UNIVERSITY OF CALIFORNIA,
IRVINE

Geographic Location and its Contribution to Disparities in Ovarian Cancer Treatment and Survival in California

DISSERTATION

submitted in partial satisfaction of the requirements
for the degree of

DOCTOR OF PHILOSOPHY

in Public Health

by

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Dissertation Committee:
Professor Verónica Vieira, Chair
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2020

DEDICATION

To

my parents,
for providing a solid and loving foundation

my partner
for being my rock and biggest champion

my brothers and sisters,
for being a source of motivation

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ACKNOWLEDGEMENTS

I would like to express my deepest appreciation to my committee chair and mentor, Professor Verónica Vieira, whose coupled genius and compassion has been a perpetual source of inspiration. Thank you for your guidance, believing in me, and willingness to share your wisdom. Without the supportive environment you foster, completion of this dissertation would not have been possible.

I would like to thank my committee member, Professor Scott Bartell, for always being extraordinarily generous with your time and knowledge. Your enthusiasm for and dedication to scholarship is simply incredible. I would also like to thank my committee member, Professor Robert Bristow, for your time, openness to new ideas, and genuine interest in understanding sources of inequities.

In addition, a thank you to Professor Argyrios Ziogas and Jenny Chang for your insights and collaboration throughout the years.

Financial Support was provided by the National Center on Minority Health and Health Disparities of the National Institutes of Health under award number: R01MD009697.

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ABSTRACT OF THE DISSERTATION

Geographic Location and its Contribution to Disparities in Ovarian Cancer Treatment and Survival in California

by

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Doctor of Philosophy in Public Health

University of California, Irvine, 2020

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Not only is ovarian cancer the 5th leading cause of cancer death in American women, it is also the deadliest of the gynecological cancers and among the malignancies of which disparities in care and outcomes in underserved populations are prominent. The aims of this dissertation were to investigate the association between residential geographic location and ovarian cancer outcomes, while considering the relationship between race and socioeconomic factors. Incident ovarian cancer cases were ascertained from the California Cancer Registry for women diagnosed between 1996 and 2014. Adherence to the National Comprehensive Cancer Network (NCCN) guidelines for treatment was used as a binary measure of receipt of quality care. Two geographic variables assessing access to care were also considered: distance traveled to receive care and the proximity of the closest high-quality-of-care (QOC) hospital. Spatial analyses using generalized additive models found geographic location to be an independent predictor of NCCN treatment adherence for women in California. Women of lower socioeconomic status and minority race/ethnicity were found to receive less quality care and to be disproportionately affected by geographic barriers. While spatial analyses identified location as an independent predictor of ovarian cancer survival, location no longer had an effect on survival after adjusting for

sociodemographic variables, receipt of NCCN care, and geographic access to care. To assess the impact of air pollution, ozone, particulate matter with diameter less than 2.5 microns (PM2.5), and nitrogen dioxide (NO2) data was extracted from California Air Resources Board's (CARB) online database, Air Quality and Meteorological Information System (AQMIS). Monthly averages of each pollutant were linked to women's residential address and calculated over their survival period. Distance to nearest major roadway was determined to account for local traffic. The analyses are suggestive of a potential association between ovarian cancer survival and NO_2 and $PM_{2.5}$ exposure in California, independent of sociodemographic and treatment factors. The impact of these pollutants was greatest among women in early stages. Null associations were observed for ozone and distance to road when examined alone, although they had marginal effects when examining them in multipollutant models.

INTRODUCTION

This dissertation investigated the relationship between residential geographic location and ovarian cancer outcomes, while considering the influence of race/ethnicity and socioeconomic factors. The most lethal of the gynecological malignancies,[1] ovarian cancer is diagnosed in approximately 22,000 women in the United States each year, and causes about 14,000 fatalities.[2] Furthermore, disparities in treatment and survival among traditionally underserved populations are prominent. This research sought to disentangle the sources of disparate outcomes observed among these women by considering the role that geographic location plays.

My dissertation used almost 20 years of retrospective cohort data from the California Cancer Registry for women 18 years of age and older diagnosed with invasive epithelial ovarian cancer. All stages of ovarian cancer diagnosed between 1996 and 2014 were considered. There are 29,844 women who had complete information on clinical variables, treatment received, and residential location. Adherence to the National Comprehensive Cancer Network (NCCN) stage-specific treatment guidelines for ovarian cancer was used to assess the quality of care received. In addition to examining the effect of women's geocoded residential location, the first two chapters also incorporated the following spatial variables to assess the impact of geographic access and barriers to care: distance traveled to receive care and proximity to closest high-quality-of-care (high QOC) hospital.

Another place-based factor that may influence ovarian cancer survival is the ambient environment. Poor air quality is increasingly being associated with adverse health outcomes. Furthermore, unexplained spatial variations in ovarian cancer mortality are observed in the literature even after controlling for known risk factors and treatment characteristics.[3,4] With

survival time being critical, it is important to understand whether women diagnosed with ovarian cancer are adversely affected by exposure to air pollutants and whether the effect is modified by race and SES. To address this, the dissertation explored the contributions of air pollution to disease-specific survival and additionally considered these sociodemographic variables.

Air pollution data from the California Air Resources Board (CARB), which has a dense monitoring network and has been systematically collecting daily measurements of air quality for decades, was used. Cumulative exposure to ambient ozone (ppm), particulate matter with diameter less than 2.5 microns ($PM_{2.5}$, μg/m3), and nitrogen dioxide (NO_2, ppm) was calculated over women's survival period. Women's residential address and survival time were linked to the spatio-temporal exposure data in order to assign and calculate exposure.

Dissertation Overview

This research makes a valuable contribution to our understanding of factors associated with survival by identifying barriers in treatment among vulnerable populations and examining how the ambient environment may play an independent role. Each chapter of this dissertation undertakes research that builds towards a better understanding of whether and how geographic location influences ovarian cancer outcomes and contributes to the disparities frequently cited in the literature. Chapter 1 examined the association between geographic location and adherence to the NCCN stage-specific treatment guidelines for ovarian cancer, taking race/ethnicity and SES into consideration. Generalized Additive Models (GAMs) were used to determine geographic variations in adherence to treatment guidelines throughout California. The analyses are additionally stage-stratified as early stages (stage 1 and 2), stage 3, and stage 4. Since NCCN adherent treatment consists of receiving both surgery and chemotherapy guideline care, separate

GAMs were used to assess differences in the association between geographic location and the two components of treatment adherence -surgery versus chemotherapy.

The aim of chapter 2 was to investigate the extent to which geographic location contributes to ovarian cancer-specific survival after accounting for treatment received. Spatial patterns were examined using Cox proportional additive hazards models. Multivariate weighted Cox regression models were used to assess the association between covariates and disease-specific survival. Models are also stratified by stage as follows: early stages (stage 1 and stage 2) and late stages (stage 3 and stage 4) and by race/ethnicity and socioeconomic status (SES). Differences in geographic barriers and access to care variables were evaluated by race/ethnicity and SES.

Chapter 3 sought to determine whether ambient $PM_{2.5}$, NO_2, and ozone concentrations play an independent role in ovarian-cancer specific survival. It additionally considers distance to major roadways as a measure of local traffic. Additional analyses were also performed that stratified separately by disease stage, race/ethnicity and SES. Cox proportional hazards models were run to study the association between the exposures and ovarian-cancer specific survival. All pollutants are studied independently and non-correlated pollutants are also modeled together.

Epidemiology of Ovarian Cancer

Given its frequent late-stage diagnosis and lethal prognosis, ovarian cancer is often referred to as the 'silent killer.'[5,6] In the United States, approximately 21,750 women are estimated to receive an ovarian cancer diagnosis by the end of 2020 and about 14,000 will die from it.[2,7] It is the 5th leading cause of death from cancer among American women.[2] Although slow, 5-year survival has consistently improved from 33.8% in 1975 to a more recent 5-year

prognosis of 48.6%.[7] Advances in ovarian cancer treatment have been a major contributing factor in the improvements observed in survival.[8] The NCCN has established stage-specific treatment guidelines (optimal debulking surgery, followed by multi-agent chemotherapy) for the standards of care that would optimize survival[9] and adherence to them has been validated as a significant predictor of ovarian cancer-specific survival.[10] Despite these evidence-based recommendations for improved care, access has not been equitable for all women, and disparities in treatment and survival have subsequently become prominent.[11]

Disparities in Ovarian Cancer Treatment and Survival

Ovarian cancer is notoriously known for having nonspecific or no symptoms at all until it is too late,[5,6] hence most women are diagnosed in late stages.[7] Screening has not been shown to decrease ovarian cancer mortality and is currently not recommended for women at average risk.[12] Treatment has therefore become a leading determinant of survival after accounting for traditional risk factors such as age and cancer characteristics.[5,12] While early detection is generally challenging, studies have consistently shown significant correlation between lower SES and late stage diagnosis.[13-15] Even after controlling for stage at diagnosis and other important determinants, reports of unequal care and shorter survival among racial and ethnic minorities, those of lower SES, and the non-privately insured persist.[3-5,8,11,16-24]

Race is one of the most frequently cited risk factors associated with ovarian cancer-specific care and mortality.[8,16-24] Compared to white women, black women are repeatedly found to have poorer prognoses,[2,11,16-22] with the survival gap continuing to grow.[8] With treatment being such an influential factor in survival, it is not surprising that black women are more likely to receive inadequate care,[8,16-18,23,24] with evidence of differences in the dose of chemotherapy received.[23] In addition to race, other factors associated with receiving adequate care are SES,[16,17]

insurance,[16,25] and characteristics of the treating hospital.[26-30] A retrospective population-based study examining women with advanced-stage ovarian cancer and predictors of receiving treatment found that those of the lowest SES were significantly more likely to receive no chemotherapy and almost twice as likely to receive no care at all compared to women of the highest SES.[18] A similar pattern is also seen with insurance status, which often directly measures the ability to access services.[25] For example, payer status was reported to be significantly associated with ovarian cancer outcomes in a study using the National Cancer Data Base, with patients using federally-funded insurance or without insurance being at a greater risk of receiving NCCN non-adherent care and shorter survival.[17]

Several hospital characteristics have become useful metrics of hospital quality, often predicting survival and the likelihood of receiving guideline-adherent care. One frequently used measure is that of hospital case volume, which refers to the number of ovarian cancer cases treated at a given hospital.[26,31,32] Receiving care at a high-volume hospital (≥20 cases a year) has been significantly associated with receiving quality care[31,32] and better survival,[26,32] even when adherent treatment is received.[32] Another noteworthy hospital quality metric is the observed-to-expected (O/E) ratio, which uses both hospital case volume and its respective rate of adherence to assess hospital quality and the likelihood of delivering NCCN guideline treatment.[28,29] High O/E hospitals have been associated with better outcomes. Hospitals are considered to have a high O/E ratio if they deliver more adherent care than expected, and treat more than 5 cases a year.[28,29] Expected cases were determined by using the probability of adherence of all patients in each respective hospital. Hospitals treating less than 5 cases are immediately considered a low O/E hospital. Additionally, teaching and research hospitals have been associated with a greater

likelihood of delivering guideline care in comparison to community and comprehensive community cancer programs.[31]

While NCCN treatment guidelines have consistently been associated with improved survival, less than half of women overall receive it [10,16] and women of minority and lower SES backgrounds are disproportionately found to receive inferior care.[16] Receiving adequate treatment is crucial to decreasing ovarian cancer mortality and the various aforementioned hospitals are more likely to deliver guideline adherent care. Understanding what factors influence their accessibility and identifying barriers to treatment among ovarian cancer patients is critical because of its direct impact on survival.

Geographic Barriers to Accessing Care

With the development of more sophisticated analysis tools and recognition of the impact of residential location on health, there has been growing appreciation of geospatial research in cancer.[33] Much of the literature examining disparities in ovarian cancer outcomes has not considered potential differences due to spatial factors. The limited research that does exist has found inequities in the spatial distribution of treatment,[16,34-37] mortality,[3,38,39] availability of services,[40,41] and geographic access to those services.[3,16,42] One study looking at spatial variations in ovarian cancer treatment delivery and mortality by Health Referral Regions found hospital region to be associated with whether or not patients received cancer-specific surgery, with women in more remote areas less likely to receive cancer-directed surgery.[34] Although there were no significant findings of variations in chemotherapy receipt by region after adjusting for demographic and clinical variables, white women were more likely to receive either surgery or chemo than non-white patients.[34] Another U.S. nationwide study emphasized the disparities in access to gynecological oncologists, highlighting that their availability was centered near

metropolitan areas, leaving vast parts of the country without specialized care.[41] They also revealed a significant positive association between increasing distance from a gynecologic oncologist and the odds of dying of ovarian cancer.[41]

Accessibility of providers, proximity to care facilities, and distance traveled for treatment have all been subjects of interest in the healthcare field for years,[33] but its application to ovarian cancer outcomes is a more recent endeavor. High-volume hospitals have repeatedly been recognized as delivering superior treatment[43] yet the relationship between proximity to higher performing hospitals and receiving quality care is more complex. In Australia, Tracey et al. found that greater distance from hospitals providing specialized care was associated with an increased likelihood of receiving services from a general hospital and consequently not receiving appropriate treatment.[42] In the United States, a comprehensive cancer center undertook a study looking at its own patient's travel distance and found that those residing furthest from the hospital had worse cervical cancer outcomes.[44] Similarly, living further from appropriate treatment facilities increased the likelihood that patients would not receive chemotherapy or surgery for lung cancer in England, although no significant associations were found between proximity and receiving care for the four other cancers examined, including ovarian cancer.[45] A California-based study looking at ovarian cancer specifically did find that greater distance from a high volume hospital increased the likelihood of not receiving NCCN guideline treatment among advanced-staged patients. They further found that the largest proportion of women living greater than 50 miles from a high volume hospital were patients of the lowest SES.[16]

Interestingly, traveling longer distances to receive care, especially to high-volume facilities,[46,47] has been consistently associated with receiving better treatment and improved survival among pancreatic,[46] breast, lung,[48] and ovarian cancer patients.[3,16,42] In California,

women who traveled longer distances for care were more likely to receive NCCN guideline-adherent treatment[16] and had a better prognosis.[3] Of particular note, Bristow and colleagues considered distance traveled to receive care in relation to race and SES and found that women of lower SES strata were significantly more likely to receive treatment closer to home and lived the furthest from a high volume hospital.[16] The respective study also found that a greater proportion of minority women lived within 5 miles from a high volume hospital, yet black women and those of lower SES were less likely to receive adherent care.[16] While in both studies, the authors only included advanced stage women and addresses were only available at the census-block level, the authors did find that geographic location alone was associated with the likelihood of receiving NCCN-guideline care and survival, even after adjusting for individual-level treatment factors.[3,16]

Role of Ambient Air in Ovarian Cancer Survival

Given the significant spatial variations in ovarian cancer mortality noted in the literature, it is essential to consider the potential impact that the environment may have on ovarian cancer survival. Air pollution has increasingly been linked with greater morbidity and mortality.[49-69] Ambient air pollutants such as ozone,[55-60] NO_2,[54,55,60,63] and $PM_{2.5}$,[50,52,54,57,62-64] have been independently linked to adverse health outcomes and increased hospitalizations in older adults and those living with chronic illnesses.[51,59] $PM_{2.5}$ is a heterogeneous mixture of tiny solid and liquid particles comprised of dust, organic compounds, smoke, and metals emitted from a multitude of sources with the potential of penetrating into the bloodstream.[68,69] In California, sources of $PM_{2.5}$ emissions include vehicles, industries such as oil refineries and energy-producing plants, agricultural activities, and wildfires.[68,69] Ambient ozone, a secondary pollutant that forms when it reacts with other pollutants, such as NO_2, in sunlight, is detrimental to health at ground-level.[68,69] NO_2 is an oxide of nitrogen, which is highly toxic, reactive, and considered

to be a well-recognized marker of vehicle and traffic emissions.[68,69] Studies have also assessed the impact of local traffic measures, such as residential proximity to traffic-related pollution and have found that increased exposure negatively influenced health outcomes.[70,71]

Air pollution is considered a carcinogen by the International Agency for Research.[67] Although the exact mechanisms are unclear, research has indicated that air pollutants may influence cancer development through their ability to induce oxidative stress, create chronic inflammation, and damage DNA.[72,73] Evidence is mounting that air pollution exposure may not only be associated with cancer incidence and mortality,[50,61,65,74,75] but that it may also independently shorten survival after a cancer diagnosis.[55,76-78] In California, ozone and $PM_{2.5}$ have both been correlated with poor outcomes among patients diagnosed with lung cancer.[55] $PM_{2.5}$ has also been found to shorten survival time after a liver cancer diagnosis in a similar California-based study.[76] A nationwide analysis of Surveillance, Epidemiology, and End Results (SEER) Program data has highlighted the deleterious effects of $PM_{2.5}$ and PM_{10} on survival from breast cancer, even after adjusting for individual-level factors.[77]

Environmental factors are increasingly being implicated in ovarian cancer outcomes. For example, an ecological study in Taiwan found a significant positive correlation between greater levels of $PM_{2.5}$ and ovarian cancer mortality.[74] In Spain, mortality differences were observed by municipality that were unexplained by individual-level or treatment factors. The authors concluded that the spatial variation could possibly be due to environmental sources.[38] Another Spain-based study used proximity to chemical facilities as a proxy for pollution exposure, finding that living within 5km of several different facility types was associated with an increased risk of ovarian cancer mortality.[49]

While most studies examining the environment's effect on ovarian cancer outcomes have focused on mortality, one population-based spatial analysis did consider ovarian cancer survival after a cancer diagnosis.[4] Specifically, the authors examined the impact of community disadvantage on survival, a score that included environmental factors.[4] The study found that indicators for census tract-level ozone and $PM_{2.5}$ were significantly correlated with worse prognosis, but additionally highlight that area-level SES was also a significant predictor.[4]

Environmental Injustice

Numerous studies have described unequal distributions of pollutants across communities, with traditionally underserved populations such as racial and ethnic minorities and those who are socioeconomically disadvantaged, disproportionately residing in areas with greater environmental contaminants and poorer air quality.[53,79-83] While overall, pollutant concentrations in the United States have decreased over time, minority communities still share an excessively larger burden.[82,83] Furthermore, environmental burden scales that combine multiple hazards have found an increased risk of cancer among those living in areas with greater cumulative burden.[51]

The Institute of Medicine has stressed that individuals living in disadvantaged communities may not only experience increased exposure to environmental pollutants, but the effects of these exposures may be amplified.[80] Cushing et al. specifically looked at the association of population vulnerability and environmental hazards in California and reported that disparities existed in the distribution of pollutants, and minority communities were more likely to live in areas with higher cumulative burden.[53] A study in Spain assessed the effects of environmental hazards on mortality by neighborhood socioeconomic status, concluding that the most disadvantaged neighborhoods had both increased exposure to environmental hazards as well as increased susceptibility.[84] The authors found that individuals living in the most affluent

areas had a 30% reduced likelihood of dying from environmental hazards compared to living in the least affluent neighborhoods.[84] Furthermore, women and those of black race have been recognized to be more vulnerable to environmental pollutants.[57,79]

Research Significance and Innovation

Research is needed to improve our understanding of the interaction of race, SES, geographic barriers, and their impact on ovarian cancer outcomes. The research from this dissertation sought to gain a better understanding of how geographic location contributes to outcome disparities among minority women and those of lower SES diagnosed with ovarian cancer, while addressing several weaknesses of prior studies. Receiving adequate and timely treatment are critical to ensuring optimal survival after an ovarian cancer diagnosis. Disparities in access to care, particularly among underserved populations, may exacerbate some of the outcome differences observed in the literature. Although researchers are increasingly examining this association and recognizing that inequities may exist between SES strata and race, the field has been limited in various regards. For instance, few studies have used a precise measure of residential location and have relied on larger units of analysis, such as census blocks and zip codes.[33] The body of work included in this dissertation used geocoded residential location, allowing for a better assessment of location.

Furthermore, compared to the commonly used measure of straight-line Euclidian distance, all the analyses presented in this dissertation used a more accurate estimate of distance traveled and proximity to services calculated with the network analyst extension in ArcGIS (version 10. 4. 1, ESRI; Redlands, CA). In addition, this research used a generalized additive model (GAM) framework, which includes a smooth term for women's residential location and allows for simultaneous adjustment of known risk factors.[85,86] The use of GAMs allows for a

flexible statistical framework to analyze the impact of geographic location on treatment adherence and survival.

Prior work examining the relationship between location and ovarian cancer outcomes has not considered several important predictors that have been found to be associated with treatment adherence and survival. Comorbid conditions, which are a significant determinant of receiving nonstandard disease-specific treatment,[31,87] is one limitation that is addressed in the current work. The analyses in this dissertation include the Deyo-adapted Charlson Comorbidity Score to assess patient comorbidity status.[88] Furthermore, instead of utilizing the hospital volume metric to assign hospital quality, the O/E measure was used, which takes into account both hospital volume and adherence.[28,29]

Another contribution of this dissertation to the larger literature is its consideration of the impact of the ambient environment on ovarian cancer survival, while examining differences by race/ethnicity and SES. Geographic location can impact outcomes in several ways, including access to providers and treatment services, but examining the relationship between women's residential outdoor environment and disease-specific survival time is a novel approach to looking at how geographic location may affect ovarian cancer outcomes. With evidence growing that minority and traditionally underserved populations are persistently exposed to greater environmental exposures, research investigating the potential interaction between air pollution exposure and sociodemographic factors is necessary in expanding our overall knowledge of factors associated with ovarian cancer survival and making recommendations for improving disease-specific survival for women, particularly those who may be more vulnerable.

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CHAPTER 1

Spatial Analysis of Ovarian Cancer Treatment Adherence

Abstract

Background: Over 14,000 American women die of ovarian cancer (OC) every year. Disparities in survival are observed by race and socioeconomic status (SES), even after adjusting for treatment received. Geographic location has been identified as an independent predictor of survival. This study aims to determine the impact of geographic location on receiving OC guideline adherent care in relation to race and socioeconomic status (SES).

Methods: Women diagnosed with epithelial OC between 1996 and 2014 were identified through the California Cancer Registry. Generalized additive models, smoothing for residential location, were used to determine the log odds of receiving adherent care at patient's geocoded residential location. We assessed the impact of distance traveled for care, distance to closest high-quality hospital (high Observed-to-Expected ratio), race, and SES on receiving quality care, adjusting for demographic and cancer characteristics.

Results: Of the 29,844 cases, 20,110 (67.4%) were diagnosed at late stages (Stage III/IV) and 38.3% received care adherent to the National Comprehensive Care Network (NCCN) treatment guidelines. Non-Hispanic black women (OR, 1.21; 95% CI, 1.06 - 1.39), those of lower SES (OR, 1.28; 95% CI, 1.16 - 1.42), and women with no insurance (OR, 1.34; 95% CI, 1.14 - 1.58) or using Medicare (OR, 1.10; 95% CI, 1.03 - 1.19) had greater odds of receiving non-adherent care. Living in northern California was protective, while women in East-Central California were at greater risk. Traveling distances >32 kilometers was associated with decreased odds (OR, 0.76; 95% CI, 0.70 - 0.84) of receiving NCCN non-adherent care, yet living further from a high-quality hospital increased the odds of substandard care. Non-Hispanic white women were more likely to receive quality care and traveled far distances to receive it. Women of the highest and

lowest SES, those using Medicare insurance, and non-Hispanic black were less likely to travel further for care. Asian/Pacific Islanders lived the closest to a high-quality hospital.

Conclusions: Among California women diagnosed with OC, traveling greater distances for care was associated with receiving better treatment. Proximity to high O/E centers was an independent determinant of receiving adherent care. Minority women and those of lower SES disproportionately received inferior care. Non-Hispanic black women are less likely to receive high-quality care despite their closer proximity, and women of lower SES lived furthest from high-quality hospitals.

Introduction

By the end of 2018, approximately 22, 240 American women are estimated to receive an ovarian cancer (OC) diagnosis.[1] Considered the most fatal of the gynecological cancers,[2] this malignancy kills more than 14,000 women in the United States each year.[1] Fortunately, substantial advances in treatment in the last four decades has led to gradual but consistent improvements in survival.[3] With screening not currently recommended for women at average risk,[2,4] treatment has become a leading determinant of survival after accounting for traditional risk factors. Stage-specific guidelines have been established by The National Comprehensive Cancer Network (NCCN)[5] for best care practices in treating OC and adherence to these recommendations has been validated as a significant predictor of disease-specific survival.[6] Despite these evidence-based guidelines, the literature increasingly notes disparities in treatment adherence and survival by race, and socioeconomic status (SES), [7–11] indicating potential inequities in access to and delivery of appropriate care still exist.

Although most efforts to understand the drivers of OC disparities have largely focused on aspatial factors, there has been growing consideration of the role that geographic location may play.[7,9,12,13] For instance, one study explored spatial variations in the delivery of OC treatment for Medicare recipients and found discrepancies existed by Hospital Referral Region. They additionally reported white women being more likely to receive either surgery or chemo than non-white patients.[13] And despite hypothetically having equal access due to being a single-payer system, differences were found in treatment practices by Health authority region in British Columbia, with one area being less likely to perform suboptimal debulking surgery and deliver multi-agent chemotherapy.[12] Even with rising consensus that receiving specialized care is critical for OC outcomes,[7,12–21] a U.S. nationwide study emphasized the disparities in access to

gynecological oncologists, highlighting their concentration in metropolitan-centers.[20] The vast areas without specialists represent a geographic barrier for those who must cover greater distances to reach them. Perhaps stressing the differential effect location may have, traveling longer distances for care, especially to high-volume facilities, has actually been associated with receiving better treatment and improved survival for ovarian cancer.[7,9]

There is mounting evidence that minority women, those of lower socioeconomic background, and with federally-funded insurance experience greater deviations from NCCN guidelines, are less likely to access specialized facilities, and may be disproportionately affected by geographic barriers.[7,9,22] Geographic location at the census block level has also recently been associated with the likelihood of receiving adherent treatment among advanced-stage ovarian cancer patients.[7] Our objective was to examine how residential geographic location contributes to adherence to NCCN treatment guidelines among women of all stages, while exploring how this may differ by race/ethnicity, SES, and insurance. This study setting is appealing because U.S. population statistics indicate that the demographic trends observed in CA provide a preview of those that will face the country as a whole in the coming decades.

Methods

Study Population

A retrospective population-based study design was used to examine the relationship between geographic location and adherence to NCCN treatment guidelines. All cases of epithelial OC diagnosed in the state of California between January 1, 1996 and December 31, 2014 were ascertained from the California Cancer Registry (CCR), with follow up data obtained through December 31, 2016. The CCR collects extensive information on demographic and

clinical data such as age, race, insurance type, tumor and disease characteristics (histology, size, grade, stage), and treatment received within 6 months of diagnosis. In California, reporting to the CCR is close to 99%, with follow up nearly as high (95%).[23,24] CCR data was linked to California's Office of Statewide Health Planning and Development (OSHPD) patient discharge data.

Women of all OC stages (International Federation of Gynecology and Obstetrics (FIGO) - Stage I-IV) were eligible for inclusion. Cases were identified using the International Classification of Disease Codes for Oncology (ICD-O-3) specifying OC (C56.9). To be included, women had to be 18 years of age and older at time of diagnosis, with complete clinical information and no prior history of OC. Of the initial pool of 36,616 women identified, cases were removed if they were obtained through death records (n=309), and had unknown stage (n=5,690), survival time (n=90) or were missing other clinical information (n=208). Germ cell and stromal tumors resulted in the exclusion of an additional 268 cases. The current study excluded 207 women due to missing information on residential location or treating hospital, resulting in a final sample of 29,844 women diagnosed with incident epithelial OC (case distribution displayed in Figure 1.1). The study was approved by the Institutional Review Board of the University of California, Irvine (UCI 14-66/HS# 2014-1476).

Study Data

The primary outcome was non-adherence to stage-specific NCCN treatment guidelines, examined as a binary variable (adherent vs non-adherent). Both surgical and chemotherapy treatment had to be adherent to the NCCN guidelines for women to be considered having received overall adherent care.[5] Surgical guideline adherence for stages I-IIIB was a minimum of oophorectomy (± hysterectomy), pelvic and/or para-aortic lymph node biopsy, and

omentectomy. Adherence for stages IIIC-IV was a minimum of oophorectomy (± hysterectomy) and omentectomy. In terms of chemotherapy, receiving no adjuvant treatment was only appropriate for early stage and grade (stages IA-IB, grades 1-2). For all other stages (stage IC-IV) and grade 3 disease, multi-agent chemotherapy was determined to be guideline adherent. Chemotherapy must have been delivered subsequent to surgery, with the exception of stages IIIC-IV, in which it could have been received before or after surgery.

The main predictor variable of interest was geographic location, examined using a smooth function of women's geocoded residential location (longitude and latitude). A Generalized Additive Model (GAM) framework was employed to estimate the log odds of not receiving adherent treatment based on geographic location. This model, which is an expansion of generalized linear models,[25,26] incorporated a locally-weighted loess smoother for the patients' geocoded address at diagnosis while also adjusting for covariates. Details of the methods used are described elsewhere.[7] Briefly, a point grid covering the state of California was created at distances of approximately 5km by 5km, each serving as a prediction point in which the log odds of adherence was computed, using the average odds for all of California in the respective analysis as the referent group. Areas with very few or no cases were not predicted for, resulting in a grid of approximately 7,500 points. The amount of smoothing depends on the span size, which represents the proportion of cases used locally to calculate the log odds at each point. A span of 0.3 was used for models. The span size was chosen because it minimized the Akaike's Information Criterion (AIC) for the majority of the models.[25,26]

Several important patient characteristics were included as predictors: age at diagnosis, race/ethnicity, marriage status, SES, insurance status, year of diagnosis, tumor stage and characteristics, and a comorbidity index. Age was determined at the time of diagnosis and was

treated as a continuous variable. Race/ethnicity was categorized as: non-Hispanic white, non-Hispanic black, Hispanic, Asian/Pacific Islander, and American Indian/other/unknown. Marital status was a binary variable recorded as married versus not married, single, divorced, or unknown. Insurance status was categorized as: managed care, Medicare, Medicaid, other Insurance, not insured, and unknown. SES was stratified into quintiles, assigned using the Yost score[27] for patients diagnosed prior to 2006 and the Yang index[28] for those with a diagnosis after 2006. The Yost score is a community-level measure available in the CCR developed through a principal components analysis of census block group-level variables (median household income, education levels, median rent, median house value, percentage with blue-collar job, proportion employed, and percent below 200% poverty level).[27] The Yang index is a comparable measure but uses block group variables from the American Community Survey.[28]

Cancer characteristics were included as categorical variables in the model: tumor grade (I, II, III, IV, or unknown), tumor size (≤50mm, 50-99mm, >100mm, or unknown), histology type (serious, mucinous, endometrioid, clear cell, adenocarcinoma/not otherwise specified, or unknown), and stage at diagnosis (FIGO Stages I-IV). To account for the possible influence of comorbid conditions on receiving adherent care, the Deyo-adapted Charlson Comorbidity Score was considered in the models. This scale was adapted from the Charlson Comorbidity Index (CCI) for use with administrative data.[29] As a measure of hospital quality, the observed-to-expected (O/E) ratio of women's initial treating hospital was included. This metric (O/E ratio) was recently calculated for each hospital in California that has treated women for OC.[18] Galvin-Turner and colleagues used the number of cases that received NCCN adherent care at each hospital and divided it by the amount expected to receive standard care for that hospital.[18] Expected cases were determined by summing the probability of adherence of all patients in each

respective hospital. Hospitals treating less than 5 cases are considered a low O/E hospital. The variable was classified as low O/E (lowest quartile), intermediate O/E (middle two quartiles), and high O/E (highest quartile).

In order to assess the role of geographic location, two distance variables were included in the models as measures of spatial accessibility and potential barriers to treatment. One variable was the distance traveled to receive care, which was calculated as the distance from each woman's geocoded residential address at the time of diagnosis to the geocoded location of their initial treating hospital. The second measure was how far each woman lived from the nearest high O/E hospital. Distances for both measures were obtained using the Streetmaps routing dataset in the network analysis extension available through ArcGIS (version 10. 4. 1, ESRI; Redlands, CA) and subsequently categorized into quintiles based on the variables' distribution.

Statistical Analysis

The initial model examined the effect of geographic location, while adjusting only for age and cancer characteristics. A second model additionally adjusted for demographic and treatment factors: SES, race/ethnicity, marriage status, quality of treating hospital, comorbidities, and the two distance variables. If these added variables did not remove the areas of increased or decreased risk, then those local areas were considered to be significant. Any differences in geographic areas of increased or decreased risk between the first and second models would suggest that the demographic and treatment factors were contributing to the geographic variation. Further stage-stratified analyses were also conducted with stage categorized as early (Stages 1 and 2), Stage 3, and Stage 4. Lastly, fully-adjusted models examining the effect of location on chemotherapy adherence versus surgery adherence were conducted.

To determine a global p-value evaluating the importance of women's geographic location, the deviance of the model with the bivariate smooth term was compared to a model without it and permuted 1,000 times while maintaining their outcome and using the same set of covariates. Without the smooth term, the models become ordinary logistic regression models. Color maps were produced for each model displaying the odds ratios for treatment non-adherence throughout the state, with geographic areas showing significant increased or decreased odds clearly outlined. MapGam package in R generates standard errors that provide contour lines highlighting local areas that exclude odds ratios of 1. The odds ratios for all maps are displayed on the same scale.

In addition to resulting maps, the stepwise effect of each additional variable on the geographic pattern of non-adherence was explored. Furthermore, summary statistics are presented for select characteristics of the complete and stage-stratified population. Secondary analyses examined the relationship between sociodemographic factors and the distance variables. Chi-square tests were conducted to test for differences between racial/ethnic, SES, and insurance groups in the distribution of distance variables. Statistical modeling and mapping were conducted in R version 3.4.0 using the MapGAM package.

