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Outdoor Air Pollution Exposure and Ovarian Cancer Incidence in a United States–Wide Prospective Cohort Study

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Introduction

Outdoor air pollution is classified as a Group 1 carcinogen based primarily on evidence of associations with lung cancer.[1] It has increasingly been associated with a higher incidence of other cancers, including breast[2,3] and uterine cancers.[4] Ovarian cancer, which shares a hormonal etiology with breast and uterine cancers,[5] is the deadliest gynecologic cancer among women, contributing to ∼12,740 deaths in the United States (US) in 2024.[6]

The literature on outdoor air pollution and ovarian cancer is sparse, with most studies evaluating mortality rather than incidence.[7] The few studies investigating disease etiology utilize cross-sectional or ecologic designs focusing on area-level observations.[7,8] A 2023 ecologic study using registry data across >700 US counties reported a positive association between county-level estimates of ambient particulate matter ≤2.5 μm in aerodynamic diameter ($PM_{2.5}$) and ovarian cancer incidence.[8] Our study expands upon the existing literature by investigating the association between individual-level residential estimates of air pollution [nitrogen dioxide (NO_2), $PM_{2.5}$, and ozone (O_3)] and incident ovarian cancer in a large, nationwide prospective cohort.

Methods

The Sister Study enrolled 50,884 women across the United States (2003–2009) who were 35–74 years of age with at least one sister who had breast cancer but no prior breast cancer themselves.[9] We excluded those who withdrew, had a history of ovarian cancer or bilateral oophorectomy at baseline, or were missing data, resulting in 40,308 eligible women (Data Release 11.1). The Sister Study was approved by the institutional review board of the National Institutes of Health. All participants provided written informed consent.

Ovarian cancer diagnoses were self-reported during annual follow-up surveys and confirmed with medical records when available (positive predictive value of 77%). For women in the contiguous United States, 12-month average ambient concentrations of NO_2 (in parts per billion), $PM_{2.5}$ (in micrograms per meter cubed), and O_3 (in parts per billion) were estimated at participants' primary residential address(es) over the follow-up period, accounting for residential mobility, using validated national spatiotemporal models. The models were extensions of regional spatiotemporal models of the Multi-Ethnic Study of Atherosclerosis and Air Pollution (MESA Air) and incorporate information from monitoring stations, satellite-derived pollutant concentrations, and several geographic characteristics.[10] Cross-validated R^2 values were 0.89, 0.87, and 0.73 for $PM_{2.5}$, NO_2, and O_3, respectively.

We used Cox proportional hazards models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between a 5-unit increase in time-varying 12-month average air pollutant concentrations and incident ovarian cancer. All models were time-scaled by person-months and stratified by age at baseline. Participants were considered at risk from enrollment to ovarian cancer diagnosis with censoring at the earliest of bilateral oophorectomy, loss to follow-up, death, or the administrative end of follow-up (June 2017). In model 1, we included covariates determined *a priori* as confounders based on prior literature, including race/ethnicity [Black, Hispanic/Latina, non-Hispanic White, or other races (American Indian/Alaskan Native, Asian, Native Hawaiian or other Pacific Islander)] given racial disparities in both air pollution exposure levels and ovarian cancer incidence, educational attainment (high school or less, some college, college degree or higher), baseline neighborhood socioeconomic status score (nSES; continuous; an index developed using 16 tract-level measures of educational attainment, occupation, income, wealth, poverty, employment status, and housing characteristics from the US Census and American Community Survey), and time-varying US Census region (Northeast, Midwest, South, West). Model 2 incorporated all covariates from model 1 and mutually adjusted for time-varying copollutants (e.g., the model for NO_2 was adjusted for both $PM_{2.5}$ and O_3 as individual continuous variables). Model 3 included all covariates from models 1 and 2, and further adjusted for ovarian cancer risk factors, including smoking (never, former, current), alcohol consumption (none, <1, 1 to <7, ≥7 drinks/week), physical activity (<5, 5 to <10, 10 to <20, ≥20 metabolic equivalent hours/week), body mass index (<25, 25 to <30, ≥30 kg/m^2), age at first birth (nulliparous, <20, 20 to <25, ≥25 y), parity (nulliparous, 1–2, ≥3 births), breastfeeding (nulliparous, <1, 1 to <7, ≥7 months), oral contraceptive use (never/ever), age at menopause (premenopausal, <50, 50 to <55, ≥55 y), age at menarche (<12, 12–13, ≥14 y), postmenopausal hormone therap1y use (never, former, current), and mother or sister with a ovarian cancer diagnosis (yes/no). We assessed effect modification by menopausal status at diagnosis (premenopausal/postmenopausal), US Census region, and self-reported residential urbanicity (urban, suburban, rural/small town/other) and

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Conclusions and opinions are those of the individual authors and do not necessarily reflect the policies or views of EHP Publishing or the National Institute of Environmental Health Sciences.

