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Contralateral Prophylactic Mastectomy is Associated with a Survival Advantage in High-Risk Women with a Personal History of Breast Cancer

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Abstract

Background—The aim of this study was to investigate whether contralateral prophylactic mastectomy (CPM) in addition to therapeutic mastectomy (TM) is associated with a survival advantage in high-risk women with breast cancer.

Methods—A total of 385 women with stage I or II breast cancer and a family history of breast cancer who underwent TM and CPM between 1971 and 1993 were evaluated and compared to 385 patients matched on age at diagnosis, tumor stage, nodal status, and year of diagnosis who underwent TM-only. Contralateral breast cancer (CBC) events and survival outcomes were compared.

Results—At a median follow-up of 17.3 years, 2 CBCs (0.5%) developed in the CPM cohort and 31 (8.1%) in the TM-only cohort, representing a 95% decreased risk of CBC (hazard ratio [HR] = 0.05, 95% confidence interval [95% CI] 0.01–0.22, $P < 0.0001$). One hundred twenty-eight women in the CPM group and 162 women in the TM-only group have died, resulting in 10-year overall survival estimates of 83 and 74%, respectively (HR 0.68, 95% CI 0.54–0.86, $P = 0.001$). This difference in overall survival persisted in multivariate analysis (HR 0.77, $P = 0.03$). Disease-free survival (DFS) was better in the CPM cohort than the TM-only group (HR 0.66, 95% CI 0.53–0.82, $P = 0.0002$) and remained significant in multivariate analysis (HR 0.67, $P = 0.0005$).

Conclusions—In this retrospective cohort study, CPM was associated with decreased CBC event and improved overall survival and disease free survival.

Women with breast cancer who undergo mastectomy increasingly opt for contralateral prophylactic mastectomy (CPM), with the rate more than doubling over the last decade both in invasive breast cancer and ductal carcinoma-in-situ.^{1,2} CPM decreases contralateral breast cancer (CBC) risk by 90–95% in women with a breast cancer family history and those with *BRCA1* or *BRCA2* mutations.^{3–7} Additionally, pathology of the CPM tissue, particularly in women younger than 40 years old, reveal high-risk histology in 3–57% of cases.^{8–12} The efficacy of CPM reducing CBC has garnered health care professional support of CPM as a viable option.¹³ Debate continues regarding whether CPM provides any survival advantage.

There are limited data for decreased mortality after CPM.¹⁴ Breast cancer-specific survival benefits were shown in one study and a trend shown in another study.^{5,6} Other small studies did not show breast cancer survival benefits associated with CPM in women with *BRCA1* mutations.^{15,16} Disease-free survival (DFS) benefits were found in one study.^{5,17} Most recently, a population-based study showed improved DFS and improved 5-year breast cancer-specific survival in young women with estrogen receptor (ER)-negative early-stage breast cancer.¹⁷ Breast cancer mortality studies, with the exception of the work of Peralta et al., are limited by mean follow-up of < 6 years.⁵

This study's aim was to investigate whether CPM is associated with improved survival in women with a family history of breast cancer undergoing therapeutic mastectomy (TM).

METHODS

Patient Cohorts

CPM Cohort—Women with a family history of breast cancer who underwent unilateral mastectomy for breast cancer (stages I or II) and prophylactic contralateral mastectomy were identified. Family history was defined as parent, sibling, or second-degree relative with breast cancer. All CPMs were performed at Mayo Clinic Rochester between 1971 and 1993. Patients were excluded if both tumor stage and number of positive nodes were unknown or if CPM occurred more than 2 years after breast cancer diagnosis. Cases with cancer found in the CPM were also excluded. The final cohort of 385 women had their therapeutic mastectomies at Mayo Clinic Rochester ($N = 302$) or another institution ($N = 83$).

