Indications for Sentinel Lymph Node Biopsy in the Setting of Prophylactic Mastectomy

Christine Laronga, MD, FACS, M Catherine Lee, MD, Kandace P McGuire, MD, Tammi Meade, BA, BS, W Bradford Carter, MD, FACS, Susan Hoover, MD, FACS, Charles E Cox, MD, FACS

BACKGROUND: Bilateral/contralateral prophylactic mastectomy (PM) is offered to high-risk women to decrease their actual or perceived breast cancer risk. When an invasive occult cancer is identified, prevailing wisdom suggests that an axillary dissection be performed. This single-institution study aims to identify patients who may benefit from sentinel node biopsy (SLNB) at the time of prophylactic mastectomy.

STUDY DESIGN: We performed a retrospective review of a prospective database of patients treated at our institution with bilateral/contralateral PM between 1995 and 2006. We examined patients' clinicopathologic characteristics in comparison with their incidence of occult cancer in the contralateral breast or axilla.

RESULTS: There were 449 patients who underwent PM and SLNB. Twenty-eight underwent bilateral PM. Of the 28, no occult cancers were identified. Occult cancers were identified in 18 of 420 (4.3%) contralateral prophylactic specimens; they were invasive in 6 (1.4%). In cases of occult carcinoma, the primary established tumor was more likely to be of invasive lobular histology. Eight of 420 (2%) patients had a positive contralateral sentinel node, and within this subset of 8 patients the majority had locally advanced disease on the known tumor side. Other features associated with a positive contralateral sentinel node included the presence of lymphovascular involvement or skin or nipple involvement and grade 2 to 3 invasive primary established tumors.

CONCLUSIONS: Overall, SLNB in patients undergoing bilateral PM or contralateral PM associated with early-stage disease is not indicated. But patients with locally advanced primary breast cancers have a significantly increased risk of occult cancer in the contralateral axilla, likely due to crossover metastasis; this select group of patients may benefit from SLNB at the time of surgery. (J Am Coll Surg 2009;209:746–752. © 2009 by the American College of Surgeons)

Bilateral prophylactic mastectomy is offered to high-risk women to decrease the actual or perceived breast cancer risk. High-risk patients are women without current or previous breast cancer, who have a genetic predisposition, such as a BRCA mutation; have a strong family history but no demonstrable genetic mutation; or have a biopsy-proved histologic high-risk lesion, such as lobular carcinoma in situ, atypical lobular hyperplasia, or atypical ductal hyperplasia. For women with current or previous breast cancer, a contralateral prophylactic mastectomy is considered for risk reduction, difficult surveillance, or to provide symmetry for women undergoing mastectomy for local control of their breast cancer. Historically, 3% to 5% of prophylactic mastectomy specimens are found to have occult carcinomas on surgical pathology; more than half of these cancers are noninvasive.[1,2] When an invasive occult cancer is identified, prevailing wisdom suggests that an axillary dissection be performed. In actuality, the incidence of axillary node involvement with metastatic disease in this scenario is quite low (< 1%), calling into question the short- and longterm risks associated with axillary node dissection versus the benefit of confirming no metastatic axillary disease.[1] Axillary node dissection in itself bears the short-term risks associated with surgery, in addition to the longterm risks of numbness, neuropathic pain, and lymphedema.

With women presenting with earlier-stage breast cancers, the risk-benefit ratio of axillary lymph node dissection for

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From the Don & Erika Wallace Comprehensive Breast Program, H Lee Moffitt Cancer Center & Research Institute, Tampa, FL (Laronga, Lee, Meade, Carter, Cox); the Department of Surgery, Division of Surgical Oncology, Magee-Womens Hospital of UPMC, Pittsburgh, PA (McGuire); and The Breast Clinic of Memphis, Germantown, TN (Hoover).

Correspondence address: Christine Laronga, MD, Comprehensive Breast Program, H Lee Moffitt Cancer Center & Research Institute, 12902 Magnolia Dr, MCC-BRPROG, Tampa, FL 33612.

