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ORIGINAL ARTICLE – BREAST ONCOLOGY

Occult Histopathology and Its Predictors in Contralateral and Bilateral Prophylactic Mastectomies

David Mattos, MD, MBA[1], Lisa Gfrerer, MD, PhD[1], Irving T. C. Ling, MBBS, MRCSEd[1], Richard G. Reish, MD[1], Kevin S. Hughes, MD[2], Elkan F. Halpern, PhD[3], Curtis Cetrulo, MD[1], Amy S. Colwell, MD[1], Jonathan M. Winograd, MD[1], Michael J. Yaremchuk, MD[1], William G. Austen Jr., MD[1], and Eric C. Liao, MD, PhD[1]

[1]Division of Plastic and Reconstructive Surgery, Massachusetts General Hospital, Boston, MA; [2]Avon Comprehensive Breast Evaluation Center, Massachusetts General Hospital, Boston, MA; [3]Institute for Technology Assessment, Massachusetts General Hospital, Boston, MA

ABSTRACT

Background. The last decade has seen an increasing prevalence of prophylactic mastectomies with decreasing age of patients treated for breast cancer. Data are limited on the prevalence of histopathologic abnormalities in this population. This study aimed to measure the prevalence of histopathologic findings in contralateral prophylactic mastectomy (CPM) and bilateral prophylactic mastectomy (BPM) patients and identify predictors of findings.

Methods. Our institution's prophylactic mastectomies from 2004 to 2011 were reviewed. Breast specimens with prior malignancies were excluded. Patient factors and pathology reports were collected. Independent predictive factors were identified with univariate and multivariate logistic analysis.

Results. A total of 524 specimens in 454 patients were identified. Malignancy was found in 7.0 % of CPM and 5.7 % of BPM specimens. In CPM patients, ipsilateral lobular carcinoma-in situ [odds ratio (OR) 4.0] and mammogram risk group (OR 2.0) were predictive of

malignancy. Age group (OR 1.5), ipsilateral lobular carcinoma-in situ (OR 2.3), and prior bilateral salpingo-oophorectomy (OR 0.3) were predictive of moderate- to high-risk histopathology. Only increasing age group was predictive of increased moderate- to high-risk histopathology in BPM patients (OR 2.3). There were no independent predictors of malignancy in BPM. *BRCA* status was not predictive in either CPM or BPM.

Conclusions. Patients with lobular carcinoma-in situ in the index breast or high-risk mammograms have a higher prevalence of malignancies. Although *BRCA* patients may benefit from prophylactic mastectomy, the genetic diagnosis does not increase the prevalence of detecting occult pathology. BPM patients can be counseled about relative risk, where occult pathology increases with age.

E. C. Liao, MD, PhD
e-mail: cliao@partners.org

As has been observed nationally, our institution has seen a significant increase in the number of prophylactic mastectomy (PM) procedures. The last decade, we observed a 260 % increase in bilateral breast reconstructions, particularly high-risk patients undergoing PMs.[1] Patients pursuing surgery are now on average 6 years younger at our institution. Similarly, patients nationwide are increasingly trying to weigh their cancer risks. With 36 % of *BRCA*-positive patients in the United States pursuing bilateral prophylactic mastectomy (BPM) and the increasing use of genetic testing, the number of BPMs is likely to continue to rise.[2] Patients undergoing BPM are often *BRCA* mutations carriers or have Li-Fraumeni syndrome, and they are more likely to pursue breast reconstruction.[3] However, many patients without a genetic diagnosis are pursuing contralateral prophylactic mastectomy (CPM), as evidenced by the 150 % increase in CPM rates from 1998 to

2003.[4] From 2003 to 2010, the percentage of women under 45 years old opting for CPM instead increased from 9.3 to 24.1 %.[5] Likely given the 0.6 % per year risk of contralateral breast cancer, younger patients pursue CPM more often, as are those with a cancer history.[4] Data are needed to guide patients', physicians', and policy makers' decisions about PMs. With an estimated 232,430 diagnoses of breast cancer in 2013, approximately 10 % of which are in *BRCA* patients, this topic is timely for many care providers.[6]