TM-Only Cohort—A comparison cohort of 385 women who underwent TM for cancer at Mayo Clinic Rochester was identified. One control patient was matched to each CPM patient on the basis of age at breast cancer diagnosis, year of diagnosis, tumor stage (I or II), and nodal status (0, 1–2, or 3+ nodes positive). Matching also ensured that a control subject had event-free follow-up at least as long as the time to CPM in the patient to whom she was matched. These controls were identified from all TM patients in the Mayo Cancer Registry and selected on similarity of matching variables to that of the case. Matching was performed by statistical personnel without knowledge of patient outcomes and by computerized programs to implement mathematically optimal matching algorithms.¹⁸

Data Collection

Mayo Clinic institutional review board approval was obtained. Patients' medical records were reviewed and eligibility criteria verified. Data abstracted included family history of breast cancer, tumor size, lymph node status, oophorectomy, and adjuvant therapy. Follow-up information on subsequent breast cancer events and survival were collected from the Mayo Cancer Registry. For the CPM cohort, a study-specific questionnaire was used to collect data on cancers and surgeries performed elsewhere.³

Because of the time frame of the cohort, overall staging used American Joint Committee on Cancer staging, 5th edition. For the 20 women in the CPM cohort whose TM was performed elsewhere and tumor stage was unknown but nodal status was available, we assumed stage I if node negative and stage II if node positive.

Bilateral oophorectomy was considered prophylactic or for benign intent if performed for any cause other than malignancy. Patients who underwent hysterectomy elsewhere without comment regarding removal of the ovaries were coded as unknown.

If recurrence date was unknown ($n = 15$), the date was imputed as the midpoint between last noted disease-free date and date recurrence was reported.

Outcome Definitions

A CBC was defined as ductal carcinoma-in-situ or invasive breast cancer in the contralateral breast, chest wall, or axilla. We classified subsequent events as recurrences if they occurred on the ipsilateral chest wall or axilla, or if they were distant metastases. Because it was not possible to reliably distinguish second primary malignancies from some recurrences (e.g., extensive chest wall disease), we censored women for second primary disease at the time of diagnosis of distant disease.

Overall survival (OS) was measured in person-years of observation and defined as time from original breast cancer diagnosis until death from any cause or last follow-up in those alive. Similarly, DFS was defined as time from original breast cancer diagnosis until any of the following events: CBC, ipsilateral breast cancer recurrence, distant metastases, or death from any cause. Breast cancer-specific survival was defined as time from original breast cancer diagnosis to death or last follow-up, with those whose death was due to breast cancer treated as events and those who died of other causes or alive at last follow-up treated as censors.

Statistical Analyses

Cox proportional hazard regression was used to estimate the effect of CPM on each outcome. Because the CPM occurred up to 2 years after breast cancer diagnosis in the CPM cohort, it was modeled as a time-dependent covariate. Hazard ratios (HR) and 95% confidence intervals (95% CIs) were estimated. Multivariate survival models adjusted for age at diagnosis, tumor stage, nodal status, estrogen and progesterone status of the original cancer; first-degree family history; diagnosis year; oophorectomy; and adjuvant treatment. Oophorectomies may have occurred during follow-up; thus, this risk-reducing variable was also handled as a time-dependent covariate. Because the Kaplan–Meier method does not accommodate a time-dependent covariate, figures showing the outcomes in the CPM and TM-only groups were created by treating the CPM as if it occurred at time 0 for that cohort. The two groups were compared with respect to characteristics such as adjuvant treatment and family history by χ^2 tests. Analyses were performed by SAS, version 9.1.3 (SAS Institute, Cary, NC). *P* values of <0.05 were considered statistically significant.

RESULTS

The CPM group consisted of 385 women with breast cancer and a family history of breast cancer who underwent TM and CPM. A total of 163 women (42%) had prophylactic subcutaneous mastectomy, and 222 women (58%) a prophylactic total mastectomy. The TM-only cohort consisted of 385 patients matched for age at diagnosis, tumor stage, nodal status, and year of diagnosis who underwent TM-only without CPM. Characteristics of the two cohorts are summarized in Table 1. All of the CPM cohort had a family history of breast cancer, whereas only 35% of the TM-only group did (*P* < 0.0001). Similarly, there was a statistically significant difference in the proportion with a first-degree family history (46% CPM vs. 22% TM-only, *P* < 0.0001). No additional variables differed significantly between the two cohorts.

