Long-term Concentrations of Ambient Air Pollutants and Incident Lung Cancer in California Adults: Results from the AHSMOG Study

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The purpose of this study was to evaluate the relationship of long-term concentrations of ambient air pollutants and risk of incident lung cancer in nonsmoking California adults. A cohort study of 6,338 nonsmoking, non-Hispanic, white Californian adults, ages 27–95, was followed from 1977 to 1992 for newly diagnosed cancers. Monthly ambient air pollution data were interpolated to zip code centroids according to home and work location histories, cumulated, and then averaged over time. The increased relative risk (RR) of incident lung cancer in males associated with an interquartile range (IQR) increase in 100 ppb ozone (O_3) was 3.56 [95% confidence interval (CI), 1.35–9.42]. Incident lung cancer in males was also positively associated with IQR increases for mean concentrations of particulate matter <10 μm (PM_{10}; RR = 5.21; CI, 1.94–13.99) and SO_2 (RR = 2.66; CI, 1.62–4.39). For females, incident lung cancer was positively associated with IQR increases for SO_2 (RR = 2.14; CI, 1.36–3.37) and IQR increases for PM_{10} exceedance frequencies of 50 μg/m^3 (RR = 1.21; CI, 0.55–2.66) and 60 μg/m^3 (RR = 1.25; CI, 0.57–2.71). Increased risks of incident lung cancer were associated with elevated long-term ambient concentrations of PM_{10} and SO_2 in both genders and with O_3 in males. The gender differences for the O_3 and PM_{10} results appeared to be partially due to gender differences in exposure. *Key words*: air pollution, lung cancer, nitrogen dioxide, ozone, particulate matter, Seventh-day Adventists, sulfur dioxide, troposphere. *Environ Health Perspect* 106:813–823 (1998). [Online 10 November 1998]
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Lung cancer has many etiological factors. Among nonsmokers, lung cancer mortality has been rising (*1*). The relationship between lung cancer and tobacco, asbestos, arsenic, radon and other radioactive materials, nickel compounds, chromates, and several other airborne chemicals (e.g., benzo[*a*]pyrene, benzene), are fairly well established, even though many issues are unresolved concerning dose–response functions, mechanisms of action, and environmental standards (*2–6*). Although lung cancer mortality has been studied, the relationship between chronic levels of ambient air pollution (especially the gaseous components) and human lung cancer incidence has not been adequately described in the literature (*7*).

Ozone (O_3) in the troposphere (0–15 km), the major oxidizing component in photochemical smog, can have various adverse health effects (*8,9*). A review by Witschi (*10*) stated that even though experimental data show that O_3 increases incidence and multiplicity of lung tumors in mice, there is not yet conclusive evidence to link O_3 exposure to lung cancer in humans. Any such link might have serious public health implications because the number of people living in areas in the United States where ambient concentrations of O_3 each year exceed the current U.S. ambient air quality standard of 120 ppb (235 μg/m^3) was estimated by the American Lung Association in 1991 to be 115–151 million (*11–13*). Positive associations between lung cancer mortality and ambient concentrations of respirable particulates (PM_{10}) and SO_2 as products of combustion have been observed (*14–17*).

To our knowledge, the Adventist Health Study on Smog (AHSMOG) is the first study to evaluate a positive relationship between long-term cumulative ambient O_3 levels and newly diagnosed respiratory cancer in humans (*18*). Estimated PM_{10} concentrations were not available for the cohort at that time. Although the ozone-incident respiratory cancer association was elevated [relative risk (RR) 2.25, 95% confidence interval (CI), 0.96–5.31], this result was based on only 17 cases and 6 years of follow-up. Cancer incidence ascertainment on this cohort has recently been extended to 15 years, resulting in a total of 36 incident cases of lung cancer. In this study we investigated the relationship between incident lung cancer (1977–1992) and cumulated levels of ambient PM_{10}, SO_2, NO_2, and O_3 since 1973.

Methods

Population. The AHSMOG study has been described in detail previously (*18–20*). In April 1977, 6,338 nonsmoking, non-Hispanic, white Seventh-day Adventist (SDA) adult residents of California were enrolled in a prospective cohort study to ascertain long-term chronic health effects of ambient air pollutants. The study participants, ages 27–95 at baseline, were part of the Adventist Health Study (AHS) (*21*). Sixty-four percent of the subjects were female. Inclusion criteria were 1) having lived 10 years or longer within 5 miles of their residence at time of enrollment; 2) residing in one of the three California air basins of San Francisco, South Coast (Los Angeles and eastward), or San Diego; or 3) being part of a 10% random sample of AHS study subjects from the rest of California who met the other inclusion criteria.

Questionnaire data. In 1976, subjects completed the AHS mailed questionnaire, which contained information on current and past dietary habits, parental history of cancer, exercise patterns, use of alcohol and tobacco, occupation, anthropometric data, and history of selected medical conditions (*21*). All AHSMOG subjects also completed a mailed respiratory symptoms questionnaire in April 1977. This latter questionnaire contained additional questions on past smoking history, history of exposure to environmental tobacco smoke, occupational history and occupational exposures, lifestyle patterns that might effect exposure to ambient air pollutants (such as hours per week spent outdoors by season), and residence and work location history. These data were updated on survivors in 1987 and 1992. Updated residence and work location histories were obtained from surrogates of deceased study subjects in 1987 and 1992.

Air pollution data. Estimates of monthly ambient concentrations of O_3 and other air pollutants were formed for study participants for the period 1966–1992 using fixed-site

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monitoring stations maintained by the California Air Resources Board (CARB). Other air pollutants studied in this report include particulate matter <10 μm in aerodynamic diameter (PM_{10}), SO_2, and NO_2.

The methods for estimating ambient air pollutants for study participants have been described earlier (*22,23*). Briefly, monthly indices of ambient air pollutant concentrations at monitoring stations were interpolated to zip code centroids according to home and work location histories, cumulated, and then averaged over time. Interpolations were restricted to zip code centroids within 50 km (31.25 miles) of a monitoring station and were not allowed to cross barriers to air flow or any topographical obstructions in excess of 250 m above the surrounding terrain as determined by CARB staff (*22*).

Concentrations of PM_{10} through 1987 were estimated using site- and season-specific regressions based on total suspended particulates (TSP) (*23*). Since 1987 PM_{10} has been monitored throughout California. For O_3 and PM_{10}, exceedance frequencies and excess concentrations above several cutoffs were estimated in addition to mean concentration. Exceedance frequencies were defined as the sum of hours above a specified cutoff for gaseous pollutants or days in excess of a cutoff for particulate pollutants. Excess concentrations were defined as the sum of concentrations above a cutoff. The cutoffs used for O_3 were 60, 80, 100, 120, and 150 ppb as well as the monthly average of the daily 8-hr average for 0900 hr to 1700 hr (used to correspond to usual hours at work locations); separate interpolations were used for work locations. The indices for PM_{10} evaluated in this report included mean concentration and average annual days per year in excess of 40, 50, 60, 80 and 100 $\mu g/m^3$ [$PM_{10}(100)$]. For a given threshold, exceedance frequencies and excess concentrations are highly correlated, so only the exceedance frequency associations are described in this report.

