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Prophylactic Versus Therapeutic Mastectomy: A Contemporary Analysis of the ACS-NSQIP Database

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Abstract

Rates of prophylactic mastectomy are increasing in the United States and might be elected for prevention in women with a hereditary predisposition to breast cancer. Using the American College of Surgeons National Surgical Quality Improvement Program database to study 30,803 patients, the data show that women who undergo prophylactic, rather than therapeutic, mastectomy, show a 5.8-fold increased risk of deep venous thrombosis.

Introduction: The objective of the study was to evaluate the morbidity, mortality, and postoperative outcomes associated with simple or subcutaneous mastectomy in the management of prophylactic versus therapeutic resection. In this study we aimed to assess if simple or subcutaneous mastectomy for prophylaxis affects perioperative outcomes compared with resection performed for biopsy proven malignancy. **Materials and Methods:** The American College of Surgeons National Surgical Quality Improvement Program database was queried for subjects who underwent simple or subcutaneous mastectomy between 2007 and 2012. Patient demographic characteristics, comorbid conditions, and postoperative complications were analyzed. **Results:** Of the 30,803 patients, 30,644 (99.5%) underwent therapeutic mastectomy and 159 (0.5%) underwent prophylactic mastectomy. Subjects who underwent prophylactic surgery were more likely to be younger (45 vs. 58 years; $P < .01$) and white (134 [84%] vs. 20,647 [67%]; $P < .01$). Surgery time was significantly greater in the prophylactic group (265 vs. 166 minutes; $P < .01$). There was no significant difference in mortality between groups. There was a trend toward greater 30-day morbidity (15 [9%] vs. 1835 [6%]; $P = .09$) and occurrence of deep venous thrombosis (DVT; 2 [1%] vs. 74 [0.2%]; $P = .06$) in those who underwent prophylactic mastectomy. After age adjustment, the prophylactic group showed a nearly sixfold increase in DVT (odds ratio [OR], 5.77; 95% confidence interval [CI], 1.37-24.22), which persisted when controlling for surgery time (OR, 4.95; 95% CI, 1.18-20.86). **Conclusion:** Prophylactic simple or subcutaneous mastectomy incurs significant additional 30-day postoperative morbidity related to perioperative DVT. Risk-mitigating strategies should be considered in the perioperative care of this patient population.

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Introduction

Breast cancer is the most common malignancy in women and is the second leading cause of cancer-related deaths in the United States.[1] Although the most cases are sporadic, approximately 5% to 10% are associated with germ line deleterious breast cancer gene (*BRCA*)*-1* and *BRCA2* mutations.[2]

For sporadic cancers, there has been a significant trend toward mastectomy in patients who are eligible for breast-conserving surgery with radiation.[3,4] This trend is most marked in those with node-negative and in situ disease.[4] Additionally, the rates of contralateral prophylactic mastectomy (CPM) have doubled over the past 6 to 10 years in women who undergo mastectomy for ipsilateral malignancy. Rates of CPM are now estimated at 12% to 56%.[2,5,6] These trends might in part be related to the evolution of

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Table 1 Patient Demographic Characteristics and Preoperative Factors

Variable	Therapeutic Mastectomy (n = 30,644)	Prophylactic Mastectomy (n = 159)	*P*
Mean Age, Years	58.4	44.6	<.01
Mean BMI	27.9	27.1	.16
Race, n (%)			<.01
White	20,647 (67.3)	134 (84.3)	
Black	2520 (8.2)	5 (3.1)	
Asian/Pacific Islander	1589 (5.2)	2 (1.3)	
American Indian	138 (0.5)	0 (0.0)	
Other/unknown	5750 (18.8)	18 (11.3)	
Current Tobacco Use	3909 (12.8)	17 (10.7)	.44
Current Alcohol Use	307 (1.0)	0 (0.0)	.41
HTN Requiring Medication	11,982 (39.1)	20 (12.6)	<.01
COPD	705 (2.3)	0.0	.06
CHF Within 30 Days	31 (0.1)	0.0	1.00
MI Within 6 Months	31 (0.1)	0.0	1.00
Angina Within 1 Month	61 (0.2)	0.0	1.00
Chronic PVD	123 (0.4)	1 (0.8)	.37
Acute Renal Failure	31 (0.1)	0.0	1.00
Current Dialysis	92 (0.3)	0.0	1.00
TIA	490 (1.6)	3 (1.7)	.71
CVD	306 (1.0)	0.0	.64
Disseminated Cancer	398 (1.3)	0.0	.27
Current Steroid Use	460 (1.5)	0.0	.18
Weight Loss > 10% Over 6 Months	123 (0.4)	1 (0.6)	.49
Bleeding Disorder	460 (1.5)	1 (0.6)	.73
Chemotherapy Within 30 Days	1226 (4.0)	1 (0.8)	.10
Radiotherapy Within 30 Days	92 (0.3)	0 (0.0)	1.00
DNR Code Status	25 (0.1)	0 (0.0)	1.00

