Predictors of Antiestrogen Recommendation in Women With Estrogen Receptor–Positive Ductal Carcinoma In Situ

Rondi M. Kauffmann, MD, MPH[a]; Leanne Goldstein, DrPH[b]; Emily Marcinkowski, MD[a]; George Somlo, MD[c]; Yuan Yuan, MD, PhD[c]; Philip H.G. Ituarte, PhD, MPH[b]; Laura Kruper, MD, MSCE[a]; Leslie Taylor, MD[a]; and Courtney Vito, MD[a]

Abstract

Background: Antiestrogen (anti-e) use in estrogen receptor–positive (ER+) ductal carcinoma in situ (DCIS) has been shown to reduce the incidence of noninvasive and invasive breast cancer. Few studies have evaluated factors associated with anti-e recommendation in ER+ DCIS. **Methods:** The California Cancer Registry was queried for female patients diagnosed with ER+ DCIS and treated with lumpectomy or unilateral mastectomy from 2004 to 2011. Patient demographics, comorbidities, and clinical characteristics were analyzed for association with anti-e recommendation. **Results:** Of 5,527 patients identified, 76.4% patients underwent lumpectomy and 23.6% underwent unilateral mastectomy. Of the total cohort, 31.6% patients were recommended anti-e therapy, 60.4% were not, and the remaining 8.0% were recommended anti-e, but administration was not documented. Performance of lumpectomy predicted anti-e use compared with mastectomy (odds ratio [OR], 2.08; 95% CI, 1.77–2.43). Asian/Pacific Islanders were more often recommended anti-e therapy when compared with whites (OR, 1.28; 95% CI, 1.10–1.49). Patients younger than 70 years were more often recommended anti-e (age, 18–49 years: OR, 1.38; CI, 1.12–1.71; and age, 50–69 years: OR, 1.43; CI, 1.20–1.71). **Conclusions:** Despite current guidelines to consider the use of anti-e therapy, recommendation of anti-e after surgical treatment of DCIS is low, having been recommended to 40% of patients, and used by fewer than one-third. Significant predictors include lumpectomy compared with unilateral mastectomy, Asian/Pacific Islander race, younger age, and number of comorbidities. Further work is merited to understand patterns of anti-e therapy recommendation by providers in patients with DCIS.

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Background

Ductal carcinoma in situ (DCIS) is a premalignant breast lesion that has been increasingly diagnosed in the era of screening mammography,[1] and accounts for 20% to 25% of all new breast cancer diagnoses.[2] Marked atypia may be seen in DCIS, which can progress to invasive cancer.[3] Surgery is typically offered to patients with DCIS, because the rate at which DCIS progresses to invasive disease is largely unknown.

Treatment for DCIS includes excision alone, lumpectomy/radiation, or mastectomy.[1] When breast conservation is used, the risk of local recurrence is higher than with mastectomy.[1] Antiestrogen (anti-e) therapy, in the form of either tamoxifen or an aromatase inhibitor (AI), may be used to reduce the risk of local recurrence and contralateral breast cancer (CBC) in patients with DCIS, particularly those that are hormone receptor–positive (HR+).[4] In 1999, investigators from the NSABP B-24 reported that the use of tamoxifen in patients with DCIS and treated with lumpectomy decreased the 5-year relative risk of ipsilateral and invasive CBC by 37%,[5] and a consideration for the use of tamoxifen in patients with DCIS was incorporated into NCCN Clinical Practuce Guidelines in Oncology (NCCN Guidelines) for Breast Cancer.[6] Data have emerged recently showing that AIs may also be used as a prevention strategy in high-risk women (including those with DCIS), although the initial trial was exemestane versus placebo.[7] An abstract presented at ASCO in 2015 reported results of a trial involving an AI versus tamoxifen, but these findings have not yet been published.[8]

From the Departments of [a]Oncologic Surgery, [b]Biostatistics and Population Sciences, and [c]Medical Oncology, City of Hope National Medical Center, Duarte, California.