In the earlier years of this time period (1966–1972), total oxidants were monitored. From 1973 to 1980, O_3 monitors gradually replaced the total oxidant monitors. Whenever ozone data were available, they were used. Ozone and total oxidants were simultaneously monitored at 5–24 stations per year throughout California between 1974 and 1979. The correlation of the 435 paired monthly values of hours in excess of 100 ppb and total oxidants in excess of the same cutoff was 0.98 (*22*).

Cancer incidence ascertainment program. We ascertained cancer incidence for the cohort from 1 April 1977 to 1 April 1992 using a combination of two methods: 1) computer-assisted record linkage with local and statewide cancer registries and 2) medical records from self-reported hospitalizations. Both were used to ensure as complete a coverage as possible.

We used computer-assisted record linkage with tumor registries to ascertain any cancers occurring in times and areas covered by them (*24*). For the years 1977–1992, these included the Los Angeles County Cancer Surveillance Program registry and the Northern California Cancer Center registry (Alameda, Contra Costa, Marin, San Francisco, and San Mateo counties). Computer-assisted record linkage was also performed for all cohort members still residing in California for the years 1988–1992 using the statewide California Cancer Registry.

In addition, we ascertained hospitalizations for study subjects by annual mailed questionnaires through 1982 and in 1987 and 1992. Phone tracing was conducted for nonrespondents to these mailed surveys. A total of 97.5% of study subjects were successfully traced, with only 156 subjects lost to follow-up. The latter were censored at date of last contact. Surrogates of deceased or incapacitated study subjects were contacted for permission to review hospital records. Medical records were requested for each hospitalization involving a tumor diagnosis. These were coded by our certified nosologist, who was blinded to the air pollution data.

A total of 36 histologically confirmed incident lung cancers [First International Classification of Diseases for Oncology (ICDO-1): 162 or Second International Classification of Diseases for Oncology (ICDO-2): C34.0–C34.9] were identified for this period.

Statistical methods. We used time-dependent, gender-specific Cox proportional hazards regression models using attained age as the time variable (*25,26*) to evaluate the association between incidence of lung cancer and the selected air pollutants (PM_{10}, SO_2, O_3, and NO_2), adjusting for the potential confounding effects of other covariates (*27*). Using attained age as the time variable enables the effects of age to be tightly controlled for in a nonparametric manner, as during analysis each lung cancer case is compared to only non-lung cancer cases of the same attained age. The PHREG procedure of SAS software (version 6.12; SAS Institute, Cary, NC) was used for these analyses (*28*). We conducted analyses by gender to satisfy the proportional hazards assumption required by the Cox proportional hazards regression model.

We chose annual average number of hours in excess of 100 ppb of O_3 [$O_3(100)$] as the primary O_3 for development of statistical models because this metric filtered out lower background levels and showed the strongest association with respiratory cancer incidence in previous analyses (*18*). Air pollutants were treated as time-dependent variables in the Cox regression models. Each time a risk set was created for a new lung cancer case, the cumulated air pollutant variable for each individual in the risk set was recomputed as the sum of the monthly data assigned to that individual from January 1973 through the following months, stopping 3 years before to the date of diagnosis of the defining case. This cumulated value was then divided by 12 to obtain an average annual ambient exposure for each individual. This averaging algorithm thus allowed for a 3-year time lag between the cumulated air pollutant and the diagnosis of lung cancer. Pack-years of past cigarette smoking and education were included as covariates in all models. Education was the best available surrogate of socioeconomic status in this cohort (*19*).

Initial gender-specific Cox proportional hazards regression models estimated RR associated with O_3 adjusting for pack-years of past tobacco smoking and education using attained age as the time variable. We evaluated the large number of potential confounders for inclusion in the final statistical model one at a time because of the small number of incident respiratory cancers (20 female; 16 male) (*29*). The primary criterion for inclusion of potential confounders in the final Cox regression model was that their inclusion changed the adjusted RR estimate associated with $O_3(100)$ by 10% or more (*30*); none of the potential confounders other than those included in the initial *a priori* model did so. A secondary criterion was that the precision of the model be significantly ($p<0.05$) increased according to the log-likelihood test. Only "current use of alcohol" met this criterion and was thus included in the final model. For comparison purposes, evaluation of the association between PM_{10}, SO_2, and O_3 and incident lung cancer used the same final model. Analyses that combined both genders in one model indicated a violation of the proportional hazards assumption of the Cox regression. Therefore, all final analyses are reported by gender.

Potential confounders identified from the literature included 1) worked for 10 years or more in an environment involving exposure to occupational air pollutants (*31,32*), 2) years lived with a smoker (*33–35*), 3) years worked with a smoker (*36–38*), 4) whether or not a doctor had ever diagnosed asthma (*39–41*), 5) parents' history of cancer (*42,43*), 6) total exercise combining work and leisure activity (*44,45*), 7) body mass index (*46,47*), 8)

indices of fruit and vegetable use (*48*), 9) antioxidant vitamin use (*49,50*), 10) current alcohol use (*51*), and 11) number of homes within a quarter-mile radius of residence as a surrogate for urban/rural classification (*52–54*).

To more accurately reflect individual exposure to the selected air pollutants, we evaluated potential interactions between the individual pollutants (PM_{10}, SO_2, NO_2, and O_3) and outdoor summer exposure variables (hours per week spent outdoors and hours per week exercising vigorously outdoors) (*55*) as well as all covariates included in the final model. None of the interaction terms significantly ($p<0.05$) improved the fit of the model according to the log-likelihood ratio test.

We checked the proportional hazards assumption by examining log[-log(survival)] curves versus time as well as the product term of each respective variable in the final model with the log of the time variable (*56,57*). In the final gender-specific models, all of these interaction terms produced a p-value >0.05 based on the Wald statistic (*58–60*), indicating that the proportional hazards assumptions was not seriously violated. This was supported further by visual inspection.

Because education and pack-years of past cigarette smoking were modeled as continuous variables, the log-linear assumption was checked by coding each of these as a series of dummy variables and plotting the regression coefficients for the dummy variables and their CIs against the midpoints of the underlying continuous variable. Inspection of these plots indicated that the log-linear assumption was appropriate because straight lines could be drawn through the resultant regression coefficient point estimates or their CIs.

Results

Selected characteristics of the study population and the incident respiratory cancer cases are given in Table 1. For females, the cases as compared to the noncases tended to be older, had lower educational levels, more years of past cigarette smoking, and increased number of years worked with a smoker. The male cases also tended to be older and have lower education levels than noncases. Male cases also tended to have worked for 10 years or more in occupations having substantial levels of airborne contaminants, consumed more alcoholic beverages, and exercised more.