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Abbreviations and Acronyms
DCIS = ductal carcinoma in situ
PM = prophylactic mastectomy
SLNB = sentinel lymph node biopsy

known invasive carcinomas has been highly scrutinized and has contributed significantly to the adoption of the sentinel lymph node biopsy (SLNB). SLNB is now the current accepted practice standard for axillary staging of early-stage invasive breast cancer.[3] This highly accurate, low-morbidity procedure is also used for noninvasive breast cancer (high-grade ductal carcinoma in situ [DCIS]) in conjunction with a mastectomy. The rationale for this approach is the upstaging rate to invasive carcinoma, seen in 8% to 38% of DCIS cases.[4-7] Currently, an ipsilateral sentinel lymph node biopsy cannot be reliably performed after mastectomy, committing the patient to an axillary lymph node dissection.

With this knowledge, what is the utility of sentinel lymph node biopsy performed in the setting of prophylactic mastectomy? Is there a benefit to adding this technique in cases where an occult cancer may be identified postmastectomy? Although the SLNB procedure has relatively low morbidity, it is not 0, and the incidence of lymphedema is higher than anticipated, ranging from 3.5% to 11%.[8-10] The goal of this study was to examine our institutional experience with prophylactic mastectomy and SLNB in hopes of identifying a subset population who would benefit significantly from the addition of SLNB at the time of a planned prophylactic operation.

METHODS

The Don & Erika Wallace Comprehensive Breast Program at the H Lee Moffitt Cancer Center & Research Institute offers all new breast cancer patients participation in an IRB-approved prospective database. With consent, a patient's current and future information is entered into the database, including detailed information regarding demographics, diagnosis, treatments, and outcomes. Data retrieval from this 19,000-plus patient database requires IRB approval for each individual research study. For this particular study, all patients were seen at the H Lee Moffitt Cancer Center from January 1995 to April 2006 and had prophylactic mastectomy and SLNB performed.

Starting in January 1995, subareolar injections of both isotope (technetium 99m filtered sulfur colloid; Cardinal Health) and blue dye (isosulfan blue; AnazaoHealth Corporation) were used to identify the sentinel lymph node in the prophylactic mastectomy setting until July 2003. Thereafter, only subareolar injections of blue dye were used in the prophylactic breast. Throughout the study period, all sentinel lymph nodes were evaluated with both hematoxylin and eosin and cytokeratin immunohistochemistry. Intraoperative assessment by frozen section or touch preparation of the sentinel nodes was not performed on the prophylactic mastectomy side.

Data examined included: 1) patient demographics; 2) characteristics of the primary established tumor (or known tumor) and the ipsilateral node status; 3) identification of a contralateral occult tumor in the prophylactic mastectomy specimen, its tumor characteristics, and its node status; 4) in the case of bilateral prophylactic mastectomies, identification of occult cancers in either mastectomy specimen and the ipsilateral nodal status; 5) the nodal status when no occult cancer was identified; and 6) reasons for having a contralateral prophylactic mastectomy. Statistical analysis was performed in a univariate manner, using Fisher's exact, chi-square, and Student's *t*-test (Graphpad Software, Inc).

RESULTS

From January 1995 to April 2006, 449 patients underwent prophylactic mastectomy and SLNB. Of the 449 patients, 28 patients underwent bilateral prophylactic mastectomy because of increased cancer risk, totaling 477 prophylactic mastectomy specimens. The median age of the 29 women having bilateral prophylactic mastectomy was 46 years (range, 27 to 73 years). Because genetic mutation carrier status is not disclosed at our institution, the percentage of confirmed genetic carriers within this cohort could not be determined, but all 28 women were followed in the High-Risk Breast Clinic (for biopsy-proved atypical hyperplasia or lobular carcinoma in situ) or the Familial Breast and Ovarian Clinic for suspected or known mutation carriers. The remainder of the patients (n = 420) elected mastectomy for a known unilateral breast cancer in addition to a contralateral prophylactic mastectomy for risk reduction.

In the 28 bilateral prophylactic mastectomy patients, no occult cancers were identified. Fifteen patients had surgery before July 2003, so they had both blue dye and radiolabeled colloid used for the sentinel lymph node procedure. After July 2003, only blue dye was used for the sentinel lymph node procedure in 14 patients. The overall sentinel lymph node identification rate, regardless of technique, in this cohort was 100% (28 of 28). The mean number of sentinel lymph nodes identified was 2.0 per nodal basin, and there were no sentinel nodes containing metastatic disease in any of the 28 patients.

