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Nipple-Sparing Mastectomy for Breast Cancer and Risk-Reducing Surgery: The Memorial Sloan-Kettering Cancer Center Experience

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ABSTRACT

Background. Nipple-sparing mastectomy (NSM) has been gathering increased recognition as an alternative to more traditional mastectomy approaches. Initially, questions concerning its oncologic safety limited the use of NSM. Nevertheless, mounting evidence supporting the practice of NSM for both prophylactic and oncologic purposes is leading to its more widespread use and broadened indications.

Methods. Using a prospectively maintained database, we reviewed our experience of 353 NSM procedures performed in 200 patients over the past 10 years.

Results. The indications for surgery were: 196 prophylactic risk-reduction (55.5%), 74 ductal carcinoma in situ (DCIS) (20.8%), 82 invasive cancer (23.2%), and 1 phyllodes tumor (0.5%). The nipple areolar complex (NAC) was entirely preserved in 341 mastectomies (96.7%). There were 11 patients (3.1%) who were found to have cancer at the nipple margin, warranting further excision. A total of 69 breasts (19.5%) had some degree of skin desquamation or necrosis, but only 12 (3.3%) required operative debridement, of which 3 breasts (1%) necessitated removal of a breast implant. Also, 6 patients (2%) were treated for infection. Of the 196 prophylactic NSMs, 11 specimens (5.6%) were found to harbor occult cancer (8 DCIS and 3 invasive cancers). One patient who underwent NSM for invasive ductal carcinoma in 2006 developed metastatic disease to her brain. No other recurrences are attributable to the 353 NSMs.

Conclusions. The trends demonstrate the increasing acceptance of NSM as a prophylactic procedure as well as for therapeutic purposes. Although NSM is not standard, our experience supports the selective use of NSM in both prophylactic and malignant settings.

The surgical management of breast cancer has evolved over the past several decades from the radical mastectomy to the acceptance of breast conservation as the achievable goal for early breast cancer. Paralleling this has been advancement in the cosmetic approaches in breast reconstruction. The majority of patients undergoing mastectomy for either therapeutic or risk-reducing prophylactic indications opt for immediate breast reconstruction. The past 15 years have shown the safety and cosmetic superiority associated with skin-sparing mastectomy (SSM).[1–3] This has led surgeons to reconsider nipple-sparing mastectomy (NSM) for prophylaxis and to now consider NSM as a therapeutic alternative to select women with breast cancer.[4] The NSM combines preservation of the nipple areolar complex (NAC) with the SSM.

Historically, the ductal system of the breast and its relationship with breast cancer have been much reviewed in the surgical, pathological, and radiological literature. The NAC has traditionally been removed as part of the mastectomy specimen. The rationale for including the NAC has been in order to decrease the risk of a local recurrence in the remaining ductal tissue beneath the nipple (harboring occult disease), as well as early studies showing centripetal lymphatic drainage toward the subareolar plexus. The cosmetic "importance" of the NAC was recognized in a procedure by which the NAC was

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autotransplanted for future reimplantation; this was later abandoned because of breast cancer development at the autotransplantation site and poor cosmetic results due to compromised blood supply to the NAC.[5,6] Subcutaneous mastectomy with preservation of the NAC was reported in the 1960s by Freeman as limited to benign disease.[7,8] Multiple series have examined NAC involvement in mastectomy specimens; the results have been conflicting because of differences in pathologic assessment techniques, the quality and quantity of the preserved mastectomy specimens, the small sample size, and the difference in inclusion and exclusion criteria.[9–20] One study by Verma et al. of 26 NACs showed no NAC involvement; however, only tumors in the periphery of the breast were included.[18] In another series, NAC involvement was reported to be as high as 58%, yet this included patients with clinically involved nipples and centrally located tumors.[20] Most other studies report NAC involvement ranging from 8% to 33%, with the majority at 25%.[12,14,19]

Prediction models to determine the likelihood of NAC have been developed. Lagios et al. found that the distance between the NAC and tumor, tumor size, multicentricity, tumor differentiation, and positive axillary lymph nodes corresponded to an increased incidence of NAC involvement. His study reports NAC involvement of 30%. Other studies during the same time period reported NAC involvement ranging from 16% to 42%, with the consistent findings being the distance between the NAC and tumor and also tumor size.[16,21]

Recent data have shown an increase in the number of bilateral mastectomies performed in the United States.[22] Many of these were initially in response to reports indicating the overall benefits to survival with prophylactic surgery in high-risk women.[23] Recent data show this trend occurring in women who are appropriate candidates for breast-conservation surgery but who are optional for therapeutic mastectomy and CPM.[22]

In 2009 we reported on our initial 42 NSMs at Memorial Sloan-Kettering Cancer Center.[10] The majority were risk-reduction prophylactic procedures. Since this first report, we have performed 353 NSMs, including 157 therapeutic NSMs. This update reviews this procedure, its minimal complications, and its long-term outcomes when available, and we describe our experience in both the prophylactic and therapeutic settings.