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Correspondence: Courtney Vito, MD, Department of Oncologic Surgery, City of Hope National Medical Center, 1500 East Duarte Road, Duarte, CA 91010-8113. E-mail: cvito@coh.org

The frequency of use of anti-e for preventing ipsilateral recurrence of DCIS or the development of invasive cancer remains unknown. Studies conducted in Australia and New Zealand have reported that only 20% of women with DCIS were taking an anti-e after lumpectomy/radiation.[9] In the United States, although reports have demonstrated that 60% to 91% of patients with DCIS are recommended anti-e, only a fraction (fewer than half) of these actually take the medication.[10–12] California is one of the most populous states in the country, and houses 4 NCCN Member Institutions and 10 NCI-designated cancer centers.[13,14] As the state with the most NCCN Member Institutions, the California Cancer Registry (CRC) provides a unique opportunity to study uptake of anti-e recommendation after surgical treatment of HR+ DCIS. We sought to determine the frequency of antihormone recommendation in women with DCIS treated in California, and to identify factors associated with recommending anti-e in patients with estrogen receptor–positive (ER+) DCIS.

Methods

This study was approved by the California Review Board (CPHS), the CCR, and by the Institutional Review board of City of Hope Comprehensive Cancer Center.

Data Source

The CCR is maintained by the California Department of Public Health's Chronic Disease Surveillance and Research Branch. This statewide population-based cancer surveillance system provides detailed data on all patients diagnosed and/or treated for any primary malignancy (excluding nonmelanoma skin cancers) in the state of California. Information reported includes patient age, sex, race/ethnicity, insurance status, socioeconomic status (SES) data, tumor site, histology, number of primary tumors, stage, treatment and sequence of chemotherapy and surgery, and survival status of all cancers diagnosed in California.[15] Because reporting of cancer care is mandated, the lost-to-follow-up rate is low, and this is one of the most complete cancer registries in the nation.[16,17] SES quintiles in the CCR are based on algorithms using American Community Survey variables at the block group level when available,[18] and otherwise Census variables at the block group level when available.[19] The California Office of Statewide Health Planning and Development (OSHPD) database is a statewide all-payer discharge data set that collects data and disseminates information regarding California's healthcare infrastructure, outcomes, and facilities.[20] This data set also contains patient-level information for hospital discharges, secondary diagnoses, and facility where healthcare was delivered.[16] The CCR and OSHPD data sets may be merged to provide comprehensive information about inpatient and outpatient treatments.

Cohort Selection

The CCR was queried for female patients diagnosed with ER+ DCIS and treated with lumpectomy or unilateral mastectomy from 2004 to 2011. Autopsy only cases were excluded. Data about patients' first DCIS were analyzed. This cohort was merged with the OSHPD data, and presence of Charlson comorbidities (except for cancer) were derived from patient ICD-9 diagnosis codes. Information regarding recommendation for anti-e was derived from the hormone therapy codes, which are documented according to the California Cancer Reporting System Standards, Volume I.[21] This coding system includes information on patients given anti-e therapy, patients to whom anti-e was recommended but was not given (due to patient/family refusal, or unknown reason), and those for whom anti-e recommendation was unknown. Patients with unknown hormone treatment information or who were contraindicated from anti-e treatment were excluded before analysis. The "recommendation for hormone" data point did not discriminate between tamoxifen and AIs, but because there were no data supporting the use of AIs in DCIS until 2015, hormone recommendation during our study period is likely to largely represent tamoxifen.

Statistical Analysis

Patient demographics and clinical characteristics were compared between patients recommended anti-e and those who were not, using chi-square tests. A multivariable logistic regression model was created to evaluate predictors associated with recommendation for anti-e therapy. Predictors included age, comorbidities, pathologic information, race, type of surgery, reconstruction, marital status, SES, and insurance status. Interactions were evaluated to assess age, marital status, SES, radiation, and insurance as

predictors independent of surgery type. All analyses were performed using the SAS statistical software (version 9.4, SAS Institute, Inc., Cary, NC). The level of statistical significance was set at a *P* value of less than 0.05.