Of the original 449 patients, 420 patients had newly diagnosed breast cancer and chose to have a contralateral prophylactic mastectomy. The median age of these women with breast cancer was 50.0 years (range, 22 to 85 years). The

Table 1. Demographic Comparisons Between the Primary Established Tumor When the Prophylactic Contralateral Mastectomy Is Benign Versus When an Occult Cancer Is Identified in the Prophylactic Mastectomy Specimen

Variable	Benign contralateral prophylactic mastectomy specimen (n = 402)	Occult cancer in the contralateral prophylactic mastectomy specimen (n = 18)	p Value
Mean age, y	52.7	51.6	0.70
Median tumor size, cm (range)	1.5 (0.2–13)	1.95 (0.03–4.00)	0.27
Positive ipsilateral sentinel node biopsy in the primary established, n (%)	189 (47)	11 (61)	0.23
Positive contralateral "prophylactic" sentinel node biopsy, n (%)	7 (2.0)	1 (5.6)	0.05
Family history breast cancer, n (%)	227 (56)	12 (67)	0.47
First-degree relative with breast cancer, n (%)	105 (26)	5 (28)	0.36

median tumor size for the primary established invasive cancers was 1.95 cm (range, 0.03 cm to 4.00 cm). Locally advanced primary breast cancer (stage IIB to IIIB) was present in 111 of 420 patients (26%). Occult cancers were identified in the contralateral prophylactic mastectomy specimen in 18 of 420 (4.3%); the occult cancers were invasive in 6 cases (1.4%) and DCIS in the remaining 12 (2.9%).

A comparison between the 18 patients with occult cancer found in the prophylactic mastectomy specimen and the 402 women with benign contralateral mastectomy specimens is seen in Table 1. Age, invasive tumor size, primary nodal status, and family history of breast cancer did not predict for identification of an occult cancer in the contralateral prophylactic breast. The histologic distribution of the primary established tumor type associated with occult cancer versus benign breast on pathologic examination of the prophylactic mastectomy is shown in Figure 1.

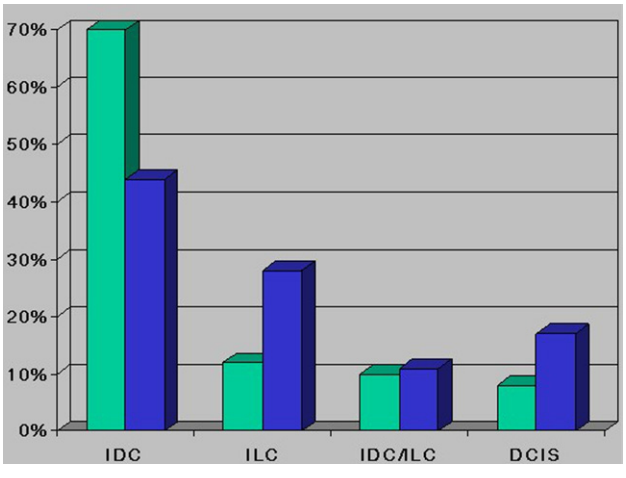

Fig 1. Comparison of primary tumor histology when the contralateral prophylactic mastectomy tissue is benign (green) versus primary tumor histology when the contralateral prophylactic mastectomy specimen contains occult carcinoma (blue). DCIS, ductal carcinoma in situ; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; PM, prophylactic mastectomy.

We did find that invasive lobular carcinoma was more common when an occult cancer was discovered in the contralateral breast.

In the 420 patients having a contralateral prophylactic mastectomy, the sentinel lymph node identification rate was 420 of 420 (100%); 205 of 420 (49%) had both blue dye and isotope, and 215 of 420 (51%) had blue dye alone. A total of 1,163 sentinel lymph nodes (mean 2.8 nodes per basin) were evaluated. One of the six patients with an occult invasive carcinoma after prophylactic mastectomy was found to have axillary disease on the prophylactic side as well. This patient had locally advanced breast cancer on the primary established breast cancer side. The occult contralateral cancer and contralateral positive sentinel lymph node were both determined by pathologic evaluation to represent metastases from the locally advanced, known primary tumor based on similar histologic features. The remaining five patients with invasive occult cancers in the contralateral prophylactic mastectomy group had negative SLNBs. So 6 of 420 patients (1.4%) would have been candidates for axillary node dissection because of the discovery of occult invasive disease.

