ORIGINAL RESEARCH & CONTRIBUTIONS

Comparative Effectiveness of Surgical Options for Patients with Ductal Carcinoma In Situ: An Instrumental Variable Approach

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ABSTRACT

Context: Many patients with ductal carcinoma in situ (DCIS) receive treatment that is too extensive.

Objective: To take a holistic approach in comparing the effectiveness in cancer prevention between mastectomy and breast-conserving surgery (BCS) for patients with DCIS.

Design: Female Kaiser Permanente Southern California members who underwent surgery for treatment of single primary DCIS from 2004 to 2014 were identified by the Kaiser Permanente Southern California cancer registry and HealthConnect database.

Method: Two-stage residual inclusion with the surgeon's preference of surgical procedure type as the instrumental variable was used to examine the effect of surgical choice on DCIS recurrence, breast cancer progression, and other cancer progression. Traditional Cox proportional hazards models were used for comparison.

Results: Of qualified subjects, 72.2% underwent BCS and 27.8% underwent mastectomy. Patients were likelier to receive BCS if their surgeon preferred to perform BCS in the past 5 years (odds ratio = 1.02, 95% confidence interval = 1.02-1.03). Although traditional Cox proportional hazards models suggested an association between BCS and higher risk of DCIS recurrence, no significant effect was observed when we adjusted for endogeneity. Neither model showed significant differences between mastectomy and BCS in progression of any cancer.

Conclusion: No significant benefit was observed with a more aggressive surgical procedure in preventing DCIS recurrence or cancer progression in a diverse population. Many patients with DCIS could benefit from BCS with preservation of their body image. Breast conservation followed-up with cancer surveillance is a rational approach to ensure affordable, effective care for patients with DCIS.

INTRODUCTION

Ductal carcinoma in situ (DCIS) is the earliest form of breast cancer presented in ductal cells. Because the cancer has not grown outside the mammary ducts, DCIS is considered noninvasive. Since the advent of mammographic screening, the DCIS incidence rate in the US markedly increased from 1.78 per 100,000 women in the 1970s to 32.5 per 100,000 women in 2004, then reached a plateau.[1-3]

According to National Comprehensive Cancer Network guidelines, options for DCIS treatment include lumpectomy with or without radiation therapy (commonly known as breast-conserving surgery [BCS]) and total mastectomy.[4] Treatment decisions are usually based on a variety of factors, including the patient's history, physical findings, bilateral mammograms, pathologic findings, tumor estrogen receptor (ER) status, genetic counseling, and results of breast magnetic resonance imaging.[4] Because DCIS is nonlethal, surgeons' attitudes regarding optimal management and patient preference may play an increased role in treatment decisions.[5]

Mastectomy is an invasive procedure that results in removal of the patient's entire breast. In addition to side effects and complications, women may feel differently about their bodies and themselves after mastectomy. These feelings may cause distress for some women, which could drastically reduce their quality of life and may trigger an additional burden in the health care system. Guidelines from the National Comprehensive Cancer Network suggested mastectomy should be the last resolution for DCIS if BCS is unsuitable or rejected. However, the study shows that since 2003, more women with a diagnosis of early-stage breast cancer who are eligible for lumpectomy chose mastectomy. The adjusted odds of mastectomy in BCS-eligible women increased by 34% from 2003 to 2011.[6]

Many patients with DCIS receive treatment that is too extensive.[7-9] In this study, we sought to challenge the misconception that mastectomy is superior to BCS in preventing cancer progression. We compared surgical effects of mastectomy and BCS for DCIS recurrence and cancer progression in real-world clinical settings. We also evaluated patient- and surgeon-specific factors associated with the choice of surgical type. The surgeon's experience and preference have effects on choice of surgical type, but the final choice is made by both parties (patient and surgeon). Finally, we used an instrumental variable to mitigate bias caused by confounding by indication for surgical choice in a nonexperimental study setting.

METHODS

Study Population

The study population included patients from Kaiser Permanente (KP) Southern California (KPSC), which is an integrated health system that serves more than 4.2 million residents of Southern California.[10] The KPSC Region includes 14 hospitals and more than 220 medical offices by a partnership of more than 6660 medical specialists. The study population from KPSC is socioeconomically, ethnically, and racially diverse, and is generally representative of the population residing in Southern

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California.[10] Membership in KPSC can be obtained by enrolling through the Kaiser Foundation Health Plan and provides its members with prepaid health care insurance and pharmaceutical benefits.

Data Sources

We used the KPSC's cancer registry and electronic medical records (EMRs) as the primary data sources for the study. Through the KPSC cancer registry, we obtained data on all patients who received a diagnosis and/or treatment of a new or prevalent cancer.