Results

A total of 5,527 patients were included. Of these, 1,748 (31.6%) were administered anti-e therapy, 3,339 (60.4%) were not, and the remaining 469 (8.0%) were recommended anti-e but administration was either not documented or refused. Surgical treatment included lumpectomy in 4,222 patients (76.4%) and unilateral mastectomy in 1,305 (23.6%). Reconstruction (tissue-based, implant, or both) was performed on 322 patients (5.8%), and no reconstruction was performed for 5,205 patients (94.2%). Of the patients who underwent lumpectomy, 60.1% also underwent radiation.

Patient Demographics

Patient characteristics by anti-e recommendation are shown in Table 1. Patients who underwent lumpectomy were more likely to be recommended anti-e (43.4%) versus mastectomy (27.3%; *P*<.0001). Younger patients were also more likely to be recommended anti-e, with 41.8% of patients aged 18 to 49 years and 42.1% of patients aged 50 to 69 years being recommended anti-e versus 30.5% of patients older than 70 years (*P*<.0001). Univariate analysis showed that most patients were not recommended anti-e, regardless of race, marital status, number of comorbidities, breast reconstruction, SES, or insurance status. Recommendation for anti-e therapy increased with increasing tumor size (*P*=.0012). Tumor differentiation did not have a clear association with provider recommendation for anti-e therapy, as anti-e was recommended to 40.7% of patients with well-differentiated, 40.3% with moderately differentiated, 41.6% with poorly differentiated, and 36.7% with undifferentiated DCIS. Recommendation for anti-e therapy varied over the study period, ranging from 35.5% in 2004 to 42.9% in 2011 (*P*=.01).

Multivariable Logistic Regression Analysis

Results of the regression model are presented in Table 2. There was no significant association between anti-e recommendation and type of mastectomy performed. Therefore, mastectomy versus lumpectomy, which was significant, is included in the model. Lumpectomy predicted anti-e when mastectomy was the reference (odds ratio [OR], 2.07; 95% CI, 1.77, 2.43). Asian/Pacific Islanders were more likely to be recommended anti-e when whites were the reference (OR, 1.26; 95% CI, 1.08, 1.47). Other races did not show significant differences in anti-e recommendation. Patients younger than 70 years were more often recommended anti-e (age 18–49 years: OR, 1.38; 95% CI, 1.12, 1.71; and age 50–69 years: OR, 1.43; 95% CI, 1.20, 1.71). Divorced women had a higher odds of being recommended anti-e than single/never married women (OR, 1.33; 95% CI, 1.06, 1.67). Patients with 3 or more comorbidities were less likely to be recommended anti-e (OR, 0.65; 95% CI, 0.50, 0.86). Patients diagnosed with ER+ DCIS in the later years of the study period (2010 and 2011) were more likely to be recommended anti-e (OR, 1.30; 95% CI, 1.01, 1.68; and OR, 1.32; 95% CI, 1.02, 1.70, respectively). Tumor grade/differentiation, and SES were not significant predictors in the model. Reconstruction was predictive of anti-e recommendation only when compared with no reconstruction (OR, 0.43; 95% CI, 0.19, 0.98). Type of reconstruction performed was not predictive. Tumor size was not predictive of anti-e, except for patients with unknown tumor size (OR, 0.83; 95% CI, 0.72, 0.95). Insurance status did not predict anti-e, except in patients with managed care/HMO/PPO (OR, 1.20; 95% CI, 1.02, 1.42). Interactions of surgery with marital status, age, SES, race, and insurance were not significant. However, there was a significant interaction between radiation and surgery. In the adjusted model, lumpectomy patients who underwent radiation were more likely to be recommended anti-e (OR, 3.446; 95% CI, 3.01, 3.95; *P*<.0001).

