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Ambient Air Pollution and Ovarian Cancer Survival in California

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Abstract

Objective: To examine whether exposure to ambient ozone, particulate matter with diameter less than 2.5 microns ($PM_{2.5}$), nitrogen dioxide (NO_2), and distance to major roadways (DTR) impact ovarian cancer-specific survival, while considering differences by stage, race/ethnicity, and socioeconomic status.

Methods: Women diagnosed with epithelial ovarian cancer from 1996-2014 were identified through the California Cancer Registry and followed through 2016. Women's geocoded addresses were linked to pollutant exposure data and averaged over the follow-up period. Pollutants were considered independently and in multi-pollutant models. Cox proportional hazards models assessed hazards of disease-specific death due to environmental exposures, controlling for important covariates, with additional models stratified by stage at diagnosis, race/ethnicity and socioeconomic status.

Results: $PM_{2.5}$ and NO_2, but not ozone or DTR, were significantly associated with survival in univariate models. In a multi-pollutant model for $PM_{2.5}$, ozone, and DTR, an interquartile range increase in $PM_{2.5}$ (Hazard Ratio [HR], 1.45; 95% Confidence Interval [CI], 1.41-1.49) was associated with worse prognosis. Similarly, in the multi-pollutant model with NO_2, ozone, and DTR, women with higher NO_2 exposures (HR for 20.0-30.0 ppb, 1.30; 95% CI, 1.25-1.36 and HR for >30.0 ppb, 2.48; 95% CI, 2.32-2.66) had greater mortality compared to the lowest exposed (<20.0 ppb). Stratified results show the effects of the pollutants differed by race/ethnicity and were magnified among women diagnosed in early stages.

Conclusions: Our analyses suggest that greater exposure to NO_2 and $PM_{2.5}$ may adversely impact ovarian cancer-specific survival, independent of sociodemographic and treatment factors. These findings warrant further study.

Keywords

Ovarian cancer; survival; air pollution; disparities; environmental risks

Introduction:

Ovarian cancer has the highest mortality of all gynecologic cancers.[1] Survival rates differ by sociodemographic variables, disproportionately impacting non-Hispanic black women[2-7] and women of lower socioeconomic status (SES), despite receiving equal treatment.[2,8] Recently, geographic location was identified as an independent predictor of ovarian cancer mortality.[8,9] Geographic variations in ovarian cancer outcomes and the unexplained differences observed by race/ethnicity and SES warrant further investigation into the potential role of the environment in ovarian cancer survival.

Ambient air pollution is considered a carcinogen by the International Agency for Research on Cancer[10] and is increasingly associated with cancer outcomes.[11-16] Carcinogenic properties of pollutants such as particulate matter (PM) may induce oxidative stress, create chronic inflammation, and damage DNA.[17,18] Studies suggest that exposure to higher levels of air pollution may also independently shorten survival after a cancer diagnosis.[9,19-22] Responsiveness to treatment may be affected by the sustained inflammatory environment,[23] with persistently enhanced oxidative stress being associated with chemoresistance in epithelial ovarian cancer cells.[24]

Limited evidence suggests that spatially-varying environmental exposures may contribute to ovarian cancer mortality. Researchers in Taiwan found that greater exposure to particulate matter with diameter less than 2.5 microns ($PM_{2.5}$) was significantly associated with ovarian cancer mortality among the general population.[25] Census tract-level ozone and $PM_{2.5}$ were correlated with worse outcomes among women diagnosed with late-staged ovarian cancer in California.[9] Our objective was to determine the impact of average residential exposure to ambient ozone, $PM_{2.5}$, nitrogen dioxide (NO_2), and distance to closest major roadway (DTR) on disease-specific ovarian cancer survival among California women of all stages, while considering differences by stage, race/ethnicity and SES.

Methods:

We used a retrospective population-based study design to determine whether air pollution is associated with ovarian cancer-specific survival. ovarian cancer cases were obtained through the California Cancer Registry (CCR) for women with newly diagnosed invasive epithelial ovarian cancer 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%).[26,27] 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 online database, Air Quality and Meteorological Information System (AQMIS).[28] 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. Analyses with $PM_{2.5}$ were conducted 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. Exposure was assigned to women by spatially joining their geocoded residential location at time of diagnosis to the exposure data. The linked monthly 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 DTR as the distance from women's geocoded residential address to the closest primary or secondary road using the United States Census Bureau's TIGER/line file® (Topographically Integrated Geographic Encoding and Referencing System) in GIS. Three women were excluded from primary analyses because of residence on Catalina Island, which requires travel by ferry to reach mainland CA.