Inpatient and outpatient clinical databases of KPSC's EMRs were searched for the diagnosis and treatment of cancer to identify cancer cases. For each new diagnosis, an abstract was prepared, and the information pertaining to it was included in the cancer registry. In addition, all data collected for the study were reported to the State of California and to the Los Angeles Surveillance, Epidemiology, and End Results Program in a standardized format no later than six months after diagnosis. The data collected contained each patient's medical record number, date of diagnosis, primary site of tumor, histologic results, cancer stage at diagnosis, date of past contact, vital status, and treatment received for each cancer. The EMRs included details of the patients' interactions with the health care system and were used to create datasets, including detailed information on inpatient and outpatient visits, diagnoses, procedures, vital signs, laboratory and imaging results, and prescriptions used. In addition, information regarding patients' external medical claims was extracted to provide the details of patients' use of services and surgeons outside KPSC.

The KPSC membership databases were used to extract information pertaining to patient demographics and Health Plan enrollment, and these data were supplemented by mapping geocoded income and education-level information collected by the census tract.

Study Design and Subjects

This was a retrospective cohort study among members of the KPSC Health Plan who were identified as receiving a diagnosis and treatment of DCIS between January 1, 1998, and June 31, 2014. Patients were followed-up from the surgery date until occurrence of the selected outcome or censoring. Patients were censored if they died or disenrolled from the KP Health Plan, or if the study ended (December 31, 2014). The study was approved by the KPSC institutional review board.

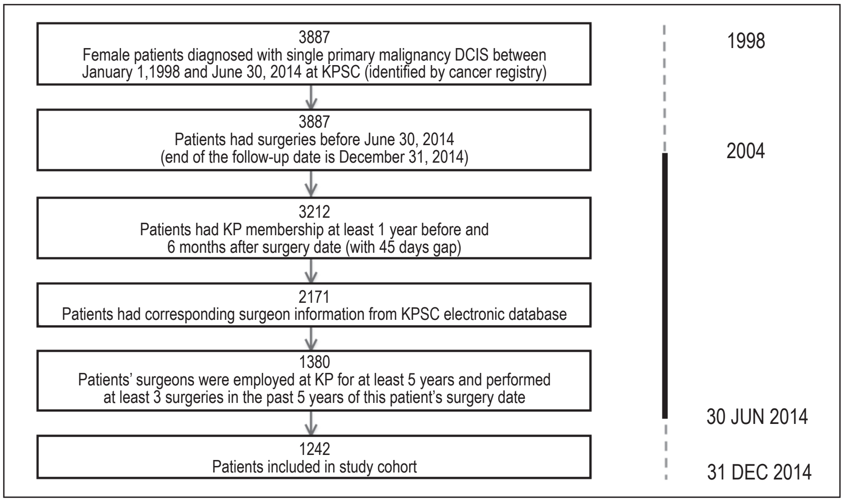

Figure 1. Flowchart of study cohort selection. Left panel (boxes) illustrates the process of study cohort selection with application of inclusion and exclusion criteria. Right panel demonstrates the timeline of patients' data inclusion. Dashed line indicates that patients' data were collected from 1998 to December 31, 2014. Solid line indicates that the study cohort included patients who received surgical treatment between 2004 and June 30, 2014, and we followed them until the end of the study (December 31, 2014).
DCIS = ductal carcinoma in situ; KP = Kaiser Permanente; KPSC = Kaiser Permanente Southern California.

Table 1A. Patient demographic characteristics of study cohort by type of surgical procedure received for ductal carcinoma in situ (N = 1242)[a]

Characteristic	BCS	Mastectomy	Total	p value
Overall	897 (72.2)	345 (27.8)	1242	
Patient demographic characteristics				
Race				
White	444 (49.7)	160 (46.4)	604 (48.7)	0.30
Nonwhite	450 (50.3)	185 (53.6)	635 (51.3)	
Partner status				
Partnered	559 (62.7)	210 (61)	769 (62.2)	0.60
Not partnered	333 (37.3)	134 (39)	467 (37.8)	
Age at diagnosis, y				
Mean (SD)	59.9 (10.44)	59.2 (11.07)	59.7 (10.62)	0.46
< 60	436 (48.6)	173 (50.1)	609 (49)	0.63
≥ 60	461 (51.4)	172 (49.9)	633 (51)	
Patient socioeconomic status				
High school graduate and above				
0%-50%	35 (3.9)	7 (2.1)	42 (3.4)	0.26
51%-75%	210 (23.5)	82 (23.8)	292 (23.6)	
76%-100%	648 (72.6)	255 (74.1)	903 (73.0)	
Median household income, US$				
≤ 45,000	194 (21.7)	65 (18.9)	259 (20.9)	0.43
45,001-80,000	424 (47.5)	176 (51.2)	600 (48.5)	
> 80,001	275 (30.8)	103 (29.9)	378 (30.6)	

[a] Data are number (percentage) unless otherwise indicated.
BCS = breast-conserving surgery; SD = standard deviation.

Using KPSC cancer registry data, we identified 3887 female adult KPSC members who received a diagnosis of single primary DCIS between January 1, 1998, and December 31, 2014 (Figure 1). To ensure that every patient had at least 6 months' follow-up until the end of the study, we excluded patients with a DCIS diagnosis obtained after June 30, 2014. A total of 3212 patients had continuous KP membership for at least 1 year before and 6 months after their surgery dates, with a 45-day gap allowed. Moreover, 2171 patients who received either lumpectomy or mastectomy were matched to the KP HealthConnect electronic database for corresponding surgeon information.