Discussion

Tamoxifen and AIs are anti-e therapies used for protection against locoregional recurrence or CBC. Historically, the use of tamoxifen was recommended for patients with ER+ DCIS undergoing lumpectomy, as first studied in the 1999 NSABP B-24 trial.[5] After this study was published, tamoxifen after lumpectomy/radiation for ER+ DCIS was rapidly incorporated into the NCCN Guidelines for Breast Cancer, published in 2000.[6] Tamoxifen was not initially

Table 1. Patient Characteristics by Hormone Recommendation Status

	N	Recommended Antiestrogen Therapy, % (N=2,188)	Not Recommended Antiestrogen Therapy, % (N=3,339)	*P* Value
Surgery				<.0001
Lumpectomy	4,222	1,831 (43.4)	2,391 (56.6)	
Mastectomy	1,305	357 (27.4)	948 (72.6)	
Radical	191	45 (23.6)	146 (76.4)	
Total sample	1,078	304 (28.2)	774 (71.8)	
Other	36	8 (22.2)	28 (78.8)	
Reconstruction				.0004
None	5,205	2,091 (40.2)	3,114 (59.8)	
Reconstruction NOS	47	7 (14.9)	40 (85.1)	
Flap	100	35 (35.0)	65 (65.0)	
Implant/combined	175	55 (31.4)	120 (68.6)	
Tumor size				.0012
<0.50 cm	4,000	1,649 (41.2)	2,351 (58.8)	
0.50–1.00 cm	212	70 (33.0)	142 (67.0)	
1.01–2.00 cm	23	10 (43.5)	13 (56.5)	
2.01–5.00 cm	13	6 (46.2)	7 (53.8)	
Unknown	1,279	453 (35.4)	826 (64.6)	
Grade/differentiation				.0408
Grade I/well	560	228 (40.7)	332 (59.3)	
Grade II/moderately	2,444	984 (40.3)	1,460 (59.7)	
Grade III/poor	1,185	493 (41.6)	692 (58.4)	
Grade IV/ undifferentiated	880	323 (36.7)	557 (63.3)	
Unknown	458	160 (34.9)	298 (65.1)	
Race				.0256
Non-Hispanic white	3,295	1,260 (38.2)	2,035 (61.8)	
Non-Hispanic black	329	125 (38.0)	204 (62.0)	
Hispanic	837	338 (40.4)	499 (59.6)	
Asian/Pacific Islander	915	404 (44.1)	511 (55.9)	
Other/unknown	151	61 (40.4)	90 (59.6)	
Age				<.0001
18–49 y	1,343	561 (41.8)	782 (58.2)	
50–69 y	3,011	1,269 (42.1)	1,742 (57.9)	
≥70 y	1173	358 (30.5)	815 (69.5)	

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Abbreviations: NOS, not otherwise specified; SES, socioeconomic; VA, Veteran's Affairs.
[a]Other than cancer.

Table 1. Patient Characteristics by Hormone Recommendation Status (cont.)