During follow-up, 36 histologically confirmed lung cancers were diagnosed (20 female, 16 male). The morphologies of the incident lung cancers are given in Table 2. Figures 1–5 show distributions of exposure to selected indices for O_3, PM_{10}, and annual mean concentration of SO_2. Subjects with more than 20% of their monthly air pollution data missing were excluded from analyses. The number of subjects thus excluded were 586 for O_3 (228 males and 358 females); 521 for PM_{10} mean concentration (198 males and 323 females); and 2,104 for SO_2 mean concentration (787 males and 1,317 females). There were no

Table 1. Distributions of selected variables in the AHSMOG Study according to noncases and cases of incident lung cancer

	Females		Males	
Variables	Percent noncases (n = 4,040)	Percent cases (n = 20)	Percent noncases (n = 2,262)	Percent cases (n = 16)
Age in 1977				
27–59	50.1	30.0	53.2	12.5
60–69	25.8	15.0	25.3	43.7
70–79	15.5	40.0	14.8	37.5
80+	8.6	15.0*	6.7	6.3**
Education				
≤High school graduate	38.6	70.0	29.1	66.7
Some college	61.4	30.0**	70.9	33.3**
Body mass index (kg/m^2)				
13.0–22.0	31.9	26.3	15.7	14.3
22.1–24.0	21.9	36.8	24.8	21.4
24.1–26.0	17.3	21.1	29.2	28.6
26.1+	28.9	15.8	30.3	35.7
Total exercise				
None/low	46.9	35.0	30.4	18.7
Moderate/high	53.1	65.0	69.6	81.3
History of cancer				
No	92.7	85.0	96.2	93.7
Yes	7.3	15.0	3.8	9.3
History of asthma				
No	91.8	90.0	92.2	100.0
Yes	8.2	10.0	7.8	0.0
Job air pollution				
No	99.1	100.0	86.3	75.0
Yes	0.9	0.0	13.7	25.0
Current alcohol use				
Never	93.0	94.1	90.1	75.0
Any	7.0	5.9	9.9	25.0*
Pack-years of cigarettes				
None	86.9	65.0	67.1	62.5
1–7	7.3	5.0	13.0	6.3
>7	5.8	30.0**	19.9	31.2
Years lived with smoker				
None	52.2	50.0	66.3	56.3
1–5	19.6	15.0	17.0	31.2
16+	28.2	35.0	16.7	12.5*
Years worked with smoker				
None	61.8	70.0	51.9	50.0
1–15	28.3	5.0	27.5	31.2
16+	9.9	25.0*	20.6	18.8
Hours outside in summer				
0–7/week	53.5	75.0	26.6	31.2
8-14/week	23.7	10.0	21.7	0.0
15+/week	22.8	15.0	51.7	68.8
Hours vigorous exercise outside in summer				
None	27.5	50.0	13.0	6.3
1–7/week	54.5	35.0	48.9	56.2
8+/week	17.9	15.0	38.1	37.5
Fruit index				
<Daily	7.2	5.9	9.1	0.0
1–2 Times daily	20.8	35.3	25.0	30.8
≥Twice daily	72.0	58.8	65.9	69.2
No. of homes within 0.25 mile radius of residence				
<5	4.1	5.0	4.2	6.7
5–10	10.4	0.0	9.4	6.7
>10	85.5	95.0	86.4	86.7

*p-Value for chi-square test comparing distributions of cases to noncases <0.05.
**p-Value for chi-square test comparing distributions of cases to noncases <0.005.

Table 2. Incident lung cancers in AHSMOG cohort, 1977–1992

Morphology		Females, past smoking		Males, past smoking		
ICDO	Description	No	Yes	No	Yes	Total
8000	Malignant neoplasm	1	1	0	0	2
8010	Carcinoma, NOS	6	0	2	2	10
8042	Oat cell carcinoma	0	0	0	1	1
8050	Papillary carcinoma, NOS	1	0	0	0	1
8070	Squamous cell carcinoma	1	0	2	3	6
8071	Squamous carcinoma (keratizing)	1	0	0	0	1
8140	Adenocarcinoma	2	1	5	0	8
8250	Bronchioloalveolar adenocarcinoma	1	3	1	0	5
8260	Papillary adenocarcinoma, NOS	0	1	0	0	1
8480	Mucinous adenocarcinoma	0	1	0	0	1
Totals		13	7	10	6	36

Abbreviations: ICDO, International Classification of Diseases for Oncology; NOS, not otherwise specified.

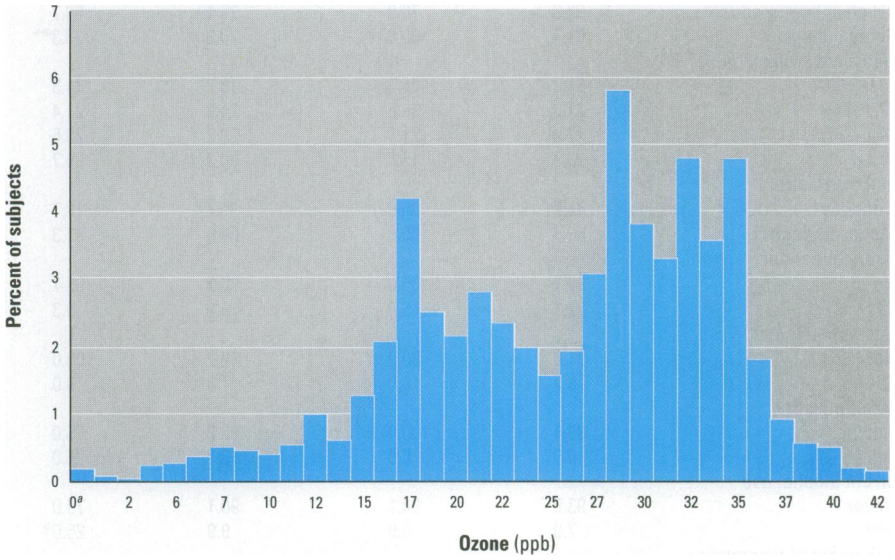

Figure 1. Average annual mean concentration of ozone experienced by subjects, 1973–1992. Numbers represent the left end of interval. Mean = 26.2; standard deviation = 7.7; n = 5,893.
[a]Unmeasured low background levels.

