A Section 508–conformant HTML version of this article is available at https://doi.org/10.1289/EHP1249.

Ambient Air Pollution and Cancer Mortality in the Cancer Prevention Study II

Michelle C. Turner,[1,2,3,4] Daniel Krewski,[1,5] W. Ryan Diver,[6] C. Arden Pope III,[7] Richard T. Burnett,[8] Michael Jerrett,[9] Julian D. Marshall,[10] and Susan M. Gapstur[6]

[1] McLaughlin Centre for Population Health Risk Assessment, University of Ottawa, Ottawa, Canada
[2] Barcelona Institute for Global Health (ISGlobal), Barcelona, Spain
[3] Universitat Pompeu Fabra (UPF), Barcelona, Spain
[4] CIBER Epidemiología y Salud Pública (CIBERESP), Madrid, Spain
[5] School of Epidemiology and Public Health, Faculty of Medicine, University of Ottawa, Ottawa, Canada
[6] Epidemiology Research Program, American Cancer Society, Atlanta, Georgia, USA
[7] Department of Economics, Brigham Young University, Provo, Utah, USA
[8] Population Studies Division, Health Canada, Ottawa, Canada
[9] Department of Environmental Health Sciences, Fielding School of Public Health, University of California Los Angeles, Los Angeles, California, USA
[10] Department of Civil and Environmental Engineering, University of Washington, Seattle, Washington, USA

Background: The International Agency for Research on Cancer classified both outdoor air pollution and airborne particulate matter as carcinogenic to humans (Group 1) for lung cancer. There may be associations with cancer at other sites; however, the epidemiological evidence is limited.

Objective: The aim of this study was to clarify whether ambient air pollution is associated with specific types of cancer other than lung cancer by examining associations of ambient air pollution with nonlung cancer death in the Cancer Prevention Study II (CPS-II).

Methods: Analysis included 623,048 CPS-II participants who were followed for 22 y (1982–2004). Modeled estimates of particulate matter with aerodynamic diameter <2.5 μm ($PM_{2.5}$) (1999–2004), nitrogen dioxide (NO_2) (2006), and ozone (O_3) (2002–2004) concentrations were linked to the participant residence at enrollment. Cox proportional hazards models were used to estimate associations per each fifth percentile–mean increment with cancer mortality at 29 anatomic sites, adjusted for individual and ecological covariates.

Results: We observed 43,320 nonlung cancer deaths. $PM_{2.5}$ was significantly positively associated with death from cancers of the kidney {adjusted hazard ratio (HR) per 4.4 $\mu g/m^3$ = 1.14 [95% confidence interval (CI): 1.03, 1.27]} and bladder [HR = 1.13 (95% CI: 1.03, 1.23)]. NO_2 was positively associated with colorectal cancer mortality [HR per 6.5 ppb = 1.06 (95% CI: 1.02, 1.10). The results were similar in two-pollutant models including $PM_{2.5}$ and NO_2 and in three-pollutant models with O_3. We observed no statistically significant positive associations with death from other types of cancer based on results from adjusted models.

Conclusions: The results from this large prospective study suggest that ambient air pollution was not associated with death from most nonlung cancers, but associations with kidney, bladder, and colorectal cancer death warrant further investigation. https://doi.org/10.1289/EHP1249

Introduction

The International Agency for Research on Cancer (IARC) classified outdoor air pollution and airborne particulate matter as carcinogenic to humans (Group 1) for lung cancer based on findings from observational and experimental studies as well as from strong mechanistic evidence (IARC 2013). Recent meta-analyses reported positive associations of particulate matter with aerodynamic diameter <2.5 μm ($PM_{2.5}$ {relative risk (RR) per 10 $\mu g/m^3$ = 1.09 [95% confidence interval (CI): 1.04, 1.14]} and nitrogen dioxide (NO_2) [RR per 10 $\mu g/m^3$ = 1.04 (95% CI: 1.01, 1.08) with lung cancer risk (Hamra et al. 2014, 2015). Similar findings were reported in other recent reviews (Cui et al. 2015; Yang et al. 2016).

Ambient air pollution represents a complex mixture of a broad range of carcinogenic and mutagenic substances that may play a role in chronic systemic inflammation, oxidative stress, and DNA damage in tissues other than the lung (Brook et al. 2010; Crouse et al. 2010; IARC 2012, 2013; Newby et al. 2015). As such, there may also be associations between ambient air pollution and other types of cancer; however, the epidemiological evidence for these associations is limited (IARC 2013).

Some previous studies reported positive associations of ambient air pollution with fatal bladder cancer (Liu et al. 2009), pancreatic cancer (Ancona et al. 2015), upper digestive tract, digestive accessory organs, and breast cancer (Wong et al. 2016), and with incident brain and cervical cancer (Raaschou-Nielsen et al. 2011), breast cancer (Crouse et al. 2010; Reding et al. 2015), hepatocellular carcinoma (Pan et al. 2015), and prostate cancer (Parent et al. 2013). Results from other studies of fatal brain cancer (McKean-Cowdin et al. 2009), incident brain tumors (Poulsen et al. 2016), and incident leukemia (Winters et al. 2015) were mixed or null. Previous studies are difficult to compare given variation in the specific cancers studied; whether outcomes were incident versus fatal cancers; and differences in study design, sample size, exposure assessment, and the availability of data on potential confounders.

We previously reported positive associations between long-term ambient air pollution exposure and lung cancer mortality in the American Cancer Society (ACS) Cancer Prevention Study II (CPS-II) (Jerrett et al. 2013; Krewski et al. 2000, 2009; Turner et al. 2011, 2014, 2016). For example, we estimated that a 10-$\mu g/m^3$ increase in $PM_{2.5}$ concentrations was associated with a

Address correspondence to M.C. Turner, McLaughlin Centre for Population Health Risk Assessment, University of Ottawa, 600 Peter Morand Cres., Room 216, Ottawa, Ontario, Canada K1G 3Z7. Telephone: 613-562-5381. Email: mturner@uottawa.ca

Supplemental Material is available online (https://doi.org/10.1289/EHP1249).

M.C.T. reports personal fees from ICF Incorporated, LLC, outside this work. D.K. reports serving as Chief Risk Scientist and CEO at Risk Sciences International (http://www.risksciences.com), a Canadian company established in 2006 in partnership with the University of Ottawa conducting work in air quality risk assessment for both public and private sector clients. D.K. also holds an Industrial Research Chair in Risk Science under a peer-reviewed university–industry partnership program administered by the Natural Sciences and Engineering Research Council of Canada, which involves methodological research in air pollution risk assessment. D.K. also recently served as Chair of the U.S. Health Effects Institute Diesel Epidemiology Panel, which conducted an evaluation of recent epidemiological evidence on quantitative risk assessment of diesel emissions and lung cancer.

All other authors declare they have no actual or potential competing financial interests.

Received 18 October 2016; Revised 31 March 2017; Accepted 31 March 2017; Published 21 August 2017.

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Table 1. Distribution of air pollution concentrations, CPS-II cohort, United States ($n = 623{,}048$).

Air pollutant (units)	Time period	Mean (SD)	Minimum	Percentiles					Maximum	Increment
				5th	25th	50th	75th	95th		5th percentile–mean
$PM_{2.5}$ ($\mu g/m^3$)	1999–2004	12.6 (2.8)	1.4	8.2	10.6	12.5	14.4	17.0	27.9	4.4
NO_2 (ppb)	2006	11.6 (5.1)	1.0	5.1	8.1	10.8	14.1	21.2	37.6	6.5
O_3 (ppb)	2002–2004	38.2 (4.0)	26.7	31.3	36.2	38.1	40.1	44.9	59.3	6.9
Near-source $PM_{2.5}$ ($\mu g/m^3$)[a]	1999–2004	12.0 (0.9)	8.6	10.4	11.6	12.0	12.5	13.5	19.7	1.6
Regional $PM_{2.5}$ ($\mu g/m^3$)[a]	1999–2004	0.5 (2.7)	−7.9	−4.0	−1.4	0.5	2.5	4.6	13.0	4.5

Note: CPS-II, Cancer Prevention Study II; NO_2, nitrogen dioxide; O_3, ozone; $PM_{2.5}$, particulate matter with aerodynamic diameter <2.5 μm.
[a]The land use regression Bayesian maximum entropy (LURBME) $PM_{2.5}$ model was created in three main steps: *a*) A base LUR model predicted $PM_{2.5}$ concentrations based on traffic within 1 km (based on modeled traffic counts) and the cube of green space within 100 m; *b*) A BME interpolation model was then used to interpolate residual spatiotemporal variation in $PM_{2.5}$ concentrations; *c*) The two estimates were then combined. Regional $PM_{2.5}$ concentrations therefore represent a residual with some observations less than zero.

9% (95% CI: 3, 16%) increase in lung cancer mortality (Turner et al. 2016, Table E4). The CPS-II is a large-scale prospective cohort in which the human health effects of ambient air pollution have been extensively investigated. The objective of this work was to clarify whether ambient air pollution is associated with specific types of cancer other than lung cancer by examining associations of ambient air pollution with nonlung cancer death among 623,048 CPS-II participants who were followed for 22 y.

Methods

Study Population

Approximately 1.2 million CPS-II participants were enrolled by 77,000 volunteers in 1982 throughout the entire United States, Washington, DC, and Puerto Rico. Participants, largely friends and family members of volunteers, were ≥30 y old with a family member ≥45 y old. A detailed self-administered questionnaire was completed at enrollment to obtain demographic, medical, and behavioral information (CPS-II questionnaires are available at https://www.cancer.org/research/we-conduct-cancer-research/epidemiology/cancer-prevention-questionnaires.html). Informed consent was implied by completion and return of the enrollment questionnaire. The Emory University School of Medicine Human Investigations Committee has approved all aspects of the CPS-II.

