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School of Public Health

THE ASSOCIATION OF LONG-TERM CONCENTRATIONS OF AMBIENT AIR POLLUTANTS AND THE INCIDENCE OF MALIGNANT NEOPLASMS IN NONSMOKING ADULTS

by

W. Lawrence Beeson

A Dissertation in Partial Fulfillment of the

Requirements for the

Degree of Doctor of Public Health

in Epidemiology

2002

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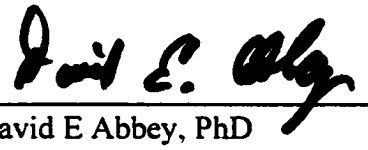

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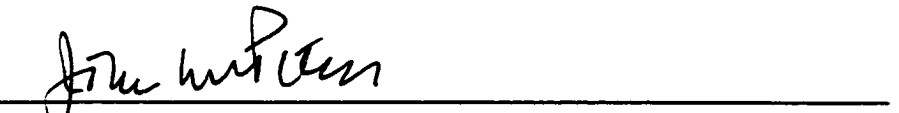

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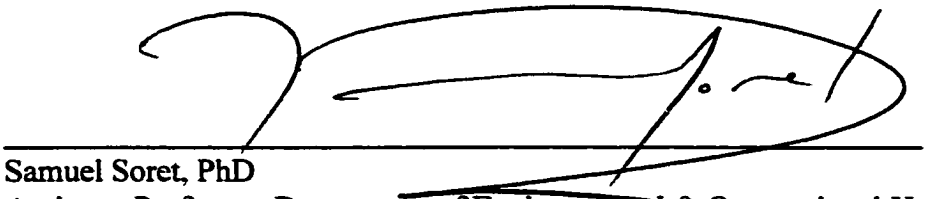

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ABSTRACT OF DISSERTATION

The Association of Long-Term Concentrations of Ambient Air

Pollutants and the Incidence of

Malignant Neoplasms in Nonsmoking Adults

by

W. Lawrence Beeson

Doctor of Public Health in Epidemiology

Loma Linda University, Loma Linda, California, 2002

David E Abbey, Chairman

A cohort of 6,338 (M=2278, F=4060) nonsmoking non-Hispanic white California adults ages 27-95 was followed from 4/77- 4/92 for newly diagnosed cancers. A total of 704 incident nonskin cancers (NSC) were identified. Of these, 36 were lung cancers (M=16, F=20).

The primary exposures investigated included exceedance frequencies and mean concentrations of ozone (O_3) and particulate matter < 10 μm in aerodynamic diameter (PM_{10}) and mean concentrations of: sulfur dioxide (SO_2), nitrogen dioxide (NO_2) and the fine ($PM_{2.5}$) and coarse ($PM_{10-2.5}$) fractions of PM_{10}.

For males, the relative risk (RR) of incident lung cancer associated with an interquartile range (IQR) increase of 100 ppb 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 PM_{10} (RR=5.21; CI: 1.94-13.99) and SO_2 (RR=2.66; CI: 1.62-4.39). The fine fraction ($PM_{2.5}$) of respirable particulates was more strongly related to lung cancer incidence than was the coarse fraction ($PM_{10-2.5}$) although the confidence limits overlapped.

For females, lung cancer incidence was positively associated with IQR increases for SO_2 (RR=2.14; CI: 1.36-3.37) and a nonsignificant increased risk with IQR increases for PM_{10} exceedance frequencies of: 50 $\mu g/m^3$ (RR=1.21; CI: 0.55-2.66) and 60 $\mu g/m^3$ (RR=1.25; CI: 0.57-2.71).

For males, the risk of NSC increased with increasing exceedance frequency thresholds of ozone reaching statistical significance with an IQR increase in average annual hours in exceedance of 150 ppb O_3 (RR=1.26; CI: 1.04-1.53). NSC was also associated with IQR increases in mean concentrations of PM_{10} (RR=1.18; CI: 1.00-1.39) and SO_2 (RR=1.85; CI: 1.64 - 2.09).

Similar to males, the risk of NSC in females also increased with increasing exceedance frequency thresholds of ozone reaching statistical significance with an IQR increase in average annual hours in exceedance of 150 ppb of O_3 (RR=1.33; CI: 1.13-1.56). NSC in females was also associated with IQR increases in mean concentrations of PM_{10} (R=1.31; CI: 1.13-1.52) and SO_2 (RR=2.28; CI: 2.07-2.52).

In summary, statistically significant increases in risk was observed for several cancer sites in both males and females associated with long-term ambient measures of gaseous and particulate air pollution.

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I would like to thank the members of my dissertation committee: Dr. David Abbey (chair), Dr. Synnove Knutsen, Dr. John Peters, and Dr Samuel Soret for their invaluable contribution to all aspects of this research including: methodology, statistical analyses, modeling, references, and presentation.

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And finally I want to express my sincere gratitude to my wife Lorna who demonstrated a great deal of patience, sacrifice and understanding during the years that I was a doctoral student. Without her constant support of my academic aspirations I would never have finished this degree.

CHAPTER 1

INTRODUCTION

A. Statement of the Problem

The factors leading to the incidence of malignant neoplasms (referred to as "cancer" throughout the rest of this dissertation) are complex and for many cancers, not fully understood. In their classic report on the "Causes of Cancer", Doll and Peto (*1*) summarized the epidemiologic literature of the time and came up with their best estimates of the proportions of cancer deaths that could be attributed to different factors. These included: diet (35%); tobacco (30%); reproductive and sexual behavior (7%); occupation (4%); alcohol (3%); geophysical factors (3%); pollution (**2%**); etc. The American Cancer Society (ACS) has estimated that 1,268,000 new cases of cancer will be diagnosed in the year 2001 in the United States and an estimated 553,400 Americans will die from cancer (*2*). Applying these estimates from ACS and from Doll and Peto, approximately 25,000 new cancer cases for 2001 could be attributed to pollution in the United States.

More recently, the U.S. Environmental Protection Agency (EPA) estimated that 0.2% of the annual incidence of cancers in the United States are attributable to the 90 toxic air pollutants that they evaluated in their report (*10*). However, this percentage would be an underestimate of the true cancer burden to the extent that unidentified pollutants and pollutants undergoing atmospheric transformation to an active carcinogen were not included in the EPA report (*8*).

The Armitage-Doll model of carcinogenesis assumes a multistage process often described as initiation, promotion, and progression (*5,6*). Some inhaled agents appear to act primarily at an early stage ("initiators") of carcinogenesis while other agents appear to act more at a later stage ("promotors') of the development of cancer. Initiation is usually considered an irreversible, normally rapid process, whereas promotion involves a series of usually reversible tissue and cellular changes during the long latency period before the appearance of the first autonomous cancer cell (*3*). There is evidence that the collection of chemicals in cigarette smoke work at both levels (*7*). The third stage of "progression" describes the stepwise evolution of cells as they become progressively more malignant.

A wide variety of known cancer-causing agents can be conveyed in the ambient air to human populations (*8*). However, the concentrations of these agents are usually assumed to be at levels below that which would cause a major impact on population cancer rates (*4*). Measurement of such an impact is difficult since concentrations can vary widely from place to place and time to time (*4*).

Most of the literature on the health effects of air pollution have focused on the short term responses (*8, 26-29*). Many of these studies are labeled as time series analyses where a change in health status of a population is evaluated with lags of zero to a few days after an air pollution "episode" or major change in the concentrations of particles (*11*-14), gases (*11-14*) or hazardous chemicals (*10,15*) in the ambient air. The effects of long-term exposures (measured in years) to low levels of ambient pollutants on the incidence of cancer are particularly difficult to observe directly since the air we breathe is a complex mixture of many different pollutants which differ geographically both in

amount and composition. Only a handful of prospective cohort studies have addressed the long-term health effects of ambient air pollution (*16-20*). Of particular concern are the respirable particles of aerodynamic diameter of 10 μm or less (PM_{10}) (*16,17*) . These small particles may have hazardous chemicals adhered to their surfaces such as cancer-causing polycyclic aromatic hydrocarbons (PAHs) that are produced in large amounts by the combustion of fossil fuels (*21-24*).

Pershagen and Simonato (*9*) summarize several ecological and aggregate studies of lung cancer mortality in urban versus rural areas. The average urban/rural lung cancer mortality ratio in these studies ranges from 1.3 to 2.0, but these types of studies usually lack adequate control of such confounders as active and passive exposure to tobacco smoke and occupational exposures. As a general rule, lung cancer mortality rates are higher in large cities and are inversely correlated to the density of the population (*25*).

Smoking is a very strong risk factor for cancer in the United States and frequently overshadows the health effects of weaker cancer-causing agents such as PAHs when these occur in air basins occupied by millions of people. The contribution of long-term exposures to particles and gases in ambient air on risk of cancer in nonsmokers needs further study. The Adventist Health and Smog (AHSMOG) study was designed to investigate the health effects (including cancer) of long-term exposure to ambient air pollution in a population of adults who are nonsmokers. This work focuses on long-term effects of ambient air pollutants on cancers, especially lung cancer.

B. Overview of Dissertation

This dissertation is organized in the two publishable paper format. Complementary analyses to the publishable papers, preliminary analyses that are in addition to the publishable papers, and other relevant work are provided in additional chapters. The present chapter includes the specific aims of this dissertation as well as a list of abbreviations.

Chapter 2 is a brief review of the literature as regards to the association of ambient air pollution and cancer. This is in addition to the references to the literature that are included in the two publishable papers (Chapters 5 & 6) and in the preliminary analysis section (Chapters 7 & 8). The primary endpoint investigated in this dissertation is lung/bronchus cancer incidence. Other organ sites are also investigated in preliminary analyses in later chapters.

Chapter 3 briefly describes how the study subjects were selected, which ambient air pollutants were investigated, and a brief description of the types of covariates available for control of confounding. Chapters 2 and 3 only contain material not already included elsewhere in the published/submitted papers chapters (i.e. chapters 4 and 5). All study subjects were nonsmokers at baseline.

Chapter 4 contains the first publishable paper which investigates the association between lung cancer incidence and long-term concentrations of ambient PM_{10}, O_3, SO_2, and NO_2. The evaluation of PM_{10} and O_3 incorporates two types of air pollution metrics: mean concentration and hours (or days) per year that a selected threshold was exceeded

(i.e. exceedance frequencies). The gaseous air pollutants of SO_2 and NO_2 are evaluated as mean concentrations only. This paper has already been published.

Chapter 5 contains the second publishable paper which extends the analysis of the association of incident lung cancer and air pollution to include the fine fraction ($PM_{2.5}$) and the coarse fraction ($PM_{10-2.5}$) of the respirable particulates. This paper has been submitted for publication and is currently in peer review.

Chapter 6 provides some additional analyses in support of the two publishable papers but which was excluded from what was submitted to the journal for publication.

Although the primary focus of this dissertation is the investigation of the association between incident lung cancer and air pollution, other cancer endpoints were also analyzed to lay the ground work for future research. Chapter 7 contains the preliminary analyses and discussion regarding the association of long-term concentrations of ambient air pollutants and risk of other non-skin neoplasms as a combined category. Skin cancer was excluded from the "all malignant neoplasm" category as we had incomplete ascertainment for skin cancer incidence.

Chapter 8 should be considered as preliminary analyses only as more work needs to be done as regards to development of statistical models, evaluation of potential confounding, sensitivity analyses, important subgroup identification, multipollutant analyses, etc. This chapter is divided into four sections, each dealing with cancer endpoints that potentially could account for a major portion of the association observed for all non-skin cancers as described in chapter 7. Section 'A' reports on the risk of smoking-related cancers (i.e. esophagus, larynx, bronchus, lung, urinary bladder,

pancreas, cervix uteri, and renal pelvis) in association with air pollutants. Section 'B' deals with breast cancer incidence, the largest (37%) single contributor to female cancer incidence and Section 'C' deals with prostate cancer incidence, the largest (48%) single contributor to male cancer incidence. Section 'D' looks at some preliminary analyses regarding non-Hodgkin's lymphoma (i.e. lymph node cancer) in relation to ambient air pollution. Non-Hodgkin's lymphoma was chosen as an *a priori* site for investigation under the hypothesis that if carcinogens and cocarcinogens permeate past the membranes of cells lining the respiratory tract, that they can be distributed systemically not only by the circulatory system, but also by the lymphatic system.

Chapter 9 describes the hospital cancer surveillance system that identified the individuals who had a cancer diagnosis after the beginning of the study in 1977. Cancer incidence for the cohort was obtained from medical records and computerized record linkage with regional cancer registries.

Chapter 10 summarizes this dissertation as regards to the statistically significant findings of the associations of selected air pollutants and incident cancer. It also offers some comments on the implications of this work and suggestions for future work.

There are also seven appendices. Appendix 'A' is a reproduction of the 1977 respiratory symptoms mailed questionnaire. The 6,338 individuals who responded to this questionnaire were enrolled into the AHSMOG study. In Appendix 'B' are the calculations for the hypothetical situation of how the relative risk might be affected if there was a 50% misclassification on the covariates. In Appendix 'C' are samples of the informed consent forms used in the Adventist Health Study and the AHSMOG study to

identify self-reported hospitalizations and to gain permission to review medical records for cancer diagnoses.

In order to facilitate access to medical records in individual hospitals for the ascertainment of cancer in our study subjects, we obtained the endorsement from the California Hospital Association (CHA). A copy of the CHA newsletter documenting this endorsement is provided in Appendix 'D'. We also sought the legal opinion from attorney's who specialize in medical law. This was done to further facilitate the access to and review of medical records. The first legal opinion was obtained in 1985 (Appendix 'E') and the second legal opinion was obtained in 1995 (Appendix 'F').

Appendix 'G' documents the permission to reproduce material in this dissertation which has already been published.

C. Specific Aims

1. To study the association between long-term (from 1973) cumulative ambient levels of PM_{10}, O_3, SO_2, NO_2 and incidence of lung cancer (4/77-4/92) separately by sex and adjusting for potential confounders (e.g. age, passive smoking, exercise, diet, etc).
2. To study the association between long-term cumulative ambient levels of $PM_{2.5}$ and $PM_{10-2.5}$ and incidence of lung cancer (4/77-4/92) separately by sex and adjusting for potential confounders.
3. To study the association between long-term cumulative ambient levels of PM_{10}, $PM_{2.5}$, O_3, SO_2, NO_2 and all non-skin cancer incidence (4/77-4/92).

4. To study the association between long-term cumulative ambient levels of PM_{10}, $PM_{2.5}$, O_3, SO_2, NO_2 and incident cancers (4/77-4/92) considered to be associated with the chemicals found in cigarette smoke (i.e. smoking-related).

5. Where numbers permit, also study the incidence of site-specific cancers (e.g. breast, lymph node) diagnosed between 4/77-4/92 and the possible association with long-term cumulative ambient levels of PM_{10}, $PM_{2.5}$, O_3, SO_2, and NO_2.

D. Abbreviations

ACS	American Cancer Society
AHS	Adventist Health Study
AHSMOG	Adventist Health and Smog Study
CARB	California Air Resources Board
CI	Confidence interval
DNA	Deoxyribonucleic acid
EPA	Environmental Protection Agency
ICDO	International Classification of Diseases for Oncology
IQR	Interquartile range
IU	International units
LDL	Low density lipoprotein
MH	Mantel-Haenszel
M-Phi	Macrophage
NAAQS	National Ambient Air Quality Standard
NO_2	Nitrogen dioxide
O_3	Ozone
$O_3(100)$	Hours/year in excess of 100 ppb
PAH	Polycyclic aromatic hydrocarbon
PPB	Parts per billion
$PM_{2.5}$	Particulate matter less than 2.5 microns in aerodynamic diameter
PM_{10}	Particulate matter less than 10 microns in aerodynamic diameter
$PM_{10}(100)$	Days/year in excess of 100 $\mu g/m^3$
RR	Relative risk
SDA	Seventh-day Adventist
SO_2	Sulfur Dioxide
SO_4	Sulfate
TSP	Total suspended particulates
$\mu g/m^3$	Micrograms per cubic meter

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CHAPTER 2

REVIEW OF THE LITERATURE

A. Literature Review Elsewhere in This Dissertation

The majority of the literature review for this dissertation is contained in the two publishable lung cancer papers found in **Chapter 4** and **5** as well as in **Chapters 7** and **8** which deal with other selected cancer endpoints and will not be replicated here. There is, however, more evidence of a chronic disease (including cancer)/air pollution association

B. Historical Perspective

The health effects attributable to ambient air pollution have been recognized for centuries. Hippocrates (460 - 377 B.C.), regarded as the father of medicine, in his treatise "On Airs, Waters, Places, and Epidemics" (*1*) broke from tradition and, instead of ascribing diseases to divine origin as was common in his day (see for example the book of Job in the Bible), discusses their environmental causes. It proposes that the town's air quality, among other things, should be considered as contributing to the disease process of its citizenry.

Moses Maimonides (1135-1204 AD), philosopher, scientist, jurist wrote: "comparing the air of cities to the air of deserts and arid lands is like comparing waters that are befouled and turbid to waters that are fine and pure" and he recommended, if at all possible, moving to the outskirts of the cities. He recognized that the foul air was contributing to the ailments of city dwellers (*2*).

London has had many notable events where excessive levels of ambient particulate mass produced an excess number of deaths in just a few days. Quantitative information of such events dates back to the London episode of 1873, although the Dec. 5-9, 1952 episode is the most infamous where there were high levels of morbidity and an excess of 4000 deaths from all causes. The number of deaths peaked in the first week and remained elevated even two weeks later (*3*). Other notable particulate fog/smog episodes causing excess morbidity and mortality include the December, 1930 "smog" episode in the Meuse Valley, Belgium (*4*) and the 1948 smog episode in Donora, Pennsylvania where 43% of the population were adversely affected; 10% severely (*5*). The Donora episode helped launch the clean air movement.

Aside from the excess deaths in the classic smog episodes noted above, a wide spectrum of health effects have been attributed to air pollution (*6, 7*). Short term effects include: annoyance of bad odors, watery eyes, headaches, congested sinuses, irritability, coughing, wheezing, shortness of breath and chest pain, among others. More long-term effects include: heart and blood decreased efficiency, brain and nervous system disorders that accompany behavior changes, lung damage (decreased lung function, pneumonia, bronchitis, emphysema, asthma, airway obstructive disease and respiratory cancer), and perhaps a decreased efficiency of the immune system leading to an increase in all malignant neoplasms.

C. Air Pollution and the Immune System

The components of the human immune system include: the thymus, spleen, tonsils, adenoids, Peyer's patches (small intestine), mucosa, bone marrow, blood, the lymph nodes (*8*) and the skin (*9*). It is our immune system that protects us from pathogens and cancer cells (*10-13*). The phagocytic immune cells that line the respiratory tract are part of the body's front line defenses against the hazardous agents found in the inspired air. Airborne contaminants may enter the body via the respiratory system as gases (e.g. O_3, SO_2), as aerosols (e.g. sulfuric acid mists, ammonium sulfate mists), or as respirable particles (e.g. diesel exhaust, cigarette smoke). These agents can then interact with the immune system resulting in both local and systemic responses (*11*). Several studies, both in animals and humans, have found associations between different air pollutants and various components of the immune system (*15,16*).

Experimental animals exposed to concentrations of $O_3 > 1$ ppm for several hours develop severe pulmonary edema and hemorrhage (*11*). This ozone exposure can then compromise the function of the respiratory phagocytes rendering them less capable to defend against foreign agents entering the lungs by way of the inhaled air (*11*). Continuous exposure to ozone has been shown to modulate alveolar macrophage-dependent lung defenses (*14*) and the generation of reactive oxygen species and biocidal properties of phagocytes have been shown to depend on the length of time of ozone exposure (*46*). The macrophage-derived mediators of interleukin-1, tumor necrosis factor-alpha, and fibronectin are thought to be important in the pathogenesis of lung

injury (*47*). The lung phagocyte production of these inflammatory mediators has been shown to be elevated following exposure to ozone (*47*).

Polycyclic aromatic hydrocarbons or PAHs are often associated with diesel exhaust particles and may function as potent immunosuppressive agents that can act directly on the respiratory lymphocytes(*17*). These pollutants can enter the circulation and be transported to the lymphoid tissues where they further degrade the immune system (*11*).

Stiller-Winkler and colleagues (*18)* investigated the influence of air pollution on the humoral immune response in blood sera of women age 55 in polluted urban areas and in a relatively unpolluted rural city in Germany. The important differences among the several cities in the study were their long-term, albeit low-level, differences in air pollution. Although the investigators did not consider cancer directly, they did observe statistically significantly higher percentages above normal values for IgG, IgA, and IgM for participants in the polluted areas compared to the rural control city. Their findings also suggested that IgE was associated with exposure to automobile exhaust in particular. Their study demonstrated a stimulation of several parameters of the humoral defense in areas with a slightly elevated degree of air pollution.

Researches from Pennsylvania State University (*19*) evaluated the effect of air pollutants on the immune system of mice. They obtained fly-ash from carbon black and filtered ambient air and studied its effect on neoplastic growth in the animals. They hypothesized that decreased cellular immune responses may lead to decreased resistance to certain neoplastic processes. The exposure of mice to increasing levels of fly-ash

resulted in alterations in immunological functions of lymphocytes and macrophages and also progressive lesions in lungs and mediastinal lymph nodes. These alterations included a decrease in the number of pulmonary macrophages capable of phagocytosis and a decreased ability to activate T cell mitogenesis after fly-ash inhalation.

In a study of 10-14 year old Austrian children, Zwick et al. (*20*) compared children from an area of high O_3 concentrations with children from an area of low O_3 concentrations. The high ozone area was characterized by a maximum ozone concentration of 188 ppb and the percentage of time with ozone > 60 ppb was 45.39%. In comparison, the low ozone area was characterized by a maximum ozone concentration of 95 ppb and the percentage of time with ozone > 60 ppb was only 0.33%. Both areas studied were characterized by the absence of large-scale industry and heavy traffic and by low levels of NO_2 and SO_2. The O_3 levels were caused more by local rather than anthropogenic factors in that the hydrocarbon precursors to the high O_3 levels were primarily from biogenic volatile organic compounds. Their results suggest that long-term exposure to high O_3 concentrations may have adverse effects on lymphocyte subpopulations in children. This was demonstrated by lower helper (CD4+) and natural killer (NK+) cells in the high ozone group. Studies in mice have indicated that even short-term O_3 inhalation can affect the T cell immune system adversely, particularly the CD4+ cells (*21*).

Even though ozone itself never reaches the systemic immune compartment, ozone can have a profound effect on systemic immunity by mechanisms not clearly understood (*22*) although ozone is known to cause free radical formation in exposed biological tissue.

When mice were continually exposed to 0.8 ppm O_3 up to 56 days, the weights of the thymus glands in these animals continued to decrease implying that production of immune cells in these organs may be hampered because of decreased organ volume (*23*). The decrease of the thymus weights in these mice chronically exposed to O_3 was related to decreased numbers of thymocytes.

Becker and Soukup (*24*) studied impairment of inflammatory functions related to ambient PM_{10}. The aerodynamic diameter of these particulates ranged from 0.2 to 0.7 μm. The alveolar macrophages and blood derived monocytes were exposed to either 33 or 100 μg/ml of environmental particulates. Their data indicate that exposure to particulate pollution is likely to impair host defense functions of alveolar macrophages and blood derived monocytes which are both important as front line defenses of the human immune system.

D. Air Pollution and Cancer

There are three major obstacles to establishing a causal link between ambient air pollution and cancer risk: 1) the latency between exposure and the diagnosis of cancer which is complicated by temporal changes in ambient air quality; 2) the difficulty in estimating cumulative personal exposure, especially in long-term cohort studies where the wearing of personal monitors is not feasible and individual data must necessarily be cumulated from fixed site monitors some distance from the home and work place; 3) control of confounding from other personal exposures, demographic characteristics, and lifestyles including active and passive exposure to tobacco products (*25*).

In spite of the obstacles noted above, there is sufficient evidence from many epidemiologic studies that ambient air pollution has contributed to the increase in human cancer (*26*). Shy (*25*) has summarized this evidence from the literature into four main areas:

"1. Known and probable human carcinogens are present in the ambient air environment. Prominent examples are organic products of incomplete combustion, arsenic, chromium, and asbestos.

2. Urban residents show a consistent lung cancer excess in comparison with rural inhabitants, even when risk estimates are appropriately adjusted for tobacco smoking and occupational exposures.

3. Among urban residents, gradients of community air pollution levels correspond with area differences in lung cancer risk.

4. Communities adjacent to certain large point sources of carcinogenic air pollutants, such as arsenic smelters, show an excess of lung cancer, adjusted for tobacco and occupational exposures, in proportion to the nearness of the household to the point source."

The U.S. Environmental Protection Agency (EPA) has estimated that the following five air pollutants: 1,3-butadiene, chromium, benzene, formaldehyde and products of incomplete combustion (PIC) account for 70% of the total estimated annual cancer cases attributable to air pollution, with the PIC accounting for 35% of the total cancer cases (*26*).

Several authors have summarized the air pollution/cancer literature so the reader is referred to their work for a listing of the specific studies (*6,7,27-31*) . Pershagen (*27,28*) summarizes both cohort and case-control studies on lung cancer in urban and rural areas where smoking is adjusted for in the statistical models. Speizer (*29*) tabulates the risk of lung cancer attributable to air pollution as estimated from nine separate studies.

Some of the highest incidence rates of lung tumors in the world has been reported in nonsmoking women in the rural country of Xuan Wei, China, where, for generations, Xuan Wei residents have been exposed to high levels of smoke emissions from unvented, open pit coal or wood fires used for cooking or heating. The epidemiologic studies showed that coal burning was used in homes inhabited by persons with the highest lung cancer mortality rates, and residents with comparatively low lung cancer mortality rates used wood or smokeless coal for cooking and heating. The unvented smoke from coal burning resulted in the highest levels of inhalable particles, organic matter and polycyclic aromatic hydrocarbons (PAHs) which had high mutagenic activity. (*32*)

Nielsen et al. (*33*) investigated heavy traffic patterns in central Copenhagen and concluded that vehicle traffic contributed an estimated 90% of polycyclic aromatic hydrocarbons (PAHs) in the street air on workdays. They estimated that approximately 5 lung cancer cases per million population could be attributed to the direct effect of PAH and other airborne mutagens.

The great majority of the air pollution/cancer literature is devoted to lung or respiratory cancer. The relationship between ambient air pollution and nonrespiratory

cancers needs further study. A review of some of this literature can be found in **Chapters 7** and **8**.

Pan et al. (*34*) collected data on the cancer deaths of children and adolescents aged 0-19 who lived near three large petrochemical complexes during the period 1971-1990 and compared these deaths with the cancer deaths of similar aged children and adolescents among the entire population of Taiwan. Almost all bone, brain, and bladder cancer deaths were located within 3 km of the three complexes. Girls who lived in these petrochemical industrial districts had bone and brain cancer rates higher than the boys even though these two cancers are believed to occur more frequently in males in the rest of the country.

In a study of iron foundry workers in Krakow, Poland, Szczeklik et al. (*35*) evaluated humoral immunity by measuring IgG, IgA, IgM, and IgE concentrations. They also assessed exposure to PAHs by personal and area monitoring methods. Workers who were exposed to higher levels of PAHs had a statistically significant ($p < 0.001$) reduction of mean serum IgG and IgA compared to workers with lower exposures to PAHs. They concluded that individuals exposed to PAHs over long periods of time will be more likely to develop immunosuppression. This may help explain the higher rate of cancer in these type of workers. It has been shown that PAHs can be distributed systemically and that comparable levels of PAH-DNA adducts have been observed across many tissues, including peripheral blood, in both experimental and human studies (*36,37*). In a study of 70 mother-newborn pairs also from Krakow, Poland, Whyatt and others (*38*) found that carcinogenic PAHs readily cross the placenta. Among the newborns of unemployed

mothers, WBC PAH-DNA adduct levels were significantly higher in newborns living in both the middle ($p=0.05$) and high ($p=0.03$) pollution areas as compared to the low pollution area. Of special note was that these newborn WBC PAH-DNA adduct levels were not associated with either active or passive smoking status of the mother or the number of cigarettes the mother smoked per day during her pregnancy. Thus, active or passive smoking status did not account for the observed association of the adduct levels with air pollution. Whyatt's study, therefore, provides evidence of significant genetic damage in newborns associated with ambient PAHs and raises concern about carcinogenic risks from *in utero* exposure to this widespread airborne contaminant.

The London surgeon Percival Pott is well known for his study of chimney sweeps who were exposed to PAH-containing soot and the subsequent development of scrotal cancer(*39*). In a more recent study of chimney sweeps, Carstensen et al. (*40*) observed that chimney sweeps have higher incidence of cancers of the lung, bladder and esophagus.

Lewtas (*41*) describes methods for assessing cancer risk associated with ambient hydrocarbons known as polycyclic organic matter (POM). The term POM encompasses a complex mixture of many diverse classes of hydrocarbons including polycyclic aromatic hydrocarbons (PAHs), substituted aromatic hydrocarbons (e.g. nitrated-PAHs), and heterocyclic aromatic compounds (e.g. aza-arenes). These carcinogenic POMs are released into the ambient air from coal combustion and pyrolysis, incomplete combustion of diesel and gasoline fuels, wood, and synthetic chemicals (e.g. plastics). In many cases, the cancer risk of these complex mixtures has been estimated without identifying the specific chemicals in the POM mixture responsible for causing cancer although the

Health Effects Institute and other organizations are pushing for more research in the future to look more closely at the source and composition of these particles and gasses.

Mastrangelo et al. (*42*) reviewed 10 recent epidemiological studies that explicitly mentioned PAH exposure and where the descriptions were in quantitative or qualitative terms. They found that risks of lung and bladder cancer were dose dependent when PAHs were measured quantitatively. These studies were generally of occupationally exposed individuals.

A wide variety of chemicals in the ambient air are known carcinogens and promoters. Benzo[a]pyrene has been frequently used as a surrogate or marker for combustion source air pollution in epidemiologic studies and for risk assessment (*43,44*). Polycyclic aromatic hydrocarbons (e.g. benzo[a]pyrene) are perhaps the most studied, but others include: radionuclides (e.g. radon), aromatic amines (e.g. naphthylamine), aldehydes (e.g. formaldehyde), phenolic compounds (e.g. phenol, catechol), and a variety of free radicals and other chemicals (e.g. arsenic, benzene, bis(chloromethyl)ether, chromium(VI), nickel, vinyl chloride, asbestos) (*45*). The general population is also exposed to carcinogenic PAHs and other chemicals in the ambient air, but usually at levels far below those found in occupational settings.

In summary, there is mounting experimental and epidemiological evidence for the carcinogenicity of air pollutants (*45*).

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CHAPTER 3

METHODS

A. Subjects and Instrumentation

In 1974, a brief demographic "Census" questionnaire was mailed to 63,530 households in California identified from 437 California Seventh-day Adventist (SDA) church membership lists. A total of 36,805 households (95,196 individuals of all ages) responded to this survey. Individuals completing this census questionnaire who were age 25 or older (n=59,081) became members of the Adventist Health Study (AHS) (*1*). AHS subjects were then mailed a more detailed "Lifestyle" questionnaire in 1976. Individuals who identified themselves as non-Hispanic white on this Lifestyle questionnaire and reported that they had lived within 5 miles of their 1976 residence for 10 years or longer were potential subjects for the following air pollution study. Potential subjects who lived in one of the following California air basins: San Diego, San Francisco, South Coast (Los Angeles and eastward), or were from a 13% random sample of AHS study subjects from the rest of California were selected to receive a third postal respiratory symptoms questionnaire (see **Appendix A)** in 1977 which contained the respiratory questions used by the American Thoracic Society.

A total of 6,338 (response rate of 87%) nonsmoking adult SDAs returned this 1977 respiratory symptoms questionnaire and they were thus enrolled into the Adventist Health and Smog (AHSMOG) substudy. This latter group thus consisted of baptized Seventh-day Adventist nonsmokers who were 25 years of age or older in 1974.

The diagnosis of incident cancer was obtained from computerized record linkage with regional and state cancer registries or manual review of medical records for self-reported hospitalizations. Living/dead status of AHSMOG study members was ascertained by obtaining death certificates for deceased AHSMOG study members identified by computerized record linkage with California state computer death certificate files and the National Death Index. All AHSMOG study subjects were first compared to the California computer death certificate files (1977 - 1992) using in-house record linkage software. Individuals who did not match to the California files were then evaluated by the National Death Index (1979 - 1992). Death certificates were ordered from the respective states for all record linkage perfect matches as well as the linkages for which the clerk needed additional information from the death certificate to make a final decision. Death certificates received from any state were further checked to see if this was in fact the same person as the AHSMOG subject. This was accomplished by checking the full name, date of birth, place of birth, gender, race, occupation, current address, and name of spouse as listed on the death certificate with our paper records. Only those death certificates that were considered a positive match were kept and entered into the AHSMOG analytical file.

B. Variables

Variables available for consideration in this research included: 1) from the AHS Census questionnaire: date of birth, gender, marital status, baptized member of the SDA church, and highest level of education attained; 2) from the AHS Lifestyle questionnaire:

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; 3) from the 1977 AHSMOG questionnaire: respiratory symptoms, past smoking history, history of exposure to environmental tobacco smoke (i.e. worked and/or lived with a smoker), occupational history and exposure to occupational air pollutants, lifestyle patterns that might affect exposure to ambient air pollutants (e.g. hours per week spent outdoors by season), and residence and work history; 4) from the California Air Resources Board: monthly air pollution data for PM_{10}, O_3, NO_2, SO_2; 5) from 9 California airports: visibility and atmospheric data from which we derived our $PM_{2.5}$ indices; 6) from death certificates: date of death, underlying cause of death; 7) from medical records or cancer registry reports: cancer diagnosis to include site and histology (if available).

The methods and techniques used for estimating air pollution indices, as well as descriptions of the air monitoring network data, are described in several AHSMOG publications (*2-6*).

C. Data Collection

The 1974 AHS Census questionnaire was obtained by mail from the respondents and optically scanned into a computer file using Opscan technology. This file was then error checked for missing data, duplicate responses, and invalid data. The 1976 AHS Lifestyle questionnaire and the 1977 AHSMOG respiratory symptoms questionnaires were double key-entered directly into the computer and then error checked for missing data, duplicate responses, and invalid data. Study subjects were contacted by phone to

resolve data errors. The AHS and AHSMOG data were then corrected and merged into a single analytical file which also contained the death certificate information (if deceased) and cancer incidence data (if cancer diagnosed).

D. Data Analysis

During any particular analysis computer run, the above analytical file was merged with one or two air pollutant files to explore exposure-disease relationships. Univariate analyses included t-tests for continuous data and Chi-square tests for categorical data. Cox proportional hazards regression models were then developed to evaluate the association between the air pollution indices and incident cancer adjusting for potential confounders.

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CHAPTER 4

PUBLISHED PAPER 'A'

A. Long-Term Concentrations of Ambient Air Pollutants and Incident Lung Cancer in California Adults: Results From the Adventist Health and Smog (AHSMOG) Study

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Environmental Health Perspectives. 106(12):813-823 (1998).

2. Abstract

Purpose: To evaluate the relationship of long-term concentrations of ambient air pollutants and risk of incident lung cancer in nonsmoking California adults.

Methods: A cohort study of 6,338 nonsmoking non-Hispanic white California adults ages 27-95 was followed from 1977-1992 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.

Results: 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; (95% CI=1.94-13.99)] and SO_2 (RR=2.66; 95% CI=1.62-4.39). For females, incident lung cancer was positively associated with IQR increases for SO_2 (RR=2.14; 95% CI=1.36-3.37) and IQR increases for PM_{10} exceedance frequencies of 50 $\mu g/m^3$ (RR=1.21; 95% CI=0.55-2.66) and 60 $\mu g/m^3$ (RR=1.25; 95% CI=0.57-2.71).

Conclusions: 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.

3. Introduction

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), 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 since 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 $\mu g/m^3$) 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 (1977-92) and cumulated levels of ambient PM_{10}, SO_2, NO_2, and O_3 since 1973.

4. Materials and Methods

a. 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.

b. 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 which 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.

c. 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 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}), sulfur dioxide (SO_2), and nitrogen dioxide (NO_2).

The methods for estimating ambient air pollutants for study participants has 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 meters 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-hour 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 was available, it was used. Ozone and total oxidants were simultaneously monitored at 5 to 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)*.

d. Cancer Incidence Ascertainment Program.

We ascertained cancer incidence for the cohort from April 1, 1977 to April 1, 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 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.

e. 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 pf 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 but stopping 3 years prior 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 utilized the same final model. Analyses which 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 95% CIs against the midpoints of the underlying continuous variable. Inspection of these plots indicated that the log-linear assumption was appropriate since straight lines could be drawn through the resultant regression coefficient point estimates or their CIs.

5. Results

Selected characteristics of the study population and the incident respiratory cancer cases are given in **Table 4.1**. 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, consume more alcoholic beverages and exercise more.

During follow-up, 36 lung cancers were diagnosed (20 female; 16 male). The morphologies of the incident lung cancers are given in **Table 4.2**. **Figures 4.1-4.5** 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 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 4.1**. 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 a RR of 3.56 (95% CI: 1.35-9.42) for 556 hours/year above 100 ppb (the IQR) controlling for pack-years of past cigarette smoking, educational level, and current alcohol use (**Table 4.3**). 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; 95% CI: 1.94-13.99) and SO_2 (RR=2.66; 95%CI: 1.62-4.39) also showed significant increased risk of incident lung cancer in males (**Table 4.4**). For males, all exceedance frequencies of PM_{10} were significantly elevated, and regression coefficients increased with higher cutoffs (see **Table 4.4**). For females, although all of the RRs for average annual mean concentration and the exceedance frequencies for PM_{10} were above 1.0, the 95% CIs all

included the null value. The largest PM_{10} associations with incident lung cancer in females were RR=1.21 (95% CI: 0.55-2.66) for 50 $\mu g/m^3$ and RR=1.25 (95% CI: 0.57-2.71) for 60 $\mu g/m^3$ (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; 95% 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 95% 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; 95% 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 4.5**) with an RR of 1.62 (95% 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 prior to enrollment in 1977.

A higher proportion of males than females reported working in occupations involving air borne contaminants (see **Table 4.1**). 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 (95% 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 hours/year compared to <90 hours/year) for males and females were 3.56 (95% CI: 1.08-11.62) and 1.09 (95% CI: 0.26-4.56) respectively.

a. 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; 95% CI 1.19-8.29 and females: RR= 0.91; 95% CI: 0.39-2.11).

b. 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; 95% 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; 95% 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; 95% CI: 1.49-5.62) compared to a RR of 2.95 for all males.

c. Multipollutant Analyses.

Because different components of air pollution frequently occur together and are highly correlated (**Table 4.6**), 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 pair-wise 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% non-missing data for both pollutants (see **Table 4.6**). Because PM_{10} was more highly correlated with O_3 than other air pollutants, an additional metric of PM_{10} [days/year in excess of 100 $\mu g/m^3$; PM_{10}(100)] was also evaluated. Two questions were addressed in the pairwise comparisons of 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 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.

6. Discussion

a. 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 4.1**). 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 (95% 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 (95% CI: 2.31-8.84) and 3.22 (95% 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; 95% CI 0.64-2.02) and with mean concentration of SO_2 (RR=2.11; 95% 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.

b. 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 hours/week versus 10.3 hours/week respectively, $p<0.0001$). They also reported more vigorous exercise outdoors in the summer compared to females (10.0 hours/week versus 5.1 hours/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).

c. 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, 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; 95% 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; 95% 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) which 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: >1000 mg/week of vitamin C or at least daily use of any dose of vitamin A or at least 200 IU/wk 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.

d. 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 5000 ppb of O_3 for 5 minutes resulted in cell transformation and concluded that O_3 is a co-carcinogen. 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.

e. Epidemiologic Studies on Respiratory Cancer and 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 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)* has 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 Cancer (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)*.

f. 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, p. 13-71)*.

g. 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.

h. Limitations of Study.

1) Possible Under Reporting of Alcohol and Tobacco Use

Shapiro et al. *(115)* have shown that under ascertainment of confounders, even when nondifferential, can result in a spurious association between disease incidence and a risk factor. Smoking tends to be under reported 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 has been underestimated in our study. However, it is unlikely that a 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 (see **Appendix B**) that if current smoking, past smoking and current alcohol use each were under reported by 50%, and this under reporting 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.

2) 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.

3) 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 re-evaluated 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 (95% 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 (95% CI: 1.06 - 7.97). Similar restrictions for females yielded a risk estimate of 1.53 (95% 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 (95% CI: 0.92 - 5.20) and it was 2.52 (95% CI: 1.19 - 5.33) for females.

4) 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 prior to 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}.

5) 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 be associated with 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) since 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)*.

7. Summary

In this report we observed significant positive associations between lung cancer incidence and the number of days/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 generally 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 95% 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 (NAAQS) 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 as regards to O_3 exposure as well as to better separate the independent effects of O_3, airborne particulate matter, SO_2, and NO_2.