Results

Patient characteristics at baseline are detailed in Table 1.1. Of the 29,844 cases identified, 20,110 (67.4%) women were diagnosed at late stages – Stage 3 (n=11,263) and Stage 4 (n=8,847). The majority of the population was non-Hispanic white (63.4%), followed by Hispanic (19.3%), Asian/Pacific Islander (11.9%), non-Hispanic black (4.7%) and American Indian, other or unknown (0.7%). The median age at time of diagnosis was 60 years old, with

younger age associated with diagnosis at earlier stages. Over one third (38.3%) of all patients received care adherent to the National Comprehensive Care Network (NCCN) treatment guidelines. Women with Stage 3 disease were more likely to receive adherent care as compared to those diagnosed in early stages or Stage 4 (52.8% versus 25.2% and 34.2%, respectively).

A total of 426 medical facilities treated women diagnosed with OC in California. Of those, 30 were considered high O/E hospitals, 92 were intermediate O/E hospitals and the remaining 304 were low O/E hospitals. The distribution of hospitals across the state of California is displayed in Figure 1.2. Most high O/E quality hospitals were centered near metropolitan regions and less than one-fifth (18.7%) of the women were treated at one of these quality locations. The majority of the study population received care at an intermediate O/E facility (n=17,275 or 57.9%). Across racial/ethnic and SES groups, Asian/Pacific Islanders and women of the highest SES were most likely to access a high quality hospital. Of patients treated at high O/E hospitals, a greater proportion of non-Hispanic white (55.2%) women, those with managed care insurance (56.1%), and of the highest SES (58.0%) received NCCN adherent care. Non-Hispanic blacks (39.3%), those with Medicaid (47.6%), and of the lowest SES (44.1%) were the least probable to receive quality care.

Travel distance between residential location and initial treating hospital ranged from <0.1 kilometers to 1,088 kilometers, with the median distance being slightly less than 13 kilometers. The distribution of distance traveled to receive care by patient characteristics are shown in Table 1.2. Among women treated at high O/E facilities, greater proportions traveled further for care. Conversely, the trend inverted among women who were treated at low O/E hospitals, where more women remained closer to home for treatment. In terms of proximity to the closest high O/E, this calculated value ranged from 0.2 to 501.0 kilometers, with half the study population

living within 19.3 kilometers from a high quality hospital. As can be seen in Table 1.3, among women treated at a high O/E hospital, more than a third (38.1%) lived within 9 kilometers of a high O/E hospital, whereas only 9.3% lived greater than 48 kilometers. In contrast, women treated at low O/E hospitals tended to live further from high O/E hospitals (31.4% in furthest category vs. 11.8% in closest).

Spatial Analysis of Treatment Adherence

In the state of California, geographic location was significantly associated with non-adherence to NCCN treatment guidelines among women of all stages diagnosed with OC. All analyses, including stage-stratified models, resulted in a highly significant global test for location (<0.001). Compared to odds ratios (ORs) only adjusted for age and cancer characteristics for the all stages combined (ORs: 0.46-1.57; Figure 1.3), odds ratios fully adjusted for sociodemographic factors, comorbidities, and distance variables were attenuated in some locations, but increased in other areas. As can be seen in Figure 1.3, the protective effects observed in northern California were attenuated and no longer present in the San Francisco Bay area after adjustment. Although the reduced risk observed in the southern-most portion of California was no longer present after adjustment, risk in northern Los Angeles County and western Kern County increased. Maps detailing the effect of each additional variable on geographic variations of NCCN non-adherence in California can be found in Appendix Figure A.1. The maps indicate that much of the reverse confounding observed in northern Los Angeles county and Western Kern county was a result of adjusting for sociodemographic variables. Maps for the fully-adjusted models of all stages combined examining the effect of location on chemotherapy adherence versus surgery adherence are shown in Appendix Figure A.2.

Patterns of geographic risk for NCCN non-adherence varied across the different stage-stratified analyses. Regions of increased and decreased risk in the early stage analyses differed from the others (comparison of Figure 1.3 to Figure 1.4). When controlling for age and cancer characteristics alone, we identified areas of increased risk of non-adherent treatment for early stage OC in mid-Central Valley. An area of decreased risk was also present in Northern California (OR range:0.49–2.90). After full adjustment of the early stage model, there is no longer an association in northern California and San Diego County; however, Ventura and Santa Barbara Counties in the Central Coast become largely protective (OR range: 0.49–2.90). Models for Stages 3 and 4 display similar patterns to those of all stages combined, although areas of higher and lower risk are smaller (Figure 1.4) and the magnitude of ORs are attenuated (OR ranges 0.61–2.13 and 0.47–1.86 for Stages 3 and 4 respectively). The effect of geographic location on risk of non-adherence was greatest among women diagnosed in early stages.

Risk Factors

For the fully adjusted model with all stages combined, increasing age was significantly associated with the likelihood of non-standard care. With every additional year, women had a 2% increase in risk of receiving care that deviated from the NCCN treatment guidelines ($p<0.001$). Overall, the fully-adjusted model shows that non-Hispanic black women (OR, 1.21; 95% Confidence Interval [CI], 1.06 - 1.39) and those of lowest SES (OR,1.28; 95% CI, 1.16 - 1.42) had greater odds of receiving non-adherent care than non-Hispanic white women and those of highest SES (referent). As compared to having managed care insurance, women with either Medicare (OR, 1.10; 95% CI, 1.03 - 1.19) or of uninsured status (OR, 1.34; 95% CI, 1.14 - 1.58) were more likely to receive substandard care. Those who were married had a decreased risk of receiving nonstandard treatment (OR, 0.85; 95% CI, 0.81 - 0.90). Table 1.4 shows the

associations between all patient and cancer characteristics and the odds of receiving non-adherent treatment for all stages combined.

Several treatment factors were also found to be significantly associated with the likelihood of treatment deviations in the final overall model. The hospital where women were initially treated had a strong effect on NCCN guideline adherence. Compared to women who obtained care at a high O/E center, women treated at intermediate (OR, 1.76; 95% CI, 1.64 - 1.89) and low (OR, 2.57; 95% CI, 2.35 - 2.81) O/E hospitals were at notably elevated risk. Women with either a Charlson Comorbidity Score of 2 or unknown were 19% and 26%, respectively, more likely than those with no comorbid conditions to get nonstandard care ($p<0.0001$). Increasing distance traveled to receive care provided protective effects from non-adherence. With patients living within 6 kilometers of their initial treating facility as the reference, those traveling over 32 kilometers had decreased odds (OR, 0.76; 95% CI, 0.70 - 0.84) of getting care that deviated from the NCCN guidelines. Conversely, the further away women lived from high-quality centers, the greater the odds of getting non-adherent care. Women who lived in the two furthest categories from the closest high O/E hospital had the greatest risk: 13% for those between 25-48 kilometers (<0.01) and 18% for patients living over 48 kilometers (<0.001). Appendix Figure A.3 displays the case distribution by whether or not women received adherent care.

The pattern of treatment adherence appears to differ when stratified by stage at diagnosis. Table 1.5 displays odds ratios for women in early stages. Accounting for all variables, being of Hispanic background increases the likelihood of non-adherence (OR, 1.15; 95%CI, 1.00 - 1.33) for women diagnosed in early stages compared to being non-Hispanic white, yet is not significant in any other stage nor all stages combined. Non-Hispanic black women only have a

marginally significant elevated risk of non-adherence at early stages (p=0.053) and no association at all in Stage 3, but at stage 4, show a stronger association (OR, 1.58; 95% CI, 1.23 - 2.04) with not receiving adherent care than non-Hispanic white women.

No association was observed between SES and guideline adherence for women in the stage-stratified analyses of early stages after adjusting for all covariates. Stages 3 and 4 models do, however, demonstrate an elevated risk for those of the lowest SES ($p<0.001$) compared to the highest SES. The importance of women's insurance type also varied by stage at diagnosis. For all stages combined, patients with Medicare or no insurance were at greater odds of deviations from treatment guidelines. When examining it by stage, only early stages are at an increased risk with Medicare insurance, whereas Stages 3 and 4 have a disadvantage when having no insurance at all. Being married was significantly protective in all models except for early stages and not being treated at a high-quality center was consistently associated with substandard care.

Regarding the spatial accessibility variables, every increasing distance category was significantly protective against receiving non-adherent care for those in early stages compared to traveling less than six kilometers, yet distance traveled had no statistically significant effect on women diagnosed at Stage 3. For those diagnosed at Stage 4, only traveling over 32 kilometers was protective (OR, 0.73; 95% CI, 0.62 - 0.89). Similar to distance to treating hospital, distance of the closest high O/E center had no association for patients who were diagnosed at Stage 3. Compared to women in closest proximity to a high quality hospital (within 9 kilometers), living greater than 48 kilometers was a significant deterrent for women diagnosed in early stages and living between 25-48 kilometers increased the risk for women diagnosed in Stage 4.

Geographic Disparities

Non-Hispanic white women and American Indian/Other/unknown race made up the largest proportions of women traveling greater than 32 kilometers for care. Non-Hispanic black women were the least likely to travel those longer distances for care, even in all of the stage-stratified cross-tabulations. The lowest and the highest quintiles of SES were the smallest percentages of those treated at locations greater than 32 kilometers. Women diagnosed in Stage 4 were the least likely to travel far, regardless of race, SES, or insurance. Additional factors associated with a decreased likelihood of being in the furthest quintile of distance traveled were being 65 and older, not married, being treated at a Low O/E hospital, having a comorbidity score of 2 or more, and proximity to a High O/E hospital.

Noteworthy is the distance of the closest high O/E hospital (Table 1.3), where Asian/Pacific Islanders (30.4%) and Non-Hispanic blacks (21.8%) made up the largest proportion of those living within 9 kilometers, followed by American Indian/other/unknown (20.0%), Hispanic (19.5%) and non-Hispanic whites (18.1%). Conversely, only 6.5% and 8.4% of Asian/Pacific Islander and Non-Hispanic black women, respectively, lived greater than 48 kilometers from a high quality hospital whereas Non-Hispanic white women (23.9%) and American Indian/Other/unknown race (31.3%) lived the furthest away. And while less than 10% of women of the highest SES lived over 48 kilometers from a High O/E hospital, more than a quarter of those in each of the two lower SES quintiles lived >48 kilometers.

Discussion

Due to a growing awareness of the impact of residential location on health and the development of more sophisticated analysis tools, the value of geospatial research in cancer is increasing.[30] With the availability of geocoded addresses and the use of GAMs, we were able to

estimate the likelihood of NCCN guideline adherence throughout the state of California. The current study found patient's residential geographic location to be significantly associated with the likelihood of receiving NCCN adherent treatment for women diagnosed with OC. We identified variations within the state demonstrating areas where women were more or less at risk of receiving non-adherent care, despite adjusting for numerous important factors and further showed that the impact of location depended on stage at diagnosis.

Differences in spatial patterns of care are increasingly being recognized in the OC literature. One population-based study exploring geographic patterns in treatment delivery and epithelial OC mortality by Health Referral Regions found hospital region to be associated with regional discrepancies in cancer-specific surgery, with women in more remote areas less likely to receive it.[13] Our results also show that women living in remote areas of central California, especially those diagnosed at early stages, are more vulnerable to receiving substandard care. Although there is a dearth of high-quality centers in nonmetropolitan areas, the risk of treatment non-adherence in California differed depending on residential location. While patients living in rural areas of Northern California had favorable odds, residing in portions of Los Angeles counties was associated with inferior care despite the availability of high O/E centers.

While Bristow and colleagues found geographic location at the census-tract level to be associated with treatment adherence among late-stage patients,[7] this study revealed that residential location is also a significant predictor in early stages, with distance traveled to receive care especially poignant in those stages. Among women diagnosed in Stages 1 and 2, every increasing category of distance traveled for first treatment significantly decreased their risk of nonstandard care. Conversely, residing farthest from centers providing quality treatment hindered the likelihood of receiving it.

It is well documented that the location of initial treatment for OC is important, in particular high-volume and high O/E centers showing superior outcomes.[15,18,21,31] The relationship between proximity to quality services and receiving standard care is more complex. For instance, living further from appropriate treatment facilities increased the likelihood that patients would not receive chemotherapy or surgery for lung cancer in England, although no additional significant associations were found between proximity and receiving care for the four other cancers examined, including ovarian.[32] A comprehensive cancer center examining its own patients' travel distance found that those residing farthest from the hospital had worse cervical cancer outcomes,[33] yet a similar analyses of gynecological malignancies treated at a National Cancer Institute-designated center found women living less than 10 miles were less likely to be treatment compliant.[34]

A retrospective cohort study looking at OC specifically did find that greater distance from a high volume hospital increased the likelihood of not receiving NCCN adherent care among late-stage patients in the United States.[7] In the referenced study, women of the lowest SES comprised the largest proportion of women living greater than 50 miles from one.[7] Although we did find that women of lower SES quintiles had larger proportions living at the greatest distances, most notable was that less than 10% of patients in the highest SES lived greater than 48 kilometers from a high quality hospital.

Place of residence has important implications for both availability of and accessibility to specialized care. Proximity to quality care facilities is not only important in receiving standard care but is also a strong determinant of using them. We found women were more likely to access a high O/E hospital if they lived close to one, an association similarly observed by Tracey and colleagues (2014).[19] They found that women who accessed Gynecological Oncology Services

(hospitals strongly correlated with better care and survival), were more likely to reside near them.[19] More than half of women living within 5km of high-quality hospitals utilized these facilities compared to 16% of women in the farthest quintile.[19] Consistent with the literature, the authors also found that hospital type predicted the receipt of extensive surgery. Race/ethnicity, however, was not a factor considered in their analysis.

In California, we further document that the advantages of proximity differ by race and SES. Similar to Bristow et al. who examined distance to high volume hospitals and found advanced-staged women in the lowest strata of SES lived the furthest from a high volume hospital and a greater proportion of minority women, including Hispanics, non-Hispanic blacks, and Asian and Pacific Islanders lived within 5 miles of one, [7] we likewise found evidence of disparities in accessibility of treatment and receiving it by these socio-demographic variables. Non-Hispanic black women were among the closest to a high quality center, yet were less likely to get treated at one and had significantly increased risk of non-adherence. Alternatively, Asian/Pacific Islander women generally lived the closest to these high quality hospitals, with more than half living within 15km, and were indeed more likely to get treated at one. Nonetheless, there was no significant difference in treatment adherence despite their proximity. And despite showing that traveling greater distances was protective, women of the highest SES were the least likely to travel >32 kilometers and made up the largest percentage of those who did receive NCCN-guideline care. They did, however, live the closest to a high quality hospital, which was significantly protective.

This may highlight how access to care can be differential. Of Penchansky and Thomas' five dimensions of access, two concern geographic access – accessibility and availability.[35] Availability refers to the quantity and appropriateness of the healthcare resources in an area,

whereas accessibility relates to their location in the context of the patients.[35] We report that discrepancies exist between availability and accessibility by race, SES, and insurance. Using the Surveillance, Epidemiology, and End Results data, Sakhuja et al. noted that availability of healthcare resources at the county-level and its effect on outcomes differed by race for women diagnosed with OC.[36] For instance, black women had fewer oncology hospitals in their vicinity but greater OB/Gyn specialist available. Once accounting for these health care access variables, there was no effect on mortality for black women, although having fewer medical doctors was detrimental for white women.[36]

Treatment adherence requires that both appropriate surgery and chemotherapy are delivered. In a California retrospective population-based examination of women with advanced stage OC and predictors of receiving care, Long and colleagues reported women of the lowest SES were significantly less likely to receive treatment, including no surgery, no chemotherapy, and almost two times as likely to receive no treatment at all as compared to the highest SES group.[37] They further noted that relative to white women, African Americans were less likely to receive appropriate surgery and were 50% more likely to only receive chemotherapy.[37]

The impact of stage at diagnosis and its relationship with receiving adequate care is also noteworthy. The effect of geographic location on non-adherence was greatest for women diagnosed in early stages with geographic risk in remote areas of central California being greater. After accounting for women's residential location, the insignificance of SES at early stages was particularly evident. Race is only marginally significant, while having no insurance is the only insurer status that was associated with non-adherence. On the other hand, women diagnosed in Stage 4 generally have a poor prognosis, with the 5 year survival rate being less than 30%.[1] Despite this, Stage 4 is where the largest disparities are seen in deviations from NCCN

guidelines. Women of black race, lowest SES, and with no insurance had the greatest risk in Stage 4.

The considerable financial challenges already faced coupled with the additional burden that travel poses for women diagnosed with OC must be acknowledged.[34] Travel is a geographic barrier to treatment and may disproportionately affect those of lower SES,[38] a point illustrated by their overall remoteness from high O/E centers. Moreover, not only must women have the financial means to travel for care, finding that traveling further is protective may additionally suggest a greater awareness of appropriate resources among those women.[16] A pilot study with mostly affluent women found 5 out of 6 OC patients recruited from a NCI-designated hospital expressed a lack of local specialists as a reason for traveling over 25 miles for OC-directed care.[39] Physicians interviewed in the respective study also identified transportation as a barrier, particularly for their low income patients.[39]

The implications of geographic access and travel are worth noting, given that women of lower SES and with federally-funded insurance were less likely to travel for care, obtain care at quality centers, or receive NCCN guideline treatment. Furthermore, women may choose to stay local for care. One study found that approximately 20% of women indicated that they would not travel over 50 miles for care, despite the potential survival advantages.[40] This may be particularly true for older women, those with comorbidities, or with limited social support. Greater distances may be less viable for women who are managing multiple conditions.[41] We found women with two or more comorbidities and over 65 years to be less likely to travel. Although this conflicts with Temkin et al.'s conclusion that elderly traveled the furthest to receive care, it is consistent with prior work that older age is associated with shorter journeys.[16,41] Wasif et al. suggest this may be due to longstanding, existing relationships with local providers.[16]

Strengths

The present study has several noteworthy features. Among them is the large sample size, with almost 20 years of data available from the CCR, a registry with demonstrated reliability. Additionally, the exploration of residential location and its differing effects on OC treatment adherence by stage and social demographics is novel. Unlike previous studies that used zip code and census block variables as spatial proxies, utilizing a precise measure of patient location allows for a more accurate assessment of the effect of geographic location. Furthermore, using the network analyst allows for a more precise calculation of travel distance. We were also able to incorporate a comorbidity index, which allowed us to control for potential confounding by comorbidity status. Erickson et al. (2014) conducted a retrospective study to identify the reasons that patients did not receive NCCN treatment guidelines and found existing comorbid conditions to be a main reason for failure to complete chemotherapy.[42] The ability to utilize the Deyo-adapted score to account for this was a strength in this work. Lastly, the GAM framework is particularly useful for investigating geographic disparities while accounting for known risk factors.

Limitations

There are several limitations worth noting in this study. Among them are the potential for reporting bias and the presence of unmeasured confounders given its retrospective nature. Another limitation is that we cannot account for several individual characteristics such as preferences for certain travel routes. Instead, the assumption is made that patients would choose the shortest route between their residence and the hospitals. Measuring travel distance has been said to capture the average situation encountered, therefore is likely a suitable metric. On the other hand, the lack of ability to accurately capture the utilization of public transportation

warrants consideration. For example, distances may appear short, but when reliable private transportation is unavailable, transportation may pose additional burdens to patients of lower SES and may subsequently misrepresent accessibility.

There are treatment related factors that present additional limitations. The first treatment is the only one captured in the registry, therefore any other treatment, whether simultaneous or after, is not accounted for. Also, the CCR does not collect information on provider characteristics, so the lack of details about providers presents an additional limitation. Neither the number of OC cases seen by the treating physician nor their medical specialty is captured in the registry data. As these characteristics have been previously found to be predictors of treatment adherence and survival,[8,32,43] their exclusion may also lead to unmeasured confounding. Moreover, few studies have examined the role of provider bias or patient-provider communication in this context. One qualitative study of OC patients' experiences with the medical system found that their interaction with providers influenced their own perception of quality care.[44] The dynamic role between patient and provider warrants further investigation, as the Institute of Medicine has suggested that in other contexts, providers have been found to perceive minority patients as less likely to adhere to treatment, and likewise the patient's themselves distrust providers.[45]

Conclusions

OC is a malignancy with poor prognosis and no current recommendations for screening; thus the treatment received directly impacts women's survival time post diagnosis. Quality care is vital to decreasing OC mortality, yet the majority of women do not receive it. Furthermore, differences in adherence were observed by race/ethnicity, insurance type, SES, marriage status and geographic location, with the effects of each varying by stage at diagnosis. Receiving care at

a high O/E hospital was significant, yet even amongst women who accessed these hospitals; there were still disparities in the likelihood of getting quality care by race. African American women may experience additional life stressors that prevent treatment adherence.[44,46] Non-Hispanic black women, those of lower SES and non-married women were found to receive inferior treatment and were less likely to travel far for care. Access to care and the ability to travel may negatively impact those of lower SES. The influence of these socio-demographic factors was more pronounced at later stages, while distance traveled to receive care was a stronger predictor in early stages. Spatial analyses of geographic barriers may provide an opportunity for targeted intervention to broaden access to care among vulnerable populations. Providing transportation, opening satellite clinics, employing patient navigators, and ensuring that those services are covered by all insurance carriers are all potential avenues to facilitate access to care with providers who have more familiarity with OC best practices, ultimately improving OC survival overall.[20,34]

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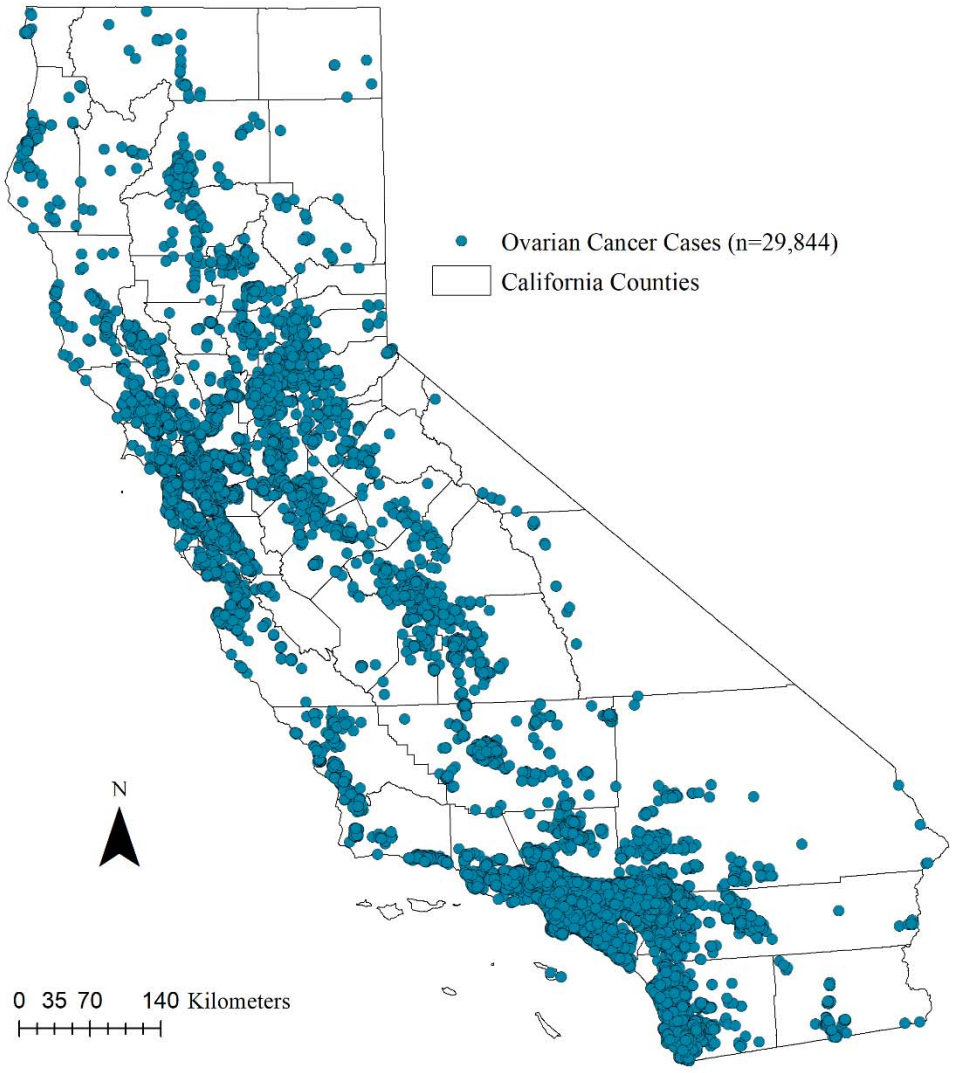


Figure 1.1: Distribution of Ovarian Cancer Cases in California, 1996-2014
This figure displays the cases of ovarian cancer diagnosed in California between the years 1996 and 2014.

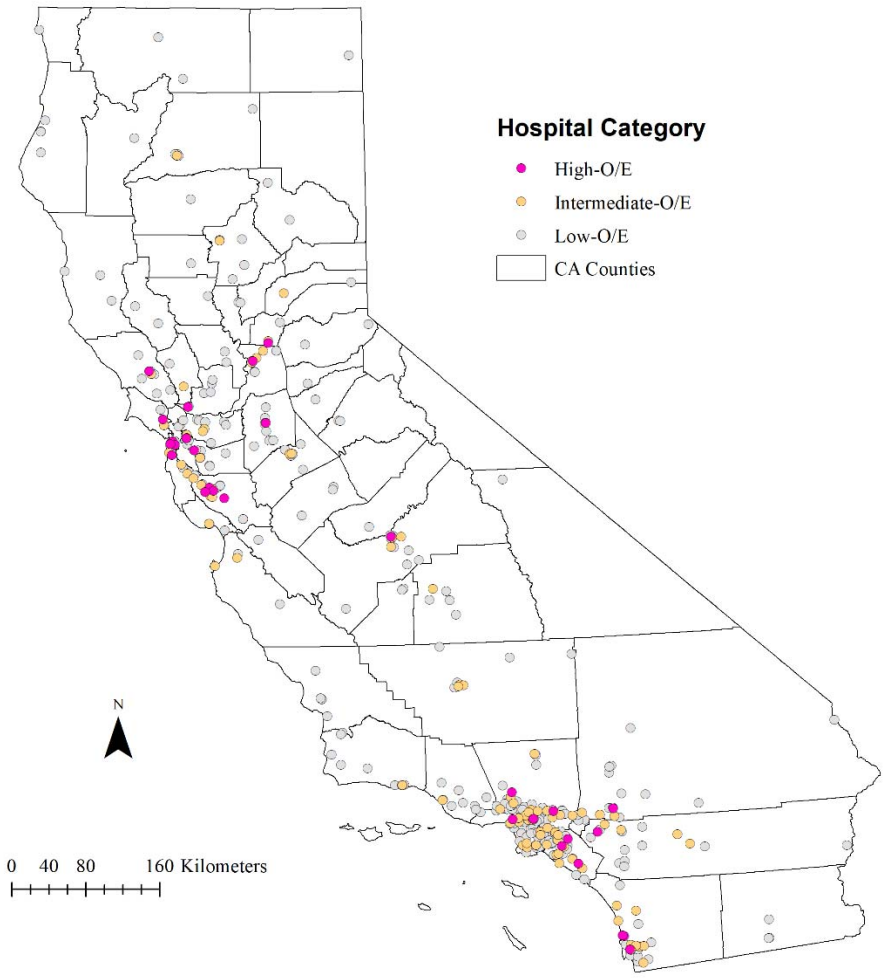
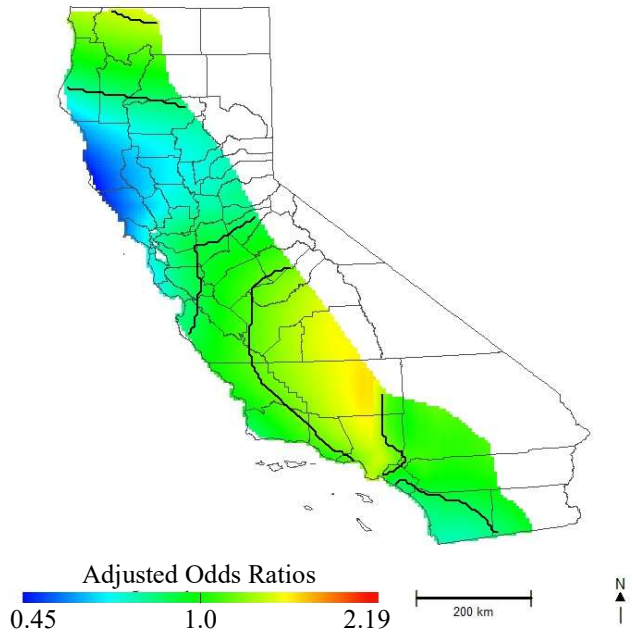


Figure 1.2: Distribution of California Hospitals by Observed-to-Expected Category
Hospitals in California (CA) treating ovarian cancer patients between 1996-2014 are shown by their Observed-to-Expected (O/E) category, a measure of hospital quality. High O/E hospitals are more likely to deliver care that meets the stage-specific National Comprehensive Cancer Network treatment guidelines than is expected for that given hospital. They are considered high-quality-of-care (QOC) hospitals. There are 30 high O/E hospitals in California during the respective time period.

(A)



(B)

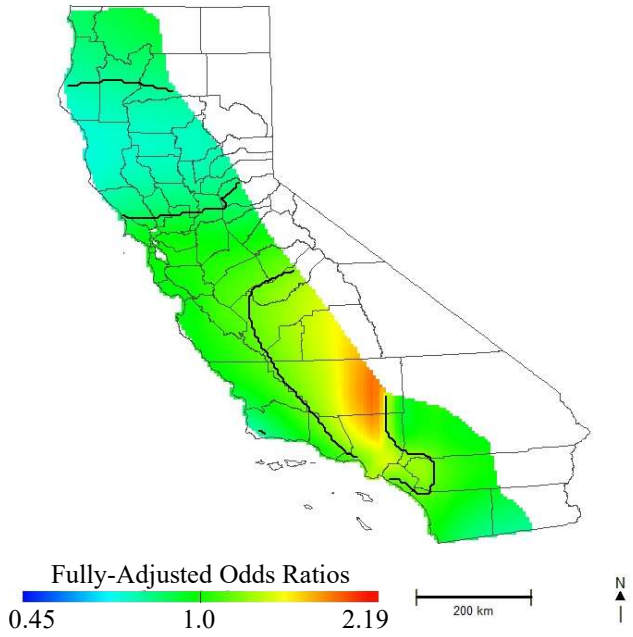


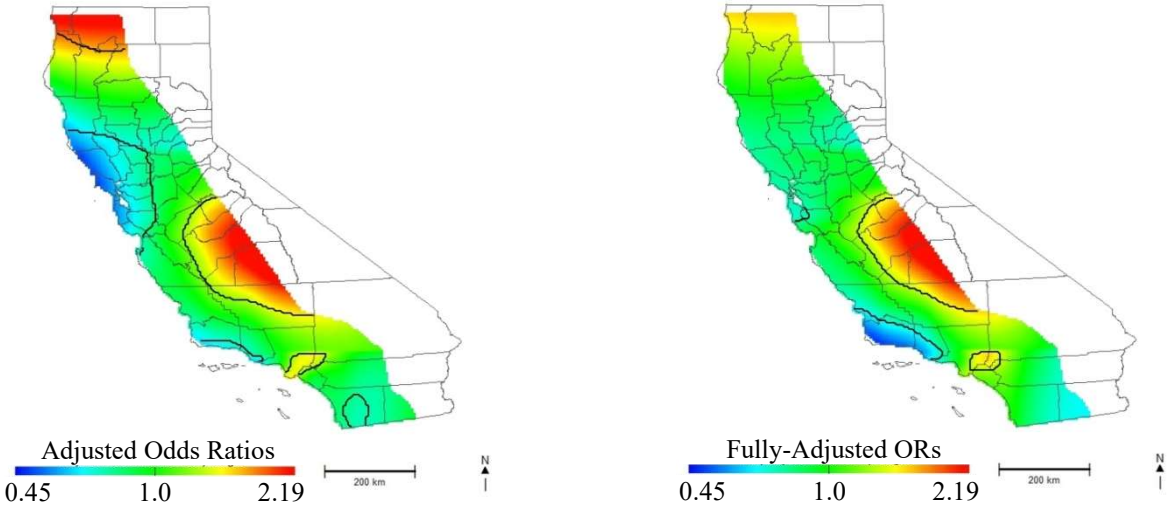
Figure 1.3: Odds of NCCN Non-Adherent Care for Ovarian Cancer in California, 1996-2014

(A) The base model, adjusted for only age and cancer characteristics and (B) the fully-adjusted model display the effect of geographic location on risk of receiving non-adherent National Comprehensive Cancer Network (NCCN) guideline treatment for epithelial ovarian cancer. Contour lines delineate geographic areas that exclude odds ratios of 1. Fully-adjusted models additionally control for race/ethnicity, socioeconomic status, insurance status, marital status, stage at diagnosis (for early stages), tumor grade, tumor histology, tumor size, comorbidity status, quality of treatment hospital, year of diagnosis, distance traveled for care, and distance of closest high quality hospital.

