LINKING ENVIRONMENTAL EXPOSURES AND HEALTH EFFECTS USING EXISTING DATA TO EXPLORE THE RELATIONSHIPS BETWEEN ENVIRONMENT AND CHRONIC DISEASES

by

Xiaohui Xu

B. Med., Zhejiang University, 1999

M. Med., Fudan University, 2002

Submitted to the Graduate Faculty of

Graduate School of Public Health in partial fulfillment

of the requirements for the degree of

Doctor of Philosophy

University of Pittsburgh

2007

UNIVERSITY OF PITTSBURGH

Graduate School of Public Health

This dissertation was presented

by

Xiaohui Xu

It was defended on

June 6th , 2007

and approved by

Dissertation Advisor:
Evelyn O. Talbott Dr. P.H., Professor
Department of Epidemiology,
Graduate School of Public Health
Universith of Pittsburgh

Committee member:
Vincent C. Arena Ph.D., Associate Professor
Department of Biostatistics, Graduate School of Public Health,
Universith of Pittsburgh

Committee member:
Devra Lee Davis Ph.D., Visiting Professor,
Department of Epidemiology, Graduate School of Public Health,
Universith of Pittsburgh

Committee member:
Ravi K. Sharma Ph.D., Assistant Professor,
Department of Behavioral Community Health Sciences,
Graduate School of Public Health, Universith of Pittsburgh

Committee member:
Conrad D Volz Dr. P.H., Assistant Professor,
Department of Environmental and Occupational Health,
Graduate School of Public Health, Universith of Pittsburgh

LINKING ENVIRONMENTAL EXPOSURES AND HEALTH EFFECTS USING EXISTING DATA TO EXPLORE THE RELATIONSHIPS BETWEEN ENVIRONMENT AND CHRONIC DISEASES

Xiaohui Xu, PhD

University of Pittsburgh, 2007

The environment plays an important role in the health of communities. However, few health systems exist at the state and/or local levels to efficiently track the potential health effects associated with environmental exposure. The objectives of this dissertation are 1) to use secondary data for assessing the possible associations between health outcomes and environmental exposure and/or hazard; 2) to explore possible methods of data linkage and analyses which can be used by state and local environmental health tracking agencies and 3) to bring positive contributions to the development of national Environmental Public Health Tracking Network (EPHT). In this project, the Three Mile Island (TMI) cohort data (1979-1995) and Pennsylvania (PA) Cancer registry data were used to evaluate the associations between cigarette smoking and adult leukemia. A case-crossover analysis was performed with PA cardiopulmonary hospital admission data and local air pollution data to assess the health effects of air pollutants on cardiopulmonary disease before and after the elimination of a major point source of air pollution. A case-control study was also conducted to examine the associations between term low birth weight and particulate air pollution. The results showed that cigarette smoking could increase the risk of acute myeloid leukemia (AML). In addition, particulate air pollution is significantly associated with cardiovascular hospitalization and low birth weight in term infant.

In conclusion, the findings suggest that environmental hazards have adverse health effects on a number of health endpoints. Secondary data can be a great resource for environmental public health tracking, which is of public health relevance. The use of existing data is an effective way to assess the potential health effects associated with environmental exposures after an appropriate study design with a feasible data linkage and correct methods of data analyses was developed.

Keyword: Environmental exposure, Secondary data, Chronic disease

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

PREFACE

I owe special thanks to all of my committee members for their great support and guidance during the dissertation process. Without their personal involvement, this work could not successfully have been done so well and so quickly. I would like to thank my advisor, Dr. Evelyn Talbott, for her patience, availability and advice. Without her great support and direction, I would not have been able to accomplish this work. I am grateful for the opportunities she has provided to me. I would also like to thank everyone in my research team, especially Dr. Jeanne V. Zborowski, whose professional suggestions and editorial support did me tremendous favor. I appreciate their support more than I can say. I am very thankful to my family and friends for their emotional and editorial support to my work.

1.0 INTRODUCTION

The environment plays an essential role in the health of community. An enormous number and variety of chemicals have been introduced into the environment with the process of industrialization and economic development. They have caused considerable concerns among the community. Exposures to environmental hazards including chemical, biological and physical agents have been linked to various adverse health outcomes such as cancer (Jurewicz and Hanke 2006; Navarro Silvera and Rohan 2007), cardiovascular diseases (Delfino et al. 2005; Monarca et al. 2006), respiratory diseases (Kunzli and Tager 2005), adverse pregnancy outcomes (Perera et al. 2005; Shi and Chia 2001; Sram et al. 2005) and others in the research literature. Efficiently tracking potential health effects associated with environmental exposure appears important, urgent and necessary.

1.1 ENVIRONMENTAL EXPOSURES AND CHRONIC DISEASES

Most chronic diseases are caused by the interaction between gene and environment, i.e. diseases result from an unfavorable combination of genetics and environment(Olden and Guthrie 2001). Population-based twin studies, which can distinguish between the contributions of genetics and environment, suggest that the environment plays a prominent role in disease development (Mucci et al. 2005; O'Brien 2000). A recent study by Lichtenstein et al found that

genetics only account for 21-42% of the risk for developing the 10 common cancers studied and shared environmental exposures could account for 58-82% of the risk (Lichtenstein et al. 2000). Environmental hazards are found not only in chemical agents used in agriculture and industrial emissions but also in household commercial products, food additives, medicine, research lab as well as natural events such as forest fire and volcano eruption. Scientific research has provided a better understanding of some environmental exposures that could cause a variety of adverse health outcomes such as arsenic and cancers in different systems (Ferreccio and Sancha 2006; Tapio and Grosche 2006), radon and lung cancer (Alavanja et al. 1994; Neuberger and Gesell 2002; Pershagen et al. 1992), lead and cognitive function (Banks et al. 1997; Rice 1996), and particulate matter and cardiopulmonary diseases (Peters and Pope 2002; Pope 2000; Pope et al. 2004). However, for many other environmental hazards, scientific evidence is less conclusive.

Billions of pounds of toxic agents are released into the environment every year where we live, eat, drink, work and play. In the report of National Survey of Public Perceptions of Environmental Health Risks, 90% of Americans believed that environmental factors like pollution, waste and chemicals are important contributors to diseases (http://healthyamericans.org/reports/files/survey0620.pdf). To address the public concerns, it is very important to systematically and efficiently identify environmental hazards that cause adverse health conditions such as mortality or morbidity in order to remove or minimize the health impacts of the toxic agents in the environment.

1.2 NATIONAL ENVIRONMENTAL PUBLIC HEALTH TRACKING NETWORK

Health tracking systems can be classified into two categories: passive and active tracking system. Passive tracking systems are usually based on a registry where local health care providers routinely report every new-onset case of a disease. Active tracking system mostly relies on population-based survey methods which include conducting personal interviews and reviewing medical records to collect information about personal characteristics, health conditions and others. Tracking in Environmental health is a strategy for the identification of hazards of the environment that cause death, disease, or disability, in order to facilitate the goal of prompt removal or reduction of exposures to the offending agents (Hertz-Picciotto 1996).

1.2.1 THE CURRENT STATUS OF ENVIRONMENTAL HEALTH TRACKING SYSTEMS

The current tracking systems in environmental health are specific only on either environmental hazards or health outcomes monitoring. For example, federal and state environmental agencies have routinely collected much environmental hazard data on air pollution, water pollution and others. In addition, federal, state and local public health agencies have developed registries focusing on health outcomes like cancer, birth defects as well as asthma etc. Some familiar examples of health effects datasets include the Surveillance, Epidemiology, and End Results (SEER) program, the Behavioral Risk Factor Surveillance System (BRFSS), the Iowa Birth Defects Registry, National Health Interview Survey (NHIS), and vital statistics data (See Appendix B: using secondary data for environmental public health tracking). However, few current tracking systems in environmental health can effectively

communicate with other tracking systems, efficiently track environmental exposures, and link environmental contaminants with health endpoints.

In 2000, after 18 months of review, the Pew Environmental Health Commission stated that the current system does not have the capability to respond adequately to environmental threats and that the environmental public health system was fragmented, neglected and ineffective. The commission recommended establishing a national environmental public health tracking (EPHT) network to link information on environmentally related diseases, human exposures and environmental hazards (McGeehin et al. 2004).

1.2.2 THE NATIONAL ENVIRONMENTAL PUBLIC HEALTH TRACKING PROGRAM

The Centers for Disease Control and Prevention (CDC) is leading the initiative to build a national EPHT network which is the ongoing systematic collection, integration, analysis, interpretation, and dissemination of data about environmental hazards, exposure to environmental hazards, and health effects potentially related to exposure to environmental hazards (McGeehin et al. 2004). The establishment of this network is a vital step to address the public health needs of the United States, track chronic diseases as well as environmental exposures and eventually reduce the burden of disease on the nation's population.

Currently there are 17 states and local health departments and four schools of public health funded to conduct activities that will form the basis of the tracking network. As one of four academic partners funded by CDC, the University of Pittsburgh/Drexel Academic Consortium for Excellence in Public Health Tracking (UPACE-EPHT) is uniquely positioned to interact with health-related agencies in a local, state and regional initiative to facilitate environmental capacity

building, to evaluate existing surveillance methodologies and to develop innovative strategies and tools to link hazards, exposures and health effects databases and conduct demonstrative studies of using secondary data to assess the potential associations between environmental hazards and health outcomes. The purpose of the Academic Partners program is to provide expertise and support to the National Environmental Public Health Tracking Program (NEPHTP) in the development and utilization of the Tracking Network.

1.3 PROPOSED THREE DEMONSTRATIVE STUDIES AND OBJECTIVES

One of the important activities of the academic partners in the CDC EPHT program is to conduct pilot/demonstration epidemiological studies using existing hazard, exposure and health outcome data. The main aims of this work are to examine the potential associations between environmental hazards/exposures and health outcomes and to explore methods of data linkage and data analyses. The techniques employed in the demonstration studies will be applicable to state and/or local environmental health tracking agencies. In this project, three pilot studies have been developed using secondary data from state or local environmental public health tracking agencies

1.3.1 CASE-CROSSOVER ANALYSIS OF AIR POLLUTION AND CARDIO-PULMONARY HOSPITAL ADMISSIONS

A case-crossover analysis is performed to assess the association between air pollution and cardiopulmonary hospital admissions in the Hazelwood neighborhood of Pittsburgh, PA. The

case-crossover design was first proposed by Maclure in 1991(Maclure 1991). The design is an attractive approach to estimating the effects of triggers of acute health outcomes by environmental exposure. In the design, only cases are involved and the exposure of each case during an at-risk "hazard period" just before the event is compared with the level on one or more reference days when the event did not occur. This self-matching approach will control for all known or unknown time-invariant confounders by design. This method is an alternative to time-series analysis in air pollution studies. The secondary datasets used in the study included the hospital admission data from the Pennsylvania Health Care Cost Containment Council, the climatic data of Pittsburgh from the U.S. National Climatic Data Center database and the air pollution data (PM_{10} and SO_2) in the Hazelwood monitor site from the Allegheny County Department of Health. The objectives of this study are to assess the health effects of air pollution on cardiopulmonary disease hospitalizations, to evaluate the effects of elimination of a major point source of air pollution, i.e. the closure of LTV coke plant, on these relationships and to examine how the different methods of control sampling in THE case-crossover design influence the results (See SECTION 2).

1.3.2 PARTICULATE AIR POLLUTION AND TERM LOW BIRTH WEIGHT IN ALLEGHENY COUNTY

Low birth weight has been reported to influence the subsequent health status of individuals including morbidity in adulthood (Barker 1995; Hales 1997). Studies across the world have consistently provided evidence of the association between particulate matter and adult health including mortality and morbidity (Chen et al. 2007; Dockery et al. 1993; Kan et al. 2007; Kettunen et al. 2007; Pope 2000; Saldiva et al. 1995). A special concern of adverse health

effects of particulate air pollution on fetal health is generated. This study focuses on the associations between exposures to particulate air pollution (PM_{10}) and term low birth weight infant and further examines the effect period of particulate matter during pregnancy. The birth registration data from the Allegheny County Health Department and the air pollution data from RAND's Center for Population Health and Health Disparities (CPHHD) are obtained in this study. (See SECTION 3)

1.3.3 CIGARETTE SMOKING AND ADULT LEUKEMIA

Benzene, a well-established carcinogen and leukemogen, has been shown to be present in cigarette smoke. Wallace observed that approximately 90% of personal exposure to benzene in the United States is due to smoking (Wallace 1996). The study was designed to assess the association between cigarette smoking and leukemia, as well as its subtype, acute myeloid leukemia (AML) and to further examine the dose-response relationship between health endpoints and smoking with the number of cigarettes per day, the number of years of smoking and pack years. The TMI cohort, assembled by the Pennsylvania Department of Health to evaluate the adverse health effects of exposure of low-level radiation emitted from the TMI nuclear power plant accident on 28 March 1979, and the PA cancer registry data are obtained in this study.