8. Acknowledgment

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Table 4.1: Distributions of Selected Variables in the AHSMOG Study According to Non-Cases and Cases of Incident Lung Cancer. part 1 of 2

Variables	FEMALES		MALES	
	Percent non-cases (n=4040)	Percent cases (n=20)	Percent non-cases (n=2262)	Percent cases (n=16)
Age in '77				
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				
≤ HS 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
Hx of cancer				
No	92.7	85.0	96.2	93.7
Yes	7.3	15.0	3.8	9.3
Hx 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				
Never	93.0	94.1	90.1	75.0
Any	7.0	5.9	9.9	25.0 *

Table 4.1: Distributions of Selected Variables in the AHSMOG Study According to Non-Cases and Cases of Incident Lung Cancer. part 2 of 2

Variables	FEMALES		MALES	
	Percent non-cases (n=4040)	Percent cases (n=20)	Percent non-cases (n=2262)	Percent cases (n=16)
Packyears of cigarettes				
None	86.9	65.0	67.1	62.5
1-7 yrs	7.3	5.0	13.0	6.3
>7 yrs	5.8	30.0 **	19.9	31.2
Yrs lived with smoker				5
None	52.2	50.0	66.3	6.3
1-15 yrs	19.6	15.0	17.0	31.2
16+ yrs	28.2	35.0	16.7	12.5 *
Yrs worked with smoker				
None	61.8	70.0	51.9	50.0
1-15 yrs	28.3	5.0	27.5	31.2
16+ yrs	9.9	25.0 *	20.6	18.8
Hrs outside in summer				
0-7 hrs/wk	53.5	75.0	26.6	31.2
8-14 hrs/wk	23.7	10.0	21.7	0.0
15+ hrs/wk	22.8	15.0	51.7	68.8
Hrs vigorous exercise outside in summer				
None	27.5	50.0	13.0	6.3
1-7 hrs/wk	54.5	35.0	48.9	56.2
8+ hrs/wk	17.9	15.0	38.1	37.5
Fruit index				
<daily	7.2	5.9	9.1	0.0
1-2 x daily	20.8	35.3	25.0	30.8
≥twice daily	72.0	58.8	65.9	69.2
# homes within 1/4 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 4.2: 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

Table 4.3: 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=2278, Cases=16).

Variable	Regression coefficient (β)	SE (β)	Increment[b]	Relative risk[c]	95% C.I for relative risk
Ozone (hrs in excess of 100 ppb) [d]	0.002284	0.0008932	556 hr/yr	**3.56** *	(1.35 - 9.42)
Pack-years of past smoking	0.015168	0.01080	10 pack-yrs	1.16	(0.94 - 1.44)
Education	-0.135385	0.08836	4 yrs	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% to 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 prior to risk set (i.e., 3-year lag)

* $p < 0.05$

Table 4.4: Relative Risks of Incident Lung Cancer Associated With Interquartile Ranges of Selected Air Pollutants[a]. Males Only. (n = 2278, cases = 16).

Variable	Regression coefficient (β)	SE (β)	Increment (interquartile range)[b]	Relative risk	95% C.I for relative risk
Ozone, hrs in excess of [c]:					
O_3 (60 ppb)	0.000814	0.0005267	935 hr/yr.	2.14	(0.82 - 5.62)
O_3 (80 ppb)	0.001433	0.0006755	756 hr/yr.	**2.96** *	(1.09 - 8.04)
O_3 (100 ppb)	0.002284	0.0008932	556 hr/yr.	**3.56** *	(1.35 - 9.42)
O_3 (120 ppb)	0.003604	0.00123	367 hr/yr.	**3.75** *	(1.55 - 9.09)
O_3 (150 ppb)	0.006945	0.00196	185 hr/yr.	**3.61** *	(1.78 - 7.35)
Ozone, 8-hr average [e]	0.287000	0.19009	2.12 ppb	2.23	(0.79 - 6.34)
Ozone, mean concentration [e]	0.041896	0.035336	8 hrs.	1.65	(0.72 - 3.80)
PM_{10}, hrs in excess of [d]:					
40 μg/m3	0.010824	0.004524	139 days/yr	**4.50** *	(1.31 - 15.44)
50 μg/m3	0.010752	0.004008	149 days/yr	**4.96** *	(1.54 - 16.00)
60 μg/m3	0.011760	0.0039672	132 days/yr	**4.72** *	(1.69 - 13.18)
80 μg/m3	0.015792	0.0045576	78 days/yr	**3.43** *	(1.71 - 6.88)
100 μg/m3	0.025176	0.0064728	43 days/yr	**2.95** *	(1.71 - 5.09)

Table 4.4: Relative Risks of Incident Lung Cancer Associated With Interquartile Ranges of Selected Air Pollutants[a]. Males Only. (n = 2278, cases = 16).

Variable	Regression coefficient (β)	SE (β)	Increment (interquartile range)[b]	Relative risk	95% C.I for relative risk
PM_{10}, mean concentration [c]	0.068759	0.02101	24 μg/m^3	**5.21** *	(1.94 - 13.99)
SO_2, mean concentration [c]	0.264594	0.06892	3.7 ppb	**2.66** *	(1.62 - 4.39)
NO_2, mean concentration [c]	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.

b Increment based on interquartile range (75%-25%) of population exposed.

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

d Average annual hours in excess of 100 μg/m^3, 1973 - 3 years prior to risk set (i.e., 3-year lag).
Because of missing data from monitoring stations, the n varies for each air pollutant (O_3: n=2050; PM_{10}: n=2080; SO_2: n=1491; NO_2: n=1971).

e All mean concentrations and O_3 8-hr average were averaged from 1973 - 3 years prior to risk set (i.e. 3-year lag)

* $p < 0.05$

Table 4.5: 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 = 2278, cases = 16).

Variable	Regression coefficient (β)	SE (β)	Increment[b]	Relative risk[c]	95% C.I for relative risk
Ozone (hrs in excess of 100 ppb)[d]	-0.000114	0.000766	556 hr/yr	0.94	(0.41 - 2.16)
Pack-years of past smoking	0.048467	0.01240	10 pack-yrs	**1.62** *	(1.27 - 2.07)
Education	-0.086790	0.08565	4 yrs	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% to 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 prior to risk set (i.e., 3-year lag)

* $p < 0.05$

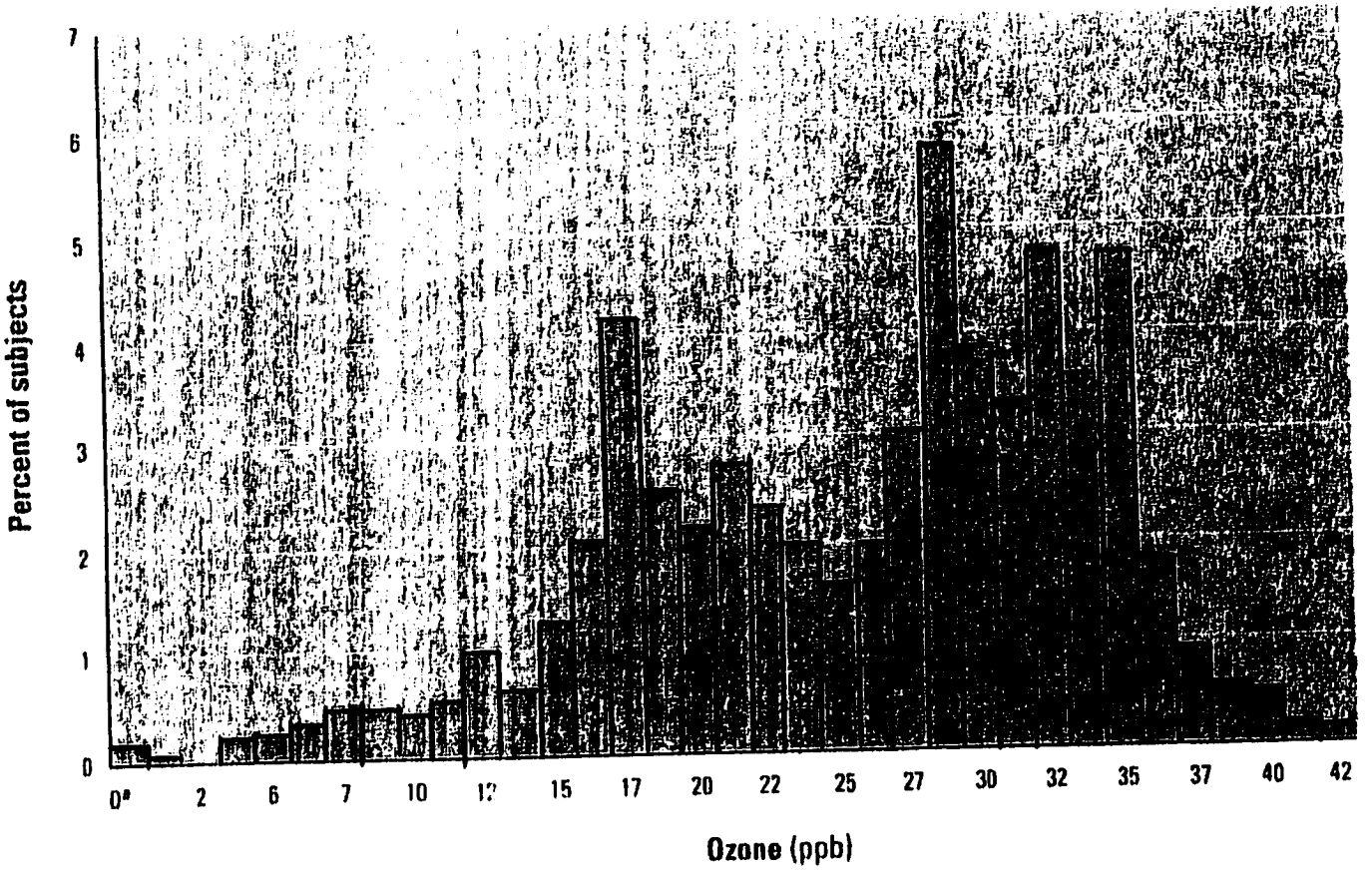
Table 4.6. Pearson Correlation Coefficients (and Sample Size) for Selected Ambient Pollutants[a], Average Annual Values for Years 1973-1992, AHSMOG Study.

Ambient air pollutant	Ozone, hrs/yr >100 ppb	Ozone, mean conc.[b] (ppb)	PM_{10}, mean conc. ($\mu g/m^3$)	PM_{10}, days/yr > 100 $\mu g/m^3$	SO_2, mean conc. (ppb)	NO_2, mean conc. (ppb)
Ozone, hrs/yr >100 ppb	1.0	0.776 (5893)	0.832 (5807)	0.834 (5807)	0.133 (4349)	0.408 (5643)
Ozone, mean conc. (ppb)	...	1.0	0.768 (5807)	0.626 (5807)	0.095 (4349)	0.360 (5643)
PM_{10}, mean conc. ($\mu g/m^3$)	...	...	1.0	0.849 (5962)	0.319 (4347)	0.567 (5638)
PM_{10}, days/yr >100 $\mu g/m^3$	...	...	...	1.0	-0.050 (4347)	0.146 (5638)
SO_2, mean conc. (ppb)	...	...	...	...	1.0	0.791 (4351)

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.

b Mean conc. = mean concentration

Figure 4.1: 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

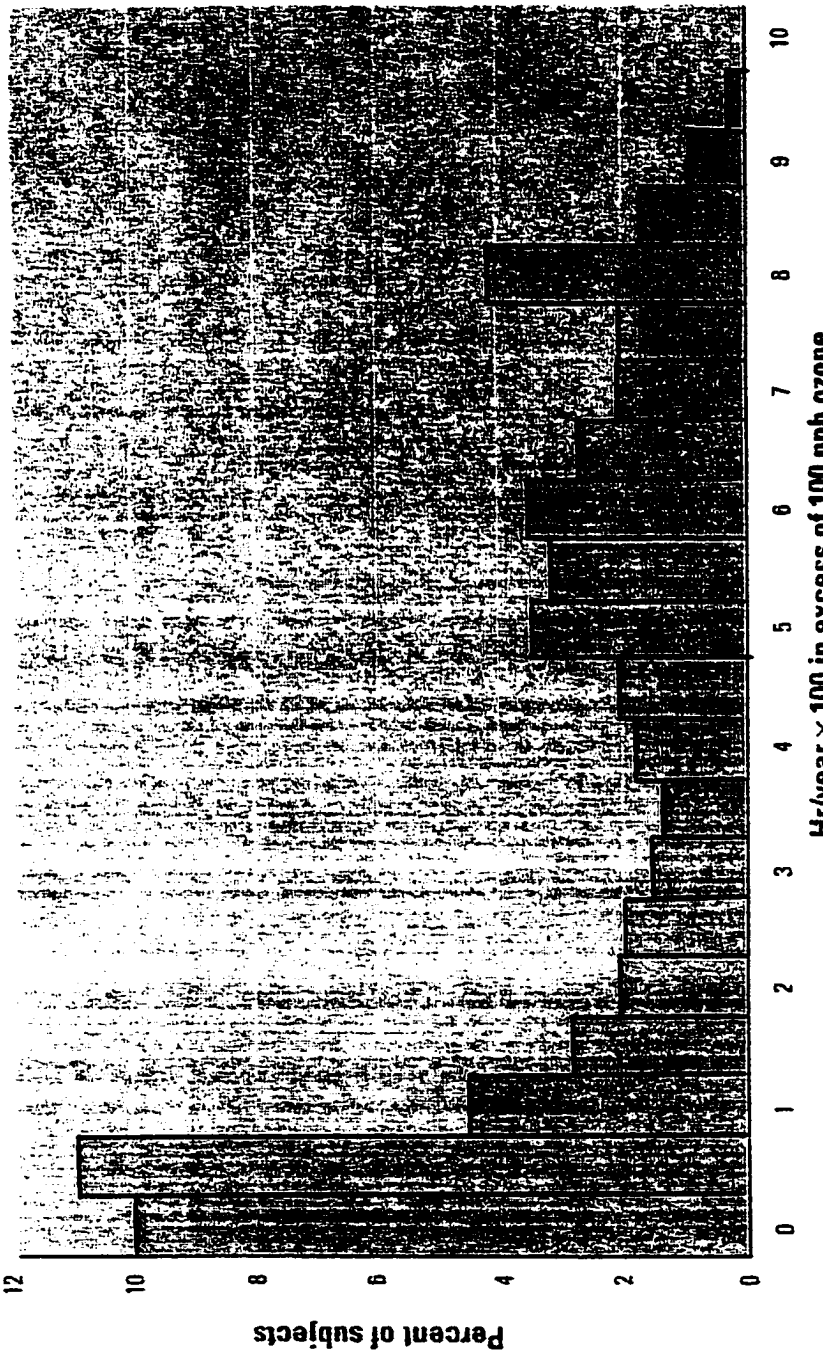
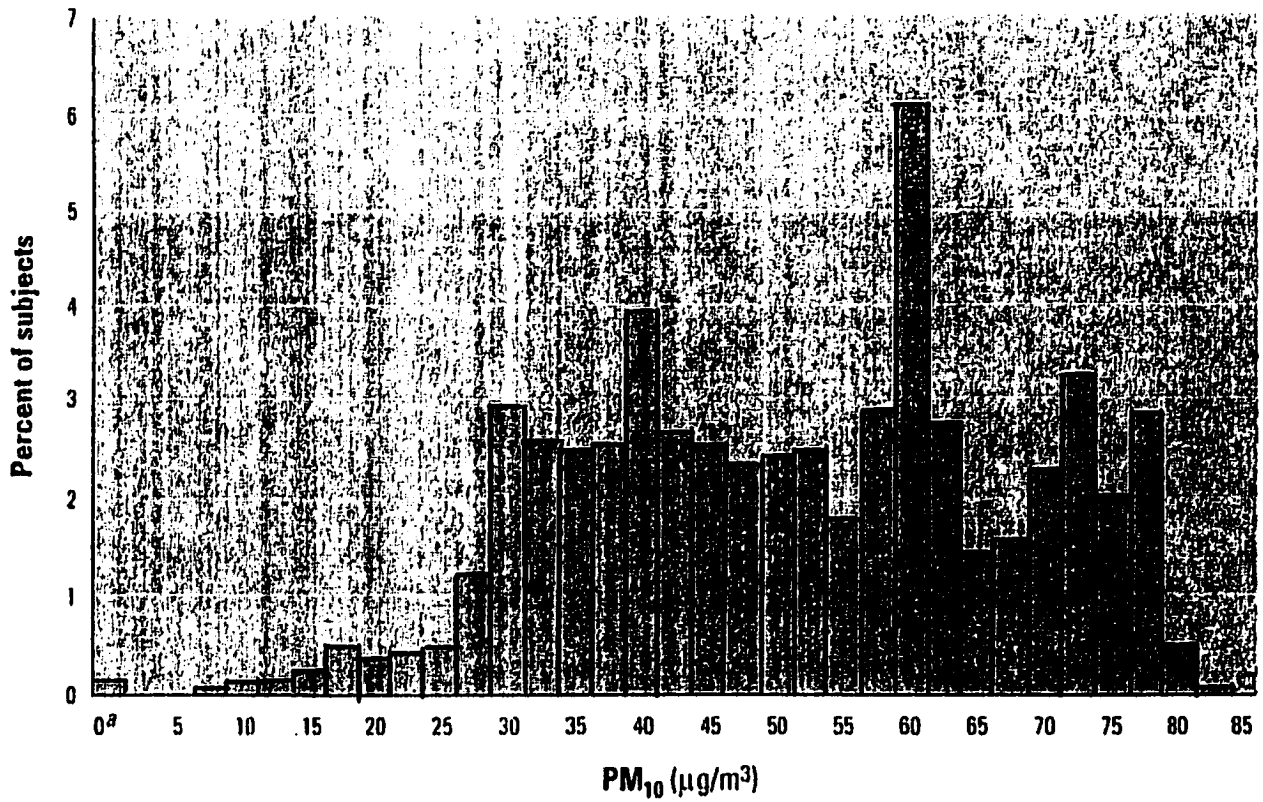


Figure 4.2: Average annual hours per year in excess of 100 ppb ozone experienced by subjects, 1973-1992. Numbers represent the left end of interval (mean=333; standard deviation=297.3; n=5,893).

Figure 4.3: 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 4.4: 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).

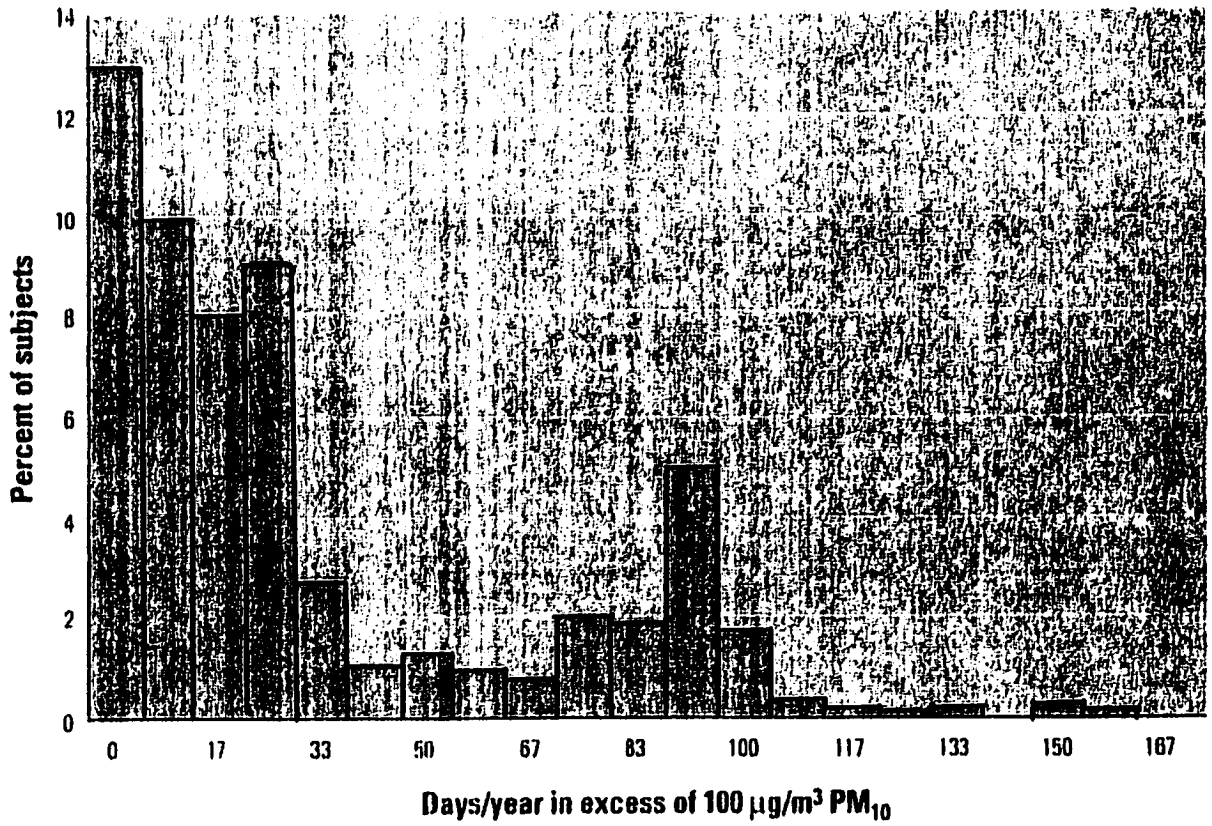
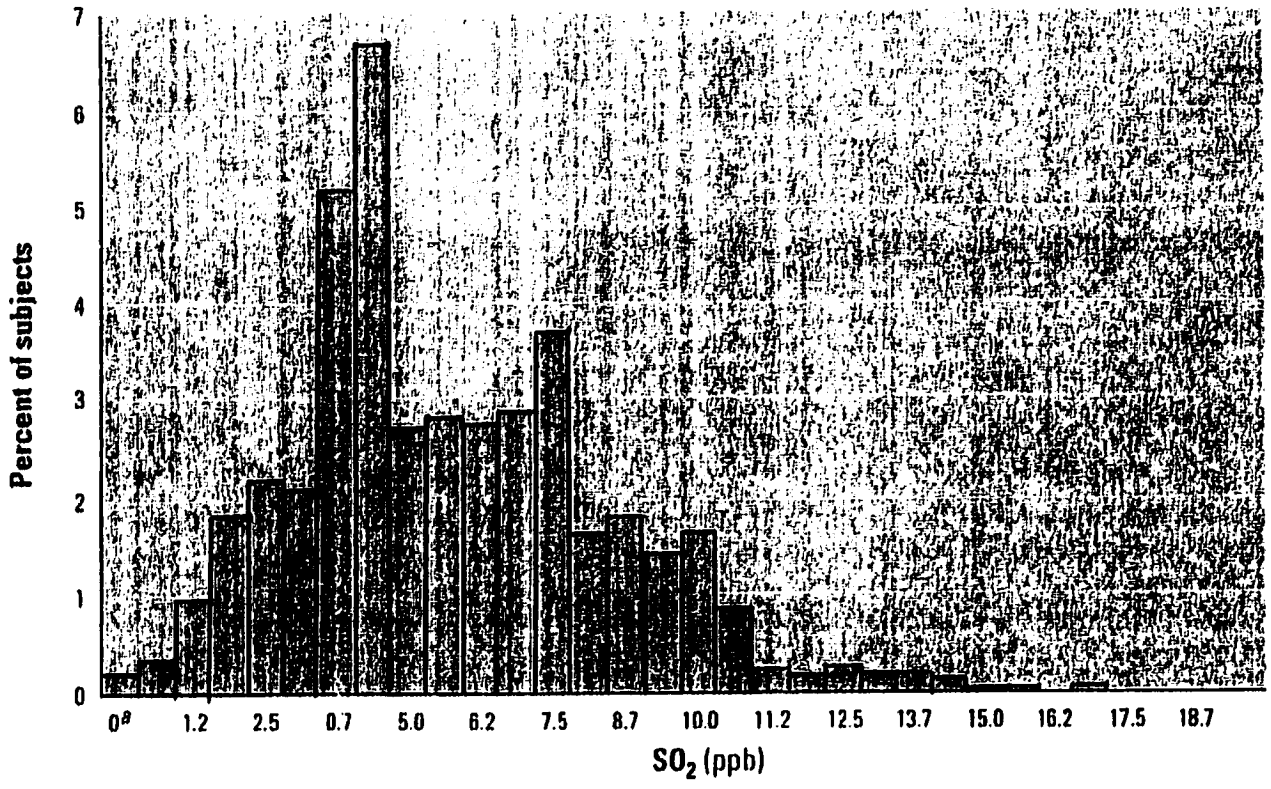


Figure 4.5: Average annual mean concentration of SO_2 experienced by subjects, 1973-1992. Numbers represent the left end of interval (mean=5.7; standard deviation=2.9; n=4,355).



a Unmeasured Low Background Levels

CHAPTER 5

SUBMITTED PAPER 'B'

A. Long-Term Mean Concentration of Ambient Fine Particulate Matter ($PM_{2.5}$) and Incidence of Lung Cancer in the Adventist Health and Smog (AHSMOG) Study

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1. Abstract

Purpose: The primary purpose of the current study was to extend previous work on PM_{10} and lung cancer incidence by considering $PM_{2.5}$ and $PM_{10-2.5}$.

Methods: We investigated the relationship of long-term concentrations of ambient $PM_{2.5}$ and $PM_{10-2.5}$ and risk of incident lung cancer in nonsmoking California adults who had lived 10 years or longer within 5 miles of their residence at time of enrollment. This prospective cohort study of 6,338 nonsmoking, non-Hispanic, white California adults, ages 27-95, was followed for newly diagnosed cancers. Twenty five incident lung cancer cases were identified during the follow-up period of 1977 to 1992. The fine fraction ($PM_{2.5}$) of respirable particulates was estimated from site- and season-specific regression equations based on airport visibility data. The coarse fraction was estimated from PM_{10} - $PM_{2.5}$. Monthly ambient air pollution data were interpolated to zip code centroids according to home and work location histories; for $PM_{2.5}$ from 1966 to 1992 and for $PM_{10-2.5}$ from 1973 to 1992. *Results:* The adjusted relative risk (RR) of incident lung cancer in males associated with an increase of 10 $\mu g/m^3$ of mean concentration of $PM_{2.5}$ lagged 3 years was 2.05 (95% CI: 1.003-4.17). The association with the coarse fraction ($PM_{10-2.5}$) was weaker (RR=1.56, 95% CI: 0.67-3.60). No statistically significant association was found in females for any of the respirable particle sizes.

Conclusion: We found elevated risks for lung cancer incidence in nonsmoking males associated with increased cumulated average mean concentration of respirable particulates that seemed to be stronger for the fine fraction ($PM_{2.5}$) compared to the coarse fraction ($PM_{10-2.5}$). No statistically significant association was found in females. The

gender differences in risk associated with ambient respirable particulates may be due in part to differences in the proportion of lung cancer cases that are histologically confirmed to be primary cancers.

Key Words: Air pollution, lung cancer incidence, Seventh-day Adventists, $PM_{2.5}$, $PM_{10-2.5}$, PM_{10}, fine fraction, coarse fraction, nonsmokers, AHSMOG.

2. Introduction

Only a few epidemiologic studies have evaluated the association between long-term ambient air pollution and lung cancer incidence or mortality. These studies include: the Six Cities Study (*1*) which followed a cohort of 8,111 adults between 1974 and 1989 from six cities located in the eastern and midwestern United States [Portage, WI; Topeka, KS; Watertown, MA; St. Louis, MO; Harriman, TN; and Steubenville, OH]; the American Cancer Society (ACS-II) Study (*2*) which followed a cohort of 552,138 adults throughout the United States and Puerto Rico from 1982 to 1989; the Adventist Health and Smog (AHSMOG) Study(*3,4*) which followed a cohort of 6,338 nonsmoking non-Hispanic white California Seventh-day Adventist (SDA) adults from 1977 to 1992; and a case-control study in Stockholm (*5*) which enrolled 1,042 male lung cancer cases and 2,364 controls from 1985 through 1990. Of these, only the AHSMOG and Stockholm studies have cancer incidence and historical exposure data at the individual level and the Stockholm study did not directly look at particulate air pollution.

There is current interest among scientists and regulatory agencies as to whether the associations observed between lung cancer and respirable particulate matter with an aerodynamic diameter less than 10 μm (PM_{10}) are primarily due to the fine fraction less than 2.5 μm ($PM_{2.5}$) or the coarse fraction between 2.5 and 10 μm ($PM_{10-2.5}$). Ambient respirable particulates contain numerous carcinogenic and mutagenic compounds (*6*) and there have been several comprehensive reviews on air pollution and lung cancer (*7-12*). Fine particles ($PM_{2.5}$) represent the component of PM_{10} which often contains the most toxic compounds and greatest load of carcinogens and thus seem to pose more significant

health risks than those measures that include the coarse particles (*13*). It is primarily those particles less than 2-3 $\mu g/m^3$ in size that penetrate to the deepest part of the lungs (*14*). Kado et al.(*15*) investigated the mutagenicity of ambient airborne particles containing benzo[a]pyrene (BaP) and other toxic chemicals. Using the Ames test for mutagenicity, they found up to 600 revertants per m^3 for fine particle extracts and virtually no activity was detected in the coarse particle extracts. Monn & Becker (*16*) suggest that the fine fraction is dominated by anthropogenic emissions from combustion such as diesel exhaust whereas the coarse fraction is dominated by natural sources including fugitive and resuspended dust and biological material such as pollen and bacteria.

Woodruff et al. (*17*) estimated the outdoor concentrations of 148 toxic air contaminants for each of the 60,803 census tracts in the contiguous United States. Using concentrations posing a one-in-a-million cancer risk as a benchmark for cancer effects, they found that estimated "concentrations of benzene, formaldehyde, and 1,3-butadiene were greater than cancer benchmark concentrations in over 90% of the census tracts" and that approximately 10% of the census tracts had estimated ambient concentrations of one or more carcinogenic air pollutants greater than a 1-in-10,000 risk level. For example, BaP originating from the burning of fossil fuels is largely adsorbed on fine particulates and hence is a widespread ambient pollutant (*18*). In experimental animals, BaP is a potent initiating carcinogen whose action is enhanced by carrier fine particles and it has been shown that the effect of small, divided doses of BaP over long periods of time is

greater than that of a single high dose (*18*). McClellan and Jackson (*19*) have recently published an excellent report on the human carcinogenic response to air pollutants.

The long-term health effects of air pollution have not been adequately studied. Künzli and Tager (*20*) suggest that studies "that follow the health status of large numbers of subjects across long periods of time (i.e., cohort studies) should be considered the key research approach to address these questions". The associations observed in the AHSMOG study between lung cancer incidence and PM_{10}, O_3, SO_2, and NO_2 have been previously described (*21*). Estimates of $PM_{2.5}$ have recently become available for this cohort. The primary purpose of the current study was to extend previous work (*22,23*) on PM_{10} and lung cancer incidence by considering $PM_{2.5}$ and $PM_{10\text{-}2.5}$.

3. Materials and Methods

a. Questionnaire Data.

The AHSMOG Study has been described in detail previously (*22,24,25*). Briefly, 6,338 nonsmoking, non-Hispanic white SDA adult residents of California who were members of the larger Adventist Health Study (AHS) (*26*) were enrolled in 1977 with the completion of a mailed respiratory symptoms questionnaire which is now part of the American Thoracic Society standardized questionnaire (*27*). Inclusion criteria were the following: 1) age 25 or older; 2) not a current smoker; 3) non-Hispanic white having lived 10 years or longer within 5 miles of their residence at time of enrollment; 4)residing in one of the three California air basins of San Francisco, South Coast (Los Angeles and

eastward), or San Diego, or 5) being part of a 10% random sample of AHS subjects from the remainder of California who met the other inclusion criteria.

Monthly residence and work location histories were obtained for each study subject for the period 1960 to April, 1992 or date of death (if subject died prior to April 1, 1992) by using mailed questionnaires (1977, 1987, and 1992), tracing by telephone, and interviewing of surrogates for deceased subjects. Residence histories of study subjects represent 1463 different zip codes throughout California. By design, approximately 68% of our study subjects lived in the South Coast air basin where they experience some of the highest particulate matter concentrations in the United States (28). Only 156 (2.5%) subjects were lost to follow-up. These latter individuals were censored at date of last contact in survival analyses.

b. Air Pollution Estimate.

From 1973 to1987, PM_{10} ambient mean concentrations were estimated using site- and season-specific regressions based on total suspended particulates (TSP) (*29*). PM_{10} was directly monitored from 1987 through the present throughout the state by the California Air Resources Board (CARB). During the time period of this study, $PM_{2.5}$ was not consistently monitored on a statewide basis. Enough monitored $PM_{2.5}$ data did exist, however, to form site- and season-specific regression estimates of $PM_{2.5}$ based on daily visibility for eleven air basins in the vicinity of nine California airports. Airport visibility data were available from 1966 through 1992. We then applied these regression equations to visibility measures when $PM_{2.5}$ was not directly monitored (i.e. all of the time period

1966-1978 and many days between 1979 and 1992). For $PM_{2.5}$, an airport subcohort of the AHSMOG study was created consisting of subjects (n=3769) living 80% of their months ('73-'77) in the air basins of nine selected airports [Alameda, Bakersfield, Fresno, Los Angeles, Long Beach, Ontario, Sacramento, San Diego and San Jose]. Because of air flow patterns, there are three separate air sheds associated with the Ontario airport region: east, central, and west Ontario. Further details of the $PM_{2.5}$ estimation methods and evaluation of their precision can be found in Abbey et al. (*30*) These estimates included adjustments for relative humidity and temperature (*4*). Daily estimates were averaged to form monthly means. Any month with nonmissing $PM_{2.5}$ estimates for more than 75% of the days were considered to have valid data. The coarse fraction of PM_{10} (i.e. $PM_{10-2.5}$) was estimated by subtracting the $PM_{2.5}$ value from the PM_{10} value for each subject in the airport cohort.

The validity of the visibility data from which the $PM_{2.5}$ estimates were derived was evaluated by comparing the computerized values to the actual log sheets completed by the respective air traffic controllers. There were no significant differences between the computerized visibility data and the actual log sheets.

Estimates of monthly ambient concentrations of nitrogen dioxide (NO_2), sulfur dioxide (SO_2) and ozone (O_3) were also formed for study participants for the period 1966-1992 using the CARB monitors which are located throughout California. The detailed methods for estimating these ambient air pollutants as well as PM_{10} for study participants are described elsewhere (*25,29-31*). Briefly, monthly indices of ambient air pollutant concentrations at 348 monitoring stations located throughout California were interpolated

to zip code centroids according to home or work location histories of study participants (3). Interpolations were restricted to zip code centroids within 50 km (31.25 mi) of a monitoring station and were not allowed to cross barriers to air flow or other topographic obstructions in excess of 250 m above the surrounding terrain (*25*). Quality ratings that reflected the distance of the nearest monitoring station from the zip code centroid were attached to all interpolations in order to allow sensitivity analyses (*25,29*). In addition to the monthly values, the data were cumulated and averaged over the time period 1973-1977.

c. Mortality Ascertainment.

Deaths during the follow-up period were ascertained using three methods: 1) computer-assisted record linkage (*32*) with the California death certificate files for the years 1977-1992; 2) computer-assisted record linkage to the National Death Index files, 1979-1992; and 3) other tracing procedures which included post office mailed returns, church records, and phone tracing. Date of death obtained from death certificates was used as a right censoring date in the calculation of risk sets in the Cox proportional hazards regression analyses.

d. Cancer Incidence Ascertainment.

We ascertained cancer incidence for the AHSMOG 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 (*32*) where cancers identified by this mechanism were considered the "gold standard"; and 2) medical records obtained from

hospitals identified via self-report by study subjects. These methods overlapped for California during the later period of the study. Cancer reporting became statewide in California in 1988. Results based on a comparison of self report in the AHSMOG study since 1988 versus record linkage with the California Cancer Registry indicated that 83.6% of tumor registry-reported cancers since 1988 were also self reported. Using both methods of case ascertainment ensured as complete a coverage as possible. Malignant cancers first diagnosed in non-California hospitals were identified via self-report only. Further details regarding cancer incidence ascertainment may be found elsewhere (*21*). Identified cancers were coded for site and morphology by a certified nosologist who was blinded to the air pollution data. The primary endpoint considered in this report was lung and bronchus cancer incidence (International Classification of Disease for Oncology, first revision = 162; second revision = C34).

e. Statistical Methods.

We used likelihood ratio chi-square tests (*33*) and t-tests in univariate analyses to evaluate potential differences between noncases and incident cancer cases for selected baseline characteristics. We estimated adjusted relative risks (RRs) by gender using Cox proportional hazards regression models with attained age as the time variable (*34*). This method gives tighter and non-parametric control for age. The PHREG procedure of SAS software (version 6.12; SAS Institute, Cary, NC) was used for these analyses (*35*). Initially, we evaluated gender-combined models, but inclusion of a gender covariate violated the proportional hazards assumption. We used the same models developed for

PM_{10} in previous reports (*4,21*) to investigate $PM_{2.5}$ and $PM_{10-2.5}$ so that comparisons could be made across the three size ranges of PM. The covariates for these models were: 1) pack-years of past cigarette smoking; 2) alcohol use at baseline (dummy coded as any versus none), and 3) years of education, as a surrogate for socioeconomic status (*24*).

The gender-specific distributions of potential covariates for lung cancer incidence amongst the total AHSMOG cohort (n=6,338) has been described elsewhere (*21*). These distributions did not change appreciably when analyses were restricted to the $PM_{2.5}$ airport subcohort. All covariates (aside from attained age) were evaluated as potential confounders by inclusion in the final statistical model one at a time (*36*). The primary criterion for inclusion of potential confounders in the final Cox regression model was that their inclusion changed the adjusted relative risk associated with a 10 $\mu g/m^3$ increase in mean concentration of $PM_{2.5}$ by 10% or more (*37*). None of the variables investigated met this criteria; thus the lung cancer relative risks described below are not significantly confounded by: body mass (kg/m^2), total exercise, history of cancer or asthma, 10 or more years in occupations with airborne contaminants, years lived or worked with a smoker, hours per week outside in summer or rest of year, or index of fruit consumption. The fruit consumption index was evaluated because it was the only dietary constituent that showed a strong, statistically significant, protective association with incident lung cancer in the parent AHS study (*38*).

The primary analyses used time dependent Cox regression models with air pollutants averaged from 1973 to 3 years prior to each risk set (i.e. 3 year lag). The 3-year lag was the maximum possible for the $PM_{10-2.5}$ analyses in order to insure at least 12

contiguous months on which to base the mean concentration estimate and because 1973 was the earliest date for which monthly PM_{10} data were available. The first incident lung cancer case was diagnosed in 1977.

f. Proportional Hazards Assumption.

We evaluated the proportional hazards assumption for the final gender-specific models by: 1) inclusion of product terms of the final model covariates with the log of the time variable (attained age) and evaluating the p-values associated with both the Wald statistic and the likelihood ratio test (*39*); and 2) visual inspection of the log[-log(survival)] plots against log(time) to evaluate whether the curves representing different categories of the covariate were approximately "parallel" (i.e. hazards are proportional).

There was some evidence from the log[-log(survival)] versus log(time) plots as well as the interaction terms of each covariate with log(time) that this assumption was not fully met for each of the variables in the final model (i.e. PM, education, packyears of past cigarette smoking, alcohol use), however, we felt that this violation did not substantially impact our results since we observed similar relationships when the analyses were rerun using logistic regression which does not incorporate a proportional hazards assumption.

4. Results

The baseline characteristics of this airport cohort for which $PM_{2.5}$ estimates for the years 1973-1992 are available are listed in **Table 5.1.** We compared descriptive characteristics at baseline between lung cancer cases and noncases. These distributions

were similar to the entire AHSMOG study population (*21*). For both females and males in the airport cohort, subjects diagnosed with lung cancer during follow-up tended to be older at baseline and have less college education compared to the noncases. For females, lung cancer cases had experienced more pack years of cigarette smoking in the 7 or more years category as well as having more years worked with a smoker compared to non-cancer cases. None of the other baseline characteristics evaluated were significantly different between lung cancer cases and non-cases for either females or males.

The airport cohort is approximately 60% of the larger AHSMOG cohort (*3*) for which PM_{10} estimates are available. We found no major differences among the population characteristics and distributions of the investigated long-term ambient air pollutants (PM_{10}, O_3, SO_2, NO_2) of the $PM_{2.5}$ airport cohort and the parent AHSMOG cohort suggesting that the airport cohort is representative of the parent cohort in both the study subject characteristics and the distributions of the ambient air pollutant concentrations. The airport cohort contributed 39,010 person years (PY) during followup (males: 13,648 PY, females: 25,362 PY). The median year of diagnosis for incident lung cancers in males and females was 1980 and 1988 respectively. The median age at lung cancer diagnosis was 70 for males and 74.5 for females.

The covariate adjusted gender-specific regression coefficients for PM_{10} (1973-1977) for incidence of lung cancer for the total AHSMOG cohort (n=6,338) and the airport cohort (n= 3,769) were similar: (β=0.02227 for AHSMOG and β= 0.02715 for the airport cohort in males; β= -0.01475 for AHSMOG and -0.01891 for the airport cohort in

females). This further supports the premise that the airport cohort is representative of the full AHSMOG cohort.