The rate of breast cancer in PM is starting to be elucidated. Most data available are for CPM, with a prevalence of occult malignancies [invasive cancer or ductal carcinoma-in situ (DCIS)] ranging from 2.2 to 5.3 % and moderate- to high-risk lesions (lobular carcinoma-in situ [LCIS], atypical ductal hyperplasia, or atypical lobular hyperplasia) ranging from 12.3 to 18.4 %.[7–14] Rai et al. evaluated 301 CPMs and found malignancies in 4.7 % and moderate- to high-risk lesions in 15.0 % of CPMs, with a mean age of 55 years among its patients and 29.9 % with first-degree family history of cancer.[11] Age >54 years and lobular histology in the index cancer were independent predictors of malignancies or moderate- to high-risk lesions. Despite varying definitions of family history—with some studies including ovarian cancer, some only breast cancer, and some first-degree relatives versus all relatives—the prevalence of malignancies and moderate- to high-risk lesions is relatively constant. Studies also found higher prevalence of findings in older patients and in those with lobular histopathologic findings in the index breast cancer. Another found estrogen receptor and progesterone receptor positivity in the index cancer to be predictive of contralateral findings.[15]

Studies evaluating BPM were more varied in their outcomes and only identified age >40 years as predictive of a higher likelihood of findings.[16] *BRCA*-positive patients make up a large percentage of those pursuing BPM, yet no relationship has been found between *BRCA* status and the occult prevalence of findings. The prevalence of occult malignancies in BPM specimens ranges from 0 to 5.6 % and in moderate- to high-risk lesions from 4.9 to 10.0 %.[8–10,16–20] Some prior studies found no predictive factors.[7] Nonetheless, patients are increasingly opting for PM despite limited oncologic justification.

This study evaluates the occult histopathology in CPM and BPM specimens at our institution. First, we aimed to determine the prevalence of occult histopathologic findings in CPM and BPM specimens. Second, we hoped to identify independent predictive factors. We hypothesized that the prevalence of occult histopathologic findings would be higher in our institution's PM patient population than in the general population, and that possible predictors would be *BRCA* gene mutation, older age, preoperative imaging, and lobular histology in the index cancer.

METHODS

Patient Population

The institutional review board approved this study. Medical records of patients who underwent mastectomy between 2004 and 2011 were retrospectively reviewed. A prospectively maintained registry of implant breast reconstructions was used to identify patients undergoing PMs. Inclusion criteria were having listed PM as the procedure in one or both breasts on the operative report and having the PM specimen's pathology report available in the electronic medical record. PM was defined as a mastectomy of a breast without a prior biopsy suggestive of DCIS or invasive cancer.

Data Collection

The following variables were collected for each patient: age, body mass index (BMI), history of radiotherapy, history of chemotherapy, history of bilateral salpingo-oophorectomy (BSO), *BRCA* status, family history of breast or ovarian cancer in first- to third-degree relatives, number of breasts treated with PM, preoperative imaging [(mammogram and magnetic resonance imaging (MRI)], and sentinel node biopsy. Preoperative imaging was considered only if done within the year before surgery. Variables were searched in the operative notes, pathology reports, anesthesia records, and office notes for each patient. For patients undergoing CPM, the index breast pathology was categorized into DCIS, invasive ductal carcinoma, or invasive lobular carcinoma. If patients had both invasive ductal carcinoma and invasive lobular carcinoma, only the lobular carcinoma was counted, as it occurs less frequently. The presence of LCIS on the index cancer side was also noted. Patient age was binned into the following age groups: 20–29, 30–39, 40–49, 50–59, and ≥60 years. The surgical pathology reports were reviewed, and the highest-risk lesion for each PM specimen was noted (lowest to highest: normal, atypia, LCIS, DCIS, carcinoma). Mammogram and MRI risks were binned into low, medium, and high depending on each prophylactic breasts recommendation for follow-up on imaging based on the breast imaging reporting and data system (BI-RADS) score. BI-RADS scores of 1 and 2 are low risk, with routine follow-up continued; 3 is medium risk, with short-interval follow-up imaging recommended; 4 and 5 are high risk, with biopsy recommended.

Statistical Analysis

Data were analyzed by STATA 12.1 for Mac (Stata-Corp, College Station, TX), using $\alpha < 0.05$ as statistically significant. Univariate logistic regression determined differences between groups defined by categorical variables. χ^2 tests were used to compared demographic variables. Statistical significance of independent predictive factors was confirmed with a multivariate logistic regression (MLR). Given that mammogram findings, MRI findings, and LCIS in the index breast cancer side correlate, only one of the three was included in each MLR analysis. The baseline analysis was done with the mammogram findings. The significance of MRI findings and ipsilateral LCIS was then evaluated using another MLR to adjust for the other variables from the baseline model. The odds ratio calculated by age group represents the change in odds of developing cancer for increase from one age group level to the next.