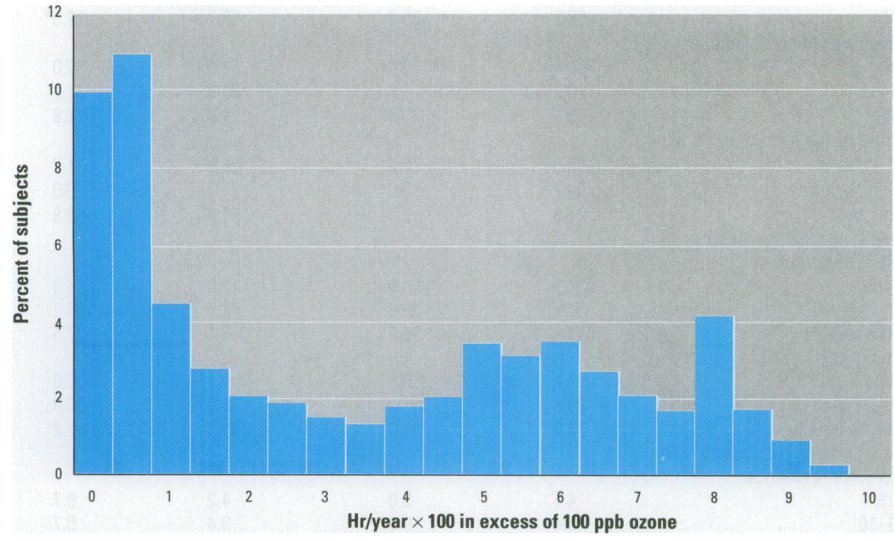

Figure 2. Average annual hours per year in excess of 100 ppb ozone experienced by subjects, 1973–1992. Numbers represent the left end of interval. Mean = 333; standard deviation = 297.3; n = 5,893.

significant differences between those who had at least 80% good air pollution data and those excluded from analyses because of incomplete air pollution data on the variables in the final models as well as other potential confounders listed in Table 1. That is, the reason for missing air pollution data appeared to be unrelated to any of the potential covariates investigated.

Ozone(100) was chosen as the primary air pollutant for comparison to our prior report (*18*). Ozone was strongly associated with incidence of lung cancer in males, with an RR of 3.56 (CI, 1.35–9.42) for 556 hr/year above 100 ppb (the IQR) controlling for pack-years of past cigarette smoking, educational level, and current alcohol use (Table 3). However, the O_3 effect did not appear to be as stable or strong as the PM_{10} and SO_2 effects (see Multipollutant Analyses below). The other metrics of O_3 and PM_{10} also showed elevated risks corresponding to increments of one IQR for incident lung cancer. Mean concentrations of PM_{10} (RR = 5.21; CI, 1.94–13.99) and SO_2 (RR = 2.66; CI, 1.62–4.39) also showed significant increased risk of incident lung cancer in males (Table 4). For males, all exceedance frequencies of PM_{10} were significantly elevated, and regression coefficients increased with higher cutoffs (see Table 4). For females, although all of the RRs for average annual mean concentration and the exceedance frequencies for PM_{10} were above 1.0, the CIs all included the null value. The largest PM_{10} associations with incident lung cancer in females were RR = 1.21 (CI, 0.55–2.66) for 50 μg/m^3 and RR = 1.25 (CI, 0.57–2.71) for 60 μg/m^3 (data not shown). But for both genders, the regression coefficients generally increased for both O_3 and PM_{10} as the exceedance frequency threshold increased. Females also showed an increased risk of incident lung cancer for one IQR increase in mean concentration of SO_2 (RR = 2.14, CI, 1.36–3.37). There was a small elevation in lung cancer risk for one IQR increase in mean concentration of NO_2 in both genders, but the CIs included the null value.

Males who used alcohol in 1977 were at increased risk of lung cancer independent of past smoking. This was demonstrated when analyses were restricted to never smokers: the association seen for alcohol remained elevated (RR = 5.29; CI, 1.04–27.02). For females, neither O_3 nor mean concentration PM_{10} was associated with incidence of lung cancer; however, pack-years of past smoking was associated with incidence of lung cancer (Table 5) with an RR of 1.62 (CI, 1.27–2.07) for each 10 pack-years of past smoking. Among subjects who were past smokers, 78.1% of males and 73.4% of females had stopped smoking more than 10 years before enrollment in 1977.

A higher proportion of males than females reported working in occupations involving airborne contaminants (see Table 1). These occupations have been previously reported and described (*19,61*). When we excluded those who had worked in these occupations, the RR of lung cancer in males associated with the IQR of O_3(100) increased to 4.73 (CI, 1.49–15.03).

Relative risks for O_3 from the Cox multivariate modeling approach were compared to gender-specific adjusted (age, pack-years, education, and alcohol) Mantel-Haenszel (MH) analyses modified for person years (*62*) and found to be similar. These analyses categorized continuous variables, and any assumptions of linear or additive effects were avoided. However, there is some loss of statistical power resulting from this categorization. The MH-adjusted RRs associated with O_3(100) (>700 hr/year compared to <90 hr/year) for males and females were 3.56 (CI, 1.08–11.62) and 1.09 (CI, 0.26–4.56), respectively.

Time on study as time variable. Because other investigators have used "time on study" as the time variable in Cox proportional hazards modeling, we reran the final gender-specific models for O_3, replacing attained age as the time variable with time on study in months. Age at baseline was then added to each model as a covariate. This approach resulted in a similar RR for an IQR increase of O_3(100) (males: RR = 3.15; CI, 1.19–8.29 and females: RR = 0.91; CI, 0.39–2.11).

Never smokers. The relationship between O_3(100) and lung cancer was reevaluated in never smokers. The RR in males increased slightly (RR = 4.48; CI, 1.25–16.04), with females again showing no relationship. When analyses were restricted to male past smokers (i.e., excluding never smokers), the results were reduced (RR = 2.15; CI, 0.42–10.89). For PM_{10}(100), restriction to never smokers resulted in no major change in RR for incident lung cancer in males (RR = 2.90, CI, 1.49–5.62), compared to an RR of 2.95 for all males.

Multipollutant analyses. Because different components of air pollution frequently occur together and are highly correlated (Table 6), the association observed with O_3(100) in males could be due instead to other air pollution components (*63*). To evaluate this, multipollutant analyses were conducted where all pairwise comparisons of O_3(100) and mean concentrations of PM_{10}, SO_2, and NO_2 were included in the time-dependent Cox regression models. Pairwise comparisons were made on that portion of the cohort having 80% nonmissing data for both pollutants (see Table 5). Because PM_{10} was more highly correlated with O_3 than with other air pollutants, an additional metric of PM_{10} [days/year in excess of 100 μg/m^3; PM_{10}(100)] was also evaluated. Two questions were addressed in the pairwise comparisons of

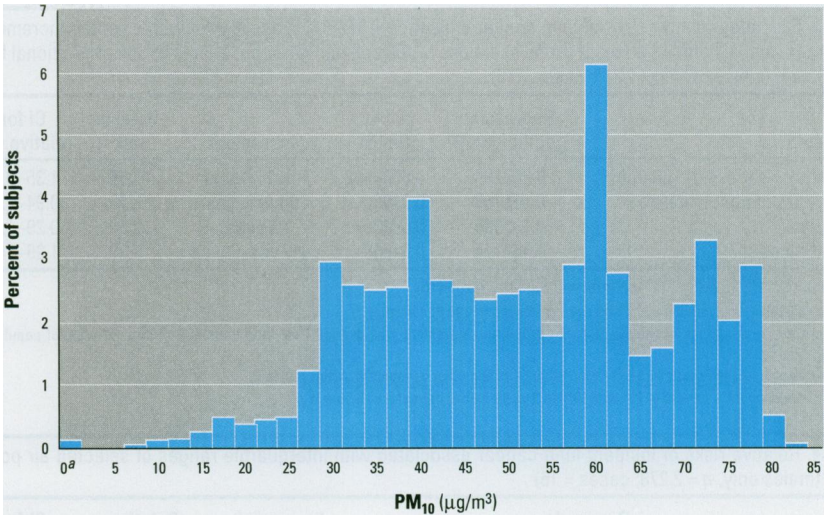

Figure 3. Average annual mean concentration of PM_{10} experienced by subjects, 1973–1992. Numbers represent the left end of interval. Mean = 51; standard deviation = 16.52; n = 5,893.
[a]Unmeasured low background levels.