Seven (7 of 420; 1.7%) additional patients had a positive contralateral sentinel lymph node without any evidence of occult disease in the prophylactic breast specimen. These seven patients all had locally advanced disease on the established primary breast cancer side, suggesting that all of these cases represent crossover metastases to the opposite axilla. In total, 8 of 420 (2%) patients had a positive contralateral sentinel lymph node; all 8 had locally advanced primary breast cancers with ipsilateral nodal involvement. Both larger invasive tumor size of the known cancer and ipsilateral nodal metastases played independent roles in contralateral nodal involvement. A comparison of the two contralateral "prophylactic" sentinel lymph node biopsy subsets between those containing metastatic disease versus no metastatic disease demonstrated additional significant risk factors. The presence of lymphovascular involvement

Table 2. Demographic Comparisons Between the Primary Established Tumor When the Prophylactic Contralateral Sentinel Node Biopsy (Axilla) Is Benign Versus When the Contralateral Sentinel Node Biopsy (Axilla) Contains Metastatic Disease (Positive)

Variable	Contralateral prophylactic axilla positive (n = 8)	Contralateral prophylactic axilla negative (n = 412)	p Value
Family history, n (%)			0.740
Yes	4 (50.0)	220 (53.4)	
No	4 (50.0)	187 (45.4)	
Unknown/adopted		5 (1.2)	
Skin/nipple involvement, n (%)			0.0004
Yes	5 (71.4)	55 (13.3)	
No	3 (28.6)	333 (80.1)	
Unknown		24 (5.8)	
Lymphatic invasion, n (%)			< 0.0001
Yes	7 (87.5)	58 (14.1)	
No	1 (13.5)	326 (79.1)	
Unknown	0 (0.0)	28 (6.3)	
Multifocal, n (%)			0.077
Yes	4 (50.0)	78 (18.9)	
No	4 (50.0)	308 (74.8)	
Unknown	0 (0.0)	26 (6.3)	
Median tumor size (invasive), cm	2.23 ± 2.72	1.50 ± 1.51	0.0053
Grade of primary tumor, n (%)			< 0.0001
1	0 (0.0)	53 (12.8)	
2	2 (25.0)	150 (36.4)	
3	6 (75.0)	144 (35.0)	
Unknown	0 (0.0)	65 (15.8)	
Ipsilateral nodes positive, n (%)			< 0.0001
0	1 (12.5)	191 (46.4)	
1–3	2 (25.0)	159 (38.6)	
4 or more	5 (62.5)	62 (15.0)	
Histology, n (%)			< 0.0001
IDC	6 (75.0)	227 (55.1)	
ILC	1 (12.5)	48 (11.7)	
IDC/ILC	1 (12.5)	37 (9.0)	
DCIS	0 (0.0)	77 (18.7)	
DCIS/LCIS	0 (0.0)	3 (0.7)	
DCIS with microinvasion	0 (0.0)	10 (2.4)	
Other	0 (0.0)	10 (2.4)	

DCIS, ductal carcinoma in situ; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; LCIS, lobular carcinoma in situ.

or skin or nipple involvement from the known cancer was associated with a positive contralateral sentinel lymph node (Table 2). Higher-grade (grades 2 to 3) invasive primary established tumors were also more likely to have a crossover metastasis. Family history and multicentricity or multifocality did not play a role.

A subset analysis of patients presenting with locally advanced disease was also performed to evaluate the incidence of crossover metastases. Patients with locally advanced disease were defined as those with a T3 or greater tumor on final pathology or those treated with neoadjuvant chemotherapy before definitive surgical therapy for clinical stage IIB or higher disease. Of the 420 patients diagnosed with cancer, 57 were identified with locally advanced disease. Within this subset of 57 patients, the contralateral sentinel lymph node positivity rate was 14% (8 of 57). On chi-square analysis, this represented a statistically significant difference ($p = 0.0002$) in comparison to the overall rate of sentinel lymph node positivity in the study population (2%, 8 of 420). The only significant difference between locally advanced breast cancer patients with and without contralateral metastasis appeared to be the incidence of ipsilateral nodes. No other clinicopathologic factors varied significantly between these 2 groups (Table 3).