Covariates

Several important covariates were included in the adjusted models. We adjusted for year of diagnosis, modeled continuously. 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[29] if diagnosed before 2006 and the Yang index[30] for those diagnosed after. The Yost score is a community-level measure using census block group-level variables[29] and the Yang index is a comparable measure but uses block group variables from the American Community Survey, which is administered more frequently.[30]

We also controlled for the following known determinants of survival: age at diagnosis (modeled continuously); stage at diagnosis (International Federation of Gynecology and Obstetrics- Stages I-IV); tumor histology, grade, and size; comorbidity status; and treatment received. Comorbidity status (no comorbidities, one comorbidity, two or more

comorbidities, and comorbidity status unknown) was assigned using the Deyo-adapted Charlson Comorbidity Score.[31] We included a binary variable indicating whether women received guideline-adherent care, defined using the National Comprehensive Cancer Network treatment guidelines and previously validated as being significantly associated with ovarian cancer-specific survival.[32] NCCN specifies stage-specific guidance for surgery and chemotherapy, both of which must be adhered to for women to be considered having received guideline-adherent care.

Statistical Analyses

Descriptive statistics were run to determine any differences in covariates and exposures by stage at diagnosis, race/ethnicity, and SES. We used chi-square tests for categorical variables and analysis of variances for continuous variables. We calculated unadjusted and adjusted hazard ratios (HRs) and 95% confidence intervals (CI) between each pollutant and ovarian cancer-specific survival using Cox Proportional Hazard models. These relationships were explored linearly and using penalized cubic splines. Based on the spline model for NO_2, exposure was categorized as: <20.0 ppb, 20.0-30.0 ppb, and >30.0 ppb. Penalized cubic splines for ozone and $PM_{2.5}$ were both approximately linear, therefore HRs for these two pollutants are reported for an interquartile range (IQR) increase in concentrations. DTR is modeled continuously with penalized cubic splines (Appendix 1).

Multi-pollutant models were additionally run for exposures not highly correlated (Appendix 2). Ozone was not correlated with $PM_{2.5}$ (Pearson's R = −0.18) or NO_2 (Pearson's R= −0.17). $PM_{2.5}$ and NO_2 were highly correlated (Pearson's R = 0.80) and were not adjusted for simultaneously in any models. Survival was the time in months from the date of diagnosis to the date of death due to ovarian cancer or date of last follow-up. We also stratified by stage at diagnosis [early stages (Stage I and Stage II), Stage III, and Stage IV], race/ethnicity, and SES. We performed sensitivity analyses stratified by residential proximity to monitoring sites. All statistical analyses were performed in R (R Software Version 3.4.4).

Results:

Patient characteristics by stage at diagnosis are presented in Table 1. Median survival among all women was 34.5 months, ranging from 73.7 months to 14.6 months for those with an early stage and stage IV diagnosis, respectively. The majority of women were non-Hispanic white (63.4%). 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 μg/m³, respectively. The average DTR was 1,337 meters. Average exposures of NO_2 and $PM_{2.5}$ significantly differed by stage

at diagnosis, while there were no differences by stage for ozone and DTR. For NO_2 and $PM_{2.5}$, concentration levels increased with advancing stage. Table 2 shows the distribution of exposures overall and stage-stratified.

Significant differences were also observed in exposure levels by sociodemographic variables (Appendix 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 $\mu g/m^3$). 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 mean NO_2 exposure of 17.4 ppb while women in the highest group had a mean 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

In adjusted single-pollutant overall models (Table 3), 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 <20.0 ppb, women who had average 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. 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; Appendix 1).

In adjusted multi-pollutant models, NO_2 and $PM_{2.5}$ remained significant predictors of survival. Adding other pollutants to models with NO_2 did not change this association (Table 4). Likewise, greater average exposure to $PM_{2.5}$ after an ovarian cancer diagnosis was associated with poorer survival in multi-pollutant models with DTR ($PM_{2.5}$ 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 4). 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, DTR was significantly associated with survival in multi-pollutant models but not in the adjusted single-pollutant model (Appendix 4). Sensitivity analyses showed consistent patterns between the pollutants and survival regardless of stratification by distance to monitors (Appendix 5).