	N	Recommended Antiestrogen Therapy, % (N=2,188)	Not Recommended Antiestrogen Therapy, % (N=3,339)	*P* Value
Insurance				<.0001
Not insured/other/unknown	423	151 (35.7)	272 (64.3)	
Private/self-pay	57	23 (40.3)	34 (59.7)	
Managed care/HMO/PPO	3,460	1,459 (42.2)	2,001 (57.8)	
Medicaid	273	113 (41.4)	160 (58.6)	
Medicare	1,260	418 (33.2)	842 (66.8)	
County/TriCare/Military/VA	54	24 (44.4)	30 (55.6)	
Marital status				.0003
Single	771	306 (39.7)	465 (60.3)	
Married	3,458	1,380 (39.9)	2,078 (60.1)	
Separated	48	17 (35.4)	31 (64.6)	
Divorced	540	250 (46.3)	290 (53.7)	
Widowed	277	195 (33.2)	393 (66.8)	
Unknown	122	40 (32.8)	82 (67.2)	
Number of comorbidities[a]				<.0001
0	3,689	1,521 (41.2)	2,168 (58.8)	
1	1,136	458 (40.3)	678 (59.7)	
2	377	124 (32.9)	253 (67.1)	
≥3	325	85 (26.1)	240 (73.9)	
SES quintile				<.0001
Lower	544	354 (65.1)	190 (34.9)	
Lower-middle	829	522 (63.0)	307 (37.0)	
Middle	1,016	616 (60.6)	400 (39.4)	
Higher-middle	1,340	800 (59.7)	540 (40.3)	
Highest	1,798	1,047 (58.2)	751 (41.8)	
Year diagnosis				.0104
2004	428	152 (35.5)	276 (64.5)	
2005	641	226 (35.3)	415 (64.7)	
2006	645	262 (40.6)	383 (59.4)	
2007	732	309 (42.2)	423 (57.8)	
2008	823	311 (37.8)	512 (62.2)	
2009	776	295 (38.0)	481 (62.0)	
2010	745	317 (42.5)	428 (57.5)	
2011	737	316 (42.9)	421 (57.1)	

Abbreviations: NOS, not otherwise specified; SES, socioeconomic; VA, Veteran's Affairs.
[a]Other than cancer.

Table 2. Multivariate Logistic Regression Model of Factors Associated With Antiestrogen Recommendation in Estrogen Receptor–Positive Ductal Carcinoma in Situ

Predictor	OR (95% CI)	*P* Value
Surgery		
Lumpectomy vs mastectomy	2.07 (1.77, 2.43)	<.0001
Reconstruction		
Reconstruction NOS vs none	0.43 (0.19, 0.98)	.0434
Flap vs none	1.29 (0.83, 2.00)	.2628
Implant/combined vs none	1.08 (0.76, 1.54)	.6686
Tumor size		
0.50–1.00 cm vs <0.50 cm	0.89 (0.65, 1.21)	.4464
1.01–2.00 cm vs <0.50 cm	1.43 (0.61, 3.34)	.4059
2.01–5.00 cm vs <0.50 cm	1.45 (0.47, 4.40)	.5174
Unknown vs <0.50 cm	0.83 (0.72, 0.95)	.0063
Grade/differentiation		
Grade II/moderately vs grade I/well	1.01 (0.83, 1.22)	.9399
Grade III/poor vs grade I/well	1.09 (0.89, 1.35)	.4016
Grade IV/undifferentiated vs grade I/well	0.93 (0.74, 1.16)	.5176
Unknown vs grade I/well	0.89 (0.69, 1.16)	.4022
Race		
Non-Hispanic black vs Non-Hispanic white	1.01 (0.79, 1.29)	.9510
Hispanic vs Non-Hispanic white	1.13 (0.95, 1.33)	.1631
Asian/Pacific Islander vs Non-Hispanic white	1.26 (1.08, 1.47)	.0033
Other/unknown vs Non-Hispanic white	1.05 (0.75, 1.48)	.7691
Age		
18–49 y vs ≥70 y	1.38 (1.12, 1.71)	.0027
50–69 y vs ≥70 y	1.43 (1.20, 1.71)	<.0001
Insurance		
Not insured/other/unknown vs Medicare	0.90 (0.70, 1.16)	.4006
Private/self-pay vs Medicare	1.06 (0.60, 1.85)	.8470
Managed care/HMO/PPO vs Medicare	1.20 (1.02, 1.42)	.0289
Medicaid vs Medicare	1.17 (0.87, 1.57)	.2918
County/TriCare/Military/VA vs Medicare	1.35 (0.76, 2.39)	.3077

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Abbreviations: NOS, not otherwise specified; OR, odds ratio; SES, socioeconomic status; VA, Veteran's Affairs.

recommended in the mastectomy setting, not even to prevent CBC. The 2007 UK/New Zealand trial evaluating the use of tamoxifen in DCIS was the first to demonstrate a reduction in CBC with tamoxifen.[9] After publication of this study, recommendations for consideration of the use of anti-e were extended to patients undergoing mastectomy to reduce the risk of CBC.[22]

We have shown that most patients (76%) undergo lumpectomy for ER+ DCIS. Fewer than half of the patients undergoing lumpectomy in our cohort were recommended anti-e. This is somewhat surpris-

Table 2. Multivariate Logistic Regression Model of Factors Associated With Antiestrogen Recommendation in Estrogen Receptor–Positive Ductal Carcinoma in Situ (cont.)