MATERIALS AND METHODS

A retrospective review of our institutional database was queried to identify patients who underwent NSM from January 2000 to December 2010. This study was approved by the Institutional Review Board of Memorial Sloan-Kettering Cancer Center. A total of 8991 mastectomies performed for any indication were identified. From these, 353 were NSMs, performed in 200 patients, representing 3.9% of all mastectomies. Information was compiled from chart review, and we recorded population and tumor characteristics, complications, and need for reoperation. Informed consent was obtained in all patients with a clear explanation of the risk of residual involved tissue in the NAC and the need to excise the NAC if this was found on permanent pathology. The NSMs were offered to selected patients with clinically negative axillas and tumors less than 3 cm in any of the 4 quadrants. In addition, tumors had to be greater than 1 cm from the NAC (prior to 2005 this distance was 2 cm). This assessment was by either clinical exam or breast imaging; mammogram, ultrasound, or magnetic resonance imaging (MRI). MRI was not required for the NSM. Patients with nipple-areolar infiltration or erosion were excluded from this procedure. Table 1 describes the patient population and the breast cancer characteristics.

TABLE 1 353 nipple-sparing mastectomies in 200 patients

Characteristic	*N*	%
Age at diagnosis, median (range) (years)	44 (23–69)	
Prophylactic	43 (23–69)	
Cancer	44 (26–56)	
Prophylactic NSM	196	55.5
Cancer NSM	157	44.5
Size, median (range) (cm)	1.1 (0.1–5.0)	
Histologic tumor type		
IDC	82	52.2
DCIS	74	47.2
Malignant phyllodes	1	0.6
BRCA status	75/200	37.5
BRCA-1	25/75	33.3
BRCA-2	11/75	14.7
BRCA negative	39/75	52
Family history		
Yes	139	69.5
No	61	30.5
Stage	353	100
0	118	59
IA	54	27
IB	8	4
IIA	12	6
IIB	6	3
IIIA	2	1

NSM nipple-sparing mastectomy, *CPM* contralateral prophylactic mastectomy, *IDC* invasive ductal carcinoma, *DCIS* ductal carcinoma in situ

All procedures were performed by a surgeon from our breast surgical service in coordination with a plastic surgeon. The NSM was not performed in patients who were found to have grade 4 ptosis, oversized breasts, or diabetes, or who were heavy smokers or obese. Periareolar, lateral, or a combination of these incisions were used; there were no inframammary incisions for the NSMs. The surgical technique was the same in both the prophylactic and therapeutic groups, with thin 5-mm flaps beneath the NAC and intraoperative frozen sections performed on a biopsy of the retroareolar ducts in the therapeutic cases. If neoplasia was both identified intraoperatively as well as on permanent final pathology, the NAC was removed. Sentinel node biopsy was performed in 108 patients (89.2%) with cancer and 34 (43%) who had prophylactic surgery. All but 1 case was reconstructed with breast implants in a 2-stage procedure; there was 1 immediate reconstruction with a transverse rectus abdominis myocutaneous (TRAM) flap. Each mastectomy was considered an individual event in patients with bilateral procedures, and CPMs were recorded as such.

RESULTS

A total of 200 women between January 2000 and December 2010 underwent 353 NSMs for either prophylaxis or the treatment of breast cancer. Of these NSMs, 56% were for breast cancer risk reduction. (Fig. 1 shows the institutional trends.) Among this group of prophylactic mastectomies, 81% had a family history of breast cancer and 36 patients (18%) were positive for a BRCA mutation (Table 2). There were 153 patients with bilateral mastectomies (76.5%). In the women choosing prophylactic mastectomy, 76% of the mastectomies were a CPM in women with a therapeutic NSM.