Stage-stratified Results

The effects of the exposure variables on survival varied by stage, with pollutants having a greater influence for women in early stages (Table 5). For example, among the highest NO_2 exposure category, 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). $PM_{2.5}$ likewise had a greater influence on survival among women diagnosed in early stages (IQR HR, 2.01; 95% CI, 1.84-2.19). While ozone's effect on survival was largely insignificant, its impact was largest among women in early stages (IQR HR, 1.05; 95% CI, 0.99-1.12). The associations between DTR and survival by stage are displayed in Appendix 6. Results for select covariates in stage-stratified NO_2 multi-pollutant analyses are presented in Appendix 7.

Race and SES-stratified Results

Several notable differences were observed in the impact of the air pollutants on survival by race/ethnicity and SES (Table 6). While overall, women with intermediate levels of average 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 multi-pollutant 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 multi-pollutant 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 multi-pollutant model with $PM_{2.5}$ (IQR HR, 1.21; 95% CI, 1.07-1.37) compared to the overall model. DTR 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 8). In the multi-pollutant model of all stages combined including NO_2, ozone, and DTR, non-Hispanic black women 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. Furthermore, being married was protective (HR, 0.91; 95% CI, 0.88-0.94).

Discussion:

We sought to determine whether exposure to air pollution after an ovarian cancer 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 DTR to influence women's outcomes, although they had marginal effects once accounting for other pollutants.

Air pollution has been linked with increased cancer risk and mortality,[13-15, 33-36] yet limited research has investigated the association between air pollution and ovarian cancer survival. In California, $PM_{2.5}$ was associated with shorter survival for patients diagnosed with lung,[19] liver,[20] and breast[22] cancers. NO_2, was also associated with shorter survival among patients diagnosed with lung cancer. We similarly found that $PM_{2.5}$ and NO_2 impacted survival. Consistent with our findings, all three studies also observed a stronger association with air pollution on women diagnosed in early stages. 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. 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. These findings, however, merit further investigation. Our results suggest that reducing exposure to air pollutants could improve ovarian cancer-specific survival overall, especially among early-staged women.

We also assessed differences in exposures by race/ethnicity and SES. Racial and ethnic minorities are often disparately affected by environmental hazards.[37-39] Consistent with the literature, non-Hispanic black, Hispanic, and women of lower SES generally had higher average exposures of $PM_{2.5}$ and NO_2 than non-Hispanic white women and those of higher SES. After adjusting for environmental exposures, race/ethnicity and SES were still significantly associated with ovarian cancer-survival, with non-Hispanic black women having worse survival and Hispanic and Asian/Pacific Islanders women having better survival. Since vulnerable communities share a larger burden of contaminants,[39,40] we assessed effect modification by race/ethnicity and SES. In race-stratified analyses, 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. Conversely, the effect of $PM_{2.5}$ and intermediate levels of NO_2 exposure were lower among non-Hispanic black women. This suggests that other competing life stressors are impacting ovarian cancer-survival among non-Hispanic black women.[41]

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.[42] To our knowledge, this is only the second study to consider the relationship between air pollution and ovarian cancer-specific survival,[9] 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, our study also addresses differences by race/ethnicity and SES, filling an important gap in the current literature.

Limitations

This study was limited by the data available in the cancer registry. Treatment data only includes first course of treatment. Any subsequent treatment received may affect survival. 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.