Follow-up

Median follow-up was 17.3 years overall (range, <1–38.8 years) and was similar in the two cohorts (CPM 18.0 years, TM-only 16.4 years).

CBC Events

A total of 33 CBC events were observed (Table 2). Median time from breast cancer diagnosis to CBC event was 7.2 years (range, 94 days–26 years). Two patients (0.5%) developed a CBC in the CPM cohort compared to 31 (8.1%) in the TM-only cohort, representing a 95% decreased risk of CBC (unadjusted HR = 0.05, 95% CI 0.01–0.22, $P < 0.0001$). This result remained strongly significant after adjusting for age, stage, nodal status, and first-degree family history (HR = 0.05, 95% CI 0.01–0.19, $P < 0.0001$).

Among the 33 women who developed CBC, 12 died during follow-up. The causes were breast cancer ($n = 5$), other causes ($n = 4$), and unknown ($n = 3$). Three patients developed distant recurrence after CBC but remained alive at last follow-up. Median tumor size of the second primary tumor was 1.3 cm (range, 0.3–3.5 cm) in the 27 patients with this information available. Nodal status was negative for 17, 1–2 positive for 6, 3+ positive for 2, and unknown for 8. Overall staging of the second primary tumor was stage 0 for 1 patient, stage 1 for 15 patients, and stage 2 for 11 patients; 8 (30%) of 27 had a higher stage for the second primary tumor than the index cancer.

OS

A total of 128 women in the CPM group and 162 women in the TM-only group have died, for 10-year OS estimates of 83 and 74%, respectively (Fig. 1a). The unadjusted HR associated with CPM vs. TM-only was 0.68 (95% CI 0.54–0.86, $P = 0.001$). This difference in OS persisted after multivariate analysis (HR 0.77, 95% CI 0.60–0.98, $P = 0.03$) (Table 3). Other variables significant in this multivariate model included age and tumor stage, as well as having more than two positive nodes versus negative nodes, and undergoing oophorectomy for a malignancy.

DFS

A total of 349 breast cancer events (148 CPM cohort, 201 TM-only cohort) were observed during follow-up. The first event was CBC in 31, local/regional recurrence in 78, distant recurrence in 136, death in 99, and recurrence of unknown type in 5. DFS difference between the two cohorts was statistically significant (Fig. 1b), with an unadjusted HR of 0.66 (95% CI 0.53–0.82, $P = 0.0002$) that remained significant in a multivariate model (HR 0.67, 95% CI 0.54–0.84, $P = 0.0005$). Other variables noted as significant for OS were also significant for DFS.

Breast Cancer-Specific Survival

Data on breast cancer-specific survival were limited as a result of the retrospective nature of this study. The cause of death was unknown for 23 (18%) of 128 deaths in the CPM cohort and 49 (30%) of 162 deaths in the TM-only cohort ($P = 0.02$). Despite this ascertainment bias and the general challenge of reliably identifying cause of death from medical records, in an analysis excluding patients with unknown cause of death, we found an unadjusted HR of 0.75 (95% CI 0.55–1.02, $P = 0.07$). This apparent benefit was attenuated after multivariate adjustment (HR = 0.82, 95% CI 0.59–1.14, $P = 0.24$).

Impact of CBC on Survival

We further evaluated the apparent survival benefit associated with CPM. We noted that the TM-only group had not only more CBC events, but also more recurrences overall, specifically distant recurrences (Table 2). There were 82 distant recurrences and 162 deaths in the TM-only cohort compared to only 60 distant recurrences and 128 deaths in the CPM cohort, despite tumor stage and nodal status being identically distributed within the two cohorts. This higher rate of distant recurrence and death is not accounted for solely by the

higher rate of CBCs. Only seven patients with a CBC event from the TM-only cohort developed distant disease and/or died of breast cancer. Even if we assume the three patients with CBC and unknown cause of death died of breast cancer, there were still 26 more deaths and 13 more distant recurrences in the TM-only cohort compared to the CPM group. When assessed in the TM-only cohort, development of a CBC modestly increased the risk of death, but not in a statistically significant manner (HR = 1.3, 95% CI 0.7–2.2, $P = 0.38$).

