Environmental Risk Factors for Lung Cancer Mortality in the Cancer Prevention Study-II

Michelle Catherine Turner

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ABSTRACT

This thesis examined associations between ecological indicators of residential radon and fine particulate matter air pollution ($PM_{2.5}$) and lung cancer mortality using data from the American Cancer Society Cancer Prevention Study-II (CPS-II) prospective cohort. Nearly 1.2 million CPS-II participants were recruited in 1982. Mean county-level residential radon concentrations were linked to study participants according to ZIP code information at enrollment (mean (SD) = 53.5 (38.0) Bq/m^3). Cox proportional hazards regression models were used to obtain adjusted hazard ratios (HRs) and 95% confidence intervals (CI) for lung cancer mortality associated with radon. After necessary exclusions, a total of 811,961 participants in 2,754 counties were retained for analysis. A significant positive linear trend was observed between categories of radon concentrations and lung cancer mortality (p = 0.02). A 15% (95% CI 1 - 31%) increase in the risk of lung cancer mortality was observed per each 100 Bq/m^3 radon. Radon was also positively associated with chronic obstructive pulmonary disease mortality (HR per each 100 Bq/m^3 = 1.13, 95% CI 1.05 - 1.21). No clear associations were observed between radon and non-respiratory mortality. In lifelong never smokers (n = 188,699), each 10 $\mu g/m^3$ increase in mean metropolitan statistical area $PM_{2.5}$ concentrations was associated with a 15-27% increase in the risk of lung cancer death which strengthened among individuals with a history of asthma or any prevalent chronic lung disease at enrollment (p for interaction < 0.05). There was no association between $PM_{2.5}$ and mortality from non-malignant respiratory disease. In conclusion, this thesis observed significant positive associations between ecological indicators of residential radon and $PM_{2.5}$ concentrations and lung cancer mortality. These findings further support efforts to reduce radon concentrations in homes to the lowest possible level and strengthens the evidence that ambient concentrations of $PM_{2.5}$ measured in recent decades are associated with small but measurable increases in lung cancer mortality.

Further research is needed to better understand possible complex inter-relationships between environmental risk factors, chronic lung disease, and lung cancer.

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ABBREVIATIONS

Adventist Health Study on Smog (AHSMOG)

air quality health index (AQHI)

attributable proportion (AP)

benzo(a)pyrene (BaP)

black smoke (BS)

benzo[a]pyrene diol epoxide (BPDE)

body mass index (BMI)

Canada-Wide Standard (CWS)

Cancer Prevention Study-II (CPS-II)

carbon monoxide (CO)

chronic obstructive pulmonary disease (COPD)

Committee on Health Risks of Exposure to Radon (BIER VI)

Committee to Assess Health Risks from Exposure to Low Levels of Ionizing Radiation (BIER VII)

confidence interval (CI)

cytochrome p450 (CYP1A1)

Environmental Protection Agency (EPA)

epidermal growth factor receptor (EGFR)

European Prospective Investigation on Cancer and Nutrition (EPIC)

excess absolute risk (EAR)

excess relative risk (ERR)

excision repair cross-complementing rodent repair deficiency (ERCC2) genes

forced expiratory volume in 1 second (FEV1)

glutathione S-transferase (GST)

hazard ratio (HR)

human papillomavirus (HPV)

incidence rate ratio (IRR)

insulin-like growth factor (IGF)

International Agency for Research on Cancer (IARC)

interquartile range (IQR)

land-use regression (LUR)

linear energy transfer (LET)

metropolitan statistical area (MSA)

microsomal epoxide hydrolase 1 (EPHX1)

myeloperoxidase (MPO)

NAD(P)H quinone reductase 1 (NQO1)

National Research Council (NRC)

Netherlands Cohort Study on Diet and Cancer (NLCS)

nitrogen dioxide (NO_2)

nitrogen oxide (NO_x)

odds ratio (OR)

ozone (O_3)

PAARC (Pollution Atmosphérique et Affections Respiratoires Chroniques)

particulate matter of ≤ 2.5 microns in diameter ($PM_{2.5}$)

particulate matter of ≤ 10 microns in diameter (PM_{10})

particulate matter of ≤ 15 microns in diameter (PM_{15})

relative excess risk due to interaction (RERI)

relative risk (RR)

sulfate (SO_4)

sulfur dioxide (SO_2)

synergy index (S)

total suspended particulate (TSP)

tumour suppressor p53 (TP53)

tyrosine kinase inhibitor (TKI)

VITamins And Lifestyle (VITAL) study

working level months (WLM)

World Health Organization (WHO)

x-ray repair cross-complementing protein group 3 (XRCC3)

xeroderma pigmentosum group D (XPD)

1. INTRODUCTION

Lung cancer is currently the leading cause of cancer death in Canada. In 2010, it was estimated that a total of 24,200 new cases and 20,600 deaths occurred[1]. Lung cancer is a highly fatal disease, with a five year survival rate (2002-2004) of just 15%[2]. Recently, the incidence rate of lung cancer for males has declined by approximately 2.1% per annum. However, the incidence rate for females has only recently begun to level off; likely reflecting differential changes in tobacco consumption by gender over the second half of the twentieth century[1]. Males continue to experience a greater lung cancer burden with an age-standardized incidence rate (mortality rate) of 66 cases (57 deaths) per 100,000 population compared to 48 cases (39 deaths) per 100,000 in females[1]. Although the majority of lung cancer cases can be attributed to active cigarette smoking, a variety of genetic and biological, social and behavioral, and environmental factors may also play a role including residential radon and fine particulate matter air pollution ($PM_{2.5}$)[3-5]. There are also lung cancer cases in never smokers[6;7]. The purpose of this thesis is to examine the association between ecological indicators of residential radon and fine particulate matter air pollution and lung cancer mortality in the American Cancer Society (ACS) Cancer Prevention Study-II (CPS-II).

Radon gas is formed during the radioactive decay of uranium-238, which is naturally present in rocks and soils in the environment. In 1988, the International Agency for Research on Cancer (IARC) determined that radon was a cause of human lung cancer, based on studies of underground miners historically exposed to high levels of the gas[8]. It was also observed that α-particles emitted from radon decay products can damage DNA in human lung tissue[8]. Radon gas enters homes through cracks and other openings in the foundation and accumulates largely in the basement and lower living areas[9]. Although there have been over 20 individual case-control studies examining the association between residential radon and lung cancer, results were limited by small sample sizes and disparate findings. Recent efforts to combine data from case-control studies have provided for the first time

strong evidence for a link[10-13]. In North America, each 100 Bq/m^3 increase in radon was associated with an 11% (95% confidence interval (CI) 0 - 28%) increase in lung cancer risk[12;13]. Results strengthened in a subset of the data with limited residential mobility and complete radon exposure histories (excess relative risk (ERR) = 21%, 95% CI 3 - 52%). Similar results were observed in Europe[10;11]. The evidence available to date suggests that radon may be responsible for 10 - 15% of the lung cancer burden, making radon the second leading cause of lung cancer after cigarette smoking[4].

Although there have been a number of residential radon case-control studies, capturing retrospective data on individual smoking habits and other lung cancer risk factors, there has been only one prospective study. Ruano-Ravina et al.[14] recently followed-up 241 control subjects from a previous case-control study of residential radon and lung cancer in Spain. An elevated, although imprecise, lung cancer risk was observed in subjects with radon concentrations above the guideline value of the US Environmental Protection Agency (EPA) (4 pCi/L = 148 Bq/m^3) (relative risk (RR) = 6.6, 95% CI 1.2 - 38) relative to those below the guideline value.

Radon may affect other malignant or non-malignant diseases besides lung cancer, however the epidemiological evidence is sparse[4;15]. Although the lung and respiratory tract experience the highest doses of ionizing radiation from the inhalation of radon and its decay products, the kidney, bone, bone marrow, and breast are also exposed, however to a substantially lesser degree, through the entrance of radon decay products into the blood stream[4;16]. There are also exposures to the stomach (ingestion) and skin (external radiation).

There is also compelling evidence from time-series and prospective studies that acute and chronic exposure to PM2.5 is associated with increased cardiopulmonary mortality[17]. However, the role of $PM_{2.5}$ in the etiology of lung cancer is less clear, particularly at concentrations that prevail in developed countries (~ 5 to 35 μg/m^3) and in never smokers[18]. In China, high levels of indoor air

pollution due to coal and biomass burning contribute to the high lung cancer rates observed even among non-smoking women[19]. There are also high background concentrations (> 100 μg/m^3) of outdoor air pollution in some industrial regions of the country[18].

Given the strong relationship between cigarette smoking and lung cancer risk, evidence of an association between $PM_{2.5}$ and lung cancer is more convincing when observed among never smokers, as compared to current or former smokers, due to possible residual confounding by cigarette smoking. A previous analysis of the CPS-II, based on 16-years of follow-up data of approximately 500,000 included participants controlling for measured parameters of active smoking, found an 8% (95% CI 1-16) increase in lung cancer mortality for each 10 μg/m^3 increase in $PM_{2.5}$ concentrations[5]. The risk was somewhat higher, although statistically insignificant when restricted to the subgroup of never smokers. An extended analysis of the Harvard Six Cities Study (n=8,096) found a positive association between $PM_{2.5}$ and lung cancer mortality (hazard ratio (HR) = 1.27, 95% CI 0.96-1.69 per each 10 μg/m^3) controlling for active smoking[20]. Naess et al.[21] observed significant positive associations between $PM_{2.5}$ and lung cancer mortality among Oslo women in a recent register-based study; however, no data on smoking history was available in this study.

Despite the possibility for residual confounding by cigarette smoking, the World Health Organization (WHO) has estimated that long-term $PM_{2.5}$ exposure is responsible for approximately 5% of all cancers of the trachea, bronchus, and lung[22]. To address the potential for residual confounding by cigarette smoking, further research examining associations between $PM_{2.5}$ and lung cancer in never smokers is needed[23;24].

Objectives

The overall objective of this thesis is to use the CPS-II cohort to examine the association between ecological indicators of residential radon and $PM_{2.5}$ and lung cancer mortality in a large-scale prospective study. Specific objectives include:

1. to examine the association between ecological indicators of residential radon and lung cancer mortality;
2. to examine the association between ecological indicators of residential radon and non-lung cancer mortality; and
3. to examine the association between ecological indicators of $PM_{2.5}$ and lung cancer mortality in never smokers.

Significance

The CPS-II is a large-scale prospective study with detailed individual-level risk factor data collected at enrollment, including cigarette smoking, passive smoking, and occupational risk factors for lung cancer. It provides a unique opportunity to further strengthen the body of evidence for an association between residential radon and lung cancer in a major cohort study and provides an excellent resource to evaluate whether residential exposure to radon is associated with fatal endpoints other than lung cancer in the general population. It also provides the opportunity to further examine the association between $PM_{2.5}$ and lung cancer mortality in lifelong never smokers in an extended 26-year follow-up time period (1982-2008).