Patients with an invasive primary breast cancer were more likely to have occult disease in their contralateral axilla ($p < 0.0001$), with invasive ductal being the most common histology. But unlike the relationship of occult cancers in the contralateral prophylactic mastectomy specimen, we found no difference in the number of patients with invasive lobular carcinoma among those with and without contralateral metastatic axillary disease.

DISCUSSION

The incidence of occult cancer in all prophylactic mastectomy specimens was 3.8% (18 of 476), similar to previously documented occult carcinoma rates. The incidence of occult carcinoma in patients undergoing bilateral prophylactic mastectomy was 0%. In the setting of contralateral prophylactic mastectomy, 4.3% (18 of 420) of patients were found to have occult disease (6 invasive cases). The presence of locally advanced cancer with ipsilateral axillary involvement on the primary side significantly increased the chances of a positive sentinel node in the contralateral axilla. We found factors such as tumor size, invasive tumor type, nuclear grade, skin and nipple involvement, number of positive ipsilateral lymph nodes, and lymphovascular invasion were significantly correlated with a positive contralateral sentinel node.

Some previous studies evaluated risk factors associated with cancer in the prophylactic breast, but none in the

Table 3. Demographic Comparisons Between the Primary Established Tumor When the Prophylactic Contralateral Sentinel Node Biopsy (Axilla) Is Benign Versus When the Contralateral Sentinel Node Biopsy (Axilla) Contains Metastatic Disease (Positive) in Locally Advanced Breast Cancer

Variable	Contralateral prophylactic axilla positive (n = 8)	Contralateral prophylactic axilla negative (n = 49)	p Value
Family history, n (%)			1.000
Yes	4 (50.0)	26 (53.1)	
No	4 (50.0)	23 (46.9)	
Skin/nipple involvement, n (%)			0.2473
Yes	5 (71.4)	18 (36.7)	
No	3 (28.6)	31 (63.3)	
Lymphatic invasion, n (%)			0.1255
Yes	7 (87.5)	27 (55.1)	
No	1 (13.5)	20 (40.8)	
Unknown	0 (0.0)	2 (4.08)	
Multifocal, n (%)			0.0914
Yes	4 (50.0)	10 (20.4)	
No	4 (50.0)	37 (75.5)	
Unknown	0 (0.0)	2 (4.08)	
Median tumor size (invasive), cm	2.23 ± 2.72	1.57 ± 2.18	0.4046
Grade of primary tumor, n (%)			
1	0 (0.0)	2 (4.08)	0.5356
2	2 (25.0)	7 (14.3)	
3	6 (75.0)	33 (67.3)	
Unknown	0 (0.0)	7 (14.3)	
Ipsilateral nodes positive, n (%)			0.0005
0	1 (12.5)	20 (40.8)	
1–3	2 (25.0)	22 (44.9)	
4 or more	5 (62.5)	7 (14.3)	
Histology, n (%)			0.1506
IDC	6 (75.0)	37 (75.5)	
ILC	1 (12.5)	5 (10.2)	
IDC/ILC	1 (12.5)	1 (2.04)	
DCIS	0 (0.0)	0 (0.0)	
DCIS/LCIS	0 (0.0)	0 (0.0)	
DCIS with microinvasion	0 (0.0)	0 (0.0)	
Other	0 (0.0)	6 (12.2)	

DCIS, ductal carcinoma in situ; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; LCIS, lobular carcinoma in situ.

contralateral axilla. A study by Yi and colleagues[11] demonstrated that age greater than 50 years, an increased Gail risk, an ipsilateral moderate- to high-risk lesion (such as lobular carcinoma in situ, atypical lobular hyperplasia, or atypical ductal hyperplasia), lobular histology, or a multicentric tumor increased the risk of breast cancer of the contralateral side in their study group. Although we found similar risk for our invasive lobular cancers, we found no correlation between these risk factors and a positive sentinel lymph node of the prophylactic side.