Frequency distributions of mean ambient concentrations (1973-1977) of $PM_{2.5}$, PM_{10} and $PM_{10-2.5}$ for participants in the airport cohort at study baseline are presented in **Figures 5.1a - 5.3b**. There were no major differences between the sex-specific distributions for any of the three size fractions. The descriptive statistics and bivariate correlations for the air pollutants investigated in this report are listed in **Table 5.2**. The correlations of PM_{10} with the fine and coarse fractions were high (> 0.80), while the correlation between the fine and course fraction was only modest (0.50).

a. Lung Cancer Incidence.

We identified a total of 25 (females: 14; males: 11) incident lung and bronchus cancers in the airport cohort during the 15-year follow-up period. Eleven of the incident lung cancers were considered carcinomas and 14 were adenocarcinomas (**Table 5.3**).

There was a statistically significant 2-fold increased risk of lung cancer in males associated with an increase of 10.0 $\mu g/m^3$ of $PM_{2.5}$ [relative risk (RR)=2.05, 95% confidence interval (CI): 1.003 - 4.17). A weaker association was found with the larger coarse-fraction particles (**Table 5.4**). Controlling for other factors (listed in Table 1) one at a time did not appreciably alter these results. In females, there was no statistical association between incident lung cancer and any of the particulate air pollutants investigated after adjustment for attained age and baseline characteristics of: pack-years of past cigarette smoking, years of education, or alcohol use (**Table 5.4**). The regression

coefficients and relative risks for all of the covariates in the final Cox PH models for both genders are shown in **Table 5.5**.

In further analyses, $PM_{2.5}$ mean concentrations were adjusted based upon the amount of time participants reported spending indoors by season at baseline. Mean indoor concentrations were assumed to be 80% of outdoor concentrations (*40*). It has been suggested (*16*) that fine particles indoors are largely derived from outdoors especially in homes where there is no tobacco consumption. Using the same covariates as in the previous models, the association of incident lung cancer in males and females with ambient $PM_{2.5}$ remained unchanged except to reflect the adjustment factor.

To further evaluate the observed gender differences in lung cancer risk associated with $PM_{2.5}$ we divided the geographic areas into three groups based upon ambient $PM_{2.5}$ mean concentration (low $\leq$ 22 $\mu g/m^3$ < medium $\leq$40 $\mu g/m^3$ < high). The observed crude lung cancer incidence rates for males for the low, medium and high pollution areas were respectively: 5.2, 4.8, and 12.5 per 10^4 person years of followup. For females, the corresponding lung cancer incidence rates were: 4.0, 9.2 and 3.3 per 10^4 person years of followup.

b. Multipollutant Analysis.

We further evaluated the relationship between incident lung cancer and $PM_{2.5}$ by the addition of a second air pollutant in the multivariate models. These two-pollutant models consisted of $PM_{2.5}$ and the mean concentration of either $PM_{10-2.5}$, ozone, sulfur dioxide or nitrogen dioxide, all averaged over 1973-1977 (i.e. fixed time period with no

lag). For males, when the fine fraction ($PM_{2.5}$) and the coarse fraction ($PM_{10-2.5}$) competed in the same model, the association with lung cancer increased slightly for $PM_{2.5}$ from 3.66 to 3.81 (CI: 0.60 - 24.10) while the relationship with $PM_{10-2.5}$ decreased from 1.21 to 0.96 (CI: 0.46 - 2.02). There was almost a 50% increase in the association with $PM_{2.5}$ (RR=5.40; CI: 0.57 - 51.30) when ozone was added to form a two-pollutant model although the 95% confidence intervals are very wide in these two pollutant models. Conversely, the association of ozone with male lung cancer incidence decreased from a RR=1.47 (CI: 0.44 - 4.97) in the single pollutant model to RR=0.65 (CI: 0.13 - 3.17) in the two-pollutant model with $PM_{2.5}$. Because of the small number of male incident lung cancer cases with non-missing SO_2 data, two pollutant models could not be analyzed for this pollutant. The $PM_{2.5}$ association did not change appreciably when NO_2 was added to form a two-pollutant model. Suspended sulfates (SO_4) were not evaluated because these data were only measured since 1977 which coincides with the date of diagnosis of the first lung cancer case.

For females, the addition of $PM_{10-2.5}$, SO_2 or NO_2 did not appreciably alter the $PM_{2.5}$ association. The association for $PM_{2.5}$ became positive (RR=1.22; CI: 0.16 - 9.15) when ozone was added to the model while the coefficient for ozone remained negative. Because of the small number of incident lung cancer cases for both males and females, the interpretation of the results from the two pollutant models should be made very cautiously.

c. Lag Times From 1966.

Our primary analyses used a lag of 3 years as explained above because we wanted to compare $PM_{2.5}$ with $PM_{10-2.5}$ and we did not have $PM_{10-2.5}$ prior to 1973. However, in focusing on $PM_{2.5}$, we have estimated data back to 1966. We therefore investigated longer lag times in the relationship of $PM_{2.5}$ to incident lung cancer. A 24-month moving average of cumulated monthly $PM_{2.5}$ data was created based on the time period from 0 to 9 years prior to date of diagnosis of the lung cancer (or date of censoring for the noncases) for each attained age risk set in the time-dependent Cox proportional hazards regression. In males, a lag of 5 years produced the largest risk (RR=5.10; CI: 1.77 - 14.72) for a 10 $\mu g/m^3$ increase in mean concentration of $PM_{2.5}$. The largest risk in females was observed for a lag of 7 years (RR=1.02; CI: 0.57 - 1.84).

d. Sensitivity Analysis.

We investigated the relationship of $PM_{2.5}$ with incident lung cancer in subgroups of the airport cohort. For males, the coefficient for $PM_{2.5}$ was reduced by only 4% when analyses were restricted to never smokers. However, there was almost a doubling of the magnitude of the regression coefficient among the males who did not consume alcohol (i.e. "alcohol" = none) and a 78% increase in the regression coefficient for men who did not work in occupations with airborne contaminants.

For females, the covariate-adjusted regression coefficient for $PM_{2.5}$ remained negative when analyses were restricted separately for never smokers, nonalcohol users, or women who were not exposed to occupational airborne contaminants. Further restricting

the analyses to no measurable exposure to tobacco smoke (i.e. never smoked and never lived nor worked with a smoker), did not alter the gender differences.

In further sensitivity analyses of the final model, we investigated the effect of $PM_{2.5}$ on lung cancer incidence when it was the only variable in the model as well as when only one or only two of the final model covariates were also included. For both males and females this did not markedly change the relationship that was observed in the final models – the relative risk for males was never lower than 2.55 and the regression coefficient for females was consistently negative.

Since five of the female incident lung cancer cases were not histologically confirmed, but were coded as carcinoma-NOS (i.e. not otherwise specified) on the hospital record, we reran the final female models excluding these five cases. The resultant association with a 10 $\mu g/m^3$ increase in $PM_{2.5}$ became stronger (RR=1.23; CI: 0.62 - 2.47) but with very low power. The associations with PM_{10} (RR=1.03; CI: 0.66 - 2.60) and $PM_{10-2.5}$ (RR=0.81; CI: 0.28 - 1.07) were weaker than that for $PM_{2.5}$. A similar exclusion of the single male lung cancer case with carcinoma-NOS resulted in an increased risk for a 10 $\mu g/m^3$ increase in $PM_{2.5}$ (RR=2.94; CI: 1.19 - 7.29).

Because of the trimodal distribution of $PM_{2.5}$ (see **Figures 5.1a & 5.1b**), we explored the relationship of lung cancer incidence to $PM_{2.5}$ by dividing the cohort into three groups based upon ambient $PM_{2.5}$ mean concentration (low $\leq$ 22 $\mu g/m^3$ < medium $\leq$40 $\mu g/m^3$ < high). Males living in areas of high $PM_{2.5}$ concentrations had the highest risk of incident lung cancer [high: (RR=3.30; CI: 0.66 - 16.52); medium: (RR=0.85; CI: 0.12 - 6.04); low: RR=1.00 (ref.)] For females, the lung cancer/$PM_{2.5}$ association was not

clear as it was the group living in areas of medium $PM_{2.5}$ concentration who had the highest risk [high:(RR=0.60; CI: 0.10 - 3.78); medium: (RR=2.31; CI: 0.60 - 8.89); low: RR=1.00 (ref.)]. Seven of the eleven male lung cancer cases lived in the high $PM_{2.5}$ areas with the remainder of the male cases being equally divided between the low and medium $PM_{2.5}$ areas whereas for females, the majority (8 of 14) of the lung cancer cases were in individuals who lived in areas of medium $PM_{2.5}$ concentration, again with the remainder of female cases being equally divided between low and high areas.

e. 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 $PM_{2.5}$ (1973-77) replacing attained age as the time variable with time on study measured in months. Age at baseline (1977) was then added to each model as a covariate. This approach resulted in similar gender-specific results for a 10 $\mu g/m^3$ increase of $PM_{2.5}$ [males: (RR=1.61; CI: 0.87 - 2.98); females: (RR=0.82; CI: 0.48 - 1.41)].

5. Discussion

We found the strongest associations between respirable particulate air pollution and incident lung cancer in males in the fine fraction. This finding is consistent with what is known about the carcinogenic properties of respirable particles as suggested by other investigators (*7,41-43*). Tomatis (*44*) notes that aside from tobacco smoke, a causal association with lung cancer has been demonstrated for eleven other carcinogenic agents which may appear in the ambient air.

The possibility that particulate air pollution might act as an independent agent in the development of lung cancer has been suggested by several investigators (*45-53*). In specific, Szczeklik and colleagues (*51*) have observed humoral immunosuppression in men exposed to polycyclic aromatic hydrocarbons (PAHs) and related airborne carcinogens in the polluted environment. $PM_{2.5}$ provides a mechanism whereby these PAHs may be delivered to the deep lung and alveolar capillaries (*52*) where they can be delivered to the lungs systemically. Urban air particulates and their extracts have been shown to cause DNA adducts and have mutagenic and carcinogenic effects in humans (*53*).

a. Other Co-Pollutants.

We have previously reported associations of lung cancer incidence with other long-term mean concentrations of ambient air pollutants (*21*). In the total AHSMOG cohort (*21*), the risk of lung cancer incidence in males associated with one IQR increase in mean concentration of ozone with a 3-year lag was 1.65 (CI: 0.72 - 3.80). Similar increases in lung cancer risk in males were observed for NO_2 (RR=1.45; CI: 0.67 - 3.14) and SO_2 (RR=2.66; CI: 1.62 - 4.39). Lung cancer in males was also associated with long-term mean concentration of PM_{10} lagged 3-years. The relative risk for a 10 $\mu g/m^3$ increase was 1.99 (CI: 1.32 - 3.00). This was similar to what was observed in the airport cohort.

For females in the total AHSMOG cohort, lung cancer incidence was not associated with mean concentration of ozone lagged 3 years (RR = 0.60; CI: 0.36 - 1.01)

nor for a 10 $\mu g/m^3$ increase in PM_{10} (RR=1.04; CI: 0.80 - 1.33). An IQR increase in mean concentration of SO_2 was associated with a statistically increased risk (RR=2.14; CI: 1.36 - 3.37) and there was a suggestion of increased risk (RR=1.57; CI: 0.79 - 3.13) for mean concentration of NO_2.

Sulfur dioxide was statistically associated with lung cancer incidence in both males and females. It has been demonstrated that SO_2 can potentiate the carcinogenicity of polycyclic aromatic hydrocarbons (PAHs) (*89*). Sulfite, the physiological form of SO_2, reacts with all classes of cellular molecules including DNA and RNA and sulfite increases the formation of benzo[a]pyrene-DNA adducts during oxidative metabolism of the carcinogen (*90*). Although SO_2 has not been shown to be carcinogenic, concurrent exposure to both SO_2 and PAHs results in a marked enhancement of respiratory tract carcinogenicity in both rats and hamsters and it is possible that this may also be true for humans (*91*). Ammonium sulfate appears to account for the largest component of the fine particle ($PM_{2.5}$) mass and the only significant source of fine particulate ammonium sulfate is the chemical conversion process of SO_2 which occurs in the atmosphere (*92*).

In the American Cancer Society's Cancer Prevention Study II, Pope and colleagues (*2*) and others (93,94,95) have observed that sulfate (SO_4^{-2}) particles generally make up the largest fraction of $PM_{2.5}$ by mass. These SO_4^{-2} particles are generally believed to be secondary products of atmospheric conversion of primary SO_2 (*2,95*). In the AHSMOG study, it is possible that our SO_2 index might be serving as a surrogate for other organic fuel combustion products even though the correlation between the mean concentrations of SO_2 and $PM_{2.5}$ was low (r=0.18).

Our multipollutant analyses in the airport cohort suggest that $PM_{2.5}$ has stronger effects than the other pollutants investigated.

b. Long-Term Studies of Lung Cancer Mortality.

We are unaware of other long-term studies of ambient air pollution and lung cancer incidence. However, the increased risk of lung cancer incidence in males associated with a 10 $\mu g/m^3$ increase in ambient $PM_{2.5}$ observed in this study is similar to the increased risk of lung cancer mortality observed in the other long-term studies already mentioned. The ACS study (*2*) also found gender differences in the risk of lung cancer mortality associated with $PM_{2.5}$. Combining never-smokers with ever-smokers as in the AHSMOG study, a comparison of the most polluted areas to the least polluted areas resulted in a negative regression coefficient for females (RR=0.90; CI=0.56-1.44) and a positive coefficient for males (RR=1.10; CI=0.81-1.47) for a 24.5 $\mu g/m^3$ increase although the confidence intervals greatly overlap. In the 6-City Study (*1*) there was a 37% increased risk of lung cancer death in both genders combined when the most polluted city was compared to the least polluted. They did not describe results by gender. The case-control Stockholm study (*5*) only investigated male lung cancers, 93% of whom were deceased at time of enrollment. Although they only investigated SO_2 and NO_x/NO_2, these gaseous pollutants can be converted into fine particulate air pollution in the atmosphere (*11*). They found a 44% increased risk (RR=1.44; CI: 1.05 - 1.99) of lung cancer for the top decile of long-term exposure to NO_2 compared to the lowest quartile. Little association was observed for SO_2. The AHSMOG study (*4*) also investigated lung

cancer mortality in relation to different levels of ambient $PM_{2.5}$. For a 24.3 $\mu g/m^3$ IQR increase in ambient $PM_{2.5}$, the observed relative risk for males was 2.23 (CI: 0.56-8.94). The association was uniformly weak or inverse for females in the AHSMOG study. This report from the AHSMOG study concluded that it was the fine fraction of respirable particles averaged over several years that was most strongly associated with the observed increased mortality on a long-term basis rather than the coarse fraction.

c. Short-Term Studies.

Most, but not all (*16*, 54) short term (or time-series) studies show that $PM_{2.5}$ is associated with a stronger health effect than is $PM_{10-2.5}$. Schwartz and Neas (*55*) investigated the relative contributions of fine and coarse particles on respiratory symptoms and peak expiratory flow in school children. They concluded that fine particles had a much stronger acute respiratory effect compared to coarse particles. Burnett et al. (*56*) compared ambient particulate matter to daily hospital admissions and found that $PM_{2.5}$ was associated with a greater increase in respiratory and cardiac admissions than was $PM_{10-2.5}$. They did not mention gender in their report. Hornberg et al. (*57*) investigated the induction of sister chromatid exchanges in human tracheal epithelial cells by different size fractions of airborne particulates in urban, industrialized and rural areas. They found that the fine fraction ($PM_{2.5}$) of ambient air from all three types of geographic areas exerted a stronger genotoxic effect compared to the coarse fraction. They also did not report on gender. Schwartz, et al. (*58*) concluded that coarse fraction particles were not associated with total daily mortality risk, which corroborated

the findings from the Six Cities study (*59*) which also looked at zero and 1-day lags and daily mortality.

A few studies have found strong toxic effects with the coarse fraction of ambient particulates. Monn and Becker (*16*) performed *in vitro* testing of different size particle extracts and cell injury. They found that significant toxicity and cytokine production was induced by outdoor $PM_{10-2.5}$, but not by outdoor $PM_{2.5}$. In geographic areas where PM_{10} is dominated by the coarse fraction such as some desert regions in southern California, health effects can still be observed. Ostro et al. (*54*) found that several measures of daily mortality were statistically significantly associated with the coarse fraction-dominated PM_{10}.

d. Possible Mechanisms.

Injury to the lung and inflammatory mediator imbalances and cytokine production have been proposed (*16*) as possible causative mechanisms of lung cancer initiation. The toxic constituents of respirable particles may include acidity, transition metals, organic and biogenic materials, and diesel soot, among others. With chronic exposure to toxic respirable particles, the normal mucociliary clearance mechanisms can be gradually overwhelmed and essentially cease, ultimately resulting in progressive buildup of particles in the lungs. It is believed that long-term health effects, including lung cancers, are due in part to chronic inflammation and other nonspecific events. Some investigators have suggested that the patchy inflammation at sites of particle accumulation is perhaps related to the adenosarcomas and squamous cell carcinomas that are observed (*60*).

Alcohol use was chosen as a covariate in all statistical models for the airport cohort as it was a significant risk factor for lung cancer incidence in the parent cohort (*21*) and it is possible that in this airport cohort, alcohol use may serve as a marker for "social" (i.e. non-work, non-home) environmental tobacco smoke (ETS) exposure not otherwise measured. In addition, several mechanisms have been described for alcohol-associated carcinogenisis including its ability to facilitate the transport of carcinogens associated with $PM_{2.5}$ across the mucosal lining (*40*).

e. Gender Differences in Response to Air Pollution.

In this study we found a statistically significant increased relative risk for incident lung cancer associated with $PM_{2.5}$ only in males. This gender difference may be due in part to the males spending more time outdoors (μ=18.9 hrs/week) than females (μ=10.3 hrs/week) ($p<0.0001$) and reporting more vigorous exercise outdoors compared to females (males: μ=10.0 hrs/week; females: μ=5.1 hrs/week) ($p<0.0001$). Although there was no significant difference between male cases and non-cases for these variables due to the small number of cases (see **Table 5.1**), the cases had substantially higher values. Brunekreef argues that fine particles readily penetrate indoors (*61*). Thus, if it is just the fine particles that are having effects, then the differences in time spent outdoors should not account for the observed gender differences. However, if ozone enhances the effects of $PM_{2.5}$ as our multipollutant analyses suggest (see **Table 6.4**), then these gender differences in time spent outdoors may partially explain the gender differences as ozone is markedly decreased indoors (*62,63*).

Since the proportion of incident lung cancer cases lacking histological conformation differed by gender (36% for females, 9% for males), a differential misclassification bias may have occurred as it is possible that females had more metastatic lung cancers from other unknown primary sites which may weaken the air pollution/lung cancer association. However, we chose to include these six carcinoma-NOS lung cancers in the primary analyses to be consistent with the way lung cancer was defined in our previous report (*21*) since the primary purpose of this paper was to look at the fine and coarse subfractions of PM_{10} and to further explore the gender differences previously observed for ambient particulate air pollution.

In a study of healthy adults, Bennett et al. (*64*) observed that fine particle deposition rates were statistically significantly higher in males than in females ($p=0.004$). When deposition per unit of area of lung tissue was evaluated, they found that males tended to receive a higher dose of fine particles and that the deposition and dose of PM_2 in the lungs of healthy adults was independent of age. Stettler et al. (*65*) studied lung particulate burdens in urban subjects with a scanning electron microscope and found that the total exogenous particle levels were statistically significantly higher in males compared to females ($p=0.015$).

Mage and Kretzschmar (*66*) also observed that males appear to be approximately 50% more at risk of smog-related mortality than females in the three classic historic air pollution episodes (Meuse Valley, Donora, London) although these were studies of short-term exposures. The gender differences we have observed for $PM_{2.5}$/incident lung cancer associations are similar to the gender differences observed for other endpoints in this

study. Greer et al. (*67*) found that elevated long-term ambient concentration of ozone was strongly associated with adult-onset asthma in men but not in women and Abbey et al. (*3*) observed that long-term mean concentrations of PM_{10}, SO_4, O_3, and NO_2 were positively associated with all natural cause mortality in males but not in females. Pershagen (*68*) reviewed several epidemiologic studies of lung cancer in relation to residential proximity to industrial point sources of air pollution. Five of these studies found relative risks in males between 1.2 and 2.0. These same studies did not consistently observe elevations in risk among women (*11*). There is epidemiologic evidence that males have an excess risk of mucous hypersecretion compared to females that is unrelated to tobacco use (*69*). The observation that males develop chronic obstructive pulmonary disease more frequently than females even with control for smoking suggests that certain chronic respiratory diseases may reflect gender-specific pathophysiologic responses and that females may be more resistant to the harmful effects of airborne chemicals and particulates (*70*).

f. Animal Studies.

In the absence of adequate data from humans, quantitative estimates of human cancer risk per unit of exposure from airborne chemicals and particles is often derived from animal carcinogenicity bioassays. However, because of many uncertainties, it is seldom appropriate to estimate human cancer risks from animal lung tumor data (*71*). Studies of inhaled particles, such as diesel exhaust, by rats and monkeys show considerable differences in the response of the lungs of these different species (*72*). Experiments with rodents have indicated that transition metal content and particle acidity

of respirable particulates cause lung inflammation and interfere with the host defense function of alveolar macrophages leading to chronic lung injury (*73*). Most of the acidic aerosols in the ambient atmosphere are in the $PM_{2.5}$ range. Chen et al. (*74*) exposed guinea pigs to different exposures of acidic aerosols and found alterations in macrophage function and changes in lung tissue morphology in the alveolar region, the major site of acid aerosol deposition. The phagocytic function of alveolar macrophages is essential to lung defense against inhaled particles which may contain carcinogens. Although there has been general concern about the generalization of findings from rodent toxicology experimentation to humans, Becker and colleagues have demonstrated that rat and human alveolar macrophages respond in a similar manner to exposure to a variety of environmental airborne particles (*75*).

g. Indoor Sources of PM.

When adjustments were made for time spent indoors, our results were not changed. The EPA PTEAM study (*76*) in southern California investigated sources of particles in personal, indoor and outdoor environments. They found that the daytime indoor $PM_{2.5}$ and PM_{10} concentration distributions were quite similar to outdoor concentrations whereas the nighttime indoor $PM_{2.5}$ and PM_{10} concentrations tended to be lower than outdoors. They summarized the indoor sources of PM into four major categories: housework (e.g. vacuuming, dusting), spraying (e.g. hair care products, deodorants), tobacco smoke, and vehicle exhaust from attached garages. The highest estimated population indoor mean PM_{10} in homes with these activities for either day or

night was associated with exposure to tobacco smoke. In the AHSMOG study, none of the participants were active smokers and exposure to second hand smoke in the home was minimal. Neither past nor passive smoking covariates altered our observed relationships with $PM_{2.5}$.

h. Measurement Error.

Any measurement error present in the estimation of air pollutants or other variables could bias our estimates of pollutant regression coefficients. There are three main sources of error in the estimation of the long-term air pollutant cummulations assigned to each subject: 1) use of indirect estimates for $PM_{2.5}$, $PM_{10-2.5}$, and PM_{10} for years 1987 and earlier; 2) interpolating monitoring station values of other air pollutants to zip code centroids; and 3) use of ambient concentrations rather than personal exposures. We discuss each of these below.

1) The $PM_{2.5}$ values used in this report were indirect estimates derived from airport visibility data using site- and season-specific regression equations in which actual monitored ambient $PM_{2.5}$ values were used to scale the daily measures of visibility. The methods and precision of using airport visibility for estimating ambient $PM_{2.5}$ mean concentrations have been described for an earlier subset of these data (*30*). Using updated (1979-1993) $PM_{2.5}$ and visibility data, we calculated a split-halves correlation coefficient of 0.72 between daily measured and estimated $PM_{2.5}$ at the monitoring sites (*4*). Another source of measurement error is our use of indirect estimates of PM_{10} based on total suspended particulates (TSP) for 1987 and earlier. These values of PM_{10} were

then utilized in the estimation of the coarse fraction ($PM_{10-2.5}$). Abbey et al. (*29*) have shown that using these indirect estimates only marginally impacts the precision of long-term cumulative averages of PM_{10}.

2) For the other pollutants investigated we interpolated monitored data to zip code centroids. This source of measurement error is discussed by Beeson et al. (*21*) and Abbey et al. (*25,29,31,77*) The accuracy of the interpolation algorithms was checked by interpolating to monitoring stations from surrounding monitoring stations, using the same interpolation algorithm. Correlations between interpolated and monitored mean concentrations for PM_{10}, O_3, SO_2, and NO_2 were: 0.88 (*29*), 0.87 (*25*) , 0.64 (*78*), and 0.92 (*31*) respectively.

3) Ambient concentrations were used for individuals instead of personal exposures. Adjustments were made for time spent indoors and time spent at work zip codes if different from residence zip codes. Several investigators (*79,80,81*) have compared personal $PM_{2.5}$ exposures to ambient concentrations. Correlations ranged from .30 to .90 based on daily averages. It is probable that monthly means would tend to be more highly correlated.

The measurement error for $PM_{10-2.5}$ may be greater than for $PM_{2.5}$ because both PM_{10} and $PM_{2.5}$ were estimated from regression equations and $PM_{10-2.5}$ was created by subtraction. This could bias the $PM_{10-2.5}$ associations either towards or away from the null depending on the direction of error in PM_{10} and $PM_{2.5}$ measurements In addition, $PM_{10-2.5}$ is more influenced by point sources than from air basin-wide phenomena as is the case for $PM_{2.5}$, so this also may increase measurement error for the coarse fraction (*82*).

All covariates, aside from the air pollution estimates, were obtained via self-report on mailed questionnaires. This may have resulted in some misclassification. Other cohort studies have found that smoking tends to be under reported (*83,84*). 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. All individuals (43 females, 49 males) reporting current smoking in 1977 were excluded from the total AHSMOG cohort. If smoking was under reported by 50% and if this under reporting occurred only in the high $PM_{2.5}$ area or only in the low $PM_{2.5}$ area, the male lung cancer RR would range from 1.75 to 4.58, respectively. These RRs were calculated by estimating how many of the observed incident lung cancer cases could be attributed to the misclassified current smokers and subtracting these cases from the calculation of the respective numerator or denominator of the RR. Nondifferential under reporting would not change the relative risk.

In the Six-Cities study (*85*) investigators found that the combustion-related components of the ambient fine particles differed geographically. In the AHSMOG study the chemical composition of $PM_{2.5}$ was not evaluated. However, in a study conducted in 1986 in the South Coast Air Basin (SCAB) which covers the greater Los Angeles area where the largest percentage of the AHSMOG study subjects resided, a PM_{10} monitoring network identified the following components (organic material, NO_3^-, SO_4^{-2}, NH_4^+, and crustal material) as accounting for more than 80% of the annual average PM_{10} mass at all mainland monitoring stations (*86*). The SCAB is recognized as having one of the worst air pollution problems in the United States. Analysis also indicated that most of the

organic material was in the $PM_{2.5}$ fraction and that $PM_{2.5}$ constituted one-half to two-thirds of PM_{10} mass at all monitoring sites (*87*).

i. Lag Times.

We used a lag of 3 years in the evaluation of ambient $PM_{2.5}$ and $PM_{10-2.5}$ and lung cancer incidence for our main analyses. This allowed the mean concentration of $PM_{2.5}$ to be based on the average of at least 12 contiguous months of $PM_{2.5}$ data from 1/73 to 3 years prior to the date of the risk set as defined by each lung cancer case. Most of the recent epidemiologic air pollution research involves time-series analyses of daily variation in air pollution concentrations where long induction lag times are not suitable (*88*). There are only a few epidemiologic studies that have estimated *long-term personal* exposure to ambient air pollutants. Aside from the AHSMOG cohort study, a recent case-control study of 1,042 lung cancers in Stockholm (*5*) was able to investigate NO_x /NO_2 as an indicator of vehicle pollution and SO_2 as an indicator of indoor heating by GIS-coding of residence histories back 30 years prior to start of study. They evaluated different lag times and found that 10-year averages of NO_2 and SO_2 lagged 20 years before the lung cancer diagnosis showed stronger effects and clearer dose-response curves compared to 30 year averages with no lag. They did not investigate particulate air pollutants directly although they believed that their NO_x / NO_2 index may be a good proxy for diesel exhaust and possibly fine or ultrafine particles.

6. Summary and Conclusions

We found elevated risks for lung cancer incidence in nonsmoking males associated with increased cumulated average mean concentration of respirable particulates that seemed to be stronger for the fine fraction ($PM_{2.5}$) compared to the coarse fraction ($PM_{10-2.5}$). No statistically significant association was found in females. The $PM_{2.5}$ data used in these analyses were not analyzed for composition. Further research is needed to identify the chemical characteristics of these potentially hazardous respirable particles. The AHSMOG study is currently updating follow-up through 1998 on the cohort to allow a larger number of cases for confirmation of these results and investigation of longer lag-times and further exploration of gender discrepancies.

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Table 5.1: Total Deaths and Baseline (1977) Characteristics for Airport Cohort Separately for Incident Lung Cancer Cases and Non-Cases. Part 1 of 2

Females[a]		Males[a]		
Non-case n=2408	Case[b] n=14	Non-case n=1336	Case[b] n=11	Characteristic
31.69	30.38	32.34	36.62	Mean concentration $PM_{2.5}$ (1973-1977) $\mu g/m^3$
34.12	32.13	34.85	42.48	Mean concentration $PM_{2.5}$ (1966-1977) $\mu g/m^3$
573	8**	367	10***	Total deaths, '77 - '92
59.2	67.4*	58.2	67.4*	Age in years at baseline, mean
70.1	76.1	68.7	72.6	Age in years at end of study, mean[c]
15.0	35.7*	35.2	27.3	% smoked in the past
11.5	26.1*	20.0	40.0	Packyears of smoking, mean for past smokers only
48.3	50.0	36.9	45.5	% ever lived with a smoker
20.0	22.0	16.1	23.6	Years lived with a smoker, mean[d]
38.3	42.9	49.3	54.6	% ever worked with a smoker
11.1	30.0***	15.8	19.5	Years worked with a smoker, mean[d]
1.0	0.0	13.3	27.3	% occupational exposure to fumes or dust > 10 years

a p-values are comparing cases to noncases within gender based on independent t-test for continuous variables and χ^2 for dichotomous (percentage) variables. (* $p < 0.05$) (** $p < 0.01$) (*** $p < 0.001$)

b A case is defined as an incident lung cancer diagnosed after '77 baseline .

c For cases, age at end of study was age at lung cancer diagnosis, for non-cases, age at end of study was the earliest of (age at death, age at 4/92 if living, or age at lost to followup)

d Mean of non-zero values.

Table 5.1: Total Deaths and Baseline (1977) Characteristics for Airport Cohort Separately for Incident Lung Cancer Cases and Non-Cases. Part 2 of 2

Females[a]		Males[a]		
Non-case n=2408	Case[b] n=14	Non-case n=1336	Case[b] n=11	Characteristic
13.2	12.4	14.4	11.4**	Years education, mean
24.6	22.4	25.0	25.0	Body mass index [(weight in kg) / (height in m)^2]
6.6	7.7	9.3	18.2	% use alcoholic beverages [any vs. none]
33.5	42.9	43.1	36.4	% high total exercise level[e]
5.0	4.3	9.7	13.2	Hours vigorous exercise outdoors/wk in summer[f], mean
4.4	2.8	8.9	12.5	Hours vigorous exercise outdoors/wk rest of year[f], mean
47.9	50.0	41.7	60.0	% High antioxidant vitamin consumption from pills[g]
33.0	35.7	28.5	54.6	% Prior heart attack, stroke, diabetes, or high blood pressure
7.8	14.3	3.8	9.1	% History of cancer
7.6	7.1	7.5	0.0	% History of asthma
64.8	65.7	61.0	45.1	Fruit index (mean servings per month)[h]

a p-values are comparing cases to noncases within gender based on independent t-test for continuous variables and χ^2 for dichotomous (percentage) variables. (* $p < 0.05$) (** $p < 0.01$) (*** $p < 0.001$)

b A case is defined as an incident lung cancer diagnosed after '77 baseline .

e Total exercise was the combination of exercise at work and at leisure. High was vigorous exercise 15+ min. three or more times per week or work involved vigorous activities "very often".

f Summer (June - Sep.), Rest of year (Oct. - May).

g (Daily consumption of vitamin A) or (>1000 mg vitamin C per week) or (≥200 IU vitamin E per week) or (1 or 2 multivitamin pills daily)

h Fruit index was a combination of monthly servings of canned or frozen fruit, dried fruit, fresh citrus fruit, fresh winter fruit, and other fresh fruit from food frequency questionnaire

Table 5.2: Correlations for Long-Term (1973-1977) Mean Concentrations of Ambient Air Pollutants Estimated for Study Participants.

	PM_{10}	$PM_{2.5}$	$PM_{10-2.5}$	Ozone	SO_2	NO_2 (ppb)
Number of subjects[a]	3727	3769	3727	3766	2685	3765
PM_{10} ($\mu g/m^3$)	1.00	0.90	0.83	0.79	0.29	0.07
$PM_{2.5}$ ($\mu g/m^3$)		1.00	0.50	0.68	0.18	-0.08
$PM_{10-2.5}$ ($\mu g/m^3$)			1.00	0.70	0.31	0.23
Ozone (ppb)				1.00	-0.13	-0.16
SO_2 (ppb)					1.00	0.86

Abbreviations: PM_{10}, $PM_{2.5}$ = particles with aerodynamic diameter less than 10 μm, 2.5 μm respectively. $PM_{10-2.5}$ = coarse fraction of PM_{10} with aerodynamic diameter between 2.5 and 10 μm.

a Number of subjects having at least 80% nonmissing (1973-1977) monthly values for calculation of correlations between two pollutants.

Table 5.3: Morphology for Incident Lung and Bronchus Cancers in Subjects in the Airport Cohort[a].

		Females smoking history		Males smoking history	
		Past (n=366)	Never (n=2056)	Past (n=473)	Never (n=874)
Site					
	Bronchus[b]	0	2	0	1
	Lung[b]	5	7	3	7
	Total	5	9	3	8
Morphology					
ICDO	Description				
8010	Carcinoma, NOS	0	5	0	1
8042	Oat cell carcinoma	0	0	1	0
8050	Papillary carcinoma	0	1	0	0
8070	Squamous cell carcinoma	0	1	2	1
8140	Adenocarcinoma	0	1	0	5
8250	Bronchioloalveolar adenocarcinoma	3	1	0	1
8260	Papillary adenocarcinoma	1	0	0	0
8480	Mucinous adenocarcinoma	1	0	0	0
	Total	5	9	3	8

Abbreviations: ICDO=International Classification of Disease for Oncology, NOS=Not otherwise specified

a Airport cohort is defined by those people living in the 11 air basins near 9 California airports (there are 3 separate air basins associated with the Ontario airport) for whom $PM_{2.5}$ data are available

b For lung cancer analyses, cancers of the bronchus and lung are combined. International Classification of Diseases for Oncology codes: 162 (1st revision), C34 (2nd revision).

Table 5.4: Adjusted[a] Relative Risks of Incident Lung Cancer[b] (1977-1992) Associated With a 10 $\mu g/m^3$ Increase of Mean Concentrations of Particle Air Pollutants of Varying Aerodynamic Diameters.

Variable	Cases/n	Regression coef. (β)	SE (β)	Relative risk (RR)	95% CI [c] for RR
Males					
$PM_{2.5}$	11/1215	0.071520	0.03634	**2.05** *	(1.003 - 4.17)
PM_{10}	11/1215	0.043211	0.02445	1.54	(0.95 - 2.49)
$PM_{10-2.5}$	11/1215	0.044195	0.04276	1.56	(0.67 - 3.60)
Females					
$PM_{2.5}$	13/2139	-0.006637	0.02860	0.94	(0.53 - 1.64)
PM_{10}	13/2139	-0.020616	0.01843	0.81	(0.57 - 1.17)
$PM_{10-2.5}$	13/2139	-0.060012	0.03411	0.55	(0.28 - 1.07)

a Relative Risks [exp(10 $\mu g/m^3$ x β)] were computed using the Cox proportional hazards regression with attained age as the time variable and controlling for baseline pack-years of past cigarette smoking, years of education and current alcohol consumption [any/none]. Same covariates for males and females. Mean concentrations averaged from 1973 to 3 years before risk set (i.e. 3-year lag) in the airport cohort.

b For lung cancer analyses, incident cancers of the bronchus and lung are combined.

c CI = Confidence Interval, RR=Relative Risk

* $p < 0.05$

Table 5.5: Relative Risks[a] of Lung Cancer Incidence (1977-1992) Associated With Selected Increments of Mean Concentration[b] of $PM_{2.5}$ and Other Covariates. (Males, n = 1215, Cases = 11) (Females, n=2139, Cases=13).

Variable	Regression coefficient (β)	SE (β)	Increment	Relative risk (RR)[c]	95% CI for RR
Males					
$PM_{2.5}$	0.071520	0.03634	10.0 (μg/m^3)	**2.05** *	1.003 - 4.17
Pack-years of past smoking	0.003427	0.01603	10 pack-years	1.04	0.76 - 1.42
Education	-0.275503	0.10446	4 Years	**0.33** *	0.15 - 0.75
Alcohol[d]	0.465905	0.80560	1=any, 0=none	1.59	0.33 - 7.73
Females					
$PM_{2.5}$	-0.006637	0.02860	10.0 (μg/m^3)	0.94	0.53 - 1.64
Pack-years of past smoking	0.064680	0.01677	10 pack-years	**1.91** *	1.38 - 2.65
Education	-0.028872	0.10656	4 years	0.89	0.39 - 2.05
Alcohol[d]	-0.315641	1.23305	1=any, 0=none	0.73	0.07 - 8.18

Abbreviations: CI = confidence interval; SE = standard error; RR = relative risk.

a Relative risks based on Cox proportional hazards regression with time variable = attained age controlling for age at entrance.

b Mean concentration of $PM_{2.5}$ averaged from 1973 with 3 year lag.

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

d "Alcohol" was a combination of current use at baseline of beer, wine, or spirits and dummy coded as "none" or "any".

* $p < 0.05$

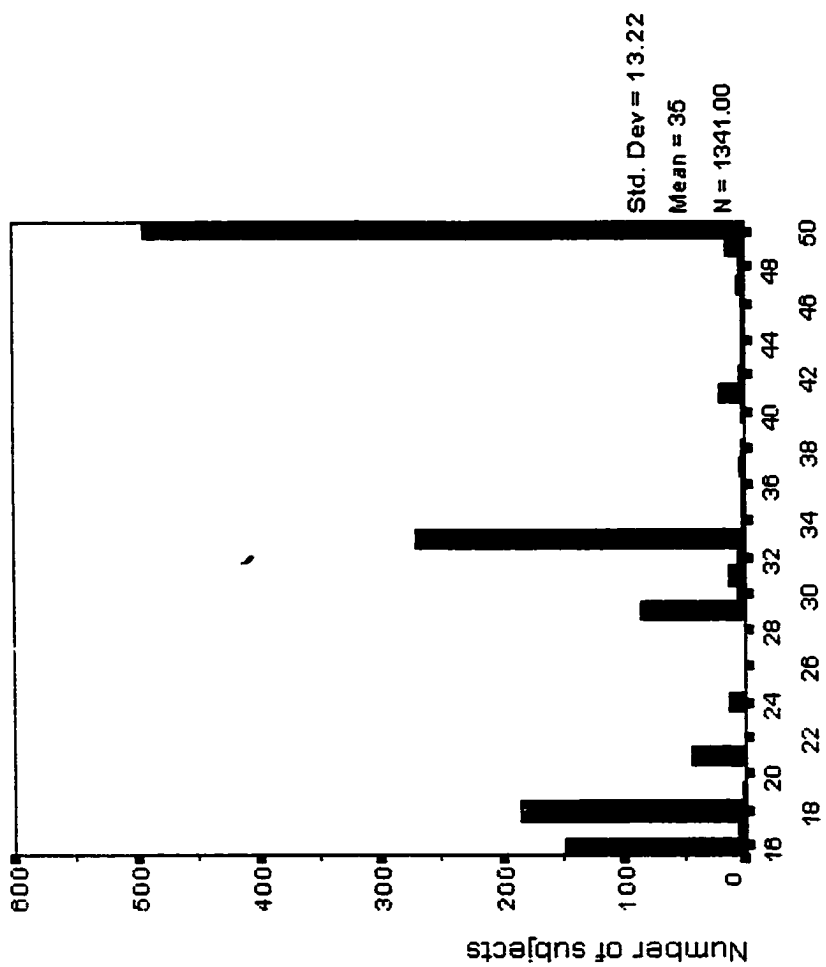

Figure 5.1a: $PM_{2.5}$ average mean concentration in $\mu g/m^3$, 1973-77. Males only.

