

# Better contralateral breast cancer risk estimation and alternative options to contralateral prophylactic mastectomy

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**Abstract:** The incidence of contralateral prophylactic mastectomy (CPM) has increased among women with breast cancer, despite uncertain survival benefit and a declining incidence of contralateral breast cancer (CBC). Patient-related reasons for undergoing CPM include an overestimation of the risk of CBC, increased cancer worry, and a desire to improve survival. We summarize the existing literature on CBC risk and outcomes and the clinical benefit of CPM among women with unilateral breast cancer who have a low-to-moderate risk of developing a secondary cancer in the contralateral breast. Published studies were retrieved from the MEDLINE database with the keywords “contralateral breast cancer” and “contralateral prophylactic mastectomy”. These include observational studies, clinical trials, survival analyses, and decision models examining the risk of CBC, the clinical and psychosocial effects of CPM, and other treatment strategies to reduce CBC risk. Studies that have evaluated CBC risk estimate it to be approximately 0.5% annually on average. Patient-related factors associated with an increased risk of CBC include carriers of *BRCA1/2* mutations, young age at breast cancer, and strong family history of breast cancer in the absence of a *BRCA1/2* mutation. Although CPM reduces the risk of CBC by approximately 94%, it may not provide a significant gain in overall survival and there is conflicting evidence that it improves disease-free survival among women with breast cancer regardless of estrogen receptor (ER) status. Therefore, alternative strategies such as the use of tamoxifen or aromatase inhibitors, which reduce the risk of CBC by approximately 50%, should be encouraged for eligible women with ER-positive breast cancers. Future research is needed to evaluate the impact of decision and educational tools that can be used for personalized counseling of patients regarding their CBC risk, the uncertain role of CPM, and alternative CBC risk reduction strategies.

**Keywords:** contralateral prophylactic mastectomy, contralateral breast cancer, endocrine therapy, sporadic breast cancer, risk assessment

## Introduction

For women with unilateral breast cancer, removal of the contralateral, cancer-free breast (contralateral prophylactic mastectomy, CPM) is a surgical option that has increased in frequency, despite uncertain survival benefit<sup>1-3</sup> and a declining incidence of contralateral breast cancer (CBC). The increasing use of CPM as a breast cancer preventative treatment<sup>4</sup> indicates a need for better estimation of the risk of CBC and knowledge of alternative CBC risk reduction treatment options for improved clinical decision-making.

Despite the increase in use of adjuvant endocrine therapy for women with estrogen receptor (ER)-positive tumors that reduces the risk of CBC by approximately 50%, the CPM rate has continued to escalate as a management therapy to prevent

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the development of cancer in the healthy breast.<sup>2</sup> Although CPM may improve health outcomes for particular subgroups, specifically younger women with a *BRCA1/2* mutation or those with a strong family history of breast cancer, the additional surgery may be unnecessary for the majority of women diagnosed with breast cancer.<sup>5,6</sup> In part, the increasing use of CPM may be due to treatment choices related to the index cancer such as desire for bilateral reconstruction or unsuccessful breast conservation rather than an increased risk of developing CBC.<sup>7,8</sup> Specific factors associated with having CPM in unselected patients include undergoing genetic testing, age, ethnicity, family history, and improved reconstruction options.<sup>9,10</sup>

Women with a family history of breast cancer, ER-negative tumors, and younger age at breast cancer diagnosis have the greatest risk for CBC.<sup>11,12</sup> In 1993, the Society of Surgical Oncology published guidelines for indications for CPM with an update issued in 2007. These include: 1) *BRCA1/2* mutation or a family history of breast or ovarian cancer in multiple first-degree relatives, 2) difficult surveillance because of high mammographic breast density or indeterminate calcifications, and 3) desire for improved symmetry or bilateral breast reconstruction.<sup>13</sup> Since CBC rates in high-risk groups have not increased over time, patients without the aforementioned indications that elect to undergo CPM, may view prophylactic surgery as beneficial for other reasons, particularly when mastectomy is required for the primary breast cancer. Indeed, Rosenberg et al<sup>14</sup> showed in a retrospective study of women with breast cancer that the reasons for CPM included the desire to reduce the risk of CBC, to improve survival, and to have peace of mind. In addition, an increased willingness of surgeons to respect their patient's preferences may contribute to the increase in CPM.