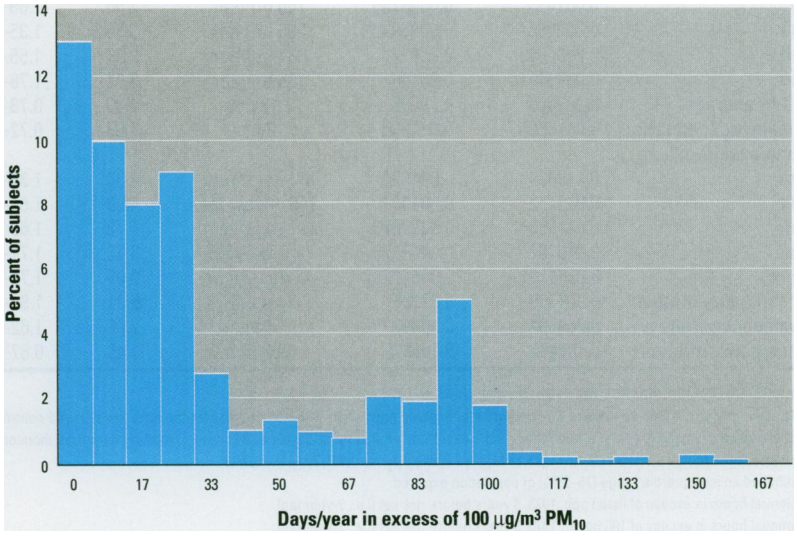

Figure 4. Average annual days per year in excess of 100 μg/m^3 of PM_{10} experienced by subjects, 1973–1992. Numbers represent the left end of interval. Mean = 31.2; standard deviation = 32.48; n = 5,962.

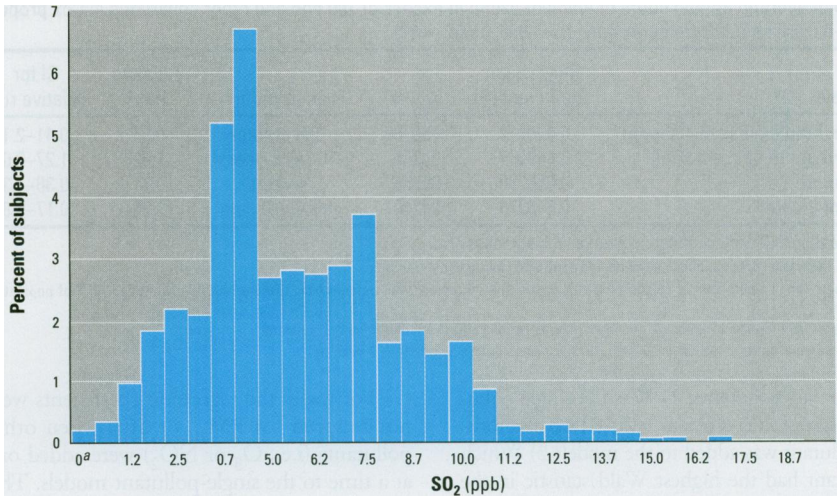

Figure 5. Average annual mean concentration of SO_2 experienced by subjects, 1973–1992. Numbers represent the left end of interval. Mean = 5.7; standard deviation = 2.9; n = 4,355.
[a]Unmeasured low background levels.

Table 3. Estimated relative risks of lung cancer incidence, 1977–1992, associated with selected increments of average annual hours of ambient ozone in excess of 100 ppb and other covariates in Cox proportional hazards model[a] (males only, $n = 2,278$; cases = 16)

Variable	Regression coefficient (β)	SE (β)	Increment[b]	Relative risk[c]	CI for relative risk
Ozone (hr in excess of 100 ppb)[d]	0.002284	0.0008932	556 hr/year	3.56	1.35–9.42
Pack-years of past smoking	0.015168	0.01080	10 pack-years	1.16	0.94–1.44
Education	-0.135385	0.08836	4 years	0.58	0.29–1.16
Current alcohol	1.462174	0.61806	1 = yes, 0 = no	4.32	1.29–14.49

Abbreviations: CI, 95% confidence interval; SE, standard error.

[a]Cox PH regression time variable = attained age controlling for age at entrance.

[b]Increment for computations of relative risk. For ozone, the increment was derived from the interquartile range (25–75% of population exposed).

[c]Relative risk of increase in exposure of one increment, holding other variables in model constant.

[d]Average annual hours in excess of 100 ppb, 1973 to 3 years before risk set (i.e., 3-year lag).

Table 4. Relative risks of incident lung cancer associated with interquartile ranges of selected air pollutants[a] (males only, $n = 2,278$; cases = 16)

Variable	Regression coefficient (β)	SE (β)	Increment (interquartile range)[b]	Relative risk	CI for relative risk
Ozone, hr in excess of[c]					
60 ppb	0.000814	0.0005267	935 hr/year	2.14	0.82–5.62
80 ppb	0.001433	0.0006755	756 hr/year	2.96	1.09–8.04
100 ppb	0.002284	0.0008932	556 hr/year	3.56	1.35–9.42
120 ppb	0.003604	0.00123	367 hr/year	3.75	1.55–9.09
150 ppb	0.006945	0.00196	185 hr/year	3.61	1.78–7.35
Ozone, 8-hr average	0.287000	0.19009	2.12 ppb	2.23	0.79–6.34
Ozone, mean concentration	0.041896	0.035336	8 hr	1.65	0.72–3.80
PM_{10}, hr in excess of[d]					
40 μg/m^3	0.010824	0.004524	139 days/year	4.50	1.31–15.44
50 μg/m^3	0.010752	0.004008	149 days/year	4.96	1.54–16.00
60 μg/m^3	0.011760	0.0039672	132 days/year	4.72	1.69–13.18
80 μg/m^3	0.015792	0.0045576	78 days/year	3.43	1.71–6.88
100 μg/m^3	0.025176	0.0064728	43 days/year	2.95	1.71–5.09
PM_{10}, mean concentration	0.068759	0.02101	24 μg/m^3	5.21	1.94–13.99
SO_2, mean concentration	0.264594	0.06892	3.7 ppb	2.66	1.62–4.39
NO_2, mean concentration	0.188802	0.19887	1.98 ppb	1.45	0.67–3.14

Abbreviations: CI, 95% confidence interval; SE, standard error.

