

# Bilateral Mastectomy for Unilateral Breast Cancer: a Perplexing Trend

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**Abstract** In the United States, there has been a trend towards the increased utilization of bilateral mastectomy for the treatment of unilateral breast cancer. Yet, breast conserving surgery rates have increased slightly, so it is among women choosing mastectomy that the use of bilateral mastectomy is increasing. Ironically, since about 1985, the risk of developing contralateral breast cancer has decreased, likely due to the widespread use of adjuvant systemic therapy for the treatment of early breast cancer. The increased utilization of bilateral mastectomy is therefore puzzling, and this article discusses factors that may account for this trend. Several observational studies have shown that bilateral mastectomy is associated with improved survival when compared to unilateral mastectomy. However, these associations are probably due to selection bias, and bilateral mastectomy is unlikely to have an independent effect in improving survival for the majority of women with unilateral breast cancer. Bilateral mastectomy might be indicated for women with a high risk of developing contralateral breast cancer, such as those with a history of mantle irradiation or mutations in the BRCA 1 or BRCA 2 genes, but it cannot be entirely justified in the majority of women with unilateral breast cancer.

**Keywords** Breast cancer · Contralateral prophylactic mastectomy · Bilateral mastectomy

The use of bilateral mastectomy for the treatment of unilateral breast cancer is increasing rapidly. In the United States, this

perplexing trend began in the late 1990s, was first reported in 2007, and has now been observed in other parts of the world as well [1–3]. Surprisingly, during this same period, the use of breast conserving surgery (lumpectomy) in the United States has slightly increased [4]. Thus, among women choosing mastectomy, there is a trend towards increased utilization of bilateral mastectomy rather than unilateral mastectomy. The surgical treatment of unilateral breast cancer is therefore becoming increasingly polarized; large numbers of women are choosing either lumpectomy or bilateral mastectomy, while the use of unilateral mastectomy is declining. The removal of the opposite uninvolved breast in women with unilateral breast cancer is often referred to as “contralateral prophylactic mastectomy (CPM)”. In this article, “CPM” will refer to bilateral mastectomy in women with unilateral breast cancer. This review discusses CPM, its implications, and possible underlying factors responsible for its increased utilization.

In 2007, Tuttle et al. reported that the overall rate of CPM in the United States increased from 1.8 % in 1998 to 4.5 % in 2003, based upon analysis of the Surveillance, Epidemiology, and End Results (SEER) database [1]. These investigators subsequently reported that the overall rate of CPM had also increased for women with ductal carcinoma in situ (DCIS), from 2.1 % in 1998 to 5.2 % in 2005 [5]. Yet, the overall rate of mastectomy in the United States decreased from 40.8 % in 2000 to 37 % in 2006 (when mastectomy rates for invasive breast cancers and DCIS were considered together), indicating that lumpectomy was still the preferred option [4]. Taken together, these results indicate that more women were choosing lumpectomy in the United States, but among those who chose mastectomy, CPM was increasingly becoming the preferred option.

Analysis of data from the California Tumor Registry shed additional light on this issue [6]. These data suggested that trends in the utilization of CPM are closely linked to age at

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the time of breast cancer diagnosis. In California, the overall rate of CPM increased from 2.0 % in 1998 to 12.3 % in 2011, about a 14.3 % annual increase during this period. However, this trend was most notable for women younger than 40 years of age at time of breast cancer diagnosis, who experienced an increase in CPM utilization from 3.6 % in 1998 to 33 % in 2011 (a nearly 10-fold increase over a 13-year period). Although CPM rates also increased in older women, the rate of increase was less pronounced, and diminished with increasing age. Moreover, the California registry indicated that White women, those with private insurance, and those who received care at a National Cancer Institute (NCI)-designated cancer center were more likely to choose CPM than other groups.

There are several possible reasons for the increased utilization of CPM. Women perhaps overestimate their risk of developing contralateral breast cancer. Indeed, that risk is now very low, as rates of contralateral breast cancer have declined by about 3.07 % per year since around the year 1985, when adjuvant systemic therapy was shown to be effective in the treatment of early breast cancer [7]. The use of adjuvant systemic therapy increased dramatically after the mid-1980s, resulting in a reduction in breast cancer mortality, ipsilateral recurrences, and incidence of contralateral breast cancer [8]. The annual risk of developing a contralateral breast cancer was about 0.5 % per year until 1985, but is now only 0.1 % per year [7]. Thus, it seems ironic that rates of CPM have dramatically increased during a period when contralateral breast cancer rates have dramatically decreased.

The wider acceptance of CPM might also be partly attributable to the better symmetry achieved with bilateral mastectomy and reconstruction versus unilateral mastectomy and reconstruction. Many women may perceive that CPM results in better cosmetic outcomes, and a recent analysis of the SEER dataset suggests that rates of mastectomy with immediate breast reconstruction are converging with rates of CPM [9]. Thus, women who choose immediate breast reconstruction are more likely to choose CPM. Yet, one might argue that improved breast symmetry can also be achieved with contralateral breast reduction, which also allows patients to maintain tactile sensation in the opposite breast, with better quality of life [10]. Plastic surgeons should present contralateral breast reduction as an option for achieving breast symmetry following unilateral mastectomy.