Predictor	OR (95% CI)	*P* Value
Marital status		
Married vs single	1.00 (0.85, 1.18)	.9916
Separated vs single	0.94 (0.50, 1.74)	.8326
Divorced vs single	1.33 (1.06, 1.67)	.0149
Widowed vs single	1.01 (0.79, 1.29)	.9333
Unknown vs single	0.78 (0.52, 1.19)	.2497
Number of comorbidities		
1 vs 0	1.06 (0.92, 1.22)	.4613
2 vs 0	0.84 (0.66, 1.06)	.1386
≥3 vs 0	0.65 (0.50, 0.86)	.0021
SES quintile		
Lower-middle vs lower	1.04 (0.82, 1.31)	.7497
Middle vs lower	1.14 (0.91, 1.43)	.2655
Higher-middle vs lower	1.14 (0.92, 1.43)	.2341
Higher vs lower	1.18 (0.95, 1.47)	.1349
Year diagnosis		
2005 vs 2004	0.94 (0.72, 1.22)	.6180
2006 vs 2004	1.16 (0.89, 1.50)	.2633
2007 vs 2004	1.25 (0.97, 1.62)	.0797
2008 vs 2004	1.04 (0.81, 1.34)	.7400
2009 vs 2004	1.03 (0.80, 1.33)	.8105
2010 vs 2004	1.30 (1.01, 1.68)	.0413
2011 vs 2004	1.32 (1.02, 1.70)	.0328

Abbreviations: NOS, not otherwise specified; OR, odds ratio; SES, socioeconomic status; VA, Veteran's Affairs.

ing given that Wapnir et al[23] demonstrated a 32% reduction in invasive ipsilateral tumor recurrence with the addition of anti-e to lumpectomy/radiation in patients with DCIS. Patients undergoing unilateral mastectomy were even less likely to be recommended anti-e, with only 27% of the patients in our cohort being recommended anti-e for prevention of CBC. The recommendation to consider anti-e after lumpectomy/radiation for HR+ DCIS has been in place for over a decade, and it is somewhat surprising that fewer than half of the patients in our cohort are recommended anti-e therapy, although the likelihood of being recommended anti-e increased in the later years of the study period. This may represent delayed adoption of the consideration for anti-e therapy after surgical treatment of HR+ DCIS, the presence of contraindications for tamoxifen/AI use, or the perception by providers that the use of anti-e for a preinvasive condition is overtreatment. This study highlights the fact that not all providers routinely recommend anti-e for treatment of HR+ DCIS, and not all guidelines endorse it strongly. This underscores the wide variability in providers' perceptions regarding the benefit of anti-e therapy relative to its side effects in the HR+ DCIS, and the ongoing controversy regarding how strongly anti-e therapy should be recommended for patients with preinvasive breast cancer.

The fact that patients who underwent radiation were more likely to be recommended anti-e suggests that anti-e is not being used in lieu of radiation. A 2007 study showed an increase in the receipt of anti-e therapy after the publication of NSABP B-24 results (24% vs 46%).[24] However, the overall rate of anti-e after lumpectomy/radiation for ER+ DCIS was 41% at the 8 NCCN Member Institutions studied. Our study suggests that despite the NCCN recommendation to *consider* anti-e therapy after surgical treatment of HR+ DCIS, this recommendation has not been widely adopted by providers. Although the use of anti-e for the prevention of CBC after mastectomy for ER+ DCIS is gaining acceptance, our study highlights the current low rates of administration in California. Although it remains true that the use of tamoxifen or AIs is associated with side effects, our study evaluated recommendations for tamoxifen, not compliance with these recommendations, and therefore reveals low adoption among providers following guideline recommendations regarding the consideration of anti-e after a diagnosis of DCIS.