Relevance to Population Health

Population health is typically defined as "*a conceptual framework for thinking about why some populations are healthier than others, as well as the policy development, research agenda, and resource allocation that flow from this*" (p. 4)[25]. Population health focuses on the full range of

factors that act to influence health status, as well as their interactions, with a particular emphasis on inequities in health status, cross-sectoral and multiple disciplinary approaches, and evidence-based decision-making[25-38]. Other authors have also emphasized notions of time (such as historical time, the lifecourse, inertia in health outcomes, and intergenerational effects)[39-43], multi-level influences on health status[40;42;44], embodiment[28;40;42;45], ecological[42;46;47], and non-linear thinking[37;48]. More recent conceptualizations of health have also referred to dynamic, positive concepts, viewing health as a "resource" or "force"[28;34;37;49].

Evans and Stoddart[50] noted the broad array of factors that influence population health status including the social environment, the physical environment, genetic endowment, and individual behavior and biology. They also highlighted the key distinction between health, disease, and well-being, with the later, the "*ultimate objective*" of health policy. The recent WHO Commission on the Social Determinants of Health[27;51] highlighted how the socioeconomic political context, social structural and intermediary factors act to generate inequities in health. Starfield[32] discusses how policies aimed at improving physical and social environments would result in greater health equity, since they do not rely on individual-level behavior change which may be influenced by level of personal resources including material wealth, education, and social connectedness. Rose[31] points out that interventions that seek to shift population distributions of adverse exposures would result in significant health gains.

We recently proposed an integrated framework for risk management and population health (Figure 1)[30]. In brief, the integrated framework depicts three broad categories of health determinants (biology and genetics, environmental and occupational, and social and behavioural) and their interactions. Health risk science examines health determinants using the best available qualitative and quantitative techniques. Health risk policy analysis then considers the most appropriate intervention strategies including regulatory, economic, advisory, community-based, and technological approaches. The

overall aim of the framework was to provide a more comprehensive approach to characterizing population health risks and to identify the most relevant opportunities for intervention in order to most effectively enhance population health status.

Outline

This thesis seeks to examine associations between ecological indicators of residential radon and $PM_{2.5}$, two major environmental risk factors, and both lung cancer and non-lung cancer mortality in the CPS-II in order to further understand the adverse health impacts of radon and air pollution and to inform further research and decision-making in Canada and elsewhere. The thesis is comprised of seven chapters. Following the introductory chapter, chapter two provides a brief overview of the epidemiology of lung cancer including genetic and biology, environmental and occupational, and social and behavioural risk factors with a particular focus on previous studies of radon and air pollution. The subsequent four chapters are comprised of the four major manuscripts emanating from this work:

1. Turner MC, Krewski D, Chen Y, Pope CA III, Gapstur S, Thun MJ. Radon and lung cancer in the American Cancer Society cohort. Cancer Epidemiol Biomarkers Prev 2011;20:438-48.
2. Turner MC, Krewski D, Chen Y, Pope CA III, Gapstur SM, Thun MJ. Radon and COPD mortality in the American Cancer Society cohort [published online ahead of print October 17, 2011]. Eur Resp J 2011;erj00582-2011; doi:10.1183/09031936.0005811.
3. Turner MC, Krewski D, Chen Y, Pope CA III, Gapstur SM, Thun MJ. Radon and non-respiratory mortality in the American Cancer Society cohort. Unpublished manuscript, 2011.
4. Turner MC, Krewski D, Pope CA III, Chen Y, Gapstur SM, Thun MJ. Long-term ambient fine particulate matter air pollution and lung cancer in a large cohort of never smokers. Am J Respir Crit Care Med 2011;184:1374-81.

Some of the results examining associations between radon and non-lung cancer mortality were also published in an abstract[52]. The final chapter (chapter seven) summarizes the main findings of the thesis, provides a brief overview of residential radon and air pollution in Canada, and provides suggestions for future work.

2. OVERVIEW

Descriptive Epidemiology

Lung cancer is currently the most common form of cancer worldwide[53]. Globally, it was estimated that there were a total of 1.61 million new lung cancer cases and 1.38 million deaths in 2008, representing some 12.7% of all new cancer cases and 18.2% of all cancer deaths[53;54]. Although incidence rates for lung cancer increase with increasing age, particularly after the age 50 years, there is also early onset lung cancer, with distinct clinical and epidemiological characteristics[55;56]. Due to the poor prognosis of the disease, primary prevention intervention strategies, as opposed to secondary or tertiary strategies, remain the most promising in terms of reducing disease burden and enhancing population health[57].

Lung cancer incidence rates largely parallel trends in tobacco consumption with an approximate 20 year lag[58]. Although, with the exception of certain occupational groups, lung cancer was a rare disease at the beginning of the twentieth century, due to increases in cigarette smoking there has been an epidemic increase in the disease since that time, peaking recently in many developed countries[58]. There is also widespread geographic variation in lung cancer rates with the highest age-standardized incidence rates observed in North America, Eastern Asia, Micronesia, and parts of Eastern and Southern Europe[53;54]. Conversely the lowest rates are observed in Africa, South America, and the Middle East[53;54]. However lung cancer rates in many developing countries are increasing and currently it is estimated that 55% of all lung cancer cases occur in the developing world[53;54].

There have also been differential trends in lung cancer subtypes over time. Although, rates of squamous cell and small cell carcinomas, arising from the central airway compartment, have been declining in males in North America and Europe, rates of adenocarcinoma, arising from the

peripheral airway compartment, have increased likely due to changes in cigarette composition (filtered/low-tar) and inhalation patterns over time[6;59]. Adenocarcinoma is also the most common form of lung cancer in never smokers[6]. Conversely, rates for all three major subtypes of lung cancer have been increasing in females[59].

There are also disparities in lung cancer according to population group and socioeconomic status. Social gradients in health, exposure, and vulnerability are well recognized[27]. There are socioeconomic patterns in cigarette smoking that are dynamic and vary by geographic region[60]. In the US, the highest lung cancer rates are observed in African American men, however rates in both white and African American women are higher compared to rates in women of Asian American and Pacific Islander, American Indian and Alaska Native, and Hispanic/Latino descent[61]. African American men and women also experience poorer lung cancer survival compared to white men and women[61]. In Canada, lung cancer was inversely associated with income adequacy and educational attainment even after adjusting for cigarette smoking and other lung cancer risk factors[62].

Although the majority of lung cancer cases can be attributed to active cigarette smoking, there is also lung cancer in never smokers, representing some 25% of all lung cancer cases[63]. A pooled analysis of data from 13 prospective studies, including over 600,000 never smoking participants, reported higher lung cancer mortality rates in males compared to females as well as in African Americans and Asians who lived in Asia compared to those of European descent[7]. There are also differential mutation patterns and frequencies of the tumour suppressor p53 (TP53), KRAS, and epidermal growth factor receptor (EGFR) genes as well as response to EGFR tyrosine kinase inhibitor (TKI) therapy in never smoking compared to smoking lung cancer cases suggesting that lung cancers in never smokers may represent a distinct disease[6].

Lung cancer patients may also be marginalized. Lung cancer patients, whether smoking or non-smoking, reported experiencing blame and stigma, with negative personal, financial, and treatment

consequences[64;65]. Lung cancers also received the highest degree of blame compared to cancers at four other sites (breast, bowel, cervical, leukemia)[66]. There is also significant morbidity, anxiety, and depression in the disease compared with other cancer groups which may be related in a complex way with both the lung cancer symptom experience, personal social support networks, and other personal and societal factors[67-69]. An overview of genetic and biological, environment and occupational, and social and behavioral risk factors for lung cancer is presented below. A summary of lung cancer risk factors is provided in Table 1.

Genetics and Biology

A variety of genetic and biological factors including specific genetic polymorphisms, chronic lung disease, allergy, mutagen sensitivity, and infections may play a role in lung cancer. Although there is some evidence for the familial aggregation of lung cancer, the influence of other shared behavioral (smoking) and environmental risk factors could not be ruled out[70;71]. A meta-analysis combining data from 41 studies reported positive associations between a family history of lung cancer and lung cancer risk overall (summary odds ratio (OR) = 1.72, 95% CI 1.56-1.88) and among non-smokers (summary OR = 1.40, 95% CI 1.17-1.68)[71]. Specific genetic factors in lung cancer, including polymorphisms of glutathione S-transferase M1 (GSTM1)[72], GST pi 1 (GSTP1)[73], GST theta 1 (GSTT1)[74], cytochrome p450 (CYP1A1)[75], microsomal epoxide hydrolase 1 (EPHX1)[76], NAD(P)H quinone reductase 1 (NQO1), x-ray repair cross-complementing protein group 3 (XRCC3), xeroderma pigmentosum group D (XPD)/excision repair cross-complementing rodent repair deficiency (ERCC2)[77], and myeloperoxidase (MPO)[78] genes and their interactions[79] may also play a role; however results are not entirely clear and further large epidemiological studies are needed. Hung et al.[80] recently suggested a role for nicotinic acetylcholine receptor genes at 15q25 as an independent risk factor for the disease. A pooled analysis of data from 10 studies from the Genetic

Susceptibility to Environmental Carcinogens database reported an inverse association between MPO G-463A and lung cancer[81].

Chronic lung diseases, including asthma, chronic bronchitis, and emphysema, may also be positively related with lung cancer, possibly due to local mechanisms of inflammation and repair; however, potential misclassification, differential recall bias, and residual confounding by smoking status remain of concern[82-84]. A meta-analysis of studies published through the year 2002 reported that never smokers with asthma experienced a significantly elevated risk of lung cancer (combined OR = 1.8, 95% CI 1.3-2.3) in case-control studies[85]. More recently, Brown et al.[86] reported a positive association between asthma and lung cancer (OR = 2.1, 95% CI 0.9 – 5.1) in non-smokers in a case-control study nested in the Adverse Childhood Experiences Study. Gorlova et al.[87] reported a significant positive association between physician-diagnosed asthma and lung cancer (OR = 1.82, 95% CI 1.05-3.15) in a US hospital-based case-control study, however results attenuated upon restriction to participants with a history of asthma (and no hay fever) only (OR = 0.92, 95% CI 0.41-2.06). Seow et al.[88] reported a positive association between a history of asthma/allergic rhinitis/atopic dermatitis and lung cancer (OR = 1.5, 95% CI 0.8-2.6) in a case-control study of never smoking Chinese women which increased to 3.1 (95% CI 1.2-8.3) in those with an interleukin-6 CG/GG genotype. A prospective study of 6,144 non-smokers in the second National Health and Nutrition Examination Survey Mortality Study reported a positive but non-significant association between physician-diagnosed asthma and lung cancer mortality (HR = 1.69, 95% CI 0.94-3.04)[89]. In a previous analysis of the CPS-II, a significant positive association was observed between a history of self-reported physician-diagnosed asthma and lung cancer mortality overall (HR = 1.11, 95% CI 1.02-1.20)[90]. When restricted to never smokers, a HR of 1.11 (95% CI 0.79-1.56) was observed.

