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Article

Spatial-Temporal Trends in Ovarian Cancer Outcomes in California

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Abstract

Background: Research suggests that geographic location may affect ovarian cancer (OC) outcomes. Insurance status often remains an important predictor of outcomes. The Affordable Care Act was enacted in 2010 to expand access to affordable health insurance. Our objective was to examine spatiotemporal trends in OC treatment nonadherence and disease-specific mortality in California (USA) among women diagnosed with OC. **Methods:** Newly diagnosed epithelial OC cases between 1996 and 2017 were identified from the California Cancer Registry. Spatiotemporal trends in adherence to treatment guidelines were examined using generalized additive models and OC-specific mortality using Cox proportional hazards additive models. Prediction grids covering California were used to display the odds ratios (ORs) and hazard ratios of location using the median value for the study area as the referent value. Seven overlapping 5-year periods and 2 larger ones (pre- and post-2013) were assessed. Analyses were stratified according to stage (early vs advanced) and used $P = .05$ to determine statistical significance. **Results:** Statistically significant spatial patterns in treatment nonadherence were observed for every time period examined ($P < .001$). Odds of treatment nonadherence associated with geographic location were highest among women with early-stage OC in southern Los Angeles County during 2014-2017 (OR max = 3.89, confidence interval = 1.04 to 7.61). For women with advanced-stage OC, residing in northern California was generally associated with lower odds ratios, whereas southern California was associated with higher odds ratios, with higher odds in the latter time period (OR range = 0.53-1.84 in 1996-2012 vs 0.49-2.37 in 2013-2017). Geographic location was not a statistically significant predictor of mortality. **Conclusions:** Residential location was statistically significantly associated with treatment received in California, with spatial patterns varying over time but not OC-specific mortality. Changes in insurance status over time were accompanied by shifts in population demographics and increased travel distances to receive care.

Despite advances in treatment and survival, ovarian cancer (OC) remains the deadliest gynecological cancer among women diagnosed in the United States. Of the 21 410 cases estimated to have been diagnosed in 2021 (1), approximately 49.1% will survive at least 5 years (2). Determinants well documented to affect OC outcomes include cancer characteristics, sociodemographic variables such as race and socioeconomic status (SES), insurance status, treating hospital and physician, and access to quality care (3-12).

In 2010, the Affordable Care Act (ACA) was signed into law by President Barack Obama with the goal of increasing access to health insurance (13). Although some initial features were introduced beforehand, most ACA mandates were passed in 2014. Nationwide, almost 20 million individuals gained insurance by 2016, with the largest increases among low-income populations (14). Furthermore, rates of patients without health insurance decreased among people newly diagnosed with cancer (15) and cancer survivors (16) in states with Medicaid expansion after 2014. Importantly, these changes were more pronounced in people of color and those with lower incomes (15-17). Even some of the earlier provisions, such as individual's ability to remain on their parent's insurance up to age 26 years, gynecologist visits without preauthorization, and coverage of preventative care (18), have been found to affect OC outcomes (19,20). For instance, using the National Cancer Database, a hospital-based registry, Smith et al. (20) observed notable improvements in the early detection of OC and initiation of treatment after the implementation of the ACA, including analyses limited to the period of 2011-2013.

Residential location has also been associated with whether women receive guideline-adherent treatment. Location can

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directly affect women's access to care by the availability of services (21,22), proximity to services (23-26), transportation barriers (27-29), and local differences in cost of care or insurance coverage (30). In California, women's location at time of diagnosis (1996-2014) statistically significantly influenced their likelihood of getting National Comprehensive Cancer Network (NCCN) guideline–adherent treatment after an OC diagnosis (23,25) and was an independent predictor of survival (24,26). Insurance status is consistently correlated with OC outcomes and often remains a determinant of receiving adequate care and disease-specific survival despite controlling for other factors (25,26). In this population, rates of uninsured women with OC started declining in 2013. Previous studies have not assessed temporal trends in the contribution of location to OC outcomes in the United States, an important consideration given the monumental changes in the health-care system since 2010 and its potential effect on access to care.

Our objective was to examine spatiotemporal trends in OC treatment adherence and OC-specific mortality in California (USA), 1 of 6 states that expanded Medicaid early (31), among women diagnosed with epithelial OC between 1996 and 2017. We investigated geographic differences in outcomes pre- and post-2013 and trends over time. Additionally, we examined the impact of insurance on OC treatment adherence and mortality.

Methods

Study Population

Using a retrospective population-based study design, we identified women through the California Cancer Registry (CCR) who were diagnosed with first or only invasive epithelial OC between 1996 and 2017, with follow-up through 2018. The CCR is a statewide population-based surveillance system with acknowledged high-quality controls (32). We included women of all OC stages [International Federation of Gynecology and Obstetrics Stage I-IV] who were aged 18 years or older at diagnosis. California's Office of Statewide Health Planning and Development patient discharge data were linked with the CCR data. Only those with complete clinical history and residential location were included. Case exclusions are outlined in Supplementary Figure 1 (available online). The study received approval from the Institutional Review Board of the University of California, Irvine (UCI 14-66/HS# 2014-1476).