Figure 1.4: Stage-Stratified Odds of Non-Adherent Care for Ovarian Cancer in California, 1996-2014

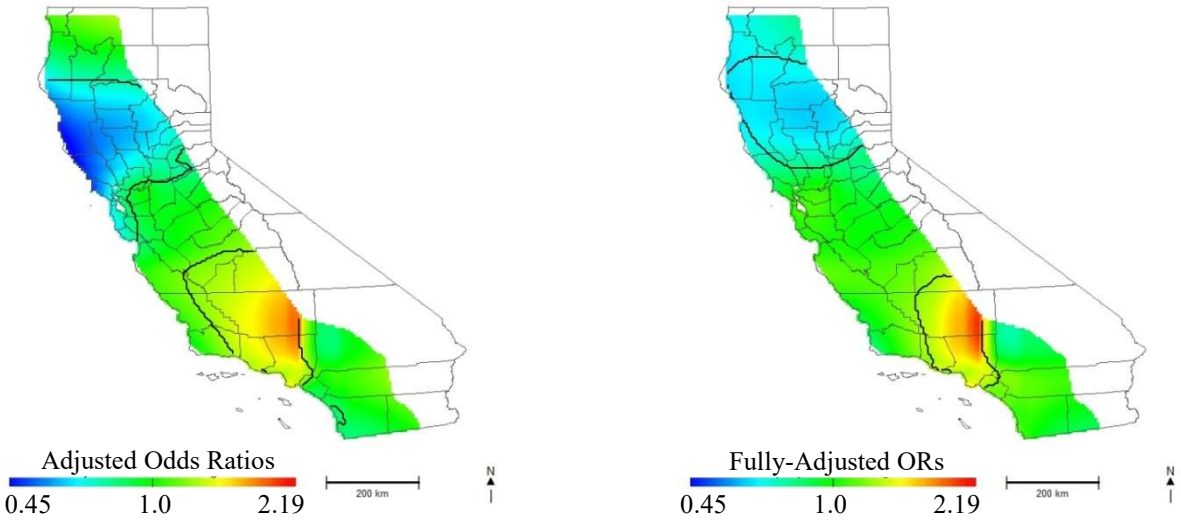
EARLY STAGES

(A) (B)



STAGE 3

(A) (B)



STAGE 4

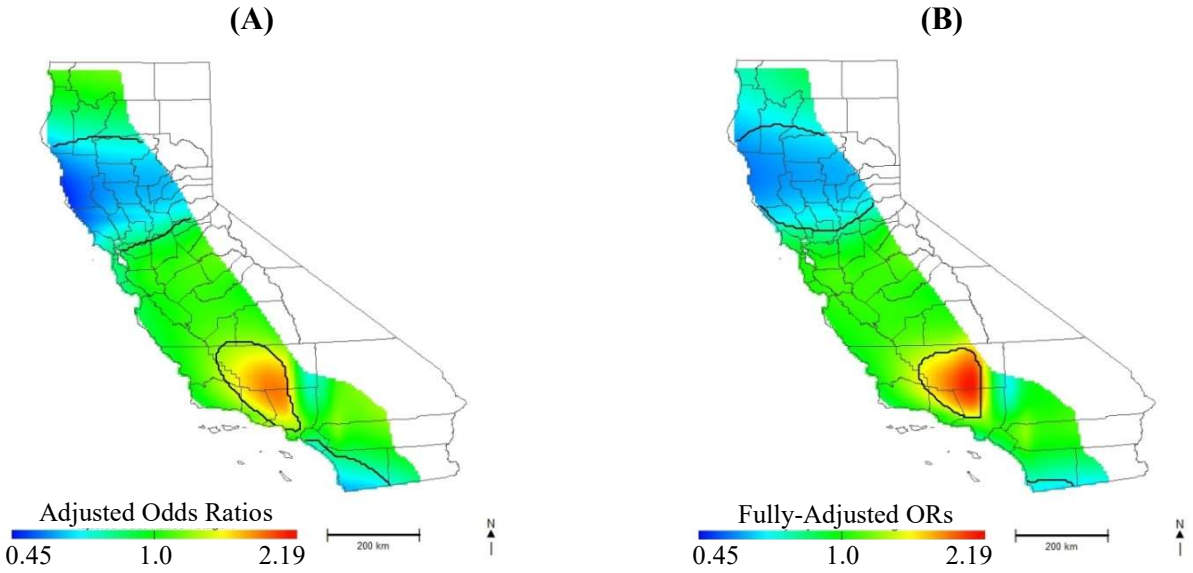


Figure 1.4: Stage-Stratified Odds of Non-Adherent Care for Ovarian Cancer in California, 1996-2014

The (A) base-adjusted and (B) fully-adjusted effect of geographic location on risk of receiving non-adherent National Comprehensive Cancer Network guideline treatment for invasive epithelial ovarian cancer, stratified by stage. Early stages include stage 1 and stage 2. Contour lines delineate geographic areas that exclude odds ratios of 1.

*Base-adjusted models control for age and cancer characteristics only. Fully-adjusted models additionally control for race/ethnicity, socioeconomic status, insurance status, marital status, stage at diagnosis (for early stages), tumor grade, tumor histology, tumor size, comorbidity status, quality of treatment hospital, year of diagnosis, distance traveled for care, and distance of closest high quality hospital.

Abbreviation: *ORs,* Odds Ratios

Table 1.1: Ovarian Cancer Patient Characteristics by NCCN Treatment Adherence, 1996-2014

Characteristic	Treatment Adherent		Treatment Non-Adherent	
	N	%	N	%
Total (n=29,844)	11419	38.3	18425	61.7
Age Group				
18-44	1511	35.9	2699	64.1
45-54	2806	43.7	3617	56.3
55-64	3359	46.5	3862	53.5
65+	3743	31.2	8247	68.8
Race/Ethnicity				
Non-Hispanic White	7533	39.8	11387	60.2
Non-Hispanic Black	424	29.9	992	70.1
Hispanic	2020	35.1	3729	64.9
Asian/ PI	1378	38.7	2186	61.3
American Indian/ Other	64	32.8	131	67.2
Socioeconomic Status				
Lowest SES	1222	30.3	2815	69.7
Lower-Middle SES	1878	34.6	3557	65.4
Middle SES	2374	37.5	3950	62.5
Higher-Middle SES	2769	40.4	4091	59.6
Highest SES	3176	44.2	4012	55.8
Insurance Type				
Managed Care	5830	41.2	8320	58.8
Medicare	2438	31.9	5215	68.1
Medicaid	1001	36.7	1724	63.3
Other Insurance	1636	42.8	2189	57.2
Not insured	275	30.9	614	69.1
Unknown	239	39.7	363	60.3
Marital Status				
Not Married	5029	34.2	9659	65.8
Married	6390	42.2	8766	57.8
Charlson Comorbidity Score				
CCS 0	5931	41.7	8288	58.3
CCS 1	2743	40.3	4064	59.7
CCS 2+	2078	30.9	4648	69.1
CCS Unknown	667	31.9	1425	68.1
Stage				
Stage 1	1720	23.8	5518	76.2
Stage 2	731	29.3	1765	70.7
Stage 3	5943	52.8	5320	47.2
Stage 4	3025	34.2	5822	65.8
Chemotherapy Adherence				
Adherent	11419	61.1	7283	38.9

Non-Adherent	0	0.0	11142	100.0
Surgery Adherence				
Adherent	11419	70.8	4700	29.2
Non-Adherent	0	0.0	13725	100.0
Hospital Quality Measure				
Low	1912	27.4	5078	72.6
Intermediate	6533	37.8	10742	62.2
High	2974	53.3	2605	46.7
Distance Traveled to Care				
<6 km	1911	32.0	4058	68.0
6-9 km	2133	35.7	3836	64.3
10-16 km	2262	37.9	3706	62.1
17-32 km	2358	39.5	3611	60.5
>32 km	2755	46.2	3214	53.8
Closest High Quality Hospital				
<9 km	2501	41.9	3468	58.1
9-14 km	2247	37.6	3722	62.4
15-24 km	2228	37.3	3740	62.7
25-48 km	2289	38.3	3680	61.7
>48 km	2154	36.1	3815	63.9

Abbreviations: *CCS,* Charlson Comorbidity Score; *km,* kilometers; *NCCN*, National Comprehensive Cancer Network; *PI*, Pacific Islander; *SES,* socioeconomic status

Table 1.2: Characteristics of Ovarian Cancer Patients by Distance Traveled to Receive Care, 1996-2014*

	<6 km		6 – 9 km		10 – 16 km		17 – 32 km		> 32 km	
Age Group	N	%	N	%	N	%	N	%	N	%
18-44	737	17.5	815	19.4	887	21.1	930	22.1	841	20.0
45-54	1148	17.9	1130	17.6	1303	20.3	1421	22.1	1421	22.1
55-64	1252	17.3	1320	18.3	1432	19.8	1535	21.3	1682	23.3
65+	2832	23.6	2704	22.6	2346	19.6	2083	17.4	2025	16.9
Race/Ethnicity										
Non-Hispanic White	3831	20.2	3716	19.6	3545	18.7	3657	19.3	4171	22.0
Non-Hispanic Black	291	20.6	293	20.7	345	24.4	300	21.2	187	13.2
Hispanic	1099	19.1	1205	21.0	1241	21.6	1226	21.3	978	17.0
Asian/ PI	715	20.1	718	20.1	804	22.6	750	21.0	577	16.2
American Indian/ Other	33	16.9	37	19.0	33	16.9	36	18.5	56	28.7
Socioeconomic Status										
Lowest SES	924	22.9	828	20.5	858	21.3	672	16.6	755	18.7
Lower-Middle SES	1127	20.7	1027	18.9	1070	19.7	1039	19.1	1172	21.6
Middle SES	1239	19.6	1212	19.2	1178	18.6	1257	19.9	1438	22.7
Higher-Middle SES	1357	19.8	1303	19.0	1382	20.1	1420	20.7	1398	20.4
Highest SES	1322	18.4	1599	22.2	1480	20.6	1581	22.0	1206	16.8
Insurance Type										
Managed Care	2528	17.9	2763	19.5	2926	20.7	3111	22.0	2822	19.9
Medicare	1913	25.0	1687	22.0	1423	18.6	1194	15.6	1436	18.8
Medicaid	604	22.2	532	19.5	534	19.6	563	20.7	492	18.1
Other Insurance	675	17.6	717	18.7	730	19.1	764	20.0	939	24.5
Not insured	145	16.3	155	17.4	202	22.7	223	25.1	164	18.4
Unknown	104	17.3	115	19.1	153	25.4	114	18.9	116	19.3
Marital Status										
Not Married	3300	22.5	3051	20.8	2905	19.8	2821	19.2	2611	17.8
Married	2669	17.6	2918	19.3	3063	20.2	3148	20.8	3358	22.2
Charlson Comorbidity Score										
CCS 0	2664	18.7	2699	19.0	2844	20.0	2967	20.9	3045	21.4
CCS 1	1360	20.0	1394	20.5	1328	19.5	1321	19.4	1404	20.6
CCS 2+	1597	23.7	1468	21.8	1338	19.9	1204	17.9	1119	16.6
CCS Unknown	348	16.6	408	19.5	458	21.9	477	22.8	401	19.2
Stage										
Stage 1	1345	18.6	1391	19.2	1485	20.5	1542	21.3	1475	20.4
Stage 2	473	19.0	480	19.2	461	18.5	548	22.0	534	21.4
Stage 3	2148	19.1	2161	19.2	2203	19.6	2238	19.9	2513	22.3
Stage 4	2003	22.6	1937	21.9	1819	20.6	1641	18.5	1447	16.4
NCCN Treatment Adherence										
Adherent	1911	16.7	2133	18.7	2262	19.8	2358	20.6	2755	24.1
Non-Adherent	4058	22.0	3836	20.8	3706	20.1	3611	19.6	3214	17.4
Hospital Quality Measure										
Low	2157	30.9	1594	22.8	1315	18.8	1121	16.0	803	11.5
Intermediate	3036	17.6	3488	20.2	3590	20.8	3597	20.8	3564	20.6
High	776	13.9	887	15.9	1063	19.1	1251	22.4	1602	28.7
Closest High Quality Hospital										
<9 km	1843	30.9	1850	31.0	975	16.3	809	13.6	492	8.2

9-14 km	1100	18.4	1240	20.8	2003	33.6	1109	18.6	517	8.7
15-24 km	860	14.4	1082	18.1	1404	23.5	1879	31.5	743	12.4
25-48 km	1023	17.1	1052	17.6	862	14.4	1375	23.0	1657	27.8
>48 km	1143	19.1	745	12.5	724	12.1	797	13.4	2560	42.9

* Chi-square tests were used to calculate statistical significance of differences between groups. *P*-values were <0.001 for all categories.

Abbreviations: *CCS,* Charlson Comorbidity Score*; km,* kilometers; *NCCN*, National Comprehensive Cancer Network; *PI*, Pacific Islander; *SES,* socioeconomic status

Table 1.3: Characteristics of Ovarian Cancer Patients by Distance to Closest High Quality Hospital, 1996-2014*

	< 9 km		9 – 14 km		15 – 24 km		25 – 48 km		> 48 km	
Age Group	N	%	N	%	N	%	N	%	N	%
18-44	877	20.8	893	21.2	895	21.3	817	19.4	728	17.3
45-54	1328	20.7	1309	20.4	1273	19.8	1353	21.1	1160	18.1
55-64	1444	20.0	1452	20.1	1455	20.1	1401	19.4	1469	20.3
65+	2320	19.3	2315	19.3	2345	19.6	2398	20.0	2612	21.8
Race/Ethnicity										
Non-Hispanic White	3418	18.1	3399	18.0	3547	18.7	4034	21.3	4522	23.9
Non-Hispanic Black	308	21.8	319	22.5	436	30.8	234	16.5	119	8.4
Hispanic	1121	19.5	1275	22.2	1267	22.0	1050	18.3	1036	18.0
Asian/ PI	1083	30.4	939	26.3	692	19.4	619	17.4	231	6.5
American Indian/ Other	39	20.0	37	19.0	26	13.3	32	16.4	61	31.3
Socioeconomic Status										
Lowest SES	814	20.2	902	22.3	691	17.1	553	13.7	1077	26.7
Lower-Middle SES	851	15.7	1094	20.1	1006	18.5	955	17.6	1529	28.1
Middle SES	1165	18.4	1163	18.4	1196	18.9	1185	18.7	1615	25.5
Higher-Middle SES	1433	20.9	1264	18.4	1480	21.6	1529	22.3	1154	16.8
Highest SES	1706	23.7	1546	21.5	1595	22.2	1747	24.3	594	8.3
Insurance Type										
Managed Care	3034	21.4	2867	20.3	3055	21.6	3166	22.4	2028	14.3
Medicare	1412	18.5	1421	18.6	1385	18.1	1393	18.2	2042	26.7
Medicaid	595	21.8	662	24.3	496	18.2	399	14.6	573	21.0
Other Insurance	647	16.9	684	17.9	702	18.4	749	19.6	1043	27.3
Not insured	166	18.7	187	21.0	203	22.8	167	18.8	166	18.7
Unknown	115	19.1	148	24.6	127	21.1	95	15.8	117	19.4
Marital Status										
Not Married	3205	21.8	3049	20.8	2926	19.9	2815	19.2	2693	18.3
Married	2764	18.2	2920	19.3	3042	20.1	3154	20.8	3276	21.6
Charlson Comorbidity Score										
CCS 0	2844	20.0	2800	19.7	2789	19.6	2925	20.6	2861	20.1
CCS 1	1324	19.5	1319	19.4	1380	20.3	1360	20.0	1424	20.9
CCS 2+	1296	19.3	1363	20.3	1407	20.9	1250	18.6	1410	21.0
CCS Unknown	505	24.1	487	23.3	392	18.7	434	20.7	274	13.1
Stage										
Stage 1	1476	20.4	1548	21.4	1500	20.7	1396	19.3	1318	18.2
Stage 2	536	21.5	502	20.1	475	19.0	477	19.1	506	20.3
Stage 3	2246	19.9	2177	19.3	2261	20.1	2312	20.5	2267	20.1
Stage 4	1711	19.3	1742	19.7	1732	19.6	1784	20.2	1878	21.2
NCCN Treatment Adherence										
Adherent	2501	21.9	2247	19.7	2228	19.5	2289	20.0	2154	18.9
Non-Adherent	3468	18.8	3722	20.2	3740	20.3	3680	20.0	3815	20.7
Chemotherapy Adherence										
Adherent	3832	20.5	3770	20.2	3735	20.0	3733	20.0	3632	19.4
Non-Adherent	2137	19.2	2199	19.7	2233	20.0	2236	20.1	2337	21.0
Surgery Adherence										
Adherent	3394	21.1	3167	19.6	3172	19.7	3236	20.1	3150	19.5
Non-Adherent	2575	18.8	2802	20.4	2796	20.4	2733	19.9	2819	20.5

Hospital Quality Measure										
Low	827	11.8	1042	14.9	1448	20.7	1477	21.1	2196	31.4
Intermediate	3017	17.5	3712	21.5	3604	20.9	3687	21.3	3255	18.8
High	2125	38.1	1215	21.8	916	16.4	805	14.4	518	9.3
Distance to Receive Care										
<6 km	1843	31.5	1100	18.8	860	14.7	1023	17.5	1023	17.5
6-9 km	1850	29.5	1240	19.8	1082	17.2	1052	16.8	1052	16.8
10-16 km	975	16.0	2003	32.8	1404	23.0	862	14.1	862	14.1
17-32 km	809	12.4	1109	16.9	1879	28.7	1375	21.0	1375	21.0
>32 km	492	9.7	517	10.2	743	14.7	1657	32.7	1657	32.7

*Chi-square tests were used to calculate statistically significant differences between groups. P-values were <0.001 for all categories

Abbreviations: *CCS,* Charlson Comorbidity Score*; km,* kilometers; *NCCN*, National Comprehensive Cancer Network; *PI*, Pacific Islander; *SES,* socioeconomic status

Table 1.4: Multivariate Analysis of NCCN Treatment Non-adherence for All Stages Combined, 1996-2014

Patient Characteristic	OR	95% Confidence Interval
Age	1.02	1.02 - 1.02
Size Category		
<50mm	1.00	Referent
50-99mm	0.93	0.85 - 1.02
100+mm	0.91	0.83 - 0.99
Size Unknown	1.12	1.03 - 1.22
Grade		
Grade I	1.00	Referent
Grade II	1.00	0.89 - 1.13
Grade III	0.85	0.76 - 0.95
Grade IV	0.73	0.65 - 0.83
Grade Unknown	2.25	2.00 - 2.54
Stage		
Stage 1	1.00	Referent
Stage 2	0.75	0.68 - 0.84
Stage 3	0.25	0.23 - 0.27
Stage 4	0.33	0.30 - 0.36
Histology		
Serous	1.00	Referent
Mucinous	1.40	1.24 - 1.58
Endometrioid	1.22	1.11 - 1.34
Clear cell	0.91	0.81 - 1.03
Adenocarcinoma, NOS	2.89	2.59 - 3.22
Others	1.78	1.66 - 1.91
Race/Ethnicity		
Non-Hispanic White	1.00	Referent
Non-Hispanic Black	1.21	1.06 - 1.39
Hispanic	1.01	0.93 - 1.09
Asian/Pacific Islander	1.02	0.93 - 1.11
American Indian/ Other	1.47	1.05 - 2.05
Socioeconomic Status		
Lowest SES	1.28	1.16 - 1.42
Lower-middle SES	1.15	1.06 - 1.26
Middle SES	1.09	1.01 - 1.19
Higher-middle SES	1.06	0.98 - 1.14
Highest SES	1.00	Referent
Insurance		
Managed Care	1.00	Referent
Medicare	1.10	1.03 - 1.19
Medicaid	1.04	0.94 - 1.15
Other Insurance	1.01	0.93 - 1.10
Not insured	1.34	1.14 - 1.58
Unknown	0.99	0.82 - 1.20
Marital Status		
Not Married	1.00	Referent
Married	0.85	0.81 - 0.90

Charlson Comorbidity Score			
CCS 0	1.00	Referent	
CCS 1	0.99	0.92 -	1.05
CCS 2+	1.19	1.10 -	1.28
CCS Unknown	1.26	1.13 -	1.41
Year of Diagnosis	1.01	1.00 -	1.01
Hospital Quality Measure			
Low	2.57	2.35 -	2.81
Intermediate	1.76	1.64 -	1.89
High	1.00	Referent	
Distance Traveled to Care			
<6 km	1.00	Referent	
6-9 km	0.92	0.85 -	1.00
10-16 km	0.89	0.82 -	0.97
17-32 km	0.91	0.84 -	1.00
>32 km	0.76	0.70 -	0.84
Closest High Quality Hospital			
<9 km	1.00	Referent	
9-14 km	1.06	0.97 -	1.15
15-24 km	1.05	0.97 -	1.15
25-48 km	1.13	1.04 -	1.23
>48 km	1.18	1.07 -	1.29

Abbreviations: *CCS*, Charlson Comorbidity Score*; km,* kilometers; *NCCN*, National Comprehensive Cancer Network; *NOS,* Not otherwise specified; *OR,* Odds Ratio

Table 1.5: Multivariate Analysis of NCCN Treatment Non-adherence for Early Stages, 2996-2014

Patient Characteristic	OR	95% Confidence Interval			P-value
Age	1.00	1.00	-	1.01	0.0373
Size Category					
<50mm	1.00	Referent			
50-99mm	0.73	0.61	-	0.87	0.0005
100+mm	0.65	0.55	-	0.76	<0.0001
Unknown	0.94	0.78	-	1.12	0.4884
Grade					
Grade I	1.00	Referent			
Grade II	1.08	0.93	-	1.24	0.3307
Grade III	1.11	0.95	-	1.30	0.1992
Grade IV	0.99	0.82	-	1.21	0.9392
Grade Unknown	2.44	2.06	-	2.89	<0.0001
Stage					
Stage 1	1.00	Referent			
Stage 2	0.72	0.64	-	0.80	<0.0001
Histology					
Serous	1.00	Referent			
Mucinous	1.01	0.84	-	1.20	0.9534
Endometrioid	0.96	0.83	-	1.12	0.6005
Clear cell	0.62	0.52	-	0.73	<0.0001
Adenocarcinoma, NOS	1.66	1.17	-	2.36	0.0047
Others	1.28	1.10	-	1.49	0.0015
Race					
Non-Hispanic White	1.00	Referent			
Non-Hispanic Black	1.34	1.00	-	1.79	0.0531
Hispanic	1.15	1.00	-	1.33	0.0483
Asian/Pacific Islander	1.10	0.95	-	1.26	0.1974
AI/other/unknown	1.65	0.89	-	3.04	0.1101
Socioeconomic Status			-		
Highest SES	1.00	Referent	-		
Lowest SES	1.05	0.87	-	1.28	0.5915
Lower-middle SES	1.12	0.95	-	1.32	0.1733
Middle SES	1.01	0.88	-	1.17	0.8543
Higher-middle SES	1.08	0.94	-	1.24	0.2654
Insurance					
Managed Care	1.00	Referent			
Medicare	1.25	1.06	-	1.47	0.0078
Medicaid	1.10	0.91	-	1.32	0.3408

Other Insurance	0.90	0.79	-	1.03	0.1340
Not insured	1.22	0.91	-	1.64	0.1764
Unknown	0.85	0.60	-	1.21	0.3723
Marriage Status					
Not Married	1.00	Referent			
Married	0.97	0.88	-	1.07	0.5372
Year of Diagnosis	0.98	0.98	-	0.99	0.0010
Charlson Comorbidity Score					
Charlson Score 0	1.00	Referent			
Charlson Score 1	1.16	1.02	-	1.33	0.0250
Charlson Score 2	1.44	1.23	-	1.68	<0.0001
Charlson Score Unknown	1.33	1.10	-	1.61	0.0031
Observed/ Expected Category					
High O/E	1.00	Referent			
Low O/E	2.34	1.99	-	2.76	<0.0001
Intermediate O/E	1.72	1.52	-	1.94	<0.0001
Distance to Care					
<6 kilometers	1.00	Referent			
6-9 kilometers	0.82	0.69	-	0.96	0.0162
10-16 kilometers	0.83	0.70	-	0.98	0.0295
17-32 kilometers	0.77	0.66	-	0.91	0.0022
>32 kilometers	0.57	0.49	-	0.68	<0.0001
Distance- Closest High O/E					
<9 kilometers	1.00	Referent			
9-14 kilometers	0.96	0.82	-	1.12	0.5873
15-24 kilometers	1.02	0.87	-	1.20	0.7964
25-48 kilometers	1.14	0.97	-	1.34	0.1183
>48 kilometers	1.25	1.05	-	1.49	0.0132

Abbreviations: *AI*, American Indian; *CCS*, Charlson Comorbidity Score; *km*, kilometers; *NCCN*, National Comprehensive Cancer Network; *NOS*, Not otherwise specified; *OE*, Observed/ Expected; *OR*, Odds Ratio

CHAPTER 2

Spatial Analysis of Ovarian Cancer Survival

Abstract

Objective: To investigate the association between geographic location and ovarian cancer-specific survival in California and examine how race/ethnicity and socioeconomic status (SES) impacts the association between survival and access to care.

Methods: Our study included 29,844 women diagnosed with epithelial ovarian cancer who were ascertained through the California Cancer Registry with follow-up through 2016. Cox proportional hazard models with a smooth term for residential location were used to identify geographic patterns in survival for crude and adjusted analyses. We report hazard ratios [HR] and 95% confidence intervals [CI] for the association between survival and distance traveled for care, distance to the closest high-quality-of-care (QOC) hospital, race/ethnicity, and SES, adjusting for receipt of National Comprehensive Cancer Network guideline care, age, and cancer characteristics. Models were also stratified by stage, race/ethnicity, and SES.

Results: Significant spatial patterns were observed across California in crude models for all stages combined (map HR range: 0.81-1.41, P=0.009) and late stages (map HR range: 0.72-1.27, P=0.002) but not in adjusted models or among early-staged patients. Across most strata, better survival was observed for patients who traveled longer distances to receive care. Associations between survival and proximity to closest high-QOC hospitals were generally null except for women in the lowest SES category living furthest away (HR, 1.22; 95% CI, 1.03-1.43).

Conclusions: Geographic disparities in ovarian cancer-specific survival were due to important predictors such as receiving quality care. Improving access to expert care and ensuring receipt of guideline-adherent treatment should be priorities in optimizing survival.

Introduction

In the United States, ovarian cancer continues to be the deadliest gynecologic malignancy.[1] Nationally, approximately 22,000 women are estimated to be given an ovarian cancer diagnosis each year.[2] While the number of deaths attributed to this disease have decreased slowly, the proportion of women overall surviving five years post-diagnosis is still below 50%.[3] Furthermore, disparities in survival by race and socioeconomic status (SES) have become prominent, with women of non-Hispanic black race and lower SES backgrounds disproportionally experiencing worse prognosis.[4–12] In an effort to find ways to reduce the immense burden ovarian cancer poses and understand the outcome differences by sociodemographic factors observed, researchers have focused on identifying sources of inequity and factors influencing ovarian cancer outcomes.

Over 40 years have passed since advances in treatment have emerged leading to slight improvements in O ovarian cancer survival.[7] It is well documented that receiving appropriate treatment for ovarian cancer is imperative to improving chances of survival.[4,7] The National Comprehensive Cancer Network (NCCN) has established stage-specific guidelines for the treatment of ovarian cancer [13] and adherence to them has been recognized as a significant predictor of prognosis.[14] Aside from age and cancer characteristics, determinants of receiving guideline care and ovarian cancer survival are multifactorial and include race, insurance,[4,5,10,15–20] individual and area-level SES,[4,9,19,21,22] proximity to services,[19,20,23,24] and characteristics of the treating hospital and physician.[22,23,25–32] Hospital characteristics such as quality, procedure volume and access to these high-performing hospitals have been found to be significantly correlated with both treatment adherence and survival. Specifically, increased odds of adherent care and better survival have been observed among women treated at hospitals with over ≥20

cases/year.[5,30–32] A more recent metric for assessing hospital quality that has been associated with improved outcomes is the Observed to Expected (O/E) Ratio, which incorporates both rate of adherence and hospital volume.[25,33]

While still in its infancy, a growing body of literature has examined spatial variations in adherence to appropriate treatment for ovarian cancer,[19,20,34–37] geographic access to care,[19,20,38] service availability,[39] and ovarian cancer outcomes.[5,35,40,41] We recently identified significant geographic disparities in the receipt of NCCN guideline-adherent care at the geocoded address-level in California.[19] We also found that cases residing further from high quality hospitals were at greater risk of nonstandard care, but cases able to travel longer distances received better care. The goal of this analysis was to investigate the effect of geographic location on ovarian cancer-specific survival, both as an independent predictor and after accounting for sociodemographic factors, disease and treatment characteristics, receipt of NCCN guideline care, and geographic barriers. We also examined the influence of geographic factors by race and SES to determine if spatial accessibility contributes to survival differences.

Methods

Study Population

We employed a retrospective population-based study design to investigate the effect of geographic location on ovarian cancer-specific survival. Cases were obtained from the California Cancer Registry (CCR) for women who had been diagnosed with invasive epithelial ovarian cancer between 1996 and 2014, with follow up available through 2016. Cases were identified from the CCR using the International Classification of Disease Codes for Oncology (ICD-O-3 C56.9). Data from the CCR, whose case reporting within 6 months is nearly 99% and follow up

approximately 95%,[42,43] was then linked to California's Office of Statewide Health Planning and Development (OSHPD) patient discharge data. This study received approval from the Institutional Review Board of the University of California, Irvine (UCI 14-66/HS# 2014-1476).

All ovarian cancer stages (International Federation of Gynecology and Obstetrics (FIGO) - Stage I-IV) were considered for inclusion. To be eligible for the spatial analysis, women had to be at least 18 years of age or older at the time of diagnosis with no prior history of ovarian cancer. Cases were then excluded for the following reasons: obtained through death records (n=309); had unknown stage (n=5,690) or were missing survival time (n=90) or other clinical information (n=208); or if tumor was classified as germ cell or stromal tumors (n=268). Women with no information available on residential location or reporting hospital were additionally removed (n=207).

Study covariates

The main independent variable of interest was women's geographic location, represented by the geocoded residential address at the time of diagnosis. We examined the independent effect of geographic location on ovarian cancer-specific survival as well as determined whether the presence of any underlying spatial patterns were due to confounding variables. Two additional variables were included to assess geographic factors that may impact access to care: the distance women traveled from their residential address to their reporting hospital and the distance from their residential address to the closest high quality hospital. The reporting hospital was the location where women received their initial treatment. The closest high-quality-of-care (high-QOC) hospital was the nearest hospital providing high quality ovarian cancer services based on the observed-to-expected (O/E) ratio of adherence to the NCCN treatment guidelines, as determined by Galvin-Turner et al.[25] The respective authors assessed hospital quality by calculating

the observed to expected (O/E) ratio of adherence to the NCCN treatment guidelines for California hospitals treating OC cases throughout the time period. This value was divided into quartiles based on the ratio of adherence and volume. Hospitals with less than 5 OC cases/year were automatically considered low O/E hospital. Hospitals with at least 5 OC cases/year and in the highest quartile of the O/E ratio were considered to be high-QOC hospitals. Details of these methods can be found elsewhere.[25] Both distance variables were calculated using the Streetmap Premium HERE street data in ArcGIS Network Analyst. (ArcGIS version 10.4.1, ESRI; Redlands, CA). Each distance variable was grouped into quintiles based on the distribution of the respective variable.

Demographic variables examined were age at diagnosis, race/ethnicity, SES, insurance status, and marriage status. Race/ethnicity was grouped into the following: non-Hispanic white, non-Hispanic black, Hispanic, Asian and Pacific Islander, and other (includes American Indian, other, and unknown race/ethnicity). Two indexes were used to assign patients into SES quintiles (Lowest, Lower-Middle, Middle, Higher-Middle, Highest). For patients with a diagnosis before 2006, the Yost score was used,[44] while the Yang index was used for those diagnosed after 2006.[45] Insurance status was grouped into six categories: managed care (including privately insured), Medicare, Medicaid, other insurance, not insured, and unknown insurance status. We also controlled for cancer characteristics traditionally known to affect survival, including histology type, tumor grade, tumor size, and stage at diagnosis (FIGO Stages I-IV).

Other clinical predictors considered were comorbidity status, quality of care received, and quality of hospital where initial treatment was received. Comorbidity status was measured using the Deyo-adapted Charlson Comorbidity Score and classified into the subsequent quartiles: no comorbidities, one comorbidity, two or more comorbidities, and unknown.[46,47] The quality of care was determined by whether the initial treatment received was adherent to the stage-specific

NCCN guidelines for ovarian cancer.[25,48–54] Both surgical and chemotherapy guidelines had to be adherent in order to be considered having received quality care. Lastly, the O/E ratio metric mentioned previously was used to assign the hospital quality where women were treated. This was grouped as low-QOC (lowest quartile of O/E ratio or <5 cases/year), intermediate-QOC (middle two quartiles of O/E ratio), and high-QOC (highest quartile of O/E ratio and > 5 cases).[25]

Statistical analyses

Spatial patterns were assessed using Cox proportional additive hazards model, an extension of the Cox proportional hazards model that includes a loess smooth term for latitude and longitude as a predictor.[5,55–57] Without the smoother for location, the models are reduced to the more common Cox proportional hazards model. Log hazards were calculated for locations across California, using the average hazards as a referent and keeping covariate values constant. The amount of smoothing selected was based on minimizing the Akaike's Information Criterion (AIC).[55,56] We did not compute the hazards for areas with low data density.[58]

We examined the effect of location on ovarian cancer-specific survival for all stages combined and stage-stratified (early vs. late stages). In order to determine whether location was an independent predictor, unadjusted models were fit using the smoother of women's geocoded address at diagnosis with no other covariates. We then adjusted the model for all covariates, including sociodemographic variables, cancer characteristics, and treatment and access to care factors. Permutations were run for each model to determine their respective global p-value for the significance of geographic location.[56] Spatio-temporal analyses were additionally conducted by two time periods (1996-2006) and (2007-2014) as well as in 5 year intervals. Maps were created to visualize the distribution of hazard ratios across California, highlighting significant

areas of higher and lower hazards of survival. All analyses and mapping were conducted using the MapGam package in R (R Software Version 3.4.4).

Aspatial multivariable weighted cox regression models without location were used to examine the association between sociodemographic, clinical, and distance variables with ovarian cancer-specific survival. These models were chosen because the cox proportional hazards assumptions were found to be violated for several variables when plotting the cumulative log hazards as well as examining the scaled Schoenfeld residuals.[59,60] These weighted models report the hazards averaged over the time period, while minimizing the influence of outlying survival times and using robust variance.[61,62] Survival time was calculated in months and ovarian cancer - specific deaths were considered events, while women were censored if they were alive at the end of the follow up period, had a death due to other causes, or were lost to follow up. The variables included in the models were age, race/ethnicity, insurance status, tumor size, grade, histology, the stage at diagnosis, marriage status, year of diagnosis, comorbidity status, and treatment adherence. Group tests were conducted using Wald chi-square tests to determine whether variables with three or more levels as a whole contributed to survival. We also ran the models stratified by race/ethnicity and SES to evaluate differences in the independent effects of the geographic access to care variables.