The aim of this review is to summarize the risk of CBC from published studies to guide patients and clinicians on the best treatment options for reducing CBC, which may include CPM or other alternatives. We focus on women with unilateral breast cancer who have a low-to-moderate risk of developing a secondary cancer in the contralateral breast. We examine the role of CPM, alternative risk reduction strategies for CBC and the need for future studies to evaluate the impact of decision-making and educational tools for personalized counseling of CBC risk.

## Methods

We retrieved published studies from the MEDLINE database using the keywords "contralateral breast cancer" or "contralateral prophylactic mastectomy". We inspected the reference

lists of identified articles published in English for further relevant articles. Any study within the last 15 years or seminal studies that evaluated the risk of CBC and/or survival, the clinical benefit of CPM, or alternative treatment options for preventing CBC or recurrence of index cancer were considered. Studies were examined for relevancy, patient cohort, methodology, and the summary of clinical outcomes, eg, risk of CBC, disease-free survival (DFS), overall survival (OS), and quality-adjusted life expectancy (QALY). These include observational studies, review papers, randomized controlled trials, survival analyses, and decision models.

## Results

### Incidence and outcomes of CBC

CBC is the most common second primary cancer in breast cancer patients, accounting for between 30% and 50% of all second cancers.<sup>15–17</sup> Commonly cited are studies that assess the annual risk of developing a CBC to be 0.5%–0.75%.<sup>5,18–23</sup> However, this may be an overestimate due to the now widespread use of adjuvant systemic therapy. In a meta-analysis performed by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG), the 15-year incidence of CBC was 6.5% in women with ER-positive disease who were randomized to no tamoxifen and approximately 7.1% in women with ER-negative disease regardless of use of tamoxifen.<sup>24</sup> In a study using the Surveillance, Epidemiology, and End Results (SEER) database (1975–2006), Nichols et al<sup>4</sup> showed a decline in CBC incidence from 1990 to 2006 driven by declines in CBC rates in patients who had ER-positive tumors. In comparison, ER-negative tumors were associated with higher rates and there were no clear declines. There were also age-specific peaks at 30 and 70 years.

A study of the SEER database (1973–1996) found that CBC occurred in 4.2% of patients with a median follow-up time of 4.5 years (0.25–23.6 years). The 5, 10, 15, and 20-year actuarial incidence rates of CBC were 3%, 6.1%, 9.1%, and 12%, respectively. Increased risk of CBC was associated with medullary carcinoma, black race, receiving radiotherapy and surviving more than 5 years after the index cancer, and age greater than 55 years at diagnosis. These specific findings of high-risk patient subgroups may have implications for the management of breast cancer patients after initial treatment.<sup>15</sup>

Prognostic significance of CBC was evaluated by Schaapveld et al<sup>17</sup> in a population-based study of Stage I–IIIA patients diagnosed in the Netherlands between 1989 and 2002 with a median follow-up time of 5.8 years. The results indicated that a higher metachronous CBC risk

(CBC diagnosed more than 6 months from initial diagnosis) was observed among women younger than 40 years of age and that it was associated with poorer survival, emphasizing the need for long-term surveillance for that patient group. The use of endocrine therapy and chemotherapy significantly reduced the incidence of metachronous CBC.

In order to evaluate the contribution of CBC in impacting overall survival, Quan et al<sup>13</sup> utilized the Oregon State Cancer Registry SEER data during the period 1996–2004, and compared the incidence and overall survival between women with a synchronous breast cancer (CBC diagnosed within 12 months of the first primary breast cancer) and those with a metachronous breast cancer (CBC diagnosed greater than 12 months after the first primary breast cancer).<sup>11</sup> The study by Quan et al<sup>13</sup> showed an incidence rate of 2.1% for synchronous CBCs and 1.2% for the metachronous CBCs. The mean age of diagnosis of initial cancers was 63.8 years, and mean time interval between diagnoses was 40.5 months for metachronous breast cancer. The mean annual incidence rate of CBC was 0.13%. This CBC incidence rate was lower than estimates from earlier studies conducted before the widespread use of adjuvant therapies<sup>7,23,25</sup> which have found an average annual incidence of 0.7%–1.8%. Among patients with an initial Stage I or II cancer, 98.7% and 86.8% of the CBCs, respectively, were Stage II or better. Those with local tumors (DCIS, stage 1) had a slightly lower 5-year survival rates (95.5% compared to 97.5%) and much lower 10-year survival (76.4% compared to 93.5%) than similar staged patients in the SEER database (1998–2003). Synchronous CBC patients had a 10% lower survival than metachronous CBC patients, perhaps associated with higher mean stage of synchronous CBCs.<sup>13</sup> Previous results from other studies evaluating the association between synchronicity and survival have been mixed. In a study of a prospectively accrued database in a UK general district hospital (1963–1999), Carmichael et al<sup>26</sup> showed a worse survival prognosis with synchronous CBC than with metachronous or unilateral breast cancer. In a study of the Geneva cancer registry (1970–2002), Verkooijen et al<sup>27</sup> did not find a significant increase in mortality risk for synchronous bilateral compared to metachronous bilateral cancers. A recent review by Narod<sup>28</sup> estimated an annual risk of 0.3%–0.8% noting that CBC risk may depend on certain factors, including patient-specific factors such as, young age at diagnosis, family history, tumor type, lobular histology, and *BRCA1*, *BRCA2*, and *CHEK2* mutation status. However, CBC incidence was not associated with reduced survival.