Outcomes

Our 2 outcomes of interest were OC treatment nonadherence and OC-specific mortality. Treatment adherence was determined by whether women received care that adhered to the NCCN stage and grade-specific guidelines. These treatment guidelines have been validated as a statistically significant predictor of survival (33). To be considered overall compliant, women must have received surgery and chemotherapy that adhered to the NCCN recommendations. Our second outcome, OC-specific mortality, was then examined after accounting for guideline-adherent care. Follow-up was considered from the date of diagnosis to the date of the event, defined as death from OC. Death from other causes or alive at the end of follow-up were censored.

Covariates

All analyses were adjusted for age at diagnosis, year of diagnosis, insurance status, SES, race and ethnicity, marital status, treatment received, comorbidities, cancer characteristics, hospital volume, distance traveled to receive treatment, and proximity to the closest high-volume hospital. Race and ethnicity, obtained from the CCR, was categorized as Asian and Pacific Islander, Hispanic, non-Hispanic Black, non-Hispanic White, other (includes American Indian and unknown). Insurance status was categorized into managed care, Medicare, Medicaid, other insurance (includes fee-for-service, TRICARE, military, Veterans Affairs, Indian/public health service, and insurance not otherwise specified), and unknown insurance status. SES was defined using a community-level index (Yost score for those diagnosed pre-2006 and the Yang Index for those diagnosed post-2006) (34,35). Cancer characteristics included histology (serous, mucinous, endometrioid, clear cell, adenocarcinoma, not otherwise specified, and others), grade, size, and stage at diagnosis (FIGO stages I-IV). Comorbidity status was categorized using the Deyo-adapted Charlson Comorbidity Score. Hospital volume was considered the OC case volume of the initial treating hospital (dichotomized into low vs high volume). High-volume hospitals were those treating 20 and more cases per year. The distance measures were categorized into quintiles. Women were stratified by early (I and II) and advanced (III and IV) stages.

Statistical Analysis

We examined differences in patient characteristics before and after 2013 by using t tests for continuous variables and χ^2 tests for categorical ones. Cox proportional hazards models without location were used to calculate the hazard ratios (HRs) between sociodemographic, treatment, geographic access variables, and OC-specific mortality. Spatiotemporal trends in NCCN treatment nonadherence and OC-specific mortality were investigated using generalized additive models with a bivariable smooth for geocoded residential location (23-25). We compared the effect of location before and after 2013, a period that coincides with the first evident drop in uninsured status after 2010 (Table 1). We additionally looked at trends over time by examining associations during 7 periods (1996-2000, 1999-2003, 2002-2006, 2005-2009, 2008-2012, 2011-2015, and 2014-2017). We used overlapping time periods to smooth the temporal analysis (36).

Evenly spaced prediction grids covering the state of California were used to display the odds ratios (ORs) and hazard ratios of geographic location. At each location, the log odds or hazards was calculated from the models. Predicted odds ratios for nonadherent treatment and hazard ratios for OC mortality were calculated for locations across California using the median odds or hazards for all of California as the referent value. We did not predict for areas in California with few or no cases. To determine statistical significance of location, we conducted permutation tests for each model. Based on previous work, we used an optimal smoothing or span size of 0.3 (25,26). Maps of California were produced for each time period, displaying either the odds of nonadherence or the hazard ratios by geographic location, indicating statistically significant areas with contour lines.

Based on previous work and preliminary findings of increased and decreased odds observed in regional areas, secondary analyses were conducted for 2 smaller geographic

Table 1. Insurance status by year of diagnosis for women diagnosed with ovarian cancer in California, 1996-2017

Year of diagnosis	Managed care, %	Medicare, %	Medicaid, %	Other insurance, %	Uninsured, %	Unknown, %
1996	41.3	31.3	8.4	9.8	4.2	5.1
1997	44.4	28.6	9.0	11.4	3.9	2.8
1998	48.7	26.8	7.8	10.8	2.5	3.3
1999	49.3	25.9	8.1	10.4	2.8	3.5
2000	51.9	26.0	7.5	9.2	2.7	2.7
2001	53.7	26.6	6.5	8.1	2.8	2.3
2002	51.7	26.8	7.6	9.0	2.7	2.3
2003	52.8	27.1	7.3	8.4	2.0	2.3
2004	43.5	28.4	9.2	13.8	2.9	2.3
2005	42.5	28.3	8.0	15.6	3.2	2.4
2006	45.1	25.5	8.7	15.3	3.4	2.0
2007	45.4	24.5	9.7	15.6	3.6	1.3
2008	46.5	26.0	8.9	13.4	3.5	1.7
2009	47.8	23.8	10.2	14.0	2.9	1.3
2010	46.7	22.1	11.6	15.2	3.2	1.2
2011	49.7	22.0	9.7	14.2	3.1	1.3
2012	45.5	24.0	10.5	15.0	3.3	1.7
2013	44.1	26.2	11.8	14.1	2.6	1.2
2014	48.6	23.3	9.6	15.8	1.5	1.2
2015	49.2	22.5	9.9	15.9	1.5	1.0
2016	50.8	23.8	8.9	14.0	1.1	1.5
2017	52.3	22.2	10.0	13.4	1.2	0.9