[a]All models above based on time-dependent Cox proportional hazards regression with attained age as the time variable and controlling for pack-years of cigarette smoking, years of education, and current use of alcohol at baseline. Because of missing data from monitoring stations, the n varies for each air pollutant (O_3; $n = 2,050$; PM_{10}; $n = 2,080$; SO_2; $n = 1,491$; NO_2; $n = 1,971$).

[b]Increment based on interquartile range (75–25%) of population exposed.

[c]Average annual hours in excess of listed ppb, 1973, 3 years before risk set (i.e., 3-year lag).

[d]Average annual hours in excess of 100 μg/m^3, 1973, 3 years before risk set (i.e., 3-year lag).

Table 5. Estimated relative risks of lung cancer incidence, 1977–1992, associated with selected increments of average annual hours of ambient ozone in excess of 100 ppb and other covariates in Cox proportional hazards model[a] (females only, $n = 4,060$; cases = 20)

Variable	Regression coefficient (β)	SE (β)	Increment[b]	Relative risk[c]	CI for relative risk
Ozone (hr in excess of 100 ppb)[d]	-0.000114	0.000766	556 hr/year	0.94	0.41–2.16
Pack-years of past smoking	0.048467	0.01240	10 pack-years	1.62	1.27–2.07
Education	-0.086790	0.08565	4 years	0.71	0.36–1.38
Current alcohol	0.246970	1.04240	1 = yes,0 = no	1.28	0.17–9.88

Abbreviations: CI, 95% confidence interval; SE, standard error.

[a]Cox PH regression time variable = attained age controlling for age at entrance.

[b]Increment for computations of relative risk; for ozone, the increment was derived from the interquartile range (25–75% of population exposed).

[c]Relative risk of increase in exposure of one increment, holding other variables in model constant.

[d]Average annual hours in excess of 100 ppb, 1973 to 3 years before risk set (i.e., 3-year lag)

selected air pollutants: 1) Was the single pollutant regression coefficient reduced when another pollutant was added to the model? 2) Which pollutant had the highest Wald statistic in the single pollutant models? The Wald statistic can be taken as a scale-free measure of the strength of association with lung cancer (*64*).

For males the regression coefficients were not reduced for PM_{10} or SO_2 when other pollutants (i.e., O_3 or NO_2) were added one at a time to the single-pollutant models. This was not true for other pollutants. When PM_{10} and SO_2 were in the same model, both coefficients remained strongly positive and significant, indicating that they may have an independent association with lung cancer. $PM_{10}(100)$ had the highest Wald statistic, indicating the strongest association with lung cancer. For females only the regression coefficient for SO_2 was not reduced when other pollutants were added one at a time to the single pollutant models. SO_2 had the highest Wald statistic, indicating the strongest association with lung cancer.

Discussion

Population Density

Our study design essentially controls for population density because more than 90% of subjects were selected from urban areas. The baseline questionnaire data did ascertain population density according to a three-category measure (see last entry in Table 1). When the final model was rerun restricted to subjects who reported living in high-density residence areas, the relative risk of $O_3(100)$ increased to 10.18 (CI, 2.44–42.45) for males and remained nonsignificant for females. When this restriction was applied to $PM_{10}(100)$ and mean concentration of SO_2 for males, the RRs increased to 4.52 (CI, 2.31–8.84) and 3.22 (CI, 1.87–5.54), respectively. A similar restriction for females living in high-density areas resulted in only a moderate increased risk of lung cancer associated with $PM_{10}(100)$ (RR = 1.13; CI, 0.64–2.02) and with mean concentration of SO_2 (RR = 2.11; CI, 1.32–3.38). This is consistent with the hypothesis that products of combustion (PM_{10} and SO_2) are associated with lung cancer incidence.

Gender Differences

The association between O_3 and lung cancer was only observed in males, whereas PM_{10} and SO_2 were associated with lung cancer for both genders. This gender difference may be due to the males spending much more time outdoors than females. This was especially true for the summer when O_3 levels are higher (18.9 hr/week versus 10.3 hr/week respectively, $p<0.0001$). They also reported more vigorous exercise outdoors in the summer compared to females (10.0 hr/week versus 5.1 hr/week, $p<0.0001$). Ozone deteriorates more rapidly in the indoor environment than PM_{10} or SO_2.

Another partial explanation could be gender differences in endogenous estrogen levels (*65*). Because estrogen is a potent antioxidant of lipids (*66*), it may help reduce possible oxidative damage caused by the action of O_3 on membrane lipids lining the respiratory tract. Sack et al. (*67*) observed that the administration of physiological levels of 17β-estradiol to postmenopausal women significantly inhibited the oxidation of low density lipoproteins (LDL). In our study

only one of the female lung cancers occurred among women identified as premenopausal at baseline. Among postmenopausal women, the effect of O_3(100) on lung cancer tended to be stronger among those who had never taken estrogen compared to those who had ever used these hormones. However, these differences were not statistically significant.

The gender differences we have observed for ozone–lung cancer associations are similar to the gender differences observed for adult-onset asthma in this study. Greer et al. (*61*) found that elevated long-term ambient concentrations of O_3 were strongly associated with adult-onset asthma in men (RR = 3.12) but not in women (RR = 0.94).

Dietary Antioxidants

Vitamin C is the major antioxidant present on the airway surface of the lung, where it could be important in protecting against exogenous oxidants such as ambient O_3 (*68*). Many ecologic, case–control, and cohort studies, and a few clinical trials have shown some benefit of antioxidant supplements on risk of epithelial cancers (*69*).

Fraser et al. (*70*) observed a reduced risk of lung cancer in the main AHS cohort for subjects who consumed fruit at least two times per day (RR = 0.26; CI, 0.10–0.70) compared to subjects who consumed fruit less than three times a week. A protective effect of fruit consumption on lung cancer was not observed in this AHSMOG cohort. This discrepancy in findings may be due to a larger range of fruit intakes in Fraser's report. When we reanalyzed the AHS lung cancer data using similar exclusions as in the AHSMOG study, the protective effect of fruit consumption was weakened (RR = 0.68; CI, 0.32–1.47). The excluded subjects tended to have lower fruit consumption, and it was the lowest category of fruit consumption (e.g., low antioxidant vitamins) that showed increased risk to lung cancer.

We created a crude antioxidant vitamin supplement index (vitamins A, C, and E) based on the food frequency questionnaire administered in 1976. High use of these vitamin supplements was defined as >1,000 mg/week of vitamin C or at least daily use of any dose of vitamin A or at least 200 IU/week of vitamin E. Low use was defined as none of the antioxidant vitamins in the high category. No protective effect was observed in males or females.