Volunteers ascertained the vital status of participants they had enrolled in 1984, 1986, and 1988, and death certificates, coded by trained nosologists, were used to determine the underlying cause of death, that is, "the disease or injury which initiated the train of morbid events leading directly to death" (WHO 1992). Since 1989, the National Death Index (NDI) has been used to determine vital status and underlying cause of death (Calle and Terrell 1993). Underlying cause of death was categorized according to the *International Classification of Diseases* (ICD) revisions 9 and 10 (WHO 1977, 1992). More than 99% of known deaths were assigned a cause.

Ambient Air Pollution Concentrations

$PM_{2.5}$ concentrations were assigned to the geocoded participant residence at enrollment based on a national-level hybrid land use regression (LUR) and Bayesian maximum entropy (BME) interpolation model (Beckerman et al. 2013) used in previous work (Jerrett et al. 2016; Pope et al. 2015; Turner et al. 2014; 2016). Details on the geocoding of participant residences are presented elsewhere (Pope et al. 2015). A total of 104,172 observations were collected monthly from 1,464 monitoring sites between 1999 and 2008. Approximately 10% of observations were reserved for cross-validation. $PM_{2.5}$ concentrations were predicted in a base LUR model that included traffic within 1 km (based on modeled traffic counts) and the cube of green space within 100 m. A BME interpolation model was then used to account for residual spatiotemporal variation in $PM_{2.5}$ concentrations, and the two estimates were combined. The cross-validation R^2 was 0.79, suggesting good spatiotemporal model prediction at locations other than those used to calibrate the model. Mean $PM_{2.5}$ concentrations at the enrollment residence for the period 1999–2004 were used in the present analysis to coincide with the cohort follow-up period.

NO_2 concentrations were assigned at the census block group level to each participant enrollment residence. A national LUR model was used that incorporated both hourly monitoring data from 423 monitors and ∼4 million satellite-based measurements in an approximate 10 km × 10 km grid scale, including additional data on population density, land use, and distance to roadways for the year 2006 (model $R^2 = 0.78$) (Novotny et al. 2011; Turner et al. 2016).

Ozone (O_3) concentrations were obtained from the U.S. Environmental Protection Agency (EPA) and Centers for Disease Control and Prevention (CDC) Environmental Public Health Tracking Network Hierarchical Bayesian space time model (HBM) combining data from national air monitoring stations/state and local air monitoring stations (NAMS/SLAMS) and the Models-3/Community Multiscale Air Quality (CMAQ) photochemical model (U.S. EPA 2011). Daily 8-h maximum concentrations at a 36 km × 36 km grid scale for the years 2002–2004 were assigned to each participant enrollment residence (Turner et al. 2016).

Statistical Methods

Both single- and multipollutant Cox proportional hazards regression models were used to estimate associations of ambient $PM_{2.5}$, NO_2, and O_3 concentrations with death from 29 specific types of cancer according to an increment of the mean minus the fifth percentile for each pollutant (4.4 $\mu g/m^3$ for $PM_{2.5}$, 6.5 ppb for NO_2, and 6.9 ppb for O_3) (Table 1). The fifth percentile–mean increment was used for comparability of results across pollutants and with previous work (Turner et al. 2016).

Models were stratified by 1-y age categories, gender, and race/ethnicity (white, black, other) to allow for separate baseline hazards according to these characteristics. In addition, in the multivariate model, we also adjusted for baseline values of education (<high school, high school, >high school); marital status (single, married, other); body mass index (BMI); BMI squared; smoking status (never cigarettes, pipes, or cigars; current cigarette smoker only; former cigarette smoker only; ever pipe/cigar); cigarettes per day and cigarettes per day squared (current and former cigarette smokers); years smoked and years smoked squared (current and former cigarette smokers); started smoking <18 y old (yes/no) (current and former cigarette smokers); passive smoking (hours per day exposed to cigarette smoke of others at home, work, or other areas); usual dietary intake of vegetables, fruit, and fiber (combined, in quintiles) and fat (quintiles), plus a

category for missing/bad dietary intake data; usual consumption of beer (yes, no, missing), wine (yes, no, missing), and liquor (yes, no, missing); occupational exposures (ever regular exposure to asbestos, chemicals/acids/solvents, coal or stone dusts, coal tar/pitch/asphalt, formaldehyde, or diesel engine exhaust) (yes/no); and an occupational dirtiness index to characterize workplace $PM_{2.5}$ exposure based on main lifetime occupation (six categories of exposure vs. a referent category, or missing) (Siemiatycki et al. 2003). In addition, we used 1990 census data to derive the following socioecomonic covariates defined at the ZIP-code level for each participant's residence at enrollment: median household income, percentage of African American residents, percentage of Hispanic residents, percentage of adults with post-secondary education, percentage of unemployed residents ≥16 y old, and percentage of residents with household incomes <125% of the poverty level. For each characteristic, we modeled the value for the ZIP code of residence and for a second variable indicating the difference between that value and the county-level mean (Jerrett et al. 2016; Pope et al. 2015; Turner et al. 2016; U.S. Department of Commerce Bureau of the Census 1993). The time axis was follow-up time in days. Participants lost to follow-up or who were alive at the end of follow-up were censored.

For analysis of death from cancers of the uterus, cervix, or ovary, participants were excluded if they reported a previous hysterectomy or an artificial (vs. a natural) menopause ($n = 108{,}956$). An additional 7,143 participants were also excluded from analysis of ovarian cancer mortality if they reported having undergone an ovarian surgery because no information was available to distinguish partial from total oophorectomy.

A sensitivity analysis was performed to examine the influence of including additional baseline variables in the model including usual physical exercise (none, slight, moderate, heavy, missing), aspirin use in the past month (yes/no), and usual dietary intake of red meat (quintiles) for analysis of all cancer sites, as well as self-reported physician-diagnosed diabetes (yes/no). Detailed reproductive and hormonal variables, including age at menarche (<12 y old, 12–13 y old, ≥14 y old, missing), parity (0, 1, 2, 3, ≥4, missing), age at first birth (none, <20 y old, 20–29 y old, ≥30 y old, missing), ever oral contraceptive use (yes, no, missing), ever postmenopausal hormone use (yes, no, missing), and postmenopausal status (yes, no, missing) were also included in models for sensitivity analysis of female reproductive cancers. Additional analyses were also performed in postmenopausal women only.

Further, we decomposed $PM_{2.5}$ concentrations into near-source and regional fractions to determine whether associations might vary for $PM_{2.5}$ from different air pollution sources (Turner et al. 2016). Near-source $PM_{2.5}$ concentrations were $PM_{2.5}$ concentrations predicted at each monitoring station based on land-use and traffic count data using the LUR model created in the first stage of the LURBME modeling process. Regional $PM_{2.5}$ was derived by subtracting the near-source $PM_{2.5}$ concentration from the total $PM_{2.5}$ concentrations from the LURBME model, thereby capturing spatial variation in $PM_{2.5}$ concentrations between monitoring stations.

Finally, where there were statistically significant positive associations observed, potential effect modification by gender, education (<high school, high school, >high school), and smoking status (never cigarettes, pipes, or cigars; current cigarette smoker only; former cigarette smoker only) was assessed on a multiplicative scale. Two-sided p-values were calculated according to the likelihood ratio statistic to compare models with and without multiplicative interaction terms between air pollutants and the potential modifiers. The proportional hazards assumption was tested by including interaction terms between ambient air pollution and follow-up time in the multivariate proportional hazards models. A p-value <0.05 was used to define statistical significance throughout this work.

SAS (version 9.2; SAS Institute Inc.) was used to conduct all analyses. Ethics approval for analysis was obtained from the Ottawa Hospital Research Ethics Board.

Results

From 1982 through 2004 there were a total of 743,543 (62.8%) participants who were alive and 438,123 (37.0%) who had died. Participants were excluded from analysis because of missing or invalid residence information ($n = 385{,}422$) or selected baseline covariate data ($n = 130{,}119$) (Jerrett et al. 2016; Pope et al. 2015; Turner et al. 2016) or having a prevalent cancer (except nonmelanoma skin cancer) at enrollment ($n = 45{,}998$). Follow-up was censored in September 1988 for 2,921 (0.2%) of participants who had insufficient information to link to the NDI. The present analysis is based on 623,048 CPS-II participants among whom 43,320 nonlung cancer deaths were observed during 11,936,799 person-years of follow-up. Follow-up ranged from 0.01 y to 22.5 y with a mean (SD) of 19.2 (5.6) y.

Mean (SD) $PM_{2.5}$, NO_2, and O_3 concentrations at the participant residence at enrollment were 12.6 (2.8) $\mu g/m^3$, 11.6 (5.1) ppb, and 38.2 (4.0) ppb, respectively (Table 1). Correlations between these air pollutants ranged from a weak inverse correlation between NO_2 and O_3 ($r = -0.09$) to a moderate positive correlation between $PM_{2.5}$ and NO_2 ($r = 0.40$) (see Table S1).

Participant characteristics are presented in Table 2 and Table S2. The majority of participants were 40 y old to 69 y old at enrollment, 94.5% of participants were white, 55.3% were female, and 57.4% had a greater than high school education. A total of 44.7% of study participants were never smokers.

There was little variation in ambient air pollution concentrations by participant characteristics, although somewhat higher $PM_{2.5}$ and NO_2 concentrations were observed in the younger and older age groups and among participants who were black or "other" race/ethnicity (Table 2). O_3 concentrations were slightly higher in older participants, in those with a low BMI (<18.5 kg/m^2), and among never smokers.