Although the majority of CBCs will be of equal or lower stage than the primary breast cancer, there may be an additive effect of having two cancers, perhaps resulting in lower survival rates. However, these results are mixed. Quan et al<sup>13</sup> surmised that if the initial tumor grade is high stage, prognosis may be largely dictated by the initial cancer. However, two low stage cancers may result in a combined effect of each cancer and the vast majority of low stage index cancers also result in low stage CBC. Finally, since the widespread use of adjuvant therapies, the annual incidence of CBC has decreased and thus survival rates may now be greatly influenced by tumor biological characteristics and the receipt of effective adjuvant therapies.

### Contralateral prophylactic mastectomy and disease-free and overall survival

Contralateral prophylactic mastectomy is estimated to reduce the risk of developing a CBC by approximately 94%.<sup>7,13,28,29</sup> Similarly, in a recent meta-analysis, focusing on patients with a personal history of unilateral breast cancer, Fayanju et al<sup>1</sup> found that CPM was associated with a 96% reduction in metachronous CBC. Although CPM reduces the risk of CBC among women with a history of breast cancer, population-based studies that have been conducted using both national and institutional databases to evaluate the effect of CPM on DFS or breast cancer survival and OS have shown conflicting results.

Some studies have shown a DFS benefit associated with CPM, but not an overall survival benefit.<sup>7,9</sup> Using the SEER database, Bedrosian and Yao<sup>30</sup> evaluated DFS benefit of CPM by patient and tumor characteristics, and showed that CPM was associated with improved breast cancer-specific survival. Patients younger than 50 years of age with Stage I or II ER-negative breast cancers had a 4.3% improvement in breast cancer survival compared to those who underwent CPM with ER-positive breast cancer, although use of adjuvant hormonal therapy was not included. Using an adjusted multivariable Cox regression analysis on patients from The University of Texas MD Anderson Cancer Center, Brewster et al<sup>31</sup> showed a significant improvement in DFS (relative risk reduction of 25%) for patients who underwent CPM compared with those who did not. The improved DFS was mostly seen among ER-negative patients compared with patients who were ER-positive. After a median follow-up time of 5 years, Yao et al<sup>3</sup> estimated a statistically significant benefit from CPM, resulting in a relative risk reduction of 12% and 5-year absolute overall survival benefit of 2% using the National Cancer Database. Similar results were obtained when stratified by hormonal therapy use.

A more recent analysis of women aged 45 years or less with Stage I or II breast cancer included in the National Cancer Database showed no overall survival benefit of CPM, and no benefit to ER-negative patients.<sup>32</sup> Zeichner et al<sup>33</sup> utilized data from patients at Mount Sinai Medical Center and found improved 10-year OS in women younger than 40 years, who are thought to be at greatest cumulative risk for secondary cancer. In a recent meta-analysis of existing studies, Fayanju et al<sup>1</sup> found that although CPM decreases metachronous CBC in patients with *BRCA* mutations and/or family history of breast cancer, it did not result in an overall or DFS benefit. These studies attempted to control for known confounders since patients who receive CPM are more likely to be white, younger than 50 years, and have certain characteristics that may predispose them to better outcomes.<sup>2,10</sup>