Among these patients, 1381 patients' surgeons were employed at KP for at least 5 years and performed at least 3 surgeries in the 5 years before this patient's surgery date. To ensure that all surgeons in the study period had complete data for the previous 5 years, the surgery data collected between 1998 and 2003 were used as a baseline for surgeons who performed surgery in 2004. A total of 1242 patients who had surgical treatment of DCIS between 2004 and 2014 remained in the final study cohort.

Table 1B. Patient clinical characteristics of study cohort by type of surgical procedure received for ductal carcinoma in situ (N = 1242)[a]

Characteristic	BCS	Mastectomy	Total	p value
Patient clinical characteristics				
Charlson Comorbidity Index (weighted)				
0 or 1	736 (82.1)	287 (83.2)	1023 (82.4)	0.64
≥ 2	161 (17.9)	58 (16.8)	219 (17.6)	
Comedo type				
Comedocarcinoma	86 (9.6)	42 (12.2)	128 (10.3)	0.18
Other	811 (90.4)	303 (87.8)	1114 (89.7)	
Lateral status, original site of primary tumor				
Right side	460 (51.3)	179 (51.9)	639 (51.4)	0.85
Left side	437 (48.7)	166 (48.1)	603 (48.6)	
Estrogen receptor status (ERα-breast)				
Positive	573 (88.2)	214 (82)	787 (86.4)	0.01
Negative	77 (11.8)	47 (18)	124 (13.6)	
Progesterone receptor status (PRα-breast)				
Positive	405 (84.2)	155 (77.9)	560 (82.4)	0.05
Negative	76 (15.8)	44 (22.1)	120 (17.6)	
Differentiation grade				
Well or moderately differentiated	535 (64.1)	170 (52.6)	705 (60.9)	< 0.01
Poorly or undifferentiated	299 (35.9)	153 (47.4)	452 (39.1)	
Tumor size				
< 2.5 cm	664 (87.4)	216 (69.2)	880 (82.1)	< 0.01
≥ 2.5 cm	96 (12.6)	96 (30.8)	192 (17.9)	
Radiation therapy status				
No	397 (44.3)	333 (96.5)	730 (74.1)	< 0.01
Yes	500 (55.7)	12 (3.5)	512 (25.9)	
Follow-up (y)				
DCIS recurrence, mean (SD)	3.6 (2.85)	3.9 (2.71)	3.7 (2.81)	0.15
Breast cancer progression, mean (SD)	4.3 (2.77)	4.0 (2.55)	4.2 (2.71)	0.06
Other cancer progression, mean (SD)	4.5 (2.81)	4.1 (2.67)	4.4 (2.78)	0.04
Patients' corresponding surgeons				
Surgical preference for BCS in last 5 y on subjects' surgery dates, mean (SD)	71.3 (16.90)	63.3 (20.44)	69.1 (18.30)	< 0.01
Years employed with KP, mean (SD)	13.9 (7.02)	13.9 (6.49)	13.9 (6.87)	0.66
Years since receiving MD, mean (SD)	20.2 (8.02)	20.2 (6.78)	20.2 (7.69)	0.35

[a] Data are number (percentage) unless otherwise indicated.
BCS = breast-conserving surgery; DCIS = ductal carcinoma in situ; KP = Kaiser Permanente; MD = medical degree; SD = standard deviation.

Outcome Measures

The outcomes of interest for this study included DCIS recurrence (International Classification of Diseases, Ninth Revision [ICD-9] Code 233.0), breast cancer progression (ICD-9 Codes 174.0-174.9), and other cancer progression (ICD-9 Codes 140-239 other than 174 and 233.0). These 3 cancer outcomes were tracked 6 months after surgery, with a diagnostic documentation requirement from 2 separate visits, at least 30 days apart, to the Oncology Department within a 180-day period.

Covariates

We examined patients' demographic characteristics (age at diagnosis, race, and partner status), patients' clinical characteristics (weighted Charlson Comorbidity Index, cancer comedo type, lateral status, tumor differentiation grade, ER and progesterone receptor [PR] status, tumor size, and radiation therapy), and patients' socioeconomic status (neighborhood high school graduation rate and neighborhood median household income range). See Tables 1A and 1B.

We used age 60 years as the cutoff point to dichotomize our age group, and grouped the race variable as white vs nonwhite, because DCIS risk increases for women older than 60 years, and white women have a higher risk of DCIS.[11] Partner status was dichotomized into partnered (married, common-law, and registered domestic partner) and nonpartnered (single, divorced, widowed, legally separated, and separated) on the basis of patients' self-reported marital status.