The increased utilization of CPM coincides with the wider use of testing for hereditary breast cancer. Approximately 10 % of all breast cancers are attributable to germline mutations, and about half of these are attributable to mutations in the BRCA 1 and BRCA 2 genes [11]. Other mutations that markedly increase breast cancer risk include those in the STK11 (Peutz-Jeghers syndrome), P53 (Li Fraumeni syndrome), PTEN (Cowden's syndrome), and CDH1 genes [11]. For patients with unilateral breast cancer who harbor these germline mutations, CPM is generally recommended.

Breast cancer patients with these mutations have a very high risk of developing contralateral breast cancer, a risk that is 3 or 4 times greater than that of the average risk patient with unilateral breast cancer. Thus, the wider use of genetic testing (and the subsequent identification of mutation carriers) may partly explain the wider use of CPM for the management of patients with unilateral early breast cancer.

In recent years, the routine use of pre-operative breast MRI for the management of primary breast cancer has generated considerable controversy [12]. However, its availability and increased utilization have likely contributed to the increased use of CPM. Pre-operative breast MRI is a far more sensitive test than traditional methods of pre-operative breast cancer evaluation (i.e., clinical breast examination, ultrasound, and mammography), and more likely to detect suspicious lesions in the ipsilateral or contralateral breast, prompting ipsilateral mastectomy and even CPM [12]. Breast MRI is associated with a greater risk of false-positives than mammography, and may also detect occult tumor foci that could have been adequately treated with systemic and/or therapy alone. Patients who undergo pre-operative breast MRI are twice more likely to undergo CPM than those who undergo standard pre-operative staging with clinical breast examination, ultrasound, and mammography [12]. Yet, it is highly unlikely that the more expansive surgery resulting from pre-operative breast MRI improves patient outcomes. The routine use of pre-operative breast MRI should therefore be discouraged, as it may result in unnecessary ipsilateral mastectomy or even CPM, when perhaps a more conservative surgical approach might have been optimal.

During the last 15 years, several observation studies have shown improved survival rates among women who undergo CPM versus unilateral mastectomy [6, 13–19]. These reports have likely influenced surgical decision-making, and may also partly account for the rapid increase in utilization of CPM. Yet, these observational studies may reflect the selection of a healthier cohort of women for CPM or women with better access to healthcare. Indeed, observational studies rely on datasets that often omit important covariates linked to breast cancer outcomes, such as a woman's health status (healthier women would be more likely to undergo CPM), and socioeconomic status (those from higher socioeconomic background may carry better healthcare insurance and therefore be preferentially selected for CPM). Thus, observational studies may produce biased estimates of the effect of CPM on breast cancer outcomes.

To further explore the association between CPM and improved breast cancer outcomes, and determine if this association is possibly attributable to selection bias, we examined associations between CPM and breast cancer-specific, all-cause, and non-cancer mortality utilizing multivariate logistic regression [20]. CPM would not be expected to reduce non-cancer mortality, and any association between CPM and

reduced non-cancer mortality would suggest that a healthier cohort of women were preferentially selected for CPM (selection bias). We utilized the 1998–2010 Surveillance Epidemiology and End Results (SEER) dataset. We identified 449,178 women with unilateral primary breast cancer in this dataset, and 25,961 of these (5.8 %) underwent CPM. When compared to unilateral surgical treatment of primary breast cancer, CPM was associated with a 16 % lower breast cancer-specific, 17 % lower all-cause, and 29 % lower non-cancer 5-year hazard of death. The stronger association between CPM and non-cancer 5-year hazard of death suggests that the reported association between CPM and improved survival might at least partly be attributable to selection bias.

The rapid increase in the utilization of CPM remains perplexing. There is no good evidence that CPM reduces breast cancer-specific or overall mortality. The reported associations between CPM and reductions in mortality appear to be at least partly attributable to selection bias. A randomized trial would be required to minimize the effect of selection bias and determine if CPM has an independent effect on mortality, but it is highly unlikely that such a trial will ever be undertaken. Moreover, the effect of CPM on quality of life is unclear, and additional studies are needed to address this issue. Although CPM may improve breast symmetry, breast reduction of the contralateral breast might be equally effective in this regard and also result in preservation of tactile sensation. CPM may, however, be justified in women who have a very high risk of developing contralateral breast cancer, such as women with the BRCA 1 or BRCA 2 mutation, or those with a history of mantle radiation [21]. Clearly, surgeons should provide women with unilateral breast cancer a balanced discussion of all local therapy options. The potential risks and benefits of CPM should be discussed, and women should be informed that its effect on mortality is uncertain. The trend towards increased utilization of CPM is not entirely justified, and will hopefully reverse in the near future.

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