The TMI cohort and PA cancer registry data was linked by the key variable of social security number (SSN). The records from these two databases refer to the same individual if the SSN is identical. This is a simple example of deterministic data linkage strategy. Due to confidentiality, this part of the work was done by the PA Department of Health. Survival analysis is performed to estimate the associations after controlling for other important confounding factors.

2.0 CASE-CROSSOVER ANALYSIS OF AIR POLLUTION AND CARDIOPULMONARY HOSPITALIZATIONS: USING ROUTINELY COLLECTED HEALTH AND ENVIRONMENTAL DATA FOR TRACKING

Xiaohui Xu, Ph.D. [1]

Evelyn O. Talbott, Dr.P.H., M.P.H[1]

Jeanne V. Zborowski, Ph.D.[1]

Vincent C. Arena, Ph.D.[2]

Judy Rager, M.P.H [1]

1. Department of Epidemiology, University of Pittsburgh Graduate School of Public Health, Pittsburgh, PA 15261

2. Department of Biostatistics, Universith of Pittsburgh Graduate School of Public Health, Pittsburgh, PA 15261

Manuscript in preparation

2.1 ABSTRACT

Background: From the early 1900s until its closure in February 1998, the LTV Steel coke oven in Pittsburgh (Hazelwood), Pennsylvania was a key source of air pollution. A case-crossover study was performed to assess the associations between daily air pollution and cardiorespiratory (ICD-9: 390-519) hospitalizations before and after plant closure and to evaluate how closure influenced these associations.

Methods: Air pollution data, climatic data and cardiorespiratory hospitalizations among Hazelwood-area residents 65 years and older were obtained for the period of 1996 through 2000. Data were analyzed using a case-crossover design and conditional logistical regression. Two distinct referent sampling approaches were compared.

Results: Significant associations were observed between the fourth quartile in PM_{10} and cardiorespiratory hospitalizations (OR: 1.12; 95%CI: 1.02-1.23) as well as cardiovascular hospitalizations only (ICD-9: 390-459) (OR: 1.13; 95%CI: 1.01-1.26) before the plant closure. After closure of the plant, PM10 was not significantly associated with cardiorespiratory or cardiovascular disease hospitalizations. Moreover, the referent sampling approaches did not greatly alter the estimations in the case-crossover analysis.

Conclusion: Existing secondary data is an economical source to assess the impact of point source polluters on the environmental landscape. The findings suggest that closure of the LTV coke plant was associated with a reduction risk of the cardiorespiratory and cardiovascular hospitalizations.

Key word: Case-Crossover Analysis Cardiopulmonary Air Pollution

2.2 INTRODUCTION

The environment plays an important role in health and human development. There are few surveillance systems that have the capability to adequately assess to environmental threats at the state or national levels in the United States. To address this gap, in 2002 the Centers for Disease Control and Prevention (CDC) began to establish the National Environmental Public Health Tracking (EPHT) Network, which is the ongoing collection, integration, analysis, interpretation, and dissemination of data on environmental hazards; exposure to those hazards; and related health effects (1). A hallmark of the Tracking Network is the use of exiting data in evaluating the relationships between exposures and health outcomes. In the present study, we demonstrated the use of data for purposes other than for which they were collected such as administrative purposes, applied available methods for linking and analyzing environmental and health outcome data, and made a positive contribution to closing gaps in methodology for conducting similar investigations within the context of the environmental public health tracking program.

Epidemiological studies consistently show that air pollutants are linked to cardiovascular and respiratory diseases (2-5). There are several potential biological mechanisms by which air pollutants cause adverse health effects. One of the potential mechanisms is related to inflammation and oxidative stress. High concentrations of oxidants and pro-oxidants contained in ambient air pollution, such as transition metals, reactive organic compounds and gases such as ozone (O_3) or nitrogen oxides (NO, NO2) can generate reactive oxygen species(ROS)(6), alter function of mitochondria(7) or NADPH-oxidase (8), activate inflammatory cells capable of generation of ROS and reactive nitrogen species(9), and promote oxidative stress and respiratory inflammatory responses, which lead to DNA damage(10). Studies show that air pollution can increase the level of blood viscosity and modify the adhesive properties of red blood cells(11),

increase blood pressure(12) and C-reactive protein level(13), and increase heart rate(14), which lead to an increased risk of cardiovascular diseases. In addition, air pollutants, interacting with lung receptors, can activate pulmonary neural reflexes and change the autonomic function resulting in an decreased heart rate variability (HRV)(15) which partly explains the observed cardiovascular effects.

Coke plants produce a by-product of coal that burns more intensely and is used in the making of steel. These plants, as a major source of air pollution, emit gaseous air pollutants such as sulfur dioxide (SO_2), nitrogen oxide (NO_2), carbon monoxide (CO), airborne particulate matter which contains organic compounds like benzo[*a*]pyrene (B[*a*]P) and other polyaromatic hydrocarbons (PAHs) (16, 17) and inorganic compounds like lead and mercury as well as other hazardous pollutants. These emissions have been linked to cardiorespiratory diseases and threaten the natural environment and overall health of the human population(18, 19).

Hazelwood is a neighborhood located in Pittsburgh, Pennsylvania. The LTV Corporation coke plant, a major local source of air pollution, was operational in the area for more than half a century. Toxic emissions from the plant led to the deterioration of the surrounding environmental landscape in the Hazelwood, Greenfield, and Squirrel Hill neighborhoods. On February 28, 1998, after eighty years of operation, the LTV plant was closed. The plant's auxiliary facilities and much of the plant itself were demolished in early 1999. The closure of the plant provided a unique opportunity to conduct a “retrospective natural intervention” study to examine whether reductions of ambient pollution concentration related to plant emissions reduced the adverse cardiorespiratory health effects in the area.

The case-crossover design was first proposed by Maclure in 1991(20). The design is an attractive approach to estimating the effects of triggers of acute health outcomes by

environmental exposure and has subsequently been widely used in air pollution studies(21-25). In this design, only cases of events are involved. The exposure of each case during an at-risk "hazard period" just before the time of the event is compared with exposure during one or more periods when the event did not occur (control periods). This self-matching approach controls by design for all known or unknown time-invariant confounders.

In the present study, a case-crossover analysis was performed to assess the association between air pollution and cardiorespiratory hospital admissions before and after the closure of this plant among the population 65 years of age and older who lived in the Hazelwood area, and to evaluate how the closure of a major point source of air pollution influences the associations. We also compared two different strategies of selecting referent periods in the case crossover analysis and evaluated how the selection of referent periods influenced the results.

Existing data used in the study included hospital admission data from the Pennsylvania Health Care Cost Containment Council, climatic data of Pittsburgh from the U.S. National Climatic Data Center Database, and a pollution monitoring data from the Allegheny County Health Department.

2.3 MATERIALS AND METHODS

2.3.1 STUDY POPULATION:

The Pennsylvania Health Care Cost Containment Council (PHC4), Special Request Unit (Harrisburg, PA) provided the cardiorespiratory hospital admission data for subjects 65 years of age and older in Hazelwood and surrounding neighborhoods in the city of Pittsburgh,

Pennsylvania. The study location included all zip codes surrounding the LTV coke plant with the plant as the center, i.e. zip codes 15207, 15120, 15217 and 15218. A dataset that included all inpatient cardiovascular and respiratory (i.e. Cardiorespiratory) hospital admissions in the Hazelwood area between 1996 and 2000 was created. The records contained a primary discharge diagnosis of the circulatory system [International Classification of Disease, 9th Revision (ICD-9) codes of 390-459] or respiratory system (ICD-9 codes of 460-519]. The study was limited to the first event for those who were hospitalized for Cardiorespiratory diseases in a one month period.

2.3.2 AIR POLLUTION AND WEATHER DATA

Ambient air levels of specific criteria pollutants were obtained in electronic format for the Hazelwood monitoring site from December 1995 through January 2001. The data collected included 24-hour values for sulfur dioxide (SO_2) and PM_{10}. The daily minimum, maximum and mean values of SO_2 and PM_{10} were computed for the present study. These daily measurements were assumed to represent the exposure level for the entire Hazelwood study area.

Daily meteorological data were obtained from the U.S. National Climatic Data Center database from the monitoring site at the Pittsburgh International Airport, Allegheny County (Coopid: 366993, Wbandid: 94,823, Latitude: 40º30', Longitude:-80º14'). The information for daily mean temperature and daily mean relative humidity was abstracted from the database for the time period of 1996-2000.

2.3.3 DATA ANALYSIS

Data were analyzed with the case-crossover technique which is an alternative to time-series analysis for assessing acute health effects of air pollution. In the design, cases serve as their own controls. A subject's exposure at the time of a health event (case-period) is compared with exposures at previous or subsequent points of time when that subject was a non-case (control-period). In the present study, the case-period is defined as the date of hospitalization for any cardiorespiratory diseases. The control periods were chosen using two methods, either the bidirectional control sampling approach or the time-stratified sampling approach in order to control relevant time-varying confounders (26). In the bidirectional control sampling approach, the control periods were selected as 7 and 14 days before and after the date of hospitalization in order to control for day-of-week effect. In the time-stratified method, the stratum is defined as the month of event. All other same days of week as the case period in the month were selected as the control periods. For example, if a case occurs in March on a Wednesday, all other Wednesdays in March are the control periods.

In the bidirectional control sampling approach, the associations between air pollutants and hospitalization for cardiovascular diseases only or respiratory diseases only as well as both combined (cardiorespiratory) were estimated for the time period January 1, 1996 to February 28, 1998 (before closure of the plant) and for the period March 1, 1998 to December 31, 2000 (after closure of the plant), respectively. The SAS conditional logistic regression procedure (Proc Phreg) was applied to estimate the associations between hospital admissions and air pollution. Air pollutants were fitted into the model as continuous variables or categorical variables (quartiles). Odds ratios (ORs) were calculated for continuous variables and the quartiles of each

pollutant during each time period with the first quartile as a reference after adjusting for daily meteorological factors including current day's mean temperature and relative humidity.

In the time-stratified control sampling approach, all analyses were performed with the Case-Crossover Analysis Tool (Beta V1.1 C-CAT), developed by Apex Epidemiology Research, LLC, in conjunction with the New York State Department of Health, to provide an easy-to-use interface to SAS software that implements time-stratified case-crossover analysis. Air pollutants were fitted into the model only as continuous variables. The results of this approach were compared with the previous approach. In addition, the impact of different referent period selections on the results was also examined.

2.4 RESULTS

Among the residents of Hazelwood area who were at least 65 years of age, there were a total of 13,437 cardiorespiratory disease admissions (9,935 cardiovascular disease admissions and 3,502 respiratory diseases admissions) during 1996-2000. Table 1 summarizes the number of admissions that had a specific diagnosis of cardiovascular disease and respiratory disease before and after the closure of the LTV coke plant. There were 4,491 and 5,444 cardiovascular disease hospitalizations before and after the closure of the plant, respectively. In addition, 1,596 and 1,906 respiratory disease hospitalizations were respectively observed before and after the closure of the plant in this study.

The distributions of air pollutants, age and meteorological variables before and after the closure of plant are described in Table 2-2. The distribution of age of hospitalizations is similar before and after the plant closure. The percentiles (10^{th}, 25^{th}, 50^{th}, 75^{th} and 90^{th}) of PM_{10} and

SO_2 were all higher before than after the closure of the plant. The daily averages of PM_{10} were 27.75 $\mu g/m^3$ before and 21.96 $\mu g/m^3$ after the plant closed, respectively. The average of SO_2 decreased to nearly half of the previous levels (from 16.4 ppb to 8.7 ppb) after the plant was closed. For considering the difference of length of time between before and after the plant closure, air pollutants and climatic factors are compared for two-year period before and after the plant closure, respectively. The results are described in Table 2-3. The change of air pollutants is the same regardless of the difference of length of time. The percentiles of daily temperature and daily relative humidity were similar in two-year period before and after the closure of the plant.

Table 2-4 shows the associations between quartiles of PM_{10} and cardiorespiratory hospitalizations after controlling for temperature and relative humidity. The results showed significant associations between the fourth quartile in PM_{10} and cardiorespiratory hospitalizations (OR: 1.12; 95%CI: 1.02-1.23) as well as cardiovascular disease hospitalization only (OR: 1.13; 95%CI: 1.01-1.26) before the closure of the plant. Moreover, significant trends for increasing risks on cardiorespiratory hospitalizations ($p=0.008$) and cardiovascular disease hospitalizations ($p=0.02$) with increasing concentration of PM_{10} were observed. After the closure of the plant, the associations with cardiorespiratory hospitalization were no longer statistically significant. In this study, no significant association between respiratory disease hospitalization and PM_{10} was found either before or after the plant closure.

The associations between SO_2 and cardiorespiratory hospitalizations were illustrated in Table 2-5. There were no significant associations between SO_2 and hospitalizations of cardiovascular diseases only or respiratory diseases only or both combined either before or after the closure of the plant.