Results

Patient characteristics

Between 1996 and 2014, 29,844 women were diagnosed with invasive epithelial ovarian cancer in California, with the median age at the time of diagnosis being 60 years (Table 2.1). The majority of women were diagnosed in late stages (67.4%) and more than half were Non-Hispanic

white (63.4%). Slightly over one-third of all women received NCCN guideline adherent care (38.3%). The median survival time among all women was 34.5 months (~2.9 years), but this varied by stage, race/ethnicity, and SES (Table 2.2). Women diagnosed in early stages had much higher survival times than those in late stages (73.7 months versus 24.6 months, respectively). The highest median survival was among Asian and Pacific Islander women (38.6 months) and those with the highest SES (40.4 months), while the lowest was among non-Hispanic black women (23.0 months) and those with the lowest SES (28.2 months).

The distribution of ovarian cancer cases and treating hospitals are displayed in Figure 2.1. A total of 426 hospitals treated women in the study population, 30 of which were considered to be high-QOC hospitals. Distance traveled to receive care ranged from 0.01 km to 1,088 km with a median of 12.7 km (Table 2.2). Women treated at a high-QOC hospital traveled further for care than those treated at low-QOC hospitals (median of 17.3 km versus 8.8 km, respectively). The median distance between residential location and the nearest high-QOC hospital was 19.3 km. Among those living closest to a high-QOC hospital were women of Asian and Pacific Islander background and those of highest SES.

Spatial analyses of OC-specific survival

Cox additive models revealed significant spatial patterns in the crude model for all stages combined (map Hazard Ratio [HR] range: 0.81-1.41, P=0.009). Areas of increased hazards of mortality included the northern part of California and the Southernmost tip (Figure 2.2A). A decreased risk of mortality was observed in the southern part of the Bay Area and in greater Los Angeles/ southern part of Central Valley. Geographic location was also significant in the late stages crude model (map HR range: 072-1.27, P=0.002; Figure 2.3A). Once the model was adjusted for covariates, significant patterns no longer existed (2.3B). Location was not associated

with survival among those diagnosed in early stages in either the crude or adjusted models (Figures 2.3C and 2.3D). The insignificant findings for location suggest that the variables examined explained the significant spatial patterns initially observed, and geographic location did not capture any residual spatial confounding. Maps displaying the hazards of location by time period are presented in Appendix Figure B.1, Appendix Figure B.2, and Appendix Figure B.3.

Determinants of ovarian cancer-specific survival

Table 2.1 reports the hazard ratios for the fully-adjusted aspatial model of all stages combined. Overall, increasing age was associated with worst outcomes (HR, 1.03; 95% confidence interval [CI], 1.02-1.03). Race/ethnicity, SES, and insurance were also significantly associated with survival. Overall, compared to non-Hispanic white women, non-Hispanic black women had a 19% increased hazards (P <0.001). An inverse association existed between SES and survival, with lower SES categories being correlated with greater hazards. Using women in the highest SES quintile as the referent, those in higher-middle, middle, lower-middle and the lowest SES groups had 11%, 9%, 19%, and 18% increased hazards of mortality, respectively. Having Medicaid insurance (HR, 1.10; 95% CI, 1.01-1.19) and not being insured (HR, 1.26; 95% CI, 1.11-1.45) were also associated with increased risk of death whereas being married was protective, with a 12% decreased risk of mortality (P<0.001).

Several cancer and treatment characteristics were associated with survival. Using women diagnosed in Stage 1 as the referent, each advancing stage of diagnosis resulted in significantly worse survival, with a Stage IV diagnoses being most detrimental (HR, 10.84; 95% CI, 9.44-12.45). Receiving non guideline-adherent care was also associated with poorer outcomes (HR, 1.29; 95% CI, 1.23-1.35), as was having a comorbidity score of 1 (HR, 1.13; 95% CI, 1.07-1.20).

Regarding access to care, longer distances traveled to receive care were associated with better outcomes. Women who traveled between 10-16 km, 17-32 km, and over 32 km had an 11%, 14%, and 13% decrease in hazards. Hazards associated with being treated at a high-QOC hospital versus a low- (HR, 1.07; 95% CI: 0.97, 1.18) or intermediate-QOC hospital (HR, 1.00; 95% CI: 0.95, 1.06) and distance to the closest high-QOC hospital (HRs for each increasing distance category = 1.02, 1.07, 0.99, 0.96, all P>0.05), however, were null when modeled with receiving non guideline-adherent care and distance traveled to receive care.

Stratified results

Across all stratified analyses, stage at diagnosis and age were the only two variables consistently predicting survival for women in the study population. With the exception of early stages and women other race, guideline adherent care was a strong determinant of survival.

Stage:

Prognosis and factors affecting it varied greatly depending on whether women were diagnosed in early stages versus late stages (Appendix Table B.1). Few variables were associated with survival among early-staged women. Sociodemographic variables such as race/ethnicity, SES, and marital status had no impact on mortality for women with early-staged disease. Insurance-wise, the only category found to influence survival was having unknown insurance status, which greatly increased risk of death (HR, 3.63; 95% CI, 2.60-5.05). While receiving NCCN-adherent treatment did not affect survival in early stages, having a Charlson comorbidity score of 1 or 2 increased hazards by 46% and 62% (P<0.001), respectively. Traveling between 10-16 km (HR, 0.73; 95% CI, 0.58-0.92) and 17-32 km (HR, 0.70; 95% CI, 0.57-0.86) to receive care was found to be protective among early-staged women. The hospital quality women

received treatment at had no significant impact on survival, however, women living between 15-24 km from a high-QOC hospital had 49 times the hazards of mortality than women living within 9 km ($p<0.001$).

Quite different associations were observed among women diagnosed in late stages than those in early stages. Non-Hispanic black women diagnosed in late stages had 21% significantly greater hazards than non-Hispanic white women. A significant inverse correlation was observed between SES and survival, with an increased risk of death associated with decreasing SES category. Compared to those in the highest quintile, women in higher-middle, middle, lower-middle, and the lowest SES categories had 9%, 14%, 21%, and 23% increased hazards. Insurance also impacted survival in later stages, with Medicaid insurance (HR,1.11; 95% CI, 1.03-1.20) and not being insured (HR, 1.24; 95% CI, 1.09-1.41) linked to worst outcomes. On the other hand, women with Medicare insurance (HR, 0.94; 95% CI, 0.89-0.98) and those who were married (HR, 0.89; 95% CI, 0.85-0.92) had better survival. Compared to early-staged women who had greater hazards when diagnosed in later years (2008-2014) versus earlier years (1996-2002), being diagnosed at late stages during that period (2008 and 2014) was protective (HR, 0.94; 95% CI, 0.89-0.98).

Treatment variables also impacted mortality among women diagnosed in late stages. Women with one comorbidity were more likely to die from ovarian cancer than women with no comorbidities (HR, 1.09; 95% CI, 1.04-1.14). Receiving care that deviated from the NCCN guidelines had a negative impact (HR, 1.36; 95% CI, 1.31-1.41) on survival. Traveling farther distances for treatment was also associated with better survival for women diagnosed in late stages, but distance from a high-QOC hospital and quality of hospital treated at was not significantly associated with survival in fully-adjusted models.

Race/Ethnicity:

Ovarian-cancer specific survival significantly differed by race and ethnicity. Among non-Hispanic black women, sociodemographic variables, such as SES, insurance, and marital status, had no impact on women's survival time. In contrast, all of these variables significantly impacted non-Hispanic white women. Every decreasing SES category significantly increased their hazards of survival. Women in the lowest SES quintile had the worst survival compared to women in the highest SES (HR, 1.30; 95% CI, 1.18-1.43). Furthermore, non-Hispanic white women with Medicaid and those who were uninsured had 29 and 55 times the hazards, respectively, of ovarian cancer-specific mortality compared to non-Hispanic white women with managed care insurance. While insurance status did not have a significant effect on survival for non-Hispanic black, Hispanic, or Asian and Pacific Islander women, being in the second to lowest SES group increased hazards of mortality for Asian and Pacific Islander women (HR, 1.23; 95% CI, 1.02-1.48). Although it should be interpreted with caution due to small numbers, among women of other race, those with no insurance had significantly increased hazards of mortality (HR, 9.92; 2.38-41.33), but SES had no statistically significant effect. Being married had a protective effect on survival, but only amongst non-Hispanic white women. For these women, there was a 15% decreased risk of ovarian cancer-specific death compared to those who were not married.

Other factors increasing hazards of mortality but differing in magnitude depending on race/ethnicity, included greater comorbidity score, receipt of non-adherent care, and treatment at an intermediate or low-QOC hospital. While overall, receiving care that deviated from the NCCN guidelines was detrimental to women, the impact was greater for non-Hispanic black (HR, 1.47; 95% CI, 1.22-1.76) and Hispanic women (HR, 1.42; 95% CI, 1.27-1.60) than for non-Hispanic white (HR, 1.27; 95% CI, 1.21-1.34) and Asian and Pacific Islander (HR, 1.23; 95%

CI, 1.08-1.41). A comorbidity index of 1 significantly increased hazards for non-Hispanic white (HR, 1.14; 95% CI, 1.08-1.20), Hispanic (HR, 1.21; 95% CI, 1.07-1.37), and Asian and Pacific Islander women (HR, 1.27; 95% CI, 1.08-1.49). Additionally, a score of 2 or more had 25 and 29 times the hazards of ovarian cancer-specific mortality for Hispanic and Asian and Pacific Islander women, respectively, compared to those having no comorbidities. For non-Hispanic black women and those of other race, the number of comorbidities had no significant influence on survival. Yet, not being treated at a high-QOC hospital negatively impacted survival. Compared to high-QOC centers, non-Hispanic black women receiving care at a low-QOC hospital had worse outcomes (HR, 1.53; 95% CI, 1.17-2.01) and for those of other race, being treated at an intermediate (HR, 3.93, p=0.051) and low quality (HR, 3.93, p=0.053) hospital had marginally significant effects. In addition, Asian and Pacific Islander women being treated at intermediate-QOC hospitals had an increased risk of ovarian cancer-specific death (HR, 1.25; 95% CI, 1.05-1.47).

While not receiving care at a high-QOC hospital had detrimental effects on survival for non-Hispanic black, Asian and Pacific Islander, and women of other race, living further away (Table 2.3) from one (between 25-48 km) only had a negative impact on survival among women of other race (HR, 4.12; 95% CI, 1.34-12.672). Furthermore, for non-Hispanic black women, greater distances from a high-QOC hospital was protective for those who lived between 15-24 km (HR, 0.72, 95% CI, 0.57-0.92) and 25-48 km away (HR, 0.70, 95% CI, 0.54-0.91). As can be seen in Table 2.3, longer distances traveled to receive care was associated with a decreased risk of mortality, but only among non-Hispanic white, Hispanic, and Asian and Pacific Islander women. Non-Hispanic white women traveling over 32 km for care had a 12% decreased hazards

of dying compared to those who were <6 km away. For Hispanic women, every increasing category of distance traveled up to 32 km had significant protective effects on survival.

Socioeconomic Status:

Differences in survival were also observed by SES. Among women in the lower two SES quintiles, few variables other than cancer characteristics, receiving NCCN guideline care, and distance traveled for care impacted survival. In the lowest SES category, being of Hispanic background was protective (HR, 0.87; 95% CI, 0.77-0.97). Additionally, traveling between 10-16 km and 17-32 km for treatment was significantly correlated with a 14% and 23% decreased hazards of mortality, respectively, while living greater than 48 km from a high-QOC hospital significantly increased hazards of mortality by 22% (Table 2.4). In the middle and higher-middle SES categories, Hispanic women no longer had a survival advantage yet non-Hispanic black women of middle and higher-middle SES had 29% and 28% increased hazards, respectively, compared to their non-Hispanic white counterparts in the same SES category. Race, however, was not associated with survival for women of highest SES.

Sociodemographic factors, such as insurance and marriage status did not show any association with survival for women in the two lowest SES categories. While relationships were not consistent across groups, these variables did significantly influence survival for women in the middle, higher-middle and highest SES categories. For instance, compared to using Managed care insurance, use of Medicaid insurance was associated with worse outcomes for women in the middle SES category (HR, 1.29; 95% CI, 1.10-1.51) and not having insurance increased hazards for women of middle (HR, 1.52; 95% CI, 1.14-2.02) and higher-middle (HR, 1.56; 95% CI, 1.19-2.03) SES. On the other hand, for women in the highest SES quintile, no insurance category increased hazards of mortality, but Medicare insurance was significantly protective (HR, 0.90;

95% CI, 0.82-0.99). In addition, having a status of married was significantly protective for the women in three upper quintiles of SES. Risk of mortality was 10% to 20% lower for women who were married compared to those who were not.

The influence of geographic access to care varied by SES category. Travel had no significant impact on women of the highest SES, yet was found to be significantly protective for women in all other SES categories. Traveling over 32km for initial treatment improved chances of survival for women of lower-middle (HR, 0.78; 95% CI, 0.68-0.89) and middle SES (HR, 0.86; 95% CI, 0.76-0.98). While traveling between 10 and 32km for care was associated with better survival for women in the lowest SES group, living greater than 48km from a high-QOC center significantly increased hazards of mortality by 22%.

Discussion

We examined the impact of women's geocoded residential address on OC-specific survival. In California, the current study found no evidence of a spatial relationship with OC survival for those with early-staged disease. It did reveal that geographic location was significantly associated with survival for women diagnosed in late stages and in models with all stages combined. The geographic patterns observed, however, were no longer statistically significant when we considered confounding by sociodemographic factors, cancer and treatment characteristics, and geographic access variables. Consistent with existing literature, several sociodemographic factors in our analyses were correlated with worse prognosis, including being of non-Hispanic black race, lower SES, and use of Medicaid insurance or having no insurance.[5,6,8–10,20] Unlike other studies,[5,17,23,32] we did not find that treatment at a high-QOC hospital improved ovarian cancer-specific survival overall; this is likely because we also

controlled for receipt of NCCN-adherent care. Overall, our findings indicate that much of the spatial variation seen was explained by patient and treatment variables and that location was not an important predictor after controlling for receipt of NCCN-adherent care. With the exception of early stages, not receiving guideline care increased the hazards of dying by at least 20% in almost all groups examined.

In British Columbia, differences in ovarian cancer survival were observed by five Health Authority Regions.[37] Despite having a universal healthcare system, the respective authors determined the geographic differences were due to variations in receipt of appropriate treatment and tumor characteristics.[37] A study of ovarian cancer mortality by Hospital Referral Region found significant geographic patterns among a Medicare population that did not persist after controlling for receipt of cancer-directed therapy.[35] In contrast, a previous spatial analysis in California using CCR data from 1996-2006, showed that geographic location at the census tract-level was associated with survival among women with late-staged disease, even after adjusting for treatment.[5] The authors, however, were unable to control for several important predictors, such as comorbidity status, which negatively impacted survival in the current study.

Some researchers have investigated geographic differences in OC mortality using sophisticated spatial models but without considering treatment. A study in Spain looked at smoothed relative risk of ovarian cancer mortality by municipality, allowing for small area variation within municipality, and found evidence of differences in the distribution of deaths but did not consider treatment.[40] The authors speculated that these findings may be attributed to environmental or occupational factors. In the United States, an age-adjusted county-level spatial analysis of ovarian cancer mortality from 2000-2014 identified several significant clusters

nationwide including one in the Pacific Northwest and northern CA, which was also elevated in our crude models.[41]

We assessed two variables to examine access to care and geographic barriers. Our results indicate that distance traveled to receive care for ovarian cancer was associated with survival and was a better predictor than the distance between residential address and the closest high-QOC hospital. Women with longer travel journeys to their initial treatment location generally had a survival advantage over those traveling the shortest distances. While not well understood, this relationship has been observed frequently in the broader cancer literature, including among pancreatic,[63,64] liver,[64] colon, breast,[65] lung,[65] and ovarian cancer patients,[5] particularly those traveling to high volume centers.[66,67] A study in Northern England, however, did not find an association between travel times to hospitals attended by patients and ovarian cancer survival and concluded that being treated at a cancer center was a better survival determinant.[65]

Traveling further to receive care has been associated with superior cancer outcomes, yet proximity to specialized care, such as high volume hospitals, cancer centers, and gynecologic oncologists, has been correlated with better survival.[5,23,38,39] Over one-third of women nationwide live >50 miles from a gynecologic oncologist.[38] A single-site study looking at patients with incident gynecologic malignancies at a National Cancer Institute-designated center in Maryland, found that women residing the greatest distances from the respective hospital were most likely to die before completing their treatment.[68] In a national analysis of proximity to gynecologic oncologists and ovarian cancer death rates, increasing distance from these specialized doctors increased the odds of dying from ovarian cancer by almost 60%.[39]

In our study population, high-QOC hospitals were not found to be distributed evenly across California, and living closer to a high-QOC hospital did not significantly improve ovarian

cancer-specific survival. Our prior work found that greater distances from these hospitals increased the likelihood of women receiving non-adherent care,[19] yet our current analysis found that it generally did not affect ovarian cancer-specific survival after accounting for treatment received. Proximity did appear to impact women in several subgroups, however. For women in the lowest SES category and those of other race, living furthest from a high-QOC hospital was associated with worse outcomes. Interestingly, among non-Hispanic black women, greater distance from these hospitals was protective. On the other hand, greater distances traveled to initial treating hospital were associated with better survival for non-Hispanic white, Hispanic and Asian and Pacific Islander women, yet there was no correlation between longer journeys and improved outcomes among non-Hispanic black women. More research is needed to better understand the association between race/ethnicity and geographic access variables.

Factors influencing patients' ability and willingness to travel are multifactorial. Some have suggested that SES, insurance status, race, and age are predictors of patient's likelihood to travel.[68] While we were unable to identify why traveling longer distances was advantageous to survival, one probable explanation is that women who are able to travel farther have more resources or awareness of them to do so, whether that is financial resources, a product of social support, or both.[64] This financial burden a cancer diagnosis poses may negatively affect women from lower SES backgrounds and make it more difficult for women to travel. A survey of cancer patients identified costs of travel to/from treatment as a top factor considered in treatment decisions.[69] Furthermore, minority women are disproportionately impacted by transportation issues. In a cross-sectional analysis of barriers to treatment among cancer patients, Hispanics and blacks were more likely than whites to report transportation as an obstacle to treatment.[70] Access to a vehicle, distance of the treating facility, and finding somebody to drive patients to care were

all cited as reasons to forgo care.[70] Women who are already more healthcare-oriented may be more likely to travel to access centers with expert care.[64] They may also be more cognizant of available resources within the centers, such as social workers who may help connect them to needed services.[68,69]

This is the first study to our knowledge examining spatial variations in ovarian cancer survival at a geocoded address-level resolution. Prior work linking location and ovarian cancer mortality have used larger units of analysis.[5,41] One possibility for the lack of association found is that individual-level data avoids the issue of induced clustering that may result from census level geocoding. Another possibility is that we may not accurately be capturing temporal variability in spatial patterns as the impact of location on survival was averaged over a long period of time. As observed in the spatio-temporal analysis (Appendix Figure B), variations in the relationship between location and survival by time period appear to exist. Future studies should further examine these trends in the relationship between geographic location, geographic access to services, and ovarian cancer survival over time, as this time period coincides with many important changes in government administrations that may impact health care access.

This work has several strengths including the large cohort size and number of years examined, which provided considerable follow-up time to examine spatial patterns in ovarian cancer mortality. In addition, the availability of geocoded location of patient's residence allowed us to examine its influence at a finer resolution than previous work, which have typically used larger units of analysis such as zip code and census block. We were also able to use a novel statistical method to test the significance of geographic location while simultaneously controlling for covariates. With the use of ArcGIS Network analyst, the distances between location and hospitals are more precise than the calculation of the Euclidian or "straight-line" distance

between two points. Lastly, we were able to adjust for the impact of comorbidities on survival, a noted gap in previous work.[5]

Our analyses were, however, limited by the data available. This is a retrospective study that uses registry data, which introduces the possibility of unmeasured confounders. We were unable to account for the use of public transportation or preferences in travel routes. We were also limited by the lack of information on physician type and specialty as this information is not included in the CCR. We were unable to determine the extent of residual disease which has been shown to affect mortality. Furthermore, the reporting hospital may not be the main facility where care was received, and the chance exists that some satellite clinics report under one hospital. These situations are considered rare and are not likely to affect our results. The CCR only collects address at time of diagnosis and we therefore could not account for patient mobility. With distances being calculated based on the patient's address at baseline and with the inability to account for relocation, some misclassification may occur.

Conclusion

While geographic location is an independent predictor of ovarian cancer mortality in CA for women overall and those diagnosed in late stages, no significant association was found between location and survival in the fully-adjusted models. We did not find any evidence for an association between geographic location and ovarian cancer survival after taking into account sociodemographic, treatment, and geographic access variables. Ensuring receipt of treatment that meets the stage-specific NCCN guidelines is crucial for optimizing outcomes. Possible strategies for better treatment may include patient navigators, provision of transportation to hospitals, increasing satellite clinics in underserved areas, or increasing access to social workers that may help connect patients to services and address other stressors that disproportionately impact

certain women. Improving access to expert care facilities is necessary to making sure women of all race/ethnicities receive guideline-adherent care, particularly among women who are socioeconomically disadvantaged.

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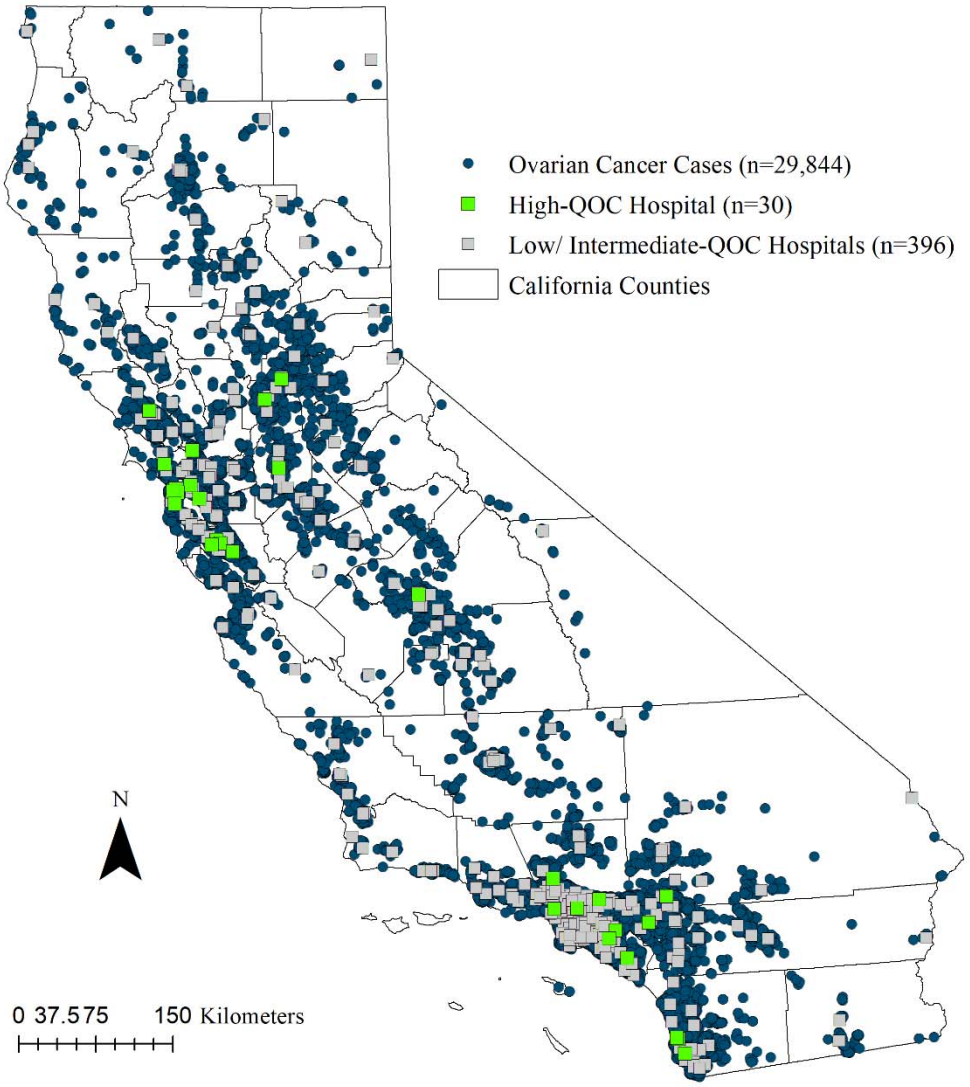

Figure 2.1 Distribution of Cases of Epithelial Ovarian Cancer and Treating Hospitals in California between 1996-2014

The distribution of epithelial ovarian cancer cases diagnosed between 1996 and 2014 in California. Hospitals treating cases during those years are displayed by the category of quality of care determined to be delivered.

Abbreviations: *QOC,* Quality of care

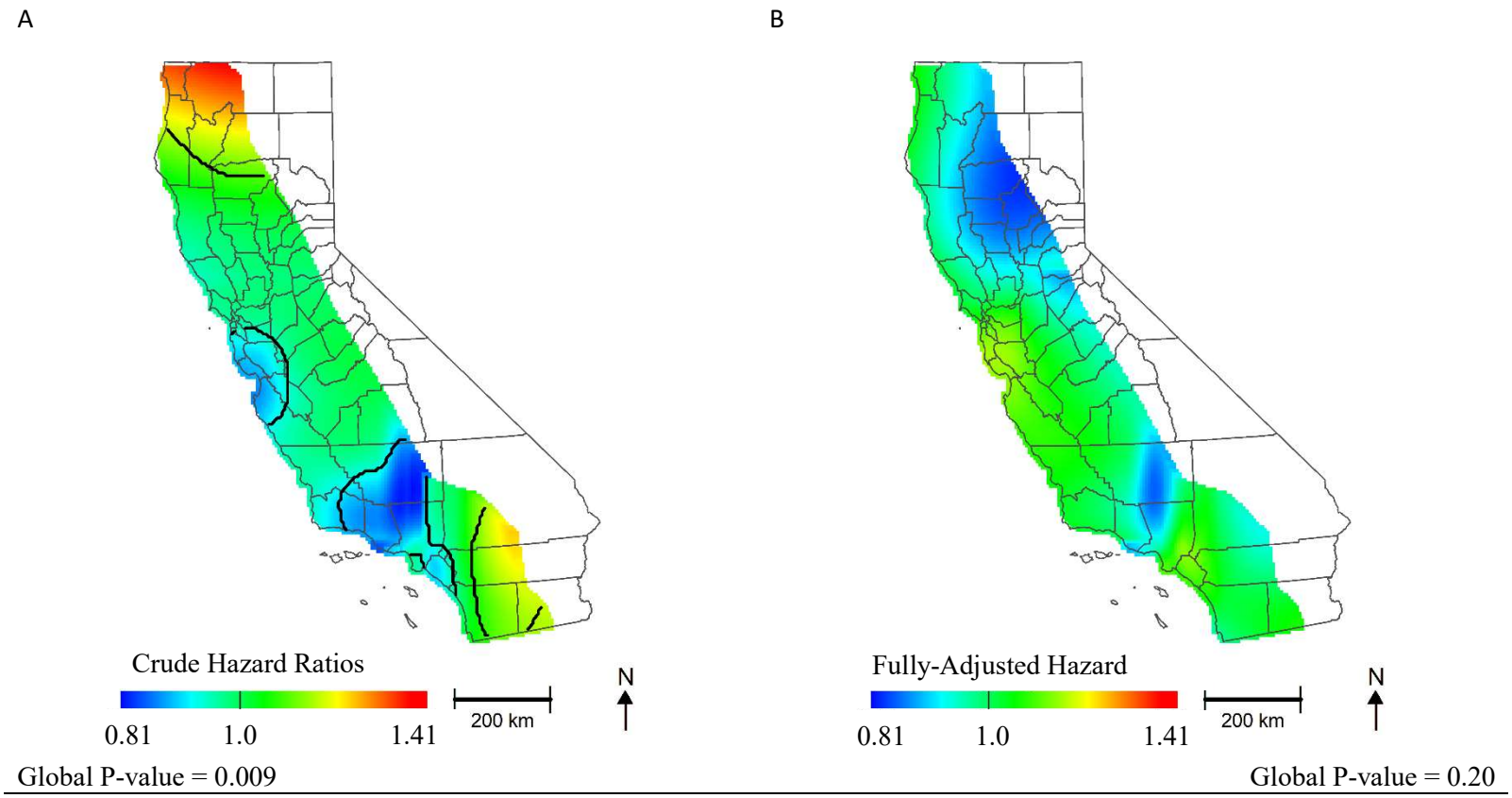

Figure 2.2: Geographic location and ovarian cancer-specific survival in California among Stages I-IV

(A) The crude and (B) fully-adjusted effect of geographic location on ovarian cancer-specific survival for all stages combined (Stages I-IV). The fully-adjusted map displays the hazard ratios for location after controlling for age, cancer stage, tumor histology, tumor grade, tumor size, race, socioeconomic status, insurance, marital status, year of diagnosis, comorbidity status, treatment adherence, hospital quality, distance traveled for care, distance of closest high quality-of-care hospital. Areas delineated by contour lines represent statistically significant geographic areas.