Animal Studies

Most of the reports relating O_3 and lung/respiratory cancer have been done in carefully controlled animal studies (*71*). Borek et al. (*72,73*) found that treatment of hamster embryo and mouse cells with 5,000 ppb of O_3 for 5 min resulted in cell transformation and concluded that O_3 is a cocarcinogen.

Table 6. Pearson correlation coefficients (and sample size) for selected ambient pollutants, average annual values for years 1973–1992, AHSMOG study[a]

	Ozone		PM_{10}		SO_2	NO_2
Air pollutant	Hr/year >100 ppb	Mean concentration (ppb)	Mean concentration (μg/m³)	Days/year >100 μg/m³	mean concentration (ppb)	mean concentration (ppb)
Ozone, hr/year >100 ppb	1.0	0.776 (5,893)	0.832 (5,807)	0.834 (5,807)	0.133 (4,349)	0.408 (5,643)
Ozone, mean concentration (ppb)	–	1.0	0.768 (5,807)	0.626 (5,807)	0.095 (4,349)	0.360 (5,643)
PM_{10}, mean concentration (μg/m³)	–	–	1.0	0.849 (5,962)	0.319 (4,347)	0.567 (5,638)
PM_{10}, days/year >100 μg/m³	–	–	–	1.0	-0.050 (4,347)	0.146 (5,638)
SO_2, mean concentration (ppb)	–	–	–	–	1.0	0.791 (4,351)

[a]Subjects whose accumulated data for specified ambient pollutant exceeded 20% missing data for the time period 1973–1992 (or date of censoring) were excluded.

Even at near-ambient concentrations (100–500 ppb), O_3 induces morphologic changes in all parts of the respiratory tract in animals and is potentially tumorigenic (*74*). Other studies on mice have reported K-*ras* mutations in lung neoplasms in mice exposed to O_3, indicating mutations in ozone-induced bronchioloalveolar adenomas and carcinomas (*75*). The cytotoxicity of natural killer cells in mice can be damaged by exposure to O_3 for 1 day (*76*). Hassett et al. (*77*) concluded that O_3 exposure at relatively high ambient concentrations (310 and 500 ppb) caused an increase in lung tumors in mice. However, there is some evidence that under certain circumstances, O_3 can also inhibit tumor formation (*78,79*).

Li and Richters (*80*) investigated subpopulations of thymocytes and spleen T lymphocytes in mice, and their findings suggested that short-term O_3 inhalation can affect the T-cell immune system adversely, particularly the $CD4^+$ cells. T-cell–dependent immune responses form an important component of the lung defense to respiratory infections and possibly also to neoplasms (*81,82*). Rajini et al. (*83*) have postulated that long-term exposure to O_3 (at least in hamsters) with its accompanying hyperplasia of respiratory tract epithelium might enhance tumor development.

Epidemiologic Studies on Respiratory Cancer and Ambient Air Pollution

A recent review paper by Cohen and Pope (*84*) indicated that the problems plaguing previous research (e.g., errors in the measurement of air pollution exposure and in the measurement of other risk factors including cigarette smoking) have limited the ability to quantify the magnitude of the excess lung cancer mortality risks associated with air pollution and that further research was needed. A recent EPA Air Quality Criteria for Ozone document concluded that the genotoxicity and carcinogenicity of O_3 (especially in humans) is inconclusive (*85*). A summarization of the literature by the EPA regarding the human health effects associated with acid aerosol exposures concluded that chronic acid aerosol exposures may promote lung cancer at high concentrations, possibly by chronic irritation of the lining of the respiratory tract or by decreasing the clearance rates in the lungs (*86*). The data referenced in this report also suggest that ambient particulate exposure may be associated with increased morbidity and mortality at PM concentrations below those previously thought to affect human health (*86*).

Lippmann (*87–89*) published a series of review articles regarding the health effects of tropospheric O_3 on animals and humans. He concluded that humans who are active outdoors during the warmer months may have greater effective O_3 exposures than test animals. Several population-based studies of lung function indicate that there may be an accelerated aging of the lung associated with living in communities with persistently elevated ambient O_3 (*90–94*).

A limited number of studies on human populations have evaluated lung cancer and ambient particulate concentrations. In a case–control study of air pollution, measured as total suspended particulates, and incident lung cancer, Vena (*95*) compared 417 male lung cancer cases with 752 controls. The author found that there was increased lung cancer risk from smoking and occupational exposure if there was also long-term exposure to particulate pollution. The effect of O_3 was not evaluated.

Our results of an association between long-term ambient concentration of PM_{10} and incidence of lung cancer are consistent with those reported by others (*14,16*). Similar findings from an analysis of 552,138 men and women drawn from the American Cancer Society (ACS) Cancer Prevention Study II showed that particulate air pollution, which

the authors concluded was particularly from combustion sources, was associated with lung cancer mortality (*14*). The authors concluded that lung cancer mortality seemed to be more strongly associated with sulfate particles than the more general index of fine particulates and that sulfate particles make up the largest fraction of fine particles by mass. Associations pertaining to O_3 have not been reported from these studies. The Six Cities Study lacked sufficiently contrasting levels of O_3 (*16*).

Possible Biologic Mechanisms

Ozone has been shown to be reactive to biomolecules, particularly those with carbon–carbon double bonds such as found in the membrane lipids (*96,97*). The toxic effects of O_3 have been attributed to its ability to cause oxidation or peroxidation of biomolecules directly or via free-radical reactions (*3,98*). In aqueous solutions, such as is found in the epithelial lining of the respiratory tract, O_3 decomposes to give hydrogen peroxide, superoxide, and hydroxy radicals, which can take part in secondary reactions (*99*). Free radicals produced within the body have been linked to the pathogenesis of cancer (*100,101*). Cellular DNA can also be damaged by O_3 (*102*) by compromising macrophage functions important in tumor surveillance. Ozone could potentially alter host susceptibility to lung cancer (*103*). Numerous investigators have provided functional and anatomical evidence to support the hypothesis that exposure to ambient O_3, respirable particulates (PM_{10}), and SO_2 can have profound effects on systemic immunity (*104–106*). Koren et al. (*107*) have shown alterations in markers associated with pulmonary inflammation in humans exposed to ambient levels of O_3.

Products of combustion of fossil fuels such as PM_{10} and SO_2 may also damage the respiratory epithelium. Respirable particles (PM_{10}) may contain benzo[*a*]pyrene and other chemicals of carcinogenic potential (*105*). Sulfur dioxide is a known respiratory irritant (*5*), which may act as a promotor or cocarcinogen. Potential mechanisms for lung cancer promotion could include slowing of mucociliary clearance, impairment of alveolar macrophage function, and other specific or nonspecific effects on the immune response such as increased epithelial permeability, which would facilitate absorption of carcinogenic components of particulate matter. Particulate matter may also transport reactive oxygen species or increase their formation (*86*).