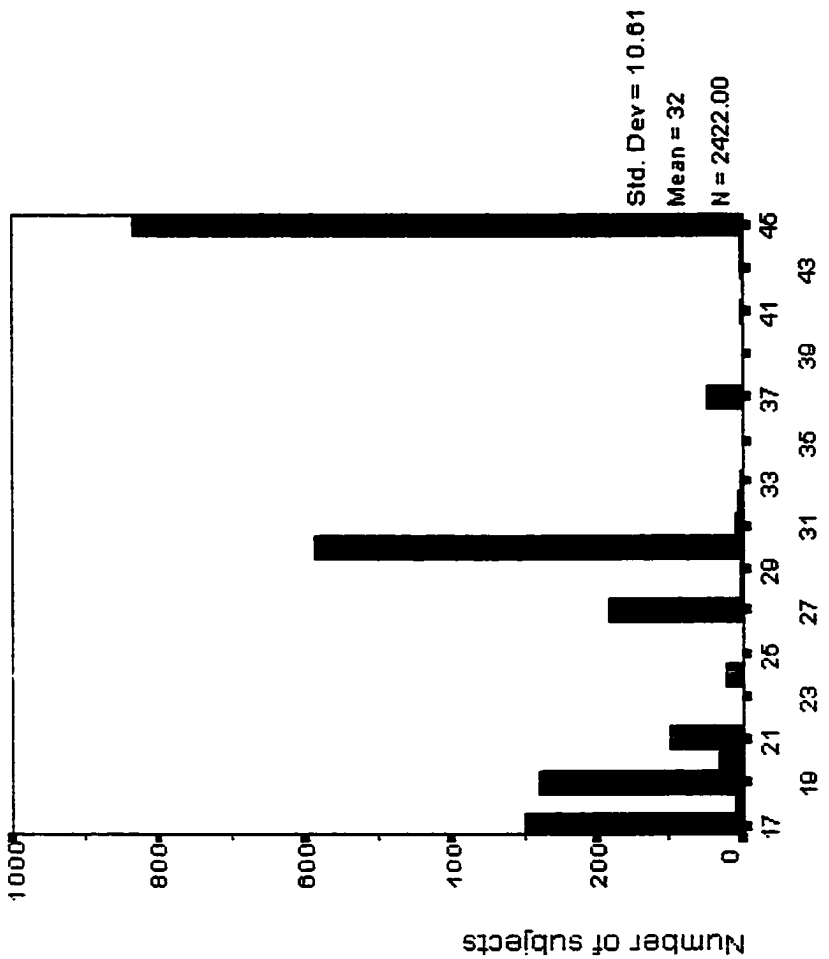

Figure 5.1b: $PM_{2.5}$ average mean concentration in $\mu g/m^3$, 1973-77. Females only.

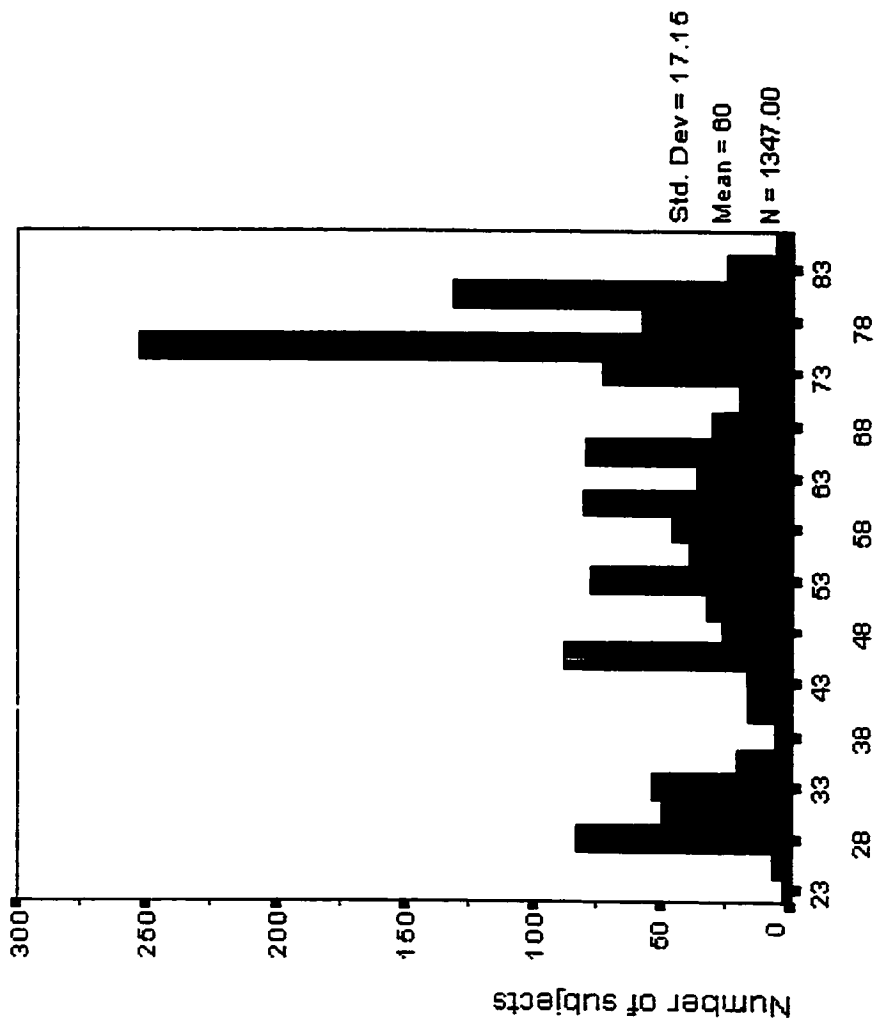

Figure 5.2a: PM_{10} average mean concentration in $\mu g/m^3$, 1973-77. Males only.

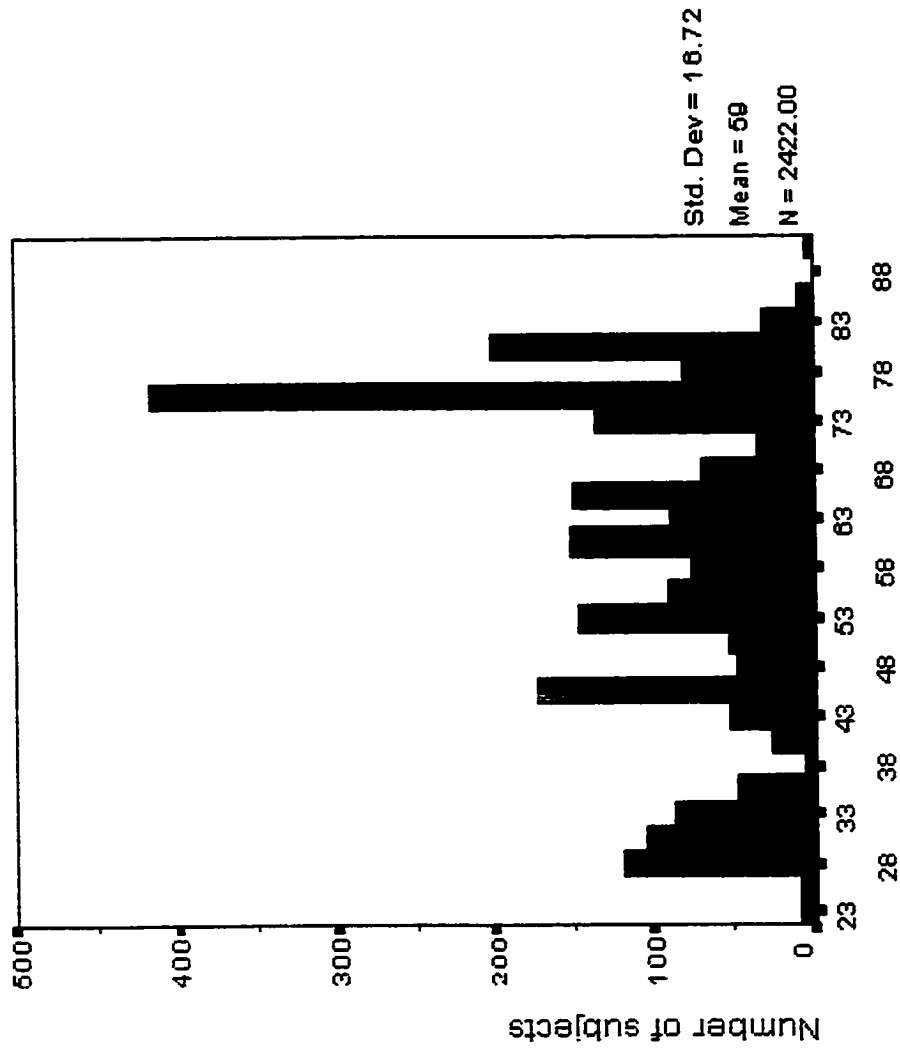

Figure 5.2b: PM_{10} average mean concentration in $\mu g/m^3$, 1973-77. Females only.

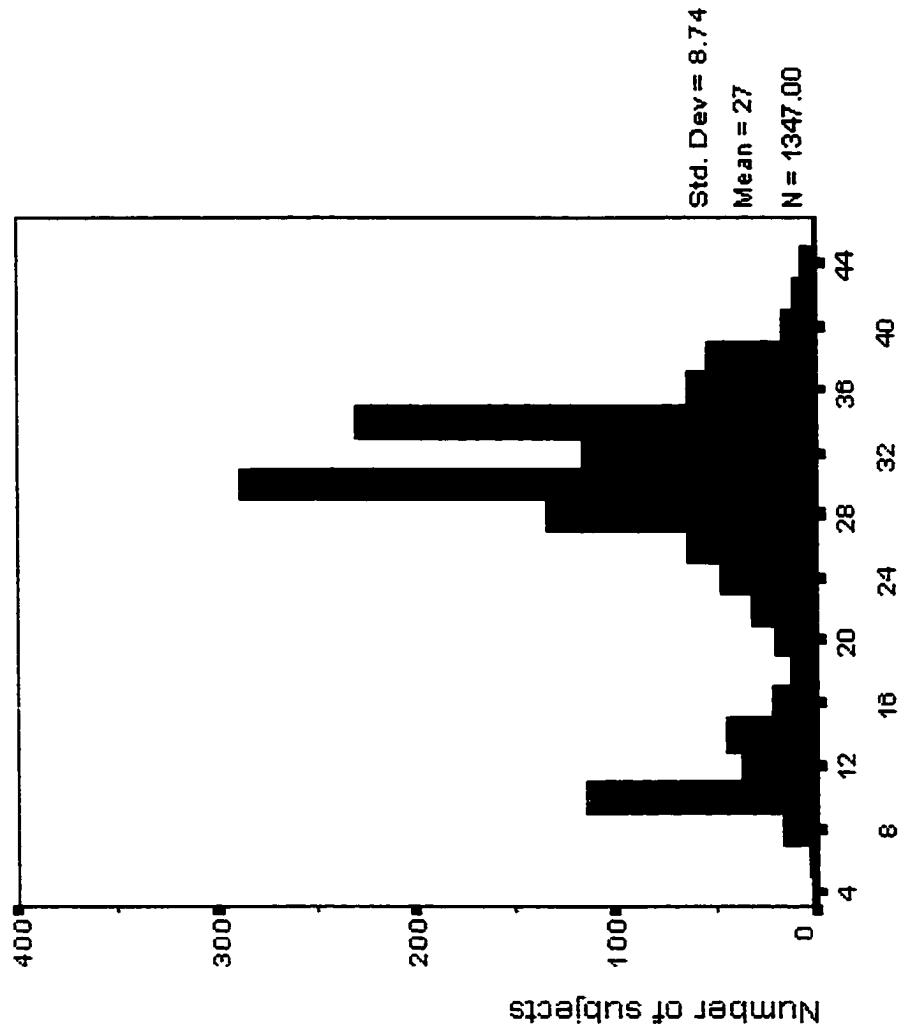

Figure 5.3a: $PM_{10-2.5}$ average mean concentration in $\mu g/m^3$, 1973-77. Males only.

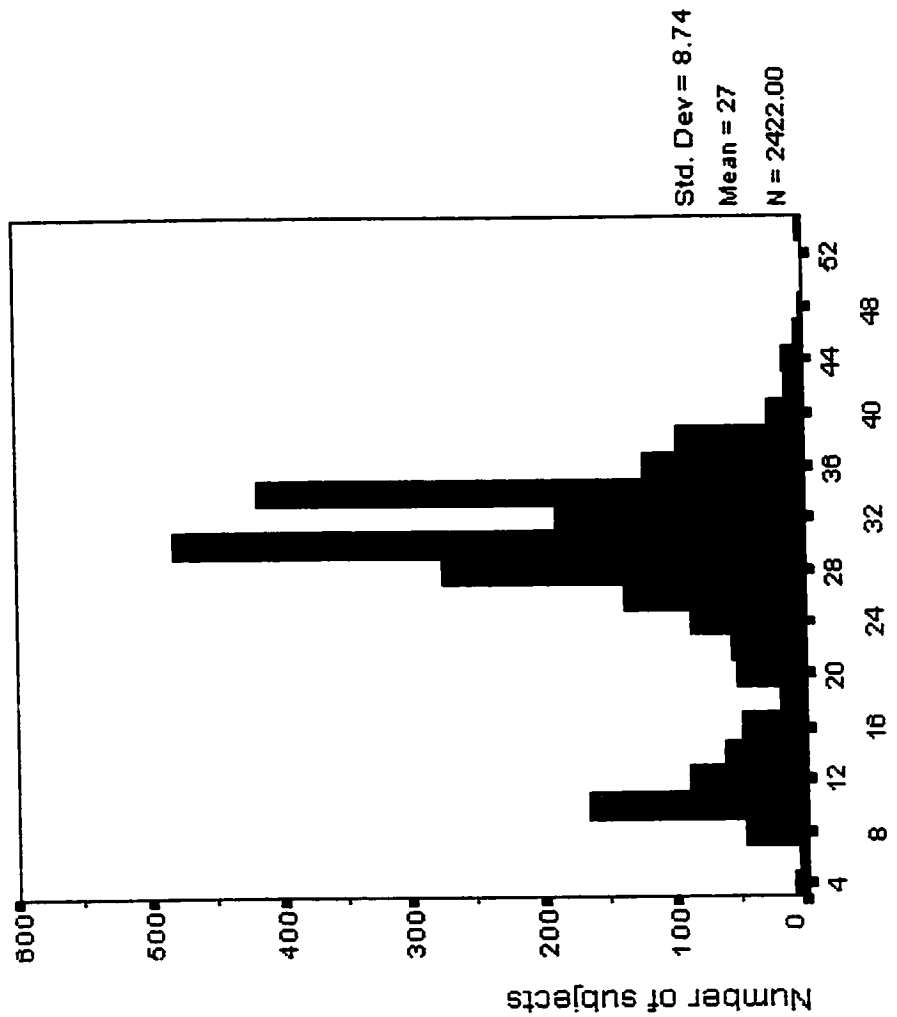

Figure 5.3b: $PM_{10-2.5}$ average mean concentration in $\mu g/m^3$, 1973-77. Females only.

CHAPTER 6

SUPPORTING TABLES TO PAPERS 'A' AND 'B'

The association between O_3, PM_{10}, SO_2 and NO_2 and incidence of lung cancer in males was described in **Table 4.4**. The comparable table for females is **Table 6.1**. The only air pollutant that was significantly associated with lung cancer incidence in females was average mean concentration of SO_2 although the RR for all metrics of PM_{10} were greater that 1.0, none reached statistical significance.

Because of the trimodal distribution of $PM_{2.5}$ (See **Figures 3B.1 & 3B.2**), the airport basins were divided into low ($\leq 22\ \mu g/m^3$), medium ($> 22\ \mu g/m^3$ & $\leq 40\ \mu g/m^3$), and high ($\geq 40\ \mu g/m^3$). The incidence rates for lung cancer incidence by geography are based on extremely low number of cases so are very unstable, but males living in high $PM_{2.5}$ areas (**Table 6.2**) had the highest lung cancer incidence rates while females who lived in the medium $PM_{2.5}$ areas (**Table 6.3**) had the highest rates.

The relationship between incident lung cancer and $PM_{2.5}$ was evaluated in two-pollutant models. Again, because of the small number of cases, the interpretation of multipollutant models should be made very cautiously, if at all. That being said, when $PM_{2.5}$ competed with $PM_{10-2.5}$, O_3, NO_2 or SO_2, the association with $PM_{2.5}$ in males (**Table 6.4**) was not appreciably altered. The same was approximately true for females (**Table 6.5**) with the observation that the association for $PM_{2.5}$ became positive

(RR=1.20; CI: 0.20 - 7.14) when ozone was added to the model indicating that there may be a synergistic effect between the two air pollutants.

Table 6.6 lists the effects on the RR of the model that evaluates the association between ozone and risk of incident lung cancer by the addition, one at a time, of potential confounders. This table was used to develop the lung cancer model for paper 'A'. The primary criteria for selection of covariates was that the inclusion of the variable changed the RR by more than 10%. None of the variables did so. A second, less important criteria, was that inclusion of the variable significantly changed the log likelihood ratio test. Only current use of alcohol at baseline for males satisfied this secondary criteria so was kept in the final model. For comparability between genders, the same final model was used for both males and females.

Tables 6.7 and **6.8** evaluate effects of different lag times for the relationship between $PM_{2.5}$ and lung cancer incidence. At enrollment into the AHSMOG study in 1977, we asked the respondents to tabulate their residence and work location histories back to 1966. We had estimated $PM_{2.5}$ back to 1966 using site- and season-specific regression equations. In males, a lag of 5 years produced the largest risk (RR=5.10; CI: 1.77-14.72) for a $10\mu g/m^3$ increase in mean concentration of $PM_{2.5}$ (**Table 6.7**). The largest risk in females was observed for a lag of 7 years (RR=1.02; CI: 0.57 - 1.84) (**Table 6.8**).

The association between $PM_{2.5}$ and incident lung cancer was investigated in selected subgroups within the airport cohort. Restricting the analysis to individuals who

had never smoked and excluding packyears of past cigarette smoking as a covariate, the RR for $PM_{2.5}$ did not appreciably change (**Table 6.9**). When males who worked in occupations with airborne contaminants were removed, the RR increased.

The final model chosen to evaluate the risk of incident lung cancer associated with an IQR increase in $PM_{2.5}$ included: packyears of past cigarette smoking, highest level of education attained, and a dummy variable for alcohol consumption at baseline while controlling for age as the time variable. The effect on the RR of modeling these covariates in different combinations is demonstrated in **Table 6.10**. The association of lung cancer with $PM_{2.5}$ was not appreciably altered for females; for males, the RR increased from 2.30 for the model that used $PM_{2.5}$ alone to 3.28 for the model with $PM_{2.5}$, education, and past smoking.

There was a discrepancy in the proportion of incident lung cancers lacking histological conformation between males and females (see **Table 5.3**). Five (36%) of the female lung cancers were coded by the nosologist as carcinoma – not otherwise specified (NOS) (ICDO = 8010), and only one (9%) male lung cancer was so coded. The medical record did not identify that a biopsy tissue was obtained. Instead, diagnosis of lung cancer was made by x-ray alone, or sputum samples. Because the lungs are frequent metastatic sites for cancer development from other unknown primary sites which may weaken the air pollution/lung cancer association, the final models were rerun excluding these 6 cases. The association with $PM_{2.5}$ became stronger in both genders (**Table 6.11**). This suggests that in future analyses relating to air pollution, the understanding of the

association between particulate air pollution and lung cancer would be strengthened when analyses were restricted to histologically confirmed cases indicating that the lungs were the primary site of origin of the cancer.

Table 6.1: Relative Risks[a] of Incident Lung Cancer Associated With Interquartile Range Increases of Selected Air Pollutants in the Total AHSMOG Cohort. Females Only. (n = 4060[b], cases = 20).

Part 1 of 2

Variable	Regression coefficient (β)	SE (β)	Increment (interquartile range)	Relative risk (RR)	95% C.I [d] for RR
Ozone, hrs in excess of [c]:					
60 ppb	-0.000565	0.0004221	935 hr/yr.	0.59	0.27 - 1.28
80 ppb	-0.000313	0.0005657	756 hr/yr.	0.79	0.34 - 1.83
100 ppb	-0.000114	0.0007655	556 hr/yr.	0.94	0.41 - 2.16
120 ppb	0.000120	0.001100	367 hr/yr.	1.05	0.47 - 2.31
150 ppb	0.000751	0.002030	185 hr/yr.	1.15	0.55 - 2.40
Ozone, 8-hr average [e]	-0.201829	0.122910	2.8 hrs.	0.57	0.29 - 1.12
Ozone, mean concentration [e]	-0.042658	0.022282	12 ppb	0.60	0.36 - 1.01

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.
b Because of missing data from monitoring stations, the n varies for each air pollutant (O_3: n=3702; PM_{10}: n=3737; SO_2: n=2743; NO_2: n=3546)
c Average annual hours in excess of listed ppb, 1973 - 3 years prior to risk set (i.e. 3-year lag).
d CI=confidence interval, RR=relative risk.
e All mean concentrations and O_3 8-hr average were averaged from 1973 - 3 years prior to risk set (i.e. 3-year lag).
* $p < 0.05$

Table 6.1. Relative Risks[a] of Incident Lung Cancer Associated With Interquartile Range Increases of Selected Air Pollutants in the Total AHSMOG Cohort. Females Only. (n = 4060[b], cases = 20).
Part 2 of 2

Variable	Regression coefficient (β)	SE (β)	Increment (interquartile range)	Relative risk (RR)	95% CI [f] for RR
PM_{10}, hrs in excess of [d]:					
40 μg/m³	0.0005572	0.0026184	139 days/yr	1.08	0.53 - 2.21
50 μg/m³	0.0012892	0.0026976	149 days/yr	1.21	0.55 - 2.66
60 μg/m³	0.0016654	0.0030096	132 days/yr	1.25	0.57 - 2.71
80 μg/m³	0.0013091	0.0041352	78 days/yr	1.11	0.59 - 2.08
100 μg/m³	0.0011841	0.0067320	43 days/yr	1.05	0.60 - 1.86
PM_{10}, mean concentration [c]	0.003457	0.012920	24.3 μg/m³	1.09	0.59 - 2.00
SO_2, mean concentration [e]	0.205832	0.062288	3.7 ppb	**2.14** *	1.36 - 3.37
NO_2, mean concentration [e]	0.227605	0.177950	1.98 ppb	1.57	0.79 - 3.13

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.
b Because of missing data from monitoring stations, the n varies for each air pollutant (O_3: n=3702; PM_{10}: n=3737; SO_2: n=2743; NO_2: n=3546)
c Average annual hours in excess of listed ppb, 1973 - 3 years prior to risk set (i.e. 3-year lag).
d Average annual hours in excess of listed μg/m³, 1973 - 3 years prior to risk set (i.e. 3-year lag).
e All mean concentrations and O_3 8-hr average were averaged from 1973 - 3 years prior to risk set (i.e. 3-year lag).
f CI=confidence interval, RR=relative risk
* $p < 0.05$

Table 6.2: Lung Cancer Incidence Rates in the Airport Cohort. Males Only.

$PM_{2.5}$ (1973-1977) mean concentration	Past smokers incidence rate / 10^6 PM[a] (cases / person months)		Never smokers incidence rate / 10^6 PM[a] (cases / person months)		Combined incidence rate / 10^6 PM[a] (cases / person months)	
$PM_{2.5}$ = low (≤22 μg/m³)	----	(0 / 18,421)	72.53	(2 / 27,573)	43.48	(2 / 45,994)
$PM_{2.5}$ = med (> 22 & ≤40 μg/m³)	98.23	(2 / 20,355)	----	(0 / 30,052)	39.68	(2 / 50,407)
$PM_{2.5}$ = hi (≥40 μg/m³)	66.94	(1 / 14,939)	114.43	(6 / 52,432)	103.90	(7 / 67,371)

a PM = person months calculated from 4/1/73 to: date of diagnosis if lung cancer case or earliest of: (date of death, 4/1/92 if living, or date of lost-to-followup)

Table 6.3: Lung Cancer Incidence Rates in the Airport Cohort. Females Only.

$PM_{2.5}$ (1973-1977) mean concentration	Past smokers incidence rate / 10^6 PM[a] (cases / person months)		Never smokers incidence rate / 10^6 PM[a] (cases / person months)		Combined incidence rate / 10^6 PM[a] (cases / person months)	
$PM_{2.5}$ = low (≤22 μg/m^3)	----	(0 / 12,948)	38.89	(3 / 77,133)	33.30	(3 / 90,081)
$PM_{2.5}$ = med (> 22 & ≤40 μg/m^3)	269.91	(5 / 18,525)	34.74	(3 / 86,355)	76.28	(8 / 104,880)
$PM_{2.5}$ = hi (≥40 μg/m^3)	----	(0 / 8,667)	29.79	(3 / 100,716)	24.43	(3 / 109,383)

a PM = person months calculated from 4/1/73 to: date of diagnosis if lung cancer case or earliest of: (date of death, 4/1/92 if living, or date of lost-to-followup)

Table 6.4: One and Two Pollutant Models[a] for Lung Cancer Incidence (1977-1992) in the Airport Cohort. Air Pollutants Averaged Over 1973-1977. Males Only.

	One pollutant model			Two pollutant model		
Pollutant	Coefficient (β)	SE (β)	RR[b] (95% CI)	Coefficient (β)	SE (β)	RR[b] (95% CI)
$PM_{2.5}$ [c]	0.04738	0.03147	3.16 (0.71 - 14.16)	0.04887	0.03441	3.28 (0.64 - 16.89)
$PM_{10\text{-}2.5}$	0.02145	0.03759	1.23 (0.60 - 2.52)	-0.00457	0.04263	0.96 (0.43 - 2.15)
$PM_{2.5}$ [c]	0.04743	0.03147	3.17 (0.71 - 14.17)	0.06164	0.04198	4.47 (0.61 - 33.03)
Ozone	0.03137	0.05043	1.47 (0.44 - 4.97)	-0.03515	0.06567	0.65 (0.13 - 3.17)
$PM_{2.5}$ [c]	0.04743	0.03147	3.17 (0.71 - 14.17)	0.04565	0.03148	3.03 (0.68 - 13.58)
NO_2	-0.01170	0.02815	0.98 (0.34 - 2.83)	-0.00778	0.03048	0.86 (0.27 - 2.72)
$PM_{2.5}$ [c]	0.10783	0.05429	Unstable[d]	0.40542	0.19989	Unstable[d]
SO_2	0.06001	0.07097	1.51 (0.58 - 3.90)	0.56061	0.29544	Unstable[d]

CI = Confidence Interval

a Adjusted for: packyears of cigarette smoking, years of education and alcohol use.

b RR=Relative Risk = exp (IQR * β), where IQR = Interquartile Range: 24.3 for $PM_{2.5}$; 12.32 for O_3; 19.29 for NO_2; 6.84 for SO_2, 9.7 for $PM_{10\text{-}2.5}$.

c The coefficients for $PM_{2.5}$ differ slightly in the single pollutant models as the 2nd air pollutant's 80% good data flag was also included in the selection criteria for both single and two-pollutant models.

d The RRs were classified as "unstable" if exp(IQR * β) > 10.

Table 6.5: One and Two Pollutant Models[a] for Lung Cancer Incidence (1977-1992) in the Airport Cohort. Air Pollutants Averaged Over 1973-1977. Females Only.

	One pollutant model			Two pollutant model		
Pollutant	Coefficient (β)	SE (β)	RR[b] (95% CI)	Coefficient (β)	SE (β)	RR[b] (95% CI)
$PM_{2.5}$[c]	-0.01891	0.02785	0.63 (0.17 - 2.38)	-0.00968	0.03206	0.79 (0.17 - 3.64)
$PM_{10-2.5}$	-0.02679	0.03029	0.77 (0.43 - 1.37)	-0.02126	0.03506	0.81 (0.42 - 1.59)
$PM_{2.5}$[c]	-0.01895	0.02785	0.63 (0.17 - 2.38)	0.00738	0.03752	1.20 (0.20 - 7.14)
Ozone	-0.05887	0.044013	0.48 (0.17 - 1.40)	-0.06579	0.05630	0.45 (0.11 - 1.73)
$PM_{2.5}$[c]	-0.01895	0.02785	0.63 (0.17 - 2.38)	-0.02237	0.03437	0.58 (0.11 - 2.98)
NO_2	0.04235	0.02097	**2.26** (1.02 - 5.00)	0.04182	0.02081	**2.24** (1.02 - 4.92)
$PM_{2.5}$[c]	-0.01221	0.03068	0.74 (0.17 - 3.20)	-0.02149	0.03556	0.59 (0.11 - 3.23)
SO_2	0.04810	0.05263	1.39 (0.69 - 2.81)	0.05321	0.05115	1.44 (0.73 - 2.86)

CI = Confidence Interval

a Adjusted for: packyears of cigarette smoking, years of education, alcohol use.

b RR=Relative Risk = exp (IQR * β), where IQR = Interquartile Range: 24.3 for $PM_{2.5}$; 12.32 for O_3; 19.29 for NO_2; 6.84 for SO_2, 9.7 for $PM_{10-2.5}$.

c The coefficients for $PM_{2.5}$ differ slightly in the single pollutant models as the 2nd air pollutant's 80% good data flag was also included in the selection criteria for both single and two-pollutant models.

Table 6.6: Effect on Relative Risk of Incident Lung Cancer Associated With Annual Average Hours in Excess of 100 ppb of Ozone by Adding Selected Potential Confounders to Reduced Model. Part 1 of 2

Model	Females			Males		
	Relative risk[a] (RR)	ΔRR[b]	LLRT p-value[c]	Relative risk[a] (RR)	ΔRR[b]	LLRT p-value[c]
Reduced model[d]	0.94	N/A	N/A	3.61	N/A	N/A
+Occupation air pollution	not done	N/A	N/A	3.63	+0.02	0.65
+Years lived with smoker	0.92	-0.02	0.77	3.71	+0.10	0.69
+Years worked with smoker	0.91	-0.03	0.09	3.73	+0.12	0.63
+Hours outdoors in summer	0.93	-0.01	0.31	3.66	+0.05	0.07
+Hours vigorous exercise outdoors in summer	0.94	0.00	0.29	3.64	+0.03	0.17

N/A Not Applicable

a RR based on an interquartile increase of 556 ppb, with a time-lag of 3-years for yearly averaging

b ΔRR = change in relative risk of the main effect (O_3) when potential confounder is added to the reduced model

c LLRT = p-value associated with the log likelihood ratio test evaluating the change from the reduced model to the model that has the additional variable

d Cox Proportional Hazards Regression Reduced model: Main effect (annual average hrs in excess of 100ppb ozone); Covariates (packyears of past cigarette smoking, education); Time variable (attained age)

Table 6.6: Effect on Relative Risk of Incident Lung Cancer Associated With Annual Average Hours in Excess of 100 ppb of Ozone by Adding Selected Potential Confounders to Reduced Model. Part 2 of 2.

Model	Females			Males		
	Relative risk[a] (RR)	ΔRR[b]	LLRT p-value[c]	Relative risk[a] (RR)	ΔRR[b]	LLRT p-value[c]
Reduced model[d]	0.94	N/A	N/A	3.61	N/A	N/A
+Hx of asthma	0.95	+0.01	0.71	3.61	0.00	0.21
+Family hx of cancer	0.94	0.00	0.30	3.61	0.00	0.86
+No. of homes near residence	0.94	0.00	0.14	3.58	-0.03	0.81
+Alcohol	0.94	0.00	0.82	3.56	-0.05	**0.03**
+Total exercise	0.94	0.00	0.37	3.56	-0.05	0.51
+Body mass index	0.87	-0.07	0.16	3.71	+0.10	0.97
+Fruit index	0.93	-0.01	0.52	3.72	+0.11	0.32

N/A Not Applicable

a RR based on an interquartile increase of 556 ppb, with a time-lag of 3-years for yearly averaging

b ΔRR = change in relative risk of the main effect (O_3) when potential confounder is added to the reduced model

c LLRT = p-value associated with the log likelihood ratio test evaluating the change from the reduced model to the model that has the additional variable

d Cox Proportional Hazards Regression Reduced model: Main effect (annual average hrs in excess of 100ppb ozone); Covariates (packyears of past cigarette smoking, education); Time variable (attained age)

Table 6.7: Adjusted[a] Relative Risks[b] of Incident Lung Cancer (1977-1992) Associated With Long-Term Ambient $PM_{2.5}$ Averaged From 1966 to Date of Diagnosis or Censoring at Different Lag Times. Males Only. (n=1189, Cases=11).

Lag time[c] (years)	Coefficient (β)	SE (β)	RR	95% CI
0	0.149641	0.05446	4.47 *	1.54 - 12.99
1	0.119776	0.04895	3.31 *	1.27 - 8.65
2	0.083660	0.03907	2.31 *	1.07 - 4.97
3	0.100569	0.04367	2.73 *	1.16 - 6.43
4	0.150128	0.05400	4.49 *	1.56 - 12.93
5	0.163004	0.05403	5.10 *	1.77 - 14.72
6	0.157059	0.04510	4.81 *	1.99 - 11.64
7	0.160982	0.04114	5.00 *	2.23 - 11.20
8	0.162471	0.04405	5.08 *	2.14 - 12.04
9	0.129744	0.04062	3.66 *	1.65 - 8.11

Abbreviations: RR=relative risk, CI=95% confidence interval.

a Models were adjusted for pack-years of past cigarette smoking, years of education and alcohol consumption with the time variable being attained age.

b Relative risks based on time-dependent Cox proportional hazards regression where the stopping time (lag) for cumulations was from 0 to 9 years prior to date of diagnosis or date of censoring and calculated as exp(k * β) where k =10.0 $\mu g/m^3$.

c The lag times were the number of years just prior to date of diagnosis or censoring that were excluded from the cumulated monthly $PM_{2.5}$ values when computing long-term averages.

* P-value < 0.05

Table 6.8: Adjusted[a] Relative Risks[b] of Incident Lung Cancer (1977-1992) Associated With Long-term Ambient $PM_{2.5}$ Averaged From 1966 to Date of Diagnosis or Censoring at Different Lag Times. Females Only. (n=2099, Cases=13).

Lag time[c] (years)	Coefficient (β)	SE (β)	RR	95% CI
0	-0.007287	0.03314	0.93	0.49 - 1.78
1	-0.007831	0.03012	0.93	0.51 - 1.67
2	-0.010876	0.02775	0.90	0.52 - 1.55
3	-0.009708	0.02846	0.91	0.52 - 1.59
4	-0.010299	0.03074	0.91	0.49 - 1.65
5	-0.011560	0.03064	0.89	0.49 - 1.62
6	-0.004561	0.03030	0.96	0.53 - 1.73
7	0.002000	0.03005	1.02	0.57 - 1.84
8	-0.002836	0.02834	0.97	0.56 - 1.69
9	-0.006223	0.02729	0.94	0.55 - 1.60

Abbreviations: RR=relative risk, CI=95% confidence interval.

a Models were adjusted for pack-years of past cigarette smoking, years of education and alcohol consumption with the time variable being attained age.

b Relative risks based on time-dependent Cox proportional hazards regression where the stopping time (lag) for cumulations was from 0 to 9 years prior to date of diagnosis or date of censoring and calculated as exp(k * β) where k =10.0 $\mu g/m^3$.

c The lag times were the number of years just prior to date of diagnosis or censoring that were excluded from the cumulated monthly $PM_{2.5}$ values when computing long-term averages.

* P-value < 0.05

Table 6.9: Sensitivity Analyses for Risk of Lung Cancer Associated With Average (1973-1977) Mean Concentration of $PM_{2.5}$ Among Airport Cohort Subgroups.

Gender & selection criteria	cases/n [a]	$PM_{2.5}$ coefficient (β)	% change in β	$PM_{2.5}$ RR[b]	95% CI
Females					
Airport cohort	13 / 2382	-0.01891	----------	0.63	0.17 - 2.38
Never smokers	8 / 2021	-0.02967	57 %	0.38	0.08 - 1.88
No occupation air pollution	13 / 2359	-0.01919	1 %	0.63	0.17 - 2.36
Males					
Airport cohort	11 / 1331	0.04738	----------	3.16	0.71 - 14.16
Never smokers	8 / 862	0.04544	4 %	3.02	0.51 - 17.97
No occupation air pollution	8 / 1154	0.08411	78 %	7.72	0.98 - 61.03

a Cases include carcinoma - not otherwise specified (NOS)

b RR = relative risk = exp (IQR * β) were IQR = Interquartile range = 24.3 $\mu g/m^3$

Table 6.10: Sensitivity Analyses: Alternate Models of $PM_{2.5}$ (1973-1977) and Risk of Incident Lung Cancer — Part 1 of 2

$PM_{2.5}$ + covariates	Coefficient (β) for $PM_{2.5}$	Relative risk (RR)[a]	95% CI
Females			
$PM_{2.5}$ alone	-0.01836	0.64	0.19 - 2.14
$PM_{2.5}$ + SMPKY6[b]	-0.00927	0.80	0.23 - 2.80
$PM_{2.5}$ + EDUCZ6[b]	-0.01750	0.65	0.19 - 2.20
$PM_{2.5}$ + ALCOHOL	-0.02614	0.53	0.15 - 1.89
$PM_{2.5}$ + SMPKY6[b] + EDUCZ6[b]	-0.00903	0.80	0.23 - 2.82
$PM_{2.5}$ + SMPKY6[b] + ALCOHOL	-0.01942	0.62	0.17 - 2.34
$PM_{2.5}$ + EDUCZ6[b] + ALCOHOL	-0.02495	0.54	0.15 - 1.96
$PM_{2.5}$ + SMPKY6[b] + EDUCZ6[b] + ALCOHOL (final model)	-0.01891	0.63	0.17 - 2.38

a Relative Risk is defined as: exp (IQR * β) where IQR = interquartile Range = 24.3 $\mu g/m^3$

b SMPKY6=smoke-pack years; EDUCZ6=education level

Table 6.10: Sensitivity Analyses: Alternate Models of $PM_{2.5}$ (1973-1977) and Risk of Incident Lung Cancer Part 2 of 2

$PM_{2.5}$ + covariates	Coefficient (β) for $PM_{2.5}$	Relative risk (RR)[a]	95% CI
Males			
$PM_{2.5}$ alone	0.03418	2.30	0.55 - 9.62
$PM_{2.5}$ + SMPKY6[b]	0.04034	2.67	0.59 - 11.99
$PM_{2.5}$ + EDUCZ6[b]	0.04706	3.14	0.72 - 13.68
$PM_{2.5}$ + ALCOHOL	0.03552	2.37	0.56 - 10.01
$PM_{2.5}$ +SMPKY6[b] + EDUCZ6[b]	0.04885	3.28	0.72 - 14.84
$PM_{2.5}$ + SMPKY6[b] + ALCOHOL	0.04064	2.69	0.60 - 12.04
$PM_{2.5}$ + EDUCZ6[b] + ALCOHOL	0.04638	3.09	0.72 - 13.32
$PM_{2.5}$ + SMPKY6[b] + EDUCZ6[b] + ALCOHOL (final model)	0.04738	3.16	0.71 - 14.16

a Relative Risk is defined as: exp (IQR * β) where IQR = interquartile Range = 24.3 $\mu g/m^3$

b SMPKY6=smoke-pack years; EDUCZ6=education level

Table 6.11: Adjusted[a] Relative Risks of Incident Lung Cancer[b] (1977-1992) Associated With a 10 $\mu g/m^3$ Increase of Mean Concentrations of Particle Air Pollutants of Varying Aerodynamic Diameters When Lung Cancers (NOS)[c] Were Excluded. [cf. Table 5.4].

Variable	cases/n	Regression coef. (β)	SE (β)	Relative risk (RR)	95% CI for RR
Males					
$PM_{2.5}$	10/1215	0.107945	0.04624	**2.94** *	1.19 - 7.29
PM_{10}	10/1215	0.070245	0.03159	**2.02** *	1.09 - 3.75
$PM_{10-2.5}$	10/1215	0.076350	0.04988	2.15	0.81 - 5.70
Females					
$PM_{2.5}$	9/2139	0.021015	0.03550	1.23	0.62 - 2.47
PM_{10}	9/2139	0.002562	0.02253	1.03	0.66 - 1.60
$PM_{10-2.5}$	9/2139	-0.020896	0.04195	0.81	0.36 - 1.85

a Relative Risks [exp(10 $\mu g/m^3$ x β)] were computed using the Cox proportional hazards regression with attained age as the time variable and controlling for baseline pack-years of past cigarette smoking, years of education and current alcohol consumption [any/none]. Same covariates for males and females. Mean concentrations averaged from 1973 to 3 years before risk set (i.e. 3-year lag) in the airport cohort.

b For lung cancer analyses, incident cancers of the bronchus and lung are combined.

c Cases labeled as "Carcinoma Not Otherwise Specified" (morphology ICDO code=8010) are excluded (F=5, M=1).

* $p < 0.05$

CHAPTER 7

LONG-TERM CONCENTRATIONS OF AMBIENT AIR POLLUTANTS AND *NON-SKIN CANCER* (NSC) RISK

A. Introduction

It has been estimated that there will be approximately 1,268,000 new cases of invasive cancer (malignant neoplasms) diagnosed in the United States in 2001 (*1*). This estimate does not include carcinoma in situ of any site except urinary bladder, nor does it include basal and squamous cell cancers of the skin. The number of new cancer cases for all sites is slightly higher in males (50.7%) than females (49.3%). The two leading organ sites in males are prostate (31%) and lung/bronchus (14%). The corresponding top two sites in females are breast (31%) and lung/bronchus (13%) (*1*).