The results from single-pollutant models per each fifth percentile–mean increment are presented in Table S3 according to the minimally adjusted model and in Table 3 according to the fully adjusted model. In the minimally adjusted model, there were several significant positive associations of $PM_{2.5}$ and colorectal, breast, cervical, and bladder cancer mortality and of NO_2 and stomach, colorectal, pancreatic, breast, and bladder cancer mortality as well as some significant inverse associations largely with O_3. Fewer significant findings were observed in the fully adjusted models, with significant positive associations of $PM_{2.5}$ and mortality from kidney [HR per 4.4 $\mu g/m^3 = 1.14$ (95% CI: 1.03, 1.27)] and bladder [HR = 1.13 (95% CI: 1.03, 1.23)] cancer observed (Table 3) [or equivalently per each 10 $\mu g/m^3$, HRs = 1.36 (95% CI: 1.06, 1.73) and 1.32 (95% CI: 1.07, 1.61), respectively]. There was a positive HR for colorectal cancer mortality [HR = 1.04 (95% CI: 1.00, 1.08)] of borderline significance ($p = 0.08$). The largest HR was observed for mortality from cervical cancer [HR = 1.34 (95% CI: 0.98, 1.83)], although this result was no longer significant and was based on a small number of deaths ($n = 115$). For NO_2, there was a weak positive association with mortality from colorectal cancer [HR per 6.5 ppb = 1.06 (95% CI: 1.02, 1.10)] [or equivalently HR = 1.09 (95% CI: 1.03, 1.16) per 10 ppb]. For O_3, HRs were generally <1, with statistically significant inverse associations with mortality from stomach cancer [HR per 6.9 ppb = 0.90 (95% CI: 0.81, 0.99)], pancreatic

Table 2. Distribution of selected participant characteristics at enrollment (1982) and air pollution concentrations, CPS-II cohort, United States ($n = 623{,}048$).

Characteristic	%	$PM_{2.5}$ ($\mu g/m^3$) Mean (SD)	NO_2 (ppb) Mean (SD)	O_3 (ppb) Mean (SD)
Age (years)				
<40	4.6	12.8 (2.9)	12.4 (5.7)	38.0 (3.9)
40–49	21.2	12.5 (2.8)	11.4 (5.1)	38.0 (3.8)
50–59	37.1	12.6 (2.8)	11.5 (5.0)	38.1 (3.9)
60–69	26.0	12.6 (2.9)	11.6 (5.1)	38.3 (4.1)
70–79	9.4	12.6 (2.9)	11.8 (5.0)	38.4 (4.2)
≥80	1.7	12.7 (2.9)	12.2 (5.1)	38.3 (4.2)
Race/ethnicity				
White	94.5	12.5 (2.8)	11.5 (5.0)	38.2 (3.9)
Black	3.9	13.7 (2.5)	13.3 (5.2)	38.1 (3.3)
Other	1.6	12.9 (4.3)	15.6 (6.4)	38.3 (5.8)
Gender				
Male	44.7	12.5 (2.8)	11.5 (5.1)	38.2 (4.0)
Female	55.3	12.6 (2.8)	11.7 (5.1)	38.2 (3.9)
Education				
<High school	11.6	12.8 (2.8)	11.6 (5.3)	38.1 (3.8)
High school	31.1	12.6 (2.7)	11.4 (5.1)	38.1 (3.7)
>High school	57.4	12.5 (2.9)	11.7 (5.0)	38.2 (4.1)
Marital status				
Single	3.3	13.0 (2.8)	13.1 (5.5)	37.5 (3.8)
Married	84.8	12.5 (2.8)	11.5 (5.0)	38.2 (3.9)
Other	11.9	12.9 (2.9)	12.4 (5.3)	38.1 (4.0)
BMI (kg/m^2)				
<18.5	1.7	12.6 (2.9)	11.7 (5.0)	38.5 (4.0)
18.5–24.9	50.3	12.5 (2.9)	11.6 (5.1)	38.2 (4.0)
25–29.9	36.5	12.6 (2.8)	11.5 (5.1)	38.1 (3.9)
≥30	11.5	12.8 (2.8)	11.7 (5.2)	38.1 (3.8)
Smoking status				
Never	44.7	12.6 (2.9)	11.5 (5.1)	38.4 (4.0)
Current cigarette smoker	19.6	12.7 (2.8)	11.8 (5.1)	38.0 (3.8)
Former cigarette smoker	25.6	12.5 (2.9)	11.7 (5.1)	38.0 (4.0)
Ever pipe/cigar	10.2	12.5 (2.8)	11.5 (5.0)	38.0 (3.8)
Cigarettes per day				
Current cigarette smoker				
<15	4.9	12.7 (2.9)	12.0 (5.3)	37.9 (3.8)
15–19	1.5	12.7 (2.8)	11.8 (5.1)	37.9 (3.9)
20–29	7.2	12.6 (2.8)	11.6 (5.0)	38.0 (3.7)
≥30	6.0	12.7 (2.8)	11.7 (5.1)	38.0 (3.8)
Former cigarette smoker				
<10	4.9	12.6 (2.9)	11.8 (5.1)	37.9 (4.0)
10–19	5.1	12.5 (2.9)	11.7 (5.1)	38.0 (4.1)
20–29	8.5	12.5 (2.9)	11.6 (5.1)	38.1 (4.0)
≥30	7.0	12.5 (2.9)	11.8 (5.2)	38.0 (4.0)
Duration of smoking (years)				
Current cigarette smoker				
<26	4.5	12.8 (2.8)	11.9 (5.3)	38.0 (3.7)
<26	4.7	12.7 (2.8)	11.7 (5.1)	37.9 (3.7)
26–32	4.7	12.7 (2.8)	11.7 (5.1)	38.0 (3.7)
33–39	5.6	12.6 (2.9)	11.8 (5.1)	38.1 (3.9)
≥40	6.1	12.5 (2.9)	11.6 (5.1)	38.0 (4.1)
Former cigarette smoker				
<12	6.7	12.5 (2.8)	11.7 (5.1)	38.0 (4.0)
21–29	5.5	12.5 (2.9)	11.8 (5.1)	37.9 (4.0)
12–20	7.3	12.5 (2.9)	11.8 (5.2)	38.0 (4.0)
≥30				
Age started smoking <18 y old				
Current cigarette smoker	7.9	12.7 (2.8)	12.0 (5.3)	37.9 (3.8)
Former cigarette smoker	9.8	12.5 (2.8)	11.9 (5.3)	37.9 (4.0)
Passive smoke exposure (hours)				
0	35.5	12.5 (2.9)	11.5 (5.1)	38.4 (4.2)
>0–3	33.8	12.5 (2.8)	11.6 (5.1)	38.0 (3.9)
>3	30.8	12.7 (2.8)	11.8 (5.2)	38.0 (3.7)
Beer consumption				
Yes	24.9	12.6 (2.9)	11.8 (5.2)	38.3 (4.1)
No	16.3	12.5 (2.8)	11.6 (5.0)	37.9 (3.8)
Missing	58.8	12.6 (2.8)	11.6 (5.1)	38.1 (3.9)
Wine consumption				
Yes	22.5	12.6 (2.8)	11.5 (5.1)	38.4 (3.9)
No	18.3	12.4 (3.0)	12.3 (5.2)	37.7 (4.3)
Missing	59.3	12.6 (2.8)	11.5 (5.0)	38.2 (3.8)

Table 2. (*Continued.*)

Characteristic	%	$PM_{2.5}$ ($\mu g/m^3$) Mean (SD)	NO_2 (ppb) Mean (SD)	O_3 (ppb) Mean (SD)
Liquor consumption				
Yes	23.6	12.7 (2.9)	11.7 (5.2)	38.4 (4.0)
No	19.7	12.3 (2.9)	11.6 (5.0)	37.8 (4.0)
Missing	56.8	12.6 (2.8)	11.6 (5.1)	38.2 (3.9)
Vegetable/fruit/fiber consumption				
1st quintile	17.2	12.8 (2.8)	11.6 (5.2)	38.1 (3.7)
2nd quintile	18.8	12.6 (2.8)	11.6 (5.1)	38.1 (3.8)
3rd quintile	18.1	12.5 (2.8)	11.6 (5.1)	38.1 (3.9)
4th quintile	18.9	12.4 (2.9)	11.6 (5.0)	38.1 (4.0)
5th quintile	18.9	12.4 (2.9)	11.6 (5.0)	38.2 (4.2)
Fat consumption				
1st quintile	17.3	12.8 (2.9)	12.2 (5.3)	38.1 (4.0)
2nd quintile	18.3	12.6 (2.9)	11.8 (5.2)	38.0 (4.0)
3rd quintile	18.6	12.5 (2.8)	11.6 (5.1)	38.1 (4.0)
4th quintile	18.8	12.5 (2.8)	11.4 (5.0)	38.2 (3.9)
5th quintile	18.8	12.5 (2.8)	11.0 (4.8)	38.4 (3.8)
Missing/bad nutrition data	8.2	12.7 (2.9)	11.8 (5.2)	38.3 (4.0)
Industrial exposures				
Yes	19.7	12.5 (2.9)	11.5 (5.1)	38.1 (4.0)
No	80.3	12.6 (2.8)	11.6 (5.1)	38.2 (3.9)
Occupational dirtiness index				
Level 0	49.9	12.6 (2.8)	11.8 (5.1)	38.1 (4.0)
Level 1	13.7	12.5 (2.8)	11.4 (5.1)	38.2 (3.9)
Level 2	11.6	12.5 (2.9)	11.5 (4.9)	38.3 (4.0)
Level 3	4.8	12.5 (2.9)	11.6 (5.1)	38.2 (4.0)
Level 4	6.2	12.4 (2.7)	10.5 (5.0)	38.2 (3.8)
Level 5	4.3	12.5 (2.8)	11.4 (5.1)	38.2 (4.0)
Level 6	1.1	12.9 (2.9)	11.4 (4.8)	38.2 (4.0)
Missing	8.4	12.8 (2.9)	12.1 (5.3)	38.0 (3.9)
Median household income (thousands, USD)				
<25	25.0	12.2 (2.8)	9.7 (4.2)	39.0 (3.3)
25–31	24.9	12.5 (2.8)	10.9 (4.4)	38.6 (3.8)
32–40	25.1	12.8 (3.0)	12.1 (4.9)	37.9 (4.2)
≥41	25.0	12.9 (2.8)	13.8 (5.8)	37.0 (4.2)
African American residents (%)				
<0.7	25.0	11.6 (2.7)	10.0 (5.1)	37.7 (3.9)
0.7–2.4	25.0	12.3 (3.0)	12.4 (5.0)	38.1 (4.5)
2.5–8.8	24.5	13.0 (2.9)	12.5 (5.1)	38.5 (4.1)
≥8.9	25.5	13.4 (2.3)	11.6 (4.8)	38.3 (3.2)
Hispanic residents (%)				
<0.8	25.0	13.2 (2.3)	9.1 (3.6)	38.5 (2.0)
0.8–1.7	25.0	12.7 (2.2)	10.4 (3.7)	37.9 (2.7)
1.8–5.8	24.6	11.9 (2.5)	12.5 (5.3)	37.1 (4.4)
≥5.9	25.4	12.5 (3.9)	14.5 (5.7)	39.1 (5.4)
Post-secondary education (%)				
<28.2	25.0	13.1 (2.6)	10.1 (4.8)	38.8 (3.1)
28.2–37.0	25.0	12.5 (2.8)	11.3 (5.1)	38.0 (3.8)
37.1–48.1	25.0	12.3 (2.9)	12.3 (5.3)	38.1 (4.2)
≥48.2	25.0	12.5 (3.0)	12.8 (4.8)	37.7 (4.5)
Unemployment (%)				
<3.6	25.0	12.7 (2.6)	11.8 (4.7)	37.2 (3.7)
3.6–4.9	25.0	12.5 (2.8)	12.1 (5.3)	38.1 (3.9)
5.0–6.6	25.0	12.3 (2.9)	11.2 (5.0)	38.7 (4.1)
≥6.7	25.0	12.8 (3.0)	11.3 (5.3)	38.7 (3.9)
Poverty (%)				
<4.6	25.0	12.8 (2.4)	13.0 (5.3)	36.9 (3.5)
4.6–8.5	25.0	12.6 (3.0)	12.1 (5.0)	38.0 (4.4)
8.6–13.9	25.0	12.3 (2.9)	10.7 (4.7)	38.6 (3.9)
≥14.0	25.0	12.6 (3.0)	10.6 (4.9)	39.0 (3.7)