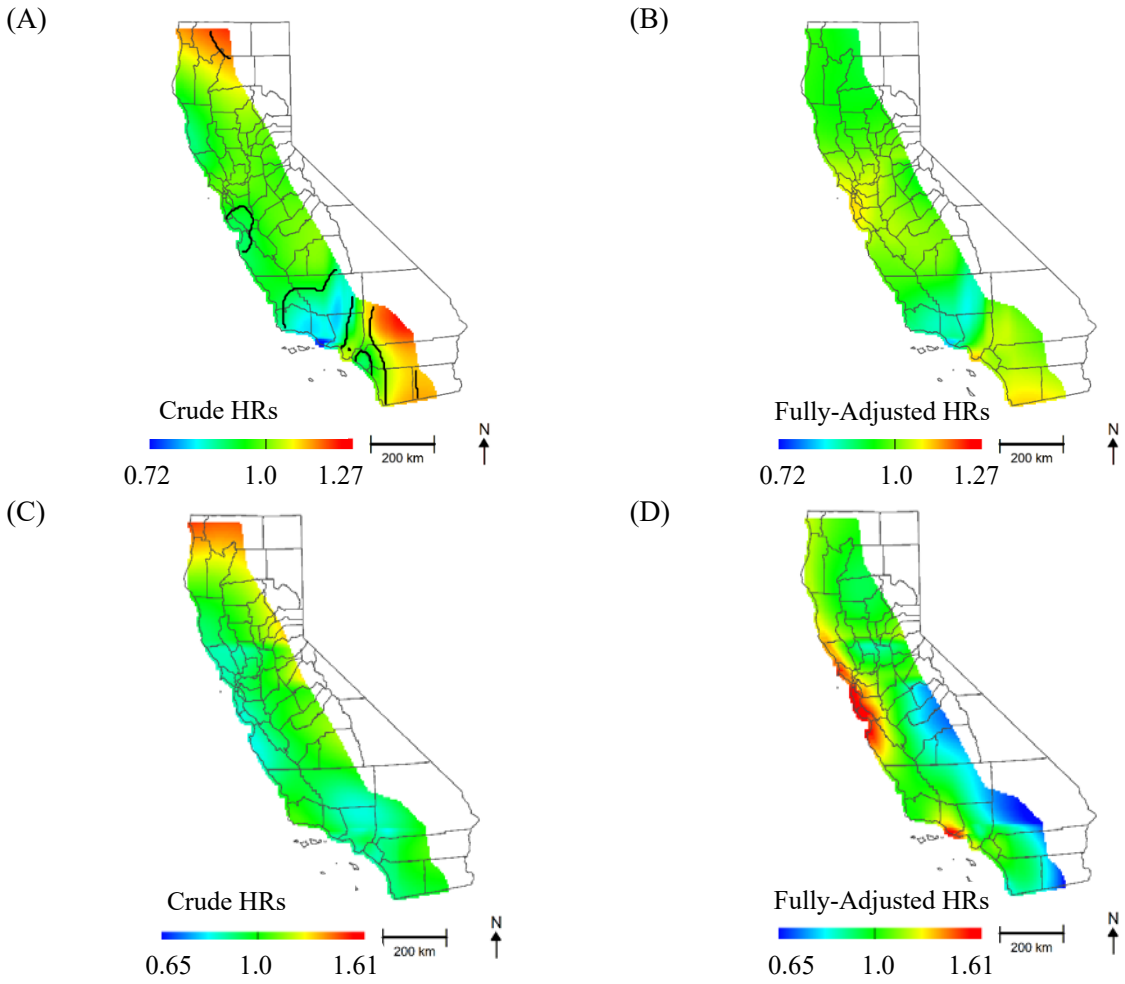

Figure 2.3: Geographic Location and Ovarian Cancer-Specific Survival in California Among Early and Late Stages, 1996-2014

(A) The crude and (B) fully-adjusted effect of geographic location on ovarian cancer-specific survival for late stages (Stages III & IV). (C) The crude and (D) fully-adjusted effect of geographic location on ovarian cancer-specific survival for early stages (Stages I & II). The fully-adjusted maps display the hazard ratios for location after controlling for age, cancer stage, tumor histology, tumor grade, tumor size, race, socioeconomic status, insurance, marital status, comorbidity status, treatment adherence, hospital quality, distance traveled for care, distance of closest high quality-of-care hospital. The global *P*-values for panels A, B, C and D are 0.002, 0.33, 0.408, and 0.98, respectively. Areas delineated by contour lines represent statistically significant geographic areas.
Abbreviations: *HR,* Hazard Ratios

Table 2.1: Patient Characteristics and Fully-Adjusted Hazard Ratios for All Stages Combined (n=29,844)

Characteristic	N (%)	HR	95% CI	*P* Value	Group *P*[a]
Age					
Median (SD)	60 (14.9)	1.03	(1.02, 1.03)	<0.001	
Race/Ethnicity					
Non-Hispanic White	18920 (63.4)	1.00	Ref		
Non-Hispanic Black	1416 (4.7)	1.19	(1.08, 1.30)	<0.001	<0.001
Hispanic	5749 (19.3)	0.96	(0.90, 1.02)	0.197	
Asian / Pacific Islander	3564 (11.9)	0.96	(0.89, 1.04)	0.351	
Other	195 (0.7)	0.87	(0.68, 1.10)	0.243	
Socioeconomic Status (SES)					
Lowest SES	4037 (13.5)	1.18	(1.10, 1.27)	<0.001	<0.001
Lower-Middle SES	5435 (18.2)	1.19	(1.12, 1.26)	<0.001	
Middle SES	6324 (21.2)	1.09	(1.03, 1.16)	0.004	
Higher-Middle SES	6860 (23.0)	1.11	(1.01, 1.21)	0.024	
Highest SES	7188 (24.1)		Ref		
Insurance Type					
Managed Care	14150 (47.4)	1.00	Ref		<0.001
Medicare	7653 (25.6)	0.97	(0.92, 1.01)	0.151	
Medicaid	2725 (9.1)	1.10	(1.01, 1.19)	0.021	
Other Insurance	3825 (12.8)	0.94	(0.88, 1.01)	0.096	
Not insured	889 (3.0)	1.26	(1.11, 1.45)	<0.001	
Unknown	602 (2.0)	1.19	(0.76, 1.87)	0.435	
Tumor Size, mm					
<50	3734 (12.5)	1.00	Ref		<0.001
50-99	5885 (19.7)	1.07	(0.96, 1.18)	0.216	
≥100	9336 (31.3)	0.98	(0.92, 1.05)	0.572	
Unknown	10889 (36.5)	1.18	(1.10, 1.26)	<0.001	
Tumor Grade					
1	10889 (8.0)	1.00	Ref		<0.001
2	4359 (14.6)	1.10	(0.72, 1.67)	0.668	
3	10051 (33.7)	1.19	(0.79, 1.79)	0.398	
4	4192 (14.0)	1.22	(0.82, 1.81)	0.329	
Unknown	8868 (29.7)	1.46	(0.97, 2.20)	0.067	
Histology					
Serous	12857 (43.1)	1.00	Ref		<0.001
Mucinous	1900 (6.4)	1.26	(1.06, 1.50)	0.007	
Endometrioid	3318 (11.1)	0.79	(0.68, 0.91)	0.001	
Clear cell	1829 (6.1)	1.26	(1.14, 1.40)	<0.001	
Adenocarcinoma, NOS	3178 (10.6)	1.39	(1.31, 1.48)	<0.001	
Others	6762 (22.7)	1.21	(1.13, 1.31)	<0.001	

Stage					
Stage 1	7238 (24.3)	1.00	Ref		<0.001
Stage 2	2496 (8.4)	2.94	(2.04, 4.23)	<0.001	
Stage 3	11263 (37.7)	6.61	(5.85, 7.48)	<0.001	
Stage 4	8847 (29.6)	10.84	(9.44, 12.45)	<0.001	
Marital Status					
Single	14688 (49.2)	1.00	Ref		
Married	15156 (50.8)	0.88	(0.83, 0.93)	<0.001	
Treatment Adherence					
Adherent	11419 (38.3)	1.00	Ref		
Non-Adherent	18425 (61.7)	1.29	(1.23, 1.35)	<0.001	
CCS					
0	14219 (47. 6)	1.00	Ref		<0.001
1	6807 (22.8)	1.13	(1.07, 1.20)	<0.001	
2+	6726 (22.5)	1.03	(0.97, 1.09)	0.289	
Unknown	2092 (7.0)	1.00	(0.92, 1.10)	0.917	
Year Category					
1996 – 2002	9557 (32.0)	1.00	Ref		0.44
2003 – 2006	8053 (27.0)	0.98	(0.93, 1.02)	0.301	
2007 – 2014	12234 (41.0)	0.97	(0.93, 1.02)	0.241	
Hospital Quality-of-Care					
Low	6990 (23.4)	1.07	(0.97, 1.18)	0.178	0.54
Intermediate	17275 (57.9)	1.00	(0.95, 1.06)	0.921	
High	5579 (18.7)	1.00	Ref		
Distance traveled to care					
<6 km	5969 (20.0)	1.00	Ref		0.01
6-9 km	5969 (20.0)	0.93	(0.84, 1.02)	0.127	
10-16 km	5968 (20.0)	0.89	(0.80, 0.98)	0.025	
17-32 km	5969 (20.0)	0.86	(0.78, 0.95)	0.003	
>32 km	5969 (20.0)	0.87	(0.79, 0.96)	0.006	
Closest High-QOC Hospital					
<9 km	5969 (20.0)	1.00	Ref		0.63
9-14 km	5969 (20.0)	1.02	(0.96, 1.09)	0.554	
15-24 km	5968 (20.0)	1.07	(0.95, 1.20)	0.259	
25-48 km	5969 (20.0)	0.99	(0.92, 1.05)	0.676	
>48 km	5969 (20.0)	0.96	(0.89, 1.04)	0.300	

[a] Group *P* are the *P*-values for the Wald chi-square tests examining the alternative hypothesis that at least one of the group levels has a direct effect on survival. These were only conducted on variables with three or more categories.

Abbreviations: *CI,* Confidence Interval*; CCS,* Charlson Comorbidity Score; *HR,* Hazard Ratios*; km,* kilometers; *NCCN*, National Comprehensive Cancer Network; *NOS,* Not Otherwise Specified; *QOC*, Quality-of-Care; *SES,* Socioeconomic Status

Table 2.2: Select Patient Characteristics by Geographic Access Variables (n=29,844)

	Median Survival	Distance Traveled to Care (km)			Closest High-QOC hospital (km)		
	(months)	Mean	Median	Range	Mean	Median	Range
Total	34.5	28.3	12.7	(0.01 - 1087.98)	37.4	19.3	(0.20 - 500.95)
Stage							
Early	73.7	28.5	13.6	(0.14 - 847.24)	35.5	18.5	(0.20 - 500.95)
Late	24.6	28.2	12.3	(0.01 - 1087.98)	38.3	19.7	(0.27 - 489.50)
Race/Ethnicity							
Non-Hispanic White	35.3	30.7	12.8	(0.17 - 1087.98)	42.6	21.6	(0.20 - 500.95)
Non-Hispanic Black	23.0	19.5	12.0	(0.01 - 583.07)	22.9	16.2	(0.61 - 282.32)
Hispanic	32.2	24.6	12.5	(0.18 - 792.78)	33.6	18.1	(0.38 - 484.07)
Asian / Pacific Islander	38.6	22.1	12.2	(0.14 - 819.64)	20.3	13.0	(0.27 - 480.84)
Other	37.1	40.8	15.2	(1.00 - 685.90)	57.7	20.9	(0.66 - 467.50)
Socioeconomic Status							
Lowest SES	28.2	28.0	11.5	(0.23 - 791.77)	43.2	17.8	(0.38 - 497.99)
Lower-Middle SES	30.1	31.4	12.9	(0.14 - 1087.98)	48.1	22.3	(0.39 - 484.07)
Middle SES	33.5	32.6	13.4	(0.01 - 808.23)	44.0	21.1	(0.20 - 500.95)
Higher-Middle SES	36.2	28.2	12.9	(0.26 - 847.24)	33.5	19.2	(0.26 - 483.74)
Highest SES	40.4	22.4	12.3	(0.23 - 955.27)	23.9	16.7	(0.23 - 258.17)

Abbreviations: *km*, kilometers; *QOC*, Quality-of-Care; *SES*, Socioeconomic Status

Table 2.3: Hazard Ratios for Geographic Access Variables by Race/Ethnicity

	Non-Hispanic White			Non-Hispanic Black			Hispanic			Asian/Pacific Islander			Other		
Distance Traveled to Receive Care															
			P = 0.05			*P* = 0.69			*P* < 0.05			*P* = 0.07			*P* = 0.98
	N(%)	HR	95% CI	N(%)	HR	95% CI	N(%)	HR	95% CI	N(%)	HR	95% CI	N(%)	HR	95% CI
<6km	3831(20.2)	1.00	Ref	291(20.6)	1.00	Ref	1099(19.1)	1.00	Ref	715(20.1)	1.00	Ref	33(16.9)	1.00	Ref
6-9 km	3716(19.6)	0.97	0.88,1.07	293(20.7)	0.91	0.71,1.16	1205(21.0)	0.86	0.75,0.99	718(20.1)	0.92	0.76,1.11	37(19.0)	0.83	0.25,2.73
10-16 km	3545(18.7)	0.91	0.81,1.02	345(24.4)	1.01	0.80,1.27	1241(21.6)	0.86	0.74,0.98	804(22.6)	0.90	0.75,1.09	33(16.9)	0.96	0.39,2.33
17-32 km	3657(19.3)	0.91	0.82,1.01	300(21.2)	0.94	0.73,1.20	1226(21.3)	0.81	0.70,0.93	750(21.0)	0.75	0.61,0.92	36(18.5)	1.14	0.42,3.14
>32 km	4171(22.0)	0.88	0.79,0.97	187(13.2)	0.85	0.64,1.12	978(17.0)	0.92	0.77,1.10	577(16.2)	0.89	0.70,1.12	56(28.7)	0.27	0.07,1.09
Distance to Nearest High-QOC Hospital															
			P = 0.47			*P* = 0.03			*P* < 0.48			*P* = 0.73			*P* = 0.10
	N(%)	HR	95% CI	N(%)	HR	95% CI	N(%)	HR	95% CI	N(%)	HR	95% CI	N(%)	HR	95% CI
<9km	3418(18.1)	1.00	Ref	308(21.8)	1.00	Ref	1121(19.5)	1.00	Ref	1083(30.4)	1.00	Ref	39(20.0)	1.00	Ref
9-14 km	3399(18.0)	1.03	0.95,1.12	319(22.5)	0.90	0.71,1.13	1275(22.2)	1.10	0.95,1.26	939(26.3)	0.88	0.73,1.05	37(19.0)	0.68	0.22,2.13
15-24 km	3547(18.7)	1.09	0.96,1.24	436(30.8)	0.72	0.57,0.92	1267(22.0)	1.14	0.98,1.31	692(19.4)	0.94	0.77,1.13	26(13.3)	1.75	0.49,6.33
25-48 km	4034(21.3)	0.99	0.92,1.06	234(16.5)	0.70	0.54,0.91	1050(18.3)	1.14	0.92,1.40	619(17.4)	0.92	0.75,1.14	32(16.4)	4.12	1.34,12.67
>48 km	4522(23.9)	0.97	0.90,1.05	119(8.4)	0.87	0.64,1.20	1036(18.0)	1.06	0.91,1.24	231(6.5)	0.96	0.74,1.25	61(31.3)	1.29	0.42,3.94

* *P*-values are for the Wald chi-square tests examining the alternative hypothesis that at least one of the levels for the distance variables has a direct effect on survival.

Abbreviations: *CI*, confidence interval; *HR*, hazard ratio; *km*, kilometers; *QOC*, quality-of-care; *Ref*, Referent
Note: Models were adjusted for age, cancer stage, tumor histology, tumor grade, tumor size, race, socioeconomic status, insurance, marital status, comorbidity status, treatment adherence, hospital quality, year of diagnosis, distance traveled for care, distance of closest high quality-of-care hospital.

Table 2.4: Hazard Ratios for Geographic Access Variables by Socioeconomic Status

	Lowest SES			Lower-Middle SES			Middle SES			Higher-Middle SES			Highest SES		
Distance Traveled to Receive Care															
			P = 0.02			*P* < 0.01			*P* < 0.05			*P* = 0.32			*P* = 0.85
	N(%)	HR	95% CI	N(%)	HR	95% CI	N(%)	HR	95% CI	N(%)	HR	95% CI	N(%)	HR	95% CI
<6km	924(22.9)	1.00	Ref	1127(20.7)	1.00	Ref	1239(19.6)	1.00	Ref	1357(19.8)	1.00	Ref	1322(18.4)	1.00	Ref
6-9 km	828(20.5)	0.96	0.83,1.11	1027(18.9)	0.93	0.82,1.07	1212(19.2)	1.01	0.89,1.15	1303(19.0)	0.88	0.77,1.01	1599(22.2)	1.03	0.92,1.16
10-16 km	858(21.3)	0.86	0.74,0.99	1070(19.7)	0.95	0.83,1.08	1178(18.6)	0.91	0.80,1.03	1382(20.1)	0.86	0.74,1.00	1480(20.6)	0.99	0.87,1.11
17-32 km	672(16.6)	0.77	0.65,0.91	1039(19.1)	0.84	0.74,0.96	1257(19.9)	0.90	0.79,1.02	1420(20.7)	0.88	0.76,1.01	1581(22.0)	0.99	0.88,1.12
>32 km	755(18.7)	0.87	0.74,1.03	1172(21.6)	0.78	0.68,0.89	1438(22.7)	0.86	0.76,0.98	1398(20.4)	0.83	0.68,1.02	1206(16.8)	1.05	0.92,1.20
Distance to Nearest High-QOC Hospital															
			P = 0.18			*P* = 0.43			*P* = 0.48			*P* = 0.38			*P* = 0.11
	N(%)	HR	95% CI	N(%)	HR	95% CI	N(%)	HR	95% CI	N(%)	HR	95% CI	N(%)	HR	95% CI
<9km	814(20.2)	1.00	Ref	851(15.7)	1.00	Ref	1165(18.4)	1.00	Ref	1433(20.9)	1.00	Ref	1706(23.7)	1.00	Ref
9-14 km	902(22.3)	1.13	0.98,1.32	1094(20.1)	0.94	0.82,1.08	1163(18.4)	1.01	0.89,1.15	1264(18.4)	1.01	0.89,1.15	1546(21.5)	1.00	0.89,1.13
15-24 km	691(17.1)	1.12	0.94,1.32	1006(18.5)	1.05	0.91,1.21	1196(18.9)	1.03	0.91,1.18	1480(21.6)	1.13	0.97,1.33	1595(22.2)	0.90	0.80,1.02
25-48 km	553(13.7)	1.08	0.90,1.30	955(17.6)	1.04	0.90,1.19	1185(18.7)	1.05	0.93,1.20	1529(22.3)	0.93	0.81,1.08	1747(24.3)	0.92	0.82,1.04
>48 km	1077(26.7)	1.22	1.03,1.43	1529(28.1)	0.97	0.84,1.11	1615(25.5)	0.95	0.83,1.08	1154(16.8)	1.01	0.87,1.16	594(8.3)	0.84	0.72,0.99

* *P*-values are for the Wald chi-square tests examining the alternative hypothesis that at least one of the levels for the distance variables has a direct effect on survival.

Abbreviations: *CI*, confidence interval; *HR*, hazard ratio; *km*, kilometers; *QOC*, quality-of-care; *Ref*, Referent; *SES*, socioeconomic status
Note: Models were adjusted for age, cancer stage, tumor histology, tumor grade, tumor size, race, socioeconomic status, insurance, marital status, comorbidity status, treatment adherence, hospital quality, year of diagnosis, distance traveled for care, distance of closest high quality-of-care hospital.

CHAPTER 3

Ambient Air Pollution and its Role in Ovarian Cancer Survival

Abstract

Background: Ovarian cancer continues to be the deadliest of the gynecological cancers. Limited evidence suggests that spatially-varying environmental exposures may contribute to ovarian cancer mortality. In addition, air pollution exposure is increasingly being examined to assess its impact on survival from various cancers. This study aims to determine the effect of cumulative exposure to ambient ozone, particulate matter with diameter less than 2.5 microns ($PM_{2.5}$), nitrogen dioxide (NO_2), and a surrogate measure of local traffic (distance to major roadways) on disease-specific survival after an ovarian cancer diagnosis.

Methods: Women diagnosed with epithelial OC between 1996 and 2014 were identified through the California Cancer Registry and followed through December 31, 2016. Ozone, $PM_{2.5}$, and NO_2 data was extracted from California Air Resources Board's (CARB) online database, Air Quality and Meteorological Information System (AQMIS). Women's geocoded addresses were linked to the exposure data. Daily maximum 8-hour values for ozone concentrations and daily means for $PM_{2.5}$ and NO_2 were averaged per month and calculated over each women's survival period. Residential distance from closest major roadways was also examined. Cox proportional hazards models were used to assess the risk of OC-specific death due to average ozone, $PM_{2.5}$, NO_2 exposure, and distance to major roadways, controlling for sociodemographic variables, disease-related factors, treatment received, and comorbidities. Pollutants were considered independently and in multipollutant models. Analyses were additionally stratified by stage of disease diagnosis, race/ethnicity and socioeconomic status (SES).

Results: Mean levels of exposure for ozone, $PM_{2.5}$, and NO_2 were 40.4 parts per billion (ppb), 12.18 $\mu g/m^3$, and 16.1 ppb, respectively. Average distance to a major roadway was 1,337 meters.

Significant differences were observed in $PM_{2.5}$ and NO_2 concentration levels by stage of diagnosis, with exposure levels increasing with advancing stage. Differences were also observed by race/ethnicity and SES. Among those living in the highest exposure quartile of $PM_{2.5}$ and NO_2 were Hispanic and Non-Hispanic black women, and those in the lower SES groups. Ozone and distance to road were not associated with survival in adjusted single pollutant models. In fully-adjusted multipollutant models including $PM_{2.5}$, ozone, and distance to nearest major road, an interquartile range (IQR) increase in $PM_{2.5}$ (Hazard Ratio [HR], 1.45; 95% Confidence Interval [CI], 1.41-1.49) and ozone (IQR HR, 1.03; 95% CI, 1.00-1.05) were associated with worse prognosis. Similarly, NO_2 was associated with poor survival in multipollutant models. The impact of the air pollutants was greatest among those diagnosed in early stages.

Conclusions: Our analyses are suggestive of a potential association between OC survival and NO_2 and $PM_{2.5}$ exposure in California, independent of sociodemographic and treatment factors. Future work should consider interventions to reduce excess exposure to air pollution among women diagnosed with ovarian cancer.

Introduction

Ovarian cancer (OC) has the highest mortality of all gynecological cancers.[1] In the United States, this malignancy is responsible for approximately 14,000 deaths a year.[2] Less than half of women diagnosed with OC will survive 5 years post-diagnosis.[3] Among the factors recognized as impacting OC survival are cancer characteristics such as stage, histology, and grade, and individual-level factors including age, race, socioeconomic status (SES), insurance, and treatment received.[1,4–8] Survival rates have been found to significantly differ by sociodemographic variables, disproportionally impacting non-Hispanic Black women[4,9–13] and women from lower SES backgrounds even when the same treatment is received.[4,5] Recently, geographic location has been implicated as an independent predictor of OC mortality.[5,14] Evidence suggesting geographic variations in OC survival and unexplained outcome differences observed by race/ethnicity and SES warrant further investigation into the potential role the environment may play in OC survival.

Evidence is mounting that air pollution exposure may not only be associated with greater morbidity, but increasingly with cancer incidence and mortality.[15–20] Ambient air pollution is considered a carcinogen by the International Agency for Research on Cancer (IARC) and environmental factors are increasingly being linked to OC mortality.[21] Although the mechanisms by which air pollutants contribute to cancer development and survival are not entirely understood, a few hypothesized pathways exist. The carcinogenic properties of pollutants such as particulate matter (PM) have been found to induce oxidative stress on epithelial cells.[22,23] This in turn produces reactive oxygen species (ROS) which have the potential to either directly damage DNA or create inflammation that then generates ROS.[22] Furthermore, the genotoxic properties of PM can promote cancer growth.[23] Ozone and Nitrogen Dioxide (NO_2) are also oxidants with

similar potential to cause genetic damage.[22] This sustained inflammatory environment may affect responsiveness to treatment,[24] with persistently enhanced oxidative stress being associated with chemoresistance in epithelial ovarian cancer cells,[25] therefore possibly affecting survival after a diagnosis.

Limited evidence suggests that spatially-varying environmental exposures may contribute to ovarian cancer mortality. Using an ecological study design, researchers in Taiwan found that greater exposure to particulate matter with diameter less than 2.5 microns ($PM_{2.5}$) was significantly associated with OC mortality among the general population.[26] In Spain, researchers could not explain spatial variations found in survival by municipality, citing possible environmental or occupational influences.[27] Furthermore, a growing body of evidence suggests that exposure to higher levels of air pollution may independently shorten survival after a cancer diagnosis.[14,28–31] In California, census-tract level ozone and $PM_{2.5}$ have been correlated with worse outcomes among women diagnosed with OC in late stages.[14]

According to the American Lung Association, the five most polluted U.S. cities in terms of ozone levels and year round particle pollution are all in California.[32] California has the most comprehensive air monitoring network nationwide, which provides a rich spatial and temporal dataset for studying the relationship between air pollution exposure and health outcomes. Our objective was to determine the impact of cumulative residential exposure to ambient ozone, nitrogen dioxide (NO_2), and $PM_{2.5}$ on disease-specific survival after an OC diagnosis among California women, while studying their effects by stage of diagnosis. We also address a gap in the cancer survival and air pollution literature by considering differences by race/ethnicity and socioeconomic status.

Methods

We used a retrospective population-based study design to examine the impact of air pollution on OC survival. OC cases were obtained through the California Cancer Registry (CCR) for women with newly diagnosed invasive epithelial OC between 1996 and 2014, with follow-up through 2016. The CCR is known to have almost complete case reporting (approximately 99%) and follow-up data nearly as high (95%).[33,34] CCR data was linked to patient discharge data from California's Office of Statewide Health Planning and Development (OSHPD). To be eligible for the study, women had to be 18 years or older at diagnosis. Women were then excluded if their case was obtained through death record (n=309), had unknown stage (n=5,690), or had a germ cell or stromal tumor classification (n=268). A total of 29,844 women had complete data on survival time, other clinical information, and residential address. This study was approved by the Institutional Review Board of the University of California, Irvine (UCI 14-66/HS# 2014-1476).

Exposure Assessment

Air pollution data was extracted from California Air Resources Board's (CARB) online database, Air Quality and Meteorological Information System (AQMIS).[35] Ambient ozone levels, measured in parts per billion (ppb), nitrogen dioxide (ppb), and concentrations of $PM_{2.5}$ ($\mu g/m^3$) were retrieved from all operating monitoring sites throughout the study period (1996-2016). We obtained daily maximum 8-hour values for ozone concentrations and daily means for $PM_{2.5}$ and NO_2. These daily values were then averaged by month for each monitoring site. Ozone and NO_2 values were available for the entire study period while $PM_{2.5}$ was only available beginning 1999. Models with $PM_{2.5}$ were run using a subset of 25,976 women who were diagnosed on or after January 1, 1999.

For all three pollutants, monthly state-wide prediction surfaces at approximately 4 x 4 km spatial resolution were created using ordinary kriging in a Geographic Information System (ArcGIS version 10.7.1, ESRI; Redlands, CA) for every month of the study period. This geostatistical interpolation method, which has shown to perform better than other exposure methods,[36] used the monthly concentrations for each respective air pollutant at the monitoring sites, assuming correlation between the sites, to create estimates of exposure throughout California. Exposure was assigned to women by spatially joining their geocoded residential location at time of diagnosis to the exposure data for analysis using ArcGIS. The linked exposure was averaged over the women's survival period, starting from the date of diagnosis to the date of death or last follow up.

As a measure of local traffic, we included residential distance from primary and secondary roads. We used the United States Census Bureau's TIGER/line file® (Topographically Integrated Geographic Encoding and Referencing System) and calculated the shortest distance from geocoded address to nearest major road using ArcGIS. Three women were excluded from primary analyses because of residence on Catalina Island, which requires travel by ferry to reach mainland CA. As a sensitivity analyses, we also examined the impact of distance from major roadways including these 3 women (n=29,844).

Covariates

Several important covariates were included in the adjusted models. Age at time of diagnosis was modeled as a continuous variable. Race/ethnicity was categorized as non-Hispanic white, non-Hispanic black, Hispanic, Asian/Pacific Islander, and other/unknown. We controlled for insurance (managed care, Medicare, Medicaid, other insurance, not insured, and unknown insurance status) and marital status. SES was grouped into quintiles based on either the Yost

Score[37] if diagnosed before 2006 and the Yang index[38] for those diagnosed after. We also controlled for the following known determinants of survival: stage at diagnosis (International Federation of Gynecology and Obstetrics- Stages I-IV), tumor histology, grade, and size, comorbidity status, and treatment received. The Deyo-adapted Charlson Comorbidity Score was used to assign comorbidity status and was grouped into quartiles (no comorbidities, one comorbidity, two or more comorbidities, and comorbidity status unknown).[39] We also included a binary variable indicating whether the women received guideline adherent care. The National Comprehensive Cancer Network treatment guidelines were used to define guideline adherence. These previously validated treatment recommendations have been found to be significantly associated with OC-specific survival.[40] They specify stage-specific guidance for surgery and chemotherapy, both of which must be adhered to for women to be considered having received guideline-adherent care. Lastly, we adjusted for the year of diagnosis.

Statistical Analyses

Descriptive statistics were run to determine any differences in covariates and exposures by stage at diagnosis. For categorical variables, chi-square tests were used whereas analysis of variances were conducted for continuous variables. Exposure levels were also assessed by race/ethnicity and SES. We used Cox Proportional Hazard models to the calculate the hazard ratios (HRs) and 95% confidence intervals (CI) between each pollutant and OC-specific survival. We explored the relationship between the different exposures (NO_2, ozone, $PM_{2.5}$, and distance to major roadways) and survival in single-pollutant models modeled as continuous linear variables and using penalized cubic splines. Multipollutant models were also fit for exposures that were not highly correlated.

We calculated survival in months from the date of diagnosis to the date of death due to OC or date of last follow up. Deaths due to other causes were censored. Models were adjusted for age at diagnosis, race/ethnicity, SES, insurance used, marital status, stage at diagnosis, tumor grade, histology, and size, comorbidity status, and treatment adherence. In secondary analyses, we also stratified by stage at diagnosis as follows: early stages (Stage I and Stage II), Stage III, and Stage IV. To assess the impact of air pollutants for select sociodemographic variables, multipollutant models were run stratified by race/ethnicity and SES. All statistical analyses were performed in R (R Software Version 3.4.4).

Results

Patient characteristics are presented in Table 3.1. The median age at diagnosis was 60 years of age, with women diagnosed at an early stage being generally younger (median of 54 years versus 66 years amongst stage IV women). Among the 29,841 women included in the analyses, 9,733 were diagnosed in early stages (21.5%), 11,262 in stage III (52.0%), and 8,846 in stage IV (26.5%). Median survival among all women was 34.5 months (2.9 years) and ranged from 73.7 months (6.1 years) among women diagnosed in early stages to 14.6 months (1.2 years) for those with a stage IV diagnosis. The majority of women were non-Hispanic white (63.4%), followed by Hispanic (19.3%), Asian/Pacific Islander (11.9%), non-Hispanic black (4.7%), and other race (0.7%). Asian/Pacific Islanders (44.7%) made up the largest proportion of women diagnosed in early stages, while non-Hispanic black women (38.6%) were the most likely to be diagnosed in Stage IV. Among women of highest SES, 26.2% were diagnosed in stage IV compared to 33.6% of women in the lowest SES quintile. Among women using Medicare insurance, 38.5% had a stage IV diagnosis compared to only 25.9% of the managed care insured women.

Distribution of Exposures

Across the study population, the mean NO_2, ozone, and $PM_{2.5}$ exposures over women's survival periods were 16.1 ppb, 40.4 ppb, and 12.18 $\mu g/m^3$, respectively. The average distance to a primary or secondary road was 1,337 meters. Cumulative exposures of NO_2 and $PM_{2.5}$ significantly differed by stage at diagnosis, while there were no differences by stage for ozone and distance from a major road. For NO_2 and $PM_{2.5}$, concentration levels increased with advancing stage of diagnosis. Table 3.2 shows the distribution of exposures overall and by stage.

Significant differences were also observed in exposure levels by sociodemographic variables (Table 3.3). Hispanic women had the highest mean levels of $PM_{2.5}$ exposure (12.85 $\mu g/m^3$) across survival time, followed by non-Hispanic black women (12.76 $\mu g/m^3$), whereas women of other race had the lowest mean concentrations (10.95 μg/m3). In contrast, women of other race had mean ozone exposures of 41.1 ppb, the highest of all racial/ethnic groups. Within each race/ethnicity, the proportion of non-Hispanic black women (34.4%) in the highest quartile of NO_2 exposure (> 19.6 ppb) was greater than that of other races. Similarly, non-Hispanic black women had the closest median distance to a major road.

Women of higher SES generally had lower levels of ambient exposure to $PM_{2.5}$ and NO_2 than women of lower SES. Among those of highest SES, about one-fifth (20.1%) were within the highest quartile of $PM_{2.5}$ exposure (> 13.91 $\mu g/m^3$) compared to over a third (34.2%) of women in the lowest SES group. Similarly, there was an inverse relationship between women's SES and the proportion living in the highest NO_2 quartile. Women in the lowest SES quintile had a median NO_2 exposure of 17.4 ppb while women in the highest group had a median of 15.9 ppb. Furthermore, as SES increased, so did distance from the nearest major roadway. There was no

significant difference in the proportion of each SES group that lived in the highest exposure quartile of ozone (P= 0.470).

Air Pollution and Survival

Penalized cubic splines relating ozone and $PM_{2.5}$ to log hazards were both approximately linear (Appendix Figure C.1). Therefore, the hazard ratios for these two pollutants are reported for an interquartile range (IQR) increase in concentrations. Based on the spline model for NO_2, exposure was categorized as: <20.0 ppb, 20.0-30.0 ppb, and >30.0 ppb. Hazard ratios for distance to a major road, modeled continuously with penalized cubic splines, are shown in Figure 3.1. $PM_{2.5}$ and NO_2 were highly correlated (Pearson's R = 0.80) and were not adjusted for simultaneously in any models. Ozone was not correlated with $PM_{2.5}$ (Pearson's R = -0.18) or NO_2 (Pearson's R= -0.22).

In single-pollutant overall models adjusted for cancer characteristics, sociodemographic and treatment factors (Table 3.4), higher $PM_{2.5}$ and NO_2 levels were significantly associated with worse prognosis. An interquartile range increase of $PM_{2.5}$ was associated with a 44% increase in hazards of survival (HR, 1.44; 95% CI, 1.40-1.47). Compared to women with overall NO_2 levels of <20.0 ppb, women who had cumulative exposures between 20.0-30.0 ppb (HR, 1.30; 95% CI, 1.25-1.36) and those with exposures >30.0 ppb (HR, 2.48; 95% CI, 2.32-2.66) had greater mortality. Adding other pollutants to the model did not change the associations for NO_2 (Table 3.5). Ozone had no independent influence on survival (IQR HR, 1.00; 95% CI, 0.98-1.02), and residential distance from primary and secondary roads was only associated with survival in the unadjusted model for distances less than 5 km (HR at median distance of 928 meters, 0.97; 95% CI, 0.96-0.98; Figure 3.1). Ozone exposure and distance from major roadways were not associated with survival when included in models with NO_2.

Greater cumulative exposure to $PM_{2.5}$ after an OC diagnosis was associated with poorer survival in multipollutant models with distance to road ($PM_{2.5}$ IQR HR, 1.45; 95% CI, 1.41-1.48), ozone ($PM_{2.5}$ IQR HR, 1.44; 95% CI, 1.41-1.48), and adjusting for both ($PM_{2.5}$ IQR HR, 1.45; 95% CI, 1.41-1.49) (Table 3.5). While ozone was not associated with survival in single-pollutant models, it became a significant determinant when added to models with $PM_{2.5}$ (IQR HR, 1.03; 95% CI, 1.00-1.05). Similarly, distance to major roads was also significantly associated with survival in multipollutant models but not in the adjusted single pollutant model. Figure 3.2 shows the hazards of dying significantly decreased as women lived further from a major roadway and then increased again at approximately 4 km. Results were similar in the sensitivity analysis including women from Catalina Island (results not shown).

Stage-stratified Results

Differences in the associations between the pollutants and survival were observed by stage at diagnosis. Results for the covariates in the stage-stratified analyses are presented in Appendix Table C.1. The effects of the exposure variables varied by stage, with pollutants having a greater influence on survival for women in early stages (Table 3.6). This was particularly true for the impact of NO_2 on survival. Among women in the highest category of exposure to NO_2 (>30.0 ppb), the adjusted hazards of dying were more than 4 times greater for early-staged women (HR, 8.13; 95% CI, 6.56-10.09; n=214) compared to those with a stage IV diagnosis (HR, 1.86; 95% CI, 1.68-2.06; n=598). Even among those with intermediate levels of NO_2 exposure, women in early stages (HR, 1.49; 95% CI, 1.30-1.70; n=1,752) had greater mortality than those with a Stage III (HR, 1.27; 95% CI, 1.19-1.35; n=2,066) or Stage IV (HR, 1.30; 95% CI, 1.22-1.39; n=1,708) diagnosis. Controlling for additional exposures in models with NO_2 did not change the magnitude of its effect (Table 3.6).

Similar to NO_2, associations between survival and $PM_{2.5}$ exposure also differed by stage at diagnosis and were statistically significant in all models. $PM_{2.5}$ likewise had a greater influence on survival among women diagnosed in early stages compared to women diagnosed in Stage III or Stage IV. Among early-staged women, mortality was higher for women with greater cumulative $PM_{2.5}$ exposure (IQR HR, 2.01; 95% CI, 1.84-2.19). Additionally, controlling for ozone and distance to major roads slightly increased the HRs of $PM_{2.5}$ (IQR HR, 2.07; 95% CI, 1.90-2.25). Greater $PM_{2.5}$ was also correlated with poorer prognosis for women in Stages III (IQR HR, 1.56; 95% CI, 1.50-1.62) and IV (IQR HR, 1.30; 95% CI, 1.25-1.35), however, adjustment for ozone and distance to nearest road did not appreciably change the hazards for $PM_{2.5}$.