Data are presented as n (%) of those with available data unless otherwise specified.
Abbreviations: BMI = body mass index; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; CVD = cerebrovascular disease; DNR = do not resuscitate; HTN = hypertension; MI = myocardial infarction; PVD = peripheral vascular disease; TIA = transient ischemic attack.

breast reconstruction and skin-sparing mastectomy, allowing for improved cosmetic outcomes.[7]

Bilateral prophylactic mastectomy (BPM) can also be offered as primary prevention in asymptomatic high-risk women with genetic mutations, most commonly *BRCA1* or *BRCA2*.[8] In these cases, BPM can reduce the risk of breast cancer development by 90%, and greatly diminish the 56% to 87% lifetime risk these women carry if left untreated.[4] As many as 50% of patients who are *BRCA1* or *BRCA2* carriers elect to undergo BPM as a means of primary prophylaxis.[8] When considering prophylactic mastectomy, the morbidity and mortality associated with the procedure are not negligible, and therefore other chemoprevention and surveillance should be considered.[9] Furthermore, because of the inherent inability to remove all breast tissue, the risk is not entirely eliminated with prophylactic mastectomy.

With the combination of improved diagnostics, less invasive surgical techniques, and the societal acceptance of surgical prophylaxis, the annual number of mastectomies performed continues to rise in the United States.[3,4] Despite the broad range of indications for a simple or subcutaneous mastectomy, there are limited data addressing perioperative outcomes stratified according to surgical indication (therapeutic vs. prophylactic). In this study used a national database to compare differences in perioperative outcomes between women who underwent therapeutic mastectomy for malignancy compared with those who underwent prophylactic mastectomy in the setting of a genetic predisposition to breast cancer.

Materials and Methods

Data Source

The American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) Participant Use Data Files were queried from 2007 to 2012. This study was conducted after approval by the institutional review board of the University of Massachusetts Medical School and a Health Insurance Portability and Accountability Act of 1996 waiver of consent was granted because the data for this study is from a deidentified national database, the ACS-NSQIP.

Table 2 Univariate Analysis of Intraoperative and Postoperative Outcomes

Variable	Therapeutic Mastectomy (n = 30,644)	Prophylactic Mastectomy (n = 159)	*P*
Mean Surgery Time, Minutes	166.3	265.2	<.01
30-Day Mortality	37 (0.1)	0 (0.0)	1.00
30-Day Morbidity	1835 (6.0)	15 (9.4)	.09
Superficial SSI	656 (2.1)	6 (3.8)	.16
Deep SSI	254 (0.8)	1 (0.6)	1.00
Organ Space SSI	147 (0.5)	0 (0.0)	1.00
Pneumonia	46 (0.2)	0 (0.0)	1.00
Reintubation	34 (0.1)	0 (0.0)	1.00
Pulmonary Embolism	40 (0.1)	0 (0.0)	1.00
Ventilator Support >48 Hours	21 (0.1)	0 (0.0)	1.00
Progressive Renal Insufficiency	12 (0.0)	0 (0.0)	1.00
Acute Renal Failure	9 (0.0)	0 (0.0)	1.00
Urinary Tract Infection	110 (0.4)	1 (0.6)	.44
CVA	21 (0.1)	0 (0.0)	1.00
Coma >24 Hours	0 (0.0)	0 (0.0)	1.00
Peripheral Nerve Injury	9 (0.0)	0 (0.0)	1.00
Cardiac Arrest	9 (0.0)	0 (0.0)	1.00
MI	12 (0.0)	0 (0.0)	1.00
Transfusion Requirement	300 (1.0)	3 (1.9)	.20
DVT	74 (0.2)	2 (1.3)	.06
Sepsis	126 (0.4)	0 (0.0)	1.00
Septic Shock	21 (0.1)	0 (0.0)	1.00
Wound Dehiscence	138 (0.5)	2 (1.3)	.16