Chronic bronchitis and emphysema may also be positively related to lung cancer[91-98], however there are few prospective studies of never smokers. In China, high rates of chronic obstructive pulmonary

disease (COPD) and lung cancer are observed in never smoking women due to high levels of indoor air pollution from coal burning and cooking fumes (below)[19;99-109]. A systematic review recently reported an inverse association between lung function (forced expiratory volume in 1 second (FEV1)) and lung cancer[110]. In a previous analysis of nearly 450,000 never smokers in the CPS-II, a significant positive association between emphysema (HR = 1.66, 95% CI 1.06-2.56) as well as a history of both chronic bronchitis and emphysema (HR = 2.44, 95% CI 1.22-4.90) and lung cancer mortality was observed although it remains unclear whether COPD may be on the lung cancer causal pathway or whether COPD and lung cancer are related to some common underlying exposure[82].

A history of allergies, but not asthma (above), as a possible indicator of enhanced immunocompetence, may be inversely related to lung cancer risk[83;84]. A large US case-control study reported an inverse association between a history of hay fever and lung cancer overall (OR = 0.58, 95% CI 0.48-0.70), that attenuated in never smokers (OR = 0.81, 95% CI 0.53-1.23)[96]. Lung cancer cases with hay fever exhibited lower mutagen sensitivity in the bleomycin and benzo[a]pyrene diol epoxide (BPDE) assays[111]. There was also a significant dose-response relationship between increasing categories of bleomycin and BPDE sensitivity overall and lung cancer risk. An inverse association was reported between a history of eczema and lung cancer in a large, multi-centre international case-control study[112]. No clear association was observed between biological indicators of atopy (allergen-specific immunoglobulin E levels, skin prick testing) and lung cancer risk in case-control[113] or cohort studies[114-117]. In the CPS-II, there was no association between a history of self-reported physician-diagnosed hay fever and lung cancer mortality in never smokers (HR = 1.02, 95% CI 0.86-1.21)[90].

Several recent reviews have examined the role of infections in lung cancer. Srinivasan et al.[118] noted considerable heterogeneity in estimates of the prevalence (0-78.3%) of human papillomavirus (HPV) in lung cancer. Although higher rates of lung cancer were observed in cervical cancer survivors, this

was attributed to higher rates of cigarette smoking in cervical cancer cases[119]. A case-control study nested in the Finnish Maternity Cohort reported no association between HPV 16 or 18 infection and lung cancer incidence adjusting for serum cotinine concentrations[120].

Liang et al.[121], in a systematic review of 41 studies, reported a significant positive association between tuberculosis and lung cancer (summary RR = 1.74, 95% CI 1.48-2.03) that remained in never smokers (summary RR = 1.78, 95% CI 1.42-2.23) based largely on results of case-control data. Results according to histologic subtype revealed positive associations with adenocarcinoma only (summary RR = 1.60, 95% CI 1.24-2.05). However there remain several potential limitations including misclassification and residual confounding by cigarette smoking status and further large prospective studies are needed. There may also be roles for *Chlamydia pneumonia* and *Helicobacter pylori* infection in lung cancer, however further research is needed[122;123].

There is no clear evidence to support an association between insulin-like growth factor (IGF) - 1 and lung cancer; however there may be an inverse association with IGF - 3[124;125].

Environment and Occupation

Radon

Radon is formed as part of the decay series of uranium-238, which is naturally present in rocks and soils in the environment. Radon has a half-life of 3.8 days and further decays into a series of radon progeny, most notably polonium-218 and polonium-214 that are deposited in the lung and emit α-particles capable of damaging DNA in human lung tissue. Alpha-particles are highly charged and deposit large amounts of energy in the cell per distance travelled (high-linear energy transfer (LET) radiation) as compared to γ rays or x-rays (low-LET radiation). Exposure to α particles may also

result in the generation of reactive oxygen species and oxidative damage to DNA through interaction with extra-nuclear targets[126].

Radon was suspected as playing a role in lung cancer for several centuries due to high rates of respiratory mortality observed in miners[4]. Modern epidemiologic investigation as well as supporting mechanistic evidence has lead to the relatively recent identification of radon as a human lung carcinogen[8]. These studies were reviewed in detail by the National Research Council (NRC)[4]. In addition to studies of miners, there have also been general population studies examining associations with residential radon using both ecological and analytical approaches including combined analyses of residential radon case-control studies conducted in North America and Europe.

Miners Studies

Studies of underground miners have observed an increased lung cancer risk associated with radon. In a combined analysis, data from 65,000 miners, including 2,700 lung cancer deaths, were combined from 11 studies conducted in North America, China, the Czech Republic, Sweden, France, and Australia[127]. Mean exposure levels ranged from 7.6 to 595.7 working level months (WLM) with an overall mean of 158.0 WLM in all studies combined (37 Bq/m^3 ~ 0.005 WL). An ERR of 0.0049 (95% CI 0.002-0.010) was observed per WLM. Results varied according to attained age, time since exposure, time since last exposure, and duration of exposure, where there were trends of decreasing risk with increasing age, time since exposure, and time since last exposure, and increasing risk with increasing exposure duration. There was also an inverse exposure rate effect, whereby for a given total cumulative dose, exposures experienced over a protracted period of time were associated with a greater lung cancer risk than exposures experienced over a shorter time period. In contrast, results did not vary according to age at first exposure, where there were no differences observed according to childhood or adult radon exposure. There was also some evidence of a supra-additive but sub-

multiplicative interaction between radon and cigarette smoking, with the joint effect larger than the sum of individual effects, but less than their product. Potential methodological limitations include limited or imputed data on radon, work histories, time/activity patterns, cigarette smoking history, and concomitant exposures that may also vary by study.

Based on miner data, the NRC Committee on Health Risks of Exposure to Radon (BIER VI) developed the following ERR model for lung cancer associated with radon:

$$ERR = \beta(w_{5\text{-}14} + \theta_{15\text{-}24}w_{15\text{-}24} + \theta_{25+}w_{25+})\varphi_{age}\gamma_z$$

where β represents the slope of weighted (θ) radon exposures (w) experienced during the previous 5-14, 15-24, and 25+ year time windows. Note that exposures experienced up to 5 years in the past are not considered relevant. The weighting of the 5-14 year time window, thought to be the most biologically relevant, is set to equal 1. The effect of radon is shown to be modified by φ_{age}, representing categories of attained age, and γ_z, representing exposure rate, with categories of either duration of exposure or average exposure concentration. Further analyses in miners exposed to lower radon levels (<50, <100 WLM) supported results based on the full cohort[128].

Although there are several uncertainties in extrapolating results to the general population, such as differences in exposure conditions, exposure rates, exposure to other lung carcinogens, and possible gender differences, it was estimated that residential radon may be responsible for 15,000 (95% CI 6,000-36,000) lung cancer deaths each year in the US. Results from more recent miner studies, with extended follow-up time periods, were consistent with previous findings[129-132].

General Population Studies

Ecological Studies

Ecological studies have examined associations between area-level residential radon concentrations and rates of lung and other cancers with mixed results reported[4]. Of particular note are a controversial series of publications by Cohen. Cohen examined the association between mean county-level residential radon concentrations (1986-1991) and county-level lung cancer mortality rates (1970-1979) in 1,601 US counties and observed a strong inverse association (β = -7.3 for males, -8.3 for females) of decreasing lung cancer mortality rates with increasing radon concentrations[133]. Results remained with adjustment for state-level cigarette smoking prevalence, 54 county-level socioeconomic variables (including population characteristics, vital and health statistics, social factors, housing factors, economics, and government expenditure), and city-level physical features (altitude, temperature, precipitation, wind, sunshine). Results were also robust to the exclusion of highly urbanized counties, upon stratification by geography, and when considering alternate radon data. Similar results were also observed in earlier publications with fewer data[134;135]. Cohen concluded that findings did not support the linear no-threshold theory for carcinogenesis. However methodological concerns including confounding by individual-level cigarette smoking, cross-level bias, model misspecification, and exposure measurement error remain[4;136-138]. A follow-up publication with updated lung cancer mortality data (1979-1994) and data on 450 socioeconomic variables also reported strong inverse associations between radon and lung cancer[139].

In order to further examine the inverse associations reported by Cohen, Puskin[140] examined the association between mean county-level residential radon concentrations and all smoking- and non-smoking related cancers combined including cancers at sites with low radon doses. Cohen's mean county-level residential radon concentrations were linked with mean county-level cancer mortality rates (1970-1994) for 1,585 counties from the National Cancer Institute. Where mortality data were sparse, an iterative weighting procedure was used to obtain an improved estimate of the county-specific mortality rate. Supporting previous observations of Gilbert[136], mortality rates for cancers that are strongly related with cigarette smoking (lung, oral cavity, pharynx, larynx, esophagus) were

inversely associated with radon whereas cancers unrelated to cigarette smoking (colon, breast, prostate), showed no negative trend. Cancers weakly related with cigarette smoking (bladder, pancreatic) were also weakly inversely related with radon. Results were unchanged with the inclusion of county-level smoking prevalence in analysis. It was concluded that confounding by individual-level cigarette smoking likely explains the strong inverse associations observed by Cohen (see also Puskin et al.[141]). Specific regional patterns in residential radon, smoking, and rates of lung cancer may also play a role.

Case-Control Studies of Residential Radon (Ecological Radon Measures)

Two studies have examined the impact of using either individual or ecological indicators of residential radon in case-control studies[142;143]. A Swedish case-control study of 1,360 lung cancer cases and 2,847 age-matched randomly selected population controls from 109 municipalities examined the association between residential radon concentrations as either the individual time-weighted average based on three month long (heating season) measurements in all residences of at least two years (individual-level) or as the mean time-weighted average value of controls by county (ecological-level) for the county of the longest time period of residence[143]. ERRs for the association between mean individual-level residential radon concentrations and lung cancer were found to range from 0.05 to 0.08 per 100 Bq/m^3 with adjustment for age, sex, and individual-level smoking, whereas no association (ERRs ranging from -0.03 to 0.00) was observed using ecological-level residential radon data. However, upon further adjustment for latitude, which may be associated with both residential radon concentrations and other lung cancer risk factors, similar point estimates for lung cancer were observed using either the individual- or ecological- data, although the ecological-estimate was notably less precise likely due to higher levels of within-, as opposed to between county variability in residential radon concentrations (ERRs individual-level = 0.07 to 0.11; ERRs ecological-level = 0.12 to 0.14). It was also noted that since findings from studies with wide

geographic study bases reflect both within-and between- area contrasts, adjustment for geographic region in analysis may aid in identifying unrecognized confounders.

Darby et al.[142] in a similar study in South-West England, examined lung cancer risk in 982 lung cancer cases who were current residents of Cornwall or Devon county of at least 20 years, and 1,486 age, sex, county- matched population controls. Individual time-weighted mean residential radon concentrations were estimated based on either radon measurements in current and previous residences over the past 35 years (individual-level) or district mean residential radon concentrations from study controls (ecological-level). Analyses were adjusted for individual-level age, sex, smoking, social class, and county of residence. Overall, similar results for lung cancer were obtained using either individual- (RR at 100 Bq/m^3 = 1.12, 95% CI 0.99-1.27) or ecological- level (RR at 100 Bq/m^3 = 1.12, 95% CI 0.69-1.82) residential radon concentrations, although findings using the ecological-level data were notably less precise. Inclusion of an additional urban-rural status indicator resulted in no change in the individual-level estimate, but increased the ecological-level estimate (RR at 100 Bq/m^3 = 1.35, 95% CI 0.81-2.23) and resulted in similar results in the two counties. Findings indicate there may be different confounding variables in individual- and ecological- analyses of residential radon and that there may be some degree of downwards bias in findings using individual-level radon measures due to exposure measurement error.