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restricted our analysis to medically confirmed diagnoses. Stratum-specific HRs were estimated by augmenting the primary model with multiplicative interaction terms and tested for heterogeneity using likelihood ratio tests. Nonlinearity was assessed by fitting restricted cubic splines with knots placement at the 5th, 27.5th, 50th, 72.5th, and 95th percentiles. Analyses were conducted in SAS (version 9.4; SAS Institute, Inc.).

Results

Over a mean ± standard deviation (SD) follow-up time of 9.8 ± 2.5 y, 249 participants were diagnosed with ovarian cancer. Baseline characteristics and the distribution of air pollutants are described in Table 1.

We observed higher incidence of ovarian cancer associated with a 5-ppb increase in NO_2 levels [HR = 1.21 (95% CI: 1.04, 1.41); model 1] (Table 2). Although the CIs were wider after adjusting for copollutants [HR = 1.21 (95% CI: 0.99, 1.47); model 2] and ovarian cancer risk factors [HR = 1.17 (95% CI: 0.95, 1.43); model 3], effect estimates were similar. $PM_{2.5}$ overall was not associated with ovarian cancer after copollutant adjustment [HR = 1.02 (95% CI: 0.65, 1.60); model 2]. However, the $PM_{2.5}$ level estimates were elevated, though imprecise, for premenopausal person-time [HR = 2.85 (95% CI: 0.98, 8.29); $p_{heterogeneity} = 0.16$] and for participants residing in the Midwest [HR = 1.40 (95% CI: 0.40, 4.89)] and West [HR = 1.63 (95% CI: 0.75, 3.52); $p_{heterogeneity} = 0.15$]. Associations with O_3 exposure were elevated for premenopausal person-time [HR = 1.36 (95% CI: 0.88, 2.10)] but were otherwise not apparent.

Discussion

To our knowledge, our study is the first to report a positive association between individual-level ambient air pollution exposure and incident ovarian cancer. Using data from a large US-wide, prospective cohort with time-varying air pollution estimates accounting for residential mobility over follow-up, we found limited evidence of an association with $PM_{2.5}$ or O_3 exposure but observed that greater levels of ambient NO_2 may be associated with higher ovarian cancer incidence. These findings are consistent with growing evidence for a role of air pollution, and for NO_2 in particular, in the incidence of hormone-dependent female cancers, including breast[2,3] and uterine cancer.[4] Although the biologic pathways underlying potential impacts of NO_2 exposure on ovarian cancer development are unclear, NO_2 levels are considered a proxy for near-road pollutant mixtures containing numerous compounds (e.g., diesel exhaust, benzene, and polycyclic aromatic hydrocarbons) with known carcinogenic or endocrine disrupting effects.[1]

Although we found limited evidence for $PM_{2.5}$ exposure overall, our findings suggest the association between $PM_{2.5}$ exposure and ovarian cancer may vary by geographic region, which has previously been observed in breast cancer studies.[3] These differences may reflect geographic variability in $PM_{2.5}$ chemical composition due to different emission sources. Further, associations with $PM_{2.5}$ and O_3 exposure were more apparent for premenopausal person-time, which has also been reported for $PM_{2.5}$ and NO_2 exposure and breast cancer.[11] Despite the large sample size, however, our study had limited power to explore relevant subgroups or consider histotypes. In addition, the exposure estimates do not capture air pollution indoors or exposures away from the home, although we expect such misclassification to be nondifferential.

In conclusion, our study provides evidence suggesting that exposure to NO_2 may be a risk factor for ovarian cancer. Given the rarity of ovarian cancer, studies that pool data from multiple prospective cohorts are needed to examine associations by tumor characteristics or other potential modifiers, including $PM_{2.5}$ chemical composition.

Table 1. Baseline characteristics of Sister Study participants by case status, enrolled 2003–2009.