The higher rates of anti-e recommendation among young patients treated with lumpectomy for DCIS is not surprising, because women younger than 40 years tend to undergo more aggressive treatment.[25,26] Although this may be partly due to more aggressive tumor biology, it may also represent differences in treatments offered to younger patients.[27] Recommendations for anti-e use after lumpectomy/radiation have been in place for well over a decade, and are expected to be more widely adopted than the relatively newer recommendations of anti-e after unilateral mastectomy. Likewise, lower rates of recommendation for anti-e in women with more comorbid conditions reflect the overall poor health of these patients. This may represent treatment choices when competing illnesses have a greater impact on overall survival than DCIS. In addition, medical conditions that may preclude the use of anti-e therapy, including deep venous thrombosis (DVT), postmenopausal bleeding, obesity, and endometrial cancer, are more common in the elderly and limit the use of antihormonal therapies in this population.[9]

We have also demonstrated a higher rate of anti-e recommendation in Asian/Pacific Islanders and divorced women. Although anti-e therapy is a fairly inexpensive, generic medication, cost/benefit analyses, whether formal or informal, do influence provider recommendations.[28] However, insurance status was not found to be significant in the final model, likely due to the co-linearity of age and insurance status, because Medicare/Medicaid coverage most often includes patients aged 65 years and older. Additionally, in our final model, SES had no significant impact on anti-e recommendation.

It is surprising that a higher rate of anti-e recommendation was observed in divorced women. Although marital status has been shown in other studies to be associated with cancer outcomes, the association between marital status and recommendation for anti-e therapy is unclear.[29] It is possible that differences in recommendation of anti-e in divorced women reflects differences in sexual and childbearing habits, but additional research is needed.

It is interesting that rates of anti-e use are higher in Asian/Pacific Islanders. This may represent differences in prescribing practices among providers treating racial minorities, or variations in tolerance of anti-e therapy. Much as genetic differences dictate response to chemotherapy, genetic variations may drive tolerance of anti-e therapy.[30] Although this analysis focuses on providers' recommendations for anti-e therapy rather than individual patient compliance with such therapy, it is possible that providers are making treatment recommendations for or against anti-e therapy based on previous experience with tolerance of said therapy in different racial groups. In addition, differences in recommendations may be explained by economics. We have shown that patients in the highest quartile for median household income were more likely to be recommended anti-e. A recent study reports that Asian Americans have the highest per capita income than any other racial group in the United States, including whites,[31] and may be more likely to be recommended anti-e due to higher median income. Additional studies are needed to define the relationship between race/ethnicity and anti-e therapy, as our analysis is unable to assess differences in tolerance of anti-e therapy or issues of compliance with recommendations.

It is important to note that tamoxifen is only one of a number of anti-e medications used for prevention of ipsilateral recurrent DCIS, invasive cancer, or CBC. The NSABP B-35 trial included the use of both tamoxifen and AIs in patients with DCIS treated with lumpectomy/radiation.[32] The primary results of this trial comparing anastrozole versus tamoxifen