RESULTS

Histopathologic Findings

A total of 524 specimens in 454 patients met the inclusion criteria. BPM patients were more likely to be *BRCA* positive, have a family history, and have a prior BSO. CPM patients were more likely to undergo chemotherapy and radiotherapy (Table 1). Two-thirds of patients who underwent CPM had invasive ductal carcinoma as the index cancer, but 20.8 % of CPM patients also had LCIS in the index cancer breast. The characteristics of the occult invasive cancers found are presented in Table 2.

Among the CPM specimens, 7 (1.8 %) had invasive cancer, 20 (5.2 %) had DCIS, 52 (13.5 %) had LCIS, and 82 (21.4 %) had atypia, for a total of 161 (41.9 %) specimens with findings. In univariate analysis, the likelihood of malignancies per specimen increased with each decade of life ($P = 0.006$), with higher-risk mammogram findings ($P = 0.025$), and when the index cancer breast had LCIS ($P < 0.001$) (Table 3). Moderate- to high-risk lesions per CPM also increased with each decade of life ($P = 0.007$) and if the index breast cancer side had LCIS ($P < 0.001$) (Table 4). The prevalence decreased in patients with a history of a BSO ($P = 0.037$). Multivariate analysis confirmed that mammogram findings ($P = 0.034$) and ipsilateral LCIS were independently predictive of malignancies ($P = 0.002$), but age group and prior BSO were not (Table 5). When only age group, family history, BSO status, and mammogram findings were in the multivariate model (*C*-statistic = 0.721), age group reached statistical significance ($P = 0.044$). For moderate- to high-risk lesions, multivariate analysis inclusive of all variables

confirmed that age group ($P = 0.018$), BSO status ($P = 0.035$), and ipsilateral LCIS ($P = 0.001$) were independently predictive of contralateral findings.

In BPM specimens, 3 (2.1 %) had invasive cancer, 5 (3.6 %) had DCIS, 15 (10.7 %) had LCIS, and 28 (20.0 %) had atypia—a total of 36.4 % of specimens. In BPM specimens, there were no predictive factors of malignancy in univariate analysis. Increasing age group was predictive of increasing prevalence of moderate- to high-risk lesions in univariate analysis ($P = 0.025$), whereas *BRCA* carriers were less likely to have similar findings ($P = 0.001$). In multivariate analysis, there were no independently predictive variables for malignancies, and only age group was predictive of findings for moderate- to high-risk lesions.

Across CPM and BPM specimens, those with *BRCA* mutations had malignancy in 4.9 % of patients, whereas *BRCA*-negative specimens had malignancies 7.6 % of the time ($P = 0.250$). Mean age for *BRCA*-positive patients was 43.2 years compared to 45.5 for non-*BRCA*-positive patients.

Sentinel nodes were assessed in 14 of the 25 PMs with DCIS, all of which were negative. Eight of ten PM specimens with invasive cancer also underwent sentinel node biopsies, two of which were positive for malignancy.

DISCUSSION

Patients are increasingly seeking proactive ways to reduce their risk of breast cancer, often driven by anxiety over breast cancer risk or recurrence. In patients with LCIS, rates of BPM have recently increased by 50 %.[21] Although satisfactory outcomes can be possible after breast reconstruction, prophylactic procedures increase surgical risks, and the decisions to pursue them should be driven by medical necessity. More information is needed regarding the presence of occult histopathologic findings and their predictors in PM. To our knowledge, this is one of the largest studies evaluating PM specimens and predictive factors of occult histopathology, and we present data not easily obtained through national patient registries.

The prevalence of histopathologic findings in CPM and BPM specimens was higher than the general population, as we hypothesized.[22] Malignancies in patients of prior reduction mammoplasty studies ranged from 0.3 to 1.0 %, and only 0.6–1.6 % had moderate- to high-risk lesions. The one study that also measured specimen-specific numbers found that 0.3 % had malignancies—significantly lower than our detection of malignancies in 6.7 % of specimens.[22–25]

The 7.0 % of malignancies in our CPMs are slightly higher compared to previous studies, which range from 2.2 to 5.3 %. The difference could be explained by a difference in patient age, as well as some other components previously found to be predictive, such as estrogen and