Possible disadvantages of CPM as a preventative treatment are the additional costs of surgery,<sup>34</sup> and in patients who decided to undergo CPM, the majority elect to have bilateral reconstruction which is associated with increased morbidity.<sup>35</sup> Frost et al<sup>36</sup> reported that 27% of women had at least one unanticipated reoperation after CPM. Barton et al<sup>37</sup> and Crosby et al<sup>38</sup> reported that 27%–66% of women had at least one complication. This means that at least one-third of patients might not have experienced a surgical complication if they had not chosen CPM. Alternatively, several studies albeit retrospectively have shown overall high patient satisfaction with CPM and a low rate of regret among high risk women.<sup>36,39</sup> Whether these psychosocial outcomes can be generalized to women at low-to-moderate risk of CBC is an active area of investigation.

## Decision analysis models of CPM

Several decision analysis models have been conducted to determine life expectancy associated with CPM in comparison to surveillance alone. For high-risk groups, women with family history and/or *BRCA1/2* genetic mutation, prophylactic surgical procedures (eg, mastectomy) have been shown to be cost-effective when compared with surveillance in terms of life expectancy and QALYs.<sup>40–44</sup> Life years can be adjusted by utilities or a qualitative evaluation of preferences for specific health states. One QALY represents a year in perfect health, with zero representing death. A year in any other intermediate state (eg, life after breast cancer or surgical treatment) would be some fraction of a QALY. Recently, Zendejas et al<sup>45</sup> developed a Markov model to determine the survival, quality of life, and cost-effectiveness of CPM for patients with sporadic, early-stage breast cancers. CPM

was cost-effective compared with surveillance for patients younger than age 70. These results were sensitive to *BRCA 1/2* mutation status and the assumption that the utility weights for the disease-free state for CPM was equal to or greater than that of surveillance.

A study conducted by Roberts et al<sup>35</sup> also presented a cost-effectiveness analysis of CPM which incorporated risks due to reconstruction following ipsilateral and contralateral mastectomy. Their results showed a reduction in QALYs for CPM and were sensitive to the rate and methods of postmastectomy reconstruction and the cost of radiologic surveillance after unilateral mastectomy. The loss of QALYs may be due to the increased rates of complications associated with bilateral reconstruction. CPM was found to be cost saving for women younger than 50 years of age with sporadic, unilateral, early stage-breast cancer, but with reduced health benefits. Thus, CPM was not considered to be a cost-effective strategy for treatment.<sup>35</sup> However, the authors' conjectured that potential QALYs gained may be more for an ER-negative patient, who has limited adjuvant treatment options, in comparison to a patient with an ER-positive tumor.

Most recently, Portschy et al<sup>6</sup> presented a decision analysis using a Markov model to simulate survival outcomes after the decision to have or forgo CPM among patients with Stage I or II breast cancer without *BRCA* mutation. The absolute 20-year survival benefits from CPM were less than 1% among all age groups, ER status groups, and cancer stage patient groups with most gains seen for ER-negative patients who have a higher risk of developing CBC. In fact, the benefit of CPM was lower for patients with Stage II compared with Stage I breast cancer because of worse prognosis associated with the primary breast cancer.<sup>6</sup> The risk of distant metastatic disease from the index tumor outweighs the risk of CBC.<sup>31</sup>

## Nonsurgical options for contralateral breast cancer risk reduction

The primary goals of systemic therapy for women with early stage breast cancer are to reduce the risk of local, regional, and distant recurrence and to improve survival. For women with an ER-positive breast cancer, an additional benefit of endocrine therapy is the reduction in the risk of developing CBC. In the EBCTCG overview of randomized trials, tamoxifen use for 5 years substantially reduced the risk of CBC by 48% ( $P < 0.00001$ ) among women with ER-positive disease. This translated into a 3.2% absolute risk reduction of CBC over 15 years (6.5% versus 9.8%) and was independent of age at diagnosis.<sup>24</sup> These data demonstrated that a carry-over effect of CBC risk reduction persists up to 10 years after