Note: BMI, body mass index; CPS-II, Cancer Prevention Study II; NO_2 , nitrogen dioxide; O_3, ozone; $PM_{2.5}$, particulate matter with aerodynamic diameter <2.5 μm; USD, U.S. dollar.

cancer [HR = 0.91 (95% CI: 0.86, 0.97)], and leukemia [HR = 0.92 (95% CI: 0.85, 0.99)].

The results were similar with further adjustment for physical exercise, aspirin use, and red meat intake for all cancer sites as well as with additional reproductive and hormonal variables for female reproductive cancers (see Tables S4 and S5). The results for female reproductive cancers were also similar upon restriction to postmenopausal women only. The results were similar in two-pollutant models including $PM_{2.5}$ and NO_2 (see Table S6) and in three-pollutant models with O_3 (see Table S7).

Upon decomposition of total $PM_{2.5}$, there were statistically significant positive associations of both bladder and kidney cancer mortality per fifth percentile–mean increment with regional $PM_{2.5}$ [HRs per 4.5 $\mu g/m^3$ = 1.14 (95% CI: 1.04, 1.25) and 1.15

Table 3. Adjusted HRs (95% CIs)[a] for nonlung cancer mortality per each fifth percentile–mean increment in air pollutant concentrations, single-pollutant models, CPS-II cohort, United States (1982–2004) ($n = 623{,}048$).

			$PM_{2.5}$		NO_2		O_3	
			Per 4.4 $\mu g/m^3$		Per 6.5 ppb		Per 6.9 ppb	
Cancer cause of death	ICD 9; ICD10	Number of deaths	HR	95% CI	HR	95% CI	HR	95% CI
Tongue and mouth	141, 143–145; C01–C06	262	1.03	0.84, 1.26	0.98	0.80, 1.19	0.93	0.74, 1.18
Salivary gland	142; C07–C08	58	0.93	0.61, 1.44	1.00	0.67, 1.48	1.44	0.91, 2.30
Pharynx	146–149; C09–C14	243	0.88	0.70, 1.10	0.86	0.69, 1.08	1.11	0.86, 1.43
Esophagus	150; C15	1,180	1.02	0.93, 1.13	1.02	0.92, 1.12	0.97	0.87, 1.08
Stomach	151; C16	1,340	1.00	0.91, 1.09	1.05	0.96, 1.15	0.90	0.81, 0.99
Colorectal	153–154; C18–C21	6,475	1.04	1.00, 1.08	1.06	1.02, 1.10	0.95	0.91, 1.00
Liver	155; C22	1,003	1.05	0.94, 1.16	1.03	0.93, 1.14	0.98	0.87, 1.10
Gallbladder	156; C23–C24	403	1.03	0.87, 1.22	1.00	0.85, 1.17	0.95	0.78, 1.14
Pancreas	157; C25	3,812	0.98	0.92, 1.03	1.04	0.98, 1.09	0.91	0.86, 0.97
Nose	160; C30–C31	46	0.65	0.37, 1.16	0.82	0.47, 1.42	1.18	0.69, 2.04
Larynx	161; C32	223	1.04	0.84, 1.30	1.07	0.86, 1.32	0.96	0.74, 1.24
Bone	170; C40–C41	81	0.81	0.55, 1.20	0.97	0.68, 1.38	0.95	0.63, 1.43
Connective tissue	171; C47, C49	377	1.06	0.89, 1.26	1.04	0.88, 1.22	0.89	0.74, 1.08
Melanoma	172; C43	862	1.05	0.94, 1.17	0.97	0.87, 1.08	1.02	0.90, 1.15
Other skin	173; C44, C46	195	1.10	0.88, 1.38	0.90	0.72, 1.14	0.97	0.75, 1.24
Breast (female)[b]	174–175; C50	3,844	1.03	0.97, 1.08	1.03	0.97, 1.08	0.99	0.93, 1.05
Uterus[b,c]	179, 182; C54–C55	611	1.04	0.91, 1.19	1.07	0.94, 1.22	0.98	0.84, 1.14
Cervix[b,c]	180; C53	115	1.34	0.98, 1.83	1.23	0.91, 1.66	1.01	0.69, 1.48
Ovary[b,c,d]	183; C56	987	1.03	0.93, 1.15	1.03	0.93, 1.14	1.01	0.90, 1.14
Prostate[b]	185; C61	1,068	0.96	0.86, 1.06	1.01	0.92, 1.12	1.03	0.92, 1.15
Bladder	188; C67	1,324	1.13	1.03, 1.23	1.03	0.94, 1.12	1.03	0.93, 1.14
Kidney	189; C64–C66, C68	927	1.14	1.03, 1.27	0.99	0.89, 1.10	0.97	0.86, 1.09
Eye	190; C69	26	1.30	0.66, 2.53	1.14	0.57, 2.28	0.76	0.38, 1.53
Brain	191; C71	1,591	1.04	0.96, 1.14	0.99	0.92, 1.08	0.98	0.89, 1.08
Thyroid	193; C73	41	0.62	0.34, 1.12	1.24	0.75, 2.05	0.96	0.54, 1.71
Non-Hodgkin's lymphoma	200, 202; C82–C85	2,840	1.00	0.94, 1.07	1.05	0.99, 1.12	0.98	0.92, 1.05
Hodgkin's disease	201; C81	125	1.12	0.82, 1.54	1.16	0.87, 1.53	1.08	0.76, 1.53
Multiple myeloma	203; C88, C90	1,421	0.97	0.89, 1.07	1.00	0.92, 1.09	0.99	0.90, 1.09
Leukemia	204–208; C91–C95	2,584	1.01	0.94, 1.07	1.00	0.94, 1.07	0.92	0.85, 0.99

Note: CI, confidence interval; CPS-II, Cancer Prevention Study II; HR, hazard ratio; ICD-9, *The International Classification of Diseases, 9th Revision*; ICD-10, *International Statistical Classification of Diseases and Related Health Problems, 10th Revision*; NO_2, nitrogen dioxide; O_3, ozone; $PM_{2.5}$, particulate matter with aerodynamic diameter <2.5 μm.
[a]Age, race/ethnicity, gender stratified and adjusted for baseline values of education; marital status; body mass index; body mass index squared; smoking status; cigarettes per day; cigarettes per day squared; duration of smoking; duration of smoking squared; age started smoking; passive smoking, vegetable/fruit/fiber consumption; fat consumption; beer, wine, liquor consumption; industrial exposures; occupation dirtiness index; and 1990 ecological covariates.
[b]As above but not gender stratified. Analysis limited to 344,593 women for analysis of breast cancer mortality, 235,637 women for analysis of uterine or cervical cancer mortality, and 228,494 women for analysis of ovarian cancer mortality. Analysis limited to 278,455 men for analysis of prostate cancer mortality.
[c]Women reporting a previous hysterectomy or an artificial menopause excluded here ($n = 108{,}956$).
[d]Women reporting having undergone an ovarian surgery also excluded here ($n = 7{,}143$).