Ozone had varying effects on survival based on the stage at diagnosis and the pollutant it was modeled with. Though not statistically significant, ozone was associated with worse outcomes when examined as the only pollutant for women with early staged (IQR HR, 1.05; 95% CI, 0.99-1.12) or Stage III (IQR HR, 1.01; 95% CI, 0.98-1.05) disease. This pollutant, however, becomes an important determinant when taking into account women's $PM_{2.5}$ exposure. A larger effect is seen for women diagnosed in early stages than those with stage III, and estimates are similar when modeled with $PM_{2.5}$ and distance to nearest major road. Among early staged women, an IQR increase in ozone when modeled with $PM_{2.5}$ and distance to major road was associated with an 11% increase in hazards of dying (95% CI, 1.04-1.18) whereas women with stage III disease had a 4% increase (95% CI, 1.00-1.08; Table 3.6). Associations among staged IV women were null.

Similar to ozone, the effect of distance to nearest primary or secondary road varied by stage, depending on co-pollutants in the model. For women in early stages, adjusting for $PM_{2.5}$

and ozone (Figure 3.3) magnified the associations observed in unadjusted and adjusted single pollutant models of distance to road. The hazards significantly and continuously decreased with increasing distance from a major road up to approximately 2,500 meters, at which point there was about a 40% decrease in hazards of dying. This protective effect was attenuated with increased distance and became significantly associated with worse survival among women in early stages at about 9,000 meters, although with wide confidence intervals.

As with early stages, residential distance from major roadways had a protective effect in models adjusting for $PM_{2.5}$ and ozone for women diagnosed in Stage III residing between 1,500 meters and 3,500 meters (Figure 3.3). Among women with Stage IV disease, distance was only an important predictor in unadjusted models, with close proximity to major roadways being significantly associated with worse outcomes. Hazard ratios then decreased with increasing distance from major roadways. Distance, however, was no longer a predictor of survival among Stage IV women after adjusting for other covariates, or in models with $PM_{2.5}$ and ozone. Across all stages, we only observed null associations for distance to primary or secondary roads when modeled with NO_2 (Appendix Figure C.2).

Race and SES-stratified Results

Results of the air pollutants stratified by race/ethnicity and SES can be found in Appendix Table C.2 and are reported for the multipollutant NO_2 and $PM_{2.5}$ models additionally adjusting for ozone and distance to major roadway. Several notable differences were observed in the impact of the air pollutants on survival by race/ethnicity. While overall, women with intermediate levels of cumulative NO_2 exposure (between 20.0-30.0 ppb) had increased hazards of dying, it was not a significant determinant among non-Hispanic black women (HR, 1.14; 95% CI, 0.95-1.37; n=342). Among women most exposed to NO_2 (>30.0 ppb), hazard ratios were

magnified among Hispanics (HR, 3.36; 95% CI, 2.84-3.97, n=332) and Asian/Pacific Islanders (HR, 3.22; 95% CI, 2.54-4.08, n=144). Ozone, which was only associated with survival in the non-stratified multipollutant models with $PM_{2.5}$, had a significant influence on survival among Asian/Pacific Islanders (IQR HR, 1.26; 95% CI, 1.10-1.45) in the NO_2 model.

With few exceptions, results for multipollutant models adjusting for $PM_{2.5}$ were similar to the overall model. Of particular note, non-Hispanic black women had attenuated hazard ratios in the multipollutant model with $PM_{2.5}$ (IQR HR, 1.21; 95% CI, 1.07-1.37) compared to the overall model. Distance to major roadway likewise did not impact survival in the respective model (median distance HR, 0.77; 95% CI, 0.38-1.55). Hazard ratios among women of other race were either larger (for $PM_{2.5}$) or null (for NO_2), however these estimates may be unreliable due to small sample sizes. Associations with survival in the SES-stratified models were similar to the overall results for the air pollutants including all data.

Other Determinants of Survival

As expected, sociodemographic factors were associated with survival and these associations were similar across exposure models (Appendix Table C.3). In the multipollutant model of all stages combined including NO_2, ozone, and distance to road, there was a significant increase in disease-specific mortality for every additional year of age at diagnosis. Women of non-Hispanic black race had 14% increased hazards of dying compared to non-Hispanic white women, while being of Asian/Pacific Islander (HR, 0.94; 95% CI, 0.89-1.00) and Hispanic (HR, 0.91; 96% CI: 0.87- 0.95) background was protective. Women from lower SES quintiles had significantly worse survival than those of higher SES. Hazards were 6%, 8%, 16%, and 13% higher for women of high-middle, middle, lower-middle, and lowest SES, respectively,

compared to those of highest SES. The effect of insurance on survival varied by type. Women with Medicare insurance had decreased hazards of dying (HR, 0.95; 95% CI, 0.91-0.99) whereas having Medicaid or not being insured was associated with worse outcomes (Appendix Table C.3). Furthermore, being married was protective (HR, 0.91; 95% CI, 0.88-0.94). Associations with sociodemographic factors in the stage-stratified analyses are presented in Appendix Table C.1.

Discussion

We sought to determine whether exposure to air pollution after an OC diagnosis was associated with disease-specific survival. This analysis found evidence that greater levels of NO_2 and $PM_{2.5}$ during follow-up time adversely impact women's survival and results were insensitive to the inclusion of additional pollutants. We also found that the impact of these pollutants was greater among women diagnosed in early stages and these findings were consistent among the various exposures examined. Overall, we did not find ozone and distance to major roads to influence women's outcomes, although they did have marginal effects once accounting for other pollutants.

Air pollution has been linked with increased cancer risk and mortality,[17–19,41–44] yet limited research has investigated the association between air pollution and cancer survival. In California, greater exposure to $PM_{2.5}$, PM_{10}, NO_2, and ozone was associated with shorter survival among patients diagnosed with lung cancer.[28] While we similarly found that $PM_{2.5}$ and NO_2 impacted survival, we did not see a significant independent association with ozone. The respective study did report that once stratifying by histology type, ozone no longer influenced lung cancer survival among many of the subgroups, while the other pollutants continued to be

significant predictors. Differences between the tissue origin of the cancers may partially explain the disparate findings, as the referenced study had similar ozone concentrations over patient's survival period (40.2 ppb versus 40.4 ppb in ours).

Another California-based study using CCR data examined the relationship between $PM_{2.5}$ exposure and survival after a liver cancer diagnosis and similarly found shorter survival among those with higher levels of exposure.[29] The hazard ratios presented, however, are smaller than the current study's in overall and stage-stratified models for a one standard deviation increase (5 $\mu g/m^3$) of $PM_{2.5}$ exposure versus our interquartile range of 4.42 $\mu g/m^3$. The reduced influence of $PM_{2.5}$ observed may be due to differences in survival time between the two cancers, with the study's reported overall median survival time being much lower (0.64 years) than the 34.5 months (2.9 years) among the current study's ovarian cancer patients. This shorter time frame may have attenuated the effect of $PM_{2.5}$ on survival. Living in areas with higher concentrations of $PM_{2.5}$ and PM_{10} was also found to be associated with adverse outcomes among women diagnosed with breast cancer.[31] Consistent with our findings, all three studies similarly found that the air pollutants had a greater impact on women diagnosed in early stages.

Each of the above referenced studies examined the independent influence of air pollutants on cancer survival yet none examined the effects of multiple exposures in the same model. While single pollutant models may be simpler and ease the interpretation of results, multipollutant models should also be considered given that people are concurrently exposed to many air pollutants.[45] Jerret et al. highlight the importance of including more than one pollutant in studies looking at health outcomes.[18] In the respective study, the authors suggest that NO_2 and ozone should be modeled together as the two pollutants are often inversely related. They also observed positive confounding when both were included in the model.[18] We similarly observed an increase

in the hazard ratios for ozone in all of the multipollutant models compared to ozone modeled alone.

The current study assessed the impact of local traffic measures by examining the role of residential distance to major roadways. Two out of the four studies specifically looking at the relationship between pollution exposure and cancer survival controlled for distance to primary and secondary US and state highways but both treated it as a confounder and did not consider its independent effect.[28,29] Interestingly, we found that distance to major roads was not an independent survival determinant in models only adjusted for individual-level factors, but became significant in multipollutant models controlling for PM2.5. We observed patterns between distance and survival that were generally the same in overall and stage-stratified models, with increasing residential distance being associated with reduced hazards, but then the risk of dying increasing again with greater distance, although mostly not significantly and with widening confidence intervals. For women overall, hazards increased after approximately 5km and 4km in the unadjusted and PM-adjusted models, respectively.

While residence near a major roadway has been found to be a detriment in other health outcomes,[46,47] our findings that risk increases at much further distances after accounting from both local and regional pollution suggest socioeconomic barriers may be at play, as these areas are generally more remote. While greater local vehicular emissions exposure is often associated with cities,[23] worse cancer outcomes have previously been observed among rural populations.[48] Previous research has found that gynecologic specialists are centered near metropolitan areas and increasing distance from a high quality hospital or appropriate care is linked to adverse ovarian cancer outcomes,[5,49,50] emphasizing that our findings may be due to potential issues with limited geographic access to needed services.

We also assessed differences in exposures by race/ethnicity and SES. Consistent with the literature, we found that women of non-Hispanic black and Hispanic backgrounds and those of lower SES generally had higher cumulative exposures of $PM_{2.5}$ and NO_2 than non-Hispanic white women and those of higher SES. Racial and ethnic minorities are often found to be disparately affected by environmental hazards. Non-Hispanic black and Hispanic women and those of lower SES often live in areas with greater environmental hazards and poorer air quality.[51–53] Data from an American-based panel study over a 20-year period found that levels of $PM_{2.5}$, PM_{10} and NO_2 were higher for black and Latino individuals compared to whites, despite overall declining pollution levels.[53] In California specifically, Cushing et al. found that minority communities disproportionately resided in areas with higher cumulative environmental burden.[51] A retrospective analysis of $PM_{2.5}$ and liver cancer survival in California additionally found that a greater proportion of patients living in places with higher $PM_{2.5}$ exposure were those of lower SES. [29]

Differences in OC survival by race, ethnicity, and SES still continue to be cited in the literature.[11–14,40] Since vulnerable communities share a larger burden of air contaminants,[53,54] we assessed whether some of the residual effects consistently observed between sociodemographic variables and disease-specific survival were potentially attributed to exposure to air pollution. We found that even after adjusting for environmental exposures such as $PM_{2.5}$ and NO_2, race/ethnicity and SES were still significantly associated with OC-survival, with non-Hispanic black women having worse survival compared to non-Hispanic white women. The hazard ratios for non-Hispanic black women were more pronounced in early stages than other races. Of particular mention, the effects from the air pollutants themselves were not as large among non-Hispanic black women in race-stratified analysis. Consideration of these two findings jointly

may emphasize the impact that other competing life stressors such as economic hardship, caretaking responsibilities, and challenging relationships, may have on non-Hispanic black women.[55]

We found that Hispanic women had reduced hazards of mortality in NO_2 and $PM_{2.5}$ models, despite having higher exposure levels compared to non-Hispanic white women. Asian/Pacific Islanders also had better outcomes in NO_2 models, although their exposure levels were slightly higher than non-Hispanic white women. Women of Asian and Latino background are increasingly associated with improved ovarian cancer outcomes,[11,56–58] although these associations are inconsistent. Hypothesized pathways are earlier age at diagnosis and potential differences in genetics which may affect responsiveness to treatment.[57,58] Other studies, however, have found comparable differences in survival between non-Hispanic white women and Hispanic[12] or Asian women[5] after adjusting for other sociodemographic factors, cancer characteristics, and treatment. Unlike non-Hispanic black women whose pollutant effects were lower in race-stratified models, exposure to the highest NO_2 levels (>30.0 ppb) had a markedly larger effect among Hispanic and Asian/Pacific Islanders, highlighting potential increased susceptibility.

Efforts to improve OC outcomes have emphasized that early diagnosis is critical to addressing the poor survival rates observed. With the majority of OC cases being diagnosed in late stages, many researchers have attempted to identify methods for early detection. The current findings that the effects of air pollution exposure are magnified among early stages is of public health concern given these women tend to have the best chances of survival. Studies assessing air pollution and overall cancer mortality have also found that higher exposure impacted those diagnosed in early stages.[43] One hypothesis is that women diagnosed in early stages live much

longer (73.7 months) compared to Stage III (33.8 months) and Stage IV (14.6 months); therefore the cumulative effects of pollution can be more easily distinguished. Recommendations to reduce exposure to air pollutants, particularly among early-staged women, would ensure that the advantages of early diagnosis are maximized. However, our study suggests that lowering exposure to high levels of $PM_{2.5}$ and NO_2 may improve survival for women diagnosed at any stage.

Strengths

The current study has several strengths. The CCR is a comprehensive cancer registry with individual-level data on many important determinants of survival. With availability of geocoded addresses, we were able to interpolate exposures to women's home addresses providing individual-level estimates. Furthermore, the study uses data from California's dense network of air monitors, which is one of the most extensive worldwide.[59] To our knowledge, this is only the second study to consider the relationship between air pollution and OC-specific survival,[14] and the first to do so using women's geocoded address and including women of all stages. Unlike other studies looking at the impact of air pollution on cancer survival that focused on single pollutant models, we also considered combinations of the pollutants. Lastly, unlike the limited studies examining the impact of air pollution exposure on cancer survival, our study also addresses differences by race/ethnicity and socioeconomic status, which fills an important gap in the current literature.

Limitations

This study was limited by the data available in the cancer registry. Treatment data was not updated after 6 months post-diagnosis, which may affect survival. Furthermore, all other

covariate values were collected at the time of diagnosis and not updated over the survival period. Furthermore, we could not account for individual behavior, such as the amount of time spent indoors versus outdoors or in traffic. Women with a cancer diagnosis may spend time indoors and therefore the potential for misclassification exists. However, this would likely drive the association towards the null. Since regional air monitors were used, air pollution exposure was calculated over a large scale which may not represent personal exposure or capture more local variations of traffic. We did, however, adjust for distance to primary and secondary roads as a proxy measure of local traffic emissions. Furthermore, there are areas in California with fewer air monitors, possibly resulting in less reliable exposures in sparse areas. Another limitation that may lead to exposure misclassification is that we were unable to adjust for residential relocation as the CCR only provides address at time of diagnosis which.

To conclude, our results provide evidence that greater levels of exposure to $PM_{2.5}$ and NO_2 may affect survival among women diagnosed with OC. Women of non-Hispanic black race and of lower SES had greater exposure to the pollutants and worse prognosis. Recommendations to reduce exposure to air pollution may provide an avenue for intervention. Future studies should examine the impact of reduced exposure interventions on OC-specific survival.[28]

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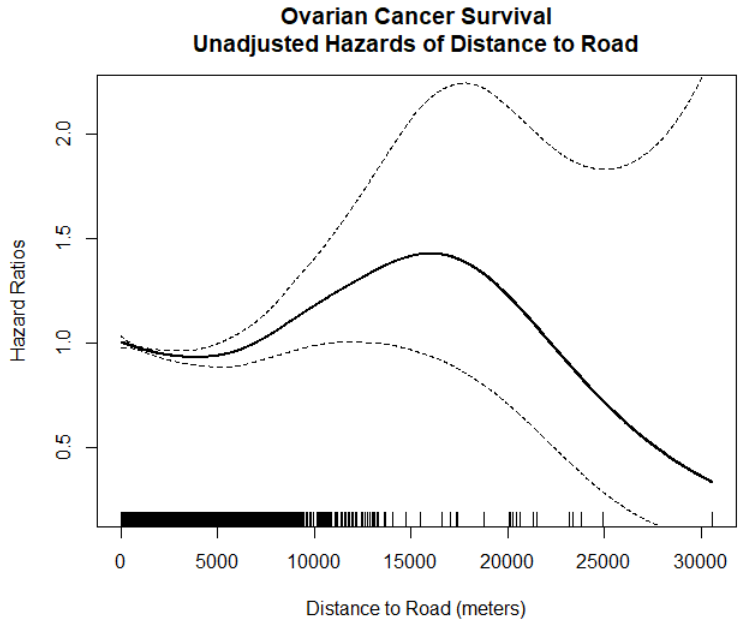
A



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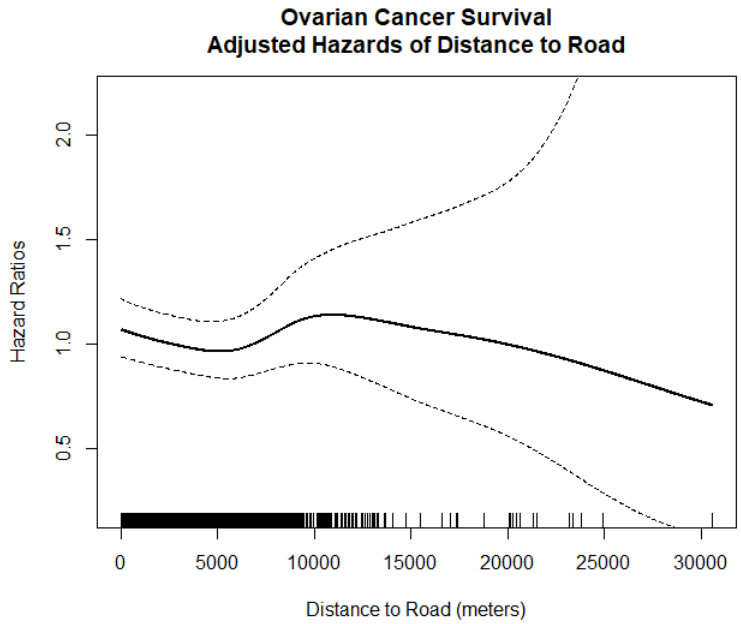


Figure 3.1: (A) Unadjusted and (B) Adjusted Hazard Ratios of Distance to Primary and Secondary Roads using Penalized Splines

This figure shows the association between residential distance from a major roadway and ovarian cancer-specific survival for women diagnosed in California between 1996-2014. The solid line represents the hazard ratios of survival and the dashed lines are the 95% confidence intervals. Residential distance from major roadways was only associated with survival in the unadjusted model (A) for distances less than 5km. The hazard ratio at the median distance of 928 meters was 0.97 (95% CI 0.96-0.98).

*The adjusted model controlled for age at diagnosis, race/ethnicity, SES, insurance status, marital status, stage at diagnosis, tumor grade, histology, size, year of diagnosis, comorbidity status, and treatment adherence.

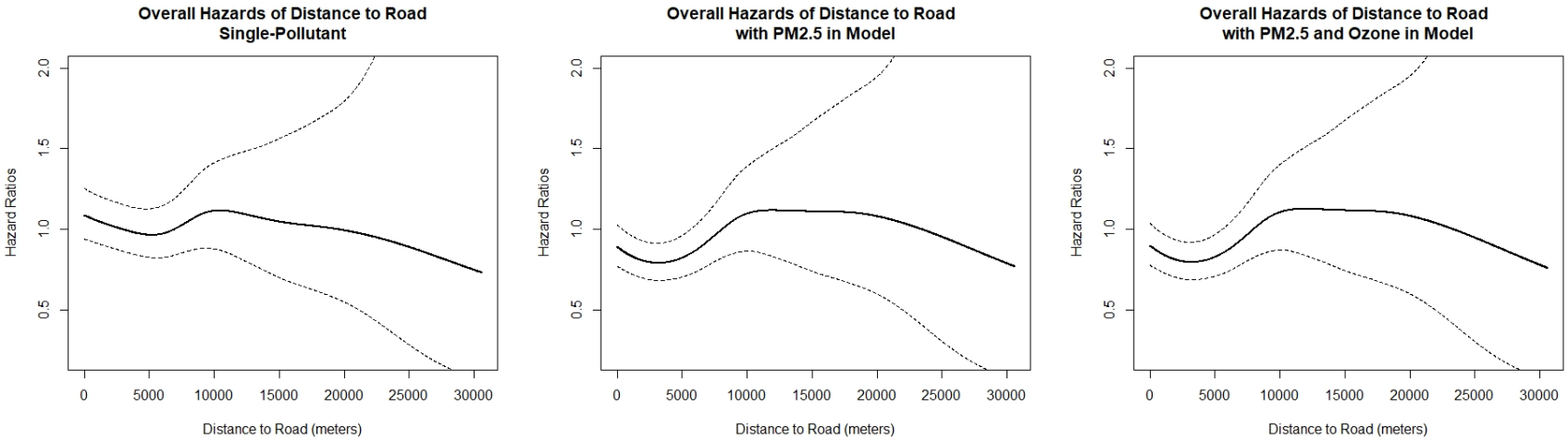
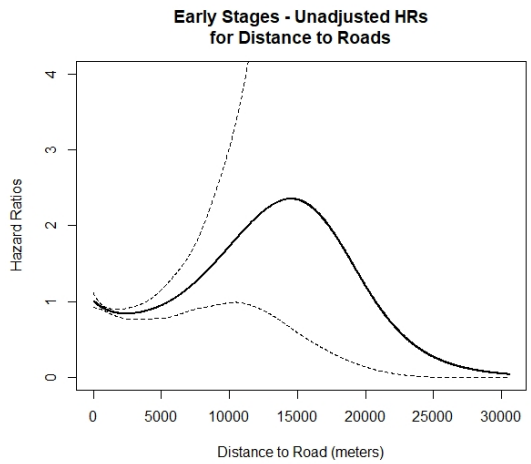
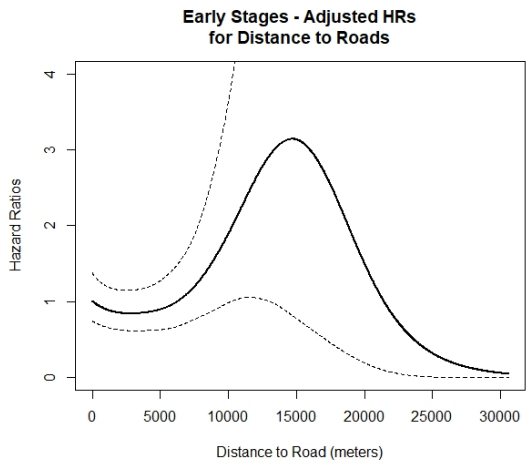


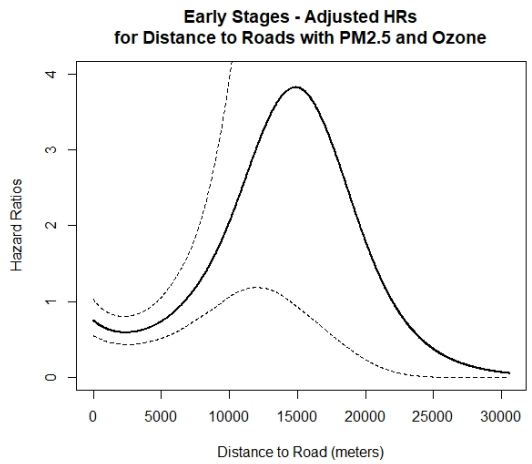
Figure 3.2: Adjusted Hazard Ratios of Distance to Primary and Secondary Major Roads using Penalized Splines for Multipollutant Model with Particulate Matter less than 2.5µm in Diameter ($PM_{2.5}$)

These figures show the association between distance from a major roadway and ovarian cancer-specific survival using penalized splines for women diagnosed in California between 1999-2014 (n=25,976) in single pollutant and multipollutant models. The first figure examines the adjusted hazards of distance alone, followed by a model including $PM_{2.5}$, and lastly one with both $PM_{2.5}$ and ozone. The solid lines represent the hazard ratios of survival and the dashed lines are the 95% confidence intervals. Models are all adjusted for age at diagnosis, race/ethnicity, socioeconomic status, insurance status, marital status, stage at diagnosis, tumor grade, tumor histology, tumor size, year of diagnosis, comorbidity status, and treatment adherence.

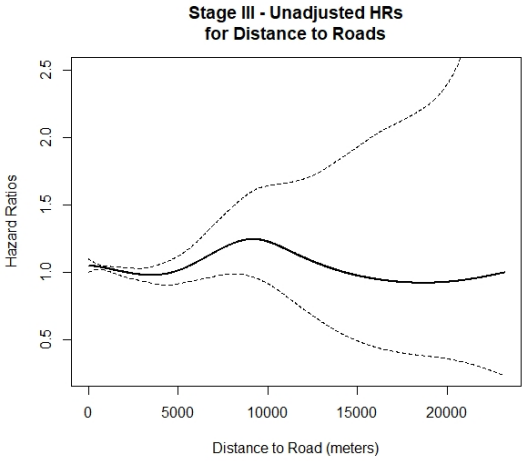
Early Stages:

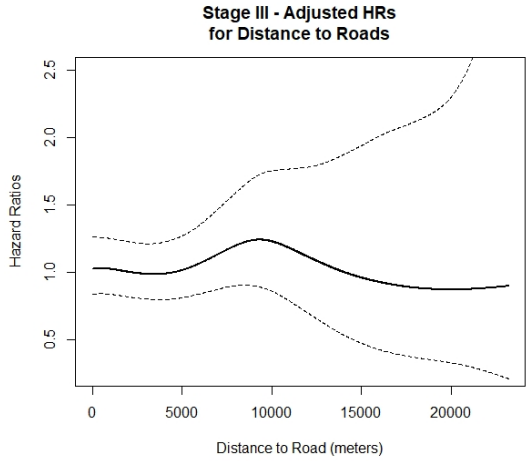


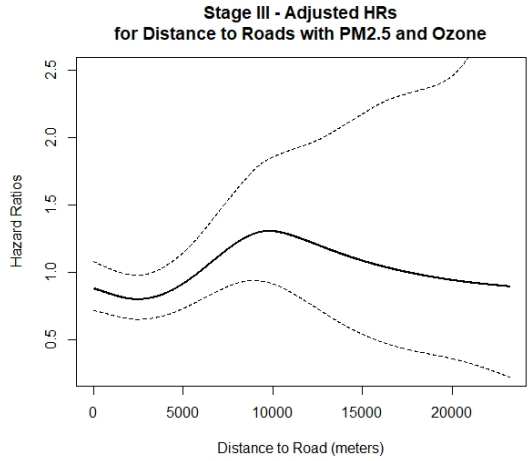




Stage III:







Stage IV:

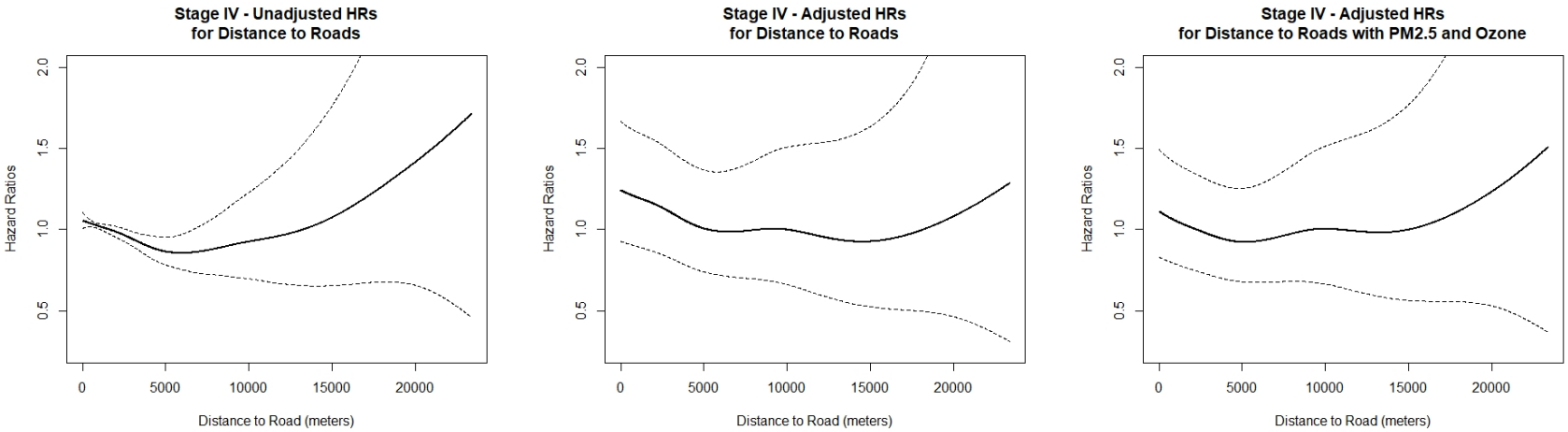


Figure 3.3: Stage-Stratified Hazard Ratios of Distance to Primary and Secondary Major Roads using Penalized Cubic Splines for Unadjusted, Adjusted, and Multipollutant Models with Particulate Matter less than 2.5µm in Diameter ($PM_{2.5}$)
These figures show the association between distance from a major roadway and ovarian cancer-specific survival using penalized cubic splines for women diagnosed in California between 1999-2014 (n=25,976) in unadjusted, single pollutant and multipollutant $PM_{2.5}$ models. The first figure within each stratification examines the unadjusted hazards of distance alone, followed by a model adjusted for sociodemographic and cancer characteristics, and lastly one with both $PM_{2.5}$ and ozone. The solid lines represent the hazard ratios of survival and the dashed lines are the 95% confidence intervals. Distance is significantly associated with survival among women with early-staged and Stage III disease in the multipollutant model and in the unadjusted model for women diagnosed in Stage IV. Adjusted models are all adjusted for age at diagnosis, race/ethnicity, socioeconomic status, insurance status, marital status, stage at diagnosis (for early stages), tumor grade, tumor histology, tumor size, year of diagnosis, comorbidity status, and treatment adherence.

Table 3.1: Patient Characteristics by Stage of Diagnosis

Characteristic	Early Stages	Stage III	Stage IV	Total	*P* Value
	N (%*)	N (%*)	N (%*)		
Total	9,733 (21.5)	11,262 (52.0)	8,846 (26.5)	29,841	
Age at Diagnosis					
Median (SD)	54 (15.3)	62 (13.9)	66 (13.8)	60 (14.9)	<0.001
Survival Time (months)					
Median (SD)	73.7 (64.4)	33.8 (48.2)	14.6 (34.7)	34.5 (56.4)	<0.001
Race/Ethnicity					
Non-Hispanic White	5,679 (30.0)	7,543 (39.9)	5,695 (30.1)	18,917	<0.001
Non-Hispanic Black	363 (25.6)	507 (35.8)	546 (38.6)	1,416	
Hispanic	2,025 (35.2)	2,022 (35.2)	1,702 (29.6)	5,749	
Asian / Pacific Islander	1,592 (44.7)	1,125 (31.6)	847 (23.8)	3,564	
Other	74 (37.9)	65 (33.3)	56 (28.7)	195	
SES					
Lowest SES	1,294 (32.1)	1,385 (34.3)	1,358 (33.6)	4,037	<0.001
Lower-Middle SES	1,742 (32.1)	1,951 (35.9)	1,741 (32.0)	5,434	
Middle SES	2,077 (32.9)	2,349 (37.2)	1,896 (30.0)	6,322	
Higher-Middle SES	2,260 (32.9)	2,632 (38.4)	1,968 (28.7)	6,860	
Highest SES	2,360 (32.8)	2,945 (41.0)	1,883 (26.2)	7,188	
Insurance					
Managed Care	5,131 (36.3)	5,347 (37.8)	3,671 (25.9)	14,149	<0.001
Medicare	1,626 (21.2)	3,077 (40.2)	2,949 (38.5)	7,652	
Medicaid	893 (32.8)	933 (34.2)	899 (33.0)	2,725	
Other Insurance	1,580 (41.3)	1,419 (37.1)	825 (21.6)	3,824	
Not insured	325 (36.6)	271 (30.5)	293 (33.0)	889	
Unknown	178 (29.6)	215 (35.7)	209 (34.7)	602	
Marital Status					
Single	4,637 (31.6)	5,264 (35.8)	4,785 (32.6)	14,686	<0.001
Married	5,096 (33.6)	5,998 (39.6)	4,061 (26.8)	15,155	
Tumor Size (mm)					
< 50	1,320 (35.4)	1,445 (38.7)	969 (26.0)	3,734	<0.001
50-99	1,850 (31.4)	2,560 (43.5)	1,474 (25.1)	5,884	
≥ 100	4,352 (46.6)	3,335 (35.7)	1,648 (17.7)	9,335	
Unknown	2,211 (20.3)	3,922 (36.0)	4,755 (43.7)	10,888	
Tumor Grade					
1	1,835 (77.3)	413 (17.4)	126 (5.3)	2,374	<0.001
2	2,228 (51.1)	1,442 (33.1)	689 (15.8)	4,359	

3	2,266 (22.5)	4,852 (48.3)	2,932 (29.2)	10,050	
4	921 (22.0)	2,156 (51.4)	1,114 (26.6)	4,191	
Unknown	2,483 (28.0)	2,399 (27.1)	3,985 (44.9)	8,867	
Histology					
Serous	2,128 (16.6)	6,885 (53.6)	3,841 (29.9)	12,854	<0.001
Mucinous	1,346 (70.8)	310 (16.3)	244 (12.8)	1,900	
Endometrioid	2,308 (69.6)	727 (21.9)	283 (8.5)	3,318	
Clear cell	1,214 (66.4)	421 (23.0)	194 (10.6)	1,829	
Adenocarcinoma, NOS	304 (9.6)	845 (26.6)	2,029 (63.8)	3,178	
Others	2,433 (36.0)	2,074 (30.7)	2,255 (33.3)	6,762	
NCCN Treatment Adherence					
Adherent	2,451 (21.5)	5,943 (52.0)	3,024 (26.5)	11,418	<0.001
Non-Adherent	7,282 (39.5)	5,319 (28.9)	5,822 (31.6)	18,423	
Charlson Comorbidity Score[b]					
CCS 0	5,444 (38.3)	5,303 (37.3)	3,471 (24.4)	14,218	<0.001
CCS 1	1,787 (26.3)	2,741 (40.3)	2,278 (33.5)	6,806	
CCS 2+	1,681 (25.0)	2,581 (38.4)	2,463 (36.6)	6,725	
CCS Unknown	821 (39.2)	637 (30.4)	634 (30.3)	2,092	
Diagnosis Year Category					
1996-1999	1,777 (33.9)	1,903 (36.3)	1,565 (29.8)	5,245	0.005
2000-2004	2,358 (31.7)	2,901 (39.0)	2,185 (29.4)	7,444	
2005-2009	2,625 (31.7)	3,192 (38.5)	2,473 (29.8)	8,290	
2010-2014	2,973 (33.5)	3,266 (36.9)	2,623 (29.6)	8,862	

*Values represent row percentages.