Data are presented as n (%) of those with available data unless otherwise specified.
Abbreviations: CVA = cerebrovascular accident; DVT = deep venous thrombosis; MI = myocardial infarction; SSI = surgical site infection.

Patient Cohort

All subjects who underwent simple or subcutaneous mastectomy were identified using Current Procedural Terminology codes 19303 and 19304. International Classification of Diseases ninth edition (ICD-9) codes for a genetic predisposition to malignant neoplasm of the breast (174, 174.0-174.9, 233, 233.0, v84.01) were then identified to stratify the cohort. Those who underwent a therapeutic mastectomy for biopsy-confirmed breast cancer or carcinoma in situ were compared with those who underwent a prophylactic mastectomy with a documented genetic predisposition to developing a malignancy. These ICD-9 codes do not identify a specific deleterious mutation(s), although it is believed that most probably have a *BRCA* mutation. Male patients were excluded. Demographic characteristics, socioeconomic factors, comorbid conditions, intraoperative characteristics, and 30-day morbidity and mortality data were abstracted for each subject. ACS-NSQIP data are limited to 30-day outcomes; therefore, the focus of this study was immediate surgical complications, rather than long-term oncologic outcomes.

Statistical Analysis

Differences in group categorical variables were compared using χ^2 and Fisher exact tests. Continuous variables were analyzed using Student *t* tests. A *P* value of .05 was considered the cutoff point for statistical significance. Logistic regression models were used to evaluate the different odds of mortality between the therapeutic and prophylactic mastectomy groups. The outcome variables were then analyzed using age-adjusted logistic regression models. Because of the potential that the significance in deep venous thrombosis (DVT) incidence might be affected by surgery time, this outcome was further analyzed using age- and surgery time-adjusted logistic regression models. Analyses were performed using STATA software (version 15.1; StataCorp LLC, College Station, TX).

Results

A total of 30,803 female subjects met inclusion criteria, of whom 30,644 (99.5%) underwent therapeutic mastectomy and 159 (0.5%) underwent prophylactic mastectomy. Within the

Table 3 Adjusted Logistic Regression Models of Postoperative DVT

Variable	Odds Ratio	*P*	95% Confidence Interval
Age-Adjusted DVT	5.77	.02	1.37-24.22
Age- and Surgery Time-Adjusted DVT	4.95	.03	1.18-20.86

Abbreviation: DVT = deep venous thrombosis.

therapeutic mastectomy group, 24,131 (78.3%) patients underwent surgical resection for a diagnosis of biopsy-confirmed breast cancer; 6513 (21.1%) were treated for in situ carcinoma. All patients in the prophylactic mastectomy group had a documented genetic predisposition to breast cancer. In a comparison of the entire cohort, 29,254 (95%) underwent simple mastectomy; 1549 (5%) underwent subcutaneous mastectomy.

The baseline characteristics of patients who underwent therapeutic or prophylactic mastectomy are shown in Table 1. Patients who underwent surgery for prophylaxis were significantly younger (45 vs. 58 years; $P < .01$) and more frequently white (134 [84%] vs. 20,647 [67%]; $P < .01$) compared with those who underwent therapeutic surgery. Patients who underwent a therapeutic mastectomy were more likely to have hypertension requiring medication (11,982 [39%] vs. 20 [13%]; $P < .01$) and showed a trend toward increased frequency of comorbid chronic obstructive pulmonary disease (705 [2%] vs. 0 [0%]; $P = .06$). There were no additional differences in preoperative variables between groups.