Case-Control Studies of Residential Radon (Individual Radon Measures)

Numerous case-control studies, with individual-level residential radon concentrations measured in homes, have been conducted in North America, Europe, and China. These studies were previously reviewed in detail elsewhere[4;144]. Although results from individual studies were limited by small sample sizes and disparate findings, combined analyses of individual case-control studies have provided strong direct evidence for a link between lung cancer and residential exposure to radon gas.

In North America, data from seven major residential radon case-control studies (Iowa, Missouri-I, Missouri-II, New Jersey, Connecticut, Utah-South Idaho, Winnipeg), including 4,081 lung cancer cases and 5,281 matched controls was combined using a common data format[12;13]. Sixty eight percent of cases were female. Approximately 44% of case questionnaire data was collected through proxy respondents. Long-term (one year) measurements of residential radon concentrations were obtained through α-track detectors placed in the main living areas of subjects' homes. Mean residential radon concentrations in the 5-30 year exposure time window ranged from 25.1 Bq/m^3 in New Jersey to 131.1 Bq/m^3 in Winnipeg. Missing radon concentrations were imputed usually based on mean observed concentrations. Overall, adjusting for age, sex, cigarette smoking, study, number of residences, and years with α-track measurements, an ERR of 0.10 (95% CI -0.01-0.26) at 100 Bq/m^3 radon was observed. There was no evidence of departure from a linear relationship. Upon restriction of the data to individuals who resided in only one or two houses in the 5-30 year exposure time window, and had measurements of residential radon concentrations for at least 20 years (1,910 cases and 2,651 controls), an ERR of 0.18 (95% CI 0.02-0.43) was observed. Further analyses using the restricted data and BIER VI weights of 1.0, 0.8, and 0.3 for exposures experienced 5-14, 15-24, and 25-30 years in the past resulted in a further increase of the ERR estimate (ERR = 0.23, 95% CI 0.03-0.55). Results according to respondent type revealed a ERR of 0.16 for subject respondents and -0.05 for proxy respondents, although the difference was not statistically significant (p = 0.47). Results did not vary significantly by age, sex, education, or cigarette smoking. In analyses by histological subtype, the largest ERR was observed for small cell carcinoma in the overall dataset (ERR = 0.23, 95% CI -0.08, 0.85) and adenocarcinoma in the restricted dataset (ERR = 0.27, 95% CI 0.02-0.73). No positive associations were observed for lung cancer of an unknown subtype.

In Europe, data from 13 major residential radon case-control studies conducted in Austria, the Czech Republic, Finland, France, East and West Germany, Italy, Spain, Sweden, and the United Kingdom including 7,148 lung cancer cases and 14,208 matched controls were combined[10;11]. Seventy-seven

percent of cases were men. Surrogate respondents were used in 39% of case interviews. Long-term (atleast two months) measurements of residential radon concentrations were obtained largely through α-track detectors placed in the main living areas of subjects' homes and used to estimate residential radon exposures in a 5-35 year time window prior to lung cancer diagnosis. Where there were missing radon data, the control subject area-specific mean value was used. Mean residential radon concentrations ranged from 50 Bq/m^3 in West Germany to 500 Bq/m^3 in the Czech Republic. Mean residential radon concentrations in cases were 104 Bq/m^3 compared to 97 Bq/m^3 for controls. Overall, an ERR of 0.08 (95% CI 0.03-0.16) was observed per each 100 Bq/m^3 radon using individual time-weighted average residential radon concentrations adjusting for study, age, sex, region, and cigarette smoking. There was no evidence of departure from a linear relationship and no evidence for a threshold. Similar results were observed for both proxy (ERR = 0.08, 95% CI 0.01-0.19) and self-respondents (ERR = 0.09, 95% CI 0.01-0.20). In analyses weighting radon data according to BIER VI (weights of 1.0, 0.75 and 0.50 for time periods of 5-14, 15-25, and 25-34 years in the past), little change in the ERR was observed (ERR = 0.08, 95% CI 0.03-0.16). Results did not vary according to age, sex, cigarette smoking, education, or employment. However, a significant association was only observed in rural (ERR = 0.13, 95% CI 0.05-0.24) as opposed to urban areas (ERR = -0.07, 95% CI <-0.07-0.06) ($p = 0.01$) and in those with a closed (ERR = 0.30, 95% CI 0.10-0.64) as opposed to an open (ERR = 0.01, 95% CI -0.03-0.13) bedroom window at night ($p = 0.03$). According to histologic subtype, the largest ERR estimate was observed for small cell carcinoma (ERR = 0.31, 95% CI 0.13-0.61), with no clear association observed for all other histological subtypes combined (ERR = 0.03, 95% CI -0.03-0.10). Upon correction for random uncertainties in residential radon concentrations using available data on the variability of radon measurements over time, the ERR increased to 0.16 (95% CI 0.05-0.31).

There are also two residential radon case-control studies conducted in China. In 2004, data from a total of 1,050 lung cancer cases and 1,996 matched controls from both the Shenyang and Gansu

studies were pooled by Lubin et al.[145]. Data on incident lung cancer cases diagnosed from 1985-1987 in Shenyang and 1994-1998 in Gansu were compiled including year-long α-track radon measurements in the main living areas of homes. Individual time-weighted average residential radon concentrations were estimated for the 5-30 year time period prior to diagnosis/reference date. Where there were missing radon data, the mean control value was used. Mean radon concentrations of 115.7 Bq/m^3 and 222.9 Bq/m^3 were observed in Shenyang and Gansu respectively. Overall, an excess OR of 0.133 (95% CI 0.010-0.136) was observed at 100 Bq/m^3. Similar results were observed for subjects who resided in their current home for atleast 30 years (excess OR = 0.132, 95% CI 0.070-0.191). Results did not vary according to sex, indoor smokiness, or cigarette smoking. However, there was some evidence that results varied by respondent type (proxy, self), and completeness of radon measurements.

Bonner et al.[146] in a case-only study of data from three residential radon case-control studies reported an interaction between GSTM1 and radon. Radon associated lung cancer risk was greater among GSTM1 null homozygotes compared to GSTM1 carriers.

Other Health Endpoints

Radon may also be associated with other malignant and non-malignant diseases beyond lung cancer. Archer et al.[147] reported a positive association between radon and non-malignant respiratory disease mortality in an early study of uranium miners in the Colorado Plateau. Mapel et al.[148] reported an inverse association between underground mining duration and lung function in a cross-sectional study of New Mexico uranium miners. There also are reports of uranium miners with chronic diffuse interstitial fibrosis, although a causal link with radon could not be established[4;149;150].

A pooled analysis of data from 11 cohorts of underground miners reported excess mortality from stomach cancer, liver cancer, and leukemia that were unrelated to radon exposure[151]. A French

cohort study showed an increased mortality from lung and kidney cancer in uranium miners that was not associated with cumulative radon exposure[132]. There was also a significant positive association between radon and mortality from cerebrovascular disease; however potential confounding by cardiovascular risk factors could not be assessed[152]. Mortality from multiple myeloma and non-Hodgkin's lymphoma was not related to cumulative radon exposure in the Colorado Plateau cohort[131]. There was no strong evidence for an association between radon and death from all extrapulmonary cancers in the German uranium miners cohort[153]. However, radon was positively associated with incident chronic lymphocytic leukemia (RR = 1.98, 95% CI 1.10-3.59) in Czech uranium miners[154].

Although ecological analyses have reported positive associations between residential radon and leukemia, case-control studies have not supported a link[155]. Excesses in total and site-specific cancer (colorectal, breast, kidney, and prostate) incidence were observed in census tracts with elevated groundwater uranium concentrations in a South Carolina study; however there were no individual-level risk factor data[156]. No association between radon or other drinking water radionuclides and leukemia, stomach, bladder, or kidney cancer risk was observed in Finland[157-159].

Ambient Air Pollution

Epidemiological investigations into potential associations between outdoor air pollution and mortality have been conducted for nearly a century with early reports suggesting that 'smokiness of the atmosphere' may represent an important factor for lung cancer[160]. A variety of methodological approaches have been used to examine potential relationships in previous studies ranging from migrant studies and studies of urban-rural comparisons to detailed analytic studies with long-term estimates of specific air pollutants measured via air pollution monitoring networks or estimated via various dispersion or land-use regression (LUR) modeling techniques.

Studies of migrants have suggested lung cancer rates in migrants between those of the country of origin and the country of residence; suggesting at least in the case of declining lung cancer rates, that some portion of risk is conserved after migration[161]. Numerous investigations have also suggested higher rates of lung cancer in urban, polluted areas compared to rural regions that do not appear to be entirely due to differences in cigarette smoking consumption[161;162]. However, other possible explanations remain including geographical differences in passive smoking or occupational exposures, or potential bias due to selective migration[161;162]. There are also studies of populations occupationally exposed to diesel and other air pollutants[161;163;164].

More recently, a variety of case-control and cohort studies have been conducted in the United States, Europe, and Asia examining associations between various measured (or estimated) indices of specific particulate and gaseous air pollutants and lung cancer incidence or mortality (Table 2). There are also studies of populations living in proximity to specific industries[105;165-172], population employment in petrochemical manufacturing[173], and petrol station density[174], as indicators of ambient air pollution exposure. Although positive associations have been reported between $PM_{2.5}$ and lung cancer, a variety of potential limitations remain including residual confounding by cigarette smoking or other individual- or ecological- risk factors, as well as other co-pollutants, uncertainty in terms of the identification of specific subpopulations that may be more susceptible to the adverse health effects of particulate matter, and which specific PM components may be most responsible for observed associations[175;176]. However, $PM_{2.5}$ is thought to represent the leading combustion-related air pollution indicator due to robust findings in previous studies and biological plausibility[5;24;177].

Hospital-Based Case-Control Studies

Hospital-based case-control studies have shown little clear evidence for an association between air pollution and lung cancer. Vena[178], in an early study of 417 prevalent lung cancer cases and 752

controls without cancer, infectious, or respiratory disease admitted to the Roswell Park Memorial Institute from 1957-1965 who were residents of Erie County, New York with measured data on total suspended particulates (1961-1963) and historical emissions data reported no clear evidence for an association between air pollution and lung cancer (RR exposure to high/medium levels of air pollution for 50 or more years compared to < 50 years or low air pollution exposure = 1.09, 95% CI 0.66-2.20). However, there was some evidence for a synergistic effect between air pollution, cigarette smoking, and occupational exposures.

Katsouyanni et al.[179] in a study of 101 prevalent female lung cancer cases and 89 orthopedic condition controls admitted to Athens hospitals between 1987-1989 who were permanent residents of Athens, reported a small, but non-significant association with lung cancer, in those in the upper two quartiles of lifelong air pollution exposure, as measured by 1983-1985 smoke and nitrogen dioxide (NO_2) concentrations, compared to those in the bottom two exposure quartiles. However no positive association was observed in nonsmokers (RR = 0.81, highest vs lowest quartile).