We generated the Charlson Comorbidity Index with modified weight to represent the burden of comorbid conditions for each patient. This index was dichotomized into good (0 or 1) vs poor (≥ 2). Comedocarcinoma is confined to the breast ducts and usually does not spread beyond but is considered a higher grade and more aggressive than other types of DCIS. Comedocarcinoma is characterized by the presence of central necrosis and identified using the patient's histologic type. Lateral status (right vs left) was considered because the frequency of occurrence of left-sided breast cancer is higher than right-sided breast cancer.[12] We considered ER and PR status because ER drives a tumor in the breast to grow and stimulates cell proliferation,[13] and PR expression is used as a biomarker of estrogen receptor-α (ERα) function and breast cancer prognosis.[14] The degree of differentiation in the final pathologic diagnosis was used to represent differentiation status of tumor grade. We categorized the tumor differentiation grade into well or moderately differentiated vs poorly differentiated or undifferentiated. Tumor size was dichotomized into large tumor size (≥ 2.5 cm) and small tumor size (< 2.5 cm). The cutoff point for tumor size was based on study results indicating that large tumor size is associated with higher risk of residual disease and recurrence,[15] as well as with microinvasion or invasive carcinoma and risk of axillary metastasis in patients with DCIS.[16] We also included radiation therapy status as one of the covariates because study findings show that radiation therapy is effective in reducing the risk of local recurrence in patients with DCIS after BCS.[17-19]

Multiple imputations using predictive mean matching[20] were performed to generate a complete dataset for analysis while filling the missing records in PR, ER, tumor size, tumor grade, race, and partner status. To avoid colinearity caused by PR and ER, only ER was included in the model.

Each patient's socioeconomic status was assessed using his/her neighborhood of residence (subject's ZIP code) from the 2000 US Census. Median household income and the proportion of residents who had a high school education or above were evaluated in the patient's ZIP code. These variables were categorized into quartiles and reported in Table 1A, but they were not included in the model.

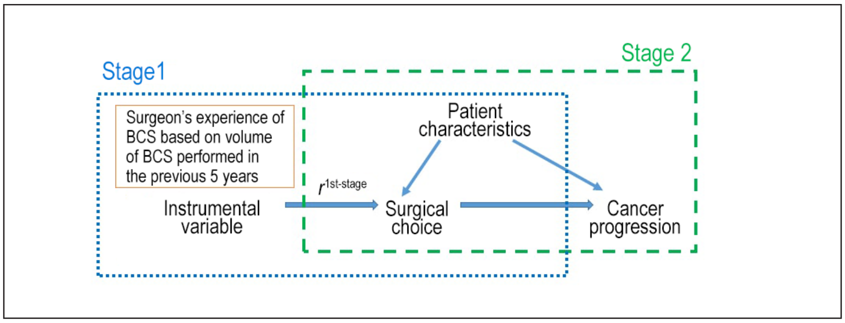

Figure 2. Model specifications. Dotted line illustrates Stage 1 model components: Patients' surgical choices were regressed on instrumental variable and observed confounders. Dashed lines demonstrates Stage 2 model specifications: Patients' cancer progression status were modeled on surgical choice with patients' characteristics and first-stage residual.
BCS = breast-conserving surgery.

Excluded Instruments

The lack of random assignment to treatment in real-world clinical settings causes bias when evaluating the treatment benefit using observational data.[21] Instrumental variable approaches were documented in multiple clinical contexts to untwine the endogeneity of unmeasured burden of illness in treatments and outcomes.[22-28] An *instrumental variable* is defined as a factor strongly associated with treatment choice but has no direct effect on outcomes (except through the endogenous exposure) and is orthogonal to the error.[29] The assumptions of instrumental variables correct for confounding and control for measurement error.[30] We considered 3 surgeon-level variables as instrumental variable candidates because they are associated with the type of treatment options and are independent to patients' characteristics and disease progression: 1) surgical preference for BCS in the last 5 years from subjects' surgery dates, 2) years since the start of KPSC employment, and 3) years since receiving a medical degree. See Table 1B.

Statistical Analysis

We investigated the association between the surgical types and patients' characteristics using the χ^2 test for categorical variables and the t-test for continuous variables. In addition, we used the Kaplan-Meier method to generate time-to-event curves to assess the unadjusted rate of cancer progression by surgical type. We also applied a conventional Cox proportional hazards (PH) model to evaluate the association between the surgical type and the hazard of cancer recurrence or progression while adjusting for relevant confounders. Separate regression models were specified for each of the three outcomes. We verified the validity of the PH assumption with log-minus-log plots for all Cox PH models.

To select a valid instrumental variable, we explored the association between the selection of surgical type and the surgeons' experience, using multiple logistic regression with confounding adjustment. The model did not support the association between surgical type and the surgeons' years since employed in KPSC, or years since receiving a medical degree. We chose the surgeon's surgical preference for BCS in the past five years as the instrumental variable in our model, because it demonstrated a statistically significant association with surgical type, and it was not independently associated with any outcomes. F statistics validated that surgeon's surgical preference for BCS in the past five years was a strong instrumental variable. We further verified its validity by examining its association with selected patient-level characteristics.