regions: the San Francisco (SF) Bay area in northern California and Orange and Los Angeles counties in southern California. We performed all analyses and mapping in R (Version 4.0.1) using the MapGAM package. Statistical significance was considered $P = .05$, and tests were 2-sided.

Results

During the 22-year period examined, 11 563 early and 23 882 advanced-staged OC cases were diagnosed in California. The 5-year OC-specific survival rate among the entire study population was 52.6%, with a median survival time of 34.3 months (64.0 months and 24.3 months among early- and late-stage women, respectively). The distribution of patient characteristics by stage (early vs advanced) and time period (pre- and post-2013) is outlined in Table 2. Among women with early-stage OC, the most notable changes between pre- and post-2013 were increases in Medicaid (8.8% vs 10.8%, $P = .001$) and other insurance (15.9% vs 18.8%, $P < .001$) and a decrease in those uninsured (3.6% vs 1.4%, $P < .001$). Women diagnosed in advanced stages similarly had statistically significant changes between time periods. Compared with pre-2013, a greater proportion of women had Managed Care insurance (46.9% vs 44.8%, $P = .003$) and other insurance (12.7% vs 10.9%, $P < .001$) in 2013-2017, and a decrease was observed in the number of patients with Medicare (27.6% vs 30.3%, $P < .001$) and those not insured (1.7% vs 2.9%, $P < .001$). We also observed a decrease in women with unknown insurance status for both early- and advanced-stage women.

Statistically significant shifts in the study's demographics were observed pre- and post-2013, including women's race and ethnicity and SES. For example, regardless of stage at diagnosis, a greater proportion of Hispanic and Asian and Pacific Islander women were diagnosed with OC post 2013 compared with before 2013 ($P < .001$). In addition, treatment adherence improved after 2013 among early-stage women (24.8% vs 31.3%, $P < .001$) but not for those diagnosed in advanced stages (44.8% vs 45.5%, $P = .35$). For both early and advanced stages of OC, a larger percentage of women were in the furthest 2 categories of distance traveled for care ($P < .001$) in the second time period compared with pre-2013.

Insurance and OC NCCN Treatment Nonadherence

Table 3 reports the odds ratios for insurance. Among women with early-stage OC, only Medicare insurance increased the odds of treatment nonadherence before 2013 (OR = 1.28, 95% CI = 1.07 to 1.52). After 2013, Medicare was no longer associated with treatment adherence (OR = 1.10, 95% CI = 0.84 to 1.44), and having other insurance was statistically significantly protective against receiving care that did not adhere to the NCCN guidelines (OR = 0.63, 95% CI = 0.50 to 0.78). Before 2013, other insurance increased the odds of nonadherence among advanced-staged women (OR = 1.13, 95% CI = 1.01 to 1.26). Although being uninsured did not affect NCCN treatment adherence among women with early-stage OC, it increased the risk for advanced-staged women pre-2013 (OR = 1.23, 95% CI = 1.00 to 1.51), and that risk increased from 2013-2017 (OR = 2.05, 95% CI = 1.27 to 3.33).

Insurance and OC-Specific Mortality

In general, insurance was correlated with survival for women in advanced stages (Table 4) and during the period of 1996-2012. Before 2013, having Medicare (HR = 0.93, 95% CI = 0.89 to 0.97) and other insurance (HR = 0.94, 95% CI = 0.88 to 1.00) were associated with a better prognosis. In contrast, women with Medicaid (HR = 1.10, 95% CI = 1.03 to 1.18) and those not insured (HR = 1.18, 95% CI = 1.05 to 1.32) had increased hazards of mortality.