One of the first authoritative lists of cancer-causing agents was prepared by a World Health Organization Expert Committee (*2*) and included tobacco smoking and atmospheric pollution. Tobacco use in the United States has been estimated to contribute directly to 21.5% of female cancer deaths and 45% of male cancer deaths (*3*).

Not all respiratory cancers can be attributed to exposure to tobacco smoke. There is growing evidence that specific chemicals and respirable particles suspended in the ambient air ("air pollution") can contribute to human carcinogenesis. Early studies failed to link air pollution to human malignancies, especially lung cancer (*4,5*). However, with improved exposure assessment and better control of the confounding effects of known risk factors (e.g. smoking, occupational exposure to industrial carcinogens, etc),

significant relationships began to emerge (*6*). The relationship between air pollution and respiratory cancer is weak compared to that of smoking and can easily be completely overshadowed by the inadequate control of confounding in the analysis. But even a small relative risk can be translated into hundreds of new cases of cancer when applied to the whole population assuming a cause-effect relationship.

Ambient air is a complex mixture containing a variety of substances, some of which are known to be carcinogenic (*7*). Currently there are over 4 million organic and inorganic chemicals in the American Chemical Society registry and the number of these chemicals increases at a rate of 6,000 per week (*8*). Acute and chronic toxicity data are available for only a minority of these chemicals. It is not unreasonable to assume that other chemicals among the thousands to which we are exposed will eventually be identified as carcinogenic to humans, besides those for which a positive association with the occurrence of cancer in humans has already been established (*8*). The U.S. Environmental Protection Agency (*9*) has published a report estimating cancer risks from outdoor exposure to airborne toxic pollutants in the United States.

There have been many epidemiologic studies in recent years that have evaluated the association between selected air pollutants and all-cause mortality (*10-20*). However, the potential relationship between cancer *incidence* and long-term ambient air pollution has been inadequately studied. The Adventist Health and Smog (AHSMOG) study is a cohort study designed to relate long-term cumulated ambient air pollutants and selected health outcomes including newly diagnosed cancers. This research seeks to gain further insight into the possible roles that long-term ambient concentrations of PM_{10}, $PM_{2.5}$, O_3,

SO_2, and NO_2 have on the incidence of all nonskin cancers in general and smoking-related cancers, lung, breast, and lymph node cancers in specific in a nonsmoking California Seventh-day Adventist population.

B. Significance

Early epidemiologic studies of the relationship between ambient airborne particulate matter (e.g. PM_{10}, $PM_{2.5}$, SO_4) and gaseous pollutants (e.g. O_3, SO_2, NO_2) and cancer in humans have been investigations that utilized the **hypothesis generating** format of cross-sectional and correlational designs (*21*). These have generally focused on acute episodes of high "smog" levels and rise in morbidity and/or mortality over relatively short periods of time (hours, days) (*22-24*). Non-malignant endpoints for many of these studies include chronic cough (*25*), bronchitis (*26*), chronic obstructive pulmonary diseases (COPD) (*27-30*), asthma attacks (*30,31*) and other chest illnesses including opportunistic infections (*32,33*). Very little is know about the effect of long-term (10-15 years) cumulative exposure to ambient airborne particulates on total cancer and especially lung cancer because very few well designed **hypothesis testing** studies have been conducted to date. The AHSMOG study was designed to be one of these long-term hypothesis testing cohort studies.

Much of the research on the adverse health effects of air pollution have been directed at the "at-risk" populations: a) preadolescent children (aged ≤ 13 years); b) elderly (aged ≥65 years); c) persons (aged ≤ 18 years) with asthma; d) persons (aged > 18

years) with asthma; and e) persons with chronic obstructive pulmonary disease (*34*). Very little is known on the effect of air pollution in the general population exposed.

Particulate matter in ambient air is known to contain substances that exhibit carcinogenic activity in experimental systems (*35*). The polycyclic aromatic hydrocarbons have received the most attention; several are known to be carcinogens in both animals and humans (*36*). A direct relationship between increasing exposure to respirable particulates which are coated with these noxious compounds and increasing cancer incidence and mortality rates would therefore be expected (*37,38*). Invasive cancers can be divided into two subclasses: 1) respiratory cancers (mouth, nose, pharynx, trachea, bronchus, lung); and 2) non-respiratory (all others). There is evidence that air pollution can stimulate non-respiratory cancers as well as the traditional respiratory cancers. For example, two known ways to induce breast cancer in animals are: a) radiation to the chest; and b) the introduction of aromatic hydrocarbons in ambient air (*39,40*). Other non-respiratory organs that have been associated with airborne contaminants include: urinary bladder (*41,42*), pancreas (*43,44*), cervix uteri (*45,46*), renal pelvis (*47-49*) and leukemia (*50,51*), colon (52), and stomach (53).

Although the majority of studies attempting to evaluate the air pollution-cancer relationship have focused on lung cancer (*54*), several studies have investigated the relationships with all cancers combined and nonrespiratory cancers. For example, Winkelstein and Kantor found that both stomach and prostate cancer mortality rates were higher in the area of Buffalo, New York, with higher total suspended particulates (TSP) pollution than in the less polluted areas (*55,56*). Other investigators noted significantly

higher mortality rates for cancers of the stomach, esophagus, and bladder in more highly polluted areas of Nashville, Tennessee, than in less polluted areas (*57*)

In a recent report by the American Cancer Society (ACS), Chao et al. (*58*) concluded that inhalation of toxic airborne chemicals in cigarette smoke may be responsible for a significant percentage (perhaps as high as 12%) of colorectal cancer. The ACS II study consisted of 781,351 adults, in whom 4,432 newly diagnosed colorectal cancers occurred between 1982 and 1996 among individuals who were cancer free at baseline. The study found that currently smoking females were more than 40% (RR= 1.41; CI: 1.26-1.58) more likely to develop colorectal cancer during follow-up compared to nonsmokers; and male smokers had more than a 30% (RR=1.32; CI: 1.16-1.49) increased risk of developing colorectal cancer compared with men who never had smoked. The associations in past smokers were less but statistically significant in both genders. These associations were not confounded by: age, race, body mass index, education, family history of colorectal cancer, exercise, aspirin and multivitamin use, alcohol consumption, and intake of vegetables, high-fiber grain foods, and fatty meats. Models among women also controlled for estrogen replacement therapy. The implication from this large cohort study is that colorectal cancer should be reconsidered for classification as a smoking-related cancer. Colorectal cancer contributes more than 20% (144/704) of the total nonskin cancers identified in the AHSMOG cohort.

One of the best studies to evaluate the relationship of air pollution and human disease is the AHSMOG Study conducted at Loma Linda University Center for Health Research. Noncancer respiratory diseases (e.g. chronic obstructive pulmonary disease,

asthma, bronchitis, emphysema, etc) were found to be associated with certain high pollution levels in this study (*59-66*).

The relationship between air pollution (specifically TSP and ozone) and all invasive cancer was also evaluated by the AHSMOG researchers (*37*). No significant association was found between ozone and sex-specific cancers (all sites combined). A significant association was observed, however, between average annual hours in excess of 200 $\mu g/m^3$ TSP (TSP-200) and all malignant neoplasms in females (RR=1.37; CI: 1.07-1.65) but not for males (RR=0.96; CI: 0.68-1,36). When analyses were restricted to respiratory cancers, both genders combined, elevated, but not statistically significant, associations were found for TSP-200 (RR=1.72; CI: 0.81-3.65) and for average annual hours in excess of 100 ppb O_3 [O_3(100)] (RR=2.25; CI: 0.96-5.31) which was of borderline statistical significance. However, these analyses were limited by low power as they were based on only 17 incident cases of respiratory cancer. Also, the simultaneous evaluation of multi-pollutants and cancer risk were not conducted.

In a later report from the AHSMOG study, Abbey and colleagues (*67*) investigated two additional air pollutants beside those described above. These included: average days/yr that PM_{10} exceeded 100 $\mu g/m^3$ [PM_{10}(100)] and mean concentration of $PM_{2.5}$. For females for all malignant neoplasms, a 15% increased risk associated with an IQR increase of PM_{10}(100) was found (RR=1.15; CI: 0.97-1.38). A 2-fold statistically significant increased risk associated with an IQR increase in mean concentration of $PM_{2.5}$ (RR=2.01; CI: 1.05-3.86) was also observed.

The primary purpose of this research in further investigating the health effects of ambient levels of several air pollutants on all cancers combined in the AHSMOG study is to investigate in more detail the gender differences observed by others. A secondary purpose of my research in further investigating all cancers combined in the AHSMOG study, separately by gender, is to see if removal of skin cancers from the definition of all malignant neoplasms would remove or reduce the gender differences previously observed (*37,67,68*) as skin cancer was incompletely ascertained in the AHSMOG study. Therefore, skin cancers were excluded from the revised definition of "all" malignant neoplasms.

C. Methods

Newly diagnosed cancers in the AHSMOG study were ascertained between March, 1977 and March, 1992, through record linkage with regional and state cancer registries and manual review of medical records from self-reported hospitalizations.

The fixed time period (1973-1977) air pollution metric of average annual hours that ambient PM_{10} exceeded 100 $\mu g.m^3$ [$PM_{10}(100)$] was chosen for statistical model development in females as that was closely related to the metric of average annual hours that total suspended particulates (TSP) exceeded 200 $\mu g/m^3$ (TSP-200) used by Abbey (*37,67*) in model development in earlier reports. The same final model that was developed for females was also applied to males for comparison. Once the final model was developed, a time dependent Cox proportional hazards model incorporating a 3 year

lag was used to evaluate the air pollution/cancer relationships. This analytical metric was therefore a 2-year moving average from 1973 lagged 3 years prior to risk set.

The *a priori* variables for the reduced model were packyears of past cigarette smoking and education as a surrogate for socioeconomic level of the study subject. Additional covariates were investigated one at a time for potential confounding effects if their inclusion changed the RR in the reduced model by more than 10%. None of the variables listed in **Table 7.1** did so. A second, less important, variable selection criterion evaluated whether the inclusion of the other variables significantly affected the fit of the model as measured by the log likelihood ratio test. The following additional variables were included in the final model based on this secondary criterion: total exercise, parental history of cancer, personal history of doctor-told asthma, current use of alcohol, antioxidant vitamin (A, C, E) supplement use, and population density as estimated by the number of homes located within a 1/4 mile radius of the study subject's home at baseline. The proportional hazards assumption of the final model was evaluated by inclusion of [variable * log(time)] product terms for each variable in the model.

D. Results

The frequency distribution of the incident cancers identified in the AHSMOG study during the followup period (1977-1992) is presented in **Table 7.2**. Because basal cell carcinoma of the skin is not reported to the regional and state cancer registries and since malignant melanoma of the skin is strongly related to exposure to ultraviolet radiation for which we have no data, skin cancers were excluded from total cancers. I

thus have limited my analyses to "all nonskin cancer" (NSC). There were a total of 704 NSC identified during followup (females=424, males=280).

Compared to females without a diagnosis of cancer, female cancer cases tended to be older, have parents with a history of cancer, and were more likely to have worked with a smoker (**Table 7.3**). Of the females who were past smokers, the cases tended to have more pack years of cigarette smoking compared to the noncase females. Male cancer cases tended to be older and have more vigorous exercise outside during the summer compared to male noncases.

The associations based on a 3-year lag between NSC and selected long-term average ambient air pollutants for males are listed in **Table 7.4**. The strength of the association with NSC monotonically increased with increasing exceedance frequencies of ozone achieving statistical significance with average hours per year ambient air exceeded 150 ppb of O_3. NSC was also significantly associated with average hours per year PM_{10} exceeded 100 $\mu g/m^3$ (RR=1.17; CI: 1.01 - 1.36) and mean concentration of SO_2 (RR = 1.85; CI: 1.64 - 2.09).

Similar findings incorporating a 3 year lag were observed in females (**Table 7.5**). NSC was significantly associated with average annual hours that ozone exceeded 150 ppb (RR= 1.33; CI: 1.13 - 1.56); average annual hours that PM_{10} exceeded 100 $\mu g/m^3$ (RR=1.33; CI: 1.17 - 1.51), and with mean concentrations of PM_{10} (RR=1.31; CI: 1.13 - 1.52) and SO_2 (RR=2.28; CI: 2.07 - 2.52).

In two-pollutant models that included hours in excess of 150 ppb O_3 with 100 $\mu g/m^3$ PM_{10}, O_3 with mean concentration of SO_2, and PM_{10} with SO_2, SO_2 appeared to

have an independent association with NSC for both genders in comparison with either O_3 or PM_{10} (**Table 7.6**). When O_3 competed with either the highest exceedance frequency of PM_{10} or with mean concentration of SO_2, it had a much lower Wald statistic compared to the competing air pollutant.

For both females and males, the association based on the fixed time period 1973-77 between ambient fine particle ($PM_{2.5}$) concentrations and all incident NSC was minimal at best, but in both cases, it was slightly higher than for the coarse particles (i.e. $PM_{10-2.5}$) . The association between all NSC and $PM_{2.5}$ was 1.06 (CI: 0.81-1.39) in females (**Table 7.7**) and 1.03 (CI: 0.74-1.43) in males (**Table 7.8**).

With the exclusion of skin cancer, the RR for all nonskin cancers in females associated with mean concentration of PM_{10} for the first time period ('77-'82) was 1.44 (CI: 0.98 - 2.13). The regression coefficient for males remained negative (RR=0.91; CI: 0.59 - 1.43).

1. Sensitivity Analyses

The current results of no association of all NSC with $PM_{2.5}$ in females does not agree with a previous report (*67*) from the AHSMOG study where we observed an increased risk (RR=2.01; CI: 1.05-3.86) of all cancers (including skin cancer) associated with an IQR increase of 45 $\mu g/m^3$ of annual concentration of the baseline time period for $PM_{2.5}$ (1973-1977) among females who were followed up from 1977 through 1982 in the AHSMOG study. When the current study was restricted to the same follow-up time period ('77-'82) and only the females in the airport subcohort (n=2,413) were included,

there was an elevated risk of all cancers (including skin cancer) associated with an IQR increase of 24.3 $\mu g/m^3$ in average ('73-'77) mean concentration of $PM_{2.5}$ (RR=1.70; CI: 1.12 - 2.58). No association was observed for $PM_{2.5}$ (1973-1977) among females for the extended follow-up period ('83-'92), and the 95% confidence intervals (CI) about the total cancer RR estimates for the follow-up time period 1977-1982 did not overlap the 95% CI for the time period 1983-1992 for $PM_{2.5}$. It is possible that inclusion of skin cancer in the "all cancer" category in the original report (*67*) may have biased the results as skin cancer was incompletely ascertained during the follow-up period.

Among males in the airport subcohort (n=1,338), the association for all cancers (including skin cancer) was strongest during the second period of follow-up ('83-'92) where the RR for an IQR increase of 24.3 $\mu g/m^3$ for $PM_{2.5}$ = 1.20 (CI: 0.85-1.71) compared to the initial follow-up period ('77-'82) where no associations were observed (RR=0.95; CI: 0.58-1.56). In this report we observed a slight difference between males and females in the lag structure of their response to ambient air pollutants, particularly when the air pollution metric was mean concentration of $PM_{2.5}$ (see **Tables 6.7** and **6.8**).

A large portion of the malignant cancers diagnosed in females were breast cancers and other hormone-associated neoplasms. The female study population was therefore separated into pre- and post-menopausal status at baseline. A women was considered to be menopausal at baseline if: a) she reported that her menstrual periods had "completely stopped"; or b) if she responded to the question as to the reasons why her menstrual periods had stopped (e.g. surgical removal of uterus, "natural change of life"); or c) she gave an age at when her periods completely stopped; or d) she was age 55 or older at

baseline. Women who were post-menopausal at baseline (n=1833) had slightly higher relative risks for all NSC (RR=1.10; CI: 0.79-1.53) for an IQR increase of $PM_{2.5}$ (1973-1977) compared to the RR experienced in the pre-menopausal (n=522) cohort (RR=0.94; CI: 0.43-2.05) although the post-menopausal confidence interval totally overlaps with the pre-menopausal confidence interval which is wide because of the low number of women in that category. These associations were not confounded by age as cases and noncases of identical ages within menopausal status were being compared in separate risk sets of the Cox proportional hazards regression.

The follow-up was then divided up into two time periods: 1977-1982, which corresponds to the initial follow-up in an earlier publication (*67*) and 1983-1992 from the current study. For comparison, identical models as in the earlier report (*67*) were used in this analysis. The variables used as covariates in the Cox model for cancer included, therefore, only years of past cigarette smoking and educational attainment with attained age as the time variable. The associations observed in the two time periods were gender specific. For females, the modest associations observed for the total time period ('77-'92) described above were strongest in the first 6-year period (**Table 7.9**).

A second issue revolves around the inclusion of skin cancer in the "all cancer" endpoint previous published. Since non-melanoma skin cancer is not a reportable cancer for the California Cancer Registry, it is underascertained in the study population. The reduction in risk of all cancer sites combined from 2.01 in the original report (*67*) to the observed estimate of 1.48 is explained by the elimination of skin cancer from the "all cancer" category in the current analysis. For example, the relative risk of all NSC

diagnosed between 1977 and 1982 was 1.48 (CI: 0.96-2.29) for $PM_{2.5}$ and less for the coarse fraction (RR=1.14; CI: 0.90-1.49) although the confidence intervals highly overlap. The regression coefficients were negative for the respective particle sizes during the second time period. The reverse was true for males. The risk of males being diagnosed with NSC during the second follow-up period ('83-'92) was again somewhat greater for fine particles (RR=1.16, CI: 0.77-1.77) than for the coarse fraction (RR=1.03; CI: 0.81-1.30) with the latter confidence interval completely contained within the former interval. The regression coefficients were negative for the respective particle sizes during the initial follow-up period of '77-'82 (**Table 7.9**).

E. Discussion

That cancer might be related to ambient air pollution has been suggested by other investigators (*69-72*). For example, Soll-Johanning, et al. (*73*) found that individuals chronically exposed to high air pollution levels, such as bus drivers and tramway employees, are at increased risk of developing several types of cancer. The possibility that particulate air pollution might act as an independent agent in the development of nonrespiratory cancers in humans has been suggested by several investigators (*73-79*). In specific, Szczeklik and colleagues (*79*) have observed humoral immuno-suppression in men exposed to polycyclic aromatic hydrocarbons (PAHs) and related airborne carcinogens in the polluted environment. PM_{10} and specifically $PM_{2.5}$ provide a mechanism whereby these PAHs may be delivered to the lung and capillaries next to the alveolar spaces.

In a study of cancers of all sites among children and adolescents 0-19 years of age who lived near three large petroleum and petrochemical complexes, Pan et al. (*80*) found that almost all bone, brain, and bladder cancer deaths were within 3 km of the 3 complexes and that bone and brain cancers in particular occurred in girls in these petrochemical industrial districts more frequently than in boys. A similar sex difference for bone cancer incidence has been described in England and Wales (*81*) where the sex differences in bone cancer risk at puberty paralleled known sex differences in skeletal growth. In the United Kingdom, adolescent skeletal growth spurts occurs, on average, two years later for boys compared to girls (*81*). These differences in growth were consistent with the observed 2-year interval between the female and the male bone cancer peaks.

The 1977-1982 time period results in Table 7.9 are consistent with what was observed in earlier reports (*69*) for the same time period of follow-up in that the associations observed for females were > 1.0 and no associations were observed for males. In the current 15-year follow-up, the median age at cancer diagnosis was 71 for males and 69 for females ($p = 0.058$). Of the NSC diagnosed in the total time period of 1977-1992, more of the male NSC cases were diagnosed in the second time period (1983-1992) compared to the females (65% versus 61%, respectively). This suggests that males may have a different latency as regards to cancer development in response to ambient air pollutants.

We evaluated the proportional hazards assumption of the final model by inclusion of [variable * log(time)] product terms for each variable in the model. None of the p-

values for these product terms were significant indicating that the variables were not time dependent and that the proportional hazards assumption of the Cox regression was not violated.

1. Particulate Matter (PM_{10})

We evaluated the associations between PM_{10} and all NSC using two different metrics: mean concentration and exceedance frequencies. For PM_{10}, both the mean concentration and the exceedance frequency [$PM_{10}(100)$] were statistically significantly associated with NSC in both genders when using a 3-year lag structure.

In multipollutant analyses, the Wald statistic can be taken as a scale-free measure of the strength of association of the competing pollutants (*67*). The observation that PM_{10} (especially the $PM_{2.5}$ component of respiratory particulates) dominates when competing in two-pollutant models is consistent with its potential to transport carcinogens to the deeper lung where they can become systemic. In males, neither O_3 nor PM_{10} were found to be predictive of NSC in the two pollutant models. The independent effect of PM_{10} found in females is consistent with that reported by others (*82-85*).

2. Ozone (O_3)

Only the exceedance frequency for ozone [$O_3(150)$] was statistically significantly associated with NSC in both genders while the mean concentration and mean 8-hour average of ozone were not associated with NSC in either gender. One may speculate that long-term exposure to high exceedance frequency levels of O_3 is a better predictor of NSC than mean concentration estimates. Other hypotheses may also be relevant. More

studies are needed on mechanisms for how O_3 might increase risk of NSC. Mean concentration of ozone appears to be not the best metric for evaluating the health effects of long-term exposure to ozone. This observation is consistent with what was observed in the lung cancer analysis (see **Table 4.4**).

For females, the association with ozone disappears when entered into the model with PM_{10} whose effect remains unchanged. These analyses suggest that ozone is not directly related to all nonskin cancer risk and that it is more probably serving as a surrogate for PM_{10}.

3. Sulfur Dioxide (SO_2)

In these analyses, we used only mean concentration of SO_2 is that metric demonstrated the highest Wald statistic when compared to the exceedance frequency metrics. In females, mean concentration of SO_2 remained independently predictive of NSC when competing with either O_3 or PM_{10}. It is not clear whether SO_2 is operating via some unknown mechanism to enhance carcinogenesis or whether it is simply a marker for a more causal factor. In the AHSMOG study, mean concentration of SO_2 was not highly correlated with the other mean concentration of air pollutants investigated (r=0.29 for PM_{10}; 0.18 for $PM_{2.5}$; 0.31 for $PM_{10-2.5}$; -0.13 for O_3; and 0.86 for NO_2 - see **Table 5.2**). The latter correlation with NO_2 does not seem important as mean concentration of NO_2 was not associated with any of the cancer endpoints investigated for either gender. The observation that mean concentration of SO_2 is an independent risk factor for lung cancer

(both genders), NSC (both genders), SRC (females and marginal in males), breast cancer (females), and non-Hodgkin's lymphoma (males) requires further study.

Sulfur dioxide is a colorless, oxygen scavenging gas that is very toxic and extremely irritating to the respiratory tract causing lung injury. The primary sources of ambient sulfur dioxide include the burning of sulfur-containing fossil fuels (mainly coal and oil) in power plants, refineries, and diesel engines. It also is produced during metal smelting and other industrial processes such as in paper bleaching and it is used to reduce chlorine in potable water, treated sewage and industrial effluent. Sulfur dioxide is also used in food processing for fumigating, preserving, and bleaching. And SO_2 can be oxidized to sulfuric acid in the presence of nitrogen compounds (*86*).

It is possible that SO_2 can be transported from its source to other geographical areas by adsorbing to ambient particulate matter (e.g. PAHs and other PM_{10}). Thus the associations observed for SO_2 and cancer may not be direct, but serve as markers for co-pollutants. Few, if any, researchers attribute carcinogenesis directly to exposures of SO_2. However, some investigators have described SO_2 as a potential tumor promotor in that exposures to SO_2 can increase transepithelial permeability of carcinogenic particles (*87*). Sulfur dioxide also produces hydroxy radicals when exposed to water (*88*). Thus it is possible that exposure to SO_2 assists in the permeation of toxic particles such as those from diesel exhaust through the alveolar epithelial cell membrane and that the hydroxy radicals promote tumorigenesis (*89*).

4. Gender Differences Observed in Earlier Analyses

In previous analyses of the AHSMOG cohort, Mills and colleagues included skin cancer in the incidence of all malignant neoplasm endpoint and found no association between it and long-term cumulations of any of the ambient pollutants studied with regard to the male subjects. In this analysis with a longer follow-up and where skin cancers were excluded, the associations in both genders between NSC and the various air pollutants generally strengthened and became statistically significant for hours/year that O_3 exceeded 150 ppb, hours/year that PM_{10} exceeded 100 $\mu g/m^3$ [$PM_{10}(100)$] , mean concentration of PM_{10}, and mean concentration of SO_2. For females, the previous association [RR=1.15; CI: 0.97-1.38] (*40*) with $PM_{10}(100)$ (1977-1982) increased to RR=1.44 (CI: 0.98-2.13) (**Table 7.9**) when PM_{10} mean concentration was evaluated in the current analysis for the same time period (1977-1982). For all three particle sizes ($PM_{2.5}$, PM_{10}, and $PM_{10-2.5}$), the air pollution association discrepancies observed in earlier reports between males and females diminished when all malignant neoplasms was evaluated in the second time period of 1983-1992. Gender differences also diminished when skin cancers were excluded for the time period 1977-1982.

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Table 7.1: Relative Risk of Non-Skin Cancers and Evaluation of Potential Covariates by Gender in the Total AHSMOG Cohort. Part 1 of 2

Model PM_{10}(100) $\mu g/m^3$[a]	Males (n=2278, cases=280) RR[b] (95% CI)	Males Δ(-2 log L) p-value	Females (n=4060, cases=424) RR[b] (95% CI)	Females Δ(-2 log L) p-value
Main effects [ME] (packyears + educ.)	1.19 (1.02-1.38)	---	1.35 (1.19-1.52)	---
ME + BMI (3 dummies)	1.19 (1.03-1.38)	9.471 p=0.024	1.35 (1.19-1.52)	2.609 p=0.456
ME + exercise (1 dummy)	1.19 (1.03-1.39)	14.97 p=0.0001	1.36 (1.20-1.53)	46.20 p<0.0001
ME + family cancer hx (dummy)	1.16 (0.99-1.34)	217.3 p<0.0001	1.35 (1.19-1.53)	338.0 p<0.0001
ME + asthma history (dummy)	1.21 (1.04-1.41)	134.0 p<0.0001	1.32 (1.16-1.49)	171.2 p<0.0001
ME + occupational air pollution	1.19 (1.02-1.38)	1.145 p=0.285	1.35 (1.19-1.52)	0.099 p=0.753
ME + alcohol (dummy)	1.17 (1.005-1.37)	151.9 p<0.0001	1.36 (1.19-1.54)	479.6 p<0.0001
ME + lived with smoker (2 dummies)	1.18 (1.02-1.38)	1.396 p=0.498	1.33 (1.18-1.50)	3.829 p=0.147
ME + worked with smoker (2 dummies)	1.20 (1.03-1.40)	6.005 p=0.0497	1.35 (1.19-1.53)	1.309 p=0.253
ME + hrs outside in summer (2 dummies)	1.19 (1.03-1.38)	0.253 p=0.881	1.35 (1.19-1.52)	0.524 p=0.770

Table 7.1: Relative Risk of Non-Skin Cancers and Evaluation of Potential Covariates by Gender in the Total AHSMOG Cohort. Part 2 of 2

Model $PM_{10}(100)$ $\mu g/m^3$[a]	Males (n=2278, cases=280) RR[b] (95% CI)	Males Δ(-2 log L) p-value	Females (n=4060, cases=424) RR[b] (95% CI)	Females Δ(-2 log L) p-value
ME + hrs exercise outside in sum. (2 dummies)	1.19 (1.02-1.38)	1.188 p=0.552	1.34 (1.19-1.52)	0.273 p=0.872
ME + fruit index-2 (continuous)	1.19 (1.02-1.38)	1.259 p=0.282	1.35 (1.19-1.52)	0.163 p=0.686
ME + fruit & vege-2 (1 dummy)	1.19 (1.02-1.38)	0.399 p=0.528	1.35 (1.19-1.52)	1.067 p=0.302
ME + fruit & vege-3 (1 dummy)	1.19 (1.02-1.38)	0.722 p=0.395	1.35 (1.19-1.52)	0.955 p=0.328
ME + total meat (2 dummies)	1.22 (1.05-1.42)	5.481 p=0.065	1.34 (1.19-1.52)	2.028 p=0.363
ME + green vege. (2 dummies)	1.18 (1.02-1.37)	2.840 p=0.242	1.34 (1.19-1.51)	1.837 p=0.399
ME + vege & salad & tomatoes (2 dummies)	1.19 (1.02-1.38)	1.046 p=0.593	1.34 (1.19-1.52)	1.251 p=0.535
ME + vit A, C, E & multiple vit. (1 dummy)	1.19 (1.03-1.38)	1.632 p=0.201	1.35 (1.20-1.53)	5.357 p=0.021
ME + green salads (2 dummies)	1.19 (1.02-1.38)	2.150 p=0.341	1.35 (1.19-1.52)	3.239 p=0.198
ME + population density (1 dummy)	1.19 (1.02-1.39)	78.8 p<0.0001	1.38 (1.22-1.56)	143.3 p<0.0001

a $PM_{10}(100)$ = average (1973-1977) hours/year when ambient PM_{10} exceeded 100 $\mu g/m^3$

b RR = exp (IQR * β), where IQR=interquartile Range = 1032 hrs/yr = 43 days/yr.

Table 7.2: Frequency of All Incident Cancers in the Total AHSMOG Cohort, 1977-1992.
Part 1 of 2

Site	ICDO-1[a] codes	ICDO-2[a] codes	Males	Females	Total
Total[b]	140-199	C00-C80	371	509	880
Skin	172-173	C44	91	85	176
Nonskin	140-199 less 172-3	C00-C80 less C44	280	424	704
Breast	174-175	C50	1	156	157
Prostate	185	C61	135	0	135
Colon	153	C18	39	58	97
Corpus uteri	182	C54	0	73	73
Rectum / Anus	154	C19-C21	20	27	47
Lung & bronchus	162	C34	16	20	36
Lymph nodes	196	C77	21	14	35
Bladder	188	C67	22	9	31
Hematopoietic	169	C42	17	13	30
Stomach	151	C16	8	14	22
Ovary	183	C56	0	21	21
Pancreas	157	C25	5	16	21
Kidney	189	C64-C65	4	10	14
Thyroid / Other endocrine	193-194	C73-C75	3	10	13
Brain	191	C71	8	2	1

Table 7.2: Frequency of All Incident Cancers in the Total AHSMOG Cohort, 1977-1992. Part 2 of 2.

Site	ICDO-1[a] codes	ICDO-2[a] codes	Males	Females	Total
Cervix uteri	180	C53	0	9	9
Lip / Oral cavity	140-149	C00-C14	5	3	8
Small intestine	152	C17	5	1	6
Connective / Soft tissue	171	C49	1	4	5
Esophagus	150	C15	2	3	5
Vulva / Vagina	184	C51-C52	0	4	4
Bone	170	C41	1	1	2
Eye	190	C69	1	1	2
Gallbladder	156	C23	0	2	2
Liver	155	C22	0	2	2
Testis	186	C62	2	0	2
Thymus	164	C37	1	0	1
Primary unknown	197-199	C80	4	13	17

a ICDO = International Classification for Disease for Oncology

b Site-specific counts for each gender do not add up to the total number of cancers because several subjects had multiple primary cancers (total includes skin cancers).

Table 7.3: Distribution of Selected Variables for Non-Cases and Cases of Incident Non-Skin Cancers in the Total AHSMOG Cohort. Part 1 of 2

Variables	FEMALES		MALES	
	Non-cases (n=3636) %	Cancer cases (n=424) %	Non-cases (n=1998) %	Cancer cases (n=280) %
Age at baseline				
27-59	51.4	39.4	55.7	37.8
60-69	25.0	31.5	24.2	31.9
70-79	14.9	20.3	13.4	23.6
80+	8.7	8.7 **	6.7	6.7 **
Education				
≤ HS graduate	39.2	35.5	28.6	33.3
≥ Some college	60.8	64.5	71.4	66.7
Body mass index				
13.0-22.0	32.4	27.5	16.5	11.8
22.1-24.0	22.1	20.7	24.4	26.5
24.1-26.0	17.1	19.1	28.5	32.9
26.1+	28.4	32.7	30.6	28.8
Total exercise				
None/Low	46.9	46.1	31.0	26.6
Moderate/High	53.1	53.9	69.0	73.4
Parents' cancer hx				
No	64.6	59.5	68.7	66.2
Yes	35.4	40.5 *	31.3	33.8
Hx of asthma				
No	92.0	91.0	92.2	93.0
Yes	8.0	9.0	7.8	7.0
Occupation air pollution				
No	93.2	92.3	86.7	83.9
Yes	6.8	7.7	13.3	16.1
Use of alcohol				
Never	93.2	92.3	90.2	89.2
Any	6.8	7.7	9.8	10.8

Table 7.3: Distribution of Selected Variables for Non-Cases and Cases of Incident Non-Skin Cancers in the Total AHSMOG Cohort. Part 2 of 2

	FEMALES		MALES	
Variables	Non-cases (n=3636) %	Cancer cases (n=424) %	Non-cases (n=1998) %	Cancer cases (n=280) %
Packyears of cigarettes				
None	86.7	86.7	67.3	65.9
1-7 yrs	7.6	5.2	13.1	12.1
> 7 yrs	5.7	8.1 *	19.7	22.0
Years lived with smoker				
None	51.5	57.0	66.4	65.0
1-15 yrs	19.9	16.9	17.2	16.7
16+ yrs	28.6	26.1	16.4	18.3
Years worked with smoker				
None	61.2	66.0	52.4	49.4
1-15 yrs	29.0	22.4	27.7	26.4
16+ yrs	9.8	11.6 **	19.9	24.2
Hours outside in summer				
0-7 hrs/wk	53.7	53.1	27.2	23.5
8-14 hrs/wk	23.6	23.3	21.7	20.7
15+ hrs/wk	22.7	23.5	51.1	55.7
Hours vigorous exercise outside in summer				
None	27.5	28.5	13.1	12.0
1-7 hrs/wk	54.5	54.3	50.0	43.3
8+ hrs/wk	18.0	17.2	36.9	44.7 *

* Likelihood Ratio Chi-Square < 0.05

** Likelihood Ratio Chi-Square < 0.01

Table 7.4: Relative Risks[a] of Incident Non-Skin Cancers Associated With Interquartile Ranges of Selected Air Pollutants in the Total AHSMOG Cohort, Two-Year Moving Average From 1973 With a Three-Year Lag Prior to Risk Set. Males Only. (n = 2278, Cases = 280).

Variable	Regression coefficient (β)	SE(β)	Increment (interquartile range)[b]	Relative risk (RR)	95% C.I. for relative risk
Ozone, hrs in excess of [c]:					
O_3, (60 ppb)	-0.0000880	0.000117	935 hrs/yr	0.92	(0.74 - 1.14)
O_3, (80 ppb)	0.0000285	0.000155	756 hrs/yr	1.02	(0.81 - 1.29)
O_3, (100 ppb)	0.000188	0.000211	556 hrs/yr	1.11	(0.88 - 1.40)
O_3, (120 ppb)	0.000415	0.000300	367 hrs/yr	1.17	(0.94 - 1.45)
O_3, (150 ppb)	0.001252	0.000540	185 hrs/yr	**1.26***	(1.04 - 1.53)
Ozone, 8-hr average	-0.048428	0.03666	2.8 ppb	0.87	(0.71 - 1.07)
Ozone, mean concentration	-0.047573	0.07170	12 ppb	0.95	(0.80 - 1.12)
PM_{10}, (hrs in excess of 100 μg/m^3)	0.000153	0.0000753	43 days/yr (1032 hrs/yr)	**1.17***	(1.01 - 1.36)
PM_{10}, mean concentration	0.006841	0.00357	29.5 μg/m^3	**1.22***	(1.00 - 1.50)
SO_2, mean concentration	0.153795	0.01547	4 ppb	**1.85***	(1.64 - 2.09)

a All models above based on time-dependent Cox Proportional Hazards Regression with attained age as the time variable and controlling for: years of education, pack-years of past cigarette smoking, total exercise, parental history of cancer, personal history of doctor-told asthma, current use of alcohol, antioxidant vitamin use (A, C, & E) and population density.

b Increment based on interquartile range (75%-25% of population exposed).

c Average annual hours in excess of listed ppb.

Table 7.5: Relative Risks[a] of Incident Non-Skin Cancers Associated With Interquartile Ranges of Selected Air Pollutants in the Total AHSMOG Cohort, Two-Year Moving Average From 1973 With a Three-Year Lag Prior to Risk Set. Females Only. (n = 4060, Cases = 424).

Variable	Regression coefficient (β)	SE(β)	Increment (interquartile range)[b]	Relative risk (RR)	95% C.I. for relative risk
Ozone, hrs in excess of[c]:					
O_3, (60 ppb)	-0.000207	0.000097	935 hrs/yr	0.82	(0.69 - 0.98)
O_3, (80 ppb)	-0.000043	0.000129	756 hrs/yr	0.97	(0.80 - 1.17)
O_3, (100 ppb)	0.000162	0.000175	556 hrs/yr	1.09	(0.90 - 1.33)
O_3, (120 ppb)	0.000456	0.000249	367 hrs/yr	1.18	(0.99 - 1.41)
O_3, (150 ppb)	0.001526	0.000447	185 hrs/yr	**1.33***	(1.13 - 1.56)
Ozone, 8-hr average	-0.089652	0.02957	2.8 ppb	0.78	(0.66 - 0.92)
Ozone, mean concentration	-0.156356	0.05689	12 ppb	0.83	(0.73 - 0.95)
PM_{10}, (hrs in excess of 100 μg/m^3)	0.000275	0.0000633	43 days/yr (1032 hrs/yr)	**1.33***	(1.17 - 1.51)
PM_{10}, mean concentration	0.011239	0.00311	29.5 μg/m^3	**1.39***	(1.16 - 1.67)
SO_2, mean concentration	0.206267	0.01244	4 ppb	**2.28***	(2.07 - 2.52)

a All models above based on time-dependent Cox Proportional Hazards Regression with attained age as the time variable and controlling for: years of education, pack-years of past cigarette smoking, total exercise, parental history of cancer, personal history of doctor-told asthma, current use of alcohol, antioxidant vitamin use (A, C, & E) and population density.

b Increment based on interquartile range (75%-25% of population exposed).

c Average annual hours in excess of listed ppb.

Table 7.6: Relative Risks[a] of Incident Non-Skin Cancers Associated With Interquartile Ranges of Selected Air Pollutants Evaluated Pairwise in Two-Pollutant Models in the Total AHSMOG Cohort. Two-Year Moving Average From 1973 With a Three-Year Lag Prior to Risk Set.

	Females (n=4060, cases=424)			Males (n=2278, cases=280)		
Pollutants	N	Wald χ^2	RR (95% CI)	N	Wald χ^2	RR (95% CI)
Model #1[b]	3314			1922		
O_3(150)[c]		0.005	1.01 (0.77-1.33)		1.086	1.19 (0.86-1.66)
PM_{10}(100)[d]		6.099	**1.32*** (1.06-1.64)		0.078	1.04 (0.80-1.34)
Model #2[b]	2482			1415		
O_3(150)[c]		9.111	**1.32*** (1.10-1.57)		0.193	1.05 (0.85-1.30)
SO_2-MC[e]		263.823	**2.27*** (2.06-2.51)		95.727	**1.84*** (1.63-2.08)
Model #3[b]	2482			1415		
PM_{10}(100)[d]		24.434	**1.33*** (1.14-1.55)		2.432	1.15 (0.99-1.38)
SO_2-MC[e]		283.059	**2.31*** (2.09-2.54)		97.435	**1.85*** (1.64-2.09)

RR = Relative Risk; CI = Confidence Interval, * $p < 0.05$

a Interquartile ranges used for increment of relative risk calculated by time-dependent Cox proportional hazards regression:
185 hrs/yr for O_3 in excess of 150 ppb
1032 hrs/yr (43 day) for PM_{10} in excess of 100 $\mu g/m^3$
4 ppb for SO_2-MC

b All models are adjusted for: years of education, pack-years of past cigarette smoking, total exercise, parental history of cancer, personal history of doctor-told asthma, current use of alcohol, antioxidant vitamin use (A, C, & E) and population density.

c O_3 (150) is average hours in exceedance of 150 ppb ozone

d PM_{10}(100) is average hours in exceedance of 100 $\mu g/m^3$ of particulate matter < 10 μm in aerodynamic diameter

e SO_2-MC is mean concentration of sulfur dioxide

Table 7.7: Adjusted Relative Risks[a] of Non-Skin Cancers (1977-1992) Associated With an Interquartile Range[b] Increase of Average (1973-1977) Mean Concentrations of Particulate Air Pollutants of Varying Aerodynamic Diameters in the Airport Cohort. Females Only. (n=2356, Cases=235).