There were 157 therapeutic NSMs performed, representing 44% of the NSMs between 2000 and 2010. There were 74 ductal carcinoma in situ (DCIS) (20.8%), 82 invasive carcinoma (23.2%), and 1 phyllodes tumor cases. Among the 82 invasive cancers, 62 were stage I (75.6%), 18 were stage II (22%), and 2 were stage III (2.4%). The 2 stage III tumors were initially less than 3 cm on imaging; however, they were greater than 5 cm on final pathology. The median tumor size was 1.1 cm (0.1–5.0 cm). A sentinel node biopsy was performed in 108 therapeutic mastectomies (89.2%) and was positive in only 6 cases (5.5%). None of the patients having sentinel node biopsies for prophylaxis had positive sentinel lymph nodes.

There were 196 prophylactic NSMs; therefore, 11 (5.6%) specimens were found to harbor occult cancer (8 DCIS and 3 invasive cancers) being that 9 identified intraoperatively with frozen section and 2 on permanent pathology. None of these had carcinoma at the NAC

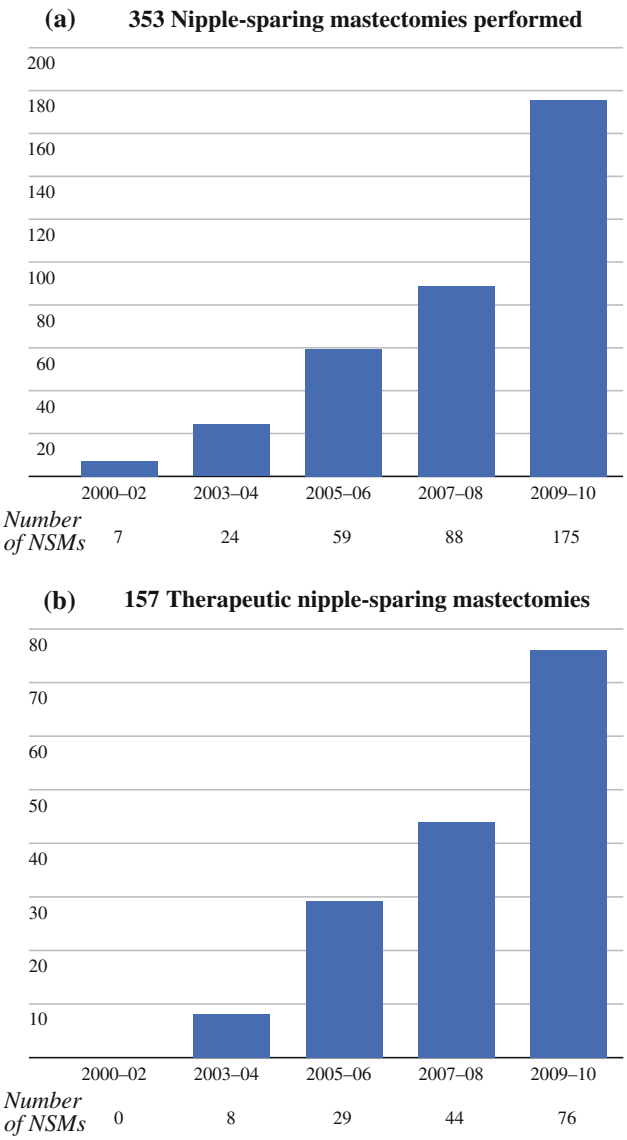

FIG. 1 Institutional trends in nipple-sparing mastectomy. **a** 353 nipple-sparing mastectomies performed. **b** 157 therapeutic nipple-sparing mastectomies performed

TABLE 2 Distribution of BRCA in the study population

	N	%
Prophylactic NSMs	79	39.5
BRCA-1	16	20.3
BRCA-2	6	7.6
Tested negative	11	13.9
Therapeutic NSMs	121	60.5
BRCA-1	9	7.5
BRCA-2	5	4.2
Tested negative	28	2.3

NSM nipple-sparing mastectomy

margin necessitating removal of the NAC. At a median follow-up of 10.38 months (range, 0–109 months), there were no reported local recurrences and 1 patient developed metastatic disease to her brain.

The NAC was entirely preserved in 341 mastectomies (96.7%). Of the mastectomies, 1 (0.2%) had partial loss of the NAC and the others were removed because of involvement of the retroareolar ductal tissue with carcinoma (Table 3). The postoperative complications were evaluated by the plastic surgeons. There were 69 of breasts (19.5%) that had some degree of skin desquamation or necrosis, but only 12 (3.3%) required operative debridement, of which 3 (1%) required removal of a tissue expander. Also, 6 patients (2%) were treated for infection. (Table 4 describes the overall complication rates.)