Table 2-6 shows the associations between PM_{10} and cardiorespiratory hospitalizations with different referent periods in the case-crossover analysis. The results from the bidirectional control sampling approach are similar to the results of the time-stratified control sampling method.

2.5 DISCUSSION

Few studies are currently available to assess how the addition or elimination of a single point major air pollution source affects the risk of adverse health effects in specific geographic area. This study, for the first time, used a case-crossover design to evaluate this relationship using existing secondary data. The case-crossover approach is a self-matched case control study, which has great advantages in comparison with a time series approach. This approach controls certain confounding factors by design rather than by modeling. With this design, personal characteristics such sex, age, race and time-invariant variables are controlled by the design. By using symmetric 7 and 14 day reference periods, the case-crossover design eliminates the confounding effects of long-term trends, seasonality and day of week(27). Therefore, the use of a case-crossover design avoids common concerns about the complex mathematical modeling and adequacy of seasonal control.

This study demonstrated that the levels of PM_{10} and SO_2 decreased in Hazelwood area after the plant was closed. PM_{10} declined an average of 6 $\mu g/m^3$ and SO_2 was reduced to half of the level when the plant was open. Significant associations between PM_{10} and cardiovascular diseases as well as cardiorespiratory disease hospitalizations were observed before the closure of plant. Moreover, a trend of increased risk for cardiovascular disease as well as cardiorespiratory

disease hospitalizations with increasing particulate matter was observed before the plant closure in the study. Interestingly, after the closure, the associations were no longer statistically significant. Sulfur dioxide did not show a significant association with any outcomes in this study either before or after the closure of the plant. Because sulfur dioxide, a highly soluble gas, can be easily and predominantly stripped out of the upper airways(28), the role of sulfur dioxide in developing adverse health effects is less coherent. Several case-crossover studies reported that there are no significant associations between sulfur dioxide and respiratory disease(22, 29) as well as cardiovascular disease hospitalization(30, 31).

The reduced health effects of PM_{10} after the plant closure could be due to two facts: the change in composition and/or concentration of particulate matter. After the elimination of the LTV coke plant, some toxic elements in the particulate matter associated with the plant emission have also been removed. The monitored data from the Allegheny County Health Department showed that the concentrations of benzo(α)pyrene [B(α)P], as a recognized carcinogen as well as respiratory, endocrine and immunological toxicant, was significantly lower after the plant closure. B(α)P can not however be used as a predictor in the study because it was measured every 7 days. Another potential fact is the reduced concentration of particulate matter in the area. At the low level of particulate matter, there might be no adverse health effect on cardiorespiratory hospitalizations or the association is too weak to be detected on this population sample size.

The findings of this study support that particulate air pollution could increase the risks of cardiorespiratory hospitalizations before the LTV coke plant closure and an elimination of a major air pollution source could lead to a reduced risk of adverse health effects, which is consistent with other epidemiological studies. Pope et al conducted a cross-sectional study to

assess how the operation of a steel mill influences the association between hospital admissions and PM10 in Utah Valley during the period April 1985-February 1988. The results showed that children's hospital admissions were two to three times higher during the winters when the mill was open compared to when it was closed (32). The findings in this study further strengthen the epidemiologic evidence of acute adverse health effects of airborne particle levels.

In this study, we also evaluated how the control sampling approaches influence the estimations in the case-crossover analysis. PM_{10} was the only pollutant used to evaluate these approaches because sulfur dioxide had no associations with the outcomes in this study and Akaike's information criterion (AIC) was increased in both methods after SO_2 was fitted as a continuous variable, suggesting a poor model fit. The estimations from the bidirectional control sampling methods are similar to those from the time-stratified method. The results of the comparison suggested that the control sampling methods in case-crossover analysis did not alter the conclusion.

A potential limitation of this study is that only one air pollution monitoring site was available in the Hazelwood area. Individual exposure was estimated by using the measurement from this fixed outdoor monitoring station. The potential misclassification of exposure due to lack of personal measurement can not be avoided. However, the bias might underestimate the association and shift the results toward the null (33, 34). In addition, we did not assess the promoting role of other pollutants such as nitrogen dioxide or ozone because the data of these pollutants from the monitor site were not available or complete. However, particulate matter is likely a reasonable indicator of other pollutants due to the high collinearity between particulate matter and other pollutants (35). Another limitation is potential for selection bias because we were unable to include all cardiorespiratory disease cases in the study if unreported to the PHC4.

Finally, another limitation of this study is that the sample size of respiratory disease hospitalization might be not large enough to have sufficient power to detect a statistically significant difference.

In summary, this study demonstrates the utility of secondary datasets and the methodology of the case-crossover approach to evaluate the associations between environmental air pollutants and acute health outcomes. This investigation demonstrated important strategies for using existing data to address different health issues and developing the methodology of data linkage and data analysis in conducting similar studies in an environmental public tracking program. Moreover, this analysis provides, for the first time, evidence of a reduction in air pollution resulting in a decrease in risk of Cardiorespiratory disease hospitalization using a case-crossover design. The findings reinforce the deleterious impact of air pollution and provide new epidemiologic information that the elimination or addition of a major point source of pollution could change a local environmental landscape and influence the health of the population living in the area. Further studies are required to confirm these findings.

Table 2-1 Distribution of specific primary diagnoses of hospital admissions among study sample in Hazelwood area, Pittsburgh, PA

Diagnosis	LTV Plant open (1/1/1996-02/28/1998)	LTV Plant closed (3/1/1998-12/31/2000)	Total
Cardiovascular	4,491	5,444	9,935
Respiratory	1,596	1,906	3,502
Combined	6,087	7,350	13,437

Table 2-2 Percentiles and means of age, daily air pollutants and weather variables in Hazelwood, PA

Variables	Time periods	10%	25%	50%	75%	90%	Mean
Age (years)	LTV Plant open	68	72	77	83	88	77.4
	LTV Plant closed	68	72	78	83	88	78.0
PM_{10}, $\mu g/m^3$	LTV Plant open	13.1	17.8	24.0	35.0	46.8	27.8
	LTV Plant closed	10.4	13.5	19.1	27.7	37.2	22.0
SO_2, ppb	LTV Plant open	4.7	8.2	14.1	22.4	30.1	16.4
	LTV Plant closed	3.4	5.0	7.7	11.0	15.3	8.7
Temperature (^oF)	LTV Plant open	26.0	35.0	48.0	65.0	72.0	48.8
	LTV Plant closed	28.0	40.0	55.0	67.0	74.0	52.5
Humidity (%)	LTV Plant open	30.0	40.0	49.0	62.0	73.0	51.1
	LTV Plant closed	29.0	37.0	48.0	60.0	72.0	49.1

Table 2-3 Distribution of daily air pollutants and weather factors in two-year period before and after the plant closure in Hazelwood, PA

Variables	Time periods	Mean	10%	25%	50%	75%	90%
PM_{10}, $\mu g/m^3$	LTV Plant open	28.2	13.5	18.2	24.6	35.4	47.4
	LTV Plant closed	21.3	10.2	13.1	18.5	26.9	36.3
SO_2, ppb	LTV Plant open	16.1	4.5	8.1	13.8	22.2	29.5
	LTV Plant closed	8.5	3.1	4.9	7.7	10.9	14.5
Temperature (^oF)	LTV Plant open	50.4	27	37	51	66	73
	LTV Plant closed	51.6	26	38	55	67	73
Humidity (%)	LTV Plant open	50.5	30	40	49	61	72
	LTV Plant closed	48.5	28	36	48	60	71

Table 2-4 ORs† (95% CIs) of cardiopulmonary hospitalizations for PM_{10} before and after the closure of the plant

Hospitalizations	Exposure levels	PM_{10}	
		LTV Plant open (01/01/1996-02/28/1998)	LTV Plant closed (03/01/1998-12/31/2000)
Cardiovascular and Respiratory diseases combined			
	<25th percentile *	1.0	1.0
	25th to 50th percentile	0.99 (0.91-1.08)	1.03 (0.96-1.11)
	50th to 75th percentile	1.08 (0.99-1.18)	1.02 (0.94-1.10)
	≥75th percentile	1.12 (1.02-1.23) §	0.96 (0.88-1.05)
	P for trend	0.008§	0.61
Cardiovascular diseases only			
	<25th percentile *	1.0	1.0
	25th to 50th percentile	1.01 (0.91-1.11)	1.09 (0.99-1.81)
	50th to 75th percentile	1.10 (0.99-1.21)	1.04 (0.95-1.14)
	≥75th percentile	1.13 (1.01-1.26) §	0.94 (0.85-1.04)
	P for trend	0.02§	0.42
Respiratory diseases only			
	<25th percentile *	1.0	1.0
	25th to 50th percentile	0.97 (0.82-1.39)	0.89 (0.78-1.03)
	50th to 75th percentile	1.05 (0.89-1.24)	0.97 (0.84-1.13)
	≥75th percentile	1.11 (0.92-1.35)	1.03 (0.87-1.22)
	P for trend	0.22	0.71

* Reference group
† Odds ratios adjusted for daily weather variables (daily mean temperature and humidity)
§ P<0.05

Table 2-5 ORs† (95% CIs) of cardiopulmonary hospitalizations for SO_2 before and after the closure of plant

Hospitalizations	Exposure levels	SO_2	
		LTV Plant open (01/01/1996-02/28/1998)	LTV Plant closed (02/28/1998-12/31/2000)
Cardiovascular and Respiratory diseases combined			
	<25th percentile *	1.0	1.0
	25th to 50th percentile	1.00 (0.92-1.09)	1.03 (0.95-1.11)
	50th to 75th percentile	1.06 (0.97-1.16)	0.99 (0.92-1.07)
	≥75th percentile	1.01 (0.93-1.11)	1.02 (0.94-1.11)
	P for trend	0.47	0.68
Cardiovascular diseases only			
	<25th percentile *	1.0	1.0
	25th to 50th percentile	1.04 (0.95-1.15)	1.03 (0.96-1.12)
	50th to 75th percentile	1.07 (0.96-1.19)	0.96 (0.88-1.05)
	≥75th percentile	1.05 (0.94-1.17)	0.99 (0.89-1.09)
	P for trend	0.25	0.59
Respiratory diseases only			
	<25th percentile *	1.0	1.0
	25th to 50th percentile	0.89 (0.75-1.05)	1.02 (0.88-1.18)
	50th to 75th percentile	1.05 (0.88-1.24)	1.09 (0.94-1.27)
	≥75th percentile	0.92 (0.77-1.10)	1.12 (0.95-1.32)
	P for trend	0.59	0.09

* Reference group

† Odds ratios adjusted for daily weather variables (daily mean temperature and humidity)

Table 2-6 ORs* (95% CIs) of cardiopulmonary hospitalizations per unit change in PM_{10} which is fitted as a continuous variable in case-crossover analyses with different control sampling approaches

Hospitalizations	Time periods	Control sampling approach	
		Bidirectional control sampling	Time-stratified control sampling
Cardiovascular and Respiratory diseases combined			
	LTV Plant open	1.003 (1.001-1.005)	1.002 (1.00-1.005)
	LTV Plant closed	0.998(0.995-1.001)	0.997 (0.994-1.00)
Cardiovascular diseases only			
	LTV Plant open	1.003 (1.00-1.006)	1.003(1.00-1.005)
	LTV Plant closed	0.997 (0.994-1.00)	0.996 (0.993-1.00)
Respiratory diseases only			
	LTV Plant open	1.003 (0.998-1.008)	1.001 (0.996-1.006)
	LTV Plant closed	1.00 (0.995-1.006)	0.998 (0.992-1.004)

* Odds ratios adjusted for daily weather variables (daily mean temperature and humidity)

2.6 REFERENCES

1. McGeehin MA, Qualters JR, Niskar AS. National environmental public health tracking program: bridging the information gap. Environ Health Perspect 2004;112:1409-13.

2. Pope CA, 3rd, Thun MJ, Namboodiri MM, et al. Particulate air pollution as a predictor of mortality in a prospective study of U.S. adults. Am J Respir Crit Care Med 1995;151:669-74.

3. Penttinen P, Timonen KL, Tiittanen P, Mirme A, Ruuskanen J, Pekkanen J. Ultrafine particles in urban air and respiratory health among adult asthmatics. Eur Respir J 2001;17:428-35.

4. Magari SR, Schwartz J, Williams PL, Hauser R, Smith TJ, Christiani DC. The association of particulate air metal concentrations with heart rate variability. Environ Health Perspect 2002;110:875-80.

5. Baldacci S, Viegi G. Respiratory effects of environmental pollution: epidemiological data. Monaldi Arch Chest Dis 2002;57:156-60.

6. Fubini B, Fenoglio I, Ceschino R, et al. Relationship between the state of the surface of four commercial quartz flours and their biological activity in vitro and in vivo. Int J Hyg Environ Health 2004;207:89-104.