[b] The Charlson Comorbidity Score was used to assign comorbidity status and is grouped into quartiles (CCS 0- no comorbidities, CCS 1- one comorbidity, CCS 2- two or more comorbidities, and CCS Unknown- comorbidity status is unknown).

Abbreviations: *CCS*, Charlson Comorbidity Score; *NCCN*, National Comprehensive Cancer Network; *NOS*, Not Otherwise Specified; *SES*, Socioeconomic Status; *SD,* Standard Deviation

Table 3.2: Distribution of Exposure Levels Overall and by Stage of Diagnosis

	Median	Mean	SD	25th Percentile	75th Percentile	*P* Value
Nitrogen Dioxide (ppb)						
Early	14.4	15.5	5.8	11.0	19.0	<0.001
Stage III	15.0	16.2	6.7	11.2	19.6	
Stage IV	15.8	16.8	7.3	11.4	20.3	
Overall	15.1	16.1	6.6	11.2	19.6	
Ozone (ppb)						
Early	40.4	40.3	8.1	34.6	44.8	0.216
Stage III	40.6	40.5	8.2	34.6	45.3	
Stage IV	40.6	40.5	8.2	34.6	45.0	
Overall	40.6	40.4	8.1	34.6	45.0	
$PM_{2.5}$ ($\mu g/m^3$)*						
Early	11.59	11.73	2.93	9.37	13.47	<0.001
Stage III	11.83	12.23	3.59	9.52	14.00	
Stage IV	12.10	12.62	4.16	9.64	14.48	
Overall	11.85	12.18	3.59	9.49	13.91	
Distance to Road (meters)						
Early	923.7	1339.9	1542.7	413.2	1782.3	0.415
Stage III	926.2	1342.4	1504.4	410.2	1756.5	
Stage IV	933.0	1371.1	1606.7	411.0	1782.3	
Overall	927.6	1337.0	1465.6	411.2	1770.2	

* Values represent a subset of women who were diagnosed during or after 1999 (n=25,976)
Abbreviations: *m,* meters; *NO2,* Nitrogen Dioxide; *$PM_{2.5}$,* particulate matter with diameter less than 2.5 microns; *ppb,* Parts per billion; *SD,* Standard Deviation

Table 3.3: Exposure Levels by Race/Ethnicity and Socioeconomic Status

	$PM_{2.5}$*			NO_2			Ozone			Distance		
Population Characteristics	Mean	Median	Highest Exposure Quartile[a]	Mean	Median	Highest Exposure Quartile[b]	Mean	Median	Highest Exposure Quartile[c]	Mean	Median	Highest Exposure Quartile[d]
	$\mu g/m^3$	$\mu g/m^3$	%*	ppb	ppb	%	ppb	ppb	%	m	m	%
Race/Ethnicity												
Non-Hispanic White	12.00	11.46	23.7	15.6	14.3	22.6	40.2	40.4	24.3	1440.8	990.9	23.9
Non-Hispanic Black	12.76	12.60	31.6	17.9	17.2	34.4	40.7	40.8	26.0	1117.3	787.3	27.6
Hispanic	12.85	12.74	30.0	17.2	16.8	30.3	40.9	40.9	26.0	1145.9	814.5	28.1
Asian/Pacific Islander	11.88	11.52	21.3	16.4	15.4	26.2	40.8	40.8	26.5	1177.2	888.8	24.7
Other	10.95	10.40	14.5	13.8	12.7	11.3	41.1	41.7	24.1	1427.6	872.5	27.2
Socioeconomic Status												
Lowest SES	13.11	12.89	34.2	17.4	16.5	31.8	40.7	40.7	24.4	1118.4	742.9	29.4
Lower-Middle SES	12.54	12.32	28.6	16.5	15.6	28.1	40.8	40.9	25.6	1322.6	848.6	28.0
Middle SES	12.09	11.62	24.3	15.8	14.4	24.5	40.7	40.8	25.3	1352.7	921.8	24.7
Higher-Middle SES	11.90	11.50	22.5	15.7	14.5	23.2	40.4	40.6	25.2	1384.6	951.7	24.9
Highest SES	11.74	11.19	20.1	15.9	14.9	21.0	39.9	40.0	24.5	1411.6	1078.2	20.6

***** Values represent a subset of women who were diagnosed during or after 1999 (n=25,976).

[a] Highest exposure quartile for $PM_{2.5}$ is > 13.91 $\mu g/m^3$

[b] Highest exposure quartile NO_2 is > 19.6 ppb

[c] Highest exposure quartile for ozone is > 45.0 ppb

[d] Highest exposure quartile is women living < 411.2 meters from a major road.

Abbreviations: *m,* meters; *NO2*, Nitrogen Dioxide; *$PM_{2.5}$*, particulate matter with diameter less than 2.5 microns; *ppb,* Parts per billion; *SES,* Socioeconomic status

Table 3.4: Unadjusted and Adjusted Hazard Ratios for Single Pollutant Models

Air Pollutant Exposures	IQR	Unadjusted HR (95% CI)	Adjusted HR (95% CI) [a]
$PM_{2.5}$ (μg/m3)[b]	4.42	1.47 (1.43–1.50)*	1.44 (1.40–1.47)*
Ozone (ppb)	10.4	1.02 (0.996–1.04)*	1.001 (0.98–1.02)*
NO_2 (ppb)			
< 20.0		1.00	1.00
20.0 – 30.0		1.20 (1.16–1.25)	1.30 (1.25–1.36)
> 30.0		3.03 (2.85–3.22)	2.48 (2.32–2.66)

* Represents the hazard ratios for an interquartile increase in concentration levels

[a] Models adjusted for age at diagnosis, race/ethnicity, SES, insurance status, marital status, stage at diagnosis, tumor grade, tumor histology, tumor size, comorbidity status, treatment adherence, and year of diagnosis.

[b] $PM_{2.5}$ models are for a subset of women who were diagnosed during or after 1999 (n=25,976)

Abbreviations: *Coef,* Coefficient; *CI,* Confidence Interval; *HR,* Hazard Ratios; *IQR,* Interquartile Range; *NO_2,* Nitrogen Dioxide; *ppb,* Parts per billion; *$PM_{2.5}$,* Particulate matter less than 2.5μm in diameter; *SE,* Standard Error

Table 3.5: Hazard Ratios for Multipollutant Overall Models

Multipollutant Models	Coef	SE	HR	95% CI
NO_2 + Distance				
NO_2 <20.0 ppb			1.00	Ref
20.0–30.0 ppb	0.26	0.02	1.30	1.25–1.36
>30.0 ppb	0.92	0.04	2.50	2.33–2.68
Distance			0.98	0.86–1.11
NO_2 + Ozone				
NO_2 <20.0 ppb			1.00	Ref
20.0–30.0 ppb	0.26	0.02	1.30	1.25–1.36
>30.0 ppb	0.91	0.04	2.49	2.32–2.67
Ozone	1.45	1.05	1.02	0.99–1.04
NO_2 + Ozone + Distance				
NO_2 <20.0 ppb			1.00	Ref
20.0–30.0 ppb	0.26	0.02	1.30	1.25–1.36
>30.0 ppb	0.92	0.04	2.50	2.33–2.69
Ozone	1.53	1.05	1.02	0.995–1.04
Distance			0.98	0.86–1.11
$PM_{2.5}$ + Distance				
$PM_{2.5}$	0.08	2.92e-03	1.45	1.41–1.48
Distance			0.84	0.73–0.97
$PM_{2.5}$ + Ozone				
$PM_{2.5}$	0.08	0.003	1.44	1.41–1.48
Ozone	2.46	1.118	1.03	1.00–1.05
$PM_{2.5}$ + Ozone + Distance				
$PM_{2.5}$	0.08	2.93e-03	1.45	1.41–1.49
Ozone	2.55	1.12	1.03	1.00–1.05
Distance			0.85	0.73–0.98

Notes: Hazard ratios for $PM_{2.5}$ and Ozone represent an interquartile increase in concentration levels. NO_2 is categorized into tertiles. The distance hazard ratios reported are for the spline distance variable predicted at the median.
-All models are additionally adjusted for age at diagnosis, race/ethnicity, SES, insurance status, marital status, stage at diagnosis, tumor grade, tumor histology, tumor size, comorbidity status, treatment adherence, and year of diagnosis.
-Hazard ratios for models with $PM_{2.5}$ represent a subset of women who were diagnosed during or after 1999 (n=25,976).

Abbreviations: *Coef,* Coefficient; *CI,* Confidence Interval; *HR,* Hazard Ratio; *IQR,* Interquartile Range; *NO_2,* Nitrogen Dioxide; *$PM_{2.5}$,* Particulate matter less than 2.5μm in diameter; *ppb,* Parts per billion; *SE,* Standard Error

Table 3.6: Hazard Ratios for Stage-Stratified Multipollutant Models

Multi Pollutant Models	EARLY STAGES (n=9,733)		STAGE III (n=11,262)		STAGE IV (n=8,846)	
	HR[a]	**(95% CI)**	**HR[a]**	**(95% CI)**	**HR[a]**	**(95% CI)**
$PM_{2.5}$						
Adjusted (SP)	2.01	(1.84–2.19)	1.56	(1.50–1.62)	1.30	(1.25–1.35)
with Distance	2.05	(1.88–2.23)	1.58	(1.51–1.64)	1.30	(1.25–1.35)
with Ozone	2.03	(1.86–2.21)	1.56	(1.50–1.63)	1.30	(1.25–1.35)
with Ozone and Distance	2.07	(1.90–2.25)	1.58	(1.52–1.65)	1.30	(1.25–1.35)
Ozone						
Adjusted (SP)	1.05	(0.99–1.12)	1.01	(0.98–1.05)	0.98	(0.95–1.01)
with $PM_{2.5}$	1.11	(1.04–1.18)	1.04	(1.01–1.08)	1.00	(0.96–1.03)
with $PM_{2.5}$ and Distance	1.11	(1.04–1.18)	1.04	(1.00–1.08)	1.00	(0.97–1.03)
with NO_2	1.06	(1.00–1.13)	1.03	(1.00–1.06)	0.99	(0.96–1.02)
with NO_2 and Distance	1.06	(1.00–1.13)	1.03	(1.00–1.06)	0.99	(0.96–1.03)
NO_2 – Category 1 (20.0-30.0 ppb)[b]						
Adjusted (SP)	1.49	(1.30–1.70)	1.27	(1.19–1.35)	1.30	(1.22–1.39)
with Distance	1.50	(1.31–1.71)	1.28	(1.20–1.36)	1.30	(1.22–1.38)
with Ozone	1.50	(1.31–1.71)	1.27	(1.19–1.36)	1.30	(1.22–1.39)
with Ozone and Distance	1.51	(1.32–1.72)	1.28	(1.20–1.37)	1.30	(1.22–1.38)
NO_2 – Category 2 (>30.0 ppb)[c]						
Adjusted (SP)	8.13	(6.56–10.09)	2.75	(2.47–3.06)	1.86	(1.68–2.06)
with Distance	8.33	(6.71–10.34)	2.78	(2.50–3.09)	1.86	(1.67–2.06)
with Ozone	8.18	(6.60–10.15)	2.77	(2.49–3.08)	1.86	(1.67–2.06)
with Ozone and Distance	8.39	(6.76–10.41)	2.79	(2.51–3.11)	1.85	(1.67–2.06)

[a] For $PM_{2.5}$ and ozone, hazard ratios and 95% confidence intervals are for an interquartile range increase in exposure levels. For NO_2, the referent category for the hazard ratios is exposure levels <20.0 ppb.
[b] Among women in NO_2 category 1 (20.0-30.0 ppb), there were 1,752 women in early stages, 2,066 in Stage III, and 1,708 in Stage IV.
[c] Among women in NO_2 category 2 (>30.0 ppb), there were 214 women in early stages, 574 in Stage III, and 598 in Stage IV.
Notes: Models with $PM_{2.5}$ represent a subset of women who were diagnosed during or after 1999 (n=25,976). Among those women, 8,423 were diagnosed in early stages, 9,870 in Stage III, and 7,683.

Abbreviations: *CI*, Confidence Interval; *HR*, Hazard Ratio; *NO_2*, Nitrogen Dioxide; *$PM_{2.5}$*, Particulate matter with diameter less than 2.5 microns; *ppb*, Parts per billion; *SD*, Standard Deviation; *SP*, Single Pollutant model

CONCLUSIONS

This dissertation examined the association between geographic location and ovarian cancer outcomes for women living in California, diagnosed between 1996 and 2014. It additionally considered the impact of race/ethnicity and socioeconomic status (SES). Two main outcomes were investigated: treatment received and disease-specific survival. The care that women receive is critical to survival and stage-specific guidelines have been outlined by the National Comprehensive Cancer Network (NCCN) for the standards of care for ovarian cancer. Disparities in both treatment and survival by sociodemographic factors continue to be cited in the literature, despite accounting for many important determinants. Using generalized additive models (GAMs), this research investigated the role that women's geocoded residential address had in the likelihood of receiving NCCN adherent care to determine whether location explained some of the disparate outcomes frequently cited. It additionally looked at two measures of spatial accessibility to determine the influence of geographic factors on access to care and barriers to treatment, as these two variables may disproportionately impact minority women and those of lower SES. The distance traveled to receive care and proximity to the closest high-quality hospital, determined as a hospital with a high Observed-to-Expected ratio, were calculated for each woman. Lastly, chapter 3 considered the impact of ambient air pollution on survival.

This research highlights geographic areas in California that are significantly associated with the odds of receiving non-adherent care, even after controlling for important covariates. Spatial patterns revealed that the likelihood of deviation from NCCN treatment was lowest in regions of Northern California, whereas non-adherence was observed in the eastern portion of the Central Valley, with the highest risk observed in northern Los Angeles and central Kern

Counties. This dissertation further identifies areas with greater risk of surgery versus chemotherapy non-adherence, revealing distinct geographic patterns between the two. Racial and socioeconomic differences were observed in the likelihood of non-adherent treatment, with non-Hispanic black women, women of lower SES, and women with no insurance or Medicare insurance most likely to receive substandard care. Furthermore, greater comorbidities and not being treated at a high quality hospital were associated with NCCN non-adherent treatment.

Geographic barriers also influenced the odds of treatment adherence, with traveling further distances generally being associated with a decreased risk of nonstandard care and women living further away from a high quality hospital being less likely to receive guideline-adherent care. Distance traveled to receive care was a stronger predictor of adherence for women in early stages, while race/ethnicity and SES had a larger influence on women diagnosed in late stages. Non-Hispanic black women were the least likely to travel far. Asian/ Pacific Islander women lived the closest to a high quality hospital and were also the most likely to be treated at one. Women of lower SES lived the furthest from a high quality hospital, while those in the highest SES quintile lived the closest.

While geographic location influenced women's likelihood of receiving NCCN-adherent care, it did not impact disease-specific survival after accounting for sociodemographic variables, NCCN treatment, and geographic variables. Utilizing Cox proportional additive hazards models, geographic location alone was not associated with survival among early-staged women, but did have a significant association with women diagnosed in late stages and all stages combined. The geographic variations seen, however, were explained by the covariates examined. In spatial analyses of survival by time period, there were significant geographic variations in survival during 2002-2006 in fully-adjusted additive models. In aspatial, multivariate weighted cox

regression models, non-Hispanic black women, those of lower SES, and women without insurance had a greater risk of mortality, even after taking treatment into account. Overall, traveling greater distances was associated with better survival, although proximity to a high quality hospital and being treated at one had no effect. Receiving adequate care remained the most important predictor. Considering the race-stratified models, the influence of geographic variables varied by race, with distance traveled to receive care being associated with survival among non-Hispanic white, Hispanic, and Asian/Pacific Islander women, but not among non-Hispanic black women or those of other race.

In addition to geographic location and spatial variables assessing barriers to care, this dissertation considered the survival impact of cumulative ambient exposure to NO_2, $PM_{2.5}$, ozone, and distance to closest primary and secondary road. Residential location in areas with greater NO_2 and $PM_{2.5}$ were found to be detrimental to survival. These impacts were greater among women diagnosed in early stages. Non-Hispanic black and Hispanic women, as well as those of lower SES. were found to disproportionately have higher levels of NO_2 and $PM_{2.5}$ pollutant exposure and live closest to a primary road, although greater susceptibility was observed among Asian/Pacific Islanders and Hispanics depending on the pollutant.

In summary, this dissertation contributes to our understanding of how geographic location may impact outcomes among women diagnosed with ovarian cancer in California. There was strong evidence of disparities by race/ethnicity and SES in all ovarian cancer outcomes examined, including the differential role of various location-based factors. It provides evidence of how women's residential location may independently influence ovarian cancer outcomes, particularly by stage as well as sociodemographic factors. This research further

suggests that exposure to $PM_{2.5}$ and NO_2 after an ovarian cancer diagnosis may be detrimental to survival. Differences by stage, race/ethnicity and SES are also highlighted.

Given the poor prognosis of ovarian cancer and the necessity of receiving adequate treatment to maximize survival time, it is imperative to identify ways to improve access to specialized care among all women, ensure receipt of appropriate guideline treatment, and identify other modifiable factors that may improve survival. With a focus on geographic location, there are some important implications that come from this work. First, centralizing the specialized care required for ovarian cancer[1] is a potential way to address the paucity of expert gynecologic oncologists in certain areas. However, providing transportation would have to be a critical component as centralization without transportation or service connection may exacerbate inequities in access among underserved population.[2] Another possibility is having a larger number of satellite clinics in underserved areas.[1,3] With either of those options, having dedicated patient navigators or social work staff to connect patients to services, address competing stressors, and following up with them would be essential.[2-4] Lastly, recommendations to limit exposure to increased air pollution is a novel approach to improving survival that should be considered,[5] although with recognition that reducing exposure and even improving indoor air may be difficult or unfeasible for some women. To conclude, in order to eliminate disparities and improve survival for all women diagnosed with ovarian cancer, it is vital to be cognizant of how any potential intervention may unintentionally harm those that are most vulnerable.

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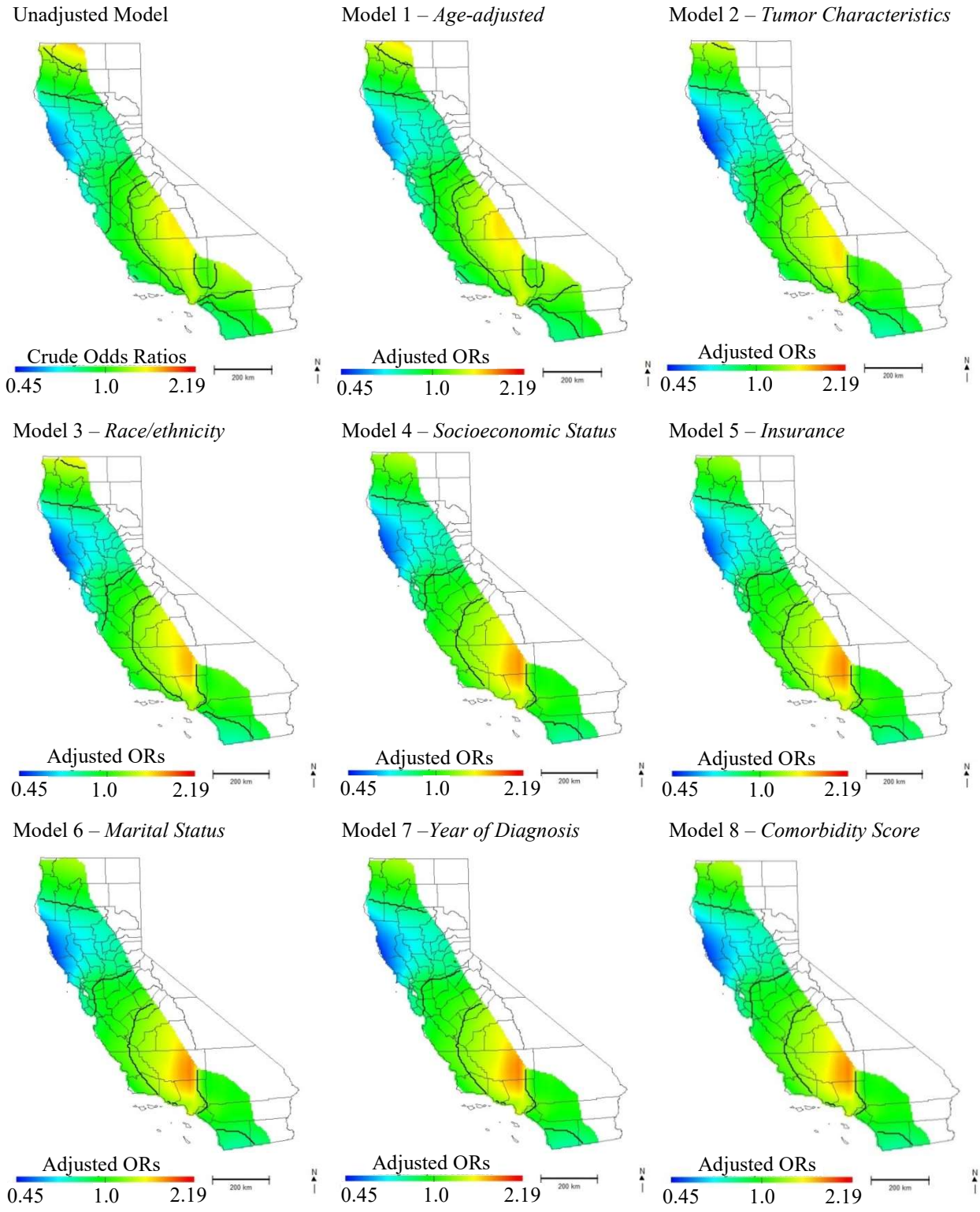
APPENDIX A – Chapter 1: Additional Spatial-Analysis of Treatment Adherence

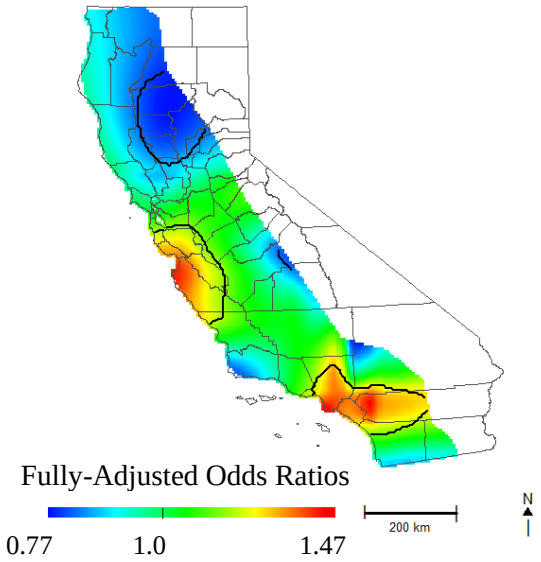
Figure A.1: Stepwise Analysis of Overall NCCN Treatment Adherence – All Stages Combined



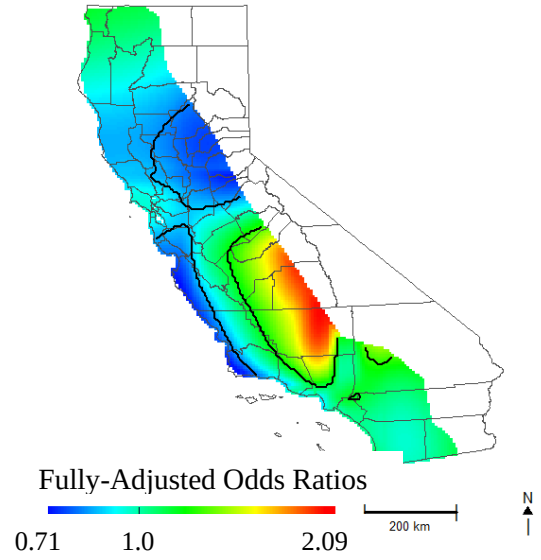
Appendix Figure A.1: Stepwise Analysis of Overall Treatment Adherence – All Stages Combined

The figures above represent the effect of each additional variable on geographic variations of overall NCCN treatment adherence. One observation of note is that reverse confounding is observed in northern Los Angeles and western Kern counties with the addition of sociodemographic variables such as race/ethnicity and socioeconomic status. The increased risk of non-adherent care observed is magnified after adjustment for sociodemographic variables. Areas delineated by contour lines represent statistically significant geographic areas.
Abbreviations: *NCCN,* National Comprehensive Cancer Network; *OR,* Odds Ratios

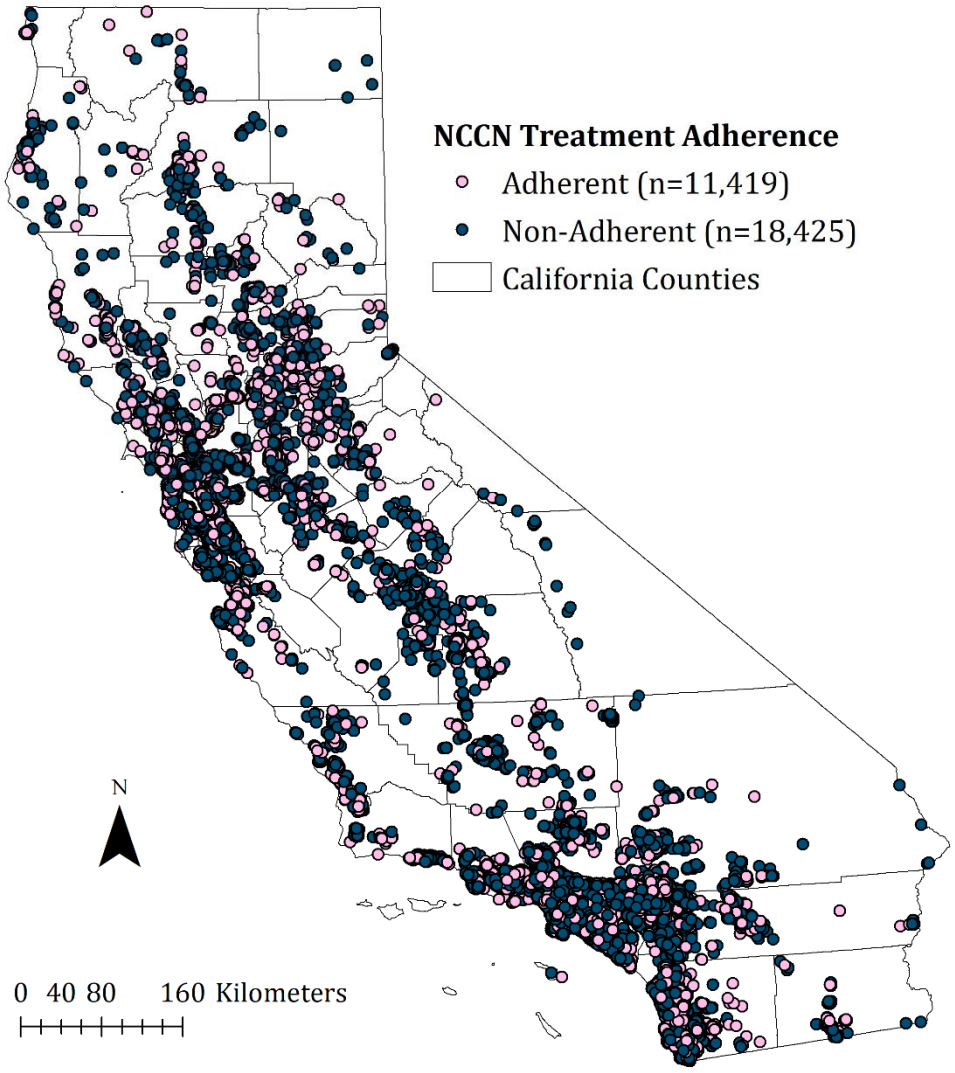
(A) Chemotherapy Non-Adherence



(B) Surgery Non-Adherence



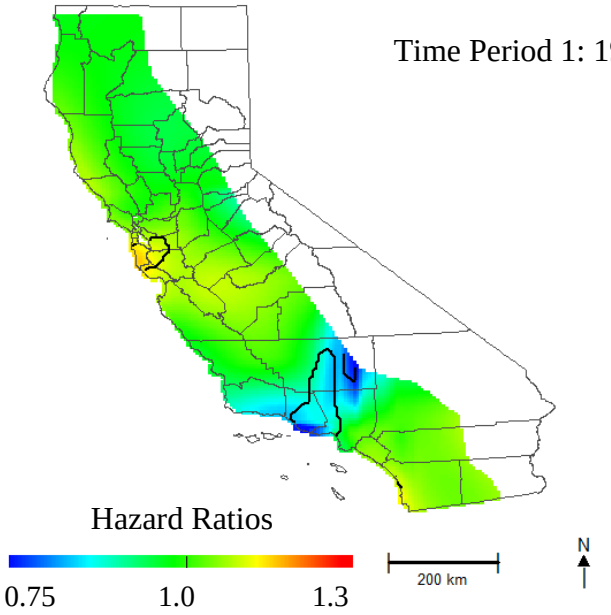
Appendix Figure A.2: Spatial-analysis of Chemotherapy versus Surgery Adherence
The fully-adjusted effect of geographic location on risk of receiving non-adherent National Comprehensive Cancer Network (A) Chemotherapy and (B) Surgery guideline treatment for invasive epithelial ovarian cancer. The figures show that areas of increased risk for chemotherapy non-adherence differ from those of surgery non-adherence by location. In particular, areas of the Central Coast that are protective against risk of non-surgery adherence have higher risk of chemo non-adherence. Similarly, higher risk of surgery non-adherence is observed in the Central Valley region, whereas the same are display either decreased or no risk of chemotherapy non-adherence. Models are adjusted for age, cancer stage, tumor histology, tumor grade, tumor size, race/ethnicity, socioeconomic status, insurance, marital status, comorbidity status, year of diagnosis, hospital quality, distance traveled for care, and distance of closest high quality hospital. Areas delineated by contour lines represent statistically significant geographic areas.



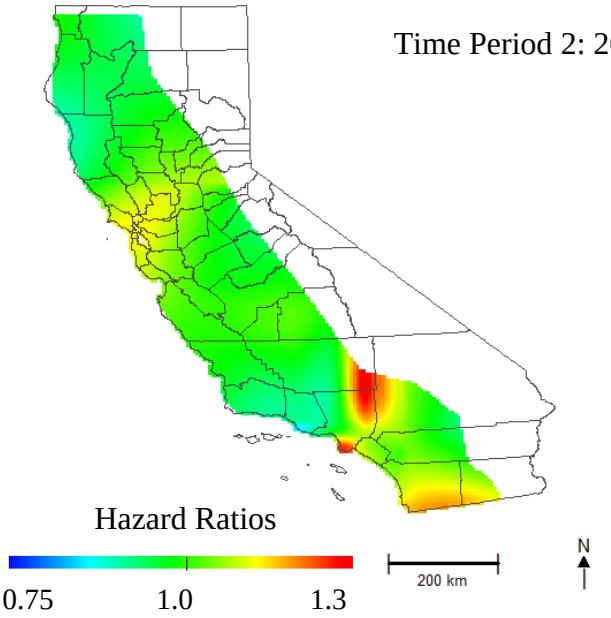
Appendix Figure A.3: Distribution of Ovarian Cancer Cases in California by adherence to the National Comprehensive Cancer Network (NCCN) guidelines, 1996-2014
This figure displays the cases of ovarian cancer diagnosed in California by whether or not they received care that adhered to the NCCN stage-specific guidelines.

APPENDIX B – Chapter 2: Spatio-Temporal Analasyis of Ovarian Cancer Mortality in California

(A)



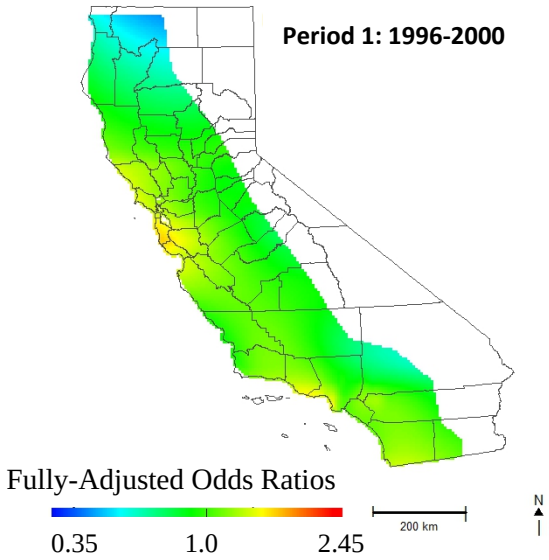
(B)



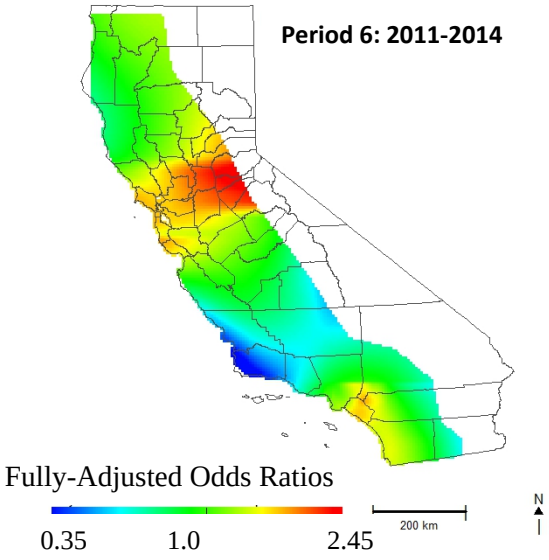
Appendix Figure B.1: Comparison of Ovarian Cancer Survival in Two Time Periods Among Women Diagnosed in Late Stages

The fully-adjusted effect of geographic location on risk of dying of ovarian cancer during (A) time period 1: 1996 and 2006 and (B) time period 2: 2007-2014. Significant geographic variations emerged in California for women diagnosed in late stagses between 1996 and 2006. Areas of decreased hazards were observed in Northern Los Angeles, Ventura, and Kern counties during 1996-2006 (global *P*-value = 0.009), although they disappeared between 2007-2014, with some regions even becoming associated with increased hazards, although not significantly (global *P*-value = 0.576).