DISCUSSION

The rate of bilateral mastectomy in women with unilateral breast cancer in the United States has increased between 1998 and 2003. Surveillance, Epidemiology, and End Results (SEER) data showed that this rate increased from 4.2% in 1998 to 11.0% in 2003.[22] Mislowsky et al. reported a significant decrease in the unilateral mastectomy with a rise in bilateral mastectomy after the period 1996–2000, attributing this to the commercial availability of BRCA1/2 testing.[24] Hartmann et al. published follow-up data on women who had prophylactic mastectomy at the Mayo Clinic and found that subcutaneous mastectomy had a protective benefit by reducing the risk of breast cancer in BRCA1/2 mutation carriers, high-risk women, and moderate-risk women.[23]

NSM represented 1% of all mastectomies performed at our institution in the early study period 2000–2005. It was used primarily in risk-reduction prophylactic procedures (81%) or in carefully selected patients with peripherally located tumors and negative retroareolar tissue.[10] NSMs represented 3.9% of all mastectomies performed at Memorial Sloan-Kettering Cancer Center during the study period 2000–2010. Of the NSMs performed after 2006, 48.2% were performed for therapeutic indications, either DCIS or invasive cancer.

TABLE 3 Nipple areolar complex in 353 nipple-sparing mastectomies

NAC in 353 NSMs	*N*	%
Preserved overall	341	96.7
NAC removed	11	3.1
Invasive cancer	8	2.3
DCIS	3	0.8

NAC nipple areolar complex, *NSM* nipple-sparing mastectomy, *DCIS* ductal carcinoma in situ

TABLE 4 Overall complication rates

Overall complication rates	Total	%
Skin desquamation	69	19.5
Necrosis requiring debridement	12	3.3
Hematoma	0	0
Removal of the implant	3	1
Infection	6	2

The patients in our study had a median tumor size of 1.1 cm, and all were carefully selected; those with peripherally located tumors, clinically negative axillas, $T < 3$ cm, and multifocality were excluded. Most of these patients would have been candidates for breast-conservation surgery. Several contributing factors for this increase in mastectomy rate and subsequent CPM include the availability of BRCA1/2 testing, perceived increased risk and anxiety, the use of MRI and detection of additional lesions/need for continued surveillance, and the improvements in reconstructive options, in particular NSM. The study of Mislowsky et al. showed that women with lymph node-negative disease, a higher portion of T1 tumors, and those who had prophylactic oophorectomy were more likely to have CPM.[24] Our data support this finding, with 76% of the prophylactic mastectomies being for CPM and 24% for risk reduction without a cancer diagnosis.

The use of NSM has expanded from prophylactic situations to the treatment of breast cancer. The question of whether this is an oncologically "safe" procedure remains. The reported rate of nipple involvement in mastectomy specimens ranges from 0% to 58%.[9–21] Much of the conflicting reports can be explained by inconsistent inclusion and exclusion criteria, the quantity and quality of the preserved mastectomy specimens, and differences in statistical reporting. Brachtel et al. examined 316 consecutive mastectomy specimens with grossly unremarkable nipples and showed that of the 21% of nipples from the therapeutic mastectomies with involved pathology, this was mainly DCIS (62%). Brachtel et al. also showed that nipple involvement with carcinoma is associated with tumor size and type, distance to the nipple, histologic grade, HER2 amplification, lymphovascular invasion, and lymph node involvement, and concluded that a retroareolar en face margin could be used for NAC involvement in NSM.[16] In a carefully selected group of patients, Laronga et al. reported the incidence of occult tumor involvement of the NAC to be 6%, with 66% of these being identifiable at the time of surgery with an intraoperative frozen assessment.[17] Our study showed involvement of the NAC in 11 of 157 patients having a therapeutic mastectomy. All were identified with intraoperative frozen section, and the NAC was removed.