7. Li N, Sioutas C, Cho A, et al. Ultrafine particulate pollutants induce oxidative stress and mitochondrial damage. Environ Health Perspect 2003;111:455-60.

8. Knaapen AM, Borm PJ, Albrecht C, Schins RP. Inhaled particles and lung cancer. Part A: Mechanisms. Int J Cancer 2004;109:799-809.

9. Schins RP, Lightbody JH, Borm PJ, Shi T, Donaldson K, Stone V. Inflammatory effects of coarse and fine particulate matter in relation to chemical and biological constituents. Toxicol Appl Pharmacol 2004;195:1-11.

10. Risom L, Moller P, Loft S. Oxidative stress-induced DNA damage by particulate air pollution. Mutat Res 2005;592:119-37.

11. Seaton A, Soutar A, Crawford V, et al. Particulate air pollution and the blood. Thorax 1999;54:1027-32.

12. Brook RD. You are what you breathe: evidence linking air pollution and blood pressure. Curr Hypertens Rep 2005;7:427-34.

13. Donaldson K, Stone V, Seaton A, MacNee W. Ambient particle inhalation and the cardiovascular system: potential mechanisms. Environ Health Perspect 2001;109 Suppl 4:523-7.

14. Peters A, Perz S, Doring A, Stieber J, Koenig W, Wichmann HE. Increases in heart rate during an air pollution episode. Am J Epidemiol 1999;150:1094-8.

15. Pope CA, 3rd, Hansen ML, Long RW, et al. Ambient particulate air pollution, heart rate variability, and blood markers of inflammation in a panel of elderly subjects. Environ Health Perspect 2004;112:339-45.

16. Liberti L, Notarnicola M, Primerano R, Zannetti P. Air pollution from a large steel factory: polycyclic aromatic hydrocarbon emissions from coke-oven batteries. J Air Waste Manag Assoc 2006;56:255-60.

17. Wang J, Zhu L, Shen X. [PAHs pollution in air of coke plant and health risk assessment]. Huan Jing Ke Xue 2003;24:135-8.

18. Bhopal RS, Phillimore P, Moffatt S, Foy C. Is living near a coking works harmful to health? A study of industrial air pollution. J Epidemiol Community Health 1994;48:237-47.

19. Dolk H, Thakrar B, Walls P, et al. Mortality among residents near cokeworks in Great Britain. Occup Environ Med 1999;56:34-40.

20. Maclure M. The case-crossover design: a method for studying transient effects on the risk of acute events. Am J Epidemiol 1991;133:144-53.

21. Lee JT, Schwartz J. Reanalysis of the effects of air pollution on daily mortality in Seoul, Korea: A case-crossover design. Environ Health Perspect 1999;107:633-6.

22. Sunyer J, Schwartz J, Tobias A, Macfarlane D, Garcia J, Anto JM. Patients with chronic obstructive pulmonary disease are at increased risk of death associated with urban particle air pollution: a case-crossover analysis. Am J Epidemiol 2000;151:50-6.

23. Neas LM, Schwartz J, Dockery D. A case-crossover analysis of air pollution and mortality in Philadelphia. Environ Health Perspect 1999;107:629-31.

24. Levy D, Sheppard L, Checkoway H, et al. A case-crossover analysis of particulate matter air pollution and out-of-hospital primary cardiac arrest. Epidemiology 2001;12:193-9.

25. Barnett AG, Williams GM, Schwartz J, et al. The effects of air pollution on hospitalizations for cardiovascular disease in elderly people in Australian and new zealand cities. Environ Health Perspect 2006;114:1018-23.

26. Levy D, Lumley T, Sheppard L, Kaufman J, Checkoway H. Referent selection in case-crossover analyses of acute health effects of air pollution. Epidemiology 2001;12:186-92.

27. Lee JT, Kim H, Schwartz J. Bidirectional case-crossover studies of air pollution: bias from skewed and incomplete waves. Environ Health Perspect 2000;108:1107-11.

28. Health effects of outdoor air pollution. Committee of the Environmental and Occupational Health Assembly of the American Thoracic Society. Am J Respir Crit Care Med 1996;153:3-50.

29. Sunyer J, Basagana X, Belmonte J, Anto JM. Effect of nitrogen dioxide and ozone on the risk of dying in patients with severe asthma. Thorax 2002;57:687-93.

30. Tsai SS, Goggins WB, Chiu HF, Yang CY. Evidence for an association between air pollution and daily stroke admissions in Kaohsiung, Taiwan. Stroke 2003;34:2612-6.

31. D'Ippoliti D, Forastiere F, Ancona C, et al. Air pollution and myocardial infarction in Rome: a case-crossover analysis. Epidemiology 2003;14:528-35.

32. Pope CA, 3rd. Respiratory disease associated with community air pollution and a steel mill, Utah Valley. Am J Public Health 1989;79:623-8.

33. Katsouyanni K, Touloumi G, Spix C, et al. Short-term effects of ambient sulphur dioxide and particulate matter on mortality in 12 European cities: results from time series data from the APHEA project. Air Pollution and Health: a European Approach. Bmj 1997;314:1658-63.

34. Zeger SL, Thomas D, Dominici F, et al. Exposure measurement error in time-series studies of air pollution: concepts and consequences. Environ Health Perspect 2000;108:419-26.

35. Gadgil AS, Jadhav RS. Street-level concentrations of suspended particulate matter (SPM), nitrogen dioxide (NO2) and sulphur dioxide (SO2) in Pune City. J Environ Sci Eng 2004;46:143-50.

3.0 LOCAL VARIATION IN PARTICULATE MATTER DURING PREGNANCY AND TERM LOW BIRTH WEIGHT IN ALLEGHENY COUNTY, PA, USA

Xiaohui Xu, Ph.D. [1]

Ravi K. Sharma Ph.D[2]

Evelyn O. Talbott, Dr.P.H., M.P.H[1]

Jeanne V. Zborowski, Ph.D.[1]

Vincent C. Arena, Ph.D.[3]

Devra Lee Davis Ph.D[1]

Conrad D Volz Dr. P.H.[4]

Judy Rager, M.P.H [1]

1. Department of Epidemiology, Graduate School of Public Health, Universith of Pittsburgh

2. Department of Behavioral Community Health Sciences, Graduate School of Public Health, Universith of Pittsburgh

3. Department of Biostatistics, Graduate School of Public Health, Universith of Pittsburgh

4. Department of Environmental and Occupational Health, Graduate School of Public Health, Universith of Pittsburgh

Manuscript in preparation

3.1 ABSTRACT

Introduction: Low birth weight has been associated with increased risks of mortality and/or morbidity in childhood and adulthood. The aim of this study is to explore the association between particulate matter (PM_{10}) and term low birth weight (birth weight <2,500g).

Methods: Birth data from the Allegheny County Health Department, Pittsburgh PA and PM_{10} air data generated with inverse-distance interpolation by RAND's Center for Population Health and Health Disparities, were obtained. The study population consisted of all term singleton live births (gestational age ≥37 weeks) born between Jan 1st, 1994 to Dec 31st, 2000. Infants with birth weight <2,500g were classified as LBW. Logistic regression was performed to estimate the association per inter-quartile range increase in PM_{10}.

Results: The results showed that the odds ratios of term LBW per inter-quartile range increase in PM_{10} were 1.13 (95%CI: 1.02-1.25) during the first trimester and 1.10 (95%CI: 1.00-1.22) during the second trimester after adjusted for other important covariates, respectively.

Conclusion: The findings of the study support that exposure to PM_{10} could increase risks of term LBW. Further studies are warrant to corroborate these findings.

Keywords: LBW PM10 air pollution Inverse-distance interpolation

3.2 INTRODUCTION

A growing body of evidence suggests that maternal exposure to air pollution is associated with adverse pregnancy outcomes. Studies conducted worldwide have investigated the health effects of air pollution on preterm delivery (PTD) (1, 2), low birth weight (3-5), intrauterine growth restriction (IUGR) (6, 7) and birth defects (8, 9). The air pollutants of concern in these studies include carbon monoxide (CO), nitrogen dioxide (NO_2), sulfur dioxide (SO2), ozone (O3), and particulate matter (PM).

Low birth weight (birth weight less than 2500 g) is comprised of the two overlapping etiologies of PTD as well as IUGR. Term LBW is caused by fetal growth retardation instead of early delivery. LBW has been widely reported to influence the health status of individuals, including increased mortality and morbidity in childhood (10, 11) and an elevated risk of hypertension, coronary heart disease, Type II diabetes in adulthood, abnormalities of lipid metabolism and blood coagulation (12-15). The public health relevance on this important health issue is evident.

Studies across the world have consistently provided evidence that exposure to particulate matter increases risks of mortality and morbidity among adults (16-23). There is a great concern about the association between particulate matter and fetal health outcomes, especially low birth weight. However, the findings of particulate matter in fetal health research are inconsistent, especially regarding the effect period and the strength of association of particulate matter. In addition, many prior studies did not account for important confounders such as maternal smoking, gestational age and weight gain. Previous studies have also had limited spatial

information on pollution sources and concentrations because the exposure mostly relied on the measurements at monitoring stations.

In the present study, we investigated the possible association between particulate matter (PM_{10}) and term LBW in Allegheny County, PA (USA). The specific purposes of this study are to use PM_{10} data spatially and temporally being generated with inverse-distance interpolation, to estimate the levels of PM_{10} corresponding to the first, second, and third trimesters of pregnancy, to evaluate the association between PM_{10} and term low birth weight, and to explore the possible techniques of data management, data linkage and data analysis for environmental public health tracking to evaluate these relationships.

3.3 MATERIALS AND METHODS

3.3.1 Live birth cohort

All live birth data in Allegheny County, PA was obtained from the birth registry data maintained by the Allegheny County Health Department, PA for the period January 1, 1994 through December 31, 2000. The information in the database includes date of birth, birth weight, gestational age, parity, birth order, maternal age, education, race and geographical location of birth (neighborhood in the city of Pittsburgh and municipality outside the city) and other reproductive data. Individual data of all singleton live births to the Allegheny County residents were abstracted from the database and used in the present study.

3.3.2 Air pollution data and geographical data

The quarterly measures of PM_{10} in census tracts in Allegheny County were obtained from the RAND's Center for Population Health and Health Disparities (CPHHD) Data Core. The geographic-specific data were derived from the publicly available Environmental Protection Agency (EPA) Air Quality System (AQS) Criteria pollutant data with the inverse-distance interpolation based on the 1990 based census tracts. The following are the basic processes used to construct the dataset.

The hourly data of PM_{10} between 1994 and 2000 were obtained from the U.S EPA AQS. The data were aggregated from daily to quarterly levels for each monitor site. The quarterly PM_{10} measures from the EPA monitor sites were used to estimate the levels at the centroids of census tracts, which represent the levels of the census tracts. All distances from the census tract centroid to the site locations were computed geospatially using ArcGIS (Version 9.1, ESRI Inc. Redlands, WA, USA). The measures from the monitor sites within 100 kilometers between the centroid and their locations are used to estimate the level of that census tract. The estimation involves various inverse distance-weighting schemes that are a function of the distance between the census tract centroid and the PM monitors (see Figure 1). Therefore, the sites further away will have less influence and thus less contribution overall to the estimation.

3.3.3 Exposure estimation

The quarterly PM_{10} data were aggregated from census tract to neighborhood in the city or municipality outside the city in geographical level. The average of the quarterly PM_{10} measures of all census tracts in each neighborhood or municipality was used to estimate the quarterly level

of that neighborhood or municipality. It assumed that all births in the same neighborhood or municipality had the same exposure at a single time.

Air pollution estimates for each individual birth were assigned using the neighborhood or municipality of the maternal residence at infant's birth. For each birth, the accumulated first 3-month, 6-month and 9-month exposures was computed by weighting the quarterly PM10 measures based on the mother's residence (neighborhood or municipality), the month, quarter and year of birth conception. The weights of estimating the accumulated exposures are shown in the table 1. The date of conception was computed based on the date of birth and gestational age. For example, for an infant who was conceived in February 1994, the accumulated first 3-month exposure is two times the first quarterly PM10 measure in 1994 plus one time the second quarterly PM10 measure in 1994. The monthly averages of trimester-specific exposures were calculated based on the accumulated exposures.

3.3.4 Statistical Analysis

In this study, our analyses were focused on the effects of PM_{10} on birth weight mediated by reduced fetal growth as opposed to early delivery. Therefore, the study population was restricted to infants who were born at term with gestational age ≥37 weeks. The relationship between particles and term low birth weight was evaluated using logistic regression analyses. Adverse pregnancy outcomes, i.e. term LBW, defined as dichotomous categories, represent dependent variables in the analysis. A term LBW infant is defined as a live-birth infant weighing <2,500g and gestational age ≥ 37 complete weeks.