Subgroup Analysis

We examined the effect of CPM in the age groups <50 vs. ≥50 years at diagnosis. There was no statistically significant interaction between age group and CPM for any of the outcomes. The adjusted OS HRs for CPM vs. TM-only were 0.78 and 0.71, respectively, in women aged <50 and those aged ≥50.

Similarly, we tested interactions between overall stage and CPM and between ER status and CPM and found them to be nonsignificant for each outcome. The adjusted OS HRs for CPM vs. TM-only were 0.73 and 0.79 in patients with stage I and II disease, respectively. They were 0.79 and 0.89 for ER-negative and -positive patients, respectively.

DISCUSSION

We report long-term survival data on 385 women with stage I or II breast cancer and a family history of breast cancer who underwent TM and CPM and a comparison cohort of 385 patients matched by age at diagnosis, tumor stage, nodal status, and year of diagnosis who underwent TM-only. This study shows that CPM patients had statistically lower incidence of CBC, improved OS and DFS compared to those undergoing TM-only. This study provides longer follow-up than all other studies evaluating CPM outcomes and has the advantage that groups are matched on breast cancer prognostic variables.

The reduction in CBC after CPM, improved OS and DFS, and trend toward disease-specific survival are consistent with previously reported data.^{3–7} Herrinton et al.⁶ published a retrospective study that used data from four health maintenance organizations comparing 908 women undergoing CPM to 46,368 women without CPM and found CPM to be associated with improved death rates from breast cancer and all-cause mortality. Peralta et al.⁵ showed a trend toward breast cancer-specific survival and statistically significant OS and DFS in a cohort of 64 women who underwent CPM compared to 182 matched patients. A recent population-based study that used the Surveillance, Epidemiology, and End Results (SEER) database with 47-month follow-up demonstrated improved DFS and a small improvement in 5-year breast cancer-specific survival mainly in young women with ER-negative breast cancer.¹⁷ In contrast to our study, it did not include family history data but showed that the benefit from CPM was mainly in younger women and in ER-negative disease. In our patients, no interaction between survival benefit from CPM and ER status or age was seen. This may be due to the difference in follow-up time; the ER-positive patients in the SEER study are less likely to have breast cancer events in the short 5-year follow-up time frame. Also, our study is limited in the ability to detect differences in ER subgroups as a result of the smaller sample size. The importance of ER status requires further attention because both our study and the SEER study had multiple patients with unknown ER status (35 and 25%, respectively).

An additional potential CPM benefit is the identification of incidental cancers. In our previous CPM report, we noted four incidental cancers within CPM in 745 women.³ These were excluded from our current study. Other authors have reported incidental cancers in CPM specimens with an incidence of 2.8–5.0%.^{5,6,11,12,19} Detection of these occult malignancies would have been delayed without CPM.

The CPM group had a higher proportion of women with a family history of breast cancer and with a first-degree family history. This should bias results toward fewer CBC events in the TM-only group because family history conveys a greater risk of a second primary tumor.^{20,21} Nevertheless, a statistically significant reduction in CBC events was still seen in the CPM group. Thus, our observed effects may be underestimates.

In addition to CPM, OS in multivariate analysis was influenced by age, disease stage, and the presence of more than two positive nodes at diagnosis. These data are consistent with the prognostic value of breast cancer stage and nodal status at time of diagnosis and of recurrence after the initial diagnosis. Although CPM reduces the risk of a new primary breast cancer, the risk of metastasis to other locations from the original breast cancer is not reduced by the CPM. Therefore, it is not surprising that CPM is less effective at preventing breast cancer mortality than preventing CBC.