Jockel et al.[180] in a German hospital-based case-control study of 194 incident lung cancer cases and 388 hospital- and population-based controls reported no association between lung cancer and sulfur dioxide (SO_2) emissions (OR high vs low = 1.01, 95% CI 0.53-1.91) or a semiquantitative air pollution index (OR high vs low = 1.16, 95% CI 0.34-2.13).

Population-Based Case-Control Studies

Population-based case-control studies have reported some associations between air pollution and lung cancer. In mortality-based studies, Jedrychowski et al.[181] examined 1,099 deaths from lung cancer and 1,073 age- and sex- matched non-respiratory deaths in Cracow, Poland from 1980-1985 with self-administered questionnaire data collected on residency, cigarette smoking, and other lung cancer risk factors from respondent proxies. Measured data on TSP and SO_2 (1973-1980) according to the

last place of residence were used to classify individuals into high, medium, and low air pollution zones. In males, a significantly increased risk for lung cancer death was observed in those with high vs low exposure to air pollution (RR = 1.46, 95% CI 1.06-1.99). However no association was observed in females. Similar, although less precise findings were observed in non-smokers.

In a case-control study of 755 male lung cancer deaths and 755 age-matched controls in Trieste, Italy there was a significant positive trend between increasing concentrations of particulate deposition and lung cancer ($p = 0.022$)[165]. A significantly elevated RR for lung cancer was observed in those in the highest tertile compared to the lowest tertile of particulate deposition concentrations (RR = 1.4, 95% CI 1.1-1.8). According to histological subtype, there were also significant increasing trends with small cell (RR highest vs lowest tertile = 1.7, 95% CI 1.1-2.5, $p = 0.016$) and large cell (RR highest vs lowest tertile = 1.7, 95% CI 0.9-3.0, $p = 0.049$) lung cancers.

Results from Taiwan studies have reported significant positive associations between indices of air pollution and female lung cancer deaths[182;183]. In 2006, Chiu et al.[182] examined 972 female lung cancer deaths and 972 age- and year of death- matched non-cancer/respiratory death controls from 1994-2003. A significant positive association was observed between lung cancer and an aggregated index of long-term air pollution, obtained as the overall average of the division the annual average of measured concentrations of particulate matter of ≤ 10 microns in diameter (PM_{10}), ozone (O_3), carbon monoxide (CO), NO_2, and SO_2 by their respective national air quality standard (OR highest vs lowest tertile = 1.28, 95% CI 1.02-1.61). In 2008, Liu et al.[183] examined a larger set of female lung cancer deaths (1,676) and matched non-cancer/respiratory death controls (1,676) and observed significant increasing trends for lung cancer with increasing categories of NO_2 and CO but a significant decreasing trend with increasing O_3 ($p < 0.05$). No associations were observed with SO_2 or PM_{10}.

Pisani et al.[184] reported no association between lung cancer and cumulative SO_2, NO_2, or total suspended particulate (TSP) in a hospital- and population-based case-control study of 211 lung cancer cases and 202 controls in rural Thailand.

In incidence-based studies, Nyberg et al.[185] examined 1,042 incident male lung cancer cases and 2,364 age-matched population-based controls (1,274 from the population register and 1,090 from the cause of death registry) diagnosed between 1985 and 1990 in Stockholm, Sweden. Estimated yearly nitrogen oxide (NO_x), NO_2, and SO_2 concentrations from 1950 to 1990, representing exposure to air pollution from road traffic and heating sources respectively, at the residential address were calculated based on emissions data and dispersion modeling techniques. There was no association observed with either long-term (30 year) average SO_2 exposure (RR per 10 $\mu g/m^3$ = 1.00, 95% CI 0.96-1.05) or with 10 year average SO_2 exposure lagged 20 years (RR = 1.01, 95% CI 0.98-1.03). For NO_2, there were elevated point estimates for long-term (30 year) average exposure (RR per 10 $\mu g/m^3$ = 1.05, 95% CI 0.93-1.18; RR 90th percentile = 1.17, 95% CI 0.84-1.62) which increased with a 20 year lag (RR per 10 $\mu g/m^3$ = 1.10, 95% CI 0.97-1.23; RR 90th percentile = 1.44, 95% CI 1.05-1.99). Results for NO_2 also strengthened in multi-pollutant models including both NO_2 and SO_2 exposures in the model simultaneously.

Cohort Studies

Results from several small, prospective studies have also provided some evidence for associations between air pollution and lung cancer. Results from the Adventist Health Study on Smog (AHSMOG), a prospective study of 6,340 non-smoking California Seventh Day Adventists followed-up for 15 years (1977-1992) reported significant positive associations between lung cancer and measured concentrations of various particulate and gaseous air pollutants, however there were few observed cancer cases (36)/deaths (30)[186-188]. Hoek et al.[189], in an eight year (1986-1994) prospective

study of 4,492 participants from the Netherlands Cohort Study on Diet and Cancer (NLCS), reported no association between lung cancer mortality and black smoke (BS) or NO_2 concentrations estimated at the level of the home address. However there were only 60 lung cancer deaths observed. Results from a study of 14,001 elderly residents of Shizuoka, Japan, followed up from 1999-2006, revealed no association between lung cancer (86 deaths) and LUR estimated NO_2 concentrations overall (HR per 10 $\mu g/m^3$ = 0.95, 95% CI 0.78-1.17)[190]. However upon restriction to never smokers, an elevated HR was observed (HR = 1.30, 95% CI 0.85-1.93).

In 1993, Dockery et al.[191] in the Harvard Six Cities Study of 8,111 randomly selected adult participants from six eastern US cities reported a positive although imprecise association between $PM_{2.5}$, as measured from study-specific monitors, and lung cancer mortality (RR highest vs least polluted city = 1.37, 95% CI 0.81-2.31). However, there were only 120 lung cancer deaths (1974-1991). In a subsequent analysis, with an extended follow-up time period through 1998, and 226 observed lung cancer deaths, a positive, non-significant association was also observed (HR per 10 $\mu g/m^3$ = 1.27, 95% CI 0.96-1.69)[20]. Although in the same study, the relative risk of mortality from cardiovascular and respiratory disease was found to decline with declining $PM_{2.5}$ concentrations over follow-up time, this was not apparent for lung cancer mortality, a disease with longer latency and less reversibility.

Nafstad et al.[192] followed up 16,209 men recruited as part of a cardiovascular disease cohort in Oslo for 26 years (1972-1998) for cancer incidence according to the Norwegian cancer register. Mean annual NO_x and SO_2 concentrations were estimated at the home address of each participant using a variety of monitoring, emissions, meteorological, and topographical data for the years 1974-1998. A total of 418 incident lung cancer cases were observed. A significant positive association was observed between lung cancer and historical NO_x (1974-1978) (HR per 10 $\mu g/m^3$ = 1.08, 95% CI 1.02-1.15) but not SO_2 exposure (HR per 10 $\mu g/m^3$ = 1.01, 95% CI 0.94 - 1.08). The positive

association between NO_x and lung cancer remained in non-smokers, but was less precise (HR = 1.20, 95% CI 0.70-2.03). Results in models using air pollution estimates from the most recent five years were attenuated. Similar results were observed for lung cancer mortality[193].

A subsequent study of all 143,842 deaths among individuals aged 51-90 years in Olso from 1992-1998 reported positive associations between estimated NO_2, PM_{10}, and $PM_{2.5}$ concentrations from dispersion models and lung cancer mortality, particularly for females[21]. There was also some evidence for a threshold in the concentration- response relationship. However there was no information on smoking history.

In a French study, Filleul et al.[194] followed up 14,284 adults in the PAARC ("Pollution Atmosphérique et Affections Respiratoires Chroniques") study for 24 years (1974-1998) for mortality according to the national register. A total of 178 lung deaths were observed. A significant positive association was observed between mean concentrations of NO_2 and lung cancer mortality (RR per 10 $\mu g/m^3$ = 1.48, 95% CI 1.05-2.06), but not SO_2, TSP, BS, acidimetric method, or NO from central monitors. Higher RR estimates for lung cancer mortality were also observed in current and former smokers, as compared to never smokers.

Vineis et al.[195], in a case-control study of 271 incident lung cancer cases who were either never or former smokers and 737 gender, age, smoking, country and time period matched controls nested in the European Prospective Investigation on Cancer and Nutrition (EPIC) reported positive associations with residence near heavy traffic roads (yes/no) (OR = 1.46, 95% CI 0.89-2.40) and NO_2 (OR per 10 $\mu g/m^3$ = 1.14, 95% CI 0.78-1.67) but not PM_{10} (OR = 0.91, 95% CI 0.70-1.18) or SO_2 (OR = 1.08, 95% CI 0.89-1.30) concentrations. Results for NO_2 strengthened in the upper tertile exposure category overall (OR upper tertile vs bottom two tertiles = 1.56, 95% CI 1.13-2.16), however upon stratification by cigarette smoking status, significant results remained only for former (OR upper

tertile = 1.59, 95% CI 1.10-2.30) but not for never smokers (OR upper tertile = 1.09, 95% CI 0.78-1.52).

Beelen et al.[196] examined the association between estimated air pollution concentrations at the geographical coordinates of the home address at enrollment and lung cancer incidence in a study of 114,378 in the NLCS. A total of 1,940 lung cancer cases were observed over the 11 year follow-up period (1986-1997). Overall, there were no clear associations between any indicator of air pollution (BS, $PM_{2.5}$, NO_2, SO_2, or traffic intensity) and lung cancer. However, in analyses stratified by cigarette smoking status, positive associations with traffic intensity in never smokers were observed, ranging from 11-55% increases in risk, and there was a significant association with BS (RR per 10 $\mu g/m^3$ = 1.47, 95% CI 1.01-2.16). There was also some evidence for higher RR's in those with lower fruit consumption. Similar results were found for lung cancer mortality[197].

Raaschou-Nielson et al.[198] examined 679 incident lung cancer cases from the Diet Cancer Health Cohort, the Copenhagen City Heart Study, and the Copenhagen Male Study with 3,481 controls from the same cohorts matched according to cohort, gender, smoking duration, and year of birth. Mean NO_x concentrations were estimated from dispersion models. Overall an incidence rate ratio (IRR) of 1.37 (95% CI 1.06-1.76) was observed per each 100 $\mu g/m^3$ increase in NO_x concentration increasing further to 1.45 (95% CI 1.12-1.88) among those above the 90^{th} percentile, compared to those below the 50^{th} percentile. By histological subtype, significant positive associations were observed for small cell (IRR per 100 $\mu g/m^3$ = 1.53, 95% CI 1.02-2.28) and squamous cell carcinoma (IRR = 2.01, 95% CI 1.27-3.43) but not adenocarcinoma. There was no notable change in results with the inclusion of a 10 year lag in air pollution concentrations.