Intraoperative factors and postoperative outcomes are summarized in Table 2. Surgery time was significantly greater in the prophylactic group (265 vs. 166 minutes; $P < .01$). Among the entire cohort, there was an extremely low 30-day mortality rate (0.12%) and no significant difference between groups (37 [0.1%] vs. 0 [0%]; $P = 1.0$). In univariate analysis, patients who underwent prophylactic mastectomy showed a trend toward greater total 30-day complications (15 [9%] vs. 1835 [6%]; $P = .09$) and a trend toward increased risk of DVT (2 [1.3%] vs. 74 [0.2%]; $P = .06$). Adjusting for age in multivariate logistic regression, patients who underwent prophylactic mastectomy carried a nearly sixfold increased risk of DVT (odds ratio [OR], 5.8; 95% confidence interval [CI], 1.4-24.2; $P = .02$; Table 3). Controlling for age and surgery time, DVT risk associated with prophylactic mastectomy persisted (OR, 5.0; 95% CI, 1.2-20.9; $P = .03$).

Discussion

To our knowledge, differences in postoperative outcomes after simple or subcutaneous mastectomy on the basis of indication for surgical resection (therapeutic or prophylactic) have not been previously reported. Herein, we present the first contemporary analysis of postoperative outcomes in a national cohort of patients who underwent mastectomy, with results stratified according to surgical indication. Although the two groups were largely similar with regard to preoperative and comorbid conditions, the data show that prophylactic mastectomy in the setting of a genetic predisposition to breast cancer might be associated with a 5.8-fold increased risk of postoperative DVT. This somewhat unexpected finding highlights a potential area to improve outcomes in a group of patients whose risk should be minimized because of the preventative nature of the intervention.

An increased risk of thromboembolic events in the setting of malignancy is a well known phenomenon.[10-13] The presence of malignancy predisposes to a hypercoagulable state through cell−cell interactions, cytokine release, and inhibition of fibrinolysis.[10,14,15] Hormonal and cytotoxic chemotherapy can increase the risk of thrombosis by 6.5-fold compared with the general population and by fourfold compared with cancer patients who do not receive chemotherapy.[10,14] Despite the rates of disseminated cancer and preoperative chemotherapy being low in this study, we hypothesized an increased risk for DVT in the therapeutic mastectomy group because of the pathophysiology associated with the presence of malignancy. Unexpectedly, we found the opposite result. The reason for this paradoxical outcome is unknown and deserves further evaluation because of the limited data available to explain these striking differences.

In an ACS-NSQIP study, Stone and colleagues investigated the rates of thromboembolic complications among various cancer surgeries and reported an overall DVT rate of 0.19% for all breast cancer surgeries.[16] Our findings are consistent with this report because the rate of DVT in the entire cohort was 0.25%. However, stratifying according to surgical indication, the rate of DVT in the prophylactic mastectomy group was 1.26%, much greater than previously reported in studies that evaluated all patients who underwent breast resection.

Although a causal relationship cannot be established by our retrospective analysis, there have been studies supporting hypotheses in which the *BRCA* mutation itself predisposes to an increased risk of thromboembolic events. Custodio et al reported that *BRCA1* mutation carriers expressed altered levels of plasma proteins associated with thrombosis and coagulation.[17] More specifically, the authors reported significantly increased expression of isotypes of fibrinogen, serotransferrin, and convertase C3/C5, and significantly decreased expression of α-1 antitrypsin, apolipoprotein, and vitamin D binding protein in *BRCA1* carriers. However, the effects of breast pathology on hypercoagulability are important when considering genetic predispositions to breast cancer. Tissue factor—the primary initiator of the coagulation cascade—has been recognized to play a major role in tumor progression from hyperplasia to invasive carcinoma.[18-21] Because studies have shown a higher prevalence of atypical hyperplasia and malignant lesions upon analysis of prophylactic mastectomy surgical specimens in unaffected high-risk women, this might be an important contributor to coagulopathy.[8,22,23] In the current study we were unable to evaluate the biological rationale for the clinical outcomes, but these previous studies suggest further investigation into the correlation of causative factors with clinical outcomes should be considered.

