RESEARCH ARTICLE

# Improved Long-term Survival with Contralateral Prophylactic Mastectomy among Young Women

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## Abstract

**Background: Despite mixed survival data, the utilization of contralateral prophylactic mastectomy (CPM) for the prevention of a contralateral breast cancer (CBC) has increased significantly over the last 15 years, especially among women less than 40. We set out to look at our own experience with CPM, focusing on outcomes in women less than 40, the sub-population with the highest cumulative lifetime risk of developing CBC. With an extended follow-up, we hoped to demonstrate differences in the long-term disease free survival (DFS) and overall survival (OS) among groups who underwent the procedure (CPM) versus those that did not (NCPM). Materials and Methods: We performed a retrospective review of all breast cancer patients less than age 40 diagnosed at Mount Sinai Medical Center between January 1, 1980 and December 31, 2010 (n=481). Among these patients, 42 were identified as having undergone CPM, while 195 were confirmed as being CPM-free during the observation period. A univariate and multivariate analyses were performed. Results: The CPM group had a significantly higher percentage of patients who were diagnosed between 2000 and 2010 (95.2% *vs* 40%, p=0.0001). The CPM group had significantly smaller tumors (0-2cm.: 41.7% *vs* 24.8%, p=0.04). Among the entire group of patients, the overall five- and 10-year DFS were 81.3% and 73.3%, respectively. CPM was significantly associated [HR 2.35 (1.02, 5.41); p=0.046] with 10-year OS, although a similar effect was not observed for five-year OS. Conclusions: We found that CPM has increased dramatically over the last 15 years, especially among white women with locally advanced disease. In patients less than 40, who are thought to be at greatest cumulative risk of secondary breast cancer, CPM provided an OS advantage, regardless of genetics, tumor or patient characteristics, and which was only seen after 10 years of follow-up.**

**Keywords:** Contralateral prophylactic mastectomy - contralateral breast cancer - young women breast cancer

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## Introduction

With an estimated 226,870 diagnoses and 39,510 deaths in 2012, breast cancer remains the most commonly occurring and second most lethal cancer among women in the United States (Howlader et al., 2011). Among those with breast cancer, patients aged less than 40 remain a particular challenge due, in part, to the inherent biologic aggressiveness of their tumors. Young women have tumors that are more likely to be high-grade histopathologically; have a higher mitotic rate with lymphovascular invasion (LVI); have more pathologic LNs; and are more likely to be hormone receptor (HR) negative/HER2 negative ("triple negative"; Colleoni et al., 2002; Carey et al., 2006; Anders et al., 2008, Kurian et al., 2009; Lund et al., 2009; Telli et al., 2011; Ademuyiwa et al., 2013; de la Rochefordiere et al., 2013). Moreover, the patients are more likely to be black, have a family history of breast cancer, and have less favorable outcomes (Adami et al., 1986; Chung et al., 1996; Althuis et al., 2003; Shavers et al., 2003).

Despite mixed survival data (Peralta et al., 2000; Bedrosian et al., 2010; Boughey et al., 2010; Narod et al., 2011; Zendejas et al., 2011), the utilization of CPM for the prevention of CBC increased significantly over the past 15 years, especially among young women (Jones et al., 2009; Katipamula et al., 2009; McLaughlin et al., 2009; Tuttle et al., 2007; 2009). In response to rising rates, the Society of Surgical Oncology (SSO) updated their position statement in 2007 and emphasized that indications for CPM should only include any of the following: *i*) BRCA mutations or other genetic susceptibility genes; *ii*) strong family history with no demonstrable mutation; and *iii*) histologic risk factors (Position Statement, 2013). However, recent evidence suggests that many patients who receive CPM don't necessarily fall into these high-risk categories (Khan et al., 2011, King et al., 2011; Katz et al., 2013).

In this retrospective, single-institution study, we

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set out to look at our own experience with CPM, in particular those women less than 40, who are at greatest cumulative lifetime risk of developing CBC. We hoped to document the prevalence of CPM within our ethnically and socioeconomically diverse community, and ultimately isolate the specific factors that were associated with its increasing prevalence. With an extended follow-up, we hoped to show differences in the long-term DFS and breast cancer specific OS among patients who underwent the procedure (CPM) versus those that did not (NCPM). We hypothesized CPM would improved long term outcomes, especially among the "high risk" patients.