TABLE 1 Patient demographics

	CPM	%	BPM	%	P value
Specimens	384	100	140	100	
Age					
Average	44.9		44.3		
SD	7.9		7.9		
≤29 years	5	1.3	2	1.4	0.825
30–39 years	90	23.4	36	25.7	
40–49 years	187	48.7	64	45.7	
50–59 years	84	21.9	34	24.3	
≥60 years	18	4.7	4	2.9	
BRCA					
Positive	78	20.3	104	74.3	<0.001
Family history					
Yes	276	71.9	138	98.6	<0.001
Prior BSO					
Yes	44	11.5	62	44.3	<0.001
BMI					
Average	25.2		24.9		
SD	4.9		4.4		
≥30 kg/m^2	45	11.7	14	10.0	0.582
Chemoradiation					
Yes	220	57.3	10	7.1	<0.001
Radiotherapy					
Yes	159	41.4	2	1.4	<0.001
SLN					
Yes	207	53.9	70	50.0	0.428
Mammogram					
Yes	250	65.1	90	64.3	0.860
MRI					
Yes	228	59.4	94	67.1	0.106
Ipsilateral LCIS					
Yes	80	20.8			
Index cancer					
DCIS	100	26.0			
IDC	259	67.4			
ILC	25	6.5			

CPM contralateral prophylactic mastectomy; *BPM* bilateral prophylactic mastectomy; *Prior BSO* bilateral salpingo-oophorectomy performed before mastectomy; *BMI* body mass index; *DCIS* ductal carcinoma-in situ; *IDC* invasive ductal carcinoma; *ILC* invasive lobular carcinoma; *Ipsilateral LCIS* patient had lobular carcinoma-in situ diagnosis on side of index cancer

progesterone receptor positivity, or lobular histology in the index breast. However, our observation of 34.9 % of CPM specimens with moderate- to high-risk lesions is far higher than the 12.3–18.4 % previously reported, perhaps suggestive of a higher-risk population of patients not explained by average age, or perhaps suggesting that the Department of Pathology's tissue handling and sectioning may have been performed differently at our institution. Our average CPM patient age was 44.9 years; prior studies often had

average patient ages of >45 years of age, not younger, suggesting that age alone does not explain the difference.

As reported in other studies, older patients were more likely to have pathologic findings, though our study only reached statistical significance in multivariate analysis for moderate- to high-risk lesions. Only ipsilateral LCIS was predictive of both malignancy and moderate- to high-risk lesions in the CPM, also consistent with prior findings. The finding that prior BSO is associated with a lower likelihood

TABLE 2 Occult invasive cancer characteristics

Type	TNM stage	Grade	ER	PR	HER2	SLN[a]	SLN Pos[b]
IDC	T1bN1M0	2	Positive	Positive	Negative	2	2
IDC	T1bN0M0	2	Positive	Positive	Negative	0	0
ILC	T1N1M1	1	Positive	Positive	Negative	1	1
IDC	T1aN0M0	2	Positive	Positive	Negative	1	0
IDC	T1aN0M0	1	Positive	Positive	Positive	3	0
IDC	T1bN0M0	3	Negative	Negative	Negative	1	0
IDC	T1aN0M0	2	Negative	Negative	Negative	1	0
Micro-ILC	TisN0 M	2	Positive	Positive	Negative	0	0
IDC	T1bN0M0	3	Negative	Negative	Negative	2	0
ILC	T1miN0M0	NA[c]	Positive	Positive	Positive	2	0

TNM tumor, node, metastasis classification system, *ER* estrogen receptor, *PR* progesterone receptor, *HER2* human epidermal growth factor receptor 2, *SLN* sentinel lymph node, *IDC* invasive ductal carcinoma, *ILC* invasive lobular carcinoma

[a] Number of SLN removed from side of prophylactic mastectomy specimen

[b] Number of removed nodes positive for malignancy

[c] Invasive sample to small to grade histologically

TABLE 3 Specimens with malignancies (DCIS or Invasive Cancer, % with findings)