In the first stage of the 2-stage residual inclusion (2SRI) model (Figure 2), we performed multiple logistic regression by regressing patients' surgical type on the selected instrumental variable (surgeon's surgical preference for BCS in last 5 years) and adjusted for age, race, partner status, Charlson Comorbidity Index, comedo type, lateral status, tumor grade, ER, tumor size, and radiation therapy. We calculated the raw residuals by subtracting the predicted likelihood of receiving BCS vs mastectomy from the actual value of the treatment received. These residuals from the first-stage model were incorporated as additional covariates, along with the endogenous surgical type variables and selected covariates. The Cox PH model was applied in the second stage to explore the relationship between time to cancer progression and surgical type. We visually verified that PH assumption was not violated by inspecting the log-minus-log plots. Three outcomes were assessed in the second stage. The instrumental variables operated as a natural randomization tool to assign patients to each type of treatment group and to compare groups of patients who differ in their likelihood of receiving treatment, rather than to compare patients on the actual treatment received where potential bias is concealed.[26,27,31-33]

For hypothesis testing, we applied the bootstrapping method to generate standard errors and 95% confidence intervals (CIs) for the hazard ratio (HR) estimates since analytical errors are undefined. A total of 2000 samples of the original cohort were bootstrapped with replacement.

Furthermore, adjusted survival curves for DCIS recurrence, breast cancer occurrence, and other cancer occurrence were obtained by a marginal approach.[34] The resulting adjusted survival curves present expected survival curves calculated on the basis of the Cox model where subgroups were balanced with respect to the confounding variables.

All statistical tests were 2-sided. A p value less than 0.05 was considered statistically significant. All analyses were performed with SAS EG (Version 9.3; SAS Institute Inc, Cary, NC) and R (R core team, R Foundation, Vienna, Austria, 2015).

RESULTS

The age of the patients in the final study cohort ranged from age 28 years to age 90 years. We identified that 49% of the patients were white and 51% nonwhite. Of the 1242 patients in the study cohort, 897 (72.2%) underwent BCS for DCIS treatment (Table 1A). Patients who underwent mastectomy had a higher rate of negative results for ER ($p = 0.01$) and PR ($p = 0.05$). Patients who received mastectomy were more likely to have a poorly differentiated or undifferentiated tumor ($p < 0.01$; Table 1B).

More patients who received BCS were treated by surgeons who preferred to perform BCS in the preceding 5 years ($p < 0.01$). No evidence was found for an association between patient's surgical type and the length of the surgeon's employment.

After adjusting for age, race, partner status, Charlson Comorbidity Index, comedo type, lateral status, tumor differentiation grade, ER status, tumor size, and radiation therapy, we found that for every 1% increase in surgeons' preference of BCS in the past 5 years, their current patients were 3% more likely to receive BCS (OR = 1.03, 95% CI = 1.02 - 1.04, Table 2). In addition, patients who had well or moderately differentiated tumors were 50% more likely to receive BCS (OR = 1.99, 95% CI = 1.41 - 2.80).

Unadjusted time-to-event curves for the 3 outcomes by type of surgical choice are illustrated in Figure 3. Without any adjustment, the Kaplan-Meier curves separated DCIS recurrence for the 2 treatment groups. For the BCS group, the probability of being DCIS free at 1 year was approximately 85%, and at 5 years was about 70%. The recurrence-free probability was around 93% at 1 year and 88% at 5 years for patients who underwent mastectomy. Both curves reached a plateau after 5 years. The breast cancer progression appeared similar for the 2 surgical groups until 9 years after treatment. The progression to other cancers seemed similar for both surgical choices. The estimates of crude HRs are consistent with these observations (Table 3).

After adjusting for the same set of confounders, the conventional Cox PH model detected that patients who received BCS were 86% more likely to encounter DCIS recurrence over time (HR = 1.86, 95% CI = 1.26 - 2.74, Table 3) than those who received mastectomy. For breast cancer (HR = 1.08, 95% CI = 0.53 - 2.23)

Table 2. Univariate and multiple logistic models for association between choice of surgical type and risk factor variables

Variable	Univariate logistic model, OR (95% CI)	Multiple logistic model, OR (95% CI)
Surgeon's surgical choice for BCS in past 5 years	1.02 (1.02-1.03)	1.03 (1.02-1.04)
Race (white vs nonwhite)	1.13 (0.88-1.45)	1.28 (0.94-1.74)
Age (> 60 vs ≤ 60 years)	1.06 (0.83-1.36)	1.10 (0.8-1.52)
Partner (partnered vs nonpartnered)	1.08 (0.84-1.4)	1.00 (0.73-1.38)
Charlson Comorbidity Index (≥ 2 vs < 2)	1.08 (0.78-1.51)	1.30 (0.87-1.97)
Comedo type (comedocarcinoma vs others)	0.77 (0.52-1.14)	0.82 (0.47-1.42)
Lateral (left vs right)	1.02 (0.8-1.31)	1.12 (0.82-1.52)
Tumor grade (well differentiated vs poorly differentiated)	1.60 (1.24-2.05)	1.99 (1.41-2.80)
Estrogen receptor status (ERα of breast, yes vs no)	1.75 (1.23-2.47)	1.75 (1.09-2.83)
Radiation therapy (yes vs no)	34.95 (20.23-66.64)	45.61 (25.69-88.98)
Tumor size (≥ 20 mm vs < 20 mm)	0.33 (0.24-0.44)	0.33 (0.22-0.48)

BCS = breast-conserving surgery; CI = confidence interval; ERα = estrogen receptor-α; OR = odds ratio.