Air Pollutant	Regression coef. (β)	SE (β)	Relative risk (RR)	95% CI for RR
All non-skin cancer				
$PM_{2.5}$	0.002349	0.00569	1.06	0.81-1.39
PM_{10}	0.001318	0.00399	1.04	0.83-1.31
$PM_{10-2.5}$	0.000061	0.00799	1.00	0.86-1.17

a Relative Risks [exp(IQR x β)] were computed using the Cox proportional hazards regression with attained age as the time variable and controlling for pack-years of past cigarette smoking and years of education.

b Interquartile range (IQR) increases used for the relative risks were: 24.3 $\mu g/m^3$ for $PM_{2.5}$; 29.49 $\mu g/m^3$ for PM_{10}; and 9.7 $\mu g/m^3$ for $PM_{10-2.5}$.

Table 7.8: Adjusted Relative Risks[a] of Non-Skin Cancers (1977-1992) Associated With an Interquartile Range[b] Increase of Average (1973-1977) Mean Concentrations of Particlulate Air Pollutants of Varying Aerodynamic Diameters in the Airport Cohort. Males Only. (n=1290, Cases=156).

Air pollutant	Regression coef. (β)	SE (β)	Relative risk (RR)	95% CI for RR
All nonskin cancer				
$PM_{2.5}$	0.001063	0.00690	1.03	0.74-1.43
PM_{10}	0.000878	0.00475	1.03	0.78-1.35
$PM_{10-2.5}$	0.000416	0.00985	1.00	0.83-1.21

a Relative Risks [exp(IQR x β)] were computed using the Cox proportional hazards regression with attained age as the time variable and controlling for pack-years of past cigarette smoking and years of education.

b Interquartile range (IQR) increases used for the relative risks were: 24.3 $\mu g/m^3$ for $PM_{2.5}$; 29.49 $\mu g/m^3$ for PM_{10}; and 9.7 $\mu g/m^3$ for $PM_{10-2.5}$.

Table 7.9: Relative Risks[a] for Incidence of Non-Skin Cancers (1973-1992) Associated With an Interquartile Range[b] Increase of Average (1973-1977) Mean Concentrations of Particulate Air Pollutants of Varying Aerodynamic Diameters and Different Follow-Up Periods in the Airport Cohort. Part 1 of 2

Gender and Years of follow-up	Cases/n	Coef. (β)	SE(β)	Wald (p-value)	RR (95% CI)
Excluding skin cancer					
Females					
$PM_{2.5}$ (fine)[c]					
'77-'82	95/2358	0.016171	0.00910	3.160 (0.076)	1.48 (0.96-2.29)
'83-'92	140/2191	-0.008250	0.00745	1.227 (0.268)	0.82 (0.57-1.17)
'77-'92	235/2358	0.002349	0.00569	0.171 (0.680)	1.06 (0.81-1.39)
PM_{10}					
'77-'82	95/2358	0.012397	0.00676	3.362 (0.067)	1.44 (0.98-2.13)
'83-'92	140/2191	-0.006090	0.00500	1.481 (0.224)	0.84 (0.63-1.12)
'77-'92	235/2358	0.001318	0.00399	0.109 (0.741)	1.04 (0.83-1.31)
$PM_{10-2.5}$ (CF)[c]					
'77-'82	95/2356	0.014795	0.01325	1.246 (0.264)	1.14 (0.90-1.49)
'83-'92	140/2189	-0.009570	0.01001	0.915 (0.339)	0.91 (0.75-1.10)
'77-'92	235/2356	0.000061	0.00799	0.001 (0.994)	1.00 (0.86-1.17)

a Relative Risks [exp(IQR x β)] were computed using the Cox proportional hazards regression with attained age as the time variable adjusting for packyears of past cigarette smoking and years of education.

b The interquartile ranges (IQR) for both genders used for the relative risks were: 24.3 $\mu g/m^3$ for $PM_{2.5}$; 29.49 $\mu g/m^3$ for PM_{10}; and 9.7 $\mu g/m^3$ for the coarse fraction ($PM_{10-2.5}$)

c Fine = fine fraction of respirable particulates, CF=coarse fraction of respirable particulates.

Table 7.9: Relative Risks[a] for Incidence of Non-Skin Cancers (1973-1992) Associated With an Interquartile Range[b] Increase of Average (1973-1977) Mean Concentrations of Particulate Air Pollutants of Varying Aerodynamic Diameters and Different Follow-Up Periods in the Airport Cohort. Part 2 of 2.

Gender and years of follow-up	Cases/n	Coef. (β)	SE(β)	Wald (p-value)	RR (95% CI)
Excluding skin cancer					
Males					
$PM_{2.5}$ (fine)[c]					
'77-'82	59/1290	-0.006274	0.01130	0.308 (0.579)	0.86 (0.50-1.47)
'83-'92	97/1175	0.006188	0.00877	0.497 (0.481)	1.16 (0.77-1.71)
'77-'92	156/1290	0.001063	0.00690	0.024 (0.878)	1.03 (0.74-1.43)
PM_{10}					
'77-'82	59/1290	-0.003057	0.00770	0.158 (0.691)	0.91 (0.59-1.43)
'83-'92	97/1175	0.003928	0.00608	0.418 (0.518)	1.12 (0.79-1.60)
'77-'92	156/1290	0.000878	0.00475	0.034 (0.853)	1.03 (0.78-1.35)
$PM_{10-2.5}$ (CF)[c]					
'77-'82	59/1289	-0.000998	0.01588	0.004 (0.950)	0.99 (0.73-1.34)
'83-'92	97/1174	0.002767	0.01253	0.049 (0.825)	1.03 (0.81-1.30)
'77-'92	156/1289	0.000416	0.00985	0.002 (0.964)	1.00 (0.83-1.21)

a Relative Risks [exp(IQR x β)] were computed using the Cox proportional hazards regression with attained age as the time variable adjusting for packyears of past cigarette smoking and years of education.

b The interquartile ranges (IQR) for both genders used for the relative risks were: 24.3 $\mu g/m^3$ for $PM_{2.5}$; 29.49 $\mu g/m^3$ for PM_{10}; and 9.7 $\mu g/m^3$ for the coarse fraction ($PM_{10-2.5}$)

c Fine = fine fraction of respirable particulates, CF=coarse fraction of respirable particulates.

CHAPTER 8

PRELIMINARY ANALYSES OF OTHER CANCER ENDPOINTS

A. Long-Term Concentrations of Ambient Air Pollutants and Risk of *Smoking-Related* Cancers (SRC)

1. Introduction

This chapter consists of preliminary investigations of cancer cites that may account for much of the gender-specific associations observed for all nonskin neoplasms. Much more work needs to be done for smoking-related cancers, breast cancers, prostate cancers, non-Hodgkin's lymphoma, as well as other cancer sites regarding the development of statistical models, evaluation of potential confounding, sensitivity analyses, important subgroup identification, multipollutant analyses, etc.

Cigarette smoke contains more than 55 established carcinogens including significant amounts of N-nitrosamines, aromatic amines, and polycyclic aromatic hydrocarbons (*1*). Using the tobacco model where human organs not in direct contact with cigarette smoke may also be adversely affected by the chemicals in cigarette smoke, and that ambient air often contains many of the same hazardous chemicals found in cigarette smoke, albeit to a much lesser concentration, we formed a group category of smoking-related cancers (SRC). Recall that none of the study participants were active smokers at baseline or throughout the study period.

2. Methods

We included the following organ sites which have been used by other investigators in their smoking-related categories because these sites have shown to be adversely affected by chemicals that initially enter the body via the respiratory tract: esophagus (*2-6*), larynx (*4-8*), bronchus (*9-11*), lung (*4-7,9-13*), urinary bladder(*14-15*), pancreas (*16-17*), cervix uteri (*18-19*), and renal pelvis (*4-6,10,11,20*). Lung and bronchus cancers make up the largest portion (35%) of SRC in the AHSMOG cohort. Even though several epidemiologic studies have reported higher leukemia and colon cancer risks among smokers compared to nonsmokers, the evidence is inconclusive (*21-24*) so these cancers are not included in our SRC category.

Most, but not all, of the results described in Chapter 5 regarding the association of long-term exposures to ambient particulates with lung cancer incidence indicated that the fine fraction ($PM_{2.5}$) appeared to be the most important component of respirable particles. However, because of small numbers of SRC in the airport cohort, the investigation in this preliminary analysis was restricted to the total cohort and the analysis started with a parsimonious model containing only a single air pollutant and the two *a priori* covariates of education and past cigarette smoking.

3. Results

After controlling for education, past cigarette smoking, exposure to passive smoking in the home and workplace and other potential confounders, we investigated the association with selected air pollutants and SRC. The gender-specific distributions of the

organ sites included in the "smoking-related" cancer classification are given in **Table 8.1.** For both genders, the majority of the SRC were in individuals who had never smoked cigarettes. This was also true for lung cancers and all nonskin cancers. Cancers of the lung/bronchus were 30% (17/56) of the SRC for females and 35% (16/46) of the SRC for males.

In females, SRC was not associated with mean concentrations of PM_{10}, O_3 nor NO_2. We did, however, observe an increased risk of SRC for mean concentration of SO_2 (RR=2.58, 95% CI: 1.51 - 4.39) (**Table 8.2**). Similarly for males, SRC was not associated with mean concentration of PM_{10}, O_3 nor NO_2. The association of SRC with SO_2 in males was elevated (RR=1.81; 95% CI: 0.98 - 3.34) but the confidence interval barely included the null value of one (**Table 8.3**). .

4. Discussion

In the single pollutant models that evaluated SRC in females, the only coefficient that was consistently significant was for past cigarette smoking. Once past cigarette smoking was controlled for in the analysis, the addition of most ambient air pollutant indices contributed little if any to the SRC risk. The only exception to this was that mean concentration of SO_2 was statistically significantly associated with SRC independent of attained age, education or past cigarette smoking.

We also did not observe any significant association between the pollutants investigated and SRC in males. After controlling for attained age, education and past cigarette smoking, the air pollutant that showed the strongest association was again mean

concentration of SO_2 with an 81% increased risk of SRC, but the 95% confidence interval was fairly wide due to the small number of cases. Past cigarette smoking was not a significant confounder in any of the male analyses.

In California, ambient levels of SO_2 are not considered to be excessively high, or at least are lower than that found on the east coast where sulfur containing coal and other fossil fuels are used for space heating more than on the west coast. There may be point sources of SO_2 to which our SRC cases might be more exposed to than the noncases, but we have no data to address that issue. It is unlikely that SO_2 is directly related to the etiology of SRC. Many of the processes that produce ambient SO_2 are the same as that which produces other products of incomplete combustion of fossil fuels such as respirable particulates and the precursors of ozone. It is not clear whether SO_2 is operating via some unknown mechanism to enhance carcinogenesis or whether it is simply a marker for a more causal factor. In the AHSMOG study, mean concentration of SO_2 was not highly correlated with the other mean concentration of air pollutants investigated (r=0.29 for PM_{10}; -0.13 for O_3, and 0.86 for NO_2 - see **Table 5.2**). If mean concentration of SO_2 is acting primarily as a marker for a more causal factor, additional research is needed to disentangle the unknown factor.

Even though ambient air may contain similar cancer-causing compounds as are found in cigarette smoke, the levels may be below the pathologic threshold for females or just overshadowed by the past smoking effect. Our preliminary analyses do not support an association between all SRC and ambient particulate air pollution. Since particulates

are vehicles for many different agents, they may be too crude a measure for use as exposure for all SRC.

As was found in the analysis of nonskin cancers (Chapter 7), the inclusion of lag times in the Cox proportional hazards analysis of risk factors for smoking-related cancers might be productive. When lag times were allowed to vary in the nonskin cancer analyses, the associations with the individual air pollutants strengthened when the few years prior to the event were excluded from the exposure metric. Future research is needed to investigate which lag structure best models the association between ambient air pollutants and smoking related cancers.

5. References

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Table 8.1: Frequency of Smoking-Related Cancers in the Total AHSMOG Cohort.

Cancer	Females (n=4060) smoking history Past/unk (n=587)	Females (n=4060) smoking history Never (n=3473)	Males (n=2278) smoking history Past/unk (n=794)	Males (n=2278) smoking history Never (n=1484)
Smoking-related	16	40	22	24
Esophagus	2	1	2	0
Larynx	0	0	2	0
Bronchus[a]	0	3	0	1
Lung[a]	7	10	6	9
Urinary bladder	0	9	11	10
Pancreas	4	11	0	4
Cervix uteri	2	6	—	—
Renal pelvis	1	0	1	0
All cancer[b]	65	359	104	176

a For lung cancer analyses, cancers of the bronchus and lung are combined.

b All cancer is defined as the incidence of all malignant neoplasms (excluding skin cancer) diagnosed between baseline (4/77) and end of follow-up (4/92)

Table 8.2: Adjusted Relative Risks[a] of Incident Smoking-Related Cancers (1977-1992) Associated With an IQR[b] Increase in Average Mean Concentrations of Selected Air Pollutants in the Total AHSMOG Cohort. Females Only .

Air pollutant	Cases/n	Regression coef (β)	SE(β)	Relative risk (RR)	95% CI for RR
SRC[c]					
PM_{10}, mean conc.	47/3938	-0.01383	0.00974	0.67	0.38 - 1.17
O_3, mean conc.	47/3933	-0.04881	0.01968	0.55	0.34 - 0.88
SO_2, mean conc.	40/2784	0.13835	0.03979	**2.58** *	1.51 - 4.39
NO_2, mean conc.	47/3878	0.02068	0.01287	1.49	0.92 - 2.43

CI: Confidence interval.

a Relative Risks [exp(IQR x β)] were computed using Cox proportional hazards regression with attained age as the time variable and controlling for packyears of past cigarette smoking and years of education; averaged from 1973 with 3-year lag.

b Interquartile range (IQR) increases used for the relative risks were: 29.5 g/m^3 for PM_{10}; 12.3 ppb for O_3; 6.84 ppb for SO_2; 19.3 ppb for NO_2.

c Smoking-related cancers (SRC): esophagus, larynx, bronchus, lung, urinary bladder, pancreas, renal pelvis, and cervix uteri.

Table 8.3: Adjusted Relative Risks[a] of Incident Smoking-Related Cancers (1977-1992) Associated With an IQR[b] Increase in Average Mean Concentrations of Selected Air Pollutants in the Total AHSMOG Cohort. Males Only .

Air pollutant	Cases/n	Regression coef (β)	SE(β)	Relative risk (RR)	95% CI for RR
SRC[c]					
PM_{10}, mean conc.	42/2199	0.00229	0.01023	1.07	0.59 - 1.93
O_3, mean conc.	43/2202	0.00150	0.02160	1.01	0.60 - 1.69
SO_2, mean conc.	34/1498	0.08663	0.04576	1.81	0.98 - 3.34
NO_2, mean conc.	43/2170	-0.00538	0.01454	0.90	0.52 - 1.56

CI: Confidence Interval

a Relative Risks [exp(IQR x β)] were computed using Cox proportional hazards regression with attained age as the time variable and controlling for packyears of past cigarette smoking and years of education; averaged from 1973 with 3-year lag.

b Interquartile range (IQR) increases used for the relative risks were: 29.5 g/m^3 for PM_{10}; 12.3 ppb for O_3; 6.84 ppb for SO_2; 19.3 ppb for NO_2.

c Smoking-related cancers (SRC): esophagus, larynx, bronchus, lung, urinary bladder, pancreas, renal pelvis, and cervix uteri.

B. Long-Term Concentrations of Ambient Air Pollutants and Risk of Female *Breast Cancer*

1. Introduction

In this nonsmoking cohort of Seventh-day Adventists, breast cancer is still the most common cancer diagnosed in women [37% (156/424) of all nonskin cancers in the total AHSMOG cohort; and similarly, 37% (89/240) of all nonskin cancers in the airport cohort]. In the total AHSMOG cohort, hormone-related cancers of the breast and uterus constituted 54% of the female non-skin cancers. The majority (77.8%) of the females in this study were post-menopausal at baseline. Since lung cancer incidence associated with air pollution was my primary *a priori* hypothesis, the following analyses on breast cancer should be considered as preliminary analyses.

Aside from increasing age, risk factors for breast cancer include personal or family history of breast cancer, atypical hyperplasia, long menstrual history associated with age at menarche and age at menopause, obesity after menopause, use of birth control pills and postmenopausal estrogen replacement, nulliparous or had first child after age 30 or consumption of alcoholic beverages (*1*). Additional factors that may be related to increased breast cancer risk include breast density, genetic predisposition (e.g. BRCA1 & BRCA2 susceptibility genes), and physical inactivity (*2-3*). The role of diet is still under investigation. However, a large multinational pooling project that included 4,980 breast cancer cases from several large cohort studies concluded that there was no evidence of a positive association between total dietary fat intake and the risk of breast cancer (*2*).

The Iowa Women's Health Study (*4*) examined the association of leisure physical activity with breast cancer incidence among 37,105 postmenopausal women. Women reporting any regular leisure-time physical activity had a RR = 0.97 (95% CI: 0.87-1.08) compared with those reporting no such regular physical activity indicating that there was little evidence that physical activity later in life was associated with breast cancer incidence to any appreciable extent.

There are large regional differences in the incidence of breast cancer. Some investigators have noted that the female breast is anatomically embedded in a major fat depot which stores and concentrates polycyclic aromatic hydrocarbons and can metabolize these hydrocarbons to carcinogenic metabolites (*5*). An earlier report from the AHSMOG study (*6*) reported a suggestion of an increased risk of breast cancer (RR=1.51, 95% CI: 0.92-2.47) associated with hours of average annual concentration of total suspended particulates in excess of 200 $\mu g/m^3$ for the follow-up time period 1977-1982. In the updated AHSMOG cohort, we now have data for the new EPA standard of PM_{10}.

2. Methods

The air pollution metric, average (1973-1977) annual hours of concentration in excess of 100 $\mu g/m^3$ of PM_{10} [$PM_{10}(100)$], was chosen for model development for breast cancer because it was the closest currently available metric to what was used before to evaluate the association between ambient particulate air pollution and risk of all nonskin cancers in the AHSMOG study. In that earlier report, Mills et al. (*3*) found a statistically

significant increase in risk of incidence of all cancers (including skin) in females (RR=1.37; CI: 1.05-1.80) associated with a 1000 hours/year increase in average hours in excess of 200 $\mu g/m^3$ of total suspended particulates (TSP) However, in 1987, the Environmental Protection Agency reviewed the existing PM air quality criteria and standards and changed the indicator for PM from TSP to PM_{10}.

The initial reduced model contained just the main effect [$PM_{10}(100)$] and the covariates packyears of past cigarette smoking and education with attained age as the time variable. Other variables identified in Chapter 3, section B, were evaluated one at a time by adding them to the reduced model and evaluating how the coefficient for the main effect changed when the additional variable was included. If the change was less than 10%, then these variables were left out of the model.

3. Results

Evaluating the same list of potential covariates as was used in all NSC, **Table 8.4** shows the effect of adding these potential covariates to the reduced model one at a time. Only history of doctor-diagnosed asthma appeared to act as a confounder as defined by a change in the regression coefficient for the main effect [$PM_{10}(100)$] of more than 10 percent. Other variables that appeared to affect the fit of the model as evidenced by a significant change in the log likelihood ratio test included: total exercise, parental history of cancer, alcohol consumption, and population density.

Female-related variables were also investigated for possible confounding effects. These are listed in **Table 8.5**. Potential confounders that produced a change in the

regression coefficient of more than 10 percent included: age at first live birth and age menses stopped. Other variables that appeared to affect the fit of the model as evidenced by a significant change in the log likelihood ratio test included: whether mother had breast cancer, subject had a previous lump or cyst in breast, age at first menses, years between menarche and age first live birth, and parity.

The association of incident breast cancer with several metrics of PM_{10}, and mean concentrations of O_3 and SO_2 incorporating a 3-year lag structure are given in **Table 8.6**. In the current 15 year follow-up of the total AHSMOG cohort of 4060 females, we observed a statistically significant 60% increased risk (RR=1.60; CI: 1.24 - 2.07) associated with mean concentration of PM_{10}. The other exceedance metrics for PM_{10} were also significantly elevated with the magnitude of the regression coefficients increasing as the PM_{10} threshold increased. There was over a two-fold increase risk of incident breast cancer associated with an IQR increase in mean concentration of SO_2 (RR=2.70; CI: 2.30 - 3.17).

4. Discussion

Aside from the several factors that have been associated with increased risk of breast cancer as mentioned in the introduction above, there are large regional differences in the incidence of breast cancer. Incidence studies among migrants who move from low- to high-incidence areas have demonstrated that the risk of developing breast cancer in the migrant population will gradually rise to the level of the population in the new locale (*7*).

This pattern of change in risk suggests that environmental factors are important in the development of breast cancer.

Experimental evidence suggests that ambient toxic chemicals including chlorinated organics and polycyclic aromatic hydrocarbons (PAHs) affect estrogen production and metabolism and thus function as zenoestrogens (*8*). Many of these compounds can potentially induce carcinogenesis in breast tissue (*9*). For example, Rundle and colleagues (*10*) observed that PAH-DNA adducts measured in breast tissue from breast cancer cases and noncases were significantly associated with breast cancer (OR=4.43; 95% CI: 1.09-18.01) after controlling for known breast cancer risk factors and current active and passive smoking and dietary PAH. Aromatic amines have also been discussed as potential mammary carcinogens (*11*). However, there remains considerable controversy regarding the role of ambient environmental exposures experienced passively by the U.S. population (*12*). The amount of these toxic chemicals in breast fat of cancer cases has been found to be significantly higher compared to noncase controls (*8*).

Polychlorinated biphenyls (PCBs) are a major health concern because of their wide distribution and persistence in the environment. The PCBs tend to build up in adipose tissue because of their lipid solubility. Holford and colleagues (*13*) investigated several PCB congeners and found that some were associated with increased risk of breast cancer. Wolff and Toniolo (*14*) have proposed that exposure to some environmental organochlorines might be part of the etiology of breast cancer.

Respirable particulates provide a mechanism whereby these hydrocarbons can be efficiently delivered to the alveolar capillaries and into the circulatory system and

ultimately stored in the body's adipose tissues. Further studies (both toxicologic and epidemiologic) and are needed to better understand the role of different metrics of particulate air pollution on breast cancer risk.

We found a statistically significant association between long-term mean concentration of SO_2 and breast cancer in the total AHSMOG cohort. A controversial hypothesis suggests that the SO_2 / breast cancer association may be partially related to vitamin D deficiencies. Sulfur dioxide absorbs ultraviolet light in the region of the spectrum (290-310 nm wavelength) which is most active in forming vitamin D on the surface of the skin (*15*). Early reports provided some evidence from *in vitro* studies as well as from case-control studies which compared excised breast tissue from malignant and benign tumors that indicates that vitamin D may have a protective role in reducing breast cancer (*16-18*). A more recent study of breast cancer cases in a United Kingdom Caucasian population observed a significant association between vitamin D receptor polymorphism and breast cancer risk (OR=2.32; 95% CI: 1.23-4.39) (*19*). Other recent studies have also shown associations between the vitamin D endocrine system and the control of proliferation of mammary epithelial cells (*20-23*). It is likely that dietary vitamin D would modify these associations.

The lowest rates of breast cancer occur in countries within 20 degrees of the equator; countries known for their high levels of sunlight, lower average social economic status, and less SO_2 production (*24*). Incidence of breast cancer in the United States tends to increase with increasing latitude (*25*).

However, since ambient SO_2 is produced by similar mechanisms as that for many other air pollutants, namely the incomplete combustion of fossil fuels, the association observed between mean concentration of SO_2 and breast cancer may simply be the result of other correlated hazardous ambient compounds and that SO_2 may be serving as a marker for a more etiologically relevant process. If the previous statement is true, it is unclear what SO_2 may be acting as a surrogate for since the observed correlations between SO_2 and the other air pollutants investigated in this report are generally low, including that for respirable particulates.

a. Future Work.

The analyses presented here are only preliminary. More modeling needs to be done to include additional covariates such as diet and important hormone/reproductive variables identified in **Table 8.5**. Sensitivity analyses have yet to be done by looking at premenopausal versus postmenopausal women within the different histological subtypes of breast cancer. Since we observed positive associations with breast cancer for both respirable particulates and mean concentration of SO_2 in the total AHSMOG cohort, multipollutant analyses need to be run to evaluate the relative strength of measured ambient air pollutants and their possible independent associations with breast cancer. With the current funding from the Environmental Protection Agency (EPA), the AHSMOG study is expected to expand cancer follow-up an additional 8 years (1993-2000). We intend to further explore the association of various air pollutants with an increased number of incident breast cancer cases.

5. References

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Table 8.4: Relative Risk of Breast Cancer Associated With Average (1973-1977) Annual Hours in Excess of 100 $\mu g/m^3$ PM_{10} and Evaluation of Potential Covariates for Females in the Total AHSMOG Cohort. (n=4060, Cases=122). Part 1 of 2

Model PM_{10} (100)[a] $\mu g/m^3$	β PM_{10}(100)	$\Delta\beta$ (%)	RR[b] (95% CI)	-2 log L p-value
Main effects (ME) (packyrs + education)	.000332	N/A	1.41 (1.14-1.74)	N/A
ME + BMI (3 dummies)	.000335	+0.9%	1.41 (1.14-1.75)	2.921 p=0.404
ME + exercise (dummy)	.000348	+4.8%	1.43 (1.16-1.77)	29.78 p<0.0001
ME + parents cancer history (dummy)	.000328	-1.2%	1.40 (1.13-1.75)	96.96 p<0.0001
ME + asthma history (dummy)	.000294	-11.4%	1.35 (1.09-1.69)	43.49 p<0.0001
ME + occupation air pollution	.000331	-0.3%	1.41 (1.14-1.74)	2.182 p=0.140
ME + alcohol (dummy)	.000342	+3.0%	1.42 (0.83-1.32)	96.60 p<0.0001
ME + lived with smoker (2 dummies)	.000311	-6.3%	1.38 (1.11-1.71)	5.156 p=0.076
ME + worked with smoker (2 dummies)	.000330	-0.6%	1.41 (1.13-1.74)	0.030 p=0.985
ME + hrs outside in summer (2 dummies)	.000334	+0.6%	1.41 (1.14-1.75)	3.597 p=0.166
ME + hrs exercise outside in sum. (2 dummies)	.000330	-0.6%	1.41 (1.14-1.74)	0.198 p=0.906
ME + fruit index-2 (continuous)	.000333	+0.3%	1.41 (1.14-1.75)	0.124 p=0.725
ME + fruit & vege-2 (1 dummy)	.000335	+0.9%	1.41 (1.14-1.75)	0.783 p=0.376

Table 8.4: Relative Risk of Breast Cancer Associated With Average (1973-1977) Annual Hours in Excess of 100 $\mu g/m^3$ PM_{10} and Evaluation of Potential Covariates for Females in the Total AHSMOG Cohort. (n=4060, Cases=122). Part 2 of 2.

Model PM_{10} (100)[a] $\mu g/m^3$	β PM_{10}(100)	$\Delta\beta$ (%)	RR[b] (95% CI)	-2 log L p-value
ME + fruit & vege-3 (1 dummy)	.000334	+0.6%	1.41 (1.14-1.75)	0.664 p=0.415
ME + total meat (2 dummies)	.000341	+2.7%	1.42 (1.14-1.77)	0.209 p=0.901
ME + green vege. (2 dummies)	.000324	-2.4%	1.40 (1.13-1.73)	2.220 p=0.330
ME + vege & salad & tomatoes (2 dummies)	.000330	-0.6%	1.41 (1.14-1.74)	1.191 p=0.551
ME + vit A, C, E & multiple vit. (1 dummy)	.000333	+0.3%	1.41 (1.14-1.75)	0.095 p=0.758
ME + green salads (2 dummies)	.000332	+0.0%	1.41 (1.14-1.74)	1.240 p=0.538
ME + population density (1 dummy	.000353	+6.3%	1.44 (1.16-1.79)	38.13 p<0.0001

a PM_{10} (100) is the average number of hours per year that PM_{10} exceeded 100 $\mu g/m^3$ over the time period 1973-1977.

b RR = exp(IQR * β) whre IQR=interquartile range increase for PM_{10}(100) = (1032 hours/yr = 43 days/year). Time variable = attained age.

Table 8.5: Relative Risk of Breast Cancer Associated With Average (1973-1977) Annual Hours in Excess of 100 $\mu g/m^3$ PM_{10} and Evaluation of Additional Potential Covariates for Females in the Total AHSMOG Cohort. (n=4060, Cases=122).

Model PM_{10} (100) [a] $\mu g/m^3$	β PM_{10} (100)	$\Delta\beta$ (%)	RR[b] (95% CI)	-2 log L p-value
Main effects (ME) (packyears+education)	.000332	N/A	1.41 (1.14-1.74)	N/A
ME + mother had breast cancer	.000351	+5.7%	1.44 (1.16-1.78)	52.928 p<0.0001
ME + lump or cyst in breast	.000330	-0.6%	1.41 (1.14-1.74)	5.575 p=0.018
ME + age menses stopped	.000371	+11.7%	1.47 (1.16-1.85)	397.9 p<0.0001
ME + age first menses	.000338	+1.8%	1.42 (1.14-1.76)	35.63 p<0.0001
ME + age at first live birth	.000290	-12.7%	1.35 (1.05-1.73)	413.1 p<0.0001
ME + years between menarche & age first live birth	.000301	-9.3%	1.36 (1.06-1.75)	447.3 p<0.0001
ME + used birth control pills (3 dummies)	.000328	-1.2%	1.40 (1.13-1.74)	2.668 p=0.102
ME + used replacement hormones (3 dummies)	.000335	+0.9%	1.41 (1.14-1.75)	5.759 p=0.124
ME + parity	.000337	+1.5%	1.42 (1.12-1.79)	322.1 p=<0.0001

a PM_{10} (100) is the average number of hours per year that PM_{10} exceeded 100 $\mu g/m^3$ over the time period 1973-1977.

b RR = exp(IQR * β) whre IQR=interquartile range increase for PM_{10}(100) = (1032 hours/yr = 43 days/year). Time variable = attained age.

Table 8.6: Relative Risks[a] for Incidence of Female Breast Cancer[b] (1977-1992) With Selected Air Pollutants in the Total AHSMOG Cohort. Exposure Averaged From 1973 With Three-Year Lag. (n=4060, Cases=122).

Pollutant	Regression coefficient (β)	SE (β)	IQR[c]	RR[d] (95% CI)
PM_{10}, hrs in excess of[e]:				
40 μg/m³	0.000129	0.0000458	139 days	**1.54** * (1.14-2.08)
50 μg/m³	0.000133	0.0000452	149 days	**1.61** * (1.17-2.21)
60 μg/m³	0.000151	0.0000492	132 days	**1.61** * (1.19-2.19)
80 μg/m³	0.000186	0.0000642	78 days	**1.42** * (1.12-1.79)
100 μg/m³	0.000271	0.0001011	43 days	**1.32** * (1.08-1.62)
PM_{10}, mean concentration	0.019638	0.00541	29.5 μg/m³	**1.79** * (1.31-2.44)
O_3 mean concentration	0.004619	0.010327	12.3 ppb	1.06 (0.83-1.35)
NO_2 mean concentration	-0.007995	0.009092	19.3 ppb	0.86 (0.61-1.21)
SO_2 mean concentration	0.268622	0.022185	3.7 ppb	**2.70** * (2.30-3.17)

a Relative Risks based on time-dependent Cox Proportional Hazards Regression using interquartile range for increment and controlling for: years of education, pack-years of past cigarette smoking, total exercise, parental history of cancer, personal history of doctor-told asthma, current use of alcohol, and population density. Time variable was attained age

b ICDO-2 [Second International Classification of Diseases for Oncology] = C50
ICDO-1 [First International Classification of Diseases for Oncology] = 174

c IQR = Interquartile Range

d RR = Relative Risk; CI = Confidence Interval

e Average annual hours in excess of listed μg/m³, 1973 to 3 years before risk set (i.e. 3-year lag)

* $p < 0.05$

C. Long-Term Concentrations of Ambient Air Pollutants and Risk of *Prostate Cancer*

1. Introduction

The causes of prostate cancer are largely unknown. Suspected etiologic factors include: the hormone dependence of the prostate since growth and function of the prostate depend on sex hormones; sexual activity; diet, especially dietary fat; smoking; ionizing radiation; occupation, especially exposures to cadmium and possibly zinc and also rubber workers; and viruses including cytomegalovirus, herpes virus type 2 and some RNA viruses (*1*). Prostate cancer incidence also differs by race, family history, religion, socioeconomic status (*2*). The strongest risk factor is increasing age with the incidence rates doubling for each decade of life after 40 (*1*). Data on migrating populations also show the importance of environmental factors. For example, Shimizu et al. (*3*) showed a shift in risk toward the U.S. rates for Japanese immigrants moving from areas, such as Japan, where the prevailing prostate cancer rates are relatively low, to the United States, where the rates are high.

Some early studies did not show significant differences in prostate cancer between urban versus rural dwellers (*4*) whereas other studies did find positive associations with suspended particulate air pollution (*5*). Two early independent studies, the Nashville Air Pollution Study (*6*) and the Erie County Air Pollution Study (*7*) found positive associations between suspended particulate air pollution and prostate and gastric cancers. However, in the last several years there has been no convincing evidence of any positive association between air pollution and prostate cancer.

2. Methods

In order to compare these findings to those in the breast cancer analysis, the same list of covariates for prostate cancer was chosen as was used in the breast cancer analysis (see **Table 8.6**). These were: years of education, pack-years of past cigarette smoking, total exercise, parental history of cancer, personal history of doctor-told asthma, current use of alcohol, and population density. The time variable in the Cox proportional hazards regression models was attained age. The ambient air pollutants were averaged from 1973 to 3 years prior to each individual risk set (i.e. 3 year lag). The rational for using a 3 year lag was that our first incident cancer cases were diagnosed in 1977 and we wanted to have a full year (i.e. minimum of 12 contiguous months) on which to base our average air pollution metrics. We chose to begin cumulating monthly air pollution values starting in 1973 as years before that time had excessive amounts of missing monthly data.

The average mean concentrations lagged 3 years for PM_{10}, O_3, SO_2, and NO_2 were investigated in the total AHSMOG cohort in relation to the incidence of prostate cancer. Incident prostate cancers were defined by International Classification of Disease for Oncology codes (1^{st} revision = 185, 2^{nd} revision = C 61).

3. Results

The association of incident prostate cancer with the average mean concentrations of PM_{10}, O_3, SO_2 and NO_2 was investigated in the total AHSMOG cohort. The regression coefficients were negative for mean concentration of PM_{10}, O_3, and NO_2 (**Table 8.7**). The

association of prostate cancer incidence with an IQR increase in mean concentration of SO_2 was elevated, but not significant (RR = 1.37; CI: 0.85-2.18).

4. Discussion

No significant positive associations were observed between prostate cancer incidence and any of the mean concentrations of O_3, SO_2, NO_2, PM_{10}. Prostate cancer is the most commonly diagnosed incident cancer in males in the AHSMOG cohort. Some investigators have noted that carcinogenic organic compounds found in the ambient air (e.g. benzene, polycyclic aromatic hydrocarbons) tend to be concentrated in the adipose deposits of the body (e.g. breast tissue) once these chemicals become systemic (*8*).

The prostate gland is composed of smooth muscle and collagen fibers in which is embedded secretory glandular tissue (*9*). There is very little adipose tissue. The female breast, which contains more fat deposits, is thus possibly more likely to store and concentrate these carcinogenic hydrocarbons than is the prostate gland (*8*). The observation that female breast cancer was positively and statistically significantly associated with PM_{10} (see Table 8.9) while prostate cancer was not is consistent with this potential mechanism. It is also possible that prostate cancer may have a different lag structure compared to breast cancer.

In the AHSMOG study, breast cancer is the most common newly diagnosed cancer in females and prostate cancer is the most common newly diagnosed cancer in males. The finding in earlier reports by Mills et al. (*10*) and Abbey et al. (*11*) that particulate air pollution was statistically significantly associated with all malignant

neoplasms in females but not in males may be partially explained by these breast and prostate cancer associations with respirable particulates.

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Table 8.7: Relative Risks[a] for Incidence of Prostate Cancer[b] (1977-1992) With Selected Air Pollutants in the Total AHSMOG Cohort. Exposure Averaged From 1973 with Three-year Lag. (n=2202, Cases= 105).

Pollutant	Coefficient (β)	SE(β)	IQR	RR (95% CI)
PM_{10} - MC	-0.024940	0.005830	29.5 $\mu g/m^3$	0.48 (0.34 - 0.67)
O_3 - MC	-0.034526	0.013542	12.3 ppb	0.65 (0.47 - 0.91)
SO_2 - MC	0.045490	0.035028	6.84 ppb	1.37 (0.85 - 2.18)
NO_2 - MC	-0.010684	0.010254	19.3 ppb	0.81 (0.55 - 1.20)

Abbreviations: IQR = Interquartile Range, RR = relative risk = exp(IQR * β), CI = 95% confidence interval, MC = mean concentration

a Adjusted for: packyears of past cigarette smoking, education, alcohol, exercise, family history of cancer, personal history of asthma, and population density.

b International Classification of Disease for Oncology (1st revision = 185, 2nd revision = C61).

D. Long-Term Concentrations of Ambient Air Pollutants and Risk of *Non-Hodgkin's Lymphoma* (NHL)

1. Introduction

Risk factors for non-Hodgkin's lymphoma (lymph node cancers) are largely unknown but in part involve reduced immune function and exposure to herbicides and pesticides such as DDT (*1*) and perhaps ambient hydrocarbons as well as exposure to certain infectious agents (*2*). It has been estimated that there will be approximately 63,600 new cases of lymphoma in 2001 including 56,200 cases of non-Hodgkin's lymphoma (*2*). In essentially all countries, the incidence rate among males is higher than that among females (*3*).

Respirable particulates (PM_{10}) provide a mechanism whereby toxic chemicals can be delivered into the deep lung. Because of the minimal air flow velocity in the deep lung, particles settle out and come into contact with the alveolar walls. These toxic chemicals can then traverse the thin membrane of the alveolar sacks and get into the blood stream and lymphatic systems where they are carried throughout the body. Again using the smoking analogy whereby toxic chemicals in cigarette smoke (e.g. polycyclic aromatic hydrocarbons) may be deposited in organs not in direct contact with the air (e.g. urinary bladder, pancreas, cervix uteri and renal pelvis), the association between the particulate air pollutants and cancer of the lymph nodes (i.e. non-Hodgkin's lymphoma) was investigated as an *a priori* hypothesis.

Cancer of the lymph nodes (ICD9-1 = 196, 200, 202, ICD9-2 = C77) is often metastatic from other organ sites. In the analyses below, only primary lymph node

cancers were included. Hodgkin's disease (ICD9-1 = 201) was excluded from the analysis. This was because Hodgkin's disease is distinguished by its atypical clinical features and unusual epidemiology with the clinical and histologic features of Hodgkin's disease suggesting a chronic infectious process (*4*). The identification of Reed-Sternberg cells distinguish Hodgkin's disease from the other lymphomas, leaving a collection of diseases regarded as non-Hodgkin's lymphomas (*5*).

2. Methods

As is stated in Section B above regarding breast cancer incidence, the same air pollution metric [$PM_{10}(100)$] was used to develop the lymphoma model. **Table 8.8** lists the effects on the RR in the model that evaluates the association between $PM_{10}(100)$ and risk of incident lymphoma by the addition, one at a time, of potential confounders. The primary criterion for selection of confounders was that the inclusion of the variable changed the RR by more than 10%. None of the variables did so. A second, less important criterion, was that inclusion of the variable significantly changed the log likelihood ratio test. Only parental history of cancer (females), personal history of doctor-told asthma (males), current use of alcohol (females) and population density (both genders) were statistically significant. These were added to the reduced model to make the final model for both genders.

3. Results

During the 15 years of follow-up (1977-1992), 34 incident lymphomas (females: n=14, males: n=20) were identified. In males in the total AHSMOG cohort, an IQR increase of average (from1973 with 3 year lag) annual hours of concentration in excess of 100 $\mu g/m^3$ of PM_{10} [$PM_{10}(100)$] was associated with a two fold increased risk which was statistically significant (RR=2.39; CI: 1.45-3.97) (**Table 8.9**). The association was elevated but not significant in females (RR=1.57; CI: 0.84-2.94).

Lymphoma was significantly associated with the highest exceedance frequency of ozone in both genders based on the average number of hours per year that ozone exceeded 150 ppb [$O_3(150)$]. For an IQR increase in $O_3(150)$, the RR for males was 3.61 (CI: 1.69-7.76) and the RR in females was 2.36 (CI: 1.02-5.50). To evaluate the effect of a more parsimonious model because of the limited number of cases, the covariates were restricted to only education and past cigarette smoking and this had little effect on the point estimates. For example, with only two covariates in the model, the association with $O_3(150)$ in males changed from 3.62 to 3.68 (CI: 1.77-7.62) and the association with $O_3(150)$ in females changed from 2.36 to 2.37 (CI: 1.11-5.07) and the width of the confidence intervals decreased only slightly.

The gender differences mentioned earlier was also observed in the AHSMOG study where males were only 35.9% of the total cohort yet contributed to 58.8% (20/34) of the lymph node cancers.