Hart et al.[199] examined associations between mean particulate and gaseous pollutants at the last known residential address and all-cause and cause specific mortality in a study of 53,814 men employed in the US trucking industry in 1985. In mortality follow-up through the year 2000, a total

of 800 lung cancer deaths were observed. Mean PM_{10}, SO_2, and NO_2 concentrations (1985-2000) were estimated using spatial smoothing and LUR techniques while mean $PM_{2.5}$ (2000) concentrations were assigned to study participants based on the nearest available monitor. Overall, positive, although non-significant associations were observed between SO_2 and NO_2 and lung cancer mortality (percent increase = 9.0, 95% CI -1.8-20.9 and 5.5, 95% CI -3.4-15.3 respectively) whereas no clear association was observed with either PM_{10} (percent increase = -0.1, 95% CI -7.9-8.2) or $PM_{2.5}$ (percent increase = 2.1, 95% CI -5.0-9.7). Results from multipollutant models, which considered PM_{10}, SO_2, and NO_2 simultaneously, attenuated with the exception of results for NO_2, which strengthened somewhat (percent increase = 7.2, 95% CI -4.6-20.5). Major limitations of the study include the fact that there was no data on individual-level covariates of interest including cigarette smoking status and other lung cancer risk factors, however, data on occupational exposures was considered.

Raaschou-Nielsen et al.[200] in a prospective analysis of 52,907 members of the Danish Diet Cancer and Health Cohort, observed positive associations between lung cancer incidence and estimated NO_x concentrations at the home address (IRR per 100 $\mu g/m^3$ = 1.09, 95% CI 0.79-1.51, IRR upper quartile = 1.30, 95% CI 1.05-1.61) as well as with proximity to a major road (IRR = 1.21, 95% CI 0.95-1.55) and traffic load (IRR linear trend = 1.03, 95% CI 0.90-1.19, IRR upper quartile = 1.17, 95% CI 0.92-1.47). There was also some limited evidence of stronger associations among non-smokers, those with a low fruit intake, and higher level of educational attainment.

Finally, in one of the largest studies conducted to date, Pope et al.[201] in an analysis of ~500,000 CPS-II participants with follow-up from 1982-1989, reported a significant positive association between MSA-level sulfate (SO_4) (1980) concentrations and lung cancer mortality (HR per 24.5 $\mu g/m^3$ = 1.36, 95% CI 1.11-1.66) with detailed adjustment for cigarette smoking and other potential confounders but no association with $PM_{2.5}$. Due to intense public scrutiny, re-analysis of the findings of both this

study and the original Harvard Six Cities Study[191], reported that following a detailed replication, validation, and sensitivity analysis protocol, that the findings of both studies were valid and supported the assertion that long-term exposure to ambient air pollution is associated with mortality health effects[202]. There was also some evidence for a modifying effect of educational attainment with stronger lung cancer mortality effects observed in those with a lower level of educational attainment; possibly due to differences in exposure misclassification, susceptibility, or residential mobility from enrollment. Subsequently in an extended 16 year follow-up (1982-1998), significant associations between lung cancer mortality and $PM_{2.5}$ were observed (HR per 10 $\mu g/m^3$ $PM_{2.5}$ (1979-1983) = 1.08, 95% CI 1.01-1.16). There was no association with coarse particles or gaseous pollutants. Most recently, in an 18 year (1982-2000) follow-up a HR of 1.08 (95% CI 1.03-1.14) was observed per each 10 $\mu g/m^3$ $PM_{2.5}$ (1979-1983)[203]. Results strengthened somewhat with the inclusion of various socio-demographic ecological–level variables in the model. Results from the CPS-II have been widely used in air pollution policy-making throughout the world[22;175;204].

Other Environment and Occupation

There are also a variety of other environmental and occupational exposures that may play a role in lung cancer etiology including environmental tobacco smoke, indoor coal and biomass burning, arsenic in drinking water, and other types of radiation exposure besides radon.

A meta-analysis of 55 studies examining lung cancer risk in never-smoking women exposed to a smoking spouse reported a summary RR of 1.27 (95% CI 1.17-1.37)[205]. Similar results were found when pooling data from cohort (summary RR = 1.22, 95% CI 1.03-1.44) or case-control (population-based) studies (summary RR = 1.18, 95% CI 1.08-1.28). Occupational exposure to passive smoke is also implicated as a definite occupational carcinogen (below)[206]. A 24% (95% CI 18-29%) increase in lung cancer risk was observed when pooling data from 22 studies of workers exposure to any

environmental tobacco smoke which increased to an approximate two-fold increase in risk for highly exposed workers[207].

In China, indoor air pollution due to coal and biomass burning, as well as volatile emissions from wok cooking, are important contributors to chronic lung disease and lung cancer even in non-smoking women[19;208]. A meta-analysis reported a combined OR of 2.27 (95% CI 1.65-2.89) for the association between indoor coal consumption and lung cancer in studies (n = 20) conducted in mainland China and Taiwan[209]. Among non-smoking women the OR was 2.93 (95% CI 1.40-6.12). Upon stratification by region, the strongest ORs were observed in south/southeastern (OR = 3.27, 95% CI 1.27-8.42) and southwestern China (OR = 2.98, 95% CI 1.18-7.53). Lung cancer risk may vary according specific smoky coal subtype. In Xuanwei, the highest lung cancer RR estimates were observed for coal from Laibin and Longtan, compared to other coal sources[210].

There is strong evidence to support a causal association between exposure to high levels of arsenic in drinking water (>150 μg/L) and lung cancer based on epidemiological studies conducted in high arsenic areas of Taiwan, Japan, Chile, and elsewhere[211-213]. Although the evidence surrounding potential associations with lower concentrations of arsenic is less consistent, Heck et al.[214] recently reported a positive association between small-cell and squamous-cell lung cancer and toenail concentrations of arsenic ≥ 0.114 μg/g (compared to toenail concentrations of < 0.05 μg/g) (OR = 2.75, 95% CI 1.00–7.57) in a US case-control study conducted in a low arsenic areas (<100 μg/L) of New Hampshire and Vermont. Chen et al.[215], in a Taiwan case-control study, reported no association between arsenic in drinking water and lung cancer at concentrations <100 μg/L, but reported positive associations in categories of arsenic concentrations of 100<300 μg/L (OR = 1.54, 95% CI 0.97-2.46) and ≥ 300 μg/L (OR = 2.25, 95% CI 1.43-3.55) relative to concentrations of < 10 μg/L. A significant linear trend was also observed. Upon examination of lung cancer histological subtype, the significant linear trend remained for small-cell and squamous-cell lung cancers but not for adenocarcinoma.

Low-LET radiation has also been implicated in lung cancer. Results from a recent analysis of 105,427 participants in the Life Span Study, a study of atomic bomb survivors in Hiroshima and Nagasaki exposed primarily to γ radiation, using an updated dosimetry system and an extended follow-up time period (1958 - 1998), revealed an ERR of 0.81 (90% CI 0.56-1.1) per Gy for lung cancer at age 70 with radiation exposure at age 30 and a corresponding excess absolute risk (EAR) of 7.5 (90% CI 5.1-10) cases per 10,000 person-years per Gy[216]. A super-multiplicative interaction with cigarette smoking was observed in light to moderate smokers (less than a pack per day) with an additive or sub-additive interaction in heavy smokers (a pack per day or more)[217]. Rather than a monotonic decreasing RR with increasing age at exposure, radiation-induced lung cancer in atomic bomb survivors increases by approximately 20% for each decade in age at exposure[216], possibly suggesting a increasing role for radiation-induced promotion of premalignant cells with increasing age[218].

Studies of medically-exposed cohorts, typically exposed to high-doses of radiation for the treatment of malignant or benign disease, have reported ERRs for second lung cancers ranging from approximately 0.1 to 0.4 per Gy[219]. It is estimated that approximately 8% of all second tumors, or 5 excess cancer cases per 1,000, are attributable to radiotherapy treatment for a first cancer[220]. No association between occupational radiation exposure and lung cancer was observed in US radiologic technologists[221].

In nuclear industry workers, results from a 15 country study including 407,391 workers, primarily exposed to external X- and γ- rays, with individual radiation monitoring data reported significant associations with mortality from all cancers (ERR/Sv = 0.97, 90% CI 0.28-1.77) as well as lung cancer (ERR/Sv = 1.86, 90% CI 0.49-3.63)[222]. There was also a significant increasing trend for lung cancer mortality with increasing radiation exposure (p = 0.009). Gilbert et al.[223] reported significant positive associations between both internal plutonium (α-particle) and external (γ-ray) radiation and

lung cancer mortality in Mayak nuclear workers. In males, an ERR/Gy of 4.7 (95% CI 3.3-6.7) at age 60 was observed for internal dose while for external dose, an ERR/Gy of 0.17 (95% 0.052-0.32) was observed at all attained ages. Results for internal and external dose were found to be compatible with estimates obtained from cohorts of underground miners and atomic bomb survivors respectively.

The NRC Committee to Assess Health Risks from Exposure to Low Levels of Ionizing Radiation (BIER VII) recently estimated that 140 (95% CI 50-380) excess lung cancer cases in males and 300 (95% CI 120-780) excess lung cancer cases in females would be observed per 100,000 population (of an age-distribution comparable to the 1999 US population) exposed to 0.1 Gy of low-LET ionizing radiation[219].

Siemiatycki et al.[206] summarized previous IARC evaluations of occupational carcinogens. There was strong evidence to implicate 17 occupational carcinogens and carcinogenic circumstances in lung cancer including aluminum production, arsenic and arsenic compounds, asbestos, beryllium, cadmium and cadmium compounds, chromium compounds - hexavalent, coal gasification, coke production, hematite mining – underground with radon exposure, involuntary (passive) smoking, ionizing radiation, iron and steel founding, selected nickel compounds, painters, silica – crystalline, soots, and talc containing asbestiform fibers. Lung cancer risk due to inhaled (occupational) or ingested (drinking water) arsenic appears to be independent of the exposure pathway but rather related to absorbed dose[224]. There was also suggestive evidence implicating a range of other potential carcinogens or carcinogenic circumstances including coal tars and pitches, diesel engine exhaust, hairdressers and barbers, nonarsenical insecticides, and the rubber industry. In contrast, there may be inverse associations between endotoxin exposure (cotton textile, agricultural industry) and lung cancer risk[225].

Social and Behavioural

Active cigarette smoking is the most predominant cause of cancer worldwide, accounting for some 90% of all lung cancer cases[226]. Other social and behavioural factors that may also play a role include diet and nutritional factors, physical activity, and reproductive and hormonal status.

Active cigarette smoking has been established as a major cause of lung cancer since the mid-twentieth century. Over 60 carcinogenic chemicals, including polycyclic aromatic hydrocarbons, heterocyclic hydrocarbons, *N*-nitrosamines, aromatic amines, *N*-heterocyclic amines, aldehydes, phenolic compounds, volatile hydrocarbons, organic compounds, metals, and radio-isotopes have been identified in cigarette smoke which vary in concentration according to cigarette formulation worldwide[6;226]. Numerous epidemiological studies have examined associations between cigarette smoking and lung cancer[226;227]. A meta-analysis of studies published through the year 2003 reported an overall nine-fold (summary RR = 8.96, 95% CI 6.73-12.11) increase in lung cancer risk for current compared to never smokers[227]. However RR estimates in individual studies vary widely according to the age distribution and cigarette smoking histories of participants in each study[226]. Lung cancer risk depends largely on cigarette smoking duration and to a lesser extent intensity (cigarettes smoked per day)[228;229]. In the CPS-II, lung cancer mortality increased according to the square of duration, but the square root of intensity in men[229]. Accordingly, it is suggested that smoking-related promotion, as opposed to the initiation, is of most relevance in lung carcinogenesis[230]. Inhalation characteristics and age at initiation are also important aspects of the association[226].