Quan et al.²², examining survival of 346 women after a CBC, found that CBCs are often detected at a lower stage than the initial cancer and that the impact of a subsequent lower-stage cancer on mortality is negligible. However, if the first cancer was of a low stage, then the impact of a second primary tumor on survival was additive, even with low-stage cancers. The stage of the second cancer in the current study was lower than the index cancer in 70% of the cases. A second primary breast cancer in the TM-only group, although not statistically significant, did modestly increase the risk of death when compared to the women in the TM-only group without a second primary tumor. Thus, in our study, although the primary cancer was the main contributor to survival, the second primary cancer also contributed to survival, although to a lesser degree.

This study demonstrates an association between CPM and survival benefit, although the underlying cause cannot be fully elucidated. This study has limitations associated with its retrospective nature. The decisions that led to the patient choosing CPM and the comorbidities are unknown, leaving the study open to selection bias and the possibility that comorbidities or overall prognosis account for some of the differences in patient outcomes. We tried to control for these factors by matching by age and stage; however, short of a randomized, controlled study, there remains a potential for selection bias on the part of the patient, surgeon, or both.

CPM is associated with potential disadvantages. The current study group is composed of a subgroup of patients from a previously established cohort, and the surgical complications and satisfaction of CPM from the larger group have been reported.²³ Overall, 27% of the group had at least one unanticipated reoperation associated with CPM, most implant related.²³ Reoperations were fairly uncommon without reconstruction (4% of the group).²⁴ Overall, most women (83%) were satisfied with their CPM. Decreased satisfaction with CPM was associated with decreased satisfaction with appearance, complications with reconstruction, reconstruction after CPM, and increased level of stress in life.²⁴

Women in this cohort had their CPM between 1971 and 1993. Since that time, women have increasingly been treated with adjuvant therapies for early-stage breast cancers. Both chemotherapy and hormone therapy have been shown to decrease the incidence of second primary tumors. However, the length of time chemotherapy provides protection is unknown, but it is not likely to be long term, and the effect of tamoxifen diminishes after 10 years.²⁵ These factors may decrease the incidence of CBC for the first 10 years of follow-up, making it more important for long-term follow-up studies when survival is the outcome of interest.

In conclusion, CPM greatly decreases the risk of CBC events. Additionally, this study shows an association between CPM and improved OS and DFS and a trend toward improved breast cancer-specific survival. Further research to elucidate which patients benefit the most from

prophylactic mastectomy and whether this is a true cause and effect or simply an association due to unmeasured factors is needed.

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FIG. 1. Kaplan–Meier curves showing overall survival (**a**) and DFS (**b**) in the CPM and TM-only cohorts

TABLE 1

Descriptive characteristics of the patient cohorts

Variable	Levels	CPM cohort (N = 385), n (%)	TM-only cohort (N = 385), n (%)	P
Age at diagnosis (years)	20–29	25 (6.5)	12 (3.1)	0.42
	30–39	71 (18.4)	70 (18.2)	
	40–49	129 (33.5)	134 (34.8)	
	50–59	90 (23.4)	96 (24.9)	
	60–69	57 (14.8)	60 (15.6)	
	70+	13 (3.4)	13 (3.4)	
Year of diagnosis	1970–1974	17 (4.4)	19 (4.9)	0.92
	1975–1979	43 (11.2)	36 (9.4)	
	1980–1984	104 (27.0)	103 (26.8)	
	1985–1989	122 (31.7)	129 (33.5)	
	1990–1994	99 (25.7)	98 (25.5)	
Tumor stage ^a	I	207 (53.8)	207 (53.8)	1.0
	II	178 (46.2)	178 (46.2)	
No. of positive nodes	0	301 (78.2)	301 (78.2)	1.0
	1–2	55 (14.3)	55 (14.3)	
	3+	29 (7.5)	29 (7.5)	
Radiotherapy	No	374 (97.1)	372 (96.6)	0.68
	Yes	11 (2.9)	13 (3.4)	
Chemotherapy	No	318 (82.6)	322 (83.6)	0.70
	Yes	67 (17.4)	63 (16.4)	
Tamoxifen	No	299 (77.7)	301 (78.2)	0.86
	Yes	86 (22.3)	84 (21.8)	
Bilateral oophorectomy	No	293 (76.1)	293 (76.1)	0.60
	Before diagnosis	30 (7.8)	34 (8.8)	
	During follow-up	44 (11.4)	35 (9.1)	
	Unknown	18 (4.7)	23 (6.0)	
Any family history	No	0	251 (65.2)	< 0.0001
	Yes	385 (100)	134 (34.8)	
First-degree family history	No	207 (53.8)	302 (78.4)	< 0.0001
	Yes	178 (46.2)	83 (21.6)	