Several known risk factors for term LBW that could potentially confound the relationship between LBW and air pollution were also included in regression models: maternal age (<20, 20-

29, 30-34,35-39, ≥40 years), maternal race (black, white, others), maternal education (<9, 9-11, 12, 13-15, ≥16 years), maternal tobacco use (yes/no), level of prenatal care (none, during first trimester, after first trimester), history of LBW or preterm infant (one or more vs. none), parity (first birth vs. second or subsequent birth), birth season, infant sex, gestational age (measured in weeks) and maternal weight gained.

Air pollution exposures were fitted into the logistic regression model as continuous variable. The odds ratios with per inter-quartile range increase in PM10, i.e. and 7 $\mu g/m^3$ increase, were estimated for each trimester.

3.4 RESULTS

A total of 100,595 singleton birth records were available for Allegheny County between 1994 and 2000. Among 92,447 singleton term births (≥37 completed weeks gestation), 47,221 were male births and 45,226 female births. The sex ration at birth is 104 per 100 females. A total of 2,058 (2.2%) low weight births occurred over the entire study period.

The mean trimester-specific exposures and 9-month period for PM10 during the study period were 28.7, 28.2, 28.1 and 28.1 $\mu g/m^3$ respectively. The inter-quartile range for each trimester is nearly 7 $\mu g/m^3$ (table 3-2).

Table 3-3 summarizes the distributions of characteristics of singleton births among term LBW. The results of crude estimations suggested that term LBW was significantly associated with maternal age, race, education, tobacco use, infant gender, previous LBW or PTD, parity, prenatal care, gestational age and weight gained. For term LBW, younger (<20) and older (≥40) maternal age, no previous birth, low levels of education and prenatal care, tobacco use and

previous LBW or PTD could increase the risks of term LBW. African-American women had a higher risk of term LBW than whites. Male infant sex was negatively associated with term LBW. Risk of term LBW decreased as the increase of gestational age and maternal weight gained (See Table 3-3).

Table 4-4 illustrates the risks of term LBW associated with per inter-quartile range increase in exposure to trimester-specific PM_{10}. Significant associations between term LBW and the first trimester exposure to PM_{10} was observed in the study after controlling for other covariates including for maternal age, maternal race, maternal education, smoking, weight gain, gender of infant, gestation age, parity, previous LBW or preterm birth, level of prenatal care and birth season. The odds ratios of term LBW for per inter-quartile range increase in PM_{10} were 1.13 (95%CI: 1.02-1.25) during the first trimester and 1.10 (95%CI: 1.00-1.22) during the second trimester, respectively. There is no significant association between term LBW and PM_{10} exposure during the third trimester (OR=1.05, 95%CI: 0.96-1.16) and 9-month period (OR=1.07, 95%CI: 0.99-1.14).

3.5 DISCUSSION

The sex ratio at birth is one of the stable parameters of a population and it should lie in a narrow range of 100-108 males per 100 females. In this study, the sex ratio is 104 per 100 females, which is similar to the national level in the USA (24). We examined associations between term low birth weight and exposure to PM_{10} at various stages of pregnancy. Increased risks of LBW were observed for mother's exposure to PM_{10} during the first trimester after adjusting for other important confounding factors including maternal age, race, education,

smoking, weight gain, infant gender, gestational age, parity, history of LBW or PTD, prenatal care and birth season. The findings of this study support that PM_{10} exposure could increase risk of term LBW.

In adverse pregnancy outcome research, it is important to identify the critical time points during pregnancy when exposure to air pollutants might be most harmful (25). Our finding of an adverse effect of ambient particulates in the first trimester on pregnancy outcomes is consistent with some previous studies. Dejmek et al conducted a study in the Treplice District of the Czech Republic and revealed that exposure to PM10 during the first month was associated with intrauterine growth retardation (IUGR) (6). The study from Seoul found that carbon monoxide, nitrogen dioxide, sulfur dioxide, and total suspended particle concentrations in the first trimester of pregnancy period are risk factors for low birth weight (26). The finding from a study in Brazil also showed that exposure from the first trimester was the most important for LBW(27). However, other studies found that exposures during the third trimester were importantly linked with birth weight. Chen et al found that exposure to PM_{10} in the third trimester of pregnancy was negatively associated with birth weight in North Nevada, USA(28). Wang and colleagues reported that concentrations of TSP and SO_2 in the last trimester of pregnancy were associated with low birth weight in Beijing, China(29). A study in Poland also found that PM2.5 exposure in the second trimester of pregnancy was negatively associated with birth weight (30). Therefore exposure during the earlier or later stage of pregnancy could present the possibility of interference with final infant weight gain.

Although the specific biological mechanisms that may account for the association between ambient air pollution and adverse pregnancy outcomes are not well known, the effect of particulate matter exposure during pregnancy on adverse pregnancy outcomes has a plausible

biological basis. It has been assumed that prenatal exposure to ambient air pollution might be similar to maternal smoking which can result in some adverse reproductive outcomes. The possible biological mechanisms of air pollution on birth weight might vary according the time of pregnancy, such as the implantation of the fetus and the formation of placenta during the first trimester as well as important weight gain during the third trimester. A study found that placental abnormalities due to exposure in the first trimester and complex vascular alterations in the second and third trimester could be the main causes of placental abnormalities and fetal growth retardation(31). PM10 contains many toxic elements including polycyclic aromatic hydrocarbons (PAHs), which could produce DNA adducts and cause DNA damage, resulting in activation of apoptotic pathways(32). Molecular epidemiological studies have been shown that the levels of DNA adducts are positively related to the risk of low birth weight(33-36). Another possible way is that toxic components and/or it metabolites may bind some receptors, which results in disruption of endocrine system and changes the placental function with decreasing exchange of oxygen and nutrients(37). Moreover, these toxic elements might also be able to provoke alveolar inflammation and release the mediators capable of increasing blood coagulability which increase blood viscosity (38). The change of viscosity can affect blood perfusion and have an adverse effect on placental functions, which may result in adverse birth outcomes. All these changes could result into consequent fetal growth retardation. Therefore, our finding of a significant effect during the first trimester is coherent with some potential mechanisms.

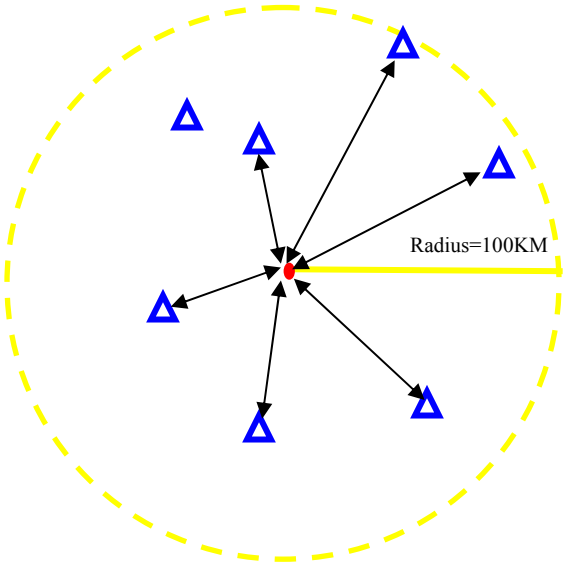
There are number of strengths to our study. First, the present study had a population based birth data with a large sample size to assess the effects of particulate air pollution on term LBW. By focusing on term LBW, the effect of PM_{10} on fetal growth independent from the effects of prematurity could be examined in this study. Second, the health effects of particulate air

pollutant on birth weight were estimated after controlling for potential confounding factors in this study. Important known risk factors for a low birth weight baby like maternal smoking and maternal weight gain were also considered in this study. Most previous studies of adverse pregnancy outcomes did not control for the information due to unavailability (3-5, 26, 27, 29). Third, our study used the inverse-distance interpolation to predict the levels of particulate air pollutant in smaller geographical resolutions, which provided a more accurate exposure assessment for individual mothers. The inverse-distance interpolation, one of the popular methods to predict spatial distribution of air pollutants, uses real pollution measurements in the neighborhoods and estimates the weight average of neighboring values for un-sampled locations(39).

While the findings of this study are in accordance with other previous studies, some methodological aspects of this study should be elucidated. A certain degree of inaccuracy of maternal exposure might occur due to invalid assumption, difference between monthly period and gestational age, and difference between personal exposure and estimated quarterly measurement. For example, one assumption of this study is that mothers did not move and stayed most of time pregnancy in the place where they resided. However, we do not have information on maternal mobility during pregnancy to assess whether the assumption is true or not. In addition, although our analyses controlled for a number of important potential confounders, information on other factors such as second hand smoking, maternal occupational exposures and nutrition are not available in this study. Therefore, the potential confounding of these factors could not be controlled. However, we adjusted for maternal weight gain in our analyses, which could partially control for the effects of maternal nutrition. Another issue in this study is that we used quarterly levels of PM_{10} to estimate maternal trimester-specific exposure.

Therefore, a certain degree of inaccuracy of maternal exposure might occur. However, such bias or inaccuracy would be non-differential and make the effects toward the null. Moreover, we applied the weight method to estimate the accumulated exposure, which could provide estimates very close to one based on monthly air data.

In conclusion, our findings suggested that exposure to PM10 during the first trimester of pregnancy is associated with an increased risk of term LBW among infants whose mothers resided in Allegheny County, PA, between 1994 and 2000. Further studies are required to elucidate this association and to corroborate the findings of potential public health significance.



Monitor sites

Points to be

Distance

$$\hat{Z}_{0\,IDp} = \frac{\sum_{i=1}^{N} Z(s_i) d_{0,i}^{-p}}{\sum d_{0,i}^{-p}}$$

$\hat{Z}_{0IDp}$ estimated value

Z(si) observed value in "i" monitor site
N: number of monitor sites
$d_{0,I}$ distance between estimated point and "i" site
p the power

Figure 3-1 Inverse-distance interpolation

Table 3-1 Weights for estimating the accumulated exposure during pregnancy

Month of conception	Accumulated Exposure first 3 months		Accumulated Exposure first 6 months			Accumulated Exposure first 9 months			
	Q_c	Q_{a1}	Q_c	Q_{a1}	Q_{a2}	Q_c	Q_{a1}	Q_{a2}	Q_{a3}
1	3	-	3	3	-	3	3	3	-
2	2	1	2	3	1	2	3	3	1
3	1	2	1	3	2	1	3	3	2
4	3	-	3	3	-	3	3	3	-
5	2	1	2	3	1	2	3	3	1
6	1	2	1	3	2	1	3	3	2
7	3	-	3	3	-	3	3	3	-
8	2	1	2	3	1	2	3	3	1
9	1	2	1	3	2	1	3	3	2
10	3	-	3	3	-	3	3	3	-
11	2	1	2	3	1	2	3	3	1
12	1	2	1	3	2	1	3	3	2

Q_c : the level of PM10 during the quarter of birth conception
Q_{a1} : the level of PM10 in the 1st quarter after the quarter of birth conception
Q_{a2} : the level of PM10 in the 2nd quarter after the quarter of birth conception
Q_{a3} : the level of PM10 in the 3rd quarter after the quarter of birth conception

Table 3-2 Distribution of trimester-specific PM_{10}, Allegheny County PA, 1994-2000

Trimester (monthly average)	Mean	25%	50%	75%	95%
1st Trimester	28.7	25.1	28.3	32.2	37.4
2nd Trimester	28.2	24.9	27.6	31.3	36.9
3rd Trimester	28.1	24.9	27.3	31.0	36.6
9-month period	28.1	25.8	27.8	30.1	33.5

Table 3-3 Distribution of characteristics of term singleton births by low birth weight status

Characteristics		Term LBW		OR (95%CI)
		CASE (N=2,058)	Control (N=90,389)	
Maternal age				
	<20	307 (14.9)	7,620 (8.4)	1.69 (1.49-1.93)
	20-29*	949 (46.1)	39,907 (44.1)	1.0
	30-34	463 (22.5)	27,628 (30.6)	0.71 (0.63-0.79)
	35-39	282 (13.7)	13,002 (14.4)	0.91 (0.80-1.04)
	≥40	57 (2.8)	2,232 (2.5)	1.07 (0.82-1.41)
Maternal race				
	White*	1,250 (60.9)	72,087 (79.8)	1.0
	Black	731 (35.6)	15,808 (17.5)	2.67 (2.43-2.93)
	Other	73 (3.5)	2,392 (2.7)	1.76 (1.38-2.24)
Maternal education				
	<9	43 (2.1)	641 (0.7)	4.51 (3.27-6.22)
	9-11	313 (15.2)	6,662 (7.4)	3.16 (2.74-3.64)
	12	761 (37.0)	27,512 (30.4)	1.86 (1.66-2.08)
	13-15	425 (20.6)	20,884 (23.1)	1.37 (1.20-1.56)
	≥16 *	516 (25.1)	34,690 (38.4)	1.0
Maternal tobacco use				
	Yes	879 (43.1)	16,103 (17.9)	3.48 (3.18-3.80)
	No	1,160 (56.9)	73892 (82.1)	1.0
Infant sex				
	Male	814 (39.6)	46,407(51.3)	0.62 (0.57-0.68)
	Female *	1,244 (60.45)	43,982 (48.7)	1.0
Parity				
	Second or subsequent birth	1,005 (48.9)	52,856 (58.5)	0.68 (0.62-0.74)
	First birth *	1,049 (51.1)	37,465 (41.5)	1.0
Birth season				
	Summer (Jun-Aug)*	534 (25.9)	23,747 (26.3)	1.0
	Autumn (Sep-Nov)	541 (26.3)	22,155 (24.5)	1.09 (0.96-1.23)
	Winter (Dec-Feb)	503 (24.4)	21,128 (23.4)	1.06 (0.94-1.20)
	Spring (Mar-May)	480 (23.3)	23,359 (25.8)	0.91 (0.81-1.03)
Previous LBW or PTD				
	Yes	53 (2.6)	364 (0.4)	6.56 (4.90-8.77)
	No	1,998 (97.4)	89,931 (99.6)	1.0
Prenatal care				
	None	45 (2.2)	517 (0.6)	3.95 (2.91-5.38)
	1st trimester *	1,945 (97.3)	88,347 (99.1)	1.0
	After 1st trimester	10 (0.5)	235 (0.3)	1.93 (1.02-3.64)
Gestational age	Mean±SD	38.2±1.1	39.4±1.2	0.40 (0.39-0.42)
Maternal weight gain	Mean±SD	26.4±11.9	31.0±12.2	0.968 (0.96-0.97)