in postmenopausal patients with DCIS undergoing lumpectomy and radiation therapy were reported at the 2015 ASCO Annual Meeting. According to the oral report presented, 5 years of anastrozole provided postmenopausal women with a significant improvement in breast cancer–free interval compared with tamoxifen, particularly in women younger than 60 years.[8] The years of our study overlapped with those of the NSABP B-35 phase III trial, and it is possible that our cohort includes patients who were enrolled in this study. We were unable to determine which patients may have been enrolled from the data set used. Furthermore, the Mammary Prevention Trial.3 (MAP.3) included postmenopausal women with DCIS who underwent unilateral mastectomy and were treated with exemestane, and found a decreased risk of invasive breast cancer and DCIS (hazard ratio [HR], 0.47). Although there was an insufficient number of patients with DCIS to allow for subgroup analysis of the effect of exemestane, the trial did determine the side effects, and suggests that it may also be beneficial in preventing ipsilateral recurrence or CBC in DCIS.[1] Our study included women for whom hormone therapy was recommended, but we are unable to determine which type of hormone (tamoxifen vs AI) was recommended. However, until the results of the NSABP B-35 trial were reported at the ASCO Annual Meeting in May 2015,[8] there were no clear indications for AIs in DCIS. Therefore, it is likely that a significant proportion of the anti-e therapy recommended during the years of our study was tamoxifen, because this has been the most common anti-e therapy used in the setting of HR+ DCIS. As the NSABP B-35 data comes to press, we may see differing strategies for hormone-based prevention, including higher use of AIs, that have better patient acceptance, lower rates of rare but life-threatening complications, and increased patient and provider acceptance.

There are several limitations to this study. Although the CCR and OSHPD linked data set includes extensive demographic and clinical information on more than 3.4 million cases of cancer diagnosed in California, potentially relevant variables are not collected. First, smoking is known to increase the risk of DVT, and therefore is a relative contraindication to anti-e. Neither the CCR nor OSPHD collects information on smoking status, history of smoking, nor previous DVT, and there may be patients in this cohort whose contraindication to anti-e therapy was based on these. Although these individuals would appropriately be included in the "anti-e not recommended" group, their inclusion in the analysis would falsely elevate the rates of non-use of anti-e. Additionally, information regarding menopausal status and type of hormone therapy administered is not included in the data set. This study also evaluates recommendation of anti-e use and not actual anti-e use, because actual anti-e use may have not been documented in the patient's records. A review of the literature reports that up to 50% of patients prescribed anti-e therapy may not be compliant with taking it for the prescribed duration, and therefore our results may overestimate the number of patients actually taking the medication.[33] In addition, only 60% of patients in our cohort who underwent lumpectomy also underwent postlumpectomy radiation therapy. This is lower than expected, although consistent with other published reports.[34] In light of this, the findings of our study may not be generalizable to populations who have undergone both lumpectomy and radiation therapy for HR+ DCIS. Previous studies have also shown low rates of accuracy for documentation of hormone administration in population-based registries, but this is improved by linking to claims.[35] Although we expect some incompleteness in documentation of hormone administration in our data set, we attempted to minimize this effect by linking the CCR and OSHPD datasets. The CCR also does not include information regarding necrosis or margins, both of which contribute to risk of recurrence. We could not control for these factors in our analysis. In addition, it is possible that some patients took an anti-e therapy at their own insistence, rather than the recommendation of a healthcare provider, and the data set did not distinguish these individuals from those who took anti-e therapy on the advice of their healthcare provider. Finally, the data set does not include actual income, but only an SES quintile based on patients' census block.

The strengths of our study include that information was obtained from a large, prospectively maintained data set, including all cases of ER+ DCIS treated in the state of California from 2004 to 2011. Additionally, we controlled for a number of comorbidities.

Conclusions

Despite current guidelines recommending consideration of its use, provider recommendation for anti-e therapy after surgery for DCIS remains low, having been recommended to 40% of patients with ER+ DCIS in our cohort, and used by fewer than one-third. Although reconstruction and insurance status have no impact on predicting anti-e recommendation, predictors include lumpectomy versus mastectomy, Asian/Pacific Islander race, younger age, and 3 or more comorbidities. This study underscores the importance of ongoing efforts to educate providers in the current NCCN Guidelines, including the consideration for tamoxifen and AIs after both lumpectomy and unilateral mastectomy for HR+ DCIS, understanding that the decision to recommend anti-e therapy is a complex one, made by providers based on conversations with each individual patient. Further work is warranted to understand patterns of anti-e recommendation for patients with HR+ DCIS among providers.

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