Another reason commonly noted for prophylactic mastectomy is a strong family history of breast cancer.[12,13] We found that a strong family history neither increased the risk of occult cancer in the contralateral breast nor in the contralateral axilla. But we were not privy to the BRCA status of our patients, which impaired our assessment of the efficacy of bilateral and contralateral prophylactic mastectomy use.[12]

The real question remains as to whether sentinel node evaluation in conjunction with contralateral mastectomy affects outcomes in most patients. This study aimed to elucidate its utility in clinical practice. The use of prophylactic mastectomy itself has come under scrunity in recent years, and a Cochrane review from 2004 showed contralateral prophylactic mastectomy decreased the incidence of contralateral breast cancer, but this decrease was not associated with improved overall or disease-specific survival.[14] In contrast, a retrospective cohort study demonstrated that contralateral prophylactic mastectomy was associated with a significant decrease in both the breast cancer mortality rate (8% versus 12%) and the overall mortality rate (13% versus 22%).[15]

In high-risk women with a BRCA diagnosis or strong family history, this risk reduction in cancer development is even more dramatic. A recent study noted a 94% relative risk reduction in contralateral breast cancer diagnoses at a median followup period of 10 years among high-risk women with a first breast cancer and family history of breast or ovarian cancer.[16] These findings were echoed in a study by Babiera and associates,[17] but also found no overall difference in survival after contralateral prophylactic mastectomy at a median followup time of 5 years.

A review of the Surveillance, Epidemiology, and End Results (SEER) database from 1999 to 2003 revealed that overall survival rates for patients with an initial diagnosis of unilateral stage II or III cancer were not changed when a metachronous lesion was found. But in patients presenting with an early stage I lesion, a second stage I lesion in the contralateral breast did affect overall survival.[18] A 30-year-old patient with early-stage breast cancer and a BRCA mutation would gain an estimated 0.6 to 2.1 additional years in life expectancy after contralateral prophylactic mastectomy.[19] So contralateral prophylactic mastectomy may confer some survival benefit in high-risk women with early-stage unilateral cancers.

The question that still remains is whether these same patients would benefit from an evaluation of their con-

tralateral nodes with SLNB. A previous study by Soran and coworkers[20] noted a 2.5% incidence of occult disease in the prophylactic axilla of 75 patients undergoing contralateral prophylactic mastectomy. Another study, by Dupont and colleagues,[21] found that 7% of patients benefited from an SLNB on their prophylactic side. Neither study, perhaps because of smaller numbers of positive contralateral sentinel nodes, investigated clinicopathologic factors that may have been associated with sentinel node positivity.

Based on our current data, SLNB in patients undergoing bilateral prophylactic mastectomy is likely not indicated, and in patients with early-stage disease, SLNB in the contralateral prophylactic mastectomy is of little benefit. Considering the 3% to 11% longterm risk of lymphedema associated with SLNB,[8-10] as well as the other potential risks, this study suggests that SLNB in all prophylactic mastectomies can be avoided in low-risk patients. Larger, prospective trials examining these data, especially in light of the increasing rates of prophylactic mastectomy, may further elucidate this topic.[22] It is interesting to note in our population that patients with locally advanced primary breast cancers have a markedly increased risk of occult cancer in the contralateral axilla, likely because of the "crossover" metastasis effect. The finding of contralateral axillary metastases significantly upstages this particular subset of patients, leading to more aggressive adjuvant therapies. So, despite few data justifying the practice of SLNB in all patients undergoing prophylactic mastectomy, SLNB should be applied in conjunction with prophylactic mastectomy for patients presenting with locally advanced primary breast cancers.

Author Contributions

Study conception and design: Laronga, Hoover, Cox, Carter
Acquisition of data: Laronga, Lee, Meade, Carter, Hoover, Cox
Analysis and interpretation of data: Laronga, Lee, McGuire, Meade
Drafting of manuscript: Laronga, Lee, McGuire, Meade
Critical revision: Laronga, Lee, McGuire, Carter, Hoover, Cox