In conclusion, our results provide evidence that higher exposure to $PM_{2.5}$ and NO_2 may affect survival among women diagnosed with ovarian cancer. Women of non-Hispanic black race and of lower SES had higher exposure to the pollutants and worse prognosis, while Hispanics, Asian/Pacific Islanders, and women diagnosed in early stages were most susceptible to the effects of the pollutants. More research is needed to better understand the association between air pollution exposure and survival after an ovarian cancer diagnosis, particularly among early-staged women. Interventions to reduce excess exposure to air pollution on ovarian cancer-specific survival should be explored,[19] with recognition that reducing exposure and even improving indoor air may be difficult or unfeasible for some women.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments:

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Highlights:

- Higher $PM_{2.5}$ and NO_2 exposure was associated with shortened ovarian cancer survival

- Largest survival differences were observed among early-staged women

- Impact of pollutants on ovarian cancer survival differed by race/ethnicity

Table 1:

Patient Characteristics by Stage at Diagnosis for California Women Diagnosed with Ovarian Cancer, 1996-2014

Characteristic[*]	Early Stages	Stage III	Stage IV	Total
	N (%[†])	N (%[†])	N (%[†])	
Total	9,733 (21.5)	11,262 (52.0)	8,846 (26.5)	29,841 (100)
Age at Diagnosis				
Median (SD)	54 (15.3)	62 (13.9)	66 (13.8)	60 (14.9)
Survival Time (months)				
Median (SD)	73.7 (64.4)	33.8 (48.2)	14.6 (34.7)	34.5 (56.4)
Race/Ethnicity				
Non-Hispanic White	5,679 (30.0)	7,543 (39.9)	5,695 (30.1)	18,917 (63.4)
Non-Hispanic Black	363 (25.6)	507 (35.8)	546 (38.6)	1,416 (4.7)
Hispanic	2,025 (35.2)	2,022 (35.2)	1,702 (29.6)	5,749 (19.3)
Asian / Pacific Islander	1,592 (44.7)	1,125 (31.6)	847 (23.8)	3,564 (11.9)
Other	74 (37.9)	65 (33.3)	56 (28.7)	195 (0.7)
SES				
Lowest SES	1,294 (32.1)	1,385 (34.3)	1,358 (33.6)	4,037 (13.5)
Lower-Middle SES	1,742 (32.1)	1,951 (35.9)	1,741 (32.0)	5,434 (18.2)
Middle SES	2,077 (32.9)	2,349 (37.2)	1,896 (30.0)	6,322 (21.2)
Higher-Middle SES	2,260 (32.9)	2,632 (38.4)	1,968 (28.7)	6,860 (23.0)
Highest SES	2,360 (32.8)	2,945 (41.0)	1,883 (26.2)	7,188 (24.1)
Insurance				
Managed Care	5,131 (36.3)	5,347 (37.8)	3,671 (25.9)	14,149 (47.4)
Medicare	1,626 (21.2)	3,077 (40.2)	2,949 (38.5)	7,652 (25.6)
Medicaid	893 (32.8)	933 (34.2)	899 (33.0)	2,725 (9.1)
Other Insurance	1,580 (41.3)	1,419 (37.1)	825 (21.6)	3,824 (12.8)
Not insured	325 (36.6)	271 (30.5)	293 (33.0)	889 (3.0)
Unknown	178 (29.6)	215 (35.7)	209 (34.7)	602 (2.0)
Marital Status				
Single	4,637 (31.6)	5,264 (35.8)	4,785 (32.6)	14,686 (49.2)
Married	5,096 (33.6)	5,998 (39.6)	4,061 (26.8)	15,155 (50.8)
Tumor Size (mm)				
< 50	1,320 (35.4)	1,445 (38.7)	969 (26.0)	3,734 (12.5)
50-99	1,850 (31.4)	2,560 (43.5)	1,474 (25.1)	5,884 (19.7)
100	4,352 (46.6)	3,335 (35.7)	1,648 (17.7)	9,335 (31.3)
Unknown	2,211 (20.3)	3,922 (36.0)	4,755 (43.7)	10,888 (36.5)
Tumor Grade				
1	1,835 (77.3)	413 (17.4)	126 (5.3)	2,374 (8.0)
2	2,228 (51.1)	1,442 (33.1)	689 (15.8)	4,359 (14.6)
3	2,266 (22.5)	4,852 (48.3)	2,932 (29.2)	10,050 (33.7)
4	921 (22.0)	2,156 (51.4)	1,114 (26.6)	4,191 (14.0)