## Materials and Methods

We performed a retrospective review of all breast cancer patients less than age 40 diagnosed at Mount Sinai Medical Center between January 1, 1980 and December 31, 2010 (n=480), with a date of last follow up of April 30, 2013. Among these patients were identified as having undergone CPM (n=42) or NCPM (n=195). The minimum and maximum follow-up times were one month, and 383 months, respectively. The median follow-up time was 93 months. Patients who were male, lost to follow-up, and/or had a history of de-novo metastases, secondary cancers, bilateral breast cancers, and one-time consults, were excluded from the study. Descriptive statistics were used to characterize the demographic and prognostic characteristics of the cohort. Results are presented as means and standard deviations for continuous variables and as frequencies and percentages for categorical variables. T-tests and chi-squared tests were used to identify differences between sub-groups.

The study was comprised of two parts: the univariate and the multivariate analyses. In the univariate section, the studied factors were analyzed through the time-to-event endpoints. Breast cancer specific OS was defined as the date of diagnosis to the date of breast cancer specific OS or date of last follow-up. DFS was defined as the date of diagnosis to the date of local or distant recurrence or date of last follow-up. For both endpoints, the median and 5- and 10-years survival rates were estimated for all variables (i.e., adjuvant treatment types, race, ethnicity, age at diagnosis, year at diagnosis, pathologic subtype, tumor size, number of metastatic nodes, histologic grade, hormone receptor status, HER2-neu status, etc.). The survival rates were estimated using the Kaplan Meier method and the survivorships were compared using nonparametric survival comparisons. The simple Cox proportional hazards models were also used to estimate the crude hazard ratios (HR) along with their corresponding 95% confidence intervals and the Wald test for significance.

The multivariate section consisted in the analysis of all prognostic factors significant at 0.05 level in the univariate analysis. We used a multiple Cox proportional hazards regression model to evaluate the relationship between CPM and DFS and OS. For this purpose, were the estimated hazard ratios were considered significant at the level of 0.10. Because the large majority (95.2%) of patients (95.2%) had undergone the CPM procedure during the most recent decade (2000-2010), only patients diagnosed during this time were included in the final multivariate model.

## Results

Of the 237 patients in our study, the median age at diagnosis was 35. Most patients were white (74.2%), non-Hispanic (68.7%), and diagnosed between 2000-2010 (49.8%; Table 1). Tumors were most often IDC (92.2%), with high-grade histology (60.4%), 2-5 cm in size (50.3%), ER positive (61.0%), HER2 negative (72.3%), and had no involved pathologic LN (54.9%). Most patients received adjuvant chemotherapy (67.6%) and radiation (67.6%), and only a small minority received CPM (17.7%). Of the 295 patients in our study, there were 66 recurrences (27.8%) and 56 deaths (23.6%).

The median age at diagnosis was 35 and 36 in the CPM and NCPM groups, respectively (Table 2). The CPM

**Table 1. Descriptive Numbers and Frequencies of a Group of 237 Patients <40 Years Old Diagnosed at MSMC From 1990-2007**

| Characteristic | | No. (%) |
|---|---|---|
| Race | White | 173 (74.2) |
| | Black | 60 (25.8) |
| | Unknown | 4 |
| Ethnicity | Non-Hispanic | 158 (68.7) |
| | Hispanic | 72 (31.3) |
| | Unknown | 7 |
| Timeframe of Diagnosis | 1980-1989 | 38 (16.0) |
| | 1990-1999 | 81 (34.2) |
| | 2000-2009 | 118 (49.8) |
| Morphology | Infiltrating Ductal | 165 (92.2) |
| | Lobular | 14 (7.8) |
| | Unknown | 58 |
| Histologic Grade | Low | 5 (5.2) |
| | Intermediate | 33 (34.4) |
| | High | 58 (60.4) |
| | Unknown | 141 |
| Size | 0-2 | 54 (28.0) |
| | 2-5 | 97 (50.3) |
| | >5 | 42 (21.8) |
| | Unknown | 44 |
| Involved LN | 0 | 113 (54.9) |
| | 1-3 | 50 (24.3) |
| | >4 | 43 (20.9) |
| | Unknown | 31 |
| ER | Positive | 75 (61.0) |
| | Negative | 48 (39.0) |
| | Unknown | 114 |
| HER2 | Positive | 18 (27.7) |
| | Negative | 47 (72.3) |
| | Unknown | 172 |
| ER/HER2 | ER+/HER2+ | 9 (14.1) |
| | ER+/HER2- | 29 (45.3) |
| | ER-/HER2+ | 9 (14.1) |
| | ER-/HER2- | 17 (26.6) |
| Surgery | CPM | 42 (17.7) |
| | No-CPM | 195 (82.3) |
| Radiation | Yes | 161 (67.6) |
| | No | 76 (32.1) |
| Chemotherapy | Yes | 161 (67.6) |
| (no targeted agents) | No | 76 (32.1) |
| Recur | Yes | 66 (27.8) |
| | No | 171 (72.2) |
| Status | Alive | 181 (76.4) |
| | Dead | 56 (23.6) |