* Reference group

** Number of missing for each variable: maternal race (106); maternal tobacco use (413); Parity (72); Previous LBW or PTD (101); Prenatal care (1348)

Table 3-4 Risks for term low birth weight [a] according to trimester-specific exposure to PM_{10}

Exposure period	OR (95%CI) *	
	OR	95% CI
1st Trimester	1.13[b]	1.02-1.25
2nd Trimester	1.10	1.00-1.22
3rd Trimester	1.05	0.96-1.16
9-month period	1.07	0.99-1.14

* ORs were estimated by per inter-quartile range increase (per 7 μg/m^3 for trimester-specific exposure and 4.3 μg/m^3 for 9-month period) after adjustment for maternal age, maternal race, maternal education, smoking, weight gain, gender of infant, gestation age, parity, previous LBW or preterm birth, level of prenatal care and birth season

[a] All singleton births with gestational age ≥37 weeks

[b] $P<0.05$

3.6 REFERENCES

1. Xu X, Ding H, Wang X. Acute effects of total suspended particles and sulfur dioxides on preterm delivery: a community-based cohort study. Arch Environ Health 1995;50:407-15.

2. Tsai SS, Yu HS, Liu CC, Yang CY. Increased incidence of preterm delivery in mothers residing in an industrialized area in Taiwan. J Toxicol Environ Health A 2003;66:987-94.

3. Bobak M. Outdoor air pollution, low birth weight, and prematurity. Environ Health Perspect 2000;108:173-6.

4. Dugandzic R, Dodds L, Stieb D, Smith-Doiron M. The association between low level exposures to ambient air pollution and term low birth weight: a retrospective cohort study. Environ Health 2006;5:3.

5. Maisonet M, Bush TJ, Correa A, Jaakkola JJ. Relation between ambient air pollution and low birth weight in the Northeastern United States. Environ Health Perspect 2001;109 Suppl 3:351-6.

6. Dejmek J, Selevan SG, Benes I, Solansky I, Sram RJ. Fetal growth and maternal exposure to particulate matter during pregnancy. Environ Health Perspect 1999;107:475-80.

7. Liu S, Krewski D, Shi Y, Chen Y, Burnett RT. Association between gaseous ambient air pollutants and adverse pregnancy outcomes in Vancouver, Canada. Environ Health Perspect 2003;111:1773-8.

8. Gilboa SM, Mendola P, Olshan AF, et al. Relation between ambient air quality and selected birth defects, seven county study, Texas, 1997-2000. Am J Epidemiol 2005;162:238-52.

9. Ritz B, Yu F, Fruin S, Chapa G, Shaw GM, Harris JA. Ambient air pollution and risk of birth defects in Southern California. Am J Epidemiol 2002;155:17-25.

10. Moore A. Changing patterns of childhood mortality in Wolverhampton. Arch Dis Child 2005;90:687-91.

11. Reynolds P, Urayama KY, Von Behren J, Feusner J. Birth characteristics and hepatoblastoma risk in young children. Cancer 2004;100:1070-6.

12. Hales CN. Fetal and infant origins of adult disease. J Clin Pathol 1997;50:359.

13. Osmond C, Barker DJ. Fetal, infant, and childhood growth are predictors of coronary heart disease, diabetes, and hypertension in adult men and women. Environ Health Perspect 2000;108 Suppl 3:545-53.

14. Morley R. Fetal origins of adult disease. Semin Fetal Neonatal Med 2006;11:73-8.

15. Barker DJ. The developmental origins of adult disease. J Am Coll Nutr 2004;23:588S-595S.

16. Chen TM, Gokhale J, Shofer S, Kuschner WG. Outdoor Air Pollution: Particulate Matter Health Effects. Am J Med Sci 2007;333:235-243.

17. Glorennec P, Monroux F. Health impact assessment of PM10 exposure in the city of Caen, France. J Toxicol Environ Health A 2007;70:359-64.

18. Zhang M, Song Y, Cai X. A health-based assessment of particulate air pollution in urban areas of Beijing in 2000-2004. Sci Total Environ 2007;376:100-8.

19. Yorifuji T, Yamamoto E, Tsuda T, Kawakami N. Health impact assessment of particulate matter in Tokyo, Japan. Arch Environ Occup Health 2005;60:179-85.

20. Chen L, Mengersen K, Tong S. Spatiotemporal relationship between particle air pollution and respiratory emergency hospital admissions in Brisbane, Australia. Sci Total Environ 2007;373:57-67.

21. Schwartz J, Slater D, Larson TV, Pierson WE, Koenig JQ. Particulate air pollution and hospital emergency room visits for asthma in Seattle. Am Rev Respir Dis 1993;147:826-31.

22. Dockery DW, Pope CA, 3rd, Xu X, et al. An association between air pollution and mortality in six U.S. cities. N Engl J Med 1993;329:1753-9.

23. Anderson HR, Spix C, Medina S, et al. Air pollution and daily admissions for chronic obstructive pulmonary disease in 6 European cities: results from the APHEA project. Eur Respir J 1997;10:1064-71.

24. Mathews TJ, Hamilton BE. Trend analysis of the sex ratio at birth in the United States. Natl Vital Stat Rep 2005;53:1-17.

25. Sram RJ, Binkova B, Dejmek J, Bobak M. Ambient air pollution and pregnancy outcomes: a review of the literature. Environ Health Perspect 2005;113:375-82.

26. Ha EH, Hong YC, Lee BE, Woo BH, Schwartz J, Christiani DC. Is air pollution a risk factor for low birth weight in Seoul? Epidemiology 2001;12:643-8.

27. Gouveia N, Bremner SA, Novaes HM. Association between ambient air pollution and birth weight in Sao Paulo, Brazil. J Epidemiol Community Health 2004;58:11-7.

28. Chen L, Yang W, Jennison BL, Goodrich A, Omaye ST. Air pollution and birth weight in northern Nevada, 1991-1999. Inhal Toxicol 2002;14:141-57.

29. Wang X, Ding H, Ryan L, Xu X. Association between air pollution and low birth weight: a community-based study. Environ Health Perspect 1997;105:514-20.

30. Jedrychowski W, Bendkowska I, Flak E, et al. Estimated risk for altered fetal growth resulting from exposure to fine particles during pregnancy: an epidemiologic prospective cohort study in Poland. Environ Health Perspect 2004;112:1398-402.

31. Lin CC, Santolaya-Forgas J. Current concepts of fetal growth restriction: part I. Causes, classification, and pathophysiology. Obstet Gynecol 1998;92:1044-55.

32. Nicol CJ, Harrison ML, Laposa RR, Gimelshtein IL, Wells PG. A teratologic suppressor role for p53 in benzo[a]pyrene-treated transgenic p53-deficient mice. Nat Genet 1995;10:181-7.

33. Whyatt RM, Bell DA, Jedrychowski W, et al. Polycyclic aromatic hydrocarbon-DNA adducts in human placenta and modulation by CYP1A1 induction and genotype. Carcinogenesis 1998;19:1389-92.

34. Whyatt RM, Santella RM, Jedrychowski W, et al. Relationship between ambient air pollution and DNA damage in Polish mothers and newborns. Environ Health Perspect 1998;106 Suppl 3:821-6.

35. Perera FP, Jedrychowski W, Rauh V, Whyatt RM. Molecular epidemiologic research on the effects of environmental pollutants on the fetus. Environ Health Perspect 1999;107 Suppl 3:451-60.

36. Perera F, Hemminki K, Jedrychowski W, et al. In utero DNA damage from environmental pollution is associated with somatic gene mutation in newborns. Cancer Epidemiol Biomarkers Prev 2002;11:1134-7.

37. Dejmek J, Solansky I, Benes I, Lenicek J, Sram RJ. The impact of polycyclic aromatic hydrocarbons and fine particles on pregnancy outcome. Environ Health Perspect 2000;108:1159-64.

38. Maisonet M, Correa A, Misra D, Jaakkola JJ. A review of the literature on the effects of ambient air pollution on fetal growth. Environ Res 2004;95:106-15.

39. Spokas K, Graff C, Morcet M, Aran C. Implications of the spatial variability of landfill emission rates on geospatial analyses. Waste Manag 2003;23:599-607.

4.0 CIGARETTE SMOKING AND THE RISK OF ADULT LEUKEMIA: RESULTS FROM THE THREE MILE ISLAND COHORT STUDY

Xiaohui Xu, M.P.H.

Evelyn O. Talbott, Dr.P.H., M.P.H.

Jeanne V. Zborowski, M.S., Ph.D.

Judy Rager, M.P.H.

Department of Epidemiology
University of Pittsburgh Graduate School of Public Health

Manuscript in preparation

4.1 ABSTRACT

Smoking is an unconfirmed risk factor for the development of leukemia. The potential link was examined using data from the TMI cohort for the period of 1979 to 1995. A total of 24,539 subjects followed up over 16 years from the TMI cohort who were 14 years or older, were eligible for this analysis. All incident leukemia cases were identified through the Pennsylvania Department of Health Cancer Registry. The Cox proportional hazards model was employed to evaluate the relationships. A total of 42 incident leukemia cases, including 15 AML cases, were observed in the cohort. After controlling for other confounding factors, current smoking was associated with an increased risk of adult AML (RR=3.47; 95% CI: 1.002-11.99). A marginally significant linear trend of risk of AML associated with the number of years smoked was also observed (p=0.06). The results from this study suggested that cigarette smoking was associated with an increased risk of adult AML. Further investigation is required to confirm these findings.

Key words: Leukemia, AML, Smoking, Cohort Study.

4.2 INTRODUCTION

Benzene, a well-established carcinogen and leukemogen, has typically been associated with acute myeloid leukemia (AML) over the past century[1,2] and has been shown to be present in cigarette smoke. Wallace observed that approximately 90% of personal exposure to benzene in the United States is due to smoking. Smokers have an average benzene body burden approximately 6-10 times that of nonsmokers [3]. Other carcinogens including ionizing radiation (polonium and lead), nitrosamines, styrene, naphthalene and urethanes are also found in cigarette smoking[4,5]. Cigarette smoking has long been suspected as an etiologic factor in leukemogenesis [6]; an association between cigarette smoking and leukemia was reported as early as 1978 [7]. Epidemiological studies to date have provided inconsistent results regarding the association between cigarette smoking and leukemia. Several case-control studies demonstrated an increased risk of leukemia among cigarette smokers[8-13]. However, other studies have observed no significant association [14,15].

Only a few cohort studies have investigated the smoking-leukemia link because of the latency period associated with the development of hematological malignancies and the large sample size required. The conclusions from available prospective studies are inconsistent and some large cohort studies were unable to detect any excess risk of leukemia related to cigarette smoking. Adami et al reported that there was no significant association between smoking status, number of cigarettes smoked per day or duration of smoking and the risk of developing leukemias in 334,957 Swedish construction workers after following up 10 years [16]. Although the study is large, all participants are male construction workers. The healthy worker effect cannot be negligible in this study. Engeland et al also found no association between smoking and leukemia in 28 year follow-up of 26,000 Norwegian men and women [17]. However, this study

failed to elucidate subtype association and the dose-response relationship of cigarette smoking. Moreover, this study was unable to control for some confounding factors such occupational radiation exposures. In summary, few cohort studies have been carried out to assess the association between cigarette smoking and subtypes of leukemia such as AML, which is more related to the exposure of benzene.