Overview	CPM patients		BPM patients	
	Pos	%	Pos	%
Totals	27	7.0	8	5.7
Variable	%	*P* value	%	*P* value
Age group				
≤29 years	0.0	0.006	0.0	0.959
30–39 years	1.1		8.3	
40–49 years	8.0		3.1	
50–59 years	9.5		8.8	
≥60 years	16.7		0.0	
BRCA				
Positive	6.4	0.810	3.8	0.121
Negative	7.2		11.1	
Family history				
Yes	8.0	0.255	5.8	NA
No	4.6		0.0	
Prior BSO				
Yes	11.4	0.239	1.6	0.098
No	6.5		9.0	
BMI				
≥30 kg/m^2	13.3	0.086	0.0	NA
<30 kg/m^2	6.2		6.3	
Mammogram risk				
Low	6.0	0.025	6.2	0.532
Medium	0.0		0.0	
High	21.7		12.5	
MRI risk				
Low	7.9	0.270	3.7	0.191
Medium	11.1		0.0	
High	16.7		25.0	

TABLE 3 continued

Variable	%	P value	%	P value
Ipsilateral LCIS				
Yes	16.3	0.001		
No	4.6			

DCIS ductal carcinoma-in situ, *CPM* contralateral prophylactic mastectomy, *BPM* bilateral prophylactic mastectomy, *Prior BSO* bilateral salpingo-oophorectomy performed before mastectomy, *BMI* body mass index, *IDC* invasive ductal carcinoma, *MRI* magnetic resonance imaging, *Ipsilateral LCIS* patient had lobular carcinoma-in situ diagnosis on side of index cancer

TABLE 4 Specimens with moderate-high risk lesions (ADH, ALH, LCIS, % with findings)

Overview	CPM Patients		BPM Patients	
	Pos	%	Pos	%
Totals	134	34.9	43	30.7
Variable	CPM		BPM	
	%	P value	%	P value
Age group				
≤29 years	20.0	0.007	0.0	0.007
30–39 years	22.2		11.1	
40–49 years	37.4		39.1	
50–59 years	42.9		32.4	
≥60 years	38.9		75.0	
BRCA				
Positive	25.6	0.057	23.1	0.001
Negative	37.3		52.8	
Family history				
Yes	34.4	0.755	30.4	0.562
No	36.1		50.0	
Prior BSO				
Yes	20.5	0.037	24.2	0.138
No	36.8		35.9	
BMI				
≥30 kg/m²	31.1	0.571	28.6	0.855
<30 kg/m²	35.4		31.0	
Mammogram risk				
Low	31.2	0.151	25.9	0.192
Medium	66.7		0.0	
High	39.1		50.0	
MRI risk				
Low	31.2	0.115	24.4	0.651
Medium	40.7		37.5	
High	50.0		25.0	
Ipsilateral LCIS				
Yes	53.8	0.001		
No	29.9			

CPM contralateral prophylactic mastectomy, *BPM* bilateral prophylactic mastectomy, *Prior BSO* bilateral salpingo-oophorectomy performed before mastectomy, *BMI* body mass index, *IDC* invasive ductal carcinoma, *MRI* magnetic resonance imaging, *Ipsilateral LCIS* patient had lobular carcinoma-in situ diagnosis on side of index cancer

TABLE 5 Multivariate analysis for malignancies (A) and moderate- to high-risk lesions (B) by specimen ($n = 524$)

Variable	CPM (C-statistic = 0.711)			BPM (C-statistic = 0.736)		
	P value	OR	95 % CI	P Value	OR	95 % CI
A						
Age group	0.058	1.784	0.98–3.25	0.685	1.304	0.36–4.71
BRCA	1.000	1.000	0.25–3.93	0.652	0.612	0.07–5.16
Family history	0.360	1.797	0.51–6.31	NA	NA	NA
Prior BSO	0.125	2.783	0.75–10.30	0.259	0.225	0.02–2.99
BMI ≥30 kg/m^2	0.649	1.363	0.36–5.18	NA	NA	NA
Mammogram (1)	0.034	2.032	1.05–3.92	0.939	1.048	0.32–3.47
MRI (2)	0.338	1.449	0.68–3.10	0.359	2.071	0.44–9.80
Ipsilateral LCIS (3)	0.002	4.013	1.70–9.47	NA	NA	NA
Variable	CPM (C-statistic = 0.677)			BPM (C-statistic = 0.720)		
	P value	OR	95 % CI	P Value	OR	95 % CI
B						
Age group	0.018	1.497	1.07–2.09	0.024	2.301	1.12–4.75
BRCA	0.159	0.565	0.26–1.25	0.149	0.418	0.12–1.37
Family history	0.520	0.823	0.45–1.49	NA	NA	NA
Prior BSO	0.028	0.271	0.09–0.87	0.907	1.076	0.3103.69
BMI ≥30 kg/m^2	0.965	0.980	0.39–2.44	0.747	0.731	0.11–4.91
Mammogram (1)	0.359	1.225	0.79–1.89	0.214	1.705	0.73–3.96
MRI (2)	0.139	1.487	0.88–2.52	0.139	1.487	0.88–2.52
Ipsilateral LCIS (3)	0.001	2.331	1.38–3.92	NA	NA	NA