**Table 2. Differences in Characteristics among Patients in the CPM Group Versus Those in the NCPM Group**

| Characteristic | | NCPM (n=195) No. (%) | CPM (n=42) No. (%) | p value* |
|---|---|---|---|---|
| Race | White | 35 (85.4) | 138 (71.9) | 0.07 |
| | Black | 6 (14.6) | 54 (28.1) | |
| | Unknown | 1 | 3 | |
| Ethnicity | | | | |
| | Non-Hispanic | 30 (71.4) | 128 (68.1) | 0.67 |
| | Hispanic | 12 (28.6) | 60 (31.9) | |
| | Unknown | | 7 | |
| Timeframe of Diagnosis | | | | |
| | 1980-1989 | 2 (4.8) | 36 (18.5) | 0.03 |
| | 1990-1999 | 0 (0) | 81 (41.5) | 0.0001 |
| | 2000-2009 | 40 (95.2) | 78 (40.0) | 0.0001 |
| Morphology | | | | |
| | Infiltrating Ductal | 31 (93.9) | 134 (91.8) | 0.68 |
| | Lobular | 2 (6.1) | 12 (8.2) | |
| | Unknown | 9 | 49 | |
| Histologic grade | | | | |
| | Low | 1 (3.8) | 4 (5.7) | 0.71 |
| | Intermediate | 10 (38.5) | 23 (32.9) | 0.61 |
| | High | 15 (57.7) | 43 (61.4) | 0.74 |
| | Unknown | 16 | 125 | |
| Size | 0-2 | 15 (41.7) | 39 (24.8) | 0.04 |
| | 2-5 | 19 (52.8) | 78 (49.7) | 0.74 |
| | >5 | 2 (5.6) | 40 (25.5) | 0.009 |
| | Unknown | 6 | 38 | |
| Involved LN | | | | |
| | 0 | 18 (45.0) | 95 (57.2) | 0.16 |
| | 1-3 | 10 (25.0) | 40 (24.1) | 0.9 |
| | >4 | 12 (30.0) | 31 (18.7) | 0.11 |
| | Unknown | 2 | 29 | |
| ER | Positive | 23 (63.9) | 52 (59.8) | |
| | Negative | 13 (36.1) | 35 (40.2) | 0.67 |
| | Unknown | 6 | 108 | |
| HER2 | Positive | 8 (30.8) | 10 (25.6) | |
| | Negative | 18 (69.2) | 29 (74.4) | 0.65 |
| | Unknown | 16 | 156 | |
| ER/HER2 | | | | |
| | ER+/HER2+ | 4 (12.9) | 5 (15.2) | 0.8 |
| | ER+/HER2- | 11 (35.5) | 18 (54.5) | 0.13 |
| | ER-/HER2+ | 5 (16.1) | 4 (12.1) | 0.64 |
| | ER-/HER2- | 11 (35.5) | 6 (18.2) | 0.12 |
| Radiation | | | | |
| | Yes | 10 (23.8) | 60 (30.8) | |
| | No | 32 (76.2) | 135 (69.2) | 0.37 |
| Chemotherapy (no targeted agents) | | | | |
| | Yes | 32 (76.2) | 129 (66.2) | 0.21 |
| | No | 10 (23.8) | 66 (33.8) | |
| Recur | Yes | 6 (14.3) | 60 (30.8) | 0.03 |
| | No | 36 (85.7) | 135 (69.2) | |
| Status | Alive | 37 (88.1) | 144 (73.8) | 0.05 |
| | Dead | 5 (11.9) | 51 (26.2) | |

*Chi-square test of independence

**Table 3. Reasons for CPM among a Group of Patients <40 Years Old Diagnosed at MSMC From 1990-2007**

| Reasons for CPM | Number (%) |
|---|---|
| BRCA Positive | 15.8 |
| Multicentric Disease | 15.8 |
| Contralateral abnormality on MRI | 2.6 |
| Unknown | 65.8 |

**Table 4. The Five and Ten-year DFS and OS among a Group of 237 Patients <40 Years Old Diagnosed at MSMC From 1990-2007**