Overall, it is estimated that the cumulative probability of lung cancer mortality in current smokers at age 85 is approximately 8-15%[231]. The RR of lung cancer declines following smoking cessation in former smokers compared with current smokers, but remains elevated in comparison with never smokers[232]. Although cigarette smoking is associated with all histologic subtypes of lung cancer, it has typically been most strongly related with small cell and squamous cell carcinoma, and with adenocarcinoma to a lesser extent[233]. However, associations with adenocarcinoma have strengthened

in recent decades[226]. There are also other tobacco products including pipe tobacco, cigars, and bidi that are also associated with the disease, with the magnitude of the association ranging from approximate 2-4 fold increases in risk[226].

The World Cancer Research Fund concluded that there was "convincing" evidence for a positive association between β-carotene supplements (in smokers) and lung cancer and "probable" evidence for an inverse association with dietary fruits and carotenoids[212]. Results from two major intervention studies, the US β-Carotene and Retinol Efficacy Trial and the Finnish α-Tocopherol, β-Carotene Cancer Prevention trial examining the impact of high-dose β-carotene supplementation (20-30 mg daily) in individuals at high risk for lung cancer reported significant increases in lung cancer risk which attenuated following cessation of the supplementation[234-237]. The association may however be limited to high risk groups with results from interventions studies of β-carotene supplementation in health professionals showing no impact on lung cancer risk[238;239]. Satia et al.[240] recently reported that long-term users of β-carotene supplements experienced a significant three-fold increase in risk for incident small-cell lung cancer in the general population VITamins And Lifestyle (VITAL) cohort study. Conversely, a meta-analysis of 25 prospective observational studies of dietary carotenoid consumption reported inverse associations between individuals in the highest compared to the lowest group of total dietary carotenoid consumption (summary RR = 0.79, 95% CI 0.71-0.87) and lung cancer risk as well as those in the highest category of total serum carotenoid concentrations (summary RR = 0.70, 95% CI 0.44-1.11)[241]. In one study, the inverse association between β-cryptoxanthin and lung cancer remained after adjustment for both self-reported cigarette smoking and pre-diagnostic spot urinary cotinine levels[242].

A pooled analysis of eight prospective cohort studies reported a significant inverse association between individuals in the highest quintile of total fruit consumption and lung cancer risk (summary RR = 0.77, 95% CI 0.67-0.87) with a weaker association observed for total vegetable consumption

(summary RR = 0.88, 95% CI 0.78-1.00)[243]. Results were not found to differ by cigarette smoking status or by lung cancer histological subtype however residual confounding by smoking status remains a concern. A significant inverse association was observed in a recent meta-analysis between individuals in the highest category of total cruciferous vegetable consumption and lung cancer risk when combining data from 12 case-control studies (summary RR = 0.78, 95% CI 0.70-0.88) that remained upon restriction of the analysis to never smokers (summary RR = 0.78, 95% CI 0.64-0.95)[244]. Results strengthened among individuals with both GSTM1 and GSTT1 null genotypes (summary RR = 0.41, 95% CI 0.26-0.65) but attenuated when combining data from prospective studies (summary RR = 0.83, 95% CI 0.64-1.08).

No association between vitamin A, C, E, and folate intake and lung cancer risk was observed in a pooled analysis of data from eight prospective studies[245]. Results from the VITAL cohort study revealed significant inverse associations between any use of glucosamine (HR = 0.74, 95% CI 0.58-0.94) or chondroitin (HR = 0.72, 95% CI 0.54-0.96) and lung cancer incidence[246]. Results of studies examining the association between aspirin and lung cancer were inconsistent[247;248].

There was also "limited" evidence for an inverse association with physical activity[212]. Although previous studies have reported inverse associations between physical activity and lung cancer, with 20 to 40% reductions in risk observed, residual confounding by cigarette smoking status remains a concern[249]. Recently, the National Institutes of Health- American Association of Retired Persons Diet and Health Study, a large prospective study of over 500,000 American men and women, reported inverse associations between physical activity and lung cancer in current and former smokers with no association observed in never smokers[250]. However results from a small case-control study of never and former smokers nested in the EPIC cohort, reported inverse associations between recreational physical activity and lung cancer risk, as well as positive associations between

recreational physical activity and red blood cell glutathione levels, although glutathione levels themselves were not independently associated with disease risk[251].

Residual confounding by cigarette smoking may also likely explain inverse associations observed between body mass index (BMI), alcohol consumption, coffee consumption and lung cancer. A meta-analysis of previous prospective studies reported a significant inverse association (RR = 0.76, 95% CI 0.67-0.85) between BMI and lung cancer incidence in smokers but no association (RR = 0.91, 95% CI 0.76-1.10) in non-smokers[252]. Alcohol consumption was not associated with lung cancer mortality in 223,216 never smoking CPS-II participants[253]. A recent meta-analysis reported a significant positive association between coffee consumption and lung cancer overall (summary RR highest versus lowest coffee intake = 1.27, 95% CI 1.04-1.54) that was attenuated in never smokers (summary RR = 0.78, 95% CI 0.60–1.00)[254].

There is increasing interest in the role of estrogens in female lung cancer[255]. Although results from observational studies examining the association between hormonal replacement therapy and lung cancer have been mixed[256;257] with few details provided on the exact nature of therapy, results from intervention studies have reported some positive findings[258;259]. Most recently, the Women's Health Initiative reported a significant positive association between combined estrogen plus progestin therapy (versus placebo) and death from non-small-cell lung cancer (HR = 1.87, 95% CI 1.22-2.88) in postmenopausal women[260]. No association was observed in women treated with estrogen alone[261]. Slatore et al.[262], in the VITAL study, recently reported a significant 50% increase in risk for incident lung cancer among women who were users of estrogen plus progestin therapy for 10 or more years. Although several case-control and cohort studies have also suggested a possible role for reproductive factors in lung cancer including parity, age at first live birth, age at menarche, and age at menopause, results are largely inconsistent [263-267].

3. ARTICLE 1

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Cancer Epidemiology, Biomarkers & Prevention

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Cancer Epidemiology, Biomarkers & Prevention

Research Article

Radon and Lung Cancer in the American Cancer Society Cohort

Michelle C. Turner[1,2], Daniel Krewski[2,3,4], Yue Chen[3], C. Arden Pope III[5], Susan Gapstur[6], and Michael J. Thun[6]

Abstract

Background: Case–control studies conducted in North America, Europe, and Asia provided evidence of increased lung cancer risk due to radon in homes. Here, the association between residential radon and lung cancer mortality was examined in a large-scale cohort study.

Methods: Nearly 1.2 million Cancer Prevention Study-II participants were recruited in 1982. Mean county-level residential radon concentrations were linked to study participants according to ZIP code information at enrollment [mean (SD) = 53.5 Bq/m^3 (38.0)]. Cox proportional hazards regression models were used to obtain adjusted HR and 95% CI for lung cancer mortality associated with radon. Potential effect modification by cigarette smoking, ambient sulfate concentrations, and other risk factors was assessed on both the additive and multiplicative scales.

Results: Through 1988, 3,493 lung cancer deaths were observed among 811,961 participants included in the analysis. A significant positive linear trend was observed between categories of radon concentrations and lung cancer mortality ($P = 0.02$). A 15% (95% CI, 1–31) increase in the risk of lung cancer mortality was observed per 100 Bq/m^3 increase in radon. Participants with mean radon concentrations above the EPA guideline value (148 Bq/m^3) experienced a 34% (95% CI, 7–68) increase in risk for lung cancer mortality relative to those below the guideline value.

Conclusions: This large prospective study showed positive associations between ecological indicators of residential radon and lung cancer.

Impact: These results further support efforts to reduce radon concentrations in homes to the lowest possible level. *Cancer Epidemiol Biomarkers Prev; 20(3); 438–48. ©2011 AACR.*

Introduction

Lung cancer is the leading cause of cancer mortality in the United States. In 2009, it was estimated that a total of 219,440 new lung cancer cases and 159,390 deaths occurred (1). Lung cancer is a highly fatal disease, with a 5-year survival ratio of 15% (1). Although incidence rates for lung cancer have been declining for males, they are only now leveling off after several decades of increase for females, most likely because of changes in cigarette smoking patterns in recent decades (1). Although the majority of lung cancer cases can be attributed to active cigarette smoking, residential radon and ambient air pollution also have been implicated as important risk factors for this disease in the general population (2–5).

Radon gas is formed during the radioactive decay of uranium-238, which is naturally present in rocks and soils in the environment. In 1988, the International Agency for Research on Cancer (IARC) determined that radon was a cause of human lung cancer, based on studies of underground miners historically exposed to high levels of the gas (2). It was also observed that α-particles emitted from radon decay products can damage DNA in human lung tissue (2). Bonner and colleagues (6) recently reported an interaction between glutathione-*S*-transferase M1 and radon, suggesting that radon may also induce lung cancer through oxidative mechanisms.

Radon gas enters homes through cracks and other openings in the foundation and accumulates largely in the basement and lower living areas (7). Although there have been more than 20 case–control studies examining the association between residential radon and lung

Authors' Affiliations: [1]Graduate and Postdoctoral Studies, [2]McLaughlin Center for Population Health Risk Assessment, Institute of Population Health, and [3]Department of Epidemiology and Community Medicine, Faculty of Medicine, University of Ottawa; [4]Risk Sciences International, Ottawa, Ontario, Canada; [5]Department of Economics, Brigham Young University, Provo, Utah; and [6]Epidemiology Research Program, American Cancer Society, Atlanta, Georgia

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Corresponding Author: Michelle C. Turner, McLaughlin Centre for Population Health Risk Assessment, Institute of Population Health, University of Ottawa, One Stewart Street, Room 313, Ottawa, Ontario, Canada K1N 6N5. Phone: 613-562-5800 ext. 2328; Fax: 613-562-5380. E-mail: mturner@uottawa.ca

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cancer, results were limited by small sample sizes and disparate findings. Recent efforts to combine data from individual case–control studies have provided for the first time strong evidence for a link (8–11). In North America, data from 7 case–control studies, involving 3,622 lung cancer cases and 4,966 controls were combined, revealing that each 100 Bq/m^3 increase in radon was associated with an 11% (95% CI, 0–28) increase in lung cancer risk (10, 11). Results strengthened in a subset of the data with limited residential mobility and complete radon exposure histories [excess relative risk (ERR) = 21%; 95% CI, 3—52]. In Europe, data from a total of 7,148 lung cancer cases and 14,208 controls were also combined with similar findings observed (8, 9). Overall, each 100 Bq/m^3 increase in radon was associated with an 8% (95% CI, 3–16) increase in lung cancer risk. The evidence available to date suggests that radon may be responsible for 10% to 15% of the lung cancer burden, making radon the second leading cause of lung cancer after cigarette smoking (3).