4. Discussion

In secondary analyses, elevated associations were observed between respirable particulate air pollution and incidence of cancer of the lymph nodes which was true for both males and females. This is consistent with other investigators. In a study of 1,570 deceased workers from the California Department of Transportation, Maizlish et al. (*6*) observed a proportional mortality ratio of 157 (95% CI: 115-210) for lymphopoietic cancers in white males who worked in dusty environment. Another study (*7*) of 2,878 cases of malignant lymphomas in Germany found suggestions of environmental cofactors in the pathogenesis of malignant lymphomas.

Air pollution can be a source of a wide variety of hazardous chemicals that may enter the blood stream. Hydrocarbons in the air have been implicated as risk factors for lymphoma. Badman and Jaffé (*8*) note that pesticides and herbicides are ubiquitous resulting in an estimated exposure rate of 90% of the U.S. population. An increased risk of non-Hodgkin's lymphoma has been associated with exposure to these chemicals (*9*).

Synthetic chlorinated hydrocarbon compounds are widespread and present throughout the United States and strong epidemiological evidence has linked exposure to these chemicals to a high incidence of non-Hodgkin's lymphoma (*10*). A number of epidemiological studies have found increased risk of Non-Hodgkin's lymphoma with exposure to a variety of solvents. Lisiewicz (*11*) reports that lymphoma risk is increased after exposure to irradiation, pesticides, electomagnetic fields, and benzene, the latter being associated with a more polluted ambient environment. Hatzissabas and colleagues (*12*) suggest that of the different patterns of lymphoma distributions, large cell

lymphomas apparently are more prominent in highly industrialized regions where there are more toxic and immunosuppressive substances in the environment.

Diet has also been investigated by other researchers in relation to the etiology of non-Hodgkin's lymphoma. In a prospective cohort study of 15,914 Norwegians followed for more than 11 years, a RR of 3.36 (p=0.007) associated with drinking 2 or more glasses of milk/day was reported for the incidence of lymphoma (*13*). And in a study of vegetable and fruit consumption, investigators found an increased smoking-adjusted risk of Non-Hodgkin's lymphoma (RR=1.5, 95% CI: 1.0-2.2) in the highest tertile of green vegetable consumption (*14*). It is possible that diet may modify the association of non-Hodgkin's lymphomas with air pollutants. The effect of these dietary factors on risk of cancer of the lymphatic tissues can be further explored in the AHSMOG study (*15*) as we have consumption of milk, fruit, cooked green vegetables, green salads, and other foods measured at baseline.

In a nested case-control study with equal follow-up time for a case and the matched controls, Raaschou-Nielsen, et al. (*16*) evaluated the effects of air pollution from traffic at the residence of children with cancer living in Denmark and found that the risk of lymphomas increased by 25 % for a doubling of the concentration of benzene (RR=1.25; CI: 0.99 - 1.58) and a 51% increase for a doubling concentration of NO_2 (RR=1.51; CI: 0.99 - 2.30). The association between risk of lymphomas and exposure in utero was more consistent than exposure during childhood where exposure cumulations for the pregnancy period were calculated from presumed date of conception until date of

birth and the exposure cumulations for the childhood period were calculated from date of birth. All analyses incorporated a 1-year lag for exposure assessment.

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Table 8.8: Change in Relative Risk of Lymph Node Cancer and Selection of Potential Covariates Associated With an IQR[a] Increase in Hours/Year PM_{10} Exceeded 100 $\mu g/m^3$ (1973-1977). Part 1 of 2

	Males (cases=20)		Females (cases=14)	
Model PM_{10} (100) $\mu g/m^3$	RR[b] (95% CI)	-2 log L p-value	RR[b] (95% CI)	-2 log L p-value
Main effects (ME) (packyears+education)	2.59 (1.51-4.43)	N/A	1.40 (0.76-2.61)	N/A
ME + BMI (3 dummies)	2.66 (1.55-4.58)	2.435 p=0.487	1.39 (0.75-2.59)	4.354 p=0.226
ME + exercise (dummy)	2.58 (1.51-4.42)	0.054 p=0.816	1.41 (0.76-2.62)	0.567 p=0.451
ME + parents cancer history (dummy)	2.58 (1.50-4.41)	2.884 p=0.089	1.30 (0.65-2.60)	32.01 p<0.0001
ME + asthma history (dummy)	2.66 (1.52-4.63)	14.377 p=0.0001	1.40 (0.75-2.61)	2.292 p=0.130
ME + occupation air pollution	2.60 (1.52-4.45)	0.145 p=0.703	1.41 (0.76-2.62)	2.227 p=0.136
ME + alcohol (dummy)	2.63 (1.55-4.47)	3.174 p=0.075	1.58 (0.85-2.94)	14.956 p=0.0001
ME + lived with smoker (2 dummies)	2.58 (1.51-4.41)	0.355 p=0.837	1.39 (0.75-2.61)	0.348 p=0.840
ME + worked with smoker (2 dummies)	2.64 (1.57-4.45)	2.707 p=0.258	1.41 (0.75-2.63)	0.184 p=0.912
ME + hrs outside in summer (2 dummies)	2.57 (1.50-4.39)	1.241 p=0.538	1.39 (0.75-2.59)	0.47 p=0.791
ME + hrs exercise outside in sum. (2 dummies)	2.57 (1.51-4.40)	0.188 p=0.910	1.40 (0.76-2.61)	0.055 p=0.973
ME + fruit index-2 (continuous)	2.59 (1.51-4.45)	0.449 p=0.503	1.39 (0.748-2.57)	1.985 p=0.159

Table 8.8: Change in Relative Risk of Lymph Node Cancer and Selection of Potential Covariates Associated With an IQR[a] Increase in Hours/Year PM_{10} Exceeded 100 $\mu g/m^3$ (1973-1977). Part 2 of 2

	Males (cases=20)		Females (cases=14)	
Model PM_{10} (100) $\mu g/m^3$	RR[b] (95% CI)	-2 log L p-value	RR[b] (95% CI)	-2 log L p-value
ME + fruit & vege-2 (1 dummy)	2.60 (1.51-4.46)	0.630 p=0.427	1.41 (0.76-2.62)	0.033 p=0.856
ME + fruit & vege-3 (1 dummy)	2.58 (1.51-4.43)	0.402 p=0.526	1.41 (0.76-3.62)	0.05 p=0.823
ME + total meat (2 dummies)	2.56 (1.48-4.44)	0.047 p=0.977	1.33 (0.71-2.49)	1.844 p=0.476
ME + green vege. (2 dummies)	2.55 (1.47-4.41)	1.635 p=0.442	1.39 (0.75-2.60)	1.408 p=0.495
ME + vege & salad & tomatoes (2 dummies)	2.57 (1.50-4.42)	2.04 p=0.361	1.40 (0.75-2.60)	4.581 p=0.101
ME + vit A, C, E & multiple vit. (1 dummy)	2.57 (1.51-4.40)	0.236 p=0.627	1.43 (0.77-2.67)	2.92 p=0.087
ME + green salads (2 dummies)	2.59 (1.51-4.44)	0.004 p=0.998	1.39 (0.75-2.59)	2.749 p=0.253
ME + population density (1 dummy)	2.67 (1.52-4.67)	11.642 p=0.0006	1.58 (0.84-2.98)	12.451 p=0.0004

a IQR=interquartile Range = 1032 hrs/yr = 43 days/yr.
b RR = exp (IQR * β), time variable = attained age.

Table 8.9: Relative Risks for Incidence of Cancer of the Lymph Nodes[a] With Selected Air Pollutants in the Total AHSMOG Study. Exposure Averaged From 1973 With Three-Year Lag.

	Males (n=2278, cases=20)		Females (n=4060, cases=14)	
Air pollutant	RR[b]	95% CI	RR	95% CI
PM_{10} (100) [c]	**2.39** *	1.45 - 3.97	1.57	0.84 - 2.94
O_3 (150) [d]	**3.62** *	1.69 - 7.76	**2.36** *	1.02 - 5.50
SO_2 - MC [e]	**2.28** *	1.56 - 3.45	1.46	0.80 - 2.66
NO_2 - MC[f]	2.34	0.99 - 5.50	1.14	0.40 - 3.21

a Lymph node cancer defined as International Classification of Disease for Oncology [ICDO] (1st edition: 196, 200, 202); ICDO (2nd edition: C77). Hodgkins lymphoma excluded.
b RR=Relative risk based on time-dependent Cox proportional hazards regression controlling for: years of education, pack-years of past cigarette smoking, and current use of alcohol for interquartile range (IQR) increases as defined below:
c Average annual hours in excess of 100 $\mu g/m^3$ of PM_{10} (IQR = 1032 hrs/yr = 43 days/yr)
d Average annual hours in excess of 150 ppb of O_3 (IQR = 185 hrs/yr)
e Average annual mean concentration of SO_2 (IQR = 6.84 ppb)
f Average annual mean concentration of NO_2 (IQR = 19.3 ppb)
* $p < 0.05$

CHAPTER 9

DESCRIPTION OF THE CANCER SURVEILLANCE SYSTEM

A. Cancer Ascertainment for the Follow-Up Period (1977-1982)

Cancer incidence for the AHSMOG study was obtained for the time period 1977 through 1992. Since study subjects for the AHSMOG cohort are also members of the larger Adventist Health Study (AHS), the follow-up can be divided into two separate time periods: 1977-1982 and 1983-1992. During the earlier time period the AHS identified incident cancers and all cause mortality. In addition to computer-assisted record linkage with regional cancer registries, we also obtained notification of hospitalizations from the respondents themselves via the return of annual mailed questionnaires which included an informed consent form (see **Appendix C**) which included their permission for our study staff to review their medical records for diagnosis of cancer. The following text describes the cancer surveillance system under the AHS and was transcribed from:

> Beeson WL, Fraser GE, Mills PK. Validation of record linkage to 2 California population-based tumor registries in a cohort study. In: *Proceedings of the 1989 Public Health Conference on Records and Statistics.* DHHS publication no. (PHS) 90-1214, 1990. pp 196-201.
>
> [Used by permission of NCHS]

1. Introduction

The Adventist Health Study (AHS) is a prospective cohort study of 34,198 non-Hispanic white Seventh-day Adventists (SDAs) followed for 6 years (1977-1982) for cancer incidence and all cause mortality (*1*). These study subjects were all California residents at the time the study began in August, 1974.

Previous reports (*1-3*) have documented lower age-adjusted sex-specific mortality rates for cancer, cardiovascular disease, and several other chronic diseases among SDAs when compared to either the total United States white population or to a comparable population of nonsmoking whites living in California..

The primary aim of the AHS is to relate the diet and other lifestyle characteristics to long-term (10-15 years) site-specific risk of cancer among the study population. During 1973 through 1988, the study has been funded by the National Cancer Institute.

2. Self-Reporting of Hospitalizations

Previous report (*1*) contains the flow chart of the overall study plan for the AHS. This report refers only to the Incidence Population portion of the larger study. The baseline questionnaire included demographic variables, information of current and past dietary habits, exercise patterns, use of prescription drugs, use of alcohol and tobacco, measures of religiosity, occupation and residential histories, anthropometric data, and menstrual and reproductive histories.

The primary procedure utilized in the effort to monitor cancer incidence in the AHS involved the completion of annual hospital history forms by the study subjects.

After collection of baseline exposure data in the fall of 1976, each member of the Incidence Population received a mailed annual hospital form beginning in 1977. This form requested participants to record whether they experienced an overnight hospitalization in the appropriate period since last contact and, if so, to provide the name and address of the hospital, and dates of last discharge. They were then requested to sign a consent fo the AHS to review these medical records.

Annual mailing of hospital history forms took place between 1977 and 1983, only 1095 subjects (3.2%) had refused to respond to these annual hospital history forms. During the six years of follow-up, 18,053 individuals had reported a total of 32,451 hospitalizations representing 27,929 separate hospital charts in 1658 different hospitals. Many individuals reported multiple admissions for a given hospital.

The AHS sought endorsement from the California Hospital Association as a bona fide research project (see **Appendix D**). This endorsement of the need for the AHS to review medical records for cancer was relayed to each of the California hospitals via the weekly newsletter published by the Association (*4*).

As members of the Incidence Population began reporting hospitalizations to the AHS, the field operation component of the AHS came into existence. This was responsible for contacting the hospitals reported by study members and sending trained AHS field representatives to these hospitals to review and microfilm pertinent sections of the relevant medical records.

3. Confidentiality and Human Subjects Considerations

Since 1973, all study procedures and forms have been annually reviewed and approved by the Loma Linda University Human Subjects Committee. All names of subjects were deleted from the copies of the tumor abstract forms obtained from the two tumor registries described below. The only unique identifier recorded on these forms was the ID number for the Adventist Health Study. Furthermore, these copies were filed separately from the Census Questionnaire (1974) and the annual follow-up forms, which are the only AHS forms that contain names of study subjects.

As a second step the AHS approached the California law partnership of Musick, Peeler & Garrett for a legal opinion regarding whether hospitals' Medical Records' Custodians may release patient identifiable information in connection with the Adventist Health Study research project, when there is no patient authorization for the disclosure (See **Appendix E**). The firm concluded that "California law and general federal and national standards of confidentiality permit the disclosures that are requested and, based upon our review of the safeguards provided by this research team for the confidentiality of the data, we have concluded that hospitals should be encouraged to provide the requested information. . .Releasing the requested records in connection with this study (AHS) is lawful, even if there is no patient authorization. In this regard, the California Confidentiality of Medical Information Act, Civil Code Section 56 *et seq.*, provides that hospitals may release patient identifiable medical information to clinical investigators for bona fide research purposes without having any patient authorization. Specifically, Civil

Code Section 56.10.c.7 provides that a health care provider does not need patient authorization and may disclose medical information . . ." (*5-6*).

The AHS followed the code of federal regulations for the protection of human subjects as set forth by the Department of Health and Human Services, the National Institutes of Health, and the Office for Protection from Research Risks (*7*). These regulations implement the amendments to the National Research Act, Public Law 93-348, July 12, 1974. Ethical principles and guidelines for the protection of human subjects of research ("The Belmont Report") was also followed by the AHS (*8*).

Epidemiology has made major contributions to the understanding of the etiology of disease through the implementation of studies in which medical records of large populations were used. Gordis and Gold have identified many studies of cancer, cardiovascular disease, infectious diseases and child health where medical record review was an important part of the research (*9*).

4. Computer-Assisted Record Linkage

Assembly Bill 136 (September, 1985) made cancer a reportable disease in the state of California. Section 211.3 of the Health and Safety Code states: "The director shall establish a statewide system for the collection of information determining the incidence of cancer, using population-based tumor registries. . .By July 1, 1990, the statewide cancer reporting system shall be fully operational." The state has been divided into 10 regions (**Figure 9.1**) and Regional Cancer Registries have been funded by the Department of Health Services to process the cancer incidence data with the 10 regions.

In an initial effort to reduce the cost of sending an AHS representative to each of the 698 California hospitals reported by AHS subjects, it was noted that 289 of these California hospitals reported to two population-based tumor registries. (See Regions 8 & 9 on **Figure 9.1**).

The Bay Area Tumor Registry (Region 8) represents 1.6A% of the area and 13.0% of the population of California. The Los Angeles Tumor Registry (Region 9) represent 2.6% of the area and 30.1% of the population of California. Approximately 23% of the AHS population ever lived in one of these two regional tumor registries compared to 43% of the general California population.

Study subjects who had cancer diagnosed or treated in one of these hospitals located in a population-based tumor registry were identified by computer-assisted record linkage with the centralized records of the two operating tumor registries in California (Resource for Cancer Epidemiology operated by the State Department of Health and Human Services in Oakland, and the Cancer Surveillance Program operated by the University of Southern California in Los Angeles). For cases identified by record linkage, we obtained documentation of the original tumor abstract which was prepared for the tumor registry by hospital staff or tumor registry staff. This enabled AHS staff to recode and process the cancer information in a comparable way to the information obtained from hospitals that do not report to a centralized population-based tumor registry.

5. Cancer Surveillance Program

Computer-assisted record linkage with this Los Angeles county tumor registry was performed by software written by the author (WLB) and included the following variables: 1) sex, 2) position 1-4 of last name, 3) position 5-8 of last name, 4) position 9-11 of last name, 5) position 1 of first name, 6) position 2-5 of first name, 7) position 6-8 of first name, 8) middle initial, 9) month of birth, 10) day of birth, 11) year of birth [± 5 years], 12) state of birth. Social Security numbers were not available in the AHS dataset.

The possible matches were resolved by clerical review by AHS staff using ancillary data including the name of spouses and addresses. Validation of a similar process (same algorithm of matching variables) used for the computerized linkage portion of ascertainment of fatal events from California death certificate files indicated that it ascertained 93.2% of known fatal events and there was no evidenced that it would not be similar for nonfatal events (*2*).

6. Resource for Cancer Epidemiology

Computer-assisted record linkage with the San Francisco-Oakland Metropolitan Statistical Area composed of five counties surrounding the Bay area was predicated on a pair-wise comparison of the same variables used in the record linkage with the Los Angeles tumor registry. The computer software for linkage was adapted from the Fellegi-Sunter record linkage model (*10*). Each file is blocked by the New York State Identification Information System (NYSIIS) surname phonetic code which is assigned to each file according to the surname and sex. NYSIIS is a phonetic coding system that

incorporates the best features of many phonetic coding systems including Soundex (*11*). The computer program generates all possible comparison pairs within each NYSIIS and sex block. Minor variations between the items of identification are accounted for in the numerical algorithm which eventually categorizes each link as: 1) not a match, 2) possible match, and 3) definite match (*12*). Possible matches were resolved by tumor registry personnel utilizing ancillary data supplied by AHS.

7. Validation of Record Linkage

Prior to the final record linkage between the AHS and the two above mentioned population-based tumor registries one of the authors (GEF) was awarded a grant from the National Heart, Lung and Blood Institute of the National Institutes of Health to evaluate the relation of many lifestyle and psychosocial characteristics to risk of fatal and non-fatal ischemic heart disease (IHD) in this nonsmoking population.

This study with IHD endpoints was an "add-on" to the already funded study of the same population with cancer endpoints. Overall, the cooperative nature of the studies has been beneficial, with the cost of the cardiovascular study being less than 20% that of the cancer study, due to the joing use of resources.

Ascertainment of suspected hospitalized IHD cases necessitated AHS field representatives to visit hospitals in the above mentioned tumor registry areas (in addition to the hospitals not reporting to a tumor registry already being visited to find cancer outcomes) to substantiate IHD diagnoses with ECG data, cardiac enzymes, doctors notes, etc. While the field representative was reviewing the chart for evidences of IHD he or

she made notice as to whether the patient had evidence of malignant neoplasm diagnosed during the study period (Lifestyle Questionnaire return date to 12/31/82).

While in the hospital the field representative completed an AHS Discharge Diagnosis Form (DDF) for each hospital record reviewed. This DDF contained 30 disease categories which were checked by the AHS field representatives for diseases occurring one or more times in a given hospital record. Copies of records for study subjects admitted to one of the 960 non-California hospitals were obtained by mail and the DDF was completed by AHS staff at Loma Linda University.

Table 9.1 shows the number of hospitals and hospitalizations reported by the study subjects during the six year follow-up period. By the end of the follow-up period, 12.0% of the population had moved out of California. This resulted in 8.6% of the reported hospitalizations in non-California hospitals where medical records were obtained by mail. Of the remaining California hospitalizations, 20.4% were in hospitals reporting to one of two population-based tumor registries.

All of the invasive cancers identified by AHS field representatives while reviewing medical records in hospitals that report to one of the two population-based tumor registries were also identified independently by the computer-assisted record linkage mechanism (**Table 9.2**). However, there were 43 incident cancers (3.1% of total ascertained) that were identified only by the computer-assisted record linkage.

Table 9.3 itemizes the different reasons why the AHS field representatives did not find these new cancer cases identified only by computer-assisted record linkage. The single most frequent reason (46.5%) was that the AHS was not aware of the

hospitalization since the study subject failed to return the annual hospital history forms which should have elicited the hospital stay information. Of particular note was that none of these non- reascertained cancers were respiratory sites (e.g. lung) which are the primary targets for the health effects of ambient air pollution.

8. Summary

Computerized record linkage with population-based tumor registries is an efficient and cost-effective means of identifying incident cancers in a geographical region. Cancer cases identified by computerized record linkage were obtained at a fraction of the cost as those obtained by visual inspection of the medical record. In no case did computerized record linkage fail to ascertain a cancer case that was identified by review of medical records by AHS trained personnel. Record linkage also identified additional cancers that would have been missed using the traditional personal review mechanism.

9. Acknowledgments

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Table 9.1: Number of Hospitals Reported by Adventist Health Study Subjects by Geographical Region, 1976-1982.

Geographical region	Number of hospitals		Number of hospitalizations reported by study subjects	
	N	%	N	%
CSP[1]	208	29.8	4,731	16.0
RCE[2]	81	11.6	1,321	4.4
Other hospitals in California	409	58.6	23,610	79.6
Subtotal Calif.	698	100.0	29,662	100.0
Subtotal non-Calif.	960	100.0	2,789	100.0
Total U.S.	1,658		32,451	

1 CSP=Cancer Surveillance Program covers the county of Los Angeles

2 RCE=Resource for Cancer Epidemiology covers the counties of Alameda, Contra Costa, Marin, San Francisco, and San Mateo.

Table 9.2: Number of New Incident Cancer Cases in the Adventist Health Study (AHS) by Geographical Region and Method of Ascertainment, 1976-1982.

Geographical region	Ascertained only by AHS field rep.	Ascertained only by record linkage	Ascertained by both	Total
CSP[1]	0	34	191	225
RCE[2]	0	9	35	44
Outside the two tumor registries	1,137	n/a	n/a	1,137
Total	1,137	43	226	1,406

1 CSP=Cancer Surveillance Program covers the country of Los Angeles

2 RCE=Resource for Cancer Epidemiology covers the counties of: Alameda, Contra Costa, Marin, San Francisco, and San Mateo.

Table 9.3: Reasons Why AHS[1] Field Representatives Did Not Reascertain the New Cancer Case Identified by Computer-Assisted Record Linkage. Part 1 of 2

Number of subjects	ICD9[2] Code	Cancer	Field representatives observations
1	153	Colon	Subject located in hospital master file but record is lost
3	169	Hemato-poietic	a) Disease of blood forming organs b) Other circulatory system disease c) Died in Mexico, never reported a hospitalization
2	171	Connective, Soft tissue	a) Digestive, genitourinary b) Musculoskeletal or connective tissue
5	173	Skin	a) No hospitalizations reported b) Nose skin cancer (outpatient only) c) Myocardial infarction d) No hospitalizations reported e) No hospitalizations reported
2	174	Breast	a) Acute myocardial infarction b) CVA, other circulatory

1 AHS = Adventist Health Study

2 ICD9 = International Classification for Disease (9th revision)

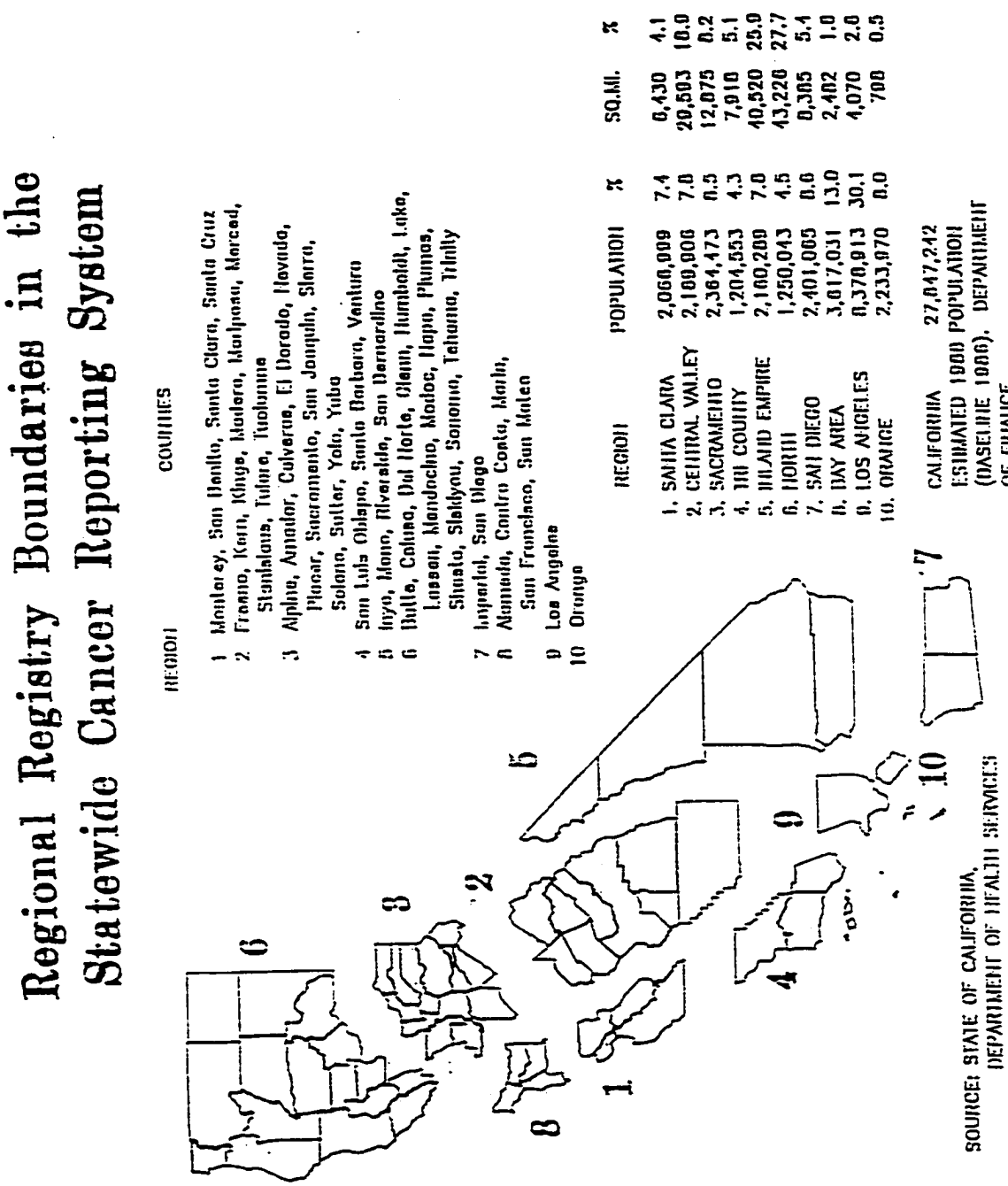
* (ICD9=153, n=1) (ICD9=154, n=2) (ICD9=158, n=1) (ICD9=162, n=3) (ICD9=169, n=2) (ICD9=174, n=3) (ICD9=180, n=3) (ICD9=182, n=1) (ICD9=185, n=2) (ICD9=191, n=1) (ICD9=193, n=1)

Table 9.3: Reasons Why AHS[1] Field Representatives Did Not Reascertain the New Cancer Case Identified by Computer-Assisted Record Linkage. Part 2 of 2

Number of subjects	ICD9[2] Code	Cancer	Field representatives observations
1	180	Cervix uteri	Outpatient only (cancer in situ - excised - patient discharged same day
1	182	Corpus uteri	Moved to Brazil right after hospitalization
1	184	Vulva	Tumor registry DX=12/17/82 but field rep.="all adm. > Dec, 1982" (i.e. after end of study)
5	185	Prostate	a) Benign prostatic hypertrophy b) Benign prostatic hypertrophy c) Died < 2 mo. after lifestyle quest. return d) Endocrine, nutritional, immunity e) no cancer reported (by phone)
1	188	Bladder	Endocrine, nutritional, immunity
1	194	Pituitary	Digestive - appendicitis
23	Subjects who returned the annual AHS Hospital History forms		
20*	Subjects who did not return the annual AHS Hospital History forms (i.e. no hospitalization reported)		
43	Total cancer cases identified only by record linkage		

1 AHS = Adventist Health Study
2 ICD9 = International Classification for Disease (9th revision)
* (ICD9=153, n=1) (ICD9=154, n=2) (ICD9=158, n=1) (ICD9=162, n=3) (ICD9=169, n=2) (ICD9=174, n=3) (ICD9=180, n=3) (ICD9=182, n=1) (ICD9=185, n=2) (ICD9=191, n=1) (ICD9=193, n=1)

Figure 9.1: Regional registry boundaries in the California statewide cancer reporting system.



B. Cancer Ascertainment for the Follow-Up Period (1983-1992)

Computer-assisted record linkage with the California Cancer Registry (CCR) resulted in 250 reportable cancers (all sites) for the total AHSMOG cohort diagnosed between January 1988 through March, 1992 . Of these, 209 (83.6%) were also identified through contact either by returned mailed questionnaire or phone call with study subject or his/her surrogate (if subject was deceased). The remaining 41 (16.4%) cancers were not reascertained through self-report or phone tracing. The reasons that these latter cancers were missed via the non-record linkage follow-up process are described in **Table 9.4** (males) and **Table 9.5** (females). The frequency distribution of these non-selfreported cancers is listed in **Table 9.6**. Again, of special note is that none of these cancers that were not self-reported were lung cancers.

We also obtained notification of hospitalization for the diagnosis and treatment of cancer by self-report of the study subjects when they returned the mailed questionnaires in 1987 and 1992. This process covered the period from 1983 through 1987 when the CCR was not fully operational. Several studies have indicated that patient's self-reports are generally fairly accurate (*1-3*)

A second legal opinion from McCutchen, Doyle, Brown & Enersen, Counselors at Law (see **Appendix F**) was obtained in 1995 to get an update on the law regarding the release of patient information from hospitals and other providers of health care services, regardless of the presence of a signed consent authorizing such release.

1. References

1. Katz JN, Chang LC, Sangha O, Fossel AH, Bates DW. Can comorbidity be measured by questionnaire rather than medical record review? Med Care 34:73-84 (1996).

2. Kriegsman DM, Penninx W, van Eijk JT, Boeke AJ, Deeg DJ. Self-reports and general practitioner information on the presence of chronic diseases in community dwelling elderly. A study on the accuracy of patients' self-reports and on determinants of inaccuracy. J Clin Epidemiol Dec; 49(12):1407-17 (1996).

3. Haapanen N, Miilunpalo S, Pasanen M, Oja P, Vuori I. Agreement between questionnaire data and medical records of chronic diseases in middle-aged and elderly Finnish men and women. Am J Epidemiol 145:762-9 (1997).

Table 9.4: Reasons Why Cancers Identified via Record Linkage With California Cancer Registry Were Not Also Self-Reported by Study Subject in AHSMOG Study (1983-1992). Males Only.

Vital status	Reason for non self-report of cancer	Freq.
Deceased	Lost-to-followup (i.e. a surrogate could not be located)	2
	Spouse surrogate said "no" to cancer question via phone call	7
	Non-spouse surrogate said "no" to cancer question via phone call (friend, brother-in-law, daughter)	3
	Died after 4/92 but response to cancer question on 4/92 questionnaire = "no"	1
Not known dead	Response to cancer question on 4/92 questionnaire = "no" *	4
	Response to cancer question via phone tracing (self) = "no"	2
Totals		**19**

* One subject changed answer from "yes" to "no" on 1992 questionnaire

Table 9.5: Reasons Why Cancers Identified via Record Linkage With California Cancer Registry Were Not Also Self-Reported by Study Subject in AHSMOG Study (1983-1992). Females Only.

Vital status	Reason for non self-report of cancer	Freq.
Deceased	Lost-to-followup (i.e. a surrogate could not be located)	2
	Spouse surrogate said "no" to cancer question via phone call	1
	Non-spouse surrogate said "no" to cancer question via phone call (friend, friend, niece, daughter, friend, grand daughter, friend)	7
	Non-spouse surrogate said "don't know" to cancer question via phone call	2
	Died after 4/92 (but non-spouse surrogate said "no" to cancer question via phone call	1
Not known dead	Lost-to-followup (could not be located)	1
	Response to cancer question on 4/92 questionnaire = "no"	7
	Response to cancer question via phone tracing (self) = "no"	1
Totals		**22**

Table 9.6: Organ Sites for Record Linkage Only Cancers in the AHSMOG Cohort (1988-1992).

Site	ICD9-2	Frequency
Stomach	C16	2
Colon	C18	4
Rectosigmoid junction	C19.9	1
Rectum	C20	2
Gallbladder	C23	2
Pancreas	C25	2
Site	C34	3
Pleura	C38	1
Bone marrow	C40	3
Skin	C44	5
Cervix uteri	C53	1
Corpus uteri	C54	1
Prostate	C61	6
Bladder	C67	5
Lymph nodes	C77	3
Total		41

Abbreviations: ICDO-2 = International Classification of Diseases for Oncology· 2nd revision

CHAPTER 10

SUMMARY AND CONCLUSIONS

A. Summary

The following cancers: lung cancer; all nonskin cancers; smoking-related cancers; breast cancer; prostate cancer; and non-Hodgkin's lymphoma were investigated in relation to long-term cumulated averages of PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, O_3, SO_2, and NO_2. **Table 10.1** gives a summary of which organ sites were associated with the individual ambient air pollutants. The analyses for smoking-related cancers, breast cancer, prostate cancer, and non-Hodgkin's lymphoma should be considered as preliminary only.

For respirable particulates (PM_{10}), statistically significant positive associations were observed for lung cancer in males, all nonskin neoplasms in both genders, breast cancer in females and non-Hodgkin's lymphoma in males. The fine fraction ($PM_{2.5}$) of respirable particulates was only significantly associated with lung cancer in males, but in general was more strongly associated with the various cancer endpoints than was the coarse fraction ($PM_{10-2.5}$).

The exceedance frequencies of ozone were associated with lung cancer in males but not females. The highest exceedance frequency for ozone (hours/year > 150 ppb) was also associated with all nonskin neoplasms in both genders and non-Hodgkin's lymphoma in both genders. It should be noted that, although the magnitude of the regression coefficients monotonically increased (i.e. dose response) as the exceedance frequency for different ozone densities increased for both genders, ozone tended to drop

out in multipollutant analyses, but not always. This observation of a general lack of independent effect along with the fact that ozone (measured in hours/year > 100 ppb) is highly correlated (r = 0.83) with PM_{10} (measured in days/year > 100 $\mu g/m^3$) and that PM_{10} demonstrated similar associations with all nonskin cancer and non-Hodgkin's lymphonma as was observed for ozone seems to imply that the associations observed for ozone may be acting a surrogates for particulate air pollution. Ozone is essentially a secondary pollutant formed in the air by the interaction of oxides of nitrogen and carbon-containing compounds in the presence of solar radiation. These precursors of ozone are frequently generated by the same process of incomplete combustion of organic fuels as what generates much of the respirable particulates. Therefore, it is likely that the ozone effects observed in this study may be serving as markers for a respirable particle effect.

The statistically significant association of mean concentration of SO_2 was consistent across the different cancer endpoints. However, because the magnitude of the concentration distribution of SO_2 observed in this study does not support a strong physiological effect, it is less likely that SO_2 was a causal factor than that it was serving as a surrogate for other pollutants in the complex mixture resulting from the combustion of fossil fuels. What SO_2 may be serving as a surrogate for may be multifactorial and synergistic in that the univariate correlations between SO_2 and the other pollutants investigated in this research tended to be quite low. Mean concentration of NO_2 had only a borderline association with non-Hodgkin's lymphoma in males. This latter observation needs more investigation.

Previous researchers have published cancer associations to air pollution which are sometimes quite different for males and females. This research suggests that any of the following possibilities might contribute to these gender differences: 1) males report spending more time outdoors compared to females; 2) inclusion of lung cancers that are not histologically confirmed may create a differential bias; 3) the synergistic or complementary effect of air pollutants on the human body may be different for males and females; 4) the lack of a lag structure in the analysis of an air pollution index as regards to cancer incidence may give a distorted picture of the true relationship of the air pollutant; 5) exclusion of skin cancers in the all malignant neoplasm category reduces the gender differences; 6) insufficient follow-up of the study population for cancer incidence may lead to transient gender differences that may diminish with a longer follow-up; and 7) major gender-specific cancer cites (e.g. breast cancer and prostate cancer) contributing to the all malignant neoplasm category may have quite different responses to the long-term effects of air pollution.

We generally breathe complex mixtures of gases and airborne particles. This research provides additional evidence that ozone and SO_2 may act either as cocarcinogens (i.e. cancer promotors) in that they may facilitate or increase the effect of a carcinogen by direct concurrent effect of the relevant tissue or may simply be markers for carcinogenic-containing air pollutants. Airborne carcinogens are most effectively delivered to the lower respiratory system via respirable particles (PM_{10} in general and $PM_{2.5}$ in specific). A suggested next step would be to identify the chemical makeup and biochemistry of these potentially hazardous particulates.

At this point in time the effects of air pollution on health in general and cancer incidence in particular is not well understood. More studies are needed with larger number of study subjects with individual measurements of air pollutants and reduced measurement error on relevant covariables.

Table 10.1: Statistically Significant ($p < 0.05$) Associations of Ambient Air Pollutants, as Measured by Mean Concentration (μ)[a] and Exceedance Frequency Statistics, With Cancer Outcomes (1977-1992) for the AHSMOG Study.

Cancer site & Gender	New cases 1977-92	PM_{10}	$PM_{2.5}$[b]	$PM_{10-2.5}$[b]	O_3	SO_2	NO_2
Lung							
M	16	40+[c], μ	μ	none[d]	80+	μ	none
F	20	none	none	none	none	μ	none
Nonskin							
M	280	100, μ	none	none	150	μ	none
F	424	100, μ	none	none	150	μ	none
Smoking-related							
M	28	none	defer[e]	defer[e]	none	border	none
F	34	none	defer[e]	defer[e]	none	μ	none
Breast							
F	156	40+, μ	defer[e]	defer[e]	none	μ	none
Prostate							
M	135	none	defer[e]	defer[e]	none	none	none
Lymph node							
M	21	100, μ	defer[e]	defer[e]	150	μ	border
F	14	none	defer[e]	defer[e]	μ	none	none

a μ = Ambient mean concentration

b Airport cohort only

c 40+, etc., Exceedance frequencies of 40 and higher are statistically significant, $p < 0.05$. Units are $\mu g/m^3$ for particulate pollutants (PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$), and ppb for gaseous pollutants (O_3, SO_2, NO_2).

d None means no statistically significant association with any metric tested.

e Because of low numbers of cases, these analyses will be deferred until the AHSMOG study extends cancer followup through 2000.

APPENDIX A

1977 AHSMOG QUESTIONNAIRE

LOMA LINDA UNIVERSITY

LOMA LINDA, CALIFORNIA 92354
(714) 796-7311 EXT. 3717

SCHOOL OF HEALTH
ADVENTIST HEALTH STUDY

Dear Friend:

You are one of a small group selected from all participants in the Adventist Health Study to help in a special substudy. This substudy is sponsored by the Air Resources Board to measure some effects of the type of air you breathe.

We have greatly appreciated your cooperation and efforts in completing the detailed lifestyle questionnaire which is helping us to determine the possible relationship between various aspects of lifestyle and health status. The enclosed questionnaire will supplement this information with some additional questions.

Most other members in your church are receiving only the back page of this questionnaire which is the first of the yearly hospital history forms being sent to all adult SDAs in California. It is extremely important for you to complete this last page because it is our only means of keeping track of the health status of California SDAs. The few minutes necessary to fill in the entire questionnaire will contribute significantly to new knowledge that may save many lives.

By completing this questionnaire NOW, you will save us the expense and effort of having to contact you personally. Please return the completed questionnaire in the enclosed self-addressed envelop. Thank you for your assistance.

Sincerely yours,

Roland L. Phillips, M.D.
Director

RESPIRATORY SYMPTOMS AND RESIDENCE
HISTORY QUESTIONNAIRE

Please answer every question.

COUGH

1. Do you usually cough first thing in the morning?

   1 [ ] Yes
   2 [ ] No

2. Do you usually cough at other times during the day or night?

   1 [ ] Yes
   2 [ ] No

3. Do you cough on most days for 3 months or more?

   1 [ ] Yes
   2 [ ] No

4. For how many years have you had a cough?

   1 [ ] Never
   2 [ ] Less than 1 year
   3 [ ] More than 1 but less than 2 years
   4 [ ] 2-5 years
   5 [ ] More than 5 years

SPUTUM

5. Do you usually bring up phlegm, sputum, or mucus from your chest first thing in the morning?

   1 [ ] Yes
   2 [ ] No

6. Do you usually bring up phlegm, sputum, or mucus from your chest at other times during the day or night?

   1 [ ] Yes
   2 [ ] No

7. Do you bring up phlegm, sputum or mucus from your chest on most days for 3 months of the year or more?

   1 [ ] Yes
   2 [ ] No

8. For how many years have you raised phlegm, sputum, or mucus from your chest?

   1 [ ] Never
   2 [ ] Less than 1 year
   3 [ ] More than 1 but less than 2 years
   4 [ ] 2-5 years
   5 [ ] More than 5 years

PLEASE GO TO TOP OF NEXT COLUMN.