| Characteristic | DFS | | | OS | | |
|---|---|---|---|---|---|---|
| | 5 yr (%) | 10 yr (%)** | p value | 5 yr (%) | 10 yr (%)** | p value |
| Overall | 81.3 | 73.3 | | 86.1 | 77.6 | |
| Race | | | | | | |
| White | 82.4 | 74.5 | 0.72 | 90.3 | 79.4 | 0.024 |
| Black | 76.7 | 71 | | 75.2 | 75.2 | |
| Ethnicity | | | | | | |
| Non-Hispanic | 83.1 | 77.8 | 0.11 | 88.3 | 82.9 | 0.73 |
| Hispanic | 78.7 | 66.9 | | 87.5 | 73.3 | |
| Timeframe of diagnosis | | | | | | |
| 1980-1989 | 70.4 | 63.3 | 0.17 | 80 | 70.6 | 0.28 |
| 1990-1999 | 75.2 | 71.1 | | 84.6 | 75.3 | |
| 2000-2009 | 89.4 | 73 | | 89.4 | 81.6 | |
| Morphology | | | | | | |
| Infiltrating ductal | 74.8 | 66 | 0.27 | 83.3 | 74.2 | 0.17 |
| Lobular | 100 | 91.7 | | 92.9 | 85.1 | |
| Histologic Grade | | | | | | |
| Low | 100 | 100 | 0.22 | 100 | 100 | 0.49 |
| Intermediate | 87.2 | 70.9 | | 96.2 | 72.2 | |
| High | 83.1 | 63.1 | | 89 | 80.6 | |
| Size | | | | | | |
| 0-2 | 87.9 | 78.5 | 0.33 | 95.6 | 80.7 | 0.49 |
| 2-5 | 83.9 | 74 | | 88.7 | 80.1 | |
| >5 | 71.5 | 65.6 | | 79.4 | 73 | |
| Involved LN | | | | | | |
| 0 | 90 | 85 | 0.003 | 95.1 | 90.1 | 0.016 |
| 1-3 | 85.9 | 72.3 | | 84 | 70.7 | |
| >4 | 73.1 | 56.4 | | 79.7 | 66.7 | |
| ER | | | | | | |
| Positive | 85.2 | 72.5 | 0.27 | 95.6 | 78.6 | 0.63 |
| Negative | 88.6 | 81 | | 90.5 | 87 | |
| HER2 | | | | | | |
| Positive | 81.7 | 71.5 | 0.03 | 94.1 | 66.5 | 0.13 |
| Negative | 97.4 | 92.3 | | 94.5 | 90.6 | |
| ER/HER2 | | | | | | |
| ER+/HER2+ | 76.2 | 50.8 | 0.06 | 100 | 41.7 | 0.15 |
| ER+/HER2- | 96 | 96 | | 91.4 | 84.9 | |
| ER-/HER2+ | 88.9 | 88.9 | | 87.5 | 87.5 | |
| ER-/HER2- | 87.5 | 87.5 | | 100 | 100 | |
| Surgery | | | | | | |
| CPM | 89.4 | 79.8 | 0.21 | 91.4 | 79.4 | 0.28 |
| No-CPM | 79.5 | 72 | | 85 | 76.8 | |
| Radiation | | | | | | |
| Yes | 82.3 | 69.8 | 0.66 | 80.1 | 69.7 | 0.09 |
| No | 81 | 74.8 | | 88.7 | 81 | |
| Chemotherapy (no targeted agents) | | | | | | |
| Yes | 80.3 | 69.9 | 0.16 | 84.9 | 76.7 | 0.98 |
| No | 83.6 | 81.6 | | 83.7 | 80 | |

*Kaplan Meier method and the nonparametric survival comparison; **Estimated

group had a greater percentage of white patients (83.3% *vs* 70.8%, p=0.07), but there were a near equal percentage of Hispanic patients. The CPM group had a significantly larger percentage of patients diagnosed between 2000-2010 (95.2% *vs* 40%, p=0.0001). Both groups had an equal percentage of patients with IDC, high-grade histology tumors, ER or HER2 positive tumors, and those with pathologically involved lymph nodes. The CPM group had significantly smaller tumors (0-2cm: 41.7% *vs* 24.8%, p=0.04). With a median follow up of 68 and 101 months,

respectively, the patients in the CPM group had fewer recurrences (14.3% *vs* 30.8%, p=0.03) and fewer deaths (11.9% *vs* 26.2%, p=0.05). Reasons for CPM included unknown (65.8%), BRCA mutation (15.8%), multicentric disease (13.2%), and contralateral abnormality on MRI (2.6%; Table 3).

The overall 5 and 10-year DFS was 81.3% and 73.3%, respectively (Table 4 and Figure 1). Meanwhile, the 5 and 10-year breast-cancer specific OS was 86.1% and 77.6%, respectively. There were no significant differences in DFS or OS among patients based on ethnicity, timeframe of diagnosis, morphology, histological grade, ER status, or radiation/chemotherapy received. Black patients had a significantly worse 10-year OS compared with white patients, that remained in our multivariate model (HR 2.83 (1.04, 7.71); p=0.024). Although not significant in our univariate analysis (Figure 2), in our final model (Table 5), there was a significant improvement in 10-year OS among patients based on the utilization of CPM (HR 2.35 (1.02, 5.41); p=0.046). Patients with tumors greater than 5cm. had a significantly worse 10-year DFS (HR 0.19 (0.05, 0.73); p=0.015) and OS (HR 0.17 (0.04, 0.65); p=0.01) compared with patients with smaller tumors. In our final model, patients with HER2 negative tumors had a significant better 10-year OS compared to those with HER2 positive tumors (HR 2.34 (1.05, 5.20); p=0.037).