Alcohol

The observation that alcohol consumption, at least in males, is a significant risk factor for lung cancer is consistent with other studies—those that did not control for smoking at the individual level (*108,109*) and those that did (*110,111*).

Alcohol may act as a promoter of lung cancer through a variety of mechanisms. From animal research, major changes in the lipid surfactant in the lung (*112*) and levels of inducible enzymes capable of activating procarcinogens and mutagens (*113*) have been demonstrated as consequences of alcohol consumption. Ziegler (*114*) has identified several other mechanisms for the alcohol-associated carcinogenesis: 1) alcohol may facilitate the transport of carcinogens (e.g., airborne particulates or tobacco-associated) across the mucosal lining; 2) alcohol may damage the liver's ability to detoxify certain carcinogens; 3) alcohol consumption may affect nutritional status by reducing intake and/or absorption of essential nutrients; and 4) in conjunction with liver disease and nutrient deficiencies, alcohol may suppress the immune response. It is also possible that in our cohort, alcohol use is serving as a marker for increased exposure to tobacco smoke.

Limitations of Study

Possible underreporting of alcohol and tobacco use. Shapiro et al. (*115*) have shown that underascertainment of confounders, even when nondifferential, can result in a spurious association between disease incidence and a risk factor. Smoking tends to be underreported in cohort studies (*116,117*). Because tobacco smoking and alcohol use are discouraged by the SDA Church, it is possible that the use of these substances has been underestimated in our study. However, it is unlikely that RRs as high as 3.56 for O_3(100) and 5.21 for mean concentration of PM_{10} would be due to unmeasured confounders (*118*) not already addressed in this report. All individuals (43 females, 49 males) reporting current smoking in 1977 were excluded from the study. We have estimated that if current smoking, past smoking, and current alcohol use each were underreported by 50% and this underreporting was not differential with respect to O_3 concentrations, the observed RR of 3.56 in males would be even higher. However, if the underreporting only occurred in the high O_3 quartile, the true RR would be reduced to 2.0.

Outdoor ambient concentrations. Ozone estimates are of outdoor ambient concentrations and may not reflect true individual exposure. Ozone is highly reactive and adsorbs rapidly onto indoor surfaces, resulting in a short indoor half-life (*119*). As a consequence, indoor/outdoor ratios of O_3 have been reported from 0.10 to 0.80 (*120*). We have rerun our final models using adjusted outdoor ambient mean concentrations obtained by applying an indoor/outdoor adjustment factor to mean concentration of O_3 according to time spent indoors as reported by season for each study participant in 1977. An indoor adjustment factor of 0.5 for O_3 was used as described by Winer et al. (*121*). Results consistent with those reported for unadjusted mean concentration were obtained. Ambient O_3 is highly correlated with products of fossil fuel combustion (PM_{10} and SO_2), and associations seen for O_3 may be partly due to uncontrolled confounding by the presence of these other air pollutants.

Interpolations from fixed site monitors. Estimates of ambient air pollution concentrations are based on interpolations from fixed-site monitoring stations. The precision of these interpolations was assessed by comparing values interpolated from surrounding stations to those monitored at a station. The correlation coefficient for 2-year average annual cumulative exceedance of O_3 >100 ppb interpolated versus actually measured at monitoring stations was r = 0.85 (*22*). Quality grades were assigned to all interpolations used in our study (*22*). When the RR of lung cancer as associated with O_3(100) was reevaluated in only the 1,751 males for whom 80% of months were "A" or "B" quality data (within 20 miles of a monitoring station), it was found to be 3.05 (CI, 1.14–8.17). There were 13 incident lung cancer cases in these males.

When analyses for mean concentration of PM_{10} were restricted to individuals having 80% A/B quality months, the observed risk of lung cancer in males was 2.91 (CI, 1.06–7.97). Similar restrictions for females yielded a risk estimate of 1.53 (CI, 0.57–4.11). The increased risk of lung cancer associated with mean concentration of SO_2 remained elevated when analyses were restricted to individuals with 80% A/B quality data. The RR for males was 2.18 (CI, 0.92–5.20), and it was 2.52 (CI, 1.19–5.33) for females.

Indirect estimates of PM_{10} before 1987. PM_{10} has been monitored on a statewide basis in California only since 1987. In this study, estimated ambient levels of PM_{10} could potentially be inaccurate because indirect estimates using site- and seasonal-specific regression prediction equations based on TSP were used before 1987. Abbey et al. (*23*), however, have shown that using these indirect estimates only marginally impacts the precision of long-term cumulative averages of PM_{10}.

Multipollutant analyses. Air pollutants included in the multipollutant analyses were limited to PM_{10}, SO_2, O_3, and NO_2. SO_2 levels are relatively low in most of California compared to other areas in eastern United States and Europe, yet were found to increase lung cancer risk in both genders.

Suspended sulfates (SO_4) were not evaluated because these data were only measured since 1977, thus not allowing sufficient latency time for cancer to develop. Also for NO_2, indoor sources must be carefully considered (more so than for other ambient air pollutants) because indoor sources contribute a substantial amount of the total personal exposure to NO_2 (*122*). Data to control for indoor sources were not collected until 1987 and thus were only available on 62% of the study population who survived until then (*123*). However, it is possible that other pollutants (e.g., polycyclic aromatic hydrocarbons) not yet widely monitored could be responsible for the increased risk of lung cancer. Differences in measurement error among the other air pollutants may account for differences in strengths of association seen for different air pollutants (*118,124*).

Summary

In this report we observed significant positive associations between lung cancer incidence and the number of days per year that respirable particulates (PM_{10}) exceeded several thresholds for males. Lung cancer incidence in males was associated with PM_{10} exceedance frequencies of 40, 50, 60, 80, and 100 $\mu g/m^3$ with the regression estimates increasing as the cutoff increased. For females, the RRs of lung cancer incidence were all above 1.0 for each of the PM_{10} thresholds investigated. However, all of the corresponding CIs included the null value. Both genders also showed increased risk of incident lung cancer for one interquartile increase in mean concentration of SO_2. Males, but not females, showed moderate associations for O_3 and incident lung cancer risk. These associations were significant for hours per year exceedance frequencies of O_3 thresholds as low as 80 ppb. Our findings suggest that the current EPA standard of 120 ppb for O_3 may not adequately protect the large portion of the U.S. male population who live or work in communities where the current standard for O_3 is frequently exceeded. Excess lung cancer risk was also observed at levels below the National Ambient Air Quality Standard of 50 $\mu g/m^3$ (annual arithmetic mean) for PM_{10}. The association between combustion-related sources of air pollution and incident lung cancer was consistent across genders. More research with a larger number of incident cases of lung cancer is needed to better understand the observed gender difference in regard to O_3 exposure as well as to better separate the independent effects of O_3, airborne particulate matter, SO_2, and NO_2.

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