Table 2. Patient characteristics by stage at diagnosis pre- and post-2013

Characteristics	Early stages			Advanced stages		
	1996-2012 No. (%)	2013-2017 No. (%)	P[c]	1996-2012 No. (%)	2013-2017 No. (%)	P[c]
Total	8539 (100)	3024 (100)		17724 (100)	6158 (100)	
Age (median, SD), y	54 (15.4)	55 (14.8)	.01	63 (14.0)	64 (13.8)	<.001
Insurance status						
Managed care	4513 (52.9)	1602 (53.0)	<.001	7933 (44.8)	2891 (46.9)	<.001
Medicare	1443 (16.9)	470 (15.5)		5364 (30.3)	1697 (27.6)	
Medicaid	749 (8.8)	326 (10.8)		1571 (8.9)	596 (9.7)	
Other insurance	1354 (15.9)	567 (18.8)		1938 (10.9)	781 (12.7)	
Not insured	305 (3.6)	41 (1.4)		507 (2.9)	105 (1.7)	
Unknown	175 (2.0)	18 (0.6)		411 (2.3)	88 (1.4)	
Race and ethnicity						
Asian/Pacific Islander	1348 (15.8)	563 (18.6)		1681 (9.5)	806 (13.1)	
Hispanic	1716 (20.1)	810 (26.8)		3155 (17.8)	1516 (24.6)	
Non-Hispanic Black	325 (3.8)	116 (3.8)		924 (5.2)	343 (5.6)	
Non-Hispanic White	5091 (59.6)	1499 (49.6)	<.001	11869 (67.0)	3435 (55.8)	<.001
Other[a]	59 (0.7)	36 (1.2)		95 (0.5)	58 (0.9)	
Socioeconomic status						
Highest	2089 (24.5)	691 (22.9)	.02	4302 (24.3)	1362 (22.1)	<.001
Higher-middle	1968 (23.0)	703 (23.2)		4068 (23.0)	1377 (22.4)	
Middle	1839 (21.5)	603 (19.9)		3740 (21.1)	1208 (19.6)	
Lower-middle	1519 (17.8)	582 (19.2)		3239 (18.3)	1223 (19.9)	
Lowest	1124 (13.2)	445 (14.7)		2375 (13.4)	988 (16.0)	
Marital status						
Single	4042 (47.3)	1501 (49.6)	.03	8783 (49.6)	3239 (52.6)	<.001
Married	4497 (52.7)	1523 (50.4)		8941 (50.4)	2919 (47.4)	
Charlson Comorbidity Score[b]						
0	4806 (56.3)	1739 (57.5)	<.001	7749 (43.7)	3354 (54.5)	<.001
1	1611 (18.9)	341 (11.3)		4480 (25.3)	941 (15.3)	
2+	1571 (18.4)	286 (9.5)		4595 (25.9)	962 (15.6)	
Unknown	551 (6.5)	658 (21.8)		900 (5.1)	901 (14.6)	
Treatment received						
NCCN adherent	2117 (24.8)	945 (31.3)	<.001	7933 (44.8)	2799 (45.5)	.35
NCCN nonadherent	6422 (75.2)	2079 (68.8)		9791 (55.2)	3359 (54.5)	
Hospital volume						
Low (annual case <20)	6846 (80.2)	2349 (77.7)	.004	14524 (81.9)	5081 (82.5)	.33
High (annual case ≥20)	1693 (19.8)	675 (22.3)		3200 (18.1)	1077 (17.5)	
Distance to closest HVH, km						
≤11	1807 (21.2)	593 (19.6)	.45	3548 (20.0)	1141 (18.5)	.006
12-19	1772 (20.8)	640 (21.2)		3465 (19.5)	1212 (19.7)	
20-36	1726 (20.2)	637 (21.1)		3536 (20.0)	1190 (19.3)	
36-84	1621 (19.0)	583 (19.3)		3537 (20.0)	1348 (21.9)	
≥85	1613 (18.9)	571 (18.9)		3638 (20.5)	1267 (20.6)	
Distance traveled to care, km						
<6	1704 (20.0)	420 (13.9)	<.001	3850 (21.7)	1115 (18.1)	<.001
6-9	1683 (19.7)	478 (15.8)		3684 (20.8)	1244 (20.2)	
10-16	1744 (20.4)	602 (19.9)		3507 (19.8)	1236 (20.1)	
17-32	1789 (21.0)	696 (23.0)		3348 (18.9)	1256 (20.4)	
>32	1619 (19.0)	828 (27.4)		3335 (18.8)	1307 (21.2)	

[a]Other race and ethnicity includes American Indian and unknown. HVH = high-volume hospital; NCCN = National Comprehensive Cancer Network.
[b]The Charlson Comorbidity Score was used to assign comorbidity status. A score of 0 = no comorbidities, 1 = 1 comorbidity, 2+ = 2 or more comorbidities, and unknown comorbidity status is unknown.
[c]P value is for differences by time period, *t* test is used for age, and χ^2 tests are used for all other variables.