In a subgroup analysis of the patients based on race (Table VII), white patients had smaller tumors (0-2: 31.7 *vs* 17.6%; p=0.056), fewer involved lymph nodes (>/=4: 17.8 *vs* 29.4%; p =0.03), more tumors that were ER+, HER2+ (50.0 *vs* 25%; p=0.04), a greater percentage of tumors that lobular morphology (10.2 *vs* 2.0; p=0.07), and were less likely to receive adjuvant radiation (20.8 *vs* 51.7%; p<0.0001).

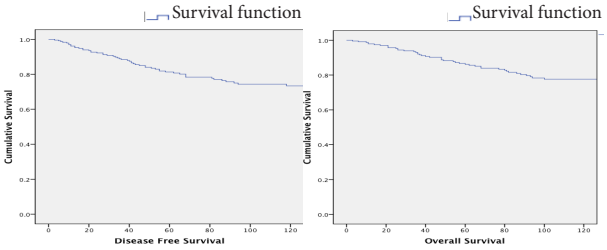


**Figure 1. The DFS and OS of a Group of Patients <40 Years Old Diagnosed at MSMC From 1990-2010**

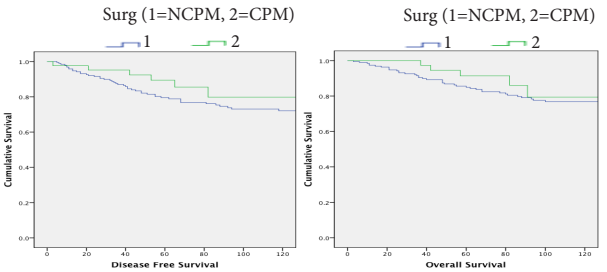


**Figure 2. The DFS and OS of a Group of Patients <40 Years Old Diagnosed at MSMC From 1990-2010 Who Either Underwent CPM or Did Not (NCPM)**

**Table 5. Multivariate Analysis among a Group of 237 Patients <40 Years Old Diagnosed at MSMC From 1990-2007**

| Characteristic | | 5-year DFS | | 10-year DFS** | | 5-year OS | | 10-year OS** | |
|---|---|---|---|---|---|---|---|---|---|
| | | HR (95% CI) | p value* | HR (95% CI) | p value* | HR (95% CI) | p value* | HR (95% CI) | p value* |
| CPM (ref.) | | 0.92 (0.44, 1.93) | 0.82 | 2.06 (0.89, 4.76) | 0.091 | 1.03 (0.50, 2.10) | 0.94 | 2.35 (1.02, 5.41) | 0.046 |
| No -CPM | | | | | | | | | |
| Race | White (ref.) | 1.60 (0.65, 3.99) | 0.31 | 2.36 (0.84, 6.61) | 0.103 | 1.51 (0.61, 3.71) | 0.37 | 2.83 (1.04, 7.71) | 0.042 |
| | Black | | | | | | | | |
| Ethnicity | Non-Hispanic | 0.69 (0.33, 1.47) | 0.34 | 0.95 (0.42, 2.18) | 0.91 | 0.71 (0.34, 1.48) | 0.36 | 0.98 (0.43, 2.23) | 0.96 |
| | Hispanic (ref.) | | | | | | | | |
| Size | 2-5cm. | 0.89 (0.46, 1.74) | 0.74 | 1.03 (0.53, 2.03) | 0.91 | 0.87 (0.45, 1.69) | 0.68 | 0.98 (0.5, 1.93) | 0.95 |
| | >5cm. | 0.50 (0.17, 1.50) | 0.22 | 0.19 (0.05, 0.73) | 0.015 | 0.54 (0.19, 1.52) | 0.24 | 0.17 (0.04, 0.65) | 0.01 |
| Involved LN | | | | | | | | | |
| | 1-3 | 0.67 (0.32, 1.38) | 0.28 | 0.69 (0.32, 1.52) | 0.36 | 0.68 (0.33, 1.37) | 0.28 | 0.70 (0.33, 1.51) | 0.37 |
| | ≥4 | 1.17 (0.49, 2.78) | 0.72 | 0.89 (0.37, 2.15) | 0.8 | 1.04 (0.45, 2.41) | 0.93 | 0.71 (0.29, 1.73) | 0.45 |
| ER | Positive | 0.73 (0.35, 1.51) | 0.4 | 0.59 (0.27, 1.31) | 0.198 | 0.77 (0.38, 1.57) | 0.47 | 0.72 (0.33, 1.56) | 0.4 |
| | Negative (ref.) | | | | | | | | |
| HER2 | Positive | 1.31 (0.62, 2.74) | 0.48 | 2.00 (0.87, 4.61) | 0.104 | 1.20 (0.61, 2.37) | 0.6 | 2.34 (1.05, 5.20) | 0.037 |
| | Negative (ref.) | | | | | | | | |
| Radiation | Yes (ref.) | 1.13 (0.47, 2.73) | 0.78 | 1.27 (0.49, 3.28) | 0.62 | 1.11 (0.47, 2.63) | 0.82 | 1.27 (0.48, 3.36) | 0.62 |
| | No | | | | | | | | |
| Chemotherapy (no targeted agents) | | | | | | | | | |
| | Yes (ref.) | 1.01 (0.44, 2.31) | 0.99 | 0.80 (0.32, 1.98) | 0.63 | 1.15 (0.49, 2.68) | 0.75 | 0.95 (0.37, 2.43) | 0.92 |
| | No | | | | | | | | |