Characteristic [*]	Early Stages	Stage III	Stage IV	Total
	N (%[†])	N (%[†])	N (%[†])	
Unknown	2,483 (28.0)	2,399 (27.1)	3,985 (44.9)	8,867 (29.7)
Histology				
Serous	2,128 (16.6)	6,885 (53.6)	3,841 (29.9)	12,854 (43.1)
Mucinous	1,346 (70.8)	310 (16.3)	244 (12.8)	1,900 (6.4)
Endometrioid	2,308 (69.6)	727 (21.9)	283 (8.5)	3,318 (11.1)
Clear cell	1,214 (66.4)	421 (23.0)	194 (10.6)	1,829 (6.1)
Adenocarcinoma, NOS	304 (9.6)	845 (26.6)	2,029 (63.8)	3,178 (10.6)
Others	2,433 (36.0)	2,074 (30.7)	2,255 (33.3)	6,762 (22.7)
NCCN Treatment Adherence				
Adherent	2,451 (21.5)	5,943 (52.0)	3,024 (26.5)	11,418 (38.3)
Non-Adherent	7,282 (39.5)	5,319 (28.9)	5,822 (31.6)	18,423 (61.7)
Charlson Comorbidity Score[‡]				
CCS 0	5,444 (38.3)	5,303 (37.3)	3,471 (24.4)	14,218 (47.6)
CCS 1	1,787 (26.3)	2,741 (40.3)	2,278 (33.5)	6,806 (22.8)
CCS 2+	1,681 (25.0)	2,581 (38.4)	2,463 (36.6)	6,725 (22.5)
CCS Unknown	821 (39.2)	637 (30.4)	634 (30.3)	2,092 (7.0)
Diagnosis Year Category				
1996-1999	1,777 (33.9)	1,903 (36.3)	1,565 (29.8)	5,245 (17.6)
2000-2004	2,358 (31.7)	2,901 (39.0)	2,185 (29.4)	7,444 (24.9)
2005-2009	2,625 (31.7)	3,192 (38.5)	2,473 (29.8)	8,290 (27.8)
2010-2014	2,973 (33.5)	3,266 (36.9)	2,623 (29.6)	8,862 (29.7)
Distance to Major Road (m)				
< 50	209 (30.6)	243 (35.6)	230 (33.7)	682 (2.3)
50-149	564 (32.6)	646 (37.4)	518 (30.0)	1728 (5.8)
150-299	993 (33.5)	1150 (38.8)	823 (27.7)	2966 (9.9)
300-499	1156 (32.3)	1306 (36.5)	1117 (31.2)	3579 (12.0)
500	6811 (32.6)	7917 (37.9)	6158 (29.5)	20886 (70.0)

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

[*] With the exception of distance to major road, each patient characteristic was statistically different by stage at diagnosis (P < 01).

[†] Values represent row percentages.

[‡] The Charlson Comorbidity Score was used to assign comorbidity status and is grouped as: CCS 0- no comorbidities, CCS 1- one comorbidity, CCS 2- two or more comorbidities, and CCS Unknown- comorbidity status is unknown.

Table 2:

Assigned Residential Pollutant Exposure Levels Overall and by Stage of Diagnosis for California Women Diagnosed with Ovarian Cancer, 1996-2014

		Median	Mean	SD	25th Percentile	75th Percentile	*P* Value
NO_2 (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	
DTR (m)							
	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	

SD, Standard Deviation; *NO2*, Nitrogen Dioxide; *ppb*, Parts per billion; *PM2.5*, particulate matter with diameter less than 2.5 microns; *μg*, microgram; *m*, meters; *DTR*, Distance to road

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

Table 3:

Unadjusted and Adjusted Hazard Ratios for Ovarian Cancer-Specific Survival in Single-pollutant Models

Air Pollutant Exposures	IQR	Unadjusted HR (95% CI)	Adjusted HR (95% CI) [*]
PM$_{2.5}$ (μg/m^3) [†]	4.42	1.47 (1.43–1.50) [‡]	1.44 (1.40–1.47) [‡]
Ozone (ppb)	0.01	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)

IQR, Interquartile Range; *HR*, Hazard Ratios; *CI*, Confidence Interval; *PM$_{2.5}$*, Particulate matter less than 2.5μm in diameter; *μg*, microgram; *m*, meters; *ppb*, Parts per billion; *NO$_2$*, Nitrogen Dioxide

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

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

[‡] Represents the hazard ratios for an interquartile increase in concentration levels

Table 4:

Multivariate Ovarian Cancer-Specific Survival in Multi-pollutant Overall Models

Multi-pollutant Models	Coef	SE	HR [*][†]	95% CI
NO₂ + DTR				
NO₂ <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
DTR			0.98	0.86–1.11
NO₂ + Ozone				
NO₂ <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
NO₂ + Ozone + DTR				
NO₂ <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
DTR			0.98	0.86–1.11
PM₂.₅ + DTR [‡]				
PM₂.₅	0.08	2.92e-03	1.45	1.41–1.48
DTR			0.84	0.73–0.97
PM₂.₅ + Ozone [‡]				
PM₂.₅	0.08	0.003	1.44	1.41–1.48
Ozone	2.46	1.118	1.03	1.00–1.05
PM₂.₅ + Ozone + DTR [‡]				
PM₂.₅	0.08	2.93e-03	1.45	1.41–1.49
Ozone	2.55	1.12	1.03	1.00–1.05
DTR			0.85	0.73–0.98

Coef, Coefficient; *SE*, Standard Error; *HR*, Hazard Ratio; *CI*, Confidence Interval; *NO₂*, Nitrogen Dioxide; *DTR*, Distance to road; *ppb*, Parts per billion; *PM₂.₅*, Particulate matter less than 2.5μm in diameter

[*] Hazard ratios for PM₂.₅ and Ozone represent an interquartile increase in concentration levels. NO₂ is categorized into tertiles. The DTR hazard ratios reported are for the spline distance variable predicted at the median.

[†] All models are additionally adjusted for age at diagnosis, race/ethnicity, socioeconomic status, 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 PM₂.₅ represent a subset of women who were diagnosed during or after 1999 (n=25,976).

Table 5:

Multivariate Ovarian Cancer-Specific Survival in Multi-pollutant Models, Stage-Stratified

Multi-pollutant Models	EARLY STAGES (n=9,733)		STAGE III (n=11,262)		STAGE IV (n=8,846)	
	HR*	(95% CI)	HR*	(95% CI)	HR*	(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 DTR	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 DTR	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 DTR	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 DTR	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) [‡]						
Adjusted (SP)	1.49	(1.30–1.70)	1.27	(1.19–1.35)	1.30	(1.22–1.39)
with DTR	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 DTR	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) [§]						
Adjusted (SP)	8.13	(6.56–10.09)	2.75	(2.47–3.06)	1.86	(1.68–2.06)
with DTR	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 DTR	8.39	(6.76–10.41)	2.79	(2.51–3.11)	1.85	(1.67–2.06)

HR, Hazard Ratio; *CI*, Confidence Interval; *PM$_{2.5}$*, Particulate matter with diameter less than 2.5 microns; *SP*, Single-pollutant model; *NO$_2$*, Nitrogen Dioxide; *ppb*, Parts per billion;

*
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.

†
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.

‡
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.

§
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.

Models are additionally adjusted for age at diagnosis, race/ethnicity, socioeconomic status, insurance status, marital status, stage at diagnosis, tumor size, tumor grade, histology, treatment adherence, Charlson Comorbidity Score, year of diagnosis.

Table 6:

Adjusted [*] -Hazard Ratios for Multi-pollutant Models Stratified by Race/Ethnicity and Socioeconomic Status for Women Diagnosed with Ovarian Cancer, 1996–2014

	NO₂: N	Model 1 [†]						Model 2 [‡]					
		20.0-30.0 ppb		>30.0 ppb		Ozone		N	PM₂.₅		Ozone		
		HR	95% CI	HR	95% CI	HR[§]	95% CI		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/PI	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					

NO₂, Nitrogen Dioxide; *ppb*, Parts per billion; *PM₂.₅* Particulate matter less than 2.5µm in diameter; *HR*, Hazard Ratio; *CI*, Confidence Interval; *PI*, Pacific Islander

[*] Models are additionally adjusted for age at diagnosis, insurance status, marital status, stage at diagnosis, tumor size, tumor grade, histology, treatment adherence, Charlson Comorbidity Score, year of diagnosis.

[†] Model 1 is the multi-pollutant model adjusting for NO₂, ozone, and distance to major roadway.

[‡] Model 2 is the multi-pollutant model adjusting for PM₂.₅, ozone, and distance to major roadway.

[§] Hazard ratios are for an interquartile increase in concentration levels.