Characteristics	Ovarian cancer cases ($n = 249$)	All ($n = 40{,}308$)[a]
Age (y) [*n* (%)]		
<40	5 (2.0)	1,966 (4.9)
40–49	52 (20.9)	10,666 (26.5)
50–59	90 (36.1)	15,701 (38.9)
60–69	79 (31.7)	9,853 (24.4)
70–79	23 (9.2)	2,122 (5.3)
Race/ethnicity [*n* (%)]		
Black, including Hispanic	20 (8.0)	3,349 (8.3)
Hispanic/Latina	5 (2.0)	1,254 (3.1)
Non-Hispanic White	220 (88.4)	34,401 (85.4)
Other races[b]	4 (1.6)	1,304 (3.2)
Educational attainment [*n* (%)]		
High school or less	46 (18.5)	5,734 (14.2)
Some college	87 (34.9)	13,176 (32.7)
College graduate or more	116 (46.6)	21,398 (53.1)
nSES score [median (IQR)][c]	−0.22 (−0.96, 0.38)	−0.29 (−1.07, 0.36)
Menopause status [*n* (%)]		
Premenopausal	80 (32.1)	16,458 (40.8)
Postmenopausal	169 (67.9)	23,845 (59.2)
US Census region [*n* (%)]		
Northeast	39 (15.7)	7,389 (18.3)
Midwest	73 (29.3)	11,040 (27.4)
South	78 (31.3)	13,105 (32.5)
West	59 (23.7)	8,774 (21.8)
Urbanicity [*n* (%)]		
Urban	39 (15.7)	7,695 (19.1)
Suburban	98 (39.3)	16,166 (40.1)
Rural/small town/other	112 (45.0)	16,447 (40.8)
12-month NO_2 concentrations (ppb) [median (IQR)]	8.9 (5.8–12.2)	8.4 (5.8–11.8)
12-month $PM_{2.5}$ concentrations ($\mu g/m^3$) [median (IQR)]	11.0 (8.8–12.8)	10.7 (8.7–12.4)
12-month O_3 concentrations (ppb) [median (IQR)]	26.3 (24.4–29.0)	26.6 (24.4–28.8)

Note: IQR, interquartile ranges; NO_2, nitrogen dioxide; nSES, neighborhood socioeconomic status; O_3, ozone; $PM_{2.5}$, particulate matter ≤2.5 μm in diameter.
[a]Excluded women who withdrew from the study ($n = 5$), had a prevalent or uncertain ovarian cancer history ($n = 235$), pre-baseline bilateral oophorectomy or unknown number of ovaries removed ($n = 9{,}010$), missing air pollutant exposure data ($n = 825$), missing race/ethnicity ($n = 13$), missing educational attainment ($n = 3$), missing nSES score ($n = 253$), missing US Census region ($n = 19$), or zero follow-up time ($n = 213$).
[b]Other races includes American Indian/Alaskan Native, Asian, and Native Hawaiian or other Pacific Islander.
[c]An index developed using 16 tract-level measures of educational attainment, occupation, income, wealth, poverty, employment status, and housing characteristics from the US Census and American Community Survey, with higher index indicating lower nSES and vice versa.

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Table 2. HRs (95% CIs) for the association between time-varying exposure to air pollutants (per 5-unit increase) and incident ovarian cancer in the Sister Study ($n = 40{,}308$, enrolled 2003–2009).