*Multivariate prognostic analysis for time-to-event data, using the extended Cox regression model; **Estimated

**Table 6. Our Data Compared with Previously Published Series**

| Study | Patients | Time | 5-year OS | 10-year OS |
|---|---|---|---|---|
| Our data | 237 (42 CPM, 195 NCPM) | 1980-2010 | 91.4% and 85.0% | 79.4% and 76.8%** |
| Boughey et al. (2010)16 | 385 (128 CPM, 162 NCPM) | 1971-1993 | - | 83% and 74%** |
| Bedrosian et al. (2010)15 | 107,106 (8902 CPM, 98204 NCPM) | 1998-2003 | 88.5% *vs* 83.7%** | - |
| Peralta et al. (2000)14 | 192 (64 CPM, 182 NCPM) | 1973-1998 | - | 64% *vs* 48%*** |

*Estimated; **Significant; ***15-year survival

**Table 7. Differences in Characteristics among Patients Based on Race**

| Characteristic | | Black (n=60) N0. % | White (n=173) N0. % | p value* |
|---|---|---|---|---|
| Size | 0-2 | 9 (17.6) | 44 (31.7) | 0.056 |
| | 2-5 | 28 (54.9) | 69 (49.6) | 0.52 |
| | >5 | 14 (27.5) | 26 (18.7) | 0.19 |
| | Unknown | 9 | 34 | |
| Involved LN | | | | |
| | 0 | 28 (54.9) | 83 (54.6) | 0.97 |
| | 1-3 | 8 (15.7) | 42 (27.6) | 0.09 |
| | >4 | 15 (29.4) | 27 (17.8) | 0.03 |
| | Unknown | 9 | 21 | |
| Timeframe of diagnosis | | | | |
| | 1980-1989 | 7 (11.7) | 29 (16.8) | 0.37 |
| | 1990-1999 | 18 (30.0) | 63 (36.4) | 0.37 |
| | 2000-2009 | 35 (58.3) | 81 (46.8) | 0.12 |
| Morphology | | | | |
| | Infiltrating ductal | 49 (98.0 | 115 (89.5) | 0.07 |
| | Lobular | 1 (2.0) | 13 (10.2) | |
| | Unknown | 10 | 45 | |
| Histologic Grade | | | | |
| | Low | 0 (0) | 5 (7.1) | 0.17 |
| | Intermediate | 8 (32.0) | 25 (35.7) | 0.74 |
| | High | 17 (68.0) | 40 (57.1) | 0.34 |
| | Unknown | 35 | 103 | |
| ER | Positive | 14 (53.8) | 60 (63.2) | 0.39 |
| | Negative | 12 (46.2) | 35 (36.8) | |
| | Unknown | 34 | 78 | |
| HER2 | Positive | 5 (41.7) | 13 (25.5) | 0.26 |
| | Negative | 7 (58.3) | 38 (74.5) | |
| | Unknown | 48 | 122 | |
| ER/HER2 | | | | |
| | ER+/HER2+ | 3 (25.0) | 25 (50.0) | 0.04 |
| | ER+/HER2- | 3 (25.0) | 6 (12.0) | 0.43 |
| | ER-/HER2+ | 4 (33.3) | 12 (6.9) | 0.83 |
| | ER-/HER2- | 2 (16.7) | 7 (14.0) | 0.95 |
| | Unknown | 48 | 123 | |
| Radiation | | | | |
| | Yes | 31 (51.7) | 36 (20.8) | <0.0001 |
| | No | 29 (48.3) | 137 (79.2) | |
| Chemotherapy (no targeted agents) | | | | |
| | Yes | 43 (71.7) | 114 (65.9) | 0.13 |
| | No | 17 (28.3) | 59 (34.1) | |