The relative benefits of prophylactic mastectomy have been debated over the past 10 years, particularly in the setting of *BRCA* mutation carriers. Although BPM can reduce the risk of breast cancer in this population by approximately 90%, a meta-analysis by Lostumbo et al suggests that because of incomplete penetrance in 70% of cases, a number of women who elect BPM are actually being overtreated.[9] Despite these data, there is an increasing trend toward prophylactic mastectomy for asymptomatic high-risk patients, such as those with a deleterious *BRCA* mutation.[24-26] Because of the current data and national trends toward partial mastectomy and chemoprevention, further discussion about routine perioperative anticoagulation or less invasive options are indicated in these specific populations with a significant risk of breast cancer.[9]

Although mastectomy for breast cancer is rather common, mastectomies for prophylactic purposes and the presence of perioperative DVTs are less frequent. Therefore, the use of the ACS-NSQIP database is beneficial because it affords the opportunity to study the population in a large, standardized, and multi-institutional manner over a number of years, adding relevance to a finding that would otherwise be challenging to study because of the infrequency.

Furthermore, the data reflect national practice trends and might be generalizable to the general population.

However, there are inherent limitations within this database including the lack of information related to additional therapies (including but not limited to preoperative thromboprophylaxis and hormonal agents), tumor staging, details on individual genetic mutations, and institution-specific practice patterns. It is possible all relevant covariates were not controlled for in the model. Furthermore, a causative mechanism between deleterious mutation carriers and increased DVT rates cannot be definitively proven in the context of this retrospective study. It is also important to note that our conclusions regarding the risk of DVT after prophylactic mastectomy are restricted to short-term outcomes, specifically 30 days after surgery. As such, these findings of increased risk cannot be extended or assumed to apply beyond this time period.

Conclusion

Our study showed a 5.8-fold increased risk of postoperative DVT in patients who elected a prophylactic mastectomy because of a genetic predisposition for malignancy. This finding is unexpected and raises the question whether there is a pathophysiologic basis for the increased risk of DVT in these patients who tend to be *BRCA* mutation carriers. Further exploration to better define the biologic basis for these findings is needed, and our results reiterate the need to properly counsel these high-risk patients and use preventative strategies to reduce the risk of complications.

Clinical Practice Points

- Because mastectomy might be elected for prevention in women with a hereditary predisposition to breast cancer, this study evaluated national outcomes for prophylactic mastectomy compared with mastectomy in the setting of malignancy.
- Rates of contralateral and BPM are increasing in the United States.
- Adjusted logistic regression revealed a 5.8-fold increased risk of DVT after prophylactic mastectomy compared with therapeutic mastectomy.

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Disclosure

The authors have stated that they have no conflicts of interest.