			NO_2 (ppb)[b]	$PM_{2.5}$ ($\mu g/m^3$)[b]	O_3 (ppb)[b]
Overall models, subgroups	Cases[a]	Person-years	HR (95% CI)	HR (95% CI)	HR (95% CI)
Overall					
Model 1[c]	249	395,950	1.21 (1.04, 1.41)	1.31 (0.90, 1.91)	0.92 (0.77, 1.09)
Model 2[d]	249	395,950	1.21 (0.99, 1.47)	1.02 (0.65, 1.60)	1.00 (0.82, 1.22)
Model 3[e]	247	391,673	1.17 (0.95, 1.43)	1.00 (0.64, 1.58)	1.00 (0.82, 1.22)
Confirmed cases[c,f]	205	395,950	1.14 (0.96, 1.35)	0.99 (0.60, 1.63)[g]	0.89 (0.73, 1.07)
Menopausal status[c,h]					
Premenopausal	43	101,436	1.14 (0.80, 1.62)	2.85 (0.98, 8.29)[g]	1.36 (0.88, 2.10)
Postmenopausal	206	294,515	1.20 (1.02, 1.42)	0.81 (0.49, 1.33)[g]	0.85 (0.70, 1.03)
$p_{heterogeneity}$			0.95	0.16	0.09
US Census region[c,h]					
Northeast	40	70,279	1.17 (0.88, 1.55)	0.56 (0.13, 2.34)[g]	0.79 (0.44, 1.44)
Midwest	71	107,060	1.61 (1.12, 2.32)	1.40 (0.40, 4.89)[g]	0.68 (0.42, 1.10)
South	78	131,080	1.20 (0.77, 1.87)	0.59 (0.23, 1.52)[g]	1.05 (0.64, 1.71)
West	60	87,531	1.10 (0.84, 1.44)	1.63 (0.75, 3.52)[g]	0.98 (0.78, 1.24)
$p_{heterogeneity}$			0.68	0.15	0.45
Urbanicity[c,h]					
Urban	39	74,811	1.44 (1.02, 2.02)	1.29 (0.47, 3.58)[g]	0.69 (0.42, 1.12)
Suburban	98	160,993	1.25 (0.93, 1.69)	1.15 (0.52, 2.54)[g]	0.93 (0.66, 1.30)
Rural/small town/other	112	160,146	1.42 (1.05, 1.91)	0.95 (0.48, 1.87)[g]	0.95 (0.73, 1.23)
$p_{heterogeneity}$			0.57	0.57	0.78

Note: CI, confidence interval; HR, hazard ratio; NO_2, nitrogen dioxide; nSES, neighborhood socioeconomic status score; O_3, ozone; $PM_{2.5}$, particulate matter <2.5 μm in diameter.
[a]Participants were considered at risk from enrollment to ovarian cancer diagnosis with censoring at the earliest of bilateral oophorectomy, loss to follow-up, death, or the administrative end of follow-up (June 2017).
[b]Spearman's rank correlation coefficients: NO_2 and $PM_{2.5} = 0.35$, NO_2 and $O_3 = -0.61$, and $PM_{2.5}$ and $O_3 = -0.20$.
[c]Cox proportional hazards model adjusted for calendar month (time scale), age (strata), race/ethnicity [Black, Hispanic/Latina, non-Hispanic White, other (including American Indian/Alaskan Native, Asian, Native Hawaiian or other Pacific Islander)], education (high school or less, some college, college degree or higher), baseline nSES (an index developed using 16 tract-level measures of educational attainment, occupation, income, wealth, poverty, employment status, and housing characteristics from the US Census and American Community Survey, with higher index indicating lower nSES and vice versa), and time-varying US Census region (Northeast, Midwest, South, West).
[d]In addition to covariates included in model 1, model 2 was mutually adjusted for time-varying copollutants (e.g., models for NO_2 were adjusted for $PM_{2.5}$ and O_3).
[e]In addition to covariates included in models 1 and 2, model 3 was adjusted for ovarian risk factors, including smoking (never, former, current), alcohol consumption (none, <1, 1 to <7, ≥7 drinks per week), physical activity (<5, 5 to <10, 10 to <20, ≥20 metabolic equivalent hours per week), body mass index (<25, 25 to <30, ≥30 kg/m^2), age at first birth (nulliparous, <20, 20 to <25, ≥25 y), parity (nulliparous, 1–2, ≥3 births), breastfeeding (nulliparous, <1, 1 to <7, ≥7 months), oral contraceptive use (never, ever), age at menopause (premenopausal, <50, 50 to <55, ≥55 y), age at menarche (<12, 12–13, ≥14 y), postmenopausal hormone therapy use (never, former, current), and mother or sister with a ovarian cancer diagnosis (yes, no).
[f]Restricted to cases confirmed by medical records; the confirmed cases include 108 serous, 14 endometrioid, 9 mucinous, and 9 clear cell carcinoma, as well as 29 other subtypes.
[g]For $PM_{2.5}$ analyses, models were additionally adjusted for time-varying NO_2 and O_3 levels, due to estimate changes observed after adjusting for these copollutants.
[h]Stratum-specific HRs were estimated by augmenting the primary model with multiplicative interaction terms and tested for heterogeneity using likelihood ratio tests.

All data necessary to reproduce the current analysis are available following procedures described on the Sister Study website (https://sisterstudy.niehs.nih.gov/English/data-requests.htm).

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