*Chi-square test of independence

## Discussion

Within the diverse study population, a relatively high proportion of patients were identified as racially black (25.8%) and ethnically Hispanic (31.3%). This is in contrast to other epidemiologic studies involving CPM, which consisted of predominantly white non-Hispanic patients (Carey et al., 2006; Kurian et al., 2009). Similar to previous epidemiologic studies (Tuttle et al., 2007; 2009; Jones et al., 2009; Katipamula et al., 2009; McLaughlin et al., 2009), our study population largely consisted of patients diagnosed between 2000-2010 (49.8%). Among this later timeframe, there was a 3-fold increase in the total number of CPM's compared with the earlier timeframes analyzed in this study. A large percentage of patients had tumors that were high-grade, moderately sized, and had more than 1 involved lymph node, which is consistent with previous studies documenting increased aggressiveness of tumors in patients less than age 40 (Anders et al., 2008; de la Rochefordiere et al., 2013). Consistent with previous reports of patients less than age 40, there were a relatively larger percentage of patients with "triple negative" disease (26.6%; Althuis et al., 2003; Lund et al., 2009). The overall rate of CPM among our patient population was expectedly elevated (17.7%), but was less than the rates seen at larger academic centers (Güth et al., 2012).

Consistent with previous studies (Barry et al., 2012; Chung et al., 2012; Morrow et al., 2011; Yao et al., 2010), there was trend toward a larger percentage of white patients in the CPM group. Also consistent with previous studies, there were significantly more patients in the CPM group diagnosed between 2000-2010. This finding suggests that the utilization of CPM at our hospital is a relatively recent phenomenon, with only 2 patients receiving the procedure before 2000 and 40 patients receiving the procedure thereafter. As opposed to some previous reports (Abbott et al., 2011), we did not observe a significantly increased percentage of patients with lobular histology who underwent CPM. Interestingly, those patients who received CPM did not have significantly worse adverse prognostic factors, such as high histologic grade, more involved LN, ER negativity, or HER2 positivity, and even had a significantly larger percentage of patients who had small tumors, a known favorable prognostic factor. This finding suggests that despite strict guidelines regarding its indication, CPM was not exclusively performed in high-risk patients, and may even been performed on patients with a very low cumulative lifetime risk of CBC. Although there appeared to be a significantly larger percentage of patients who recurred and ultimately died in the NCPM group, it is highly likely that this was exclusively the result of differences in follow-up. As opposed to a median follow-up of 101 months in the NCPM group, the CPM group only had a median follow-up of 68 months. To correct differences in follow-up, our final multivariate model only looked at patients diagnosed in the latest timeframe (CPM median follow-up: 67 months; NCPM median follow-up: 78 months).

Studies have repeatedly shown that patients undergo CPM for a variety of reasons; some medically justified, while others based on personal psychosocial factors (Metcalfe et al., 2008; Frost et al., 2011; Brewster et al., 2012; Katz et al., 2013; Rosenberg et al., 2013). Patients often overestimate their risk of second primary cancer, although women are, in fact, at the greatest risk of systemic recurrence and death from initial breast cancer, for which CPM makes no difference (Adami et al., 1986) and underestimate the adverse effects of aggressive surgical treatment (infection, re-operation, chest pain, cosmesis, adverse effects on feelings of feminity and sexual relationships, decrease in quality of life (QOL; Metcalfe et al., 2008; Brewster et al., 2012; Katz et al., 2013). Clinicians and researchers have generated several hypothesis for this apparent disconnect, including an accelerated decision-making process time, increased media coverage of high-profile patients, severe fear about recurrence and desire to avoid future regret, plastic reconstructive concerns, and anguish over future

surveillance of the contralateral breast (Abbott et al., 2011; Frost et al., 2011; Katz et al., 2013).

Multiple large epidemiologic studies have shown that risk-factors for CPM include Caucasian ethnicity, age less than 40, prior mantle radiation, in-situ disease, prior breast biopsies, lobular histology, tumor multicentricity, high socioeconomic status with private or managed care insurance plans, a family history of breast cancer, treatment at an academic center, receiving magnetic resonance imaging (MRI) at diagnosis, and previous prophylactic oophorectomy in BRCA mutated patients (Nichols et al., 2011; Brewster et al., 2012; Reiner et al., 2013). In our study population, we attempted to isolate reasons for CPM and found that only a small minority of patients harbored a BRCA mutation (15.8%). BRCA mutation is a generally accepted, cost-effective (Zendejas et al., 2011) indication for CPM, as patients are found to have a 3%/year or a cumulative 24-31% ten-year risk of secondary breast cancer (Brewster et al., 2012). However, the risk of CBC in non-BRCA mutated early-stage breast cancer is low at 0.5-0.75% per year, with a 10-year cumulative risk of CBC ranging from 1-15%, with higher figures seen among patients with a family history of breast cancer (Abbott et al., 2011, Nichols et al., 2011; Reiner et al., 2013). However these numbers are likely artificially elevated as they fail to take into account adjuvant therapy, which has substantially reduced risk of CBC (Silber et al., 2013). Additionally, bilateral oophorectomy in premenopausal women has been shown to offer a 60% risk reduction in the development of CBC (Brewster et al., 2012).