Table 3. Analysis of time to DCIS recurrence, breast cancer progression, and other cancer progression after surgery

	Cox proportional hazards model		2SRI
Outcome	Crude HR (95% CI)	Adjusted HR[a] (95% CI)	Adjusted HR[a] (95% CI[b])
DCIS recurrence	2.47 (1.75-3.48)	1.86 (1.26-2.74)	0.57 (0.13-1.97)
Breast cancer progression	1.27 (0.68-2.35)	1.08 (0.53-2.23)	0.38 (0.03-3.82)
Other cancer progression	0.97 (0.35-2.71)	1.18 (0.37-3.76)	0.05 (0.001-1.61)

[a] Models were adjusted for subject age, race, partner status, Charlson Comorbidity Index, cancer grade, estrogen receptor status, lateral status (left vs right), tumor size, and radiation therapy status.
[b] Confidence interval for 2SRI method was obtained by bootstrapping with 2000 iterations.
CI = confidence interval; DCIS = ductal carcinoma in situ; HR = hazard ratio; 2SRI = two-stage residual inclusion estimation instrumental variable analysis.

and other cancer progression (HR = 1.18, 95% CI = 0.37 - 3.76), the Cox PH model failed to uncover any significant beneficial effect of mastectomy over BCS.

Interestingly, after applying the instrumental variable method to account for endogeneity in the model, the 2SRI model framework altered the directions of the estimated treatment effects of BCS and mastectomy from the conventional Cox PH model for all 3 outcomes: DCIS recurrence (HR = 0.57, 95% CI = 0.13 - 1.97), breast cancer progression (HR = 0.38, 95% CI = 0.03 - 3.82), and other cancer progression (HR = 0.05, 95% CI = 0.001 - 1.61). The expected survival curves adjusted for confounders (Figure 4) showed agreement with the model estimates. BCS appeared to contribute to a higher risk of DCIS recurrence compared with mastectomy in the conventional Cox PH model; however, this effect was overturned in the 2SRI model. The conventional Cox PH model did not clearly separate the event-free probabilities between BCS and mastectomy for breast cancer progression and other cancer progression. The separations are pronounced with the 2SRI model framework, where BCS appeared to be associated with lower risks of breast and other cancer progression.

DISCUSSION

In this study, we compared the disease-free survival of patients with DCIS who received BCS vs those who received mastectomy. The goal of DCIS treatment is to prevent DCIS recurrence and cancer progression. Previous studies found that BCS resulted in lower disease-free survival rates than mastectomy in patients with DCIS.[5,35] Such a finding may have led many women to believe that mastectomy is the last resort for breast cancer treatment, even at a very early stage. However, the estimates generated by our 2SRI model framework favored BCS over time. Our results demonstrated no significant difference in disease-free survival rates comparing BCS and mastectomy for patients with DCIS in real-world clinical practice. The estimated HRs suggested that BCS may contribute to longer adjusted disease-free survival than mastectomy, although these findings were not statistically significant.

Studies in value-based care have raised the attention of health care policy makers to seek ways to balance cost (efficiency) and clinical benefit (effectiveness).[36,37] Compared with BCS in the longer term, mastectomy was found to be associated with higher complication risk[38,39] and greater adjusted total cost and complication-related cost.[40,41] The results from our study, combined with the fact that reliable prediction methods of DCIS recurrence for women treated with BCS are now plausible,[42] suggest that BCS followed-up with cancer surveillance is a rational approach to ensure affordable and effective care for patients with DCIS.

Previous studies found substantial differences among surgeons in surgical treatment.[5,43] It is unclear how strictly surgeons comply with standard treatment guidelines. The guideline-based surgical options for DCIS generally come from recommendations rather than from evidence from randomized clinical trials. Therefore, surgeons are often uncertain about the best clinical management for patients with DCIS because of the lack of evidence base for the recommendations. On the other hand, experienced surgeons may be more confident in performing the type of surgery with which they have seen better results in the past. Our results support this implication by showing that the likelihood for a surgeon to perform BCS increases if s/he was more experienced with BCS in the past.