Geographic Location and OC NCCN Treatment Nonadherence

Statistically significant spatial patterns in OC NCCN treatment nonadherence were observed for every time period examined ($P < .001$), even after controlling for known predictors of treatment adherence (Figures 1-3). Overall, the impact of where women lived on the odds of nonadherence were higher among women diagnosed in early stages compared with those who were diagnosed in advanced stages. Supplementary Table 1 (available online) outlines the odds ratios for residential

Table 3. Adjusted odds of NCCN treatment nonadherence by time period and insurance status among women diagnosed with early- and advanced-stage ovarian cancer in California, 1996-2017

Insurance status	1996-2012 OR[a] (95% CI)	2013-2017 OR (95% CI)
Early stages		
Managed care	1.00 (Referent)	1.00 (Referent)
Medicare	1.28 (1.07 to 1.52)	1.10 (0.84 to 1.44)
Medicaid	1.10 (0.90 to 1.35)	0.90 (0.68 to 1.21)
Other	0.97 (0.84 to 1.12)	0.63 (0.50 to 0.78)
Not insured	1.15 (0.85 to 1.55)	1.21 (0.55 to 2.67)
Unknown insurance	0.86 (0.60 to 1.23)	1.69 (0.47 to 6.16)
Advanced stages		
Managed care	1.00 (Referent)	1.00 (Referent)
Medicare	1.09 (0.99 to 1.18)	1.21 (1.03 to 1.41)
Medicaid	1.05 (0.93 to 1.19)	1.14 (0.92 to 1.41)
Other	1.13 (1.01 to 1.26)	0.89 (0.74 to 1.07)
Not insured	1.23 (1.00 to 1.51)	2.05 (1.27 to 3.33)
Unknown insurance	1.09 (0.87 to 1.36)	1.05 (0.63 to 1.72)

[a]The odds ratios (ORs) are obtained from the generalized additive models that additionally adjust for location, diagnosis year, age, socioeconomic status, marital status, tumor size, grade, histology, and stage at diagnosis, Charlson Comorbidity Score, year of diagnosis, hospital volume, distance to closest high-volume hospital, and distance traveled to care. CI = confidence interval; NCCN = National Comprehensive Cancer Network.

Table 4. Adjusted hazard ratios for insurance by time period and insurance status among women diagnosed with early- and advanced-stage ovarian cancer in California, 1996-2017

Insurance status	1996-2012 HR[a] (95% CI)	2013-2017 HR (95% CI)
Early stages		
Managed care	1.00 (Referent)	1.00 (Referent)
Medicare	1.08 (0.95 to 1.24)	1.04 (0.74 to 1.47)
Medicaid	1.08 (0.88 to 1.32)	1.25 (0.76 to 2.08)
Other	1.04 (0.88 to 1.22)	0.91 (0.59 to 1.43)
Not insured	1.25 (0.94 to 1.68)	0.57 (0.08 to 4.15)
Unknown insurance	1.04 (0.70 to 1.54)	7.10 (2.97 to 16.99)
Advanced stages		
Managed care	1.00 (Referent)	1.00 (Referent)
Medicare	0.93 (0.89 to 0.97)	0.96 (0.87 to 1.06)
Medicaid	1.10 (1.03 to 1.18)	1.08 (0.93 to 1.26)
Other	0.94 (0.88 to 1.00)	1.09 (0.95 to 1.25)
Not insured	1.18 (1.05 to 1.32)	1.09 (0.79 to 1.50)
Unknown insurance	0.90 (0.80 to 1.02)	1.02 (0.73 to 1.43)

[a]The hazard ratios (HRs) are obtained from Cox proportional hazards models that additionally adjust for diagnosis year, age, socioeconomic status, marital status, tumor size, grade, and histology, stage at diagnosis, Charlson Comorbidity Score, year of diagnosis, hospital volume, distance to closest high-volume hospital, distance traveled to care, and receipt of National Comprehensive Cancer Network guideline–adherent care. Models did not adjust for location. CI = confidence interval.

location for each time period among early- and advanced-staged women. Among women with early-stage OC, we identified areas of increased odds in the Central Valley before 2013 (OR range = 0.55-2.45) that were no longer present for those diagnosed between 2013 and 2017 (Figure 1). There were also areas with lower odds of nonadherence in northern California before 2013 that grew in 2013-2017. Other areas with statistically significantly lower odds ratios for treatment nonadherence altogether became statistically insignificant in southern parts of the Central Coast after 2013. For women diagnosed in advanced stages (Figure 2), geographic risk increased in the latter time period (OR range = 0.53-1.84 in 1996-2012 vs 0.49-2.37 in 2013-2017), similar to early stages. Residing in northern California was generally associated with lower odds ratios, whereas southern California was associated with higher odds ratios.

In our analysis of trends over time (Figure 3), among all time periods examined, the greatest odds of receiving nonadherent care among women with early-stage OC was in southern Los Angeles County during 2014-2017 (OR max = 3.89). Geographic location was also statistically significantly associated with receiving NCCN-adherent treatment among women diagnosed in advanced stages, yet the spatial patterns differed from those in early stages, with no increase in the Central Valley. Living in northern California was associated with lower odds ratios over time.