In our series, there were no reported local recurrences, albeit with a limited follow-up period. There was 1 patient who developed a brain metastasis and death due to metastatic disease. Several studies have shown that local recurrence after SSM is similar to that of a conventional mastectomy and breast conservation: 5.5–6.2%. The local recurrence rates after NSMs range from 0.0% to 24.1%, with lower rates in the studies with strict inclusion criteria.[9,12,13,15–19] Voltura et al. studied 31 NSMs for breast cancer stages 0–3A and reported a 5.9% local recurrence, concluding that the local recurrence is most likely a manifestation of the tumor biology rather than preservation of the skin and NAC.[9]

Preservation of the NAC and its importance within the context of a woman's body image has been addressed in several studies.[25–30] Didier et al. report that patients expressed a very high level of satisfaction with nipple preservation and perceived NSM as helpful to better cope with the traumatic experience of breast cancer and loss of a breast.[31] Patient satisfaction with NSM has been rated good–excellent in 78.6% of patients, and 42.9% of patients retained nipple sensation.[32] In an earlier report from Memorial Sloan-Kettering Cancer Center with its first 42 NSMs, cosmetic results were excellent in 30 mastectomies, good in 7, acceptable in 8, and poor in 2.[10] The NAC was preserved in 96.7% of patients, with 0.2% having partial loss as a result of the surgical procedure. The complication rate for NSM has been reported to be about 10%. In our series, 69 (19.5%) had some degree of skin desquamation or necrosis, but only 12 (3.3%) required operative debridement, of which only 3 breasts (1%) had the breast implant removed.

In conclusion, the oncologic safety of the NSM continues to be controversial. Most of the published series are limited because of insufficient long-term follow-up regarding local recurrence. Selection criteria for NSM continue to evolve, with tumor size and nipple–tumor distance being significant factors. This series limited tumor size to < 3 cm, and tumor distance from the nipple was 1 cm or greater and did not include patients with neoadjuvant treatment. The reported involvement of the NAC is minimal and can be managed appropriately with intraoperative frozen assessment of the retroareolar tissue. NSM has a positive impact on patient satisfaction and body image, yet longer follow-up is needed and patients should be counseled about the controversies and complications prior to performing this procedure.

REFERENCES

1. Eldor L, Spiegel A. Breast reconstruction after bilateral prophylactic mastectomy in women at high risk for breast cancer. *Breast J.* 2009;15:S81–9.
2. Lostumbo L, Carbine NE, Wallace J. Prophylactic mastectomy for the prevention of breast cancer. *Cochrane Database Syst Rev.* 2010;(11):CD002748.
3. Morrow M, Mehrara B. Prophylactic mastectomy and the timing of breast reconstruction. *Br J Surg.* 2009;96:1–2.
4. Rusby JE, Smith BL, Gui GP. Nipple-sparing mastectomy. *Br J Surg.* 2010;97:305–16.
5. Cucin RL, Guthrie RH, Jr, Luterman A, Shires GT, Goulian D, Jr. Transplantation of the cryopreserved nipple-areolar complex. *Ann Plast Surg.* 1980;4:391–5.
6. Rose JH, Jr. Carcinoma in a transplanted nipple. *Arch Surg.* 1980;115:1131–2.
7. Freeman BS. Subcutaneous mastectomy for benign breast lesions with immediate or delayed prosthetic replacement. *Plast Reconstr Surg Transplant Bull.* 1962;30:676–82.
8. Freeman BS. Complications of subcutaneous mastectomy with prosthetic replacement, immediate or delayed. *South Med J.* 1967;60:1277–80.
9. Voltura AM, Tsangaris TN, Rosson GD, Jacobs LK, Flores JI, Singh NK, et al. Nipple-sparing mastectomy: critical assessment of 51 procedures and implications for selection criteria. *Ann Surg Oncol.* 2008;15:3396–401.
10. Garcia-Etienne CA, Cody HS, III, Disa JJ, Cordeiro P, Sacchini V. Nipple-sparing mastectomy: initial experience at the Memorial Sloan-Kettering Cancer Center and a comprehensive review of literature. *Breast J.* 2009;15:440–9.
11. Edge SB. Nipple-sparing mastectomy: how often is the nipple involved? *J Clin Oncol.* 2009;27:4930–2.
12. Crowe JP, Patrick RJ, Yetman RJ, Djohan R. Nipple-sparing mastectomy update: one hundred forty-nine procedures and clinical outcomes. *Arch Surg.* 2008;143:1106–10; discussion 10.
13. Petit JY, Veronesi U, Orecchia R, Rey P, Martella S, Didier F, et al. Nipple sparing mastectomy with nipple areola intraoperative radiotherapy: one thousand and one cases of a five years experience at the European institute of oncology of Milan (EIO). *Breast Cancer Res Treat.* 2009;117:333–8.
14. Gerber B, Krause A, Dieterich M, Reimer T, Kundt G. The oncological safety of skin sparing mastectomy with conservation of the nipple-areola complex and autologous reconstruction: an extended follow-up study. *Ann Surg.* 2009;249:461–8.
15. Sacchini V, Pinotti JA, Barros AC, Luini A, Pluchinotta A, Pinotti M, et al. Nipple-sparing mastectomy for breast cancer and risk reduction: oncologic or technical problem? *J Am Coll Surg.* 2006;203:704–14.
16. Brachtel EF, Rusby JE, Michaelson JS, Chen LL, Muzikansky A, Smith BL, et al. Occult nipple involvement in breast cancer: clinicopathologic findings in 316 consecutive mastectomy specimens. *J Clin Oncol.* 2009;27:4948–54.
17. Laronga C, Kemp B, Johnston D, Robb GL, Singletary SE. The incidence of occult nipple–areola complex involvement in breast cancer patients receiving a skin-sparing mastectomy. *Ann Surg Oncol.* 1999;6:609–13.
18. Verma GR, Kumar A, Joshi K. Nipple involvement in peripheral breast carcinoma: a prospective study. *Indian J Cancer.* 1997;34:1–5.
19. Lagios MD, Gates EA, Westdahl PR, Richards V, Alpert BS. A guide to the frequency of nipple involvement in breast cancer. A study of 149 consecutive mastectomies using a serial subgross and correlated radiographic technique. *Am J Surg.* 1979;138:135–42.
20. Menon RS, van Geel AN. Cancer of the breast with nipple involvement. *Br J Cancer.* 1989;59:81–4.
21. Gulben K, Yildirim E, Berberoglu U. Prediction of occult nipple-areola complex involvement in breast cancer patients. *Neoplasma.* 2009;56:72–5.
22. Tuttle TM, Habermann EB, Grund EH, Morris TJ, Virnig BA. Increasing use of contralateral prophylactic mastectomy for