WHEEZING

9. Does your breathing ever sound wheezy or whistling?

   1 [ ] Yes
   2 [ ] No

10. Have you ever had attacks of shortness of breath with wheezing?

   1 [ ] Yes
   2 [ ] No

BREATHLESSNESS

11. Are you troubled by shortness of breath when hurrying on level ground or walking up a slight hill?

   1 [ ] Yes
   2 [ ] No

12. Do you get short of breath when walking at a normal pace with other people of your own age on level ground?

   1 [ ] Yes
   2 [ ] No

RESPIRATORY ILLNESS

13. During the PAST YEAR, how often were you unable to do your usual activities because of illnesses such as chest colds, bronchitis, or pneumonia?

   1 [ ] None
   2 [ ] 1 time
   3 [ ] 2-5 times
   4 [ ] More than 5 times

14. Do you think you have ever had any of these chest disorders--asthma, any kind of bronchial condition, or emphysema?

   1 [ ] Yes
   2 [ ] No

15. Has a doctor ever told you that you had asthma, some kind of bronchial condition, or emphysema?

   1 [ ] No

   IF YES, please check [✓] which conditions.

   2 [ ] Asthma
   3 [ ] Bronchial condition
   4 [ ] Emphysema

1

16. How many days per month during the SUMMER (June thru September) are you bothered by stuffy nose or post-nasal drip (i.e. drainage from the back of your nose into your throat)?

1[ ] None
2[ ] 1-5 days
3[ ] 6-10 days
4[ ] 11-20 days
5[ ] 21 days or more

17. How many days per month during the WINTER (October thru May) are you bothered by stuffy nose or post-nasal drip (i.e. drainage from the back of your nose into your throat)?

1[ ] None
2[ ] 1-5 days
3[ ] 6-10 days
4[ ] 11-20 days
5[ ] 21 days or more

ve you EVER regularly smoked cigarettes, es, or cigars (aside from possibly ying them once or twice)?

	Yes	No	
18.	1[ ]	2[ ]	Cigarettes
19.	1[ ]	2[ ]	Pipes
20.	1[ ]	2[ ]	Cigars

ring the PAST YEAR, how many times have have had the following illnesses? (Please eck [✓] the appropriate box for EACH)

21. Head cold (e.g. runny nose, sore throat, etc.)

None 1 2 3 or more
0[ ] 1[ ] 2[ ] 3[ ]

22. Chest cold (acute bronchitis e.g. cough and sputum associated with respiratory infection)

None 1 2 3 or more
0[ ] 1[ ] 2[ ] 3[ ]

23. Pneumonia

None 1 2 3 or more
0[ ] 1[ ] 2[ ] 3[ ]

24. How many times was this pneumonia diagnosed by a physician using a chest x-ray?

None 1 2 3 or more
0[ ] 1[ ] 2[ ] 3[ ]

PLEASE GO TO TOP OF NEXT COLUMN.

25. Are you usually away from home for more than 2 weeks during the summer (June thru September)?

1[ ] No
2[ ] Yes

26. IF YES, how long are you usually away?

1[ ] 3-4 weeks
2[ ] 5-6 weeks
3[ ] 7-8 weeks
4[ ] 9 weeks or more

27. How many hours per DAY during the work week do you usually spend driving or riding on CROWDED roadways? (Check the nearest category.)

1[ ] None
2[ ] Less than 15 minutes
3[ ] 15 minutes to one hour
4[ ] 2 hours
5[ ] 3 hours
6[ ] 4 hours
7[ ] 5 hours
8[ ] 6 hours or more

28. On a typical WEEKEND, how many hours per day do you spend driving or riding on CROWDED roadways? (Check the nearest category.)

1[ ] None
2[ ] Less than 15 minutes
3[ ] 15-29 minutes
4[ ] 30-59 minutes
5[ ] 1-2 hours
6[ ] 3-4 hours
7[ ] 5-6 hours
8[ ] 6 hours or more

29. How often do you use aerosol sprays (e.g. hair spray, cleaning spray, deodorant, spray paint, etc.)?

1[ ] Daily
2[ ] Several times a week
3[ ] Once a week
4[ ] a few times a month
5[ ] Rarely or never

30. What is your usual or main occupation? (Do not write "retired". If retired or not now working, give your usual occupation when you were working.)

Job Title, _____

Major duties or responsibilities: _____

2

	31. SUMMER (June thru September)	32. REST OF YEAR (October thru May)
How many hours per WEEK, including weekends, do you exercise vigorously or do heavy physical labor (e.g. jogging, tennis, gardening, etc.) in the open air?	[ ] None [ ] 1-7 hours [ ] 8-14 hours [ ] 15-21 hours [ ] 22-28 hours [ ] 29-35 hours [ ] 36-42 hours [ ] More than 42 hours	[ ] None [ ] 1-7 hours [ ] 8-14 hours [ ] 15-21 hours [ ] 22-28 hours [ ] 29-35 hours [ ] 36-42 hours [ ] More than 42 hours
	33. SUMMER (June thru September)	34. REST OF YEAR (October thru May)
How many hours per WEEK, including weekends, are you outside of buildings?	[ ] None [ ] 1-7 hours [ ] 8-14 hours [ ] 15-21 hours [ ] 22-28 hours [ ] 29-35 hours [ ] 36-42 hours [ ] More than 42 hours	[ ] None [ ] 1-7 hours [ ] 8-14 hours [ ] 15-21 hours [ ] 22-28 hours [ ] 29-35 hours [ ] 36-42 hours [ ] More than 42 hours

35. Have you ever lived for one year or more with someone who smoked?

[ ] No
[ ] Yes ------> How many years?_____

36. Have you worked in the same room with someone who smoked?

[ ] No
[ ] Yes ------> How many years?_____

37. Have you ever worked where you were exposed much of the time to various types of contaminated air such as chemical fumes, paint fumes, welding, wood or rock dust, etc.

[ ] No
[ ] Yes ------> How many years?_____

IF YES, please list:

38. Type of work_____

39. Type of contamination_____

If you have worked more than 5 miles from home in the past 10 years, please give the work locations and dates

	Started Job: MONTH	YEAR	Ended Job: MONTH	YEAR	TOWN OF WORK	STATE	ZIP CODE PLACE OF WORK
40.	____	____	____	____	_____	_____	_____
41.	____	____	____	____	_____	_____	_____
42.	____	____	____	____	_____	_____	_____
43.	____	____	____	____	_____	_____	_____
44.	____	____	____	____	_____	_____	_____
45.	____	____	____	____	_____	_____	_____

For each community you have lived in since 1960, please give the information requested below. For large cities, please give the section of the city. If the town was so small that it did not have a post office, give the nearest post office

Please start with your current place of residence.

	TOWN	STATE	ZIP	Moved to this town MONTH	YEAR
46.					
47.					
48.					
49.					
50.					
51.					

52. For each of the following, please indicate with a [✓] which years you have:

	Never	Prior to 66	1966	67	68	69	70	71	72	73	74	75	76	77
a. Lived in a home with evaporative water cooling.	a☐	☐	☐	☐	☐	a☐	☐	☐	☐	☐	a☐	☐	☐	☐
b. Lived in a home with refrigerated air-conditioning.	b☐	☐	☐	☐	☐	b☐	☐	☐	☐	☐	b☐	☐	☐	☐
c. Worked in a building with air-conditioning.	c☐	☐	☐	☐	☐	c☐	☐	☐	☐	☐	c☐	☐	☐	☐
d. Lived with someone who smoked.	d☐	☐	☐	☐	☐	d☐	☐	☐	☐	☐	d☐	☐	☐	☐
e. Worked in the same room with someone who smoked.	e☐	☐	☐	☐	☐	e☐	☐	☐	☐	☐	e☐	☐	☐	☐
f. Worked more than 5 miles from home.	f☐	☐	☐	☐	☐	f☐	☐	☐	☐	☐	f☐	☐	☐	☐
g. Worked where you were exposed much of the time to various types of contaminated air such as chemical fumes, paint fumes, welding, wood or rock dust, etc.	g☐	☐	☐	☐	☐	g☐	☐	☐	☐	☐	g☐	☐	☐	☐
	52	53	54	55	56	57	58	59	60	61	62	63	64	65

APPENDIX B

NON-DIFFERENTIAL & DIFFERENTIAL MISCLASSIFICATION

CALCULATION FOR PAPER 'A'

Assuming non-differential misclassification

The following is a hypothetical situation that addresses the question: What would be the effect on the relative risk estimate if there was a 50% under-reporting on important covariates in the statistical model that relates ozone to lung cancer incidence?

Adjustment to RR for O_3 and lung cancer allowing for 50% non-differential under-reporting of current smoking and alcohol use:

92 individuals were excluded from the study because of reported current smoking in 1977:

43 females
49 males
92

6338 remaining subjects in study
4060 females
2278 males
6338

Prevalence of reported current smoking in males in 1977:

$$\frac{49}{2278 + 49} = 0.021$$

If this were under-reported by 50% then true % current smokers in males = 4.2%, but half of these already reported smoking and were excluded.

The 1977-92 cumulative incidence rate of lung cancer in reported never smokers using percent distribution of male cases and noncases for "packyears of cigarettes" in **Table 4.1** is:

$$\frac{0.625 * 16}{(0.671 * 2262) + (0.625 * 16)} = 0.00655 \text{ (CIR)}$$

Assume cumulative incidence rate (CIR) in current smokers = 10* nonsmokers

= 10*0.00655 = 0.0655

In highest quartile of ozone in males we have: 0.021 (smoking prevalence) * 0.25 (upper quartile) * 2278 (males) = 11.96 unreported smokers who would have:

0.0655 * 11.96 = 0.78 lung cancers

The entire cohort could have::

0.021 * 2278 = 48 unreported smokers

with:

0.0655 * 48 = 3 lung cancers (2 of which are in the lower 3 quartiles of O_3).

Among non-current smoking males who have never reported smoking (N=1484, see attached crosstabs of PACKYRS * ALCOHOL), 108 reported current alcohol use. The prevalence of alcohol use is therefore: 108/1484 = 0.073 = 7.3%.

Those who under-report current alcohol use and report past smoking do not bias the ozone coefficient because their alcohol effect is picked up by reporting past smoking. If current alcohol use was under-reported by 50%, then there was 7.3% not reported in never smokers. We don't need to consider past smokers because we have a variable for them.

The number of unreported current alcohol users in reported never smoking (or missing alcohol) males = 1315 (never alcohol) + 108 (ever alcohol) + 106 (missing alcohol) = 1529

and: 1529 * 0.073 = 112

Incidence of lung cancer in current male alcohol users:

where: 0.25 (proportion male lung cancer cases reporting any alcohol use)

16 (male lung cancer cases)

0.099 (proportion male non-cases reporting any alcohol use)

2262 (male non-cases)

$$\frac{0.25 * 16}{(0.099 * 2262) + (0.25 * 16)} = \frac{4}{224 + 4} = 0.0175$$

Expected number of lung cancers in 112 non-reported alcohol users = 0.0175 * 112 = 2.0.

One quarter (0.25 * 2.0) = 0.5 of these would be in the high ozone quartile.

One-quarter of the 112 = 28 males who unreported current alcohol would be expected to be in the "high" ozone quartile.

Observed relative risk (RR) for high ozone from Cox model (from **Table 4.3**) = 3.56

Number of males in high quartile ozone is 0.25 * 2278 = 570

Number of males in lower 3 quartiles ozone is 2278 - 570 = 1708

Half of the male lung cancer cases = 0.5 * 16 = 8

$$RR = \frac{8 / 570}{8 / 1708} = 3.00$$

Assuming differential misclassification

Assume differential under-reporting (i.e. under-reporting only in high ozone quartile).

Remove unreported current smoking and alcohol from high ozone quartile:

2278 total males / 4 quartiles = 570 males per quartile

570 (males) - 11.96 (unreported smoking) - 28.0 (unreported alcohol) = 530

and number of lung cancers in the above = 0.78 (smoking) + 0.50 (alcohol) = 1.3

Prevalence of past smoking among males who report no current alcohol is (from attached crosstabs):

$$\frac{240 + 348}{1955} = 0.301 = 30.1\%$$

If this is under-reported by 50%, then another 30.1% needs to be removed from the high ozone:

(0.301 * 530) = 160 possible past smokers who didn't report as such

530 - 160 = 370

From **Table 4.1**:

6.3% + 31.2% = 37.5% (male lung cancer cases who were past smokers)

13.0% + 19.9% = 32.9% (non-lung cancer cases male past smokers)

0.329 * 2262 (male non-lung cancer cases) = 744

0.375 * 16 (male lung cancer cases) = 6

744 + 6 = 750 (reported past-smokers)

Then the number of lung cancers in these 160 men due to past smoking is:

$$\frac{0.375 * 16 \text{ (cases)} * 160}{750} = 1.3 \quad \text{(using incidence rates from Table 4.1)}$$

This would be the number of expected lung cancer cases in the high ozone quartile due to unreported past smoking in those who did not report alcohol or cigarette use.

Adding up all the lung cancers in the high ozone quartile due to under-reporting of current smoking, past smoking, or current alcohol use, we have:

$$0.78 + 0.50 + 1.3 = 2.6$$

The number at risk removed is:

$$570 - (11.96 + 28.0 + 160) = 370$$

Number of adjusted cases: $8 - 2.6 = 5.4$

$$\text{Relative Risk} = \frac{5.4/370}{8/1708} = 3.12$$

So the RR increases from 3.00 to 3.12 if leave in those at risk. That is because ozone RR is higher than past smoking RR (see **Table 4.3**)

If we left men who unreported in but just excluded lung cancers in high ozone quartile (which could be due to under-reporting), then we have 8 - 2.6 = 5.4 lung cancers in high ozone quartile which could be due to under-reporting:

$$\text{Relative Risk} = \frac{5.4/570}{8/1708} = 2.02$$

Thus, differential under-reporting of current smoking, past smoking, and current alcohol use could reduce the RR for high ozone exposure from 3.00 to 2.02. Non-differential under-reporting would increase the RR.

CONTROLLING FOR SEXM=M

PACKYRS ALCOHOL(BEERWINE + HARDLIQ)

Frequency Percent Row Pct Col Pct	MISSING	NEVER	EVER	Total
MISSING	8	52	5	65
	0.35	2.28	0.22	2.85
	12.31	80.00	7.69	
	7.55	2.66	2.30	
NONE	61	1315	108	1484
	2.68	57.73	4.74	65.14
	4.11	88.61	7.28	
	57.55	67.26	49.77	
<= 7	14	240	32	286
	0.61	10.54	1.40	12.55
	4.90	83.92	11.19	
	13.21	12.28	14.75	
> 7	23	348	72	443
	1.01	15.28	3.16	19.45
	5.19	78.56	16.25	
	21.70	17.80	33.18	
Total	106	1955	217	2278
	4.65	85.82	9.53	100.00

APPENDIX B (CONT.)

NON-DIFFERENTIAL & DIFFERENTIAL MISCLASSIFICATION

CALCULATION FOR PAPER 'B'

For paper 'B' (chapter 5), the calculations for hypothesized under-reporting of covariates in the statistical model were similar to that done for paper 'A' (chapter 4) except that we compared the highest versus the lowest quartile of the air pollutant rather than the highest versus the lower three quartiles.

APPENDIX C

SAMPLES OF INFORMED CONSENT FORMS USED IN AHS/AHSMOG

ADVENTIST HEALTH STUDY HOSPITAL HISTORY FORM (SHORT FORM) # 5

FLAGGED | PROCESSED | VERIFIED

1. Have you stayed overnight in a hospital during the last ☐ Yes ☐ No

2. If yes, please fill out the information below. If you have stayed in the same hospital more than once, list only your most recent stay in that hospital. Please include date. → Date of Last Discharge (MONTH / YEAR)

1 HOSPITAL NAME — CITY — STATE

2 HOSPITAL NAME — CITY — STATE

3 HOSPITAL NAME — CITY — STATE

3. Please carefully check and correct the hospitals you have reported on previous forms. They are listed below. Also record the date of your last discharge from each of these hospitals and add any others which you have stayed in since January, 1976.

APPROXIMATE DATE OF LAST DISCHARGE

APPROXIMATE DATE OF LAST DISCHARGE

APPROXIMATE DATE OF LAST DISCHARGE

APPROXIMATE DATE OF LAST DISCHARGE

4. Is your name, address, church, and telephone number correct as printed here? ☐ Yes ☐ No

5. Please read consent statement and write your signature and today's date below.

I, the undersigned, hereby authorize any hospital mentioned on either side of this form to provide to a representative of the Adventist Health Study of Loma Linda University, in Loma Linda, California, any medical diagnoses, medical histories, physical examination findings, reports of operative procedures, and reports of all diagnostic procedures. I understand that the information from my medical record will be used solely by the Adventist Health Study to compile statistical reports for medical research regarding the health and disease status of large groups of people. Furthermore, I understand that my name will never appear on any reports from this research project. This authorization shall be valid until December 31, 1985; however it shall apply solely to portions of my medical record which exist as of the date this form was signed. I understand that no further authorization is made than this form specifically indicates and that I am entitled to a copy of this signed authorization upon request.

X _____ SIGNATURE

_____ TODAY'S DATE

CIRCLE ONE → SELF • SPOUSE • PARENT • NEXT OF KIN • CONSERVATOR • GUARDIAN • OTHER REPRESENTATIVE

Current Church Membership:

Name, Address, and Telephone CORRECTIONS

6. PLEASE TURN OVER AND CONTINUE ON OTHER SIDE

LOMA LINDA UNIVERSITY

Center for Health Research
Adventist Health Study

Ezzat Hall, Room 204/215
Loma Linda, California 92350
(909) 824-4983
(909) 824-4268
(800) 247-1699
FAX: (909) 478-4268

Date

ID
Name
Address
City, State, Zip

Dear Mr.:

We have greatly appreciated your faithful participation in the Adventist Health Study over the last several years. Your efforts have made many new discoveries concerning the development of cancer possible. The Adventist Health Study at Loma Linda University is currently updating cancer incidence data on study participants. As part of that investigation you were contacted by phone during the last few months. During that phone interview you indicated that you had been told by a doctor that you had a tumor or cancer diagnosed after 1982.

In order to keep track of the occurrence of every tumor or cancer (whether benign or malignant) among participants in this study and to ascertain the specific cellular type of cancer, we need to have our medical records specialist review your medical record that pertains to the cancer diagnosis. Please sign the statement on the back of this letter giving permission to our study to review these specific sections of your medical record.

We will not be reviewing other parts of your medical record prior to the first diagnosis of this cancer or after your signature date.

If you do not wish to give permission you may so indicate and return the form unsigned. In order for this study to be valid and accepted by the scientific community, however, it is important to have diagnostic information on every new case of cancer, so we will greatly appreciate your permission.

If you have any questions you may call the Adventist Health Study during normal working hours at: 1-800-247-1699.

Sincerely

Synnove Knutsen, MD, PhD
Principal Investigator

I, the undersigned, hereby authorize the hospital or doctor's office mentioned below to provide to a representative of the Adventist Health Study of Loma Linda University, in Loma Linda, California, any medical diagnoses, medical histories, physical examination findings, reports of operative procedures, and reports of diagnostic procedures that pertain to cancer or tumor diagnosis. I understand that the information from my medical record will be used solely by the Adventist Health Study to compile statistical reports for medical research regarding the health and disease status of large groups of people. Furthermore, I understand that my name will never appear on any reports from this research project. This authorization shall be valid until December 31, 2000; however, it shall apply solely to portions of my medical records which exist as of the date this form was signed. I understand that no further authorization is made than this form specifically indicates and that I am entitled to a copy of this signed authorization upon request.

_____ _____

Signature Today's Date

Please review the information you previously provided as recorded below and make any needed corrections.

Name and address of hospital or physician where cancer diagnosis was made

_____

_____

_____

_____

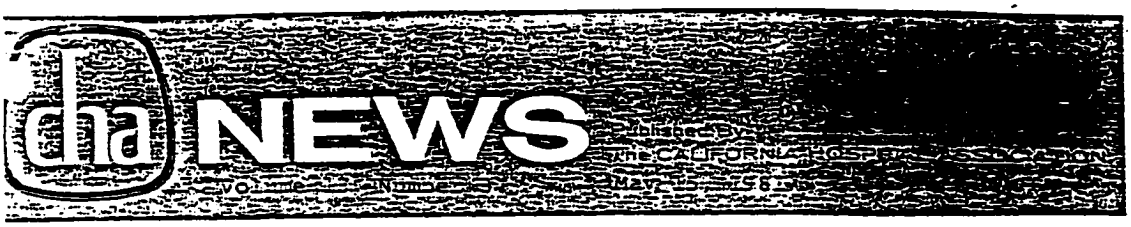
_____

_____

APPENDIX D

CALIFORNIA HOSPITAL ASSOCIATION

WEEKLY NEWSLETTER



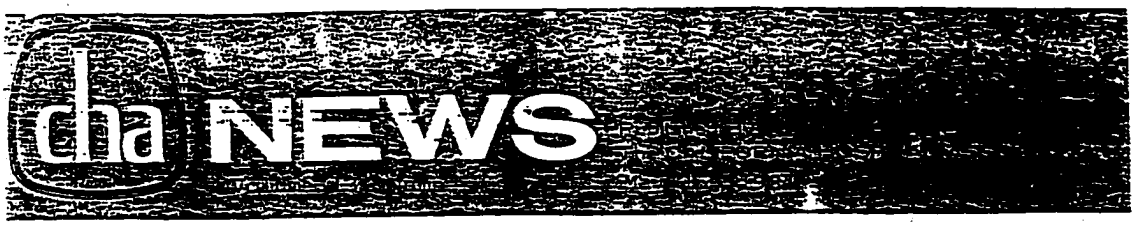
JSC And Loma Linda University Research Surveys Are Endorsed By CHA

Two current research surveys have been endorsed by CHA: one, by the University of Southern California, asks assistance in identifying patients under 65 who have survived a first myocardial infarction during the past five years, for a study on hyperlipidemias; the other is by Loma Linda University on the epidemiology of cancer in Adventists.

August 13, 1982 Volume 15 Number 16

CHA Endorses Surveys On Health Disease And Occupational Employment Statistics

Expansion of an ongoing study of cancer in 34,532 California Seventh-day Adventists to include heart disease has been endorsed by CHA. In the Loma Linda University study, specified medical records are reviewed by Adventist Health Study personnel. CHA also endorsed a hospital employment survey by the state Employment Development Department. The survey of the number and types of hospital employees will be used to project occupational and educational needs.



CHA Urges Opposition To Two Medicaid Cuts With A Drastic Impact On California

There are a number of ways the Reagan Administration is proposing to cut back on Medicare reimbursement to hospitals, among them: eliminating the 8½ percent nursing service differential, paying for all renal dialysis at the clinic rate, and reducing payments for inappropriate hospital services. But in a letter to member hospitals this week, CHA President Paul Ward pointed out that two Medicaid (Medi-Cal in California) cuts adopted by the Senate Finance Committee would create greater dislocations for California and should be aggressively opposed by hospitals.

One proposal would lower the minimum federal matching rate for Medicaid from 50 percent to 40 percent, and cost Medi-Cal $338 million in fiscal year 1982. The matching rate varies among states from 50 to 83 percent. The higher a state's per capita income, the lower its matching rate; so California, with a high per capita income, receives funds at the 50 percent rate. If the minimum is dropped to 40 percent, the federal share of Medi-Cal will drop to 41.8 percent for California. For fiscal year 1982, California would be socked with 32 percent of the projected nationwide total cut of $651 million. The other proposal would put a 9 percent cap on Medicaid in 1981, and thereafter limit federal increases to the rate of inflation. In 1982, the projected national impact would be $1 billion, and California would lose $150 million of that. By 1986, the nationwide impact would be over $5 billion and California would forego over $750 million.

"We must aggressively oppose these arbitrary and inequitable proposals which would shift a large burden of the nation's economic recovery program to those individuals and institutions least able to afford them" said Ward. He urged hospitals to contact the House of Representatives to oppose the Senate proposals, and thus force the issues to a joint Senate-House conference committee.

Rules For Private Sterilizations Go Into Effect June 1st--Assuming No More Mix-Ups

New state regulations on sterilizations for private patients were quietly filed last month to go into effect this Monday, May 18th. There's been considerable controversy over the procedures since April of 1980, when the Department of Health Services originally proposed to repeal the regulations entirely. Then in October the state adopted federal standards for Medi-Cal patients, leaving California residents with two sets of procedures: a minimum age of 21 for Medi-Cal patients, 18 for private patients; and a 30-day, non-waivable Medi-Cal waiting period, compared to 14 days, waivable to 3, for private patients.

The Department proposed new private patient rules late last year, which were rejected by the Office of Administrative Law because the Department "did not provide legally adequate notice of its intended action" (CHA News, October 10). New hearings were held in December; the regulations were filed with the Secretary of State April 17. CHA's Bob Kimball learned of the filing only this week, and calls to the Department of Health Services disclosed that no notices had been sent to hospitals. Embarrassed officials agreed to suspend enforcement until June 1, to allow hospitals time to notify physicians and patients. Under the new rules, private patients must be at least 18, as before, but the waiting period is extended to 30 days, waivable to 3. CHA will send out a legal memo on the new procedures next week.

CHA NEWS, published weekly at [illegible] 12th Street, [illegible] Sacramento, California 95814 (916) [illegible]-4011. Subscription price $10.00 per year for members [illegible] California Hospital Association; $15.00 per year for non-members. Second-class postage paid at Sacramento, California. USPS (095-[illegible])

A New Law Wipes Out The Required Reporting Of Sexual Activity Of Young Women

Governor Brown has signed SB 323 into law, ending the requirement that physicians and other providers report to law enforcement agencies any unmarried, minor females known to be engaged in sexual activities. The urgency legislation, authored by Senator Omer Rains, D-Ventura, corrects language in a previously enacted child abuse reporting law. The state court last month stayed enforcement of the reporting provision as a result of a suit by the California Medical Association.

Medi-Cal Reimbursements Can Be Cut In An Emergency, The Court Says

A state appeals court has upheld the authority of the Director of Health Services to reduce Medi-Cal reimbursements up to 10 percent and postpone elective services when there is a "reasonable basis" for believing the costs of the program will exceed available funds. In a ruling on Alta Bates Hospital vs. Lackner, a class action suit filed in 1973, the Third District Court of Appeal said the director has authority to take such action "in consultation with representatives of concerned provider groups." Alta Bates and 19 other hospitals, supported by CHA, had contended the 10 percent cut in 1970-71 was invalid because the Administrative Procedures Act, requiring public notice and hearings, hadn't been followed. The trial court agreed with the hospitals and awarded damages to those who had filed claims against the government--but not to all hospitals. The restrictions on damages was appealed, and became moot when the Third District Court of Appeal overturned the trial court ruling. "By its very nature, (the law authorizing the director's action) is useless if its mechanism is not utilized as soon as the fiscal emergency is discovered," the appellate court ruled.

A Continuing--And Difficult--Battle For Tort Reform

For several legislative sessions, the CHA has been supporting reform of California tort law, the rules governing how liability suits are tried. It's been an uphill battle ever since passage of AB 1x, the 1975 Medical Injury Compensation Reform Act, which was aimed at solving the problem of skyrocketing medical malpractice awards. Several "tort reform" bills have been introduced this session and four were up for hearings this week: SB 500 by Senator Robert Beverly, R-Manhattan Beach, AB 85 and AB 86 by Assemblyman Allister McAllister, D-San Jose; and AB 417 by Assemblyman Patrick Nolan, R-Glendale. Three of the four died in the Assembly Judiciary Committee: McAllister's AB 85 and 86, dealing with joint and several liability; and Nolan's AB 417, limiting damages for non-economic losses to $5,000 or the amount of damages for economic losses, whichever is greater.

Beverly's SB 500 only did a little bit better in the Senate Judiciary Committee, where it takes five votes to pass or kill a bill. SB 500 got four ayes and three noes, allowing the author to ask for a reconsideration. That request will be heard next week. SB 500 would abolish the rule of "joint liability" and establishes the rule of "several liability," under which defendants in a negligence action pay according to their degree of fault. Under joint liability, each negligent defendant is liable for all the damages regardless of the degree of fault.

USC And Loma Linda University Research Surveys Are Endorsed By CHA

Two current research surveys have been endorsed by CHA: one, by the University of Southern California, asks assistance in identifying patients under 65 who have survived a first myocardial infarction during the past five years, for a study on hyperlipidemias; the other is by Loma Linda University on the epidemiology of cancer in Adventists.

June's The Month For Seminars On Legal Issues, Liability And Safety

CHA's Education and Conference Planning Division has scheduled three major seminars in June. The Institute on Nursing Liability and Malpractice will be held June 2 in Los Angeles, June 3 in Newport Beach, June 9 in Burlingame and June 11 in Sacramento. Tuition is $75 per person for CHA members. The Institute for Hospital/Medical Staff Legal Issues is set for June 10 in Los Angeles and June 11 in San Francisco; tuition is $75. Two one-day workshops on hospital safety standards of the Joint Commission for Accreditation of Hospitals (JCAH) are scheduled June 18 and 19 in Los Angeles: Safety Clinic 1 will address the major topics of life safety; Safety Clinic 2 focuses on safety policy and system. Tuition for each clinic is $175, or $300 per person for both. For registration, contact Catherine Colburn at CHA.

The State Administration Unveils Its Version Of Prepaid Medi-Cal Contracts

The Deukmejian Administration yesterday made available the text of its version of privately-run, prepaid, capitated health plans for Medi-Cal. As expected (CHA News, Aug. 5), the proposal would phase in plans over 20 percent of the state's geographical area by January 1, 1986. An additional 20 percent of the state would be phased in every two years thereafter. The Administration wants to run the prepaid contracts out of the Department of Health Services; to accomplish that the proposal would immediately wipe out the California Medical Assistance Commission created last year, and transfer its responsibilities to the Department.

The proposal would give Medi-Cal recipients in an area a choice of plans--but would assign those who do not make a choice, so the end result is mandatory enrollment. The present "voluntary" co-payments of $5 for non-emergency visits to an emergency room, and $1 for outpatient visits would be made "mandatory": those amounts would automatically be deducted from hospital reimbursement, so hospitals would be liable for their collection. And the Director of the Department of Health Services would be required to negotiate contracts costing less than the estimated costs under fee-for-service care. The Administration's proposal will be amended into AB 516, by Assemblyman William Filante, and will be heard on Wednesday in the Senate Health and Welfare Committee along with AB 614, another prepaid capitation proposal for Medi-Cal by Assemblyman Richard Robinson.

Bills Signed To Ease Philanthropy, Allow Radiologic Technologist Assistance

Grants and annuities societies, under which a donor makes an irrevocable gift of money or property in exchange for a lifetime annuity, are sometimes used by hospitals to obtain philanthropic contributions. But a 1981 law raised state fees for a "certificate of authority" to set up such arrangements from $255 to $5,745. After the bill passed, the Insurance Commissioner recommended a more reasonable fee of $1,500, but it was too late to change. CHA sponsored a bill this year, SB 825 by state Senator Gary Hart, to correct that mistake. Governor Deukmejian signed the urgency measure into law on July 26.

The Governor also signed the CHA-supported AB 2143, by Assemblyman Curtis Tucker, which will allow a certified radiologic technologist to assist in administering an injection of contrast materials. Technologists still cannot perform arterial or venipuncture, however, and must be under direct physician supervision.

CHA Endorses Surveys On Health Disease And Occupational Employment Statistics

Expansion of an ongoing study of cancer in 24,532 California Seventh-day Adventists to include heart disease has been endorsed by CHA. In the Loma Linda University study, specified medical records are reviewed by Adventist Health Study personnel. CHA also endorsed a hospital employment survey by the state Employment Development Department. The survey of the number and types of hospital employees will be used to project occupational and educational needs.

Tax Refunds May Be Available For Non-Profit Hospitals With Employee Annuity Plans

Non-profit hospitals may be eligible for refunds of Social Security taxes paid since 1979 in connection with contributions to a tax-sheltered annuity plan for employees. A 1981 Supreme Court decision in Bowen Companies, Inc. v. United States, 452 U.S. 247, said that items excluded from wages for income tax purposes were also excludable for FICA tax purposes. Since the ruling Congress passed the Social Security Amendments of 1983, which specify that such payments are part of the Social Security wage base--but the provision doesn't go into effect until January 1. It's not clear how the Internal Revenue Service will respond to refund claims, but CHA recommends hospitals consider filing a claim to protect their rights. Hospitals should consult legal counsel on filing requirements.

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APPENDIX E

LEGAL OPINION BY MUSICK, PEELER & GARRETT

1985

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STUART S. MUSICK

WRITER'S DIRECT DIAL NUMBER

(213)629-7875

May 27, 1985

Medical Records Custodian

Re: Release of Medical Records to the Adventist Health Study

Dear Custodian of Medical Records:

Roland L. Phillips, M.D., the Director of the Adventist Health Study, asked me to provide our legal opinion regarding whether hospitals' Medical Records Custodians may release patient identifiable medical information to him in connection with the Adventist Health Study research project, when there is no patient authorization for the disclosure. As is discussed below, we have determined that California law and general federal and national standards of confidentiality permit the disclosures that are requested and, based upon our review of the safeguards provided by this research team for the confidentiality of the data, we have concluded that hospitals should be encouraged to provide the requested information.

The objectives of the Adventist Health Study are to identify the specific elements of lifestyles that relate to the risks of cancer and ischemic heart disease in order to obtain knowledge regarding the causes of these conditions which may be used to help prevent them. The study was initiated in 1973, when approximately 35,000 persons volunteered to complete a comprehensive health and lifestyle questionnaire and to continue to provide information over the next ten years regarding their health status. The study is sponsored by the National Heart, Lung and Blood Institute and the National Cancer Institute.

As a part of the research, the Adventist Health Study research team has sent annual questionnaires to each participant, asking whether the person has been hospitalized and, if so, whether the research team may have access to the hospital records. If the person or his or her legal representative authorizes disclosure of the hospital records, the research team requests access to inspect the record and copy portions which are needed for the research study. Currently, the research team is

collecting the final data from hospitals, and specifically is asking permission either to copy relevant portions of the patients' records or to have copies sent to the Study.

The problem that has arisen is that during this final stage, the research team does not have current authorizations for the disclosures that are requested. This usually occurs since the team requested consents for release of medical information which had a short duration, and the team was unable to complete the data collection process before the authorizations expired. We are satisfied, as a result of our review of the research protocol and interviews with the research team, that they are not seeking access to any records when a patient refused to authorize release.

Releasing the requested records in connection with this study is lawful, even if there is no patient authorization. In this regard, the California Confidentiality of Medical Information Act, Civil Code Section 56 et seq., provides that hospitals may release patient identifiable medical information to clinical investigators for bona fide research purposes without having any patient authorization. Specifically, Civil Code Section 56.10(c)(7) provides that a health care provider does not need patient authorization and may disclose medical information as follows:

> "The information may be disclosed to public agencies, clinical investigators, health care research organizations, and accredited public and private nonprofit educational and health care institutions for bona fide research purposes. However, no information so disclosed shall be further disclosed by the recipient in any way which would permit identification of the patient."

The Adventist Health Study clearly is bona fide research that is being conducted by clinical investigators associated with an accredited private nonprofit educational institution. Accordingly, information may be disclosed to the research team without requiring patient authorization.

Further, we are satisfied that the research team will not further disclose the information in any way which would permit identification of the patient. In this regard, we note that the research protocol provides ample safeguards for maintaining the confidentiality of the patient-identifiable information that is being collected. Specifically, the detailed information pertaining to individuals' health and lifestyles is

identified only by a code number, generated by a computer. Information pertaining to the patient's identity, which is necessary in order to connect the follow-up information with the data that has previously been collected, is protected by maintaining it in a file room which is locked 24 hours a day and filing it under a special code number. The patient identifying information and the medical information may be linked only by use of a computer and a complex mathemtical formula.

Other state laws and federal standards governing confidentiality of medical information are consistent with the approach used in California. Thus, data generally may be disclosed for research purposes, provided the research team will not further redisclose patient identifiable information. Specifically, the disclosure requested by the research team complies with the guidelines issued by the American Medical Record Association in its Position Statement, "Confidentiality of Patient Health Information," (Revised August, 1981). The AMRA stated, in pertinent part, that:

> "3.13 Health records shall be made available for research to individuals who have obtained approval for their research projects from an institutional review board .... "

This project meets this requirement since it has been approved by a qualified Institutional Review Board. In addition, the safeguards for the collected data comply with the standards described by AMRA in "Confidentiality and Security of Secondary Health Records," March 1984.

Accordingly, we have concluded that hospitals may release the information requested by the Adventist Health Study, and in view of the potential benefits of the research and the excellent safeguards used to maintain confidentiality, we encourage hospitals to cooperate fully.

Very truly yours,

Suzanne F. West

Suzanne F. West
for MUSICK, PEELER & GARRETT

APPENDIX F

LEGAL OPINION BY McCUTCHEN, DOYLE, BROWN & ENERSON

1995

McCUTCHEN, DOYLE, BROWN & ENERSEN
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October 23, 1995

VIA FACSIMILE AND FIRST-CLASS MAIL

Synnove Knutsen, M.D., Ph.D.
Medical Director/Co-Investigator
Adventist Health Study
Center for Health Research
Loma Linda University
Loma Linda, CA 92350

Release of Medical Records to Adventist Health Study

Dear Dr Knutsen

This will follow up on several conversations I have had with Larry Beeson concerning the Adventist Health Study, and your desire for a legal opinion regarding access to patient medical records for research purposes. Specifically, you are in the final phase of this Study, which began in 1974 as research to document incidents of cancer in a defined population of patients. For a number of patient participants in the Study, you either have consents which are quite dated or, in some cases, no specific consents to access medical information. In many of the cases, the patients are deceased and so it is impossible to obtain or update consent forms. Therefore, you have asked our opinion regarding your ability to access patient information for research purposes when a consent is either outdated or does not exist.

You last sought an opinion on this issue in 1985, and that legal opinion concluded that it was permissible to obtain access to patient records for research purposes, even in situations where a current patient consent could not be obtained. In the ten years since you obtained that legal opinion, the law has, if anything, become clearer regarding the permissibility of obtaining access to patient charts for purposes of medical research. This is true even in situations where no specific patient consent can be presented by the Study team. Let me briefly explain the current state of the law, and various safeguards which your study must, and has, met.

Certain statutes are precisely applicable to your question. It is most direct to refer to these statutes in light of your question. They are as follows:

1. California Civil Code Section 56.10(c)(7) - This Section of the California Confidentiality of Medical Information Act provides that clinical investigators may obtain medical information for "bona-fide research purposes." As long as there is no

further disclosure which would permit identification of the patient, patient consent is not required. You have indicated that there will be no disclosure of patient information beyond the study. The research is clearly "bona fide" given its IRB approval, purpose, and sponsorship by a recognized University and LCME accredited School of Medicine. Accordingly, this Section clearly permits hospitals and other providers to release medical information to the Adventist Health Study even without a specific patient consent.

2. Special Situations/Conditions - Dr. Beeson indicates that the Adventist Health Study is only interested in documenting incidents of cancer in the Study participants, and is seeking no records other than those regarding diagnosis and treatment of cancer (neoplasm). Accordingly, the Study is not seeking information which may be subject to special protections under confidentiality laws (e.g. mental illness, alcohol/substance abuse, HIV status) and, therefore, any prohibitions related to such particular conditions should not apply. Even if such sensitive records were sought, there are research exceptions which allow the release of patient-specific information regarding these sensitive conditions for legitimate research purposes. (Alcohol/substance Abuse - information may be released for research purposes - 42 C.F.R. Section 2.52; Mental health information releasable for research purposes - California Welfare and Institutions Code Section 5328(e); HIV information releasable for research purposes - California Health and Safety Code Section 199.30 et seq.). These exceptions underscore the strong policy position that medical records may be released for legitimate research purposes even in the most sensitive of situations.

3. Federal Law - You have indicated that the Adventist Health Study is subject to review and has been approved by Loma Linda University's Institutional Review Board ("IRB") and that patient information collected will not be released in any patient identifiable form. Under these circumstances, federal law and applicable government-sponsored research regulations would permit the obtaining of patient identifiable information even without the patient's consent. 45 C.F.R. Sections 46.101(b)(4) and 46.116(d).

4. Law of Other States - The vast majority of States have provisions similar to California's allowing for the release of patient identifiable information for projects such as the Adventist Health Study. To the extent that information is sought from a provider in another State, we should be able to provide the appropriate statutory provision in short order. Moreover, the federal statutes referenced above are obviously applicable in all States.

The Adventist Health Study involves the collection of patient-specific information regarding cancer, is subject to IRB safeguards and review, has procedures to guard the confidentiality of patient information, and will not result in the further release of patient-identifiable information. Under these circumstances, it is our opinion that hospitals and other providers of health care services are permitted to release patient information to the Adventist

Health Study, regardless of the presence of a signed consent authorizing such release. I hope this opinion is of assistance to you and the Adventist Health Study. If you require additional information or have any questions, please do not hesitate to contact me.

Sincerely yours,

Ross E. Campbell

APPENDIX G

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DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

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Sharon Ramirez
Chief, Population-based Statistics Section
Data Dissemination Branch

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