(95% CI: 1.02, 1.29), respectively] of similar magnitude per unit increment to those of total $PM_{2.5}$ but not with near-source $PM_{2.5}$ [HRs per 1.6 $\mu g/m^3 = 1.02$ (95% CI: 0.92, 1.13) and 1.05 (95% CI: 0.92, 1.13), respectively] (see Table S8). There were also significant positive associations of near-source $PM_{2.5}$ and mortality from cancer of the stomach [HR per 1.6 $\mu g/m^3 = 1.13$ (95% CI: 1.02, 1.26)] and colorectum [HR = 1.09 (95% CI: 1.04, 1.15)] but not with regional $PM_{2.5}$ [HRs per 4.5 $\mu g/m^3 = 0.97$ (95% CI: 0.88, 1.06) and 1.02 (95% CI: 0.97, 1.07), respectively]. There was also a positive HR for pancreatic cancer mortality with near-source $PM_{2.5}$ [HR = 1.06 (95% CI: 1.00, 1.13)] of borderline significance ($p = 0.06$), but not with regional $PM_{2.5}$ [HR = 0.96 (95% CI: 0.90, 1.01)].

In stratified analyses of associations of $PM_{2.5}$ with kidney and bladder cancer mortality and of NO_2 with colorectal cancer mortality, associations of $PM_{2.5}$ with kidney and bladder cancer mortality appeared to be limited to men [HR = 1.23 (95% CI: 1.08, 1.40) and HR = 1.16 (95% CI: 1.05, 1.29), respectively], with little or no evidence of associations in women [HR = 1.00 (95% CI: 0.83, 1.20) and HR = 1.03 (95% CI: 0.86, 1.23), respectively], although differences between men and women were not significant (interaction p-values of 0.13 and 0.25, respectively) (see Table S9). There was no clear evidence of effect modification according to categories of smoking status (interaction p-values ≥0.30). Associations of NO_2 with colorectal cancer mortality were somewhat stronger among those with a <high school or high school level of education [HR = 1.12 (95% CI: 1.01, 1.24) and HR = 1.15 (95% CI: 1.07, 1.23), respectively] compared with a >high school level of education [HR = 0.99 (95% CI: 0.94, 1.05); p for interaction = 0.03]. There was no evidence that the proportional hazards assumption was violated for associations at these sites ($p > 0.05$) (data not shown).

Discussion

Ambient air pollution was not associated with death from most nonlung cancers in our large prospective study population. However, there were statistically significant positive associations between $PM_{2.5}$ and death from bladder and kidney cancer, ranging from 13–14% increases in risk per each fifth percentile–mean increment (4.4 $\mu g/m^3$). For NO_2, there was a statistically significant positive association with colorectal cancer mortality of 6% per 6.5 ppb. The results were similar in two-pollutant models including both $PM_{2.5}$ and NO_2 as well as in three-pollutant models with O_3. The magnitudes of the associations here were somewhat stronger than, although compatible with, those of $PM_{2.5}$ and lung cancer mortality observed in previous work [9% (95% CI: 3, 16%) per 10 $\mu g/m^3$ or equivalently, 4% (95% CI: 1, 7%) per 4.4 $\mu g/m^3$] (Turner et al. 2016).

A small but growing body of literature has examined associations between ambient air pollution and nonlung cancer risk; however, the evidence for such associations is limited. For bladder cancer, a Spanish hospital-based case–control study including 1,219 incident cases and 1,271 controls reported that living

>40 y in a city of >100,000 inhabitants was associated with a significantly higher risk of the disease [odds ratio (OR) = 1.30 (95% CI: 1.04, 1.63)] (Castaño-Vinyals et al. 2008). In a death certificate–based case–control study in Taiwan, including 680 bladder cancer deaths and 680 matched noncancer or nongenitourinary death controls, there were significant positive trends with increasing tertiles of particulate matter with aerodynamic diameter <10 μm (PM_{10}), NO_2, and sulfur dioxide (SO_2), but not with carbon monoxide (CO) or O_3 concentrations (Liu et al. 2009). There was a positive, nonsignificant association between nitrogen oxides (NO_x) concentrations and bladder cancer incidence (n = 221) [incidence rate ratio (IRR) per 100 $\mu g/m^3$ = 1.32 (95% CI: 0.80, 2.19)] in an analysis of 54,304 participants in the Danish Diet Cancer and Health cohort (Raaschou-Nielsen et al. 2011). In a retrospective cohort study of 85,559 individuals in Malagrotta (Rome, Italy), there was a positive association between hydrogen sulfide (H_2S) concentrations from a municipal waste landfill and bladder cancer mortality in women [HR per 0.043 $\mu g/m^3$ = 1.35 (95% CI: 1.00, 1.82), n = 12], but not in men [HR = 0.88 (95% CI: 0.51, 1.52), n = 61] (Ancona et al. 2015). Taken together, the results from our study and those from most previous studies are generally consistent with the recent IARC evaluation noting a positive association in studies of outdoor air pollution and bladder cancer risk (IARC 2013).

There was no association [HR per 10 $\mu g/m^3$ = 0.98 (95% CI: 0.58, 1.64)] between $PM_{2.5}$ and urinary cancer mortality (including 155 bladder and kidney cancer deaths combined) in a cohort of 66,820 elderly Hong Kong residents (Wong et al. 2016). The Danish Diet Cancer and Health cohort reported a positive, although imprecise, association of NO_x with kidney cancer incidence [IRR = 1.73 (95% CI: 0.89, 3.73) per 100 $\mu g/m^3$ (Raaschou-Nielsen et al. 2011). A total of 95 kidney cancer cases were observed in that study.

Few studies of colorectal cancer have been reported to date. Although our study showed a significant positive association between NO_2 and death from colorectal cancer and a borderline association with $PM_{2.5}$, a Hong Kong cohort reported no association [HR per 10 $\mu g/m^3$ = 1.01 (95% CI: 0.79, 1.30)] between $PM_{2.5}$ concentrations and mortality from cancers of the lower digestive tract (n = 719) (Wong et al. 2016). There were nonsignificant inverse associations in men and women for PM_{10} concentrations from a waste incinerator and colorectal cancer mortality (n = 149 deaths in men and 95 deaths in women) in Malagrotta (Ancona et al. 2015). There were also nonsignificant inverse associations for NO_x concentrations and both colon and rectal cancer incidence in Denmark (n = 414 and 246 cases, respectively) (Raaschou-Nielsen et al. 2011). The number of included colorectal cancer deaths (>6,000) in CPS-II here is substantially larger than the numbers of cases/deaths in previous studies.

When $PM_{2.5}$ concentrations were decomposed into near-source and regional components, there were stronger associations for near-source $PM_{2.5}$ with colorectal (and stomach) cancer mortality, supporting similar findings for NO_2, and for regional $PM_{2.5}$ with both bladder and kidney cancer mortality. Little is known regarding the role of different air pollution sources or components in cancer, including at sites other than the lung. We have not specifically examined what $PM_{2.5}$ sources were further related to this decomposition.

Studies of occupational exposure to diesel engine exhaust and polycyclic aromatic hydrocarbons (PAHs), which are formed during incomplete combustion processes, have suggested positive associations with both bladder and kidney cancer (Brown et al. 2012; IARC 2005; Siemiatycki et al. 2004). Recent population-based case–control studies of men in Canada reported positive associations between any exposure to high concentrations of occupational diesel exhaust and both bladder [OR = 1.64 (95% CI: 0.87, 3.08), n = 658 cases and 1,360 controls] and rectal [OR = 1.98 (95% CI: 1.09, 3.60), n = 840 cases and 1,360 controls] cancer incidence, which increased among those with >10 years of exposure (Kachuri et al. 2016; Latifovic et al. 2015). Studies of workers in dusty occupations (e.g., mineral dust, wood dust), as well as in steel and iron processing, have also noted positive associations with colorectal and stomach cancer (Kreuzer et al. 2012; Oddone et al. 2014; Raj et al. 2003; Santibañez et al. 2012).

The largest HR was for $PM_{2.5}$ in relation to death from cervical cancer, although the findings were based on only 115 deaths and were not statistically significant. The positive association with NO_2 was weaker. In the Danish Diet Cancer and Health study, the strongest association was between NO_x and cervical cancer incidence [i.e., IRR = 2.45 (95% CI: 1.01, 5.93) per 100 $\mu g/m^3$], but it was based on only 35 cases (Raaschou-Nielsen et al. 2011). In both studies, there were no data on human papillomavirus (HPV) infection (or on other potentially relevant infections for cancer mortality at other sites, e.g., *Helicobacter pylori* for stomach cancer or hepatitis B or C for liver cancer), and confounding cannot be ruled out. There was also no information on access to or compliance with cervical cancer screening programs, which may differ in areas with differing levels of ambient air pollution. However, we adjusted our models for a range of area-level socioecomonic covariates and screening rates in a subset of CPS-II participants for both breast (>90%) and colorectal (>65%) cancer were high (Patel et al. 2003; Stevens et al. 2011). A recent cross-sectional study of women from a clinical trial of cervical disease diagnostic techniques in Texas reported a positive association of cervical dysplasia with residential census-tract level estimates of ambient benzene, diesel particulate matter, and PAH concentrations (Scheurer et al. 2014).

Although we found no significant associations with death from breast cancer based on fully adjusted models, other studies reported positive associations between ambient air pollution and breast cancer incidence (Crouse et al. 2010; Mordukhovich et al. 2016; Reding et al. 2015). Crouse et al. (2010) reported a positive association between NO_2 concentrations and postmenopausal breast cancer incidence [OR per 5 ppb = 1.31 (95% CI: 1.00, 1.71)] in a hospital-based case–control study including 383 case and 416 control participants. The prospective U.S. Sister Study reported no association between PM_{10}, $PM_{2.5}$, or NO_2 concentrations and incident breast cancer overall in an analysis of 47,591 participants including 1,749 breast cancer cases, but a positive association was reported between NO_2 and estrogen receptor (ER) + / progesterone receptor (PR) + disease [HR per 5.8 ppb = 1.10 (95% CI: 1.02, 1.19)] (Reding et al. 2015). In our mortality-based study, no information on ER or PR status was available.

