophylactic mastectomy reduces occurrence of contralateral breast cancer.

Study	Number of CPMs	Risk reduction of contralateral breast cancer (%)	Comparison group	Ref.
Goldflam *et al.* (2004)	239	91	Surveillance Epidemiology End Results Cancer Registry	[12]
		94	Anderson–Badzioch Model	
Peralta *et al.* (2000)	64	83	Matched controls	[5]
Van Sprundel *et al.* (2005)	79	91	BRCA patients who underwent surveillance	[8]
McDonnell *et al.* (2001)	745	94 (premenopausal); 96 (postmenopausal)	Anderson-Badzioch Model	[6]
Herrinton *et al.* (2005)	1072	97	Case–cohort	[7]

CPM: Contralateral prophylactic mastectomy.

In an analysis of the Surveillance Epidemiology End Results (SEER) registry, the CPM rate doubled from 1998 to 2003 in the USA [33]. Many factors probably contribute to the increased use of CPM for unilateral breast cancer. The availability of genetic counseling and BRCA testing has increased in recent years. Breast cancer patients with *BRCA1* or *BRCA2* mutations have a significantly increased risk of developing contralateral breast cancer and may elect to undergo CPM more frequently. The increased availability of breast reconstruction may also partially explain increased CPM rates. Furthermore, since obesity rates have increased in recent years in the USA, more obese women may choose to undergo CPM to achieve balance and symmetry. In patients with unilateral breast cancer, MRI frequently identifies abnormal findings in the contralateral breast. Although most of these abnormal findings are not malignant, some patients may undergo CPM to eliminate the stress of additional surveillance and future biopsy.

The decision to undergo CPM is complex, and many factors likely contribute to its increased use. In a review of the National Prophylactic Mastectomy Registry, Montgomery *et al.* reported that the most common reasons for CPM were [30]:

- Physicians' advice
- Patients' fear of more breast cancer
- Desire for cosmetic symmetry
- Family history
- Fibrocystic breast disease

Using data from the Connecticut Tumor Registry, Polednak reported that young age and lobular type histology were associated with higher CPM rates [34]. In another study, Geiger *et al.* reported that patients who underwent CPM were more likely to be white and to have breast reconstruction, compared with patients who did not undergo CPM [31].

To date, no study has prospectively evaluated the decision-making processes that lead to CPM among the general population of breast cancer patients. In a retrospective survey from the National Cancer Institute Cancer Research Network of 11 health maintenance organizations, Nekhlyudov *et al.* examined decision-making processes among women who underwent CPM [35]. In this study, most women reported active or shared roles in decision-making. Young age, college-education and recent treatment were associated with active or shared decision-making roles. The only prospective study evaluating decision-making processes was reported by Schwartz *et al.* in a selected cohort of patients referred for genetic counseling and BRCA testing [36]. The *BRCA* test results, number of first-degree relatives with breast cancer, cancer stage and physician recommendations were associated with bilateral mastectomy (CPM).

Alternatives to contralateral prophylactic mastectomy

Patients with unilateral breast cancer have options that are less extreme than CPM. Surveillance with clinical breast examination, mammography and newer imaging modalities, such as breast MRI, may detect cancers at earlier stages [37,38]. Several studies have shown that patients with unilateral breast cancer who were closely monitored developed significantly smaller tumors in the contralateral breast and had lower rates of axillary lymph node metastasis compared with their unscreened counterparts [37,39]. Because the annual risk of contralateral breast cancer is relatively constant, surveillance should continue indefinitely or until age- or other health-related issues significantly impair life expectancy.

Several prospective randomized trials demonstrated that tamoxifen, given as adjuvant therapy for estrogen receptor-positive breast cancer, significantly reduces the rate of malignancy in the contralateral breast [40–42]. In the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14 study, 2892 women with node-negative, estrogen receptor-positive breast tumors were randomly assigned to either tamoxifen (20 mg/day) or placebo for at least 5 years [40]. After an average follow-up of 53 months, 55 contralateral breast tumors were found in placebo-treated women and 28 were found in the tamoxifen-treated women ($p = 0.001$). Furthermore, the incidence of contralateral tumors was reduced in patients both younger and older than 50 years. Tamoxifen may also reduce the risk of contralateral breast cancer in women with *BRCA* mutations and unilateral breast cancer. In a case–control study, Narod *et al.* compared 209 women with bilateral breast cancer and BRCA mutations with 384 women with unilateral breast cancer and *BRCA* mutations [43]. The risk of contralateral breast cancer was reduced by 75% in tamoxifen-treated women.

Aromatase inhibitors may reduce the risk of contralateral breast cancer as much as, or even more than, tamoxifen [44]. The Anastrozole, Tamoxifen Alone or in Combination (ATAC) Trial demonstrated that anastrozole was superior to tamoxifen in preventing contralateral breast cancer in postmenopausal women. Ovarian ablation and cytotoxic chemotherapy also reduce the risk of contralateral breast cancer [45,46].

Expert commentary

Many breast cancer patients request CPM to prevent contralateral breast cancer. Indeed, CPM does reduce the risk of contralateral breast cancer, but probably does not impact breast cancer survival rates. Controversy exists about whether the physician or patient should initiate the discussion of CPM. If a patient appropriately chooses breast-conserving surgery, then CPM is not a relevant treatment. For patients who undergo mastectomy, CPM may be a reasonable option, particularly if a patient has a *BRCA* mutation, strong family history or is obese, or if imaging of the contralateral breast is difficult. Presently, we do not recommend SLN biopsy at the time of CPM for patients with normal mammograms and MRIs. Physicians must provide breast cancer patients with accurate information on the risk of contralateral breast cancer and on the risks and benefits of CPM and breast reconstruction. In addition, physicians should encourage appropriate patients to consider less extreme options (e.g., endocrine therapy) to prevent contralateral breast cancer.

Five-year view

We anticipate that CPM rates will increase within the next 5 years due to multiple factors: increased availability of reconstructive surgery, increased utilization of breast MRI, more *BRCA* testing and increasing obesity rates. To date, no study has prospectively evaluated the decision-making processes that led to CPM among the general population of breast cancer patients. Future research should be directed to the development of unique models and instruments to elucidate these decision-making processes in breast cancer patients. Moreover, no research has prospectively evaluated the surgeon's influence on the decision to undergo CPM. Decision-analysis research is important and timely because it may ultimately provide decision aids for breast cancer patients and their physicians.

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Key issues

- For patients with unilateral breast cancer, the annual risk of contralateral breast cancer is approximately 0.7%.
- The risk of contralateral breast cancer is higher for some patients: *BRCA* mutations, family history of breast cancer, lobular histology and multicentric breast cancer.
- Contralateral prophylactic mastectomy (CPM) reduces the rate of contralateral breast cancer by more than 90%.
- CPM probably does not reduce breast cancer mortality.
- Most patients are satisfied with their decision to undergo CPM.
- Endocrine therapy with tamoxifen or aromatase inhibitors reduces the risk of contralateral breast cancer by approximately 50%.
- The most common reasons that patients cite for CPM are physician's advice, fear of more breast cancer, desire for cosmetic symmetry and family history.
- The utility of sentinel node staging for CPM, especially in the setting of a normal breast MRI, is very low.

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