It is unrealistic to conduct randomized clinical trials in all situations where evidence is needed to guide health care. The instrumental variable approach used in this study adjusted for unmeasured confounders and accounted for endogeneity in the

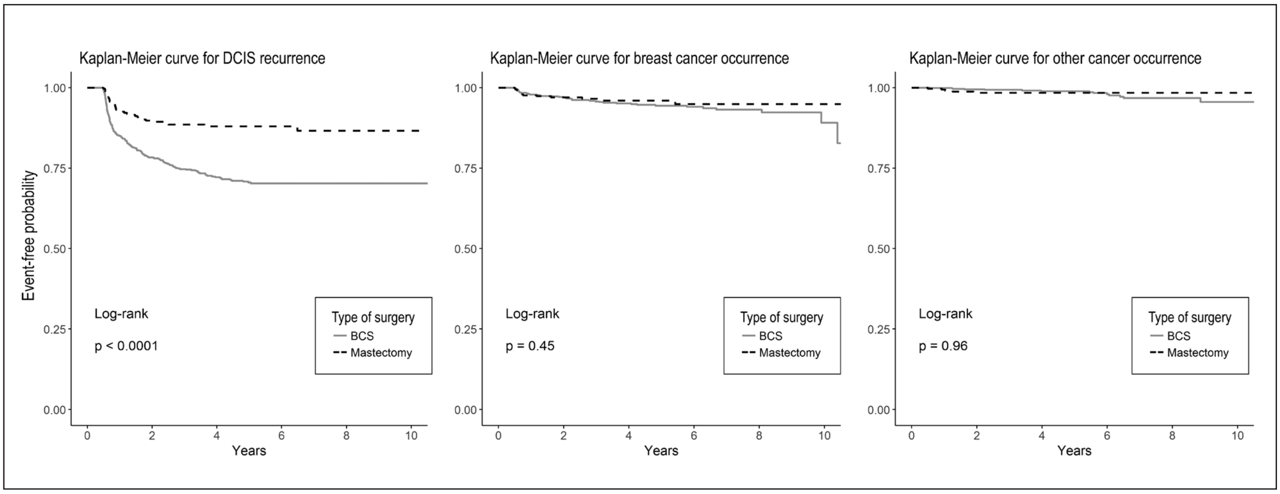

Figure 3. Kaplan-Meier unadjusted time-to-event curves stratified by type of surgical procedure received for treatment of single primary ductal carcinoma in situ (DCIS). Left curve illustrates event-free probability for DCIS recurrence; middle and right curves demonstrate event-free probability for breast cancer progression and other cancer progression, respectively. Solid lines represent that patients received breast-conserving surgery (BCS); dashed lines represent that patients received mastectomy. The p values were generated using a Cox proportional hazards model to assess the statistical significance for the difference between patients who received BCS and those who received mastectomy.

model using observational data, which maintained one of the usual benefits of randomized clinical trials. We identified each surgeon's surgical preference as a strong instrumental variable to adjust for endogeneity in the relationship between cancer progression and treatment options. We concluded that the prevention of DCIS recurrence does not necessarily benefit from more invasive surgical procedures. Furthermore, in prevention of breast cancer and other cancer progression, BCS may contribute to higher cancer-free survival than does mastectomy. Our study provides a strong evidence base for recommendations in standard guidelines about selecting treatment type for both clinicians and patients while making individual treatment plans.

Compared with traditional methods, our instrumental variable approach accounted for endogeneity and obtained consistent estimates. We were able to identify a strong instrumental variable true to how physicians practice: The volume of past experience is representative of the surgical preference. In addition, there are many advantages in using KPSC data. The KPSC cancer registry and KP HealthConnect database ensured rich data resources and adequate sample size (supplemental methods). We were able to identify a heterogeneous population, which includes younger women and a variety of races, whereas many previous studies were restricted by rules and regulation of Medicare, Medicaid, or other insurance policies. Moreover, because KP surgeons are not affected by the insurance reimbursement, the choice for surgical type will not be affected by the difference in procedure costs. Furthermore, KPSC Medical Centers have facilities equipped with surgeons and surgical equipment all over the KPSC service area; therefore, the choice for surgical type will not be limited to the availability of and accessibility for one type of surgery over the other.

We used the 2SRI method to incorporate our instrumental variable of selection in a nonparametric model. A more popular method to implement instrumental variables in linear regression modes is a 2-stage least-squares model, because it serves as the basis for most practitioners' understanding of assumptions and implementation of instrumental variable models. However, nonlinear regression models, including generalized linear models, are often more appropriate for many questions in health care research. Conventional 2-stage least squares fails to account for event time and disregards censoring, which may produce biased estimates in these inherently nonlinear situations.[44] On the other hand, 2SRI, a rote extension of 2-stage least squares with modifications, focuses especially on correcting for endogeneity bias in nonlinear models.[45] The consistency of 2SRI estimation ensures its superiority in nonlinear models.[45-47]

We encountered a number of limitations in this study. First, our dataset came with incomplete records for some important clinical factors such as tumor size and status of ER and PR. We subsequently performed multiple imputation to mitigate this limitation. Second, a diverse distribution of physician experience was observed. We assumed a normal distribution for the numbers of surgeries performed for each surgeon in the past years. Third, the weight of patients' predilection in their