There was no positive association of any ambient air pollutant and total leukemia mortality in the present study. There was a positive association of NO_2 concentrations at the residence with incident adult acute myeloid leukemia [OR per 10 mg/m^3 = 1.31 (95% CI: 1.02, 1.65), n = 531] but not with other leukemia subtypes in a Danish case-control study (Raaschou-Nielsen et al. 2016). There was no positive association of $PM_{2.5}$ with total incident leukemia or with chronic lymphocytic leukemia in a Canadian case–control study of 1,064 total case and 5,039 control participants (Winters et al. 2015). There was no information on leukemia subtype in CPS-II.

There was no association of any ambient air pollutant with total brain cancer mortality in this analysis, which included 1,591 brain cancer deaths. The Danish Diet Cancer and Health cohort reported a positive association of NO_x with incident brain tumor risk [IRR per 100 $\mu g/m^3$ NO_x = 2.28 (95% CI: 1.25, 4.19)] (Raaschou-Nielsen

et al. 2011), although there were few brain tumor cases ($n = 95$). A subsequent national case–control study in Denmark with a larger number of incident brain tumor cases ($n = 4{,}183$) reported a significant positive association of NO_x concentrations $\geq 100\ \mu g/m^3$ with nongliomas [OR = 2.30 (95% CI: 1.15, 4.59)] but not with gliomas [OR = 0.89 (95% CI: 0.44, 1.77)] (Poulsen et al. 2016). There was no information on tumor histology or cranial location in CPS-II.

In the present study, there were no clear positive, and some cases there were significant inverse, associations observed with O_3 in both single- and multipollutant models possibly owing to broader spatial patterns in ambient air pollution concentrations, to negative correlations with other air pollutants, and to the larger spatial scale of O_3 concentrations, which were unable to capture fine-scale variation and scavenging effects in urban areas (Williams et al. 2014). O_3 is thought to increase DNA damage (U.S. EPA 2013), which plays a role in several types of cancer. However, in previous studies of the CPS-II cohort, O_3 was not associated with lung cancer death (Jerrett et al. 2013; Krewski et al. 2009; Pope et al. 2002; Turner et al. 2016). A positive association between ambient O_3 and incident male lung cancer was reported in the Adventist Health Study on Smog (AHSMOG), although few lung cancers were observed ($n = 16$) (Beeson et al. 1998).

Strengths of this study include a large-scale, well-established cohort design with large numbers of nonlung cancer deaths observed at many cancer sites. Air pollution exposures were estimated at each participant's residence using national-level exposure surfaces that have previously been used to examine mortality associations in CPS-II (Jerrett et al. 2016; Pope et al. 2015; Turner et al. 2014; 2016). Detailed data were collected at enrollment on a variety of cancer risk factors including cigarette smoking, occupation, diet, and various hormonal and reproductive factors.

The main limitation of this study is the use of cancer mortality rather than cancer incidence end points, with inferences of associations of ambient air pollution here reflecting both disease incidence and survival following diagnosis. Because lung cancer is rapidly fatal, with 5-y survival rates ranging from $\sim$13–18% for the periods 1987–1989 and 2005–2011 respectively, the use of mortality data reasonably approximates disease incidence (American Cancer Society 2016). Other rapidly fatal cancer sites include the pancreas (5-year survival = 4–8%), the liver and intrahepatic bile duct (5–18%), the esophagus (10–20%), the stomach (20–30%), and the brain and other nervous system sites (29–35%) (American Cancer Society 2016). In contrast, survival is greater for cancer at other sites, including the urinary bladder, the kidney and renal pelvis, and the colorectum, of interest here (5-y survival ranging from 57–79%), with survival from disease playing an increasing role in associations with ambient air pollution observed here (American Cancer Society 2016).

There is little research on whether ambient air pollution may be related to cancer progression or survival. One recent study of >350,000 California lung cancer patients reported that higher residential ambient air pollution concentrations (NO_2, $PM_{2.5}$, PM_{10}) were associated with poorer survival, particularly among patients diagnosed in earlier disease states (i.e., with localized disease) (Eckel et al. 2016). Mean ambient air pollution concentrations were also somewhat higher among those diagnosed with more advanced disease and among those with an unknown stage at diagnosis (i.e., either patients who were dying before stage information was obtained or who had limited workup performed), possibly reflecting differences in access to medical care, which may vary by levels of ambient air pollution. Little is known regarding possible impacts at other cancer sites, although reduced breast cancer survival was associated with higher $PM_{2.5}$ and PM_{10} concentrations in another study (Hu et al. 2013). Further studies of nonlung cancer incidence are needed to disentangle the observed associations with ambient air pollution.

Covariate data were only available at enrollment and were not updated over the follow-up period in CPS-II. It is unlikely that CPS-II participants would begin smoking cigarettes over the follow-up time, given the mean age of >55 years at enrollment, although participants may increasingly become former smokers. There were also limited data on occupational exposure history. Participant residence data were also only available at enrollment. Changes in participant residence after enrollment as well as changes in coding of the underlying cause of death over the follow-up period would likely be nondifferential and would result in attenuation of the magnitude of the associations observed. A Canadian study observed little impact of accounting for residential mobility on $PM_{2.5}$ or O_3 mortality associations; however, associations with more spatially resolved NO_2 strengthened somewhat (Crouse et al. 2015).

There is also a lack of historical ambient air pollution data, although correlations between $PM_{2.5}$ and O_3 concentrations assigned to CPS-II participants over recent decades were moderately strong, ranging from approximately 0.6 to >0.8, indicating that the use of more recent ambient air pollution estimates may be reflective of longer-term exposure patterns (Krewski et al. 2009; Pope et al. 2002; Turner et al. 2016). The rank ordering of U.S. cities was also similar over time in the context of generally declining ambient air pollution concentrations. The use of recent ambient air pollution estimates may result in somewhat inflated HRs because increments of recent concentrations represent greater contrasts of historically higher concentrations (Krewski et al. 2009; Pope et al. 2002; Turner et al. 2016). Little is known regarding potential latency periods for cancer development in relation with ambient air pollution concentrations, which may also differ from those of lung cancer.

Correlations among pollutants were generally weak. Ambient air pollution concentrations were estimated using different approaches at different time periods and different geographic units of scale, possibly complicating interpretation of the correlation structure among pollutants. The LURBME model outperformed a range of other geostatistical and remote sensing $PM_{2.5}$ models in the CPS-II (Jerrett et al. 2016). Similar positive cardiorespiratory mortality–O_3 associations were observed in recent work with O_3 concentrations estimated at either 12 km × 12 km or 36 km × 36 km scales in the Eastern United States (Turner et al. 2016).

Owing to multiple testing and to the large number of cancer sites evaluated ($n = 29$), it is possible that some of the significant associations observed may be due to chance. As such, the results of this study should be replicated in other studies, particularly in studies of cancer incidence. Finally, our findings may not be entirely generalizable because CPS-II participants are of generally higher socioeconomic status and more limited racial/ethnic composition than the broader U.S. population.

Potential mechanisms through which ambient air pollution may be associated with other nonlung cancers remain to be fully elucidated; however, ambient air pollution represents a complex mixture of exposure to a broad range of carcinogenic and mutagenic substances, including PAHs and other aromatic hydrocarbons, benzene, metals, and xenoestrogens, which may be transported and metabolized in the body (Crouse et al. 2010; IARC 2012, 2013). Populations exposed to outdoor air pollutants and to diesel engine exhaust have elevated urinary 1-hydroxypyrene and hemoglobin adducts of nitro-PAHs and low-molecular-weight alkenes (Ciarrocca et al. 2014; Duan et al. 2016; IARC 2012, 2013). A recent study of 23,820 participants in Taiwan, including 464 incident hepatocellular carcinoma (HCC) cases, reported a positive association of $PM_{2.5}$ with HCC incidence, which may

have been mediated by alanine transaminase levels, suggesting that $PM_{2.5}$ exposure may lead to HCC via chronic inflammation (Pan et al. 2015).

Active cigarette smoking has also been associated with a range of other nonlung cancers, including cancers in various urinary and digestive sites such as the bladder, the kidney, and the colorectum, among others (Carter et al. 2015; IARC 2009). However, levels of exposure to $PM_{2.5}$ from ambient air pollution are substantially lower and of differing chemical composition and toxicity compared with those from active cigarette smoking or occupational exposure (Pope et al. 2011).

Patients with a history of diabetes, which has also been linked with ambient air pollution (Eze et al. 2015; Pope et al. 2015), have also been observed to be at increased risk for bladder, kidney, and colorectal cancers, although it is unclear whether this is due to shared underlying risk factors (such as obesity) or to other metabolic features of the disease (such as hyperinsulinemia, hyperglycemia, or chronic inflammation) (Campbell et al. 2012; Giovannucci et al. 2010). The results herein were virtually unchanged with further adjustment for prevalent diabetes at enrollment (not shown).

Conclusion

The results from this large prospective study suggest that ambient air pollution was not associated with most nonlung cancer causes of death. Nonetheless, observed associations with mortality from kidney, bladder, and colorectal cancer merit further research, particularly in studies of cancer incidence.

Acknowledgments

The authors thank Y. Shi for programming assistance.

M.C.T. was funded by a Canadian Institutes of Health Research Fellowship. D.K. is the McLaughlin Chair in Risk Science at the University of Ottawa. Health Canada, the Centers for Disease Control and Prevention, grant 200-2010-37394, and the National Institutes of Health, grant 5R01ES019573-04, funded the development of the $PM_{2.5}$ exposure model. The American Cancer Society funded the creation, maintenance, and follow-up of the Cancer Prevention Study II cohort.

References

American Cancer Society. 2016. *Cancer Facts & Figures 2016*. Atlanta, GA: American Cancer Society.