A malignancies, *B* moderate to high-risk lesions, *CPM* contralateral prophylactic mastectomy, *BPM* bilateral prophylactic mastectomy, *CPM* contralateral prophylactic mastectomy, *BPM* bilateral prophylactic mastectomy, *OR* odds ratio, *CI* confidence interval, *Prior BSO* bilateral salpingo-oophorectomy performed before mastectomy, *BMI* body mass index, *MRI* magnetic resonance imaging, *Ipsilateral LCIS* patient had lobular carcinoma-in situ diagnosis on side of index cancer, *NA* variable with no positive outcomes, analysis not possible, or collinearity

of moderate- to high-risk lesions had not been identified in prior PM studies, but it is consistent with data that suggest that BSO decreases breast cancer risk by up to 50 % in high-risk patients.[26]

For BPM, prior studies reported malignancies in 0–5.6 % of specimens and moderate- to high-risk lesions in 4.9–10.0 % of specimens, both of which are also lower than our observations of 5.7 and 30.7 %, respectively. The higher rate of detecting malignancies may be somewhat explained by age, as our patients were slightly older, at 44.3 years, whereas only one of the studies we used as a comparison had an average patient age of >41 years. However, the difference in moderate- to high-risk lesions is too large to be simply explained by age, as our odds ratio increase per decade of life was only 2.3.

Our hypothesis that *BRCA*-positive patients may have higher likelihood of findings was not demonstrated. *BRCA*-positive malignancies in other studies ranged from 2.7 to 3.0 %, slightly below our 4.9 % of specimens.[10,16,17] In our study, *BRCA*-negative patients had a higher odds ratio of malignancies and moderate- to high-risk lesions, even after

adjusting for other variables. However, the difference was not statistically significant. Larger sample sizes will be necessary to settle that question, given that *BRCA* mutations do increase a patient's lifetime risk of cancer.

Overall, these findings suggest that patients with LCIS in the index cancer breast have the highest likelihood of malignancies and moderate- to high-risk findings in the contralateral breast, as well as patients with concerning mammogram findings on the CPM side, and thus derive benefit from CPM. Also, although not measured in our study, tamoxifen chemoprevention has also been shown to decrease the risk of breast cancer among *BRCA* carriers, and it is an alternative to BPM or prophylactic BSO that all patients should also consider.

This study is limited by multiple factors. For one, a small percentage of patients have neoplastic cells in their nipples, so the higher use of nipple-sparing mastectomies at our institution may underestimate the prevalence of histopathologic findings.[27] Also, although we defined PM as no history of biopsy-proven DCIS or invasive cancer, given that mastectomy after LCIS is still considered risk reducing,

some studies defined it differently—for example, patients with no radiologic or clinical evidence of disease, which may predispose our subjects to a higher prevalence of findings in our study because these were not considered exclusion criteria. Additionally, our registry included patients who underwent immediate prosthetic-based reconstructions and did not include patients who underwent autologous reconstruction or no reconstruction, which potentially skews our findings against patients with higher BMI, the elderly, or those with comorbid medical conditions. The lower BMI of our patients may limit the study's detection effect on occult breast cancer. Patients with higher BMIs may opt for autologous reconstruction, and older patients more commonly do not opt for reconstruction.[28] Both BMI and age can affect breast cancer risk, so this cohort may have slightly different rates of findings.[29,30] Rate and method of reconstruction can also vary by surgeon and region, but our institution's patients mostly undergo immediate, prosthetic-based reconstruction, which is the dominant method in the United States and worldwide, so the findings of this study should still generally be applicable.[31]

This study provides data on detecting occult pathology after PM, documenting a low incidence for younger patients, where pharmacologic treatment may further reduce risk. In contrast, LCIS is a marker for future breast cancer, and consideration of CPM may be appropriate. Preoperatively, mammogram findings are still critical in helping patients decide whether to pursue CPM. Nonetheless, PM remains a difficult and personal decision for many patients, as it has many physical and psychologic implications that can only be appropriately weighed by individual patients with counsel from their physicians, whom this study aims to inform.

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