While published evidence for leukemia and cigarette smoking is inconclusive, several case-control studies suggest a weak association between AML and tobacco use [9,18,19]. The subtypes of leukemia vary in histological, molecular and clinical characteristics as well as in prognosis. The emphasis of etiologic studies on histological subtypes must be taken into consideration.

To further explore the role of cigarette smoking in the development of adult leukemia, we analyzed the risk of total leukemia and specifically acute myeloid leukemia (AML) as well as the dose-response relationship between cigarette smoking and adult leukemia in the large Three Mile Island (TMI) (Pennsylvania, U.S.A) cohort, which provided detailed information on tobacco use at baseline and the incidence of cancer with long-term follow-up.

4.3 METHODS

4.3.1 Study Population

The TMI cohort was assembled by the Pennsylvania Department of Health (PADoH) to evaluate the adverse health effects of exposure of low-level radiation emitted from the TMI nuclear power plant accident on 28 March 1979. The cohort consisted of 32,135 individuals in the 1979 TMI census [18] who were followed up from 1979 to 1995. The estimated average likely

and maximum gamma doses from the accident were 0.09 mSv (9 mrem) and 0.25 mSv (25 mrem) respectively. These exposures were therefore considered overall minimal (less than the dose of 2-3 chest X-rays). Previous mortality studies in these subjects also found no significant evidence of the association between the level of accident radiation exposure and leukemia mortality risk [18,19]. In this study, all analyses presented are based on cohort members aged 14 years or older (n= 24,539). Data collected included individual information at baseline on smoking status, demographic characteristics (age, gender and race etc), residential history, background radiation exposure, previous occupational or treatment radiation exposure, and estimated radiation exposure from the TMI nuclear power plant accident.

4.3.2 Smoking Information

Data on personal smoking history was collected in 1979 at baseline. Cigarette smoking in individuals was assessed as never smoked, former smoker and current smoker. Former smoker was defined as ever smoked at least 100 cigarettes. For those who ever or currently smoked, The number of cigarettes smoked per day as well as total number of years smoked was also obtained. Based on this information, a new variable of "pack-year" was created by multiplying total number of years smoked with number of cigarettes smoked per day then divided by 20.

4.3.3 Total Leukemia and AML Subtype Identification

The TMI cohort was followed up from March 1979 through December 1995 to determine vital status and cancer incidence. All cases of adult-onset leukemia (International Classification of Diseases for Oncology, Second Edition, and Code 980-994) and AML (ICD-O-2, code 9861,

9864, 9866, 9867 and 9891) diagnosed between March 1979 through December 1995 were identified through the Pennsylvania Cancer Registry (PCR)., which is complete for those individuals who remain within Pennsylvania. Not Otherwise Specified (NOS) leukemia cases (ICD-O-2: 9800 and 9801) are further clarified as AML when subject died from AML (International Classification of Diseases, version 9: 205.0) in the National Death Index. The PADoH, along with the U.S. Postal Service, annually obtained the current addresses of persons to maintain follow-up of the cohort. The address confirmation was updated through December 1995. We verified that 92.1% of subjects remained in Pennsylvania during the 1979-1995 follow-up period.

4.3.4 Statistical analysis

Comparison of the distribution of demographic and other characteristics among each smoking status category was made using ANOVA for continuous variables and the Chi square test for categorical variables respectively. Total leukemia and AML were analyzed separately. The Cox proportional hazards model was employed to estimate Relative Risk (RR) with 95% Confidence Intervals (CI) for the association of adult leukemia and its subtype AML with cigarette smoking after controlling for potential confounding factors. Smoking status was assessed as a dummy variable in the model. The number of cigarettes smoked per day, number of years smoked and number of pack-years were also fit as ordinal categorical variables to evaluate the dose-response relationship between cigarette smoking and total leukemia as well as AML. All final models were adjusted for age, gender, race, education, background radiation exposure (<8 μR/hr vs. ≥ 8 μR/hr), occupational exposure, and estimated maxima gamma radiation and likely gamma radiation.

Subjects with missing values were excluded from relevant analyses. The statistical tests were two-sided with a 0.05 significant level. The SAS 8.02 software package (SAS Institute Inc., 100 SAS Campus Drive Cary, NC 27513) was used to analyze the collected data.

4.4 RESULTS

Within the study population, 33% (n=8,083) of the individuals were current smokers, 18% (n=4,330) were ever smokers and 49% (11,913) were non-smokers at baseline. More than 95 percent of subjects in the cohort are white. Table 4-1 shows the distribution of baseline characteristics among each group by smoking status. The results of the ANOVA and χ^2 tests indicated that age, education level, race, occupational radiation exposure were significantly different among smoking groups. The percentages of female are 60% among never smokers, 36% among former smoker and 46% among current smokers respectively. There are 5.4% participants among never smokers, 7.4% among former smokers and 6.8% among current smokers who had experience of occupational radiation. The estimated Maximum and likely gamma exposure emitted from the TMI nuclear power plant accident was slightly higher among nonsmokers than smokers. However, the distributions of background radiation exposure were similar among each smoking group.

Table 4-2 describes the distributions of lymphatic and hematopoietic neoplasm incident cases occurred during study period. A total of 42 leukemia cases including 15 AML cases were observed within follow-up time period in the cohort.

The distributions of total leukemia among each status of cigarette smoking and risks of total leukemia associated with cigarette smoking are presented in table 4-3. We found higher proportion of leukemia cases among the current smoker group as compared with those who had never smoked (table 4-3). Of these, the cumulative incidences of total leukemia are 0.21% in current smokers, 0.14% in former smokers and 0.16% in non-smokers respectively.

To examine the association between dose of cigarette smoking and total leukemia, the age and sex adjusted model showed that a positive association between current cigarette smoking and total leukemia was suggestive but not statistically significant by using a dummy variable of smoking status (RR=1.49, 95% CI: 0.76-2.96 in current smoker). After controlling for other risk factors in the fully adjusted model, current cigarette smoking is still positively but not statistically significantly associated with total leukemia (RR=1.39, 95%CI: 0.69-2.82). Furthermore, a more powerful analysis using the number of cigarettes smoked per day, the number of years smoked and pack years of smoking was performed to provide evidence of an association between cigarette smoking and total leukemia. The results showed that there is no evidence of significant positive associations between cigarette smoking and total leukemia either in the age-sex adjusted model or in the fully adjusted model.

Table 4-4 reported the results of the distribution of the subtype of leukemia, i.e. AML among each cigarette smoking group and risk of AML associated with cigarette smoking. Only 15 AML cases were observed within follow-up time period in the cohort. The age-sex adjusted model indicated a significantly positive association between current cigarette smoking and AML using a dummy variable of smoke status (AML: RR=3.26, 95% CI: 1.05-10.17 in current smoker). After controlling for other risk factors in the fully adjusted model, the association between current cigarette smoking and AML is still significant (RR=3.47, 95% CI: 1.002-11.99).

An association between cigarette smoking and AML was further explored with a more powerful analysis using the number of cigarettes smoked per day, the number of years smoked and pack years of smoking. The age-sex adjusted models showed that those who smoked 11-20 pack years have a higher risk of AML as comparing with non-smokers (RR=4.25, 95%CI: 1.11-16.35) after controlling for other risk factors. In addition, there is a significant dose-response relationship between the number years of cigarette smoking and risk of AML (p=0.04) (see Fig 1). However, there is no evidence for a linear trend of risk of AML associated with the number of cigarettes per day as well as the pack years of smoking. We further analyzed the risk of AML associated with cigarette smoking after controlling for some other potential confounders, including age, gender, education level, race, occupational radiation, background radiation, estimated maximum and likely gamma exposures. In these analyses, we found a statistically increased risk of AML among those who smoked 1-10 cigarettes per day or 11-20 pack years (RR=5.02, 95% CI: 1.11-22.64; RR=5.07, 95% CI: 1.22-21.01). More interestingly, a dose-response relationship between the number year of smoking and risk of AML was marginally statistically significant (p=0.06). However, we found no evidence of any dose-response relationship between the number cigarettes per day or pack years of smoking and risk of AML.

4.5 DISCUSSION

In this large cohort study, 42 incident leukemia cases occurred during the study period. The Not Otherwise Specified (NOS) leukemia was further determined as its subtypes by scrutinizing PA Cancer Registry for cell type and death certificates for underlying cause of death (UCOD). Five NOS leukemia cases were determined as AML (UCOD: 205.0). A total of 15 AML cases

out of 42 leukemia cases were found in this study. The percentage of AML in leukemia is 35.7%, which is close to general population. The analyses of this study emphasized on AML because it had the largest number of cases in leukemia subtypes and epidemiological evidence suggested that AML is more likely linked to cigarette smoking.

In this study, the age-sex adjusted model and the fully adjusted model were applied to assess the associations between leukemia as well as AML and cigarette smoking. The estimations from these two models are very similar. It suggested that age and sex are the factors which confound the associations between smoking and leukemia as well as AML. In this study, neither the age-sex adjusted models nor the fully adjusted models could provide any evidence of a significantly positive association between cigarette smoking and total leukemia after adjusting for other confounders. Indeed, significant association between current cigarette smoking and AML is demonstrated after controlling for other risk factors. It also suggested that there is a significant dose-response relationship between the number year of cigarette smoking and risk of AML (trend p=0.04) after adjusted for age and sex. This linear relationship between the number years of cigarette smoking and risk of AML are still marginally significant (p=0.06) after controlling for other risk factors. However, there are no statistically significant linear relationships between AML and cigarettes smoked per day as well as pack years. Cigarettes smoked per day, number years of smoked, and pack years have their own limitations and strengths when they are used to estimate the dose of cigarette smoking. Cigarettes smoked per day have information on daily consumption but does not include information on duration of smoking. Number years of smoked emphasizes information on duration of smoking but neglects daily consumption. Pack years is a comprehensive indicator that combines information on daily consumption with duration of smoking. But inaccurate recalls in either cigarettes smoked per day or number years of smoked

could result into a misclassification of pack years. In this study, it could be possible that the recall of years smoked was more accurate than number of cigarettes smoked per day.

The findings of the present study are in agreement with the results from some other studies. The cohort study of 34,000 Seventh-Day Adventists demonstrated that a higher risk of myeloid leukemia was associated with cigarette smoking (RR=2.24, 95% CI 0.91-5.53)[22]. Several case-control studies reported an increased risk of AML among cigarette smokers [6,8,9,13,15,23]. Moreover, the childhood leukemia studies also provided significant evidence of an association between parental smoking and childhood leukemia. Chang et al found that parental preconception smoking was significantly associated with an increased risk of AML (OR=3.84, 95%:1.04-14.17) [10]. Ji et al reported that paternal preconception smoking was related to a significantly elevated risk of childhood cancers, particularly acute leukemia and lymphoma [24]. These data are consistent with a possible mechanism linking cigarette smoking to an increased risk of leukemia in human subject.

On the other hand, a few studies reported that the risk of leukemia induced by cigarette smoking decreases or ceases after smoking cessation. Kane et al showed that the odds ratio was decreased as the number of years 'stopped smoking' increased, falling to 1.0 amongst those who had given up smoking for more than 10 years [25]. Bjork et al found that the risk of AML declined in 5-10 years after smoking cessation among subjects with smoking history long enough to give a substantially elevated AML risk [1]. These studies provided supporting evidence of an association between AML and cigarette smoking.

The number of cigarettes per day, the number of years smoked and pack years of cigarette smoking have been previously used to evaluate the dose-response relationship for leukemia and AML. Our study found no evidence of a trend in risk with number of cigarettes smoked per day

and pack years, which was similar to the majority of studies[9,14,26] . A number of studies reported that there were significant increasing trends in risk with increasing number of years smoked [13,22]. These findings were consistent with the results from our study, which provided additional support for an association between cigarette smoking and leukemia.

The mechanism by which cigarette smoking increases risk of leukemia or AML are unknown. Cigarette smoke contained some known or suspected leukemogens, including benzene[3], ionizing radiation[5] and other carcinogens (nitrosamines, styrene, naphthalene and urethanes) [4,27]. It was reported that the level of trans, trans-muconic acid (t,t-MA), a urinary benzene metabolite, were about 3 times higher than those in nonsmokers[28]. Other studies found higher level of polonium and lead in tissues from smokers[29]. In addition, chromosomal defects in the peripheral blood were also observed to be increased in smokers [30,31]. All these findings suggested a possible leukemogenic effect of cigarette smoking.

There are several strengths to the study. First, the study was considered noteworthy, as it included a large sample size of cohort and a relatively long period of follow-up, i.e. over 16 years complete follow-up. Second, the rate of loss of follow-up is low in this study. Ninety three percent of participants in the cohort were verified for leukemia outcome using the population-based Pennsylvania Cancer Registry system. Third, we assessed the risk of AML among cigarette smokers and further evaluated the dose-response relationship between cigarette smoking and outcomes, as this form of leukemia has more specifically been linked to benzene exposure in occupational and community setting. In addition, personal information about natural background radiation, TMI accidental exposure and previous occupational radiation was collected in the study and was able to be included in the final statistical models.