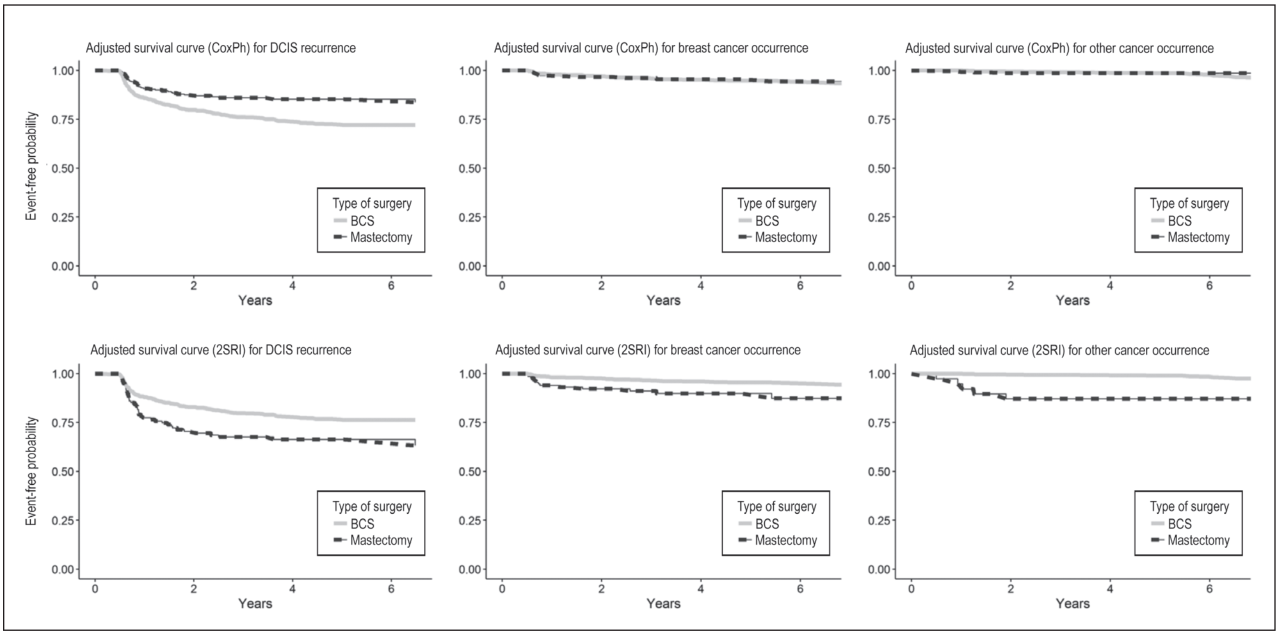

Figure 4. Expected survival curves adjusted for confounders. The upper panel illustrates event-free probability using conventional CoxPH adjusting for confounders for DCIS recurrence, breast cancer progression, and other cancer progression, respectively. The lower panel illustrates event-free probability using 2SRI framework with instruments adjusting for confounders for DCIS recurrence, breast cancer progression, and other cancer progression, respectively. Solid lines represent that patients received breast-conserving surgery (BCS); the dashed lines represent that patients received mastectomy.

CoxPH = Cox proportional hazards model; DCIS = ductal carcinoma in situ; 2SRI = two-stage residual inclusion estimation instrumental variable analysis.

treatment selection was not quantified. Patients have different priorities in life and different levels of pain tolerance. The heterogeneity of their attitudes play a role in their choice of health management style. This may potentially be accounted for by a patient-level instrumental variable, which requires further exploration.

In addition, radiation therapy is currently included in our model framework as a confounder, because radiation treatment after lumpectomy has resulted in increased disease-free survival for patients compared with lumpectomy only.[5] For future studies, we will consider incorporating radiation therapy as an element for treatment stratifications. This requires us to redefine instrumental variables and reconstruct our model, but the fundamental idea remains.

Last but not least, antihormonal therapy use was not included in our model. Tamoxifen treatment was found to reduce the risk of new DCIS events[48] and contralateral invasive breast cancers,[49,50] but it was also accompanied with a significantly adverse effect on the quality of life.[51] Future studies are needed to investigate treatment effects on cancer progression with consideration of these additional treatment levels, and to compare the cost-effectiveness in terms of the prevention power and the trade-off for quality of life.

CONCLUSION

Despite the limitations, the results from this study provide supportive evidence to improve standard treatment guidelines, and to help physicians to present cogent statistical evidence while discussing treatment options with their patients. Our results have shown that BCS is a notably favored surgical option among experienced surgeons for treating DCIS. Above all, we have demonstrated that a more invasive surgical procedure (mastectomy) does not guarantee better results of cancer prevention. Further studies are needed to investigate the roles and implications of relevant risk factors associated with the likelihood of recurrence and progression in patients with early-stage breast cancer, so that patients and surgeons can make evidence-based decisions regarding treatment options without making the avoidable sacrifice of quality of life. ❖

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

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If Not Treated

It is better not to apply any treatment in cases of occult cancer; for, if treated, the patients die quickly; but if not treated, they hold out for a long time.

— Hippocrates of Kos, 460 BC – 370 BC, Greek physician of the Age of Pericles