breast cancer patients: a trend toward more aggressive surgical treatment. *J Clin Oncol.* 2007;25:5203–9.
23. Hartmann LC, Schaid DJ, Woods JE, Crotty TP, Myers JL, Arnold PG, et al. Efficacy of bilateral prophylactic mastectomy in women with a family history of breast cancer. *N Engl J Med.* 1999;340:77–84.
24. Mislowsky A, Domchek S, Stroede C, Bergey MR, Sonnad SS, Wu L, et al. Breast cancer surgery trend changes since the introduction of BRCA1/2 mutation screening: a retrospective cohort analysis of 158 mutation carriers treated at a single institution. *Ann Surg Oncol.* 2011;18:745–51.
25. Morimoto T, Komaki K, Inui K, Umemoto A, Yamamoto H, Harada K, et al. Involvement of nipple and areola in early breast cancer. *Cancer.* 1985;55:2459–63.
26. Luttges J, Kalbfleisch H, Prinz P. Nipple involvement and multicentricity in breast cancer. A study on whole organ sections. *J Cancer Res Clin Oncol.* 1987;113:481–7.
27. Santini D, Taffurelli M, Gelli MC, Grassigli A, Giosa F, Marrano D, et al. Neoplastic involvement of nipple-areolar complex in invasive breast cancer. *Am J Surg.* 1989;158:399–403.
28. Vyas JJ, Chinoy RF, Vaidya JS. Prediction of nipple and areola involvement in breast cancer. *Eur J Surg Oncol.* 1998;24:15–6.
29. Benediktsson KP, Perbeck L. Survival in breast cancer after nipple-sparing subcutaneous mastectomy and immediate reconstruction with implants: a prospective trial with 13 years median follow-up in 216 patients. *Eur J Surg Oncol.* 2008;34:143–8.
30. Petit JY, Veronesi U, Rey P, Rotmensz N, Botteri E, Rietjens M, et al. Nipple-sparing mastectomy: risk of nipple-areolar recurrences in a series of 579 cases. *Breast Cancer Res Treat.* 2009; 114:97–101.
31. Didier F, Radice D, Gandini S, Bedolis R, Rotmensz N, Maldifassi A, et al. Does nipple preservation in mastectomy improve satisfaction with cosmetic results, psychological adjustment, body image and sexuality? *Breast Cancer Res Treat.* 2009;118: 623–33.
32. Nahabedian MY, Tsangaris TN. Breast reconstruction following subcutaneous mastectomy for cancer: a critical appraisal of the nipple-areola complex. *Plast Reconstr Surg.* 2006;117:1083–90.