^aDisease of women with unknown stage were coded as stage I if nodes were negative and stage II if nodes were positive

CPM contralateral prophylactic mastectomy; TM therapeutic mastectomy

TABLE 2

Number of events observed during follow-up

Event	Overall (N = 770)	CPM cohort (N = 385)	TM-only cohort (N = 385)
Contralateral breast cancer	33	2	31
Breast cancer recurrence	227	104	123
Local/regional ^a	79	42	37
Distant ^a	142	60	82
Unknown type	6	2	4
Death	290	128	162
Breast-cancer death	163	77	86
Other cause death	55	28	27
Unknown cause of death	72	23	49
Any breast cancer event or death	349	148	201

^aData collection only included first recurrence, so data from patients with locoregional recurrence who may have gone on to experience distant disease recurrence would only be counted as locoregional recurrence

CPM contralateral prophylactic mastectomy; TM therapeutic mastectomy

TABLE 3

Multivariate analysis results for the outcome of overall survival and DFS

Variable	Overall survival		Disease-free survival	
	Hazard ratio (95% CI)	P	Hazard ratio (95% CI)	P
Contralateral prophylactic mastectomy vs. therapeutic mastectomy only	0.77 (0.60, 0.98)	0.03	0.67 (0.54, 0.84)	0.0005
Age, per year	1.03 (1.02, 1.04)	<0.0001	1.02 (1.01, 1.03)	0.0005
Tumor stage 2 vs. 1	1.53 (1.13, 2.06)	0.006	1.50 (1.15, 1.96)	0.003
Positive nodes				
1–2 vs. 0	0.93 (0.59, 1.46)	0.75	0.96 (0.65, 1.43)	0.84
3+ vs. 0	2.54 (1.55, 4.17)	0.0002	2.47 (1.59, 3.85)	<0.0001
Diagnosis year, per calendar year	0.98 (0.95, 1.01)	0.17	0.97 (0.94, 0.99)	0.007
Radiotherapy	1.15 (0.63, 2.10)	0.65	1.26 (0.71, 2.23)	0.44
Chemotherapy	0.85 (0.53, 1.37)	0.50	0.96 (0.64, 1.46)	0.86
Tamoxifen	1.17 (0.76, 1.79)	0.48	1.40 (0.94, 2.08)	0.10
Estrogen receptor				
Positive vs. negative	0.84 (0.52, 1.34)	0.46	1.03 (0.68, 1.58)	0.88
Unknown vs. negative	0.58 (0.35, 0.98)	0.04	0.69 (0.44, 1.09)	0.11
Progesterone receptor				
Positive vs. negative	0.80 (0.48, 1.34)	0.39	0.93 (0.58, 1.50)	0.78
Unknown vs. negative	0.96 (0.58, 1.60)	0.89	1.19 (0.74, 1.92)	0.48
First-degree family history	1.01 (0.79, 1.30)	0.93	0.97 (0.77, 1.21)	0.76
Oophorectomy				
Yes for prophylactic/benign causes vs. no	1.05 (0.73, 1.51)	0.81	0.84 (0.60, 1.17)	0.30
Yes, malignancy treatment, vs. no	3.87 (2.34, 6.40)	<0.0001	2.62 (1.63, 4.23)	<0.0001
Unknown vs. no	1.15 (0.76, 1.72)	0.51	0.93 (0.64, 1.34)	0.69

95% CI 95% confidence interval