Geographic Location and OC-Specific Survival

Overall, geographic location was not a statistically significant predictor of disease-specific mortality (Supplementary Table 2; Supplementary Figures 2 and 3, available online). After adjusting for covariates, no statistically significant spatial patterns remained for most time periods (Supplementary Figure 2, available online).

Secondary Analyses

A total of 12 538 and 7672 women were diagnosed with OC in Los Angeles and Orange counties and the SF Bay area, respectively (Supplementary Figure 4, available online). In both regions, geographic location was statistically significantly associated with greater odds of noncompliant care although with varying spatial patterns between the 2 time periods. Geographic location was only associated with OC-specific mortality for women diagnosed between 2013 and 2017 in the SF Bay area.

Discussion

This study examined spatiotemporal trends in OC treatment adherence and OC-specific mortality in California. Geographic location statistically significantly affected women's odds of receiving care, with the locations of higher and lower odds changing over time and differing by stage at diagnosis. Overall, geographic location was not statistically significantly associated with OC mortality, but the patterns did vary by time period.

For both early- and advanced-stage women, the increased odds of nonadherence generally became concentrated in southern Los Angeles County. This study also shows an area of higher odds among early-stage women in the Central Valley from 1996 to 2012 that was no longer associated with treatment adherence in later years. Because rates of treatment adherence among early-stage patients increased from pre- to post-2013, 1 potential explanation for the decreased odds associated with this more remote area could be improvements in geographic access to quality care, particularly adequate surgery. Better access to surgery is possibly a result of increased insurance coverage, service and provider availability, or ability to travel. Women diagnosed with OC who reside in remote locations have been found less likely to receive cancer-directed surgery (37,38). Surgery, a crucial component of treatment adherence, is ideally

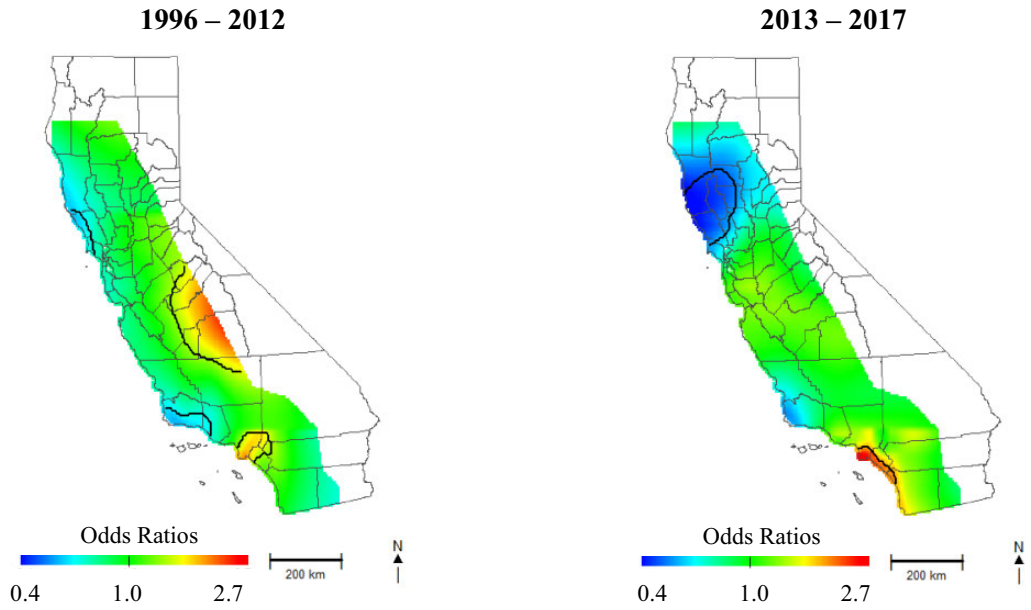

Figure 1. Geographic location and odds of National Comprehensive Cancer Network (NCCN) treatment nonadherence for women diagnosed with early-stage ovarian cancer (OC). The fully adjusted effect of geographic location on the odds of receiving care that did not adhere to the NCCN treatment guidelines among women with early-staged OC (stages I and II) is shown. Models are adjusted for insurance status, age, race and ethnicity, socioeconomic status, marital status, tumor characteristics, Charlson Comorbidity Score, year of diagnosis, treatment at a high-volume hospital, proximity of closest high-volume hospital, and distance traveled to receive care. Statistically significant locations are outlined by **contour lines.**