the discontinuation of tamoxifen. The ATLAS (adjuvant tamoxifen: longer against shorter) study which randomized women with early breast cancer who had completed 5 years of tamoxifen to either continue tamoxifen to 10 years or to stop at 5 years, showed a 3.7% absolute reduction in the risk of recurrence during years 5–14.<sup>46</sup> Although the definition of the endpoint of recurrence included the development of CBC, the CBC event was not reported separately and therefore the benefit of extended tamoxifen use on CBC risk is unclear. In the adjuvant setting, the aromatase inhibitors have also been shown to lower the risk of local regional and distant recurrence, and CBC in women with ER-positive breast cancers when compared to tamoxifen.<sup>47</sup> In the 10-year analysis of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial, women randomized to receive anastrozole versus tamoxifen had a sustained statistically significant 32% reduction in CBC.<sup>48</sup> The absolute risk reduction of CBC for the anastrozole versus tamoxifen arms at 5 and 10 years of follow-up was 0.8% and 1.7% respectively. The extended adjuvant trial of letrozole versus placebo in women with early stage breast cancer who had completed 5 years of tamoxifen, estimated a statistically significant 42% reduction in the risk of CBC for those women receiving letrozole.<sup>49</sup> There appears to be no superiority of the steroidal (eg, anastrozole) versus nonsteroidal (eg, exemestane) class of aromatase inhibitors on CBC risk when given as initial adjuvant therapy.<sup>50</sup>

Observational studies have demonstrated a reduced incidence of breast cancer among healthy women receiving bisphosphonate therapy for the prevention and treatment of bone loss.<sup>51–53</sup> The Women's Health Initiative (WHI), showed that bisphosphonate use was associated with a 32% reduction ( $P < 0.01$ ) in the incidence of invasive breast cancer after adjusting for potential confounders such as hip fracture prediction score (surrogate for bone mineral density), menopausal hormone replacement therapy, and breast cancer risk factors.<sup>51</sup> Monsees et al<sup>54</sup> conducted a nested case-control study among women diagnosed with a first primary ER-positive invasive breast cancer and showed that use of any nitrogenous bisphosphonate was associated with a 59% reduction in risk of CBC and the risk further declined with longer duration of bisphosphonate use. However, there have been several randomized studies evaluating the role of bisphosphonates in the adjuvant setting for reducing risk of recurrence; however, none of the trials showing a positive benefit on breast cancer DFS have reported a reduction in the risk of CBC associated with bisphosphonate use.<sup>55–57</sup> Therefore, there is no indication for the use of bisphosphonate therapy for CBC risk reduction at this time.

## Limitations

Although several population-based studies have been conducted to estimate risks of CBC and the benefit of CPM, these observational studies are not without limitations. Risks of CBC have been largely estimated using North American and European (specifically, Swedish) databases and institutions with their inherent limitations. For instance, SEER does not contain information on adjuvant hormonal therapy or comorbidities and there is incomplete data on Her2/neu status. Thus, regardless of techniques used to minimize bias, it is difficult to account for known prognostic and therapeutic variables.<sup>30</sup> The National Cancer Database does not contain information regarding the development of CBC and it is not possible to estimate CBC incidence or breast cancer DFS.<sup>3</sup> Limitations of prior epidemiologic studies evaluating the clinical benefit of CPM have included small sample sizes, short-term follow-up, as well as the aforementioned incomplete information on tumor characteristics, systematic treatment, and comorbidities.<sup>30</sup> Finally, there is a diversity of information in the literature in terms of risks, rates, time period of measurement, and patient cohort of interest which can make interpretation of the data difficult for both clinicians and the general public.

## Conclusion

The decision to have CPM continues to increase in popularity among women with unilateral breast cancer who have a low-to-moderate risk of developing a secondary cancer in the contralateral breast. Since it is highly unlikely that a randomized trial will ever be conducted to evaluate the clinical benefit of CPM, decision models that incorporate survival differences for particular subgroups can provide realistic estimates of the benefits of CPM and identify patient groups most likely to benefit. In addition, efforts should be made by health care providers to optimize breast conservation, minimize unnecessary tests, and improve patient education about their risk of CBC and the surgical complications associated with CPM and reconstruction for informed patient-decision making.<sup>8,35</sup> Decision making tools that incorporate the results of CBC risk models and the effect of CPM and adjuvant endocrine therapy on CBC risk, DFS, and OS may be helpful in determining the best course of treatment for an individual patient.

## Acknowledgments

The financial support for this study was provided by Patient-Centered Outcomes Research Institute and National Cancer Institute grant R21 CA149803. The funding agreements

ensured the authors' independence in study design, data interpretation, and writing of the paper.

## Disclosure

The authors report no conflicts of interest in this work.

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