Ancona C, Badaloni C, Mataloni F, Bolignano A, Bucci S, Cesaroni G, et al. 2015. Mortality and morbidity in a population exposed to multiple sources of air pollution: a retrospective cohort study using air dispersion models. Environ Res 137:467–474, PMID: 25701728, https://doi.org/10.1016/j.envres.2014.10.036.

Beckerman BS, Jerrett M, Serre M, Martin RV, Lee SJ, van Donkelaar A, et al. 2013. A hybrid approach to estimating national scale spatiotemporal variability of $PM_{2.5}$ in the contiguous United States. Environ Sci Technol 47(13):7233–7241, PMID: 23701364, https://doi.org/10.1021/es400039u.

Beeson WL, Abbey DE, Knutsen SF. 1998. Long-term concentrations of ambient air pollutants and incident lung cancer in California adults: results from the AHSMOG study. Adventist Health Study on Smog. Environ Health Perspect 106(12):813–822, PMID: 9831542.

Brook RD, Rajagopalan S, Pope CA III, Brook JR, Bhatnagar A, Diez-Roux AV, et al. 2010. Particulate matter air pollution and cardiovascular disease: an update to the Scientific Statement from the American Heart Association. Circulation 121(21):2331–2378, PMID: 20458016, https://doi.org/10.1161/CIR.0b013e3181dbece1.

Brown T, Slack R, Rushton L. British Occupational Cancer Burden Study Group, 2012. Occupational cancer in Britain. Urinary tract cancers: bladder and kidney. Br J Cancer 107(Suppl 1):S76–S84, PMID: 22710682, https://doi.org/10.1038/bjc.2012.121.

Calle E, Terrell D. 1993. Utility of the National Death Index for ascertainment of mortality among Cancer Prevention Study II participants. Am J Epidemiol 137(2):235–241, PMID: 8452128, https://doi.org/10.1093/oxfordjournals.aje.a116664.

Campbell PT, Newton CC, Patel AV, Jacobs EJ, Gapstur SM. 2012. Diabetes and cause-specific mortality in a prospective cohort of one million U.S. adults. Diabetes Care 35(9):1835–1844, PMID: 22699290, https://doi.org/10.2337/dc12-0002.

Carter BD, Abnet CC, Feskanich D, Freedman ND, Hartge P, Lewis CE, et al. 2015. Smoking and mortality–beyond established causes. N Engl J Med 372(7):631–640, PMID: 25671255, https://doi.org/10.1056/NEJMsa1407211.

Castaño-Vinyals G, Cantor KP, Tardon A, Garcia-Closas R, Serra C, Carrato A, et al. 2008. Air pollution and risk of urinary bladder cancer in a case-control study in Spain. Occup Environ Med 65(1):56–60, PMID: 17634245, https://doi.org/10.1136/oem.2007.034348.

Ciarrocca M, Rosati MV, Tomei F, Capozzella A, Andreozzi G, Tomei G, et al. 2014. Is urinary 1-hydroxypyrene a valid biomarker for exposure to air pollution in outdoor workers? A meta-analysis. J Expo Sci Environ Epidemiol 24(1):17–26, PMID: 23299300, https://doi.org/10.1038/jes.2012.111.

Crouse DL, Goldberg MS, Ross NA, Chen H, Labrèche F. 2010. Postmenopausal breast cancer is associated with exposure to traffic-related air pollution in Montreal, Canada: a case–control study. Environ Health Perspect 118(11):1578–1583, PMID: 20923746, https://doi.org/10.1289/ehp.1002221.

Crouse DL, Peters PA, Hystad P, Brook JR, van Donkelaar A, Martin RV, et al. 2015. Ambient $PM_{2.5}$, O_3, and NO_2 exposures and associations with mortality over 16 years of follow-up in the Canadian Census Health and Environment Cohort (CanCHEC). Environ Health Perspect 123(11):1180–1186, PMID: 26528712, https://doi.org/10.1289/ehp.1409276.

Cui P, Huang Y, Han J, Song F, Chen K. 2015. Ambient particulate matter and lung cancer incidence and mortality: a meta-analysis of prospective studies. Eur J Public Health 25(2):324–329, PMID: 25201901, https://doi.org/10.1093/eurpub/cku145.

Duan H, Jia X, Zhai Q, Ma L, Wang S, Huang C, et al. 2016. Long-term exposure to diesel engine exhaust induces primary DNA damage: a population-based study. Occup Environ Med 73(2):83–90, PMID: 26491144, https://doi.org/10.1136/oemed-2015-102919.

Eckel SP, Cockburn M, Shu YH, Deng H, Lurmann FW, Liu L, et al. 2016. Air pollution affects lung cancer survival. Thorax 71(10):891–898, PMID: 27491839, https://doi.org/10.1136/thoraxjnl-2015-207927.

Eze IC, Hemkens LG, Bucher HC, Hoffmann B, Schindler C, Kunzli N, et al. 2015. Association between ambient air pollution and diabetes mellitus in Europe and North America: systematic review and meta-analysis. Environ Health Perspect 123(5):381–389, PMID: 25625876, https://doi.org/10.1289/ehp.1307823.

Giovannucci E, Harlan DM, Archer MC, Bergenstal RM, Gapstur SM, Habel LA, et al. 2010. Diabetes and cancer: a consensus report. Diabetes Care 33(7):1674–1685, PMID: 20587728, https://doi.org/10.2337/dc10-0666.

Hamra GB, Guha N, Cohen A, Laden F, Raaschou-Nielsen O, Samet JM, et al. 2014. Outdoor particulate matter exposure and lung cancer: a systematic review and meta-analysis. Environ Health Perspect 122(9):906–911, PMID: 24911630, https://doi.org/10.1289/ehp.1408092.

Hamra GB, Laden F, Cohen AJ, Raaschou-Nielsen O, Brauer M, Loomis D. 2015. Lung cancer and exposure to nitrogen dioxide and traffic: a systematic review and meta-analysis. Environ Health Perspect 123(11):1107–1112, PMID: 25870974, https://doi.org/10.1289/ehp.1408882.

Hu H, Dailey AB, Kan H, Xu X. 2013. The effect of atmospheric particulate matter on survival of breast cancer among US females. Breast Cancer Res Treat 139(1):217–226, PMID: 23592372, https://doi.org/10.1007/s10549-013-2527-9.

IARC (International Agency for Research on Cancer). 2005. Some non-heterocyclic polycyclic aromatic hydrocarbons and some related exposures. IARC Monogr Eval Carcinog Risk Hum 92:1–868. https://monographs.iarc.fr/ENG/Monographs/vol92/mono92.pdf [accessed 18 October 2016].

IARC. 2009. A review of human carcinogens. Part E: Personal habits and indoor combustions. IARC Monogr Eval Carcinog Risk Hum 100E:1–598. http://monographs.iarc.fr/ENG/Monographs/vol100E/mono100E.pdf [accessed 6 August 2016].

IARC. 2012. Diesel and gasoline engine exhausts and some nitroarenes. IARC Monogr Eval Carcinog Risk Hum 105:1–714. https://monographs.iarc.fr/ENG/Monographs/vol105/mono105.pdf [accessed 4 June 2016].

IARC. 2013. Outdoor air pollution. IARC Monogr Eval Carcinog Risk Hum 109: 1–454. https://monographs.iarc.fr/ENG/Monographs/vol109/mono109-F01.pdf [accessed 19 March 2016].

Jerrett M, Burnett RT, Beckerman B, Turner MC, Krewski D, Thurston G, et al. 2013. Spatial analysis of air pollution and mortality in California. Am J Respir Crit Care Med 188(5):593–599, PMID: 23805824, https://doi.org/10.1164/rccm.201303-0609OC.

Jerrett M, Turner MC, Beckerman BS, Pope CA, van Dondelaar A, Martin RV, et al. 2017. Comparing the health effects of ambient particulate matter estimated using ground-based versus remote sensing exposure estimates. Environ Health Perspect 125(4):552–559, PMID: 27611476, https://doi.org/10.1289/EHP575.

Kachuri L, Villeneuve PJ, Parent MÉ, Johnson KC, Canadian Cancer Registries Epidemiology Research Group, Harris SA. 2016. Workplace exposure to diesel and