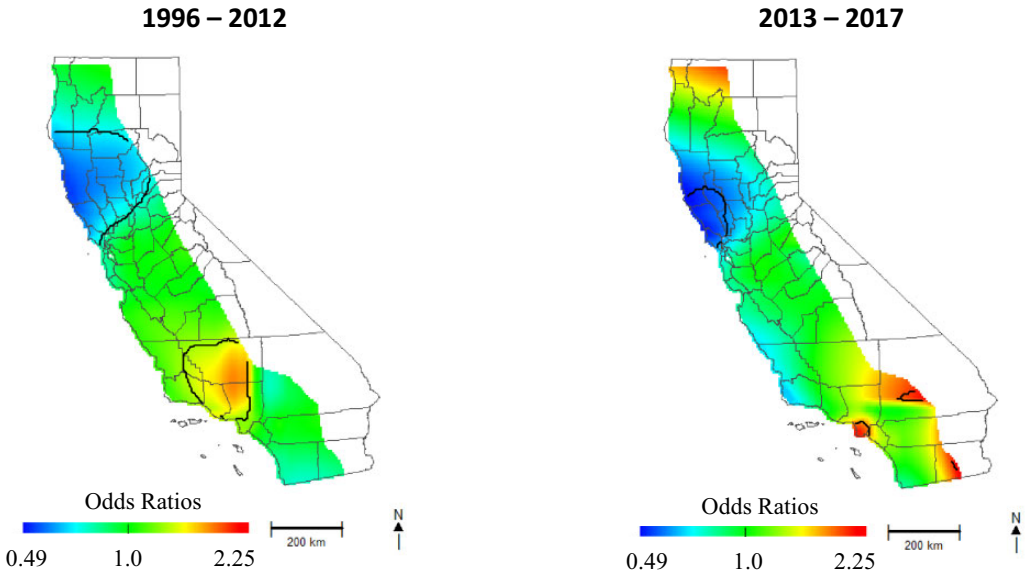

Figure 2. Geographic location and odds of National Comprehensive Cancer Network (NCCN) treatment nonadherence for women diagnosed with advanced-staged ovarian cancer (OC). The fully adjusted effect of geographic location on the odds of receiving care that did not adhere to the NCCN treatment guidelines among women with advanced-staged OC (stages III and IV) is shown. Models are adjusted for insurance status, age, race and ethnicity, socioeconomic status, marital status, tumor characteristics, Charlson Comorbidity Score, year of diagnosis, treatment at a high-volume hospital, proximity of closest high-volume hospital, and distance traveled to receive care. Statistically significant locations are outlined by **contour lines.**

performed by a gynecologic oncologist (39-41) and at a high-performing hospital (26,42) to maximize outcomes. Unfortunately, OC patients in rural locations have lower odds of receiving surgery from specialists (38). Furthermore, there are limited hospitals providing high-quality OC care in the respective area (26).

Although we were unable in this study to determine whether there was a shift in specialist availability by time period, we did observe statistically significant changes in insurance status, including a decrease in rates of uninsured women. The ACA expanded access to health insurance for millions of people, largely benefiting individuals of lower income and people of color (16,43). Changes in insurance status among OC patients could have potentially led to greater access to surgical specialists and hospitals. One study examining the impact of the ACA Medicaid Expansion on cancer admissions and