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REFERENCES

1. McLaughlin SA, Stempel M, Morris EA, et al. Can magnetic resonance imaging be used to select patients for sentinel lymph node biopsy in prophylactic mastectomy? Cancer 2008;112:1214–1221.
2. Boughey JC, Khakpour N, Meric-Bernstam F, et al. Selective use of sentinel lymph node surgery during prophylactic mastectomy. Cancer 2006;107:1440–1447.
3. Swenson KK, Nissen MJ, Ceronsky C, et al. Comparison of side effects between sentinel lymph node and axillary lymph node dissection for breast cancer. Ann Surg Oncol 2002;9:745–753.
4. Rutstein LA, Johnson RR, Poller WR, et al. Predictors of residual invasive disease after core needle biopsy diagnosis of ductal carcinoma in situ. Breast J 2007;13:251–257.
5. Huo L, Sneige N, Hunt KK, et al. Predictors of invasion in patients with core-needle biopsy-diagnosed ductal carcinoma in situ and recommendations for a selective approach to sentinel lymph node biopsy in ductal carcinoma in situ. Cancer 2006;107:1760–1768.
6. Sakr R, Antoine M, Barranger E, et al. Value of sentinel lymph node biopsy in breast ductal carcinoma in situ upstaged to invasive carcinoma. Breast J 2008;14:55–60.
7. Goyal A, Douglas-Jones A, Monypenny I, et al. Is there a role of sentinel lymph node biopsy in ductal carcinoma in situ?: analysis of 587 cases. Breast Cancer Res Treat 2006;98:311–314.
8. Langer I, Guller U, Berclaz G, et al. Morbidity if sentinel lymph node biopsy (SLN) alone versus SLN and completion axillary lymph node dissection after breast cancer surgery: a prospective Swiss multicenter study of 659 patients. Ann Surg 2007;245:452–461.
9. Mansel RE, Fallowfield L, Kissin M, et al. Randomized multicenter trial of sentinel node biopsy versus standard axillary treatment in operable breast cancer: the ALMANAC Trial. J Natl Cancer Inst 2006;98:599–609.
10. McLaughlin SA, Wright MJ, Morris KT, et al. Prevalence of lymphedema in women with breast cancer 5 years after sentinel lymph node biopsy or axillary dissection: objective measurements. J Clin Oncol 2008;26:5213–5219.
11. Yi M, Meric-Bernstam F, Middleton LP, et al. Predictors of contralateral breast cancer in patients with unilateral breast cancer undergoing contralateral prophylactic mastectomy. Cancer 2009;115:962–971.
12. Graves K, Peshkin B, Halbert C, et al. Predictors and outcomes of contralateral prophylactic mastectomy among breast cancer survivors. Breast Cancer Res Treat 2007;104:321–329.
13. Frost MH, Slezak JM, Tran NV, et al. Satisfaction after contralateral prophylactic mastectomy: the significance of mastectomy type, reconstructive complications, and body appearance. J Clin Oncol 2005;23:7849–7856.
14. Lostumbo L, Carbine N, Wallace J, Ezzo J. Prophylactic mastectomy for the prevention of breast cancer. Cochrane Database Syst Rev 2004:CD002748.
15. Herrinton LJ, Barlow WE, Yu O, et al. Efficacy of prophylactic mastectomy in women with unilateral breast cancer: a cancer research network project. J Clin Oncol 2005;23:4275–4286.
16. McDonnell SK, Schaid D, Myers JL, et al. Efficacy of contralateral prophylactic mastectomy in women with a personal and family history of breast cancer. J Clin Oncol 2001;19:3938–3943.
17. Babiera G, Rao R, Feng L, et al. Effect of primary tumor extirpation in breast cancer patients who present with stage IV disease and an intact primary tumor. Ann Surg Oncol 2006;13:776–782.

18. Quan G, Pommier SJ, Pommier RF. Incidence and outcomes of contralateral breast cancers. Am J Surg 2008;195:645–650.
19. Schrag D, Kuntz KM, Garber JE, Weeks JC. Life expectancy gains from cancer prevention strategies for women with breast cancer and BRCA1 or BRCA2 mutations. JAMA 2000;283:617–624.
20. Soran A, Falk J, Bonaventura M, et al. Is routine sentinel lymph node biopsy indicated in women undergoing contralateral prophylactic mastectomy? Magee-Womens Hospital Experience. Ann Surg Oncol 2007;14:646–651.
21. Dupont EL, Kuhn MA, McCann C, et al. The role of sentinel lymph node biopsy in women undergoing prophylactic mastectomy. Am J Surg 2000;180:274–277.
22. Tuttle TM, Habermann EB, Grund EH, et al. Increasing use of contralateral prophylactic mastectomy for breast cancer patients: a trend toward more aggressive surgical treatment. J Clin Oncol 2007;25:5203–5209.