The 5- and 10-year DFS and OS observed in our study population was consistent with reports during the same timeframe (Peralta et al., 2000; Bedrosian et al., 2010; Boughey et al., 2010) (Table 6). Our final model showed a significantly improved 10-year survival among patients who underwent CPM. This finding is consistent with some (Peralta et al., 2000; Bedrosian et al., 2010; Boughey et al., 2010; Brewster et al., 2012), but not all reports (Eley et al., 2004; van Sprundel et al., 2006). This finding suggests that in patients less than 40, who are thought to be at greatest cumulative risk of CBC, CPM provides an OS advantage, regardless of genetics, tumor or patient characteristics, and which is only seen after 10 years of follow-up. Consistent with previous reports (Eley et al., 2004; Silber et al., 2013), there was a statistically significant worse 10-year OS among black patients compared with white patients. Upon subgroup analysis (Table 7), black patients were found to present with larger tumors with more involved lymph nodes, two of the most prognostic determinants of DFS and OS in breast cancer. Although there was a non-significant difference in the percentage of patients with tumors that were ER-/HER2-, white patients did have more patients that were ER+/HER2+. Therefore, black patients likely had worse OS from their primary tumors due to multiple other reasons including lack of potential therapeutic agents, late presentation, inherent tumor biological aggressiveness, and/or socioeconomic factors. Despite apparent improvements in diagnosis and treatment options, there was not a significant improvement in DFS or OS in the later timeframe compared with earlier timeframe. This surprising finding it likely due to either: *i*) Lack of long term follow-up that is often needed to detect survival outcomes in breast cancer patients, especially those who are HR positive; *ii*) Newer agents made no significant impact on long-term outcomes in this particular group of breast cancer patients; *iii*) Long-term improvement in outcomes only occurred among a select subset of patients; or *iv*) The sample size was not large enough to detect differences between the groups. Consistent with previously established staging classifications (Edge et al., 2010), tumor size at diagnosis was the most important determinant in both 10-year DFS and OS, where larger tumors did significantly worse, which is likely due to high rates of local and distant recurrence from patient's primary tumors. Interestingly, LN status did not prove to be a significant long-term prognostic determinant in this subset of patients. Patients with ER positive tumors did not have significantly improved long-term outcomes, which is in contrast to previous studies (Loi et al., 2007) and may be unique to our young patient population. Patients in our study population with HER2 positive tumors had a significantly worse 10-year OS, without a significant difference in DFS, compared with those with HER2 negative tumors. Not surprisingly, when further subdivided based on both HR/HER2 status, it was evident that the primary driver of favorable outcomes came from ER+/HER2- patients. Therefore, this finding suggests that despite the game changing effect of the introduction of trastuzumab to the breast cancer armamentarium, HER2 positivity continues to be a predictor of worse patient outcome. Meanwhile, despite a hypothesized improvement in chemoradiation agents and techniques over the past 15 years, we found no significant differences in long-term outcomes among patients receiving these therapies.

In this our study we were able to successfully document the prevalence of CPM among a young, diverse patient population. We were able to identify specific characteristics that were more commonly seen among patients with CPM. We also were able to document long-term outcomes in patients in our study population based on many different factors. We were able to replicate previous studies documenting the worse overall survival for patients who were black, had large tumors at diagnosis, and who had HER2+ disease. Our study had the inherent limitations of being a small retrospective, single institution study with less than 10 years of median follow-up. As with most retrospective analyses, we were faced with missing data for many patients, such is why we were unable to elucidate the exact reason for CPM among all patients in our study population. Overall, we found that CPM has increased dramatically over the past 15 years, especially among white women with locally advanced disease. Less than half of the patients who underwent the procedure were considered high-risk. In patients less than 40, who are thought to be at greatest cumulative risk of secondary breast cancer, CPM provides an OS advantage, regardless of genetics, tumor or patient characteristics, and which is only seen after 10 years of follow-up. Future studies evaluating CPM in young, high-risk patients need at least 10 years of follow-up to determine clinical utility.

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