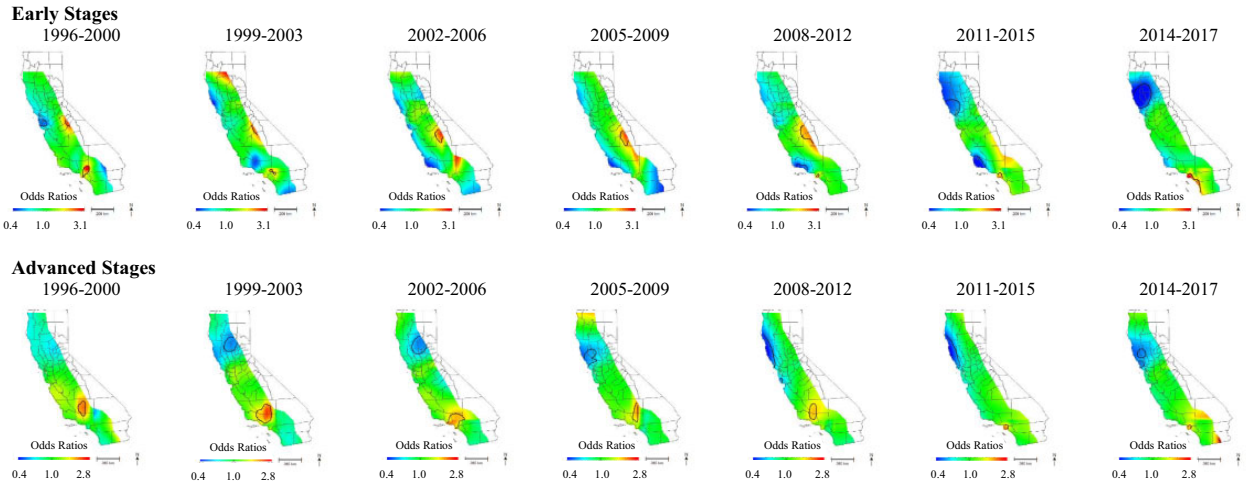

Figure 3. Time series of geographic risk of National Comprehensive Cancer Network (NCCN) treatment nonadherence for women diagnosed with ovarian cancer in California. The fully adjusted effect of geographic location on women's risk of receiving care that did not adhere to the NCCN treatment guidelines over time and by early (stages I and II) vs advanced stages (stages III and IV) is shown. We examined 7 periods that overlapped by 2 years over a 22-year period. The last period, 2014-2017, is consistent with the implementation of all the Affordable Care Act initiatives. Models are adjusted for insurance status, age, race and ethnicity, socioeconomic status, marital status, tumor characteristics, Charlson Comorbidity Score, year of diagnosis, treatment at a high-volume hospital, proximity of closest high volume hospital, and distance traveled to receive care. Statistically significant locations are outlined by **contour lines.**

surgeries observed increases in surgery rates among low-income patients, attributing it to ACA's Medicaid expansion (44). Additionally, several studies found that women diagnosed with gynecologic cancers had improved insurance coverage after the ACA's enactment (15,19). The findings of Smith et al. (20) that the ACA was associated with earlier detection among OC patients additionally supports the notion that access to surgery may have improved with the ACA, because it is required for OC staging.

However, our results showed that not all regions saw improved adherent care after ACA. Increased insurance coverage may not have translated into increased access to quality cancer care for all women. Researchers of an analysis investigating hospitals covered by federal exchange plans available through the ACA found that only 41% of plans had National Cancer Institute-Designated Cancer Centers, and HMO plans were less likely to have them (45). Yasaitis and colleagues (46) examined exchange plans that contained National Cancer Institute-Designated and NCCN Cancer Centers, determining that oncologists affiliated with either one was less likely to be covered by narrower networks. Furthermore, many insurance plans do not include an in-network gynecologic oncologist, and some networks provide no access to one at all (17).

Although we found changes in the impact of insurance status on OC outcomes over time, we acknowledge that other factors may have contributed to the different spatiotemporal patterns observed. A statistically significant demographic shift in our study population over time may have affected a location's association with OC outcomes. We also found statistically significant changes in travel patterns. Women became more likely to travel the furthest distances for care over time, and fewer advanced-staged women lived less than 11 km from a high-volume hospital. Although the number of hospitals with American College of Surgeons-accredited cancer programs increased nationwide by 6.7% from 2005 to 2015, almost twice as many people lived more than a 60-minute drive from one in the later years (47).

An important strength of this study is the decades of data included in the analysis. This span provided sufficient data to examine the effect of location on OC outcomes before and after 2013. Another strength is in the approach, which also assessed location across several overlapping periods during the 22-year period. In addition, location is available at the individual address level, allowing for continuous spatial analyses. To our knowledge, this study is the first to examine spatio-temporal trends in OC treatment adherence and mortality at a geocoded resolution. Our use of sophisticated statistical techniques allowed the examination of the effect of location while adjusting for covariates. The study also benefitted from the availability of several important risk factors.

One potential limitation is that our analyses combined all women older than 18 years. The ACA would have theoretically affected women younger than 65 years the most, because women aged 65 years and older would have automatically been eligible for Medicare insurance before the ACA. We chose not to restrict our analyses by age because the ACA provided measures for Medicare recipients, such as the introduction of free preventative services and lower drug costs, beginning in 2011 that may have affected outcomes. It is also possible that women older than 65 years had supplemental insurance changes through the ACA. Additionally, both insurance status and geographic location were available only at the time of diagnosis, which may result in some misclassification if women's insurance status changed or if they moved. We were also unable to control for provider specialty. Last, given the extensive period examined, several variables assessed using Schoenfeld residuals violated the Cox proportional hazards assumptions. Hazard ratios reported for insurance should be interpreted with caution.

In summary, this study found that statistically significant spatial patterns of care changed over time in California. Locations with greater or lower odds of inadequate care differed by time period, and increased insurance coverage may have influenced these findings. Rates of uninsured women decreased after 2013. Improvements in adherence to the NCCN treatment guidelines were observed for early-stage women during that same time period. However, our study shows that most women are still not receiving standard care, and no improvements were

observed among advanced-stage women, the majority of those diagnosed with OC. Despite improvements in access to care provided by the ACA, barriers to getting adequate care are still present. Future research should examine potential sources of increased geographic risk of treatment nonadherence still present in later years.

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Data Availability

The data that support these findings were provided and are available from the California Cancer Registry and California's Office of Statewide Health Planning and Development. Contact details can be obtained from the corresponding author upon request.

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