One of the limitations of our study lies in the fact that the baseline cigarette smoking information was only able to obtain in 1979. Any changes in smoking status during the follow-up (1979-1995) were not available. This could result into some misclassification bias in the analyses based on duration of smoking and pack-years of smoking. Second, an additional 12 years of follow up would be very beneficial and improve the power of the study if the cohort could be followed up until now. However, formal follow up of the cohort ceased in l995 when the PA Department of Health ceased funding formal follow up through post offices of the cohort. Thus, there would no longer be complete ascertainment of the denominator of the population. Third, the analysis was based on leukemia cases identified through the Pennsylvania Cancer Registry (PCR), 1979-1995. Only individuals who remained in Pennsylvania were included in the case ascertainment. In this study, 1,960 cases (7.9%) left the state and lost to follow-up during the study period. The cigarette smoking status and mortality experience were assessed among these individuals of loss follow-up. The distributions of smoking status among these cases are 34% current smokers, 17% former smokers and 49% non-smokers, which is similar to the distributions of the cohort. Moreover, 179 deaths among 7.9% loss follow-up were identified and only one case that died from myeloid leukemia in current smoking group by scrutinizing death certificate for diagnostic code. This result suggested that the study could potentially underestimate the association between cigarette smoking and leukemia. Fourth, although there was a large cohort in this study, only a few new AML cases (n=15) were identified during the follow-up time period because of the low incidence of AML, i.e. 1 to 15 cases per 100,000 persons in the general population[32]. It resulted into a wide range of 95% Confidence Interval of hazard ratios. However, we had statistical power to detect the risk difference among cigarette smoking groups. Finally, information regarding other potential risk factors of leukemia, such as

diet and medicine, was not obtained in the study. Thus, their potential confounding effects could not be ruled out.

In conclusion, the present study suggests that cigarette smoking is associated with AML. Moreover, the risk of AML was observed to be increased with the increasing number of years smoked. Further well-designed studies are needed to support the establishment of causal association between cigarette smoking and AML.

Table 4-1 Distribution of baseline characteristics among smoking groups

	Never smoked (n=11,913)	Former smoker (n=4,330)	Current smokier (n=8,083)	P-value
Age ($\overline{X}$ ±SD)	40.60 ± 20.73	46.55 ± 17.33	38.43 ± 15.52	<0.001
Gender				
Male (%)	4,746 (39.84)	2,770 (63.97)	4,382 (54.21)	<0.001
Female (%)	7,167 (60.16)	1,560 (36.03)	3,701 (45.79)	
Education level				
≤9 yr (%)	2,019 (17.39)	795 (18.51)	1,233 (15.42)	
10-12 yr (%)	7,037 (60.62)	2,587 (60.25)	5,615 (70.24)	<0.001
>12 yr (%)	2,553 (21.99)	912 (21.24)	1,146 (14.34)	
Race				
White	11,621 (97.55)	4,227 (97.62)	7,836 (96.94)	0.016
Non-white	292 (2.45)	103 (2.38)	247 (3.06)	
Occupational radiation				
Yes	642 (5.39)	321 (7.41)	555 (6.87)	<0.001
No	11,271 (94.61)	4,009(92.59)	7,528 (93.13)	
Background radiation				
<8 mrem	9,039 (76.12)	3,331 (77.11)	6,191 (76.85)	0.30
≥8 mrem	2,836 (23.88)	989 (22.89)	1,865 (23.15)	
Maximum gamma exposure ($\overline{X}$ ±SD)	25.59±22.08	24.70±21.85	24.67±21.75	0.005
Likely gamma exposure ($\overline{X}$ ±SD)	10.93±10.40	10.61±10.14	10.58±10.25	0.04

Note: χ^2 test for the categorical variables and ANOVA test for the continuous variables

Table 4-2 Distribution of lymphatic and hematopoietic neoplasm incident cases occur during study period (1979-1995)

Types of Cancer	Number	ICD-O-2
Leukemia	42	980-994
Acute myeloid leukemia(AML)*	15	9861, 9864, 9866, 9867 and 9891
Chronic lymphocytic leukemia(CLL)	11	9823
Chronic myeloid leukemia (CML)	7	9863
Other leukemia	9	-
Mutiple Myeloma	12	9732
Other Lymphatic Neoplasm	3	-
Total	57	C42.1

* Leukemia NOS (ICD-O-2: 9800, 9801) cases are clarified with death index (ICD-9:205.0)

Table 4-3 Distribution and risk of total leukemia among each status of cigarette smoking

	Total No.	Leukemia		Adjusted RR[1] (95% CI)	Adjusted RR[2] (95% CI)
		No.	%		
Smoking status					
Never smoked (%)	11,913	19	0.16	1.0	1.0
Former smoker (%)	4,330	6	0.14	0.60 (0.23-1.54)	0.58 (0.22-1.50)
Current smoker (%)	8,083	17	0.21	1.49 (0.76-2.96)	1.39 (0.69-2.82)
Number cigarettes per day					
0	11,913	19	0.16	1.0	1.0
<10	1,749	4	0.23	1.37 (0.46-4.05)	1.42 (0.48-4.20)
10-19	2,843	7	0.25	1.61 (0.67-3.86)	1.62 (0.67-3.93)
>=20	7,821	12	0.15	0.84 (0.39-1.78)	0.73 (0.34-1.60)
P value for trend test				0.79	0.57
Number of years smoked					
0	11,913	19	0.16	1.0	1.0
1-19 yrs	7,608	5	0.07	0.55 (0.20-1.52)	0.56 (0.20-1.55)
20-29 yrs	2,015	8	0.40	1.76 (0.76-4.10)	1.73 (0.74-4.07)
>=30 yrs	2,790	10	0.36	1.29 (0.58-2.88)	1.11 (0.48-2.57)
P value for trend test				0.33	0.53
Pack-Year *					
0	11,913	19	0.16	1.0	1.0
≤10	5,897	7	0.12	0.998 (0.41-2.43)	1.02 (0.42-2.50)
11-20	2,358	7	0.30	1.74 (0.72-4.22)	1.74 (0.71-4.27)
>20	4,158	9	0.22	0.88(0.39-2.0)	0.73 (0.31-1.74)
P value for trend test				0.98	0.73

Note: * *"Pack-year" is 20 cigarettes per day for one year.*

1. "Adjusted RRs" were derived from Cox proportional hazards model after controlling for age and gender.

2. "Adjusted RRs" were derived from Cox proportional hazards model, adjusting for age, gender, education level, race, occupational radiation, background radiation, estimated maximum and likely gamma exposures.

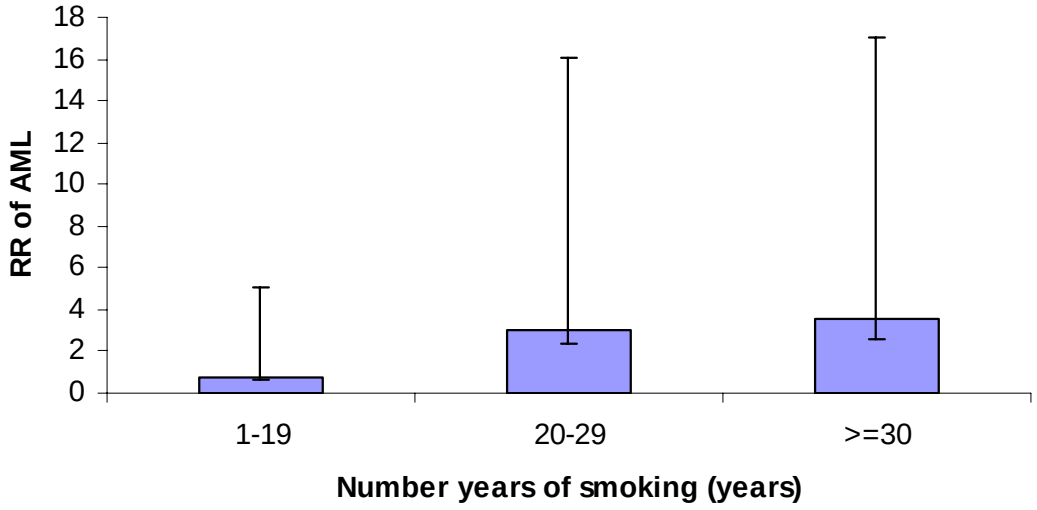
Table 4-4 Distribution and risk of AML among each status of cigarette smoking

	Total No.	AML		Adjusted RR[1] (95% CI)	Adjusted RR[2] (95% CI)
		No	%		
Smoking status					
Never smoked (%)	11,913	5	0.04	1.0	1.0
Former smoker (%)	4,330	1	0.02	0.48 (0.05-4.20)	0.54 (0.06-4.98)
Current smoker (%)	8,083	9	0.11	3.26 (1.05-10.17)	3.47 (1.002-11.99)
Number cigarettes per day					
0	11,913	5	0.04	1.0	1.0
<10	1,749	3	0.17	4.13 (0.98-17.42)	5.02 (1.11-22.64)
10-19	2,843	3	0.11	2.77 (0.65-11.75)	3.31 (0.73-14.99)
>=20	7,821	4	0.05	1.26 (0.32-4.90)	1.07 (0.23-5.01)
P value for trend test				0.67	0.82
Number years of smoking					
0	11,913	5	0.04	1.0	1.0
1-19 yrs	7,608	2	0.03	0.79 (0.15-4.27)	0.91 (0.16-5.19)
20-29 yrs	2,015	3	0.15	3.03 (0.71-12.98)	3.79 (0.82-17.61)
>=30 yrs	2,790	5	0.18	3.58 (0.95-13.50)	3.64 (0.80-16.49)
P value for trend test				0.04	0.06
Pack-Year*					
0	11,913	5	0.04	1.0	1.0
≤10	5,897	3	0.05	1.67 (0.38-7.27)	1.95 (0.42-9.03)
11-20	2,358	4	0.17	4.25 (1.11-16.35)	5.07 (1.22-21.01)
>20	4,158	3	0.07	1.44 (0.33-6.30)	1.11 (0.19-6.36)
P value for trend test				0.32	0.45

Note: * *"Pack-year" is 20 cigarettes per day for one year.*

1. *"Adjusted RRs" were derived from Cox proportional hazards model after controlling for age and gender.*
2. *"Adjusted RRs" were derived from Cox proportional hazards model, adjusting for age, gender, education level, race, occupational radiation, background radiation, estimated maximum and likely gamma exposures.*

Fig 1. the association of risk of AML and the number years of smoking



4.6 REFERENCES

1. Albin M, Bjork J, Welinder H, Tinnerberg H, Mauritzson N, Johansson B, Billstrom R, Stromberg U, Mikoczy Z, Ahlgren T, Nilsson PG, Mitelman F, Hagmar L. Acute myeloid leukemia and clonal chromosome aberrations in relation to past exposure to organic solvents. Scand J Work Environ Health 2000;26(6):482-91.

2. Rangan U, Snyder R. Scientific update on benzene. Ann N Y Acad Sci 1997;837:105-13.

3. Wallace L. Environmental exposure to benzene: an update. Environ Health Perspect 1996;104 Suppl 6:1129-36.

4. Austin H, Cole P. Cigarette smoking and leukemia. J Chronic Dis 1986;39(6):417-21.

5. Paffenbarger RS, Jr., Brand RJ, Sholtz RI, Jung DL. Energy expenditure, cigarette smoking, and blood pressure level as related to death from specific diseases. Am J Epidemiol 1978;108(1):12-8.

6. Brown LM, Gibson R, Blair A, Burmeister LF, Schuman LM, Cantor KP, Fraumeni JF, Jr. Smoking and risk of leukemia. Am J Epidemiol 1992;135(7):763-8.

7. Brownson RC, Chang JC, Davis JR. Cigarette smoking and risk of adult leukemia. Am J Epidemiol 1991;134(9):938-41.

8. Chang JS, Selvin S, Metayer C, Crouse V, Golembesky A, Buffler PA. Parental smoking and the risk of childhood leukemia. Am J Epidemiol 2006;163(12):1091-100.

9. Pogoda JM, Preston-Martin S, Nichols PW, Ross RK. Smoking and risk of acute myeloid leukemia: results from a Los Angeles County case-control study. Am J Epidemiol 2002;155(6):546-53.

10. Severson RK, Buckley JD, Woods WG, Benjamin D, Robison LL. Cigarette smoking and alcohol consumption by parents of children with acute myeloid leukemia: an analysis within morphological subgroups--a report from the Childrens Cancer Group. Cancer Epidemiol Biomarkers Prev 1993;2(5):433-9.

11. Severson RK, Davis S, Heuser L, Daling JR, Thomas DB. Cigarette smoking and acute nonlymphocytic leukemia. Am J Epidemiol 1990;132(3):418-22.

12. Kabat GC, Augustine A, Hebert JR. Smoking and adult leukemia: a case-control study. J Clin Epidemiol 1988;41(9):907-14.