gasoline engine exhausts and the risk of colorectal cancer in Canadian men. Environ Health 15:4, PMID: 26762540, https://doi.org/10.1186/s12940-016-0088-1.
Kreuzer M, Straif K, Marsh JW, Dufey F, Grosche B, Nosske D, et al. 2012. Occupational dust and radiation exposure and mortality from stomach cancer among German uranium miners, 1946–2003. Occup Environ Med 69(3):217–223, PMID: 22172952, https://doi.org/10.1136/oemed-2011-100051.
Krewski D, Burnett RT, Goldberg MS, Hoover K, Siemiatycki J, Jerrett M, et al. 2000. *Reanalysis of the Harvard Six Cities Study and the American Cancer Society Study of Particulate Air Pollution and Mortality: Special Report*. Cambridge, MA:Health Effects Institute.
Krewski D, Jerrett M, Burnett RT, MA R, Hughes E, Shi Y, et al. 2009. Extended follow-up and spatial analysis of the American Cancer Society study linking particulate air pollution and mortality. Res Rep Health Eff Inst 140:5–114, PMID: 19627030.
Latifovic L, Villeneuve PJ, Parent MÉ, Johnson KC, Kachuri L, Canadian Cancer Registries Epidemiology Group, et al. 2015. Bladder cancer and occupational exposure to diesel and gasoline engine emissions among Canadian men. Cancer Med 4(12):1948–1962, PMID: 26511593, https://doi.org/10.1002/cam4.544.
Liu CC, Tsai SS, Chiu HF, Wu TN, Chen CC, Yang CY. 2009. Ambient exposure to criteria air pollutants and risk of death from bladder cancer in Taiwan. Inhal Toxicol 21(1):48–54, PMID: 18923949, https://doi.org/10.1080/08958370802207326.
McKean-Cowdin R, Calle EE, Peters JM, Henley J, Hannan L, Thurston GD, et al. 2009. Ambient air pollution and brain cancer mortality. Cancer Causes Control 20(9):1645–1651, PMID: 19685148, https://doi.org/10.1007/s10552-009-9412-1.
Mordukhovich I, Beyea J, Herring AH, Hatch M, Stellman SD, Teitelbaum SL, et al. 2016. Vehicular traffic-related polycyclic aromatic hydrocarbon exposure and breast cancer incidence: The Long Island Breast Cancer Study Project (LIBCSP). Environ Health Perspect 124(1):30–38, PMID: 26008800, https://doi.org/10.1289/ehp.1307736.
Newby DE, Mannucci PM, Tell GS, Baccarelli AA, Brook RD, Donaldson K, et al. 2015. Expert position paper on air pollution and cardiovascular disease. Eur Heart J 36(2):83–93b, PMID: 25492627, https://doi.org/10.1093/eurheartj/ehu458.
Novotny EV, Bechle MJ, Millet DB, Marshall JD. 2011. National satellite-based land-use regression: NO_2 in the United States. Environ Sci Technol 45(10):4407–4414, PMID: 21520942, https://doi.org/10.1021/es103578x.
Oddone E, Modonesi C, Gatta G. 2014. Occupational exposures and colorectal cancers: a quantitative overview of epidemiological evidence. World J Gastroenterol 20(35):12431–12444, PMID: 25253943, https://doi.org/10.3748/wjg.v20.i35.12431.
Pan WC, Wu CD, Chen MJ, Huang YT, Chen CJ, Su HJ, et al. 2015. Fine particle pollution, alanine transaminase, and liver cancer: a Taiwanese prospective cohort study (REVEAL-HBV). J Natl Cancer Inst 108(3):djv341, PMID: 26561636, https://doi.org/10.1093/jnci/djv341.
Patel AV, Calle EE, Bernstein L, Wu AH, Thun MJ. 2003. Recreational physical activity and risk of postmenopausal breast cancer in a large cohort of US women. Cancer Causes Control 14(6):519–529, PMID: 12948283, https://doi.org/10.1023/A:1024895613663.
Parent MÉ, Goldberg MS, Crouse DL, Ross NA, Chen H, Valois MF, et al. 2013. Traffic-related air pollution and prostate cancer risk: a case-control study in Montreal, Canada. Occup Environ Med 70(7):511–518, PMID: 23531743, https://doi.org/10.1136/oemed-2012-101211.
Pope CA III, Turner MC, Burnett RT, Jerrett M, Gapstur SM, Diver WR, et al. 2015. Relationships between fine particulate air pollution, cardiometabolic disorders, and cardiovascular mortality. Circ Res 116(1):108–115, PMID: 25348167, https://doi.org/10.1161/CIRCRESAHA.116.305060.
Pope CA III, Burnett RT, Thun MJ, Calle EE, Krewski D, Ito K, et al. 2002. Lung cancer, cardiopulmonary mortality, and long-term exposure to fine particulate air pollution. JAMA 287(9):1132–1141, PMID: 11879110, https://doi.org/10.1001/jama.287.9.1132.
Pope CA III, Burnett RT, Turner MC, Cohen A, Krewski D, Jerrett M, et al. 2011. Lung cancer and cardiovascular disease mortality associated with ambient air pollution and cigarette smoke: shape of the exposure-response relationships. Environ Health Perspect 119(11):1616–1621, PMID: 21768054, https://doi.org/10.1289/ehp.1103639.
Poulsen AH, Sørensen M, Andersen ZJ, Ketzel M, Raaschou-Nielsen O. 2016. Air pollution from traffic and risk for brain tumors: a nationwide study in Denmark. Cancer Causes Control 27(4):473–480, PMID: 26892605, https://doi.org/10.1007/s10552-016-0721-x.
Raaschou-Nielsen O et al. 2011. Air pollution from traffic and cancer incidence: a Danish cohort study. Environ Health 10:67, PMID: 21771295, https://doi.org/10.1186/1476-069X-10-67.
Raaschou-Nielsen O, Ketzel M, Harbo Poulsen A, Sørensen M. 2016. Traffic-related air pollution and risk for leukaemia of an adult population. Int J Cancer 138(5):1111–1117, PMID: 26415047, https://doi.org/10.1002/ijc.29867.
Raj A, Mayberry JF, Podas T. 2003. Occupation and gastric cancer. Postgrad Med J 79(931):252–258, PMID: 12782770, https://doi.org/10.1136/pmj.79.931.252.
Reding KW, Young MT, Szpiro AA, Han CJ, DeRoo LA, Weinberg C, et al. 2015. Breast cancer risk in relation to ambient air pollution exposure at residences in the Sister Study Cohort. Cancer Epidemiol Biomarkers Prev 24(12):1907–1909, PMID: 26464427, https://doi.org/10.1158/1055-9965.EPI-15-0787.
Santibañez M, Alguacil J, de la Hera MG, Navarrete-Muñoz EM, Llorca J, Aragonés N, et al. 2012. Occupational exposures and risk of stomach cancer by histological type. Occup Environ Med 69(4):268–275, PMID: 22068174, https://doi.org/10.1136/oemed-2011-100071.
Scheurer ME, Danysh HE, Follen M, Lupo PJ. 2014. Association of traffic-related hazardous air pollutants and cervical dysplasia in an urban multiethnic population: a cross-sectional study. Environ Health 13(1):52, PMID: 24924773, https://doi.org/10.1186/1476-069X-13-52.
Siemiatycki J, Krewski D, Shi Y, Goldberg MS, Nadon L, Lakhani R. 2003. Controlling for potential confounding by occupational exposures. J Toxicol Environ Health Part A 66(16–19):1591–1603, PMID: 12959831, https://doi.org/10.1080/15287390306428.
Siemiatycki J, Richardson L, Straif K, Latreille B, Lakhani R, Campbell S, et al. 2004. Listing occupational carcinogens. Environ Health Perspect 112(15):1447–1459, PMID: 15531427, https://doi.org/10.1289/ehp.7047.
Stevens VL, McCullough ML, Sun J, Jacobs EJ, Campbell PT, Gapstur SM. 2011. High levels of folate from supplements and fortification are not associated with increased risk of colorectal cancer. Gastroenterology 141(1):98–105, PMID: 21586288, https://doi.org/10.1053/j.gastro.2011.04.004.
Turner MC, Cohen A, Jerrett M, Gapstur SM, Diver WR, Pope CA 3rd, et al. 2014. Interactions between cigarette smoking and fine particulate matter in the risk of lung cancer mortality in Cancer Prevention Study II. Am J Epidemiol 180(12):1145–1149, PMID: 25395026, https://doi.org/10.1093/aje/kwu275.
Turner MC, Jerrett M, Pope CA 3rd, Krewski D, Gapstur SM, Diver WR, et al. 2016. Long-term ozone exposure and mortality in a large prospective study. Am J Respir Crit Care Med 193(10):1134–1142, PMID: 26680605, https://doi.org/10.1164/rccm.201508-1633OC.
Turner MC, Krewski D, Pope CA, III, Chen Y, Gapstur SM, Thun MJ. 2011. Long-term ambient fine particulate matter air pollution and lung cancer in a large cohort of never-smokers. Am J Respir Crit Care Med 184(12):1374–1381, PMID: 21980033, https://doi.org/10.1164/rccm.201106-1011OC.
U.S. Census Bureau. 1993. *Census of Population and Housing, 1990 (United States): Summary Tape File 3B. ICPSR Version*. Ann Arbor, MI:Institute for Social Research, University of Michigan.
U.S. EPA (U.S. Environmental Protection Agency). 2011. Air quality data for the CDC National Environmental Public Health Tracking Network. http://www.epa.gov/heasd/research/cdc.html. [accessed 13 October 2011].
U.S. EPA. 2013. "Final Report: Integrated Science Assessment of Ozone and Related Photochemical Oxidants". EPA/600/R-10/076F. https://cfpub.epa.gov/ncea/isa/recordisplay.cfm?deid=247492 [accessed 18 October 2016].
Williams ML, Atkinson RW, Anderson HR, Kelly FJ. 2014. Associations between daily mortality in London and combined oxidant capacity, ozone and nitrogen dioxide. Air Qual Atmos Health 7(4):407–414, PMID: 25431629, https://doi.org/10.1007/s11869-014-0249-8.
Winters N, Goldberg MS, Hystad P, Villeneuve PJ, Johnson KC. Canadian Cancer Registries Epidemiology Group, 2015. Exposure to ambient air pollution in Canada and the risk of adult leukemia. Sci Total Environ 526:153–176, PMID: 25955692, https://doi.org/10.1016/j.scitotenv.2015.03.149.
Wong CM, Tsang H, Lai HK, Thomas GN, Lam KB, Chan KP, et al. 2016. Cancer mortality risks from long-term exposure to ambient fine particle. Cancer Epidemiol Biomarkers Prev 25(5):839–845, PMID: 27197138, https://doi.org/10.1158/1055-9965.EPI-15-0626.
WHO (World Health Organization). 1977. *The International Classification of Diseases, 9th Revision*. Geneva, Switzerland:World Health Organization.
WHO. 1992. *International Statistical Classification of Diseases and Related Health Problems, 10th revision*. Geneva, Switzerland:World Health Organization.
Yang WS, Zhao H, Wang X, Deng Q, Fan WY, Wang L. 2016. An evidence-based assessment for the association between long-term exposure to outdoor air pollution and the risk of lung cancer. Eur J Cancer Prev 25(3):163–172, PMID: 25757194, https://doi.org/10.1097/CEJ.0000000000000158.