References

1. Surveillance, Epidemiology, and End Results (SEER) Program Populations (1969-2014), National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, released March 2016. Available at: https://seer.cancer.gov/data/citation.html, Accessed: February 22, 2018.
2. Boccardo C, Gentilini O. Contralateral risk reducing mastectomy in patients with sporadic breast cancer. Benefits and hazards. *Eur J Surg Oncol* 2016; 42:913-8.
3. Katz SJ, Lantz PM, Janz NK, et al. Patient involvement in surgery treatment decisions for breast cancer. *J Clin Oncol* 2005; 23:5526-33.
4. Kummerow KL, Du L, Penson DF, Shyr Y, Hooks MA. Nationwide trends in mastectomy for early-stage breast cancer. *JAMA Surg* 2015; 150:9-16.
5. Jones NB, Wilson J, Kotur L, Stephens J, Farrar WB, Agnese DM. Contralateral prophylactic mastectomy for unilateral breast cancer: an increasing trend at a single institution. *Ann Surg Oncol* 2009; 16:2691-6.
6. Briasoulis E, Roukos DH. Contralateral prophylactic mastectomy: mind the genetics. *J Clin Oncol* 2008; 26:1909-10.
7. Manning A, Sacchini VS. Conservative mastectomies for breast cancer and risk-reducing surgery: the Memorial Sloan Kettering Cancer Center experience. *Gland Surg* 2016; 5:55-62.
8. Meijers-Heijboer H, van Geel B, van Putten WL, et al. Breast cancer after prophylactic bilateral mastectomy in women with a *BRCA1* or *BRCA2* mutation. *N Engl J Med* 2001; 345:159-64.
9. Lostumbo L, Carbine NE, Wallace J. Prophylactic mastectomy for the prevention of breast cancer. *Cochrane Database Syst Rev* 2010; 11:CD002748.
10. Caine GJ, Stonelake PS, Rea D, et al. Coagulopathic complications in breast cancer. *Cancer* 2003; 98:1578-86.
11. Rickles FR, Edwards RL. Activation of blood coagulation in cancer: Trousseau's syndrome revisited. *Blood* 1983; 62:14-31.
12. Andtbacka RH, Babiera G, Kuerer HM. Incidence and prevention of venous thromboembolism in patients undergoing breast cancer surgery and treated according to clinical pathways. *Ann Surg* 2006; 243:96-101.
13. Lip GY, Chin BS, Blann AD. Cancer and the prothrombotic state. *Lancet Oncol* 2002; 3:27-34.
14. Osborne NH, Wakefield TW, Henke PK. Venous thromboembolism in cancer patients undergoing major surgery. *Ann Surg Oncol* 2008; 15:3567-78.
15. McEachron TA, Pawlinski R, Richards KL, Church FC, Mackman N. Protease-activated receptors mediate crosstalk between coagulation and fibrinolysis. *Blood* 2010; 116:5037-44.
16. De Martino RR, Goodney PP, Spangler EL, et al. Variation in thromboembolic complications among patients undergoing commonly performed cancer operations. *J Vasc Surg* 2011; 55:1035-40.
17. Custodio A, López-Farré AJ, Zamorano-León JJ, et al. Changes in the expression of plasma proteins associated with thrombosis in BRCA1 mutation carriers. *J Cancer Res Clin Oncol* 2012; 138:867-75.
18. Bluff JE, Brown NJ, Reed MW, Staton CA. Tissue factor, angiogenesis and tumour progression. *Breast Cancer Res* 2008; 10:204.
19. Cole M, Bromberg M. Tissue factor as a novel target for treatment of breast cancer. *Oncologist* 2013; 18:14-8.
20. van den Berg YW, Osanto S, Reitsma PH, Verstee HH. The relationship between tissue factor and cancer progression: insights from bench and bedside. *Blood* 2012; 119:924-32.
21. Bluff JE, Cross SS, Brown NJ, Reed MW, Staton CA. Assessment of angiogenesis in the hyperplasia preinvasive, invasive breast carcinoma sequence. *Breast Cancer Res* 2008; 10(suppl 2):(Abstract P46).
22. Klijn JG, Janin N, Cortes-Funes H, Colomer R. Should prophylactic surgery be used in women with a high risk of breast cancer? *Eur J Cancer* 1997; 33:2149-59.
23. Khurana KK, Loosmann A, Numann PJ, Khan SA. Prophylactic mastectomy: pathologic findings in high-risk patients. *Arch Pathol Lab Med* 2000; 124:378-81.
24. Evans DG, Wisely J, Clancy T, et al. Longer term effects of the Angelina Jolie effect: increased risk-reducing mastectomy rates in BRCA carriers and other high-risk women. *Breast Cancer Res* 2015; 17:143.
25. Evans DG, Barwell J, Eccles DM, et al. The Angelina Jolie effect: how high celebrity profile can have a major impact on provision of cancer related services. *Breast Cancer Res* 2014; 16:442.
26. Evans DG, Lalloo F, Ashcroft L, et al. Uptake of risk reducing surgery in unaffected women at high risk of breast and ovarian cancer is risk, age and time dependent. *Cancer Epidemiol Biomarkers Prev* 2009; 18:2318-24.