(A)

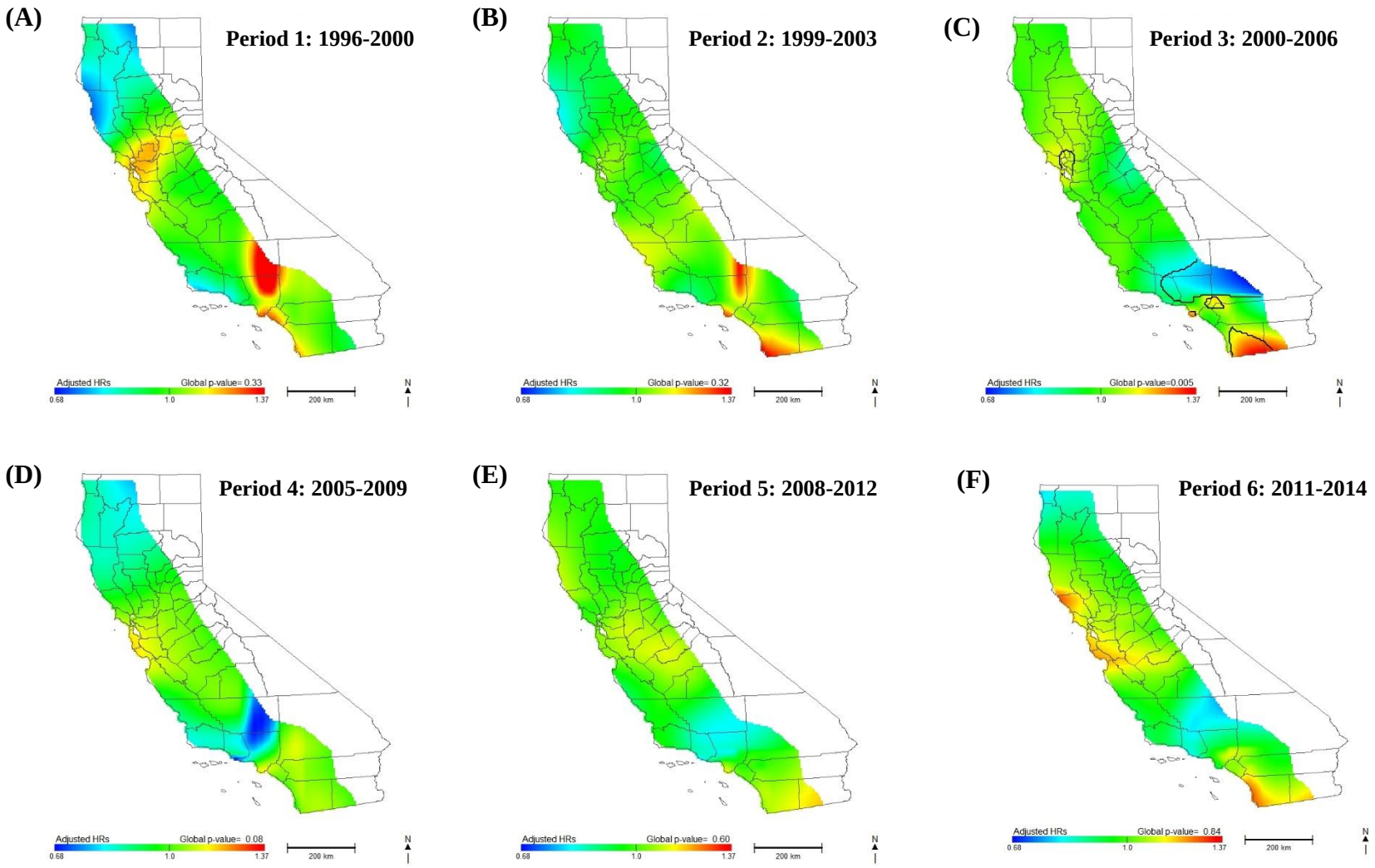


(B)



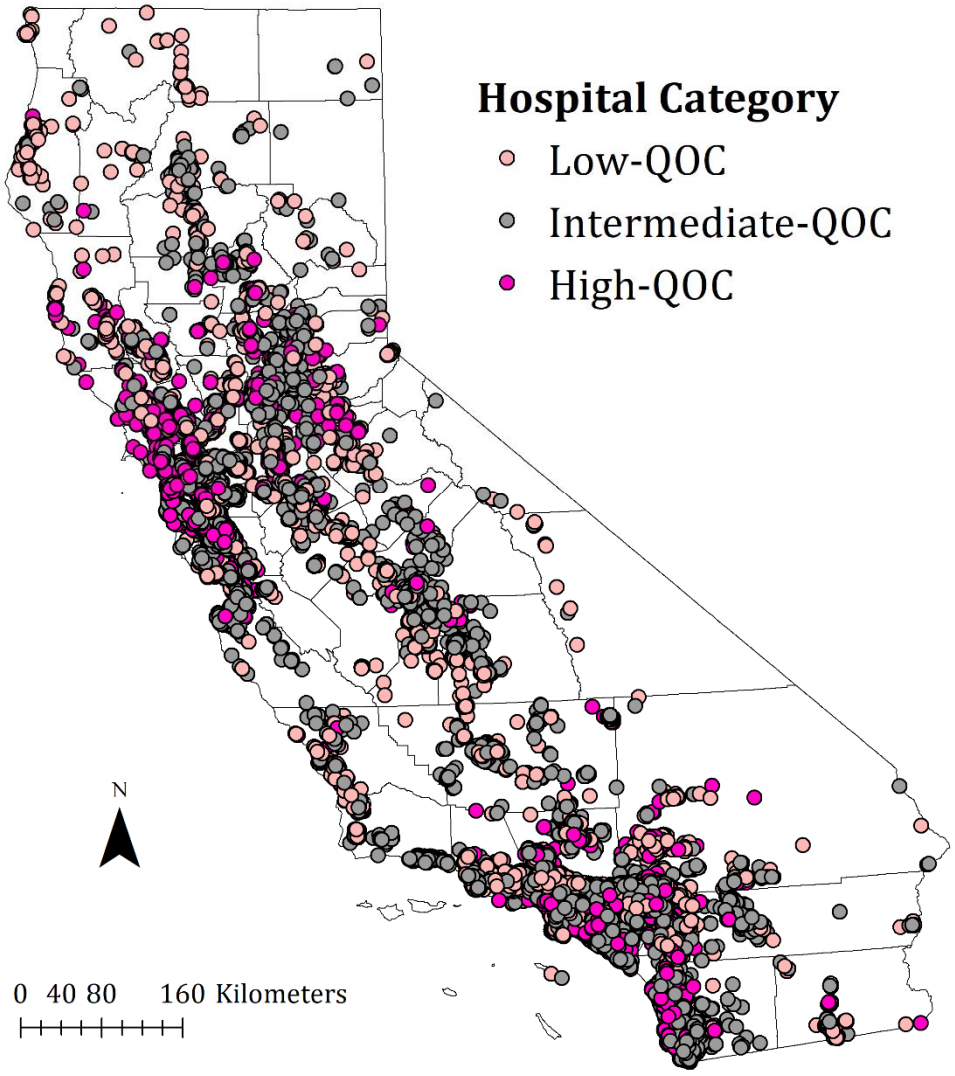
Appendix Figure B.2: Spatio-temporal analysis of ovarian cancer mortality among women diagnosed in early stages

The fully-adjusted effect of geographic location on risk of dying of ovarian cancer between (A) time period 1: 1996 and 2000 and (B) time period 2: 2011-2014. Although associations were not significant, spatial patterns emerged in California for women diagnosed in early stages. There was an increased hazards of death in northern California, whereas residing in the Central Coast region decreased hazards (global value ranges: 0.10 – 0.27).



Appendix Figure B.3: Spatio-temporal analysis of ovarian cancer mortality among women diagnosed in late stages

Geographic location was significantly associated with mortality among women diagnosed in advanced-stages for each time period. After adjusting for covariates, location only remained an independent predictor between 2002-2006 (Figure (C), global p-value: 0.005). Regions of increased mortality during that time (delineated with black contour lines) were observed in the San Francisco Bay area, southern San Diego County and southern Los Angeles County. Residing in northern Los Angeles and western San Bernardino Counties was significantly protective.



Appendix Figure B.4: Distribution of Ovarian Cancer Cases in California by Quality of Treating Hospital, 1996-2014
This figure displays the cases of ovarian cancer diagnosed in California by the quality of the treating hospital.
Abbreviations: *QOC*, Quality of care

Appendix Table B.1: Stage-Stratified Hazard Ratios of Early versus Late Stages for Women in Diagnosed in California with Ovarian Cancer between 1996 and 2014

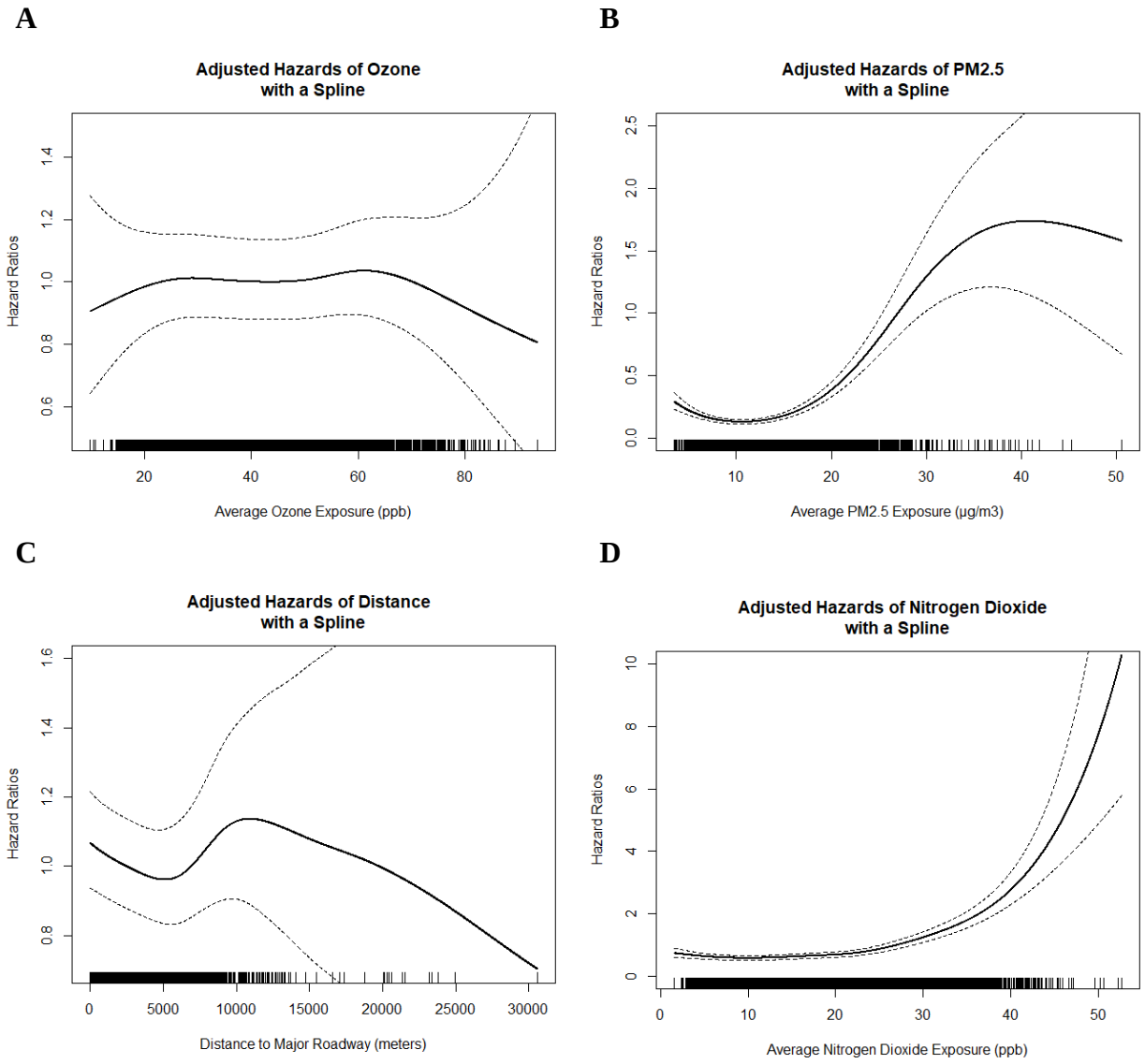
	Early Stages		Late Stages	
	HR	95% CI	HR	95% CI
Age	1.02	(1.02-1.03)	1.03	(1.02-1.03)
Race/Ethnicity				
Non-Hispanic White	1.00	Referent	1.00	Referent
Non-Hispanic Black	1.37	(0.95-1.97)	1.21	(1.10-1.32)
Hispanic	0.98	(0.68-1.40)	0.96	(0.90-1.01)
Asian/ Pacific Islander	0.87	(0.71-1.06)	1.00	(0.93-1.07)
Other	1.15	(0.50-2.64)	0.83	(0.65-1.07)
Socioeconomic Status				
Lowest SES	0.88	(0.67-1.17)	1.23	(1.14-1.32)
Lower-Middle SES	1.08	(0.85-1.36)	1.21	(1.13-1.28)
Middle SES	0.85	(0.69-1.05)	1.14	(1.07-1.21)
Higher-Middle SES	1.08	(0.85-1.36)	1.09	(1.04-1.16)
Highest SES	1.00	Referent	1.00	Referent
Insurance Type				
Managed Care	1.00	Referent	1.00	Referent
Medicare	1.12	(0.93-1.36)	0.94	(0.89-0.98)
Medicaid	1.05	(0.76-1.46)	1.11	(1.03-1.20)
Other Insurance	0.86	(0.69-1.08)	0.96	(0.90-1.02)
Not insured	1.60	(0.84-3.02)	1.24	(1.09-1.41)
Unknown	3.63	(2.60-5.05)	0.92	(0.80-1.06)
Tumor Size, mm				
<50	1.00	Referent	1.00	Referent
50-99	1.23	(0.96-1.57)	1.02	(0.95-1.10)
≥100	1.12	(0.88-1.41)	0.96	(0.90-1.03)
Unknown	1.34	(0.99-1.80)	1.17	(1.10-1.25)
Tumor Grade				
1	1.00	Referent	1.00	Referent
2	0.84	(0.59-1.18)	1.67	(1.44-1.94)
3	1.13	(0.85-1.50)	1.75	(1.53-2.02)
4	1.19	(0.89-1.59)	1.78	(1.54-2.05)
Unknown	1.00	(0.74-1.35)	2.29	(1.99-2.65)
Histology				
Serous	1.00	Referent	1.00	Referent
Mucinous	0.67	(0.50-0.91)	1.75	(1.53-2.00)
Endometrioid	0.59	(0.45-0.77)	0.87	(0.80-0.96)
Clear cell	0.88	(0.70-1.10)	1.54	(1.37-1.74)
Adenocarcinoma, NOS	1.19	(0.90-1.58)	1.45	(1.36-1.54)
Others	0.77	(0.64-0.93)	1.37	(1.30-1.44)
Stage				
Stage 1 or Stage 3	1.00	Referent	1.00	Referent

Stage 2 or Stage 4	2.40	(2.06-2.80)	1.64	(1.57-1.70)
Marital Status				
Single	1.00	Referent	1.00	Referent
Married	0.89	(0.77-1.04)	0.89	(0.85-0.92)
Treatment Adherence				
Adherent	1.00	Referent	1.00	Referent
Non-Adherent	1.18	(0.96-1.45)	1.36	(1.31-1.41)
Charlson Comorbidity Score[a]				
CCS 0	1.00	Referent	1.00	Referent
CCS 1	1.46	(1.22-1.75)	1.09	(1.04-1.14)
CCS 2+	1.62	(1.24-2.13)	0.98	(0.93-1.02)
CCS Unknown	0.97	(0.73-1.28)	0.99	(0.90-1.09)
Year Category				
1996 – 2002	1.00	Referent	1.00	Referent
2003 – 2006	1.14	(0.99-1.31)	0.95	(0.91-1.00)
2007 – 2014	1.39	(1.20-1.61)	0.94	(0.89-0.98)
Observed/ Expected Category				
Low	1.13	(0.80-1.61)	1.03	(0.97-1.10)
Intermediate	0.92	(0.66-1.29)	1.00	(0.95-1.06)
High	1.00	Referent	1.00	Referent
Distance traveled to care				
<6 km	1.00	Referent	1.00	Referent
6-9 km	0.87	(0.70-1.07)	0.96	(0.90-1.02)
10-16 km	0.73	(0.58-0.92)	0.93	(0.87-0.99)
17-32 km	0.70	(0.57-0.86)	0.91	(0.85-0.97)
>32 km	0.84	(0.66-1.06)	0.90	(0.84-0.96)
Closest High O/E Hospital				
<9 km	1.00	Referent	1.00	Referent
9-14 km	1.20	(0.96-1.48)	1.00	(0.94-1.06)
15-24 km	1.49	(1.19-1.86)	0.98	(0.92-1.05)
25-48 km	1.02	(0.74-1.41)	0.99	(0.93-1.05)
>48 km	0.92	(0.74-1.16)	0.97	(0.90-1.04)

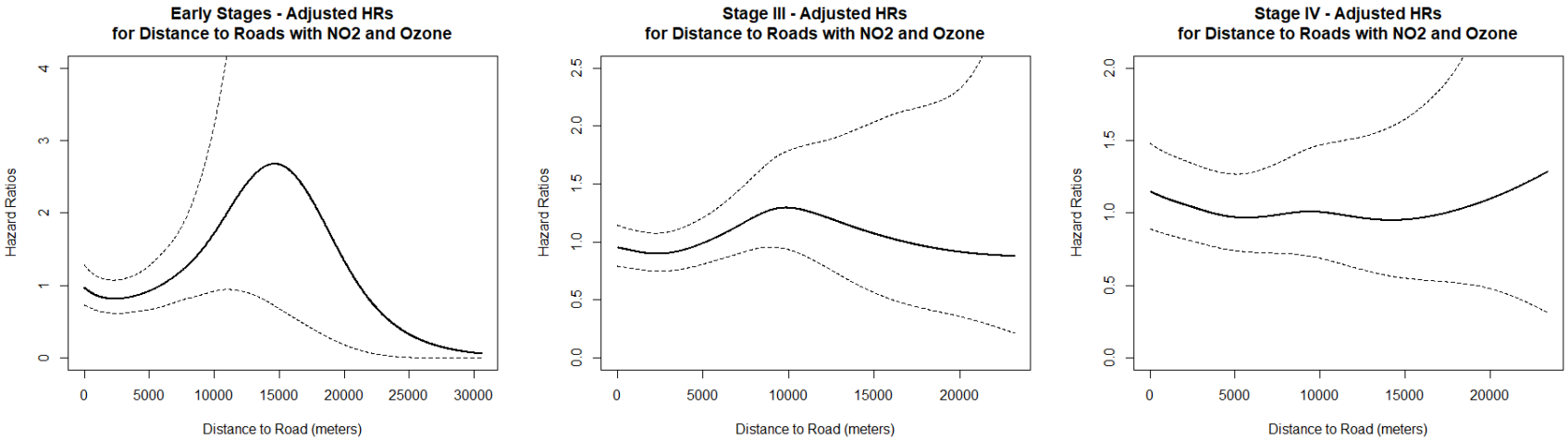
[a] The Charlson Comorbidity Score was used to assign comorbidity status and is grouped into quartiles (CCS 0- no comorbidities, CCS 1- one comorbidity, CCS 2- two or more comorbidities, and CCS Unknown- comorbidity status is unknown).

Abbreviations: *CI*, Confidence Interval*; CCS*, Charlson Comorbidity Score; *HR*, Hazard Ratios*; km*, kilometers; *NCCN*, National Comprehensive Cancer Network; *NOS*, Not Otherwise Specified; *O/E*, Observed to Expected; *QOC*, Quality-of-Care; *SES*, Socioeconomic Status

APPENDIX C – Chapter 3: Supplementary Material for Pollutant Exposures



Appendix Figure C.1: Analyses of Exposures using Penalized Cubic Splines
This figure shows each exposure assessed using a penalized cubic spline. Panel (A) for ozone and panel (B) for $PM_{2.5}$ show no or approximate linear relationships with survival. Panel (C) displays a nonlinear association between distance and survival, while panel (D) shows a sharp increase in hazards at higher exposures of nitrogen dioxide.



Appendix Figure C.2: Stage-Stratified Hazard Ratios of Distance to Primary and Secondary Major Roads using Penalized Cubic Splines for Unadjusted, Adjusted, and Multipollutant Nitrogen Dioxide (NO_2) Models

These figures show the stage-stratified associations between distance from a major roadway and ovarian cancer-specific survival using penalized cubic splines for women diagnosed in California between 1996-2014 (n=29,841). The solid lines represent the hazard ratios of survival and the dashed lines are the 95% confidence intervals. No significant association exists in any of the stage-stratified analyses between distance to major roadway and survival in multipollutant models adjusting for NO_2 and ozone. Models are all additionally adjusted for age at diagnosis, race/ethnicity, socioeconomic status, insurance status, marital status, stage at diagnosis (early stages only), tumor grade, tumor histology, tumor size, year of diagnosis, comorbidity status, and treatment adherence.

Appendix Table C.1: Adjusted Hazard Ratios for Select Sociodemographic Variables in the Nitrogen Dioxide Multipollutant Model by Stage of Diagnosis and Overall

	Early Stages		Stage III		Stage IV		Overall	
	(n=9,733)		(n=11,262)		(n=8,846)		(n=29,841)	
Characteristic	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**
Age*	1.02	(1.02, 1.03)	1.03	(1.02, 1.03)	1.02	(1.02, 1.02)	1.02	(1.02, 1.03)
Race/Ethnicity								
Non-Hispanic White	1.00	Ref	1.00	Ref	1.00	Ref	1.00	Ref
Non-Hispanic Black	1.32	(1.06, 1.66)	1.21	(1.08, 1.36)	1.04	(0.94, 1.16)	1.14	(1.06, 1.23)
Hispanic	0.83	(0.71, 0.96)	0.97	(0.90, 1.04)	0.86	(0.80, 0.93)	0.91	(0.87, 0.95)
Asian/Pacific Islander	0.86	(0.74, 1.01)	0.94	(0.86, 1.02)	0.97	(0.88, 1.05)	0.94	(0.89, 1.00)
Other	0.97	(0.50, 1.88)	0.89	(0.62, 1.27)	0.81	(0.58, 1.13)	0.84	(0.67, 1.06)
Socioeconomic Status								
Lowest SES	0.98	(0.82, 1.17)	1.10	(1.01, 1.21)	1.19	(1.09, 1.30)	1.13	(1.06, 1.20)
Lower-Middle SES	1.07	(0.92, 1.25)	1.13	(1.05, 1.22)	1.19	(1.10, 1.28)	1.16	(1.10, 1.22)
Middle SES	0.86	(0.74, 1.00)	1.10	(1.03, 1.18)	1.11	(1.02, 1.19)	1.08	(1.03, 1.13)
Higher-Middle SES	0.89	(0.77, 1.03)	1.08	(1.01, 1.16)	1.09	(1.01, 1.17)	1.06	(1.01, 1.11)
Highest SES	1.00	Ref	1.00	Ref	1.00	Ref	1.00	Ref
Insurance Type								
Managed Care	1.00	Ref	1.00	Ref	1.00	Ref	1.00	Ref
Medicare	1.05	(0.92, 1.20)	0.97	(0.91, 1.03)	0.90	(0.85, 0.96)	0.95	(0.91, 0.99)
Medicaid	1.17	(0.96, 1.44)	1.13	(1.02, 1.25)	1.08	(0.99, 1.19)	1.13	(1.06, 1.20)
Other Insurance	1.08	(0.93, 1.27)	0.95	(0.88, 1.03)	0.98	(0.89, 1.07)	0.97	(0.92, 1.03)
Not insured	1.23	(0.92, 1.65)	1.03	(0.87, 1.23)	1.21	(1.05, 1.40)	1.16	(1.05, 1.29)
Unknown	1.06	(0.71, 1.58)	1.00	(0.84, 1.18)	0.87	(0.73, 1.02)	0.93	(0.83, 1.04)
Marital Status								
Single	1.00	Ref	1.00	Ref	1.00	Ref	1.00	Ref
Married	0.91	(0.82, 1.00)	0.91	(0.87, 0.96)	0.91	(0.86, 0.95)	0.91	(0.88, 0.94)

Note: Models are additionally adjusted for ozone, distance to major roadway, stage at diagnosis, tumor size, tumor grade, histology, treatment adherence, Charlson Comorbidity Score, year of diagnosis

* Hazards and confidence intervals are identical due to rounding

Abbreviations: *CI,* Confidence Interval; *HR,* Hazard Ratios; *SES,* Socioeconomic Status

Appendix Table C.2: Race/Ethnicity and Socioeconomic Status Stage-Stratified Hazard Ratios for Multipollutant Models

	Model 1[a]							Model 2[b]			
	NO_2:	20.0-30.0 ppb		>30.0 ppb		Ozone			$PM_{2.5}$		Ozone	
	N	HR	95% CI	HR	95% CI	HR*	95% CI	N	HR*	95% CI	HR*	95% CI
Race/Ethnicity												
White	18,917	1.34	(1.27-1.42)	2.31	(2.12-2.53)	1.01	(0.99-1.04)	16170	1.45	(1.41-1.50)	1.03	(1.00-1.06)
Black	1,416	1.14	(0.95-1.37)	2.56	(1.93-3.40)	1.07	(0.97-1.17)	1238	1.21	(1.07-1.37)	1.05	(0.96-1.16)
Hispanic	5,749	1.37	(1.24-1.52)	3.36	(2.84-3.97)	1.03	(0.98-1.08)	5184	1.52	(1.43-1.62)	1.05	(0.96-1.14)
Asian	3,564	1.26	(1.10-1.45)	3.22	(2.54-4.08)	1.26	(1.10-1.45)	3205	1.41	(1.32-1.51)	0.94	(0.88-1.01)
Other	195	1.66	(0.52-5.24)	0.96	(0.20-4.63)	1.66	(0.52-5.24)	179	1.88	(1.24-2.85)	1.49	(1.12-1.97)
Total:	29,841							25976				
Socioeconomic Status												
Lowest	4,037	1.21	(1.08-1.36)	2.69	(2.24-3.23)	1.03	(0.97-1.09)	3526	1.51	(1.41-1.63)	1.03	(0.98-1.09)
Lower-Middle	5,434	1.30	(1.18-1.43)	2.73	(2.33-3.19)	1.04	(0.99-1.09)	4736	1.37	(1.30-1.45)	1.01	(0.96-1.06)
Middle	6,322	1.33	(1.21-1.47)	2.49	(2.15-2.88)	1.02	(0.97-1.06)	5512	1.49	(1.41-1.57)	1.03	(0.98-1.08)
Higher-Middle	6,860	1.33	(1.21-1.45)	2.57	(2.20-2.99)	1.01	(0.96-1.05)	5971	1.42	(1.34-1.50)	1.03	(0.98-1.07)
Highest	7,188	1.40	(1.28-1.53)	2.37	(2.01-2.79)	1.01	(0.96-1.06)	6231	1.46	(1.38-1.54)	1.03	(0.98-1.08)
Total:	29,841							25976				

* Hazard ratios are for an interquartile increase in concentration levels.
[a] Model is the multipollutant model adjusting for NO_2, ozone, and distance to major roadway.
[b] Model is the multipollutant model adjusting for $PM_{2.5}$, ozone, and distance to major roadway.
Note: Models are additionally adjusted for age, marital status, stage at diagnosis, tumor size, tumor grade, histology, treatment adherence, Charlson Comorbidity Score, year of diagnosis.

Abbreviations: *CI*, Confidence Interval; *HR*, Hazard Ratio; *NO_2*, Nitrogen Dioxide; *$PM_{2.5}$*, Particulate matter less than 2.5μm in diameter; *ppb*, Parts per billion; *SES*, Socioeconomic Status

Appendix Table C.3: Hazard Ratios for Covariates of Multipollutant Overall Models for Women in Diagnosed in California with Ovarian Cancer between 1996 and 2014

	$PM_{2.5}$ + Ozone + Distance			NO_2 + Ozone + Distance		
Characteristics	HR	95% CI	P Value	HR	95% CI	P Value
Age*	1.03	(1.02, 1.03)	<0.001	1.02	(1.02, 1.03)	<0.001
Race/Ethnicity						
Non-Hispanic White	1.00	Ref		1.00	Ref	
Non-Hispanic Black	1.15	(1.06, 1.24)	0.001	1.14	(1.06, 1.23)	<0.001
Hispanic	0.87	(0.83, 0.92)	<0.001	0.91	(0.87,0.95)	<0.001
Asian/Pacific Islander	0.96	(0.90, 1.02)	0.180	0.94	(0.89, 1.00)	0.038
Other	0.93	(0.73, 1.18)	0.540	0.84	(0.67, 1.06)	0.140
Socioeconomic Status						
Lowest SES	1.10	(1.03, 1.17)	0.004	1.13	(1.06, 1.20)	<0.001
Lower-Middle SES	1.13	(1.07, 1.20)	<0.001	1.16	(1.10, 1.22)	<0.001
Middle SES	1.08	(1.02, 1.14)	0.007	1.08	(1.03, 1.13)	0.003
Higher-Middle SES	1.06	(1.01, 1.11)	0.030	1.06	(1.01, 1.11)	0.022
Highest SES	1.00	Ref		1.00	Ref	
Insurance Type						
Managed Care	1.00	Ref		1.00	Ref	
Medicare	0.94	(0.90, 0.98)	0.003	0.95	(0.91, 0.99)	0.013
Medicaid	1.14	(1.06, 1.22)	<0.001	1.13	(1.06, 1.20)	<0.001
Other Insurance	0.98	(0.92, 1.04)	0.500	0.97	(0.92, 1.03)	0.320
Not insured	1.16	(1.03, 1.30)	0.012	1.16	(1.05, 1.29)	0.004
Unknown	0.94	(0.82, 1.07)	0.360	0.93	(0.83, 1.04)	0.180
Marital Status						
Single	1.00	Ref		1.00	Ref	
Married	0.91	(0.88, 0.94)	<0.001	0.91	(0.88, 0.94)	<0.001
Stage						
Stage 1	1.00	Ref		1.00	Ref	
Stage 2	2.49	(2.23, 2.77)	<0.001	2.49	(2.25, 2.74)	<0.001
Stage 3	6.45	(5.93, 7.00)	<0.001	6.58	(6.10, 7.09)	<0.001
Stage 4	10.20	(9.37, 11.10)	<0.001	10.59	(9.80, 11.44)	<0.001
Tumor Size, mm						
<50	1.00	Ref		1.00	Ref	
50-99	1.03	(0.96, 1.10)	0.390	1.03	(0.97, 1.09)	0.400
≥100	0.97	(0.91, 1.03)	0.330	0.98	(0.93, 1.04)	0.560
Unknown	1.20	(1.13, 1.27)	<0.001	1.21	(1.14, 1.27)	<0.001
Tumor Grade						
1	1.00	Ref		1.00	Ref	
2	1.65	(1.45, 1.87)	<0.001	1.61	(1.44, 1.80)	<0.001
3	1.82	(1.61, 2.05)	<0.001	1.79	(1.61, 2.00)	<0.001
4	1.90	(1.67, 2.15)	<0.001	1.81	(1.61, 2.02)	<0.001
Unknown	2.23	(1.98,2.53)	<0.001	2.16	(1.94, 2.41)	<0.001

Histology						
Serous	1.00	Ref		1.00	Ref	
Mucinous	1.49	(1.35, 1.65)	<0.001	1.42	(1.29, 1.56)	<0.001
Endometrioid	0.83	(0.76, 0.90)	<0.001	0.83	(0.77, 0.89)	<0.001
Clear cell	1.29	(1.17, 1.42)	<0.001	1.30	(1.19, 1.42)	<0.001
Adenocarcinoma, NOS	1.42	(1.34, 1.50)	<0.001	1.40	(1.33, 1.47)	<0.001
Others	1.28	(1.22, 1.34)	<0.001	1.24	(1.19, 1.30)	<0.001
Treatment Adherence						
Adherent	1.00	Ref		1.00	Ref	
Non-Adherent	1.22	(1.18, 1.27)	<0.001	1.23	(1.19, 1.28)	<0.001
Charlson Comorbidity Score[a]						
CCS 0	1.00	Ref		1.00	Ref	
CCS 1	1.15	(1.10, 1.21)	<0.001	1.13	(1.08, 1.17)	<0.001
CCS 2+	1.07	(1.02, 1.12)	0.003	1.02	(0.98, 1.06)	0.420
CCS Unknown	1.04	(0.96, 1.13)	0.340	0.95	(0.88, 1.03)	0.200
Year of Diagnosis	1.03	(1.03, 1.04)	<0.001	1.02	(1.01, 1.02)	<0.001

Notes: Hazard Ratios for models with $PM_{2.5}$ represent a subset of women who were diagnosed during or after 1999 (n=25,976).
* Hazards and confidence intervals are identical due to rounding
[a] The Charlson Comorbidity Score was used to assign comorbidity status and is grouped into quartiles (CCS 0- no comorbidities, CCS 1- one comorbidity, CCS 2- two or more comorbidities, and CCS Unknown- comorbidity status is unknown).

Abbreviations: *CI,* Confidence Interval; *CCS*, Charlson Comorbidity Score; *HR,* Hazard Ratio; *IQR,* Interquartile Range; *NO_2,* Nitrogen Dioxide; *NOS,* Not otherwise specified; *$PM_{2.5}$,* Particulate matter less than 2.5μm in diameter; *ppm,* Parts per million; *SE,* Standard Error