Although there have been a number of residential case–control studies capturing retrospective data on individual smoking habits and other lung cancer risk factors, there has been only one prospective study in the general population. Ruano-Ravina and colleagues (12) recently followed up 241 control subjects from a previous case–control study of residential radon and lung cancer in Spain. An elevated, although imprecise, lung cancer risk was observed in subjects with radon concentrations above the guideline value of the U.S. Environmental Protection Agency (EPA; 4 pCi/L = 148 Bq/m^3; RR = 6.6; 95% CI, 1.2–38) relative to subjects below the guideline value.

There have also been few studies to examine the joint effects of residential radon and other inhalable environmental agents including passive smoke and ambient air pollution (13, 14). The question remains as to whether such agents may interact, thereby producing additive or multiplicative effects on lung cancer risk. Radon decay products may also attach to aerosols present in the environment, possibly influencing lung deposition and dose characteristics relevant for lung cancer (4, 15–16).

The purpose of this article is to examine the association between residential radon and lung cancer mortality in a large-scale prospective study. The American Cancer Society Cancer Prevention Study-II (CPS-II) is a large, well-established cohort, with detailed individual-level risk factor data collected at enrollment, including cigarette smoking, passive smoking, and occupational risk factors for lung cancer. It provides a unique opportunity to further strengthen the body of evidence for an association between residential radon and lung cancer and allows for an examination of the potential confounding or modifying effects of a range of individual and ecological-level risk factors including passive smoking and ambient air pollution. Results examining associations between residential radon and other malignant and nonmalignant mortality outcomes other than lung cancer will be presented separately (Turner and colleagues, unpublished data).

Materials and Methods

Study population

The CPS-II is a prospective study comprised of nearly 1.2 million participants enrolled by more than 77,000 volunteers in 1982. This cohort has been extensively studied to examine the long-term health effects of ambient air pollution (5, 17, 18). Ethics approval for the CPS-II was obtained from the Emory University School of Medicine Human Investigations Committee. Participants were recruited in all 50 U.S. states as well as the District of Columbia and Puerto Rico. Participants were largely friends and family members of the volunteers. For inclusion in CPS-II, participants were at least 30 years of age and had at least one family member ages 45 years or more. A 4-page self-administered questionnaire completed at enrollment captured data on a range of demographic, lifestyle, medical, and other personal and family characteristics including ZIP code of residence.

Because no updated information was collected on cigarette smoking status from enrollment, follow-up in the present study is restricted to the first 6 years of follow-up only (1982–1988; ref. 19). In CPS-II, follow-up of study participants for vital status has been conducted every 2 years. In 1984, 1986, and 1988, vital status was obtained from the study volunteers, confirmed by obtaining the corresponding death certificate. Subsequent to 1988, follow-up has been conducted through computerized linkage to the National Death Index (20). More than 99% of all known deaths have been assigned a cause. Lung cancer deaths were classified by the underlying cause of death according to ICD-9 162 (International Classification of Disease; ref. 21).

Of a total of 1,184,881 CPS-II participants, subjects were excluded due to missing vital status (419), prevalent cancer (except nonmelanoma skin cancer) at enrollment (82,329), missing ZIP code (99,479) or county data (22,872), or missing data on radon (5,836) or individual-level covariates of interest (161,985). A total of 811,961 participants in 2,754 counties were retained for analysis, among which 3,493 lung cancer deaths were observed.

Ecological measures of residential radon

Study participants were assigned to a primary county of residence using 5-digit ZIP code information provided at enrollment according to the ZIP code boundaries (STF3B) of the 1980 U.S. Census (22). Ecological indicators of residential radon concentrations were obtained from the Lawrence Berkeley National Laboratory (LBL) and the University of Pittsburgh.

Because long-term residential radon monitoring data in the United States is sparse, researchers at the LBL sought to estimate the annual average radon concentrations in the main living areas of homes by county using available data (23, 24). More specifically, both short-term

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and long-term indoor radon monitoring data were used along with a variety of geological, soil, meteorologic, and housing data to predict mean residential radon concentrations in a statistical model. Data from the EPA State Residential Radon Survey (SRRS), involving a random sample of approximately 60,000 short-term screening measurements from homes in the mid- to late 1980s, were combined with geological data, including estimated radium concentrations, and location of screening measurements within the home, as well as a short- to long-term radon monitoring data conversion factor estimated on the basis of the relationship between radon concentrations observed in the SRRS and in the U.S. National Residential Radon Survey (NRRS; 1989–1990), the only long-term residential radon survey conducted in the United States to date with representative data collected on nearly 5,700 homes in 125 counties (7), to predict annual average radon concentrations in homes in 3,079 U.S. counties.

At the University of Pittsburgh, Cohen (25, 26, 27) compiled a database of mean county-level residential radon concentrations for 1,601 U.S. counties based on a series of screening measurements made in a nonrandom sample of homes obtained from 3 independent data sources from the mid- to late 1980s: the University of Pittsburgh (272,000 measurements in 1,217 counties), the U.S. EPA (40,000 measurements in 1,141 counties), and measurements obtained from various other state-level sources (Florida, New Jersey, South Carolina, New Hampshire, New York, Iowa, Idaho, Ohio, Utah). Mean county-level residential radon concentrations were estimated by averaging all available data in each county with at least 10 available measurements. Data from the states of Florida, California, and Arizona were excluded in the final available county-level dataset by Cohen (25, 26) because of concerns surrounding the representativeness of data for individuals in states with high rates of migration (mainly due to retirement). Mean county-level residential radon concentrations were normalized to the data of the U.S. NRRS (7). Mean county-level residential radon concentrations from both data sources were linked to study participants as indicators of historic residential radon exposure.

Sociodemographic ecological covariates

Data on a range of social and demographic ecological covariates were compiled for 20,561 participant ZIP codes from the 1980 U.S. Census including median household income, and percent air conditioning, nonwhite, black, Hispanic, post–secondary education, unemployment, poverty, urban, moving, and homes with a well (22). The selection of ecological covariates was informed by previous air pollution studies in the CPS-II cohort (17, 18).

Air pollution

Average ambient sulfate (SO_4) data for 149 U.S. metropolitan statistical areas were previously compiled by members of our research team based on the data of the Inhalable Particle Monitoring Network and the National Aerometric Database for the years 1980 and 1981 (5, 17, 18). Sulfate air pollution was previously found to be associated with lung cancer mortality in the CPS-II cohort in the follow-up time period of interest here (28). Mean sulfate concentrations ranged from 1.4 to 15.6 $\mu g/m^3$ with an average value (SD) of 6.5 (2.8) $\mu g/m^3$.

Statistical analysis

Cox proportional hazards regression models were used to examine the independent effects of residential radon on lung cancer mortality by using SAS PROC PHREG (29). The baseline hazard in the proportional hazards models was stratified by 1-year age categories, sex, and race (white, black, other). Follow-up time since enrollment (1982) was used as the time axis. The survival times of those still alive at the end of follow-up were censored. Residential radon concentrations were examined in 3 ways: as a continuous variable (per 100 Bq/m^3), as a 7-level categorical variable where the reference category was <25 Bq/m^3 (10, 11), and as a dichotomous variable where the cutpoint was at the U.S. EPA residential radon guideline value (148 Bq/m^3).

Estimated HRs and 95% CIs were adjusted for a range of individual-level risk factors including education, marital status, body mass index (BMI), BMI squared, cigarette smoking status, cigarettes per day (current and former smokers), cigarettes per day squared (current and former smokers), years smoked (current and former smokers),

Table 1. Distribution of mean county-level residential radon concentrations (LBL; Bq/m^3), at enrollment (1982), by region, CPS-II cohort, United States

Radon measure	Total (n = 811,961)	Northeast (n = 170,281)	South (n = 257,243)	Midwest (n = 234,952)	West (n = 149,485)
Mean (SD)	53.5 (38.0)	58.3 (42.3)	35.6 (21.7)	73.7 (36.6)	46.9 (40.3)
Minimum	6.3	17.8	6.3	18.9	9.6
First quartile	26.6	33.7	19.6	42.9	18.1
Second quartile	41.4	46.2	28.9	66.2	27.4
Third quartile	70.3	62.9	43.3	100.6	62.2
Maximum	265.7	265.7	143.9	221.6	232.0
Counties $\geq$ 148 Bq/m^3 (%)	3.1	3.7	0.0	7.0	2.9

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Table 2. Distribution (*n*, %) of selected participant characteristics at enrollment (1982), CPS-II cohort, United States

Characteristic	*n* (%)	Mean (SD) radon (Bq/m^3)
Age, y		
<40	37,262 (4.6)	50.1 (35.4)
40–49	173,768 (21.4)	54.0 (37.9)
50–59	297,108 (36.6)	54.2 (38.5)
60–69	213,231 (26.3)	53.1 (38.0)
70–79	76,633 (9.4)	52.4 (37.5)
≥80	13,959 (1.7)	51.9 (36.9)
Race		
White	770,352 (94.9)	54.2 (38.2)
Black	29,832 (3.7)	40.2 (28.3)
Other	11,777 (1.5)	39.3 (32.1)
Sex		
Male	362,600 (44.7)	53.8 (38.2)
Female	449,361 (55.3)	53.2 (37.8)
Education		
<High school	106,668 (13.1)	55.2 (38.9)
High school	262,853 (32.4)	56.8 (39.5)
≥High school	442,440 (54.5)	51.1 (36.6)
BMI, kg/m^2		
<18.5	13,685 (1.7)	50.3 (36.1)
18.5–24.9	402,003 (49.5)	52.2 (37.2)
25–29.9	299,755 (36.9)	54.6 (38.6)
≥30	96,518 (11.9)	55.6 (39.1)
Marital status		
Single	25,564 (3.2)	51.7 (36.7)
Married	691,267 (85.1)	54.1 (38.2)
Other	95,130 (11.7)	49.7 (36.0)
Cigarette smoking status		
Never	375,087 (46.2)	55.5 (39.0)
Current	152,033 (18.7)	51.5 (36.4)
Former	203,253 (25.0)	51.2 (36.9)
Pipe/cigar only	81,588 (10.1)	53.4 (37.9)
Passive smoking		
Yes	512,908 (63.2)	53.9 (38.4)
No	299,053 (36.8)	53.2 (37.7)
Vegetable/fruit/fiber consumption[a]		
First quintile	135,142 (16.6)	52.9 (37.8)
Second quintile	148,206 (18.2)	53.7 (37.9)
Third quintile	152,650 (18.8)	54.0 (38.1)
Fourth quintile	157,772 (19.4)	54.0 (38.4)
Fifth quintile	150,677 (18.6)	53.8 (38.5)
Fat consumption[a]		
First quintile	139,237 (17.2)	50.4 (36.9)
Second quintile	148,677 (18.3)	52.6 (37.8)
Third quintile	151,545 (18.7)	54.2 (38.6)
Fourth quintile	152,749 (18.8)	55.1 (38.6)
Fifth quintile	152,239 (18.8)	55.9 (38.5)
Industrial exposures		
Yes	166,660 (20.5)	55.5 (39.4)
No	645,301 (79.5)	53.0 (37.6)
Occupational dirtiness index[a]		
Level 0	394,828 (48.6)	52.3 (37.4)
Level 1	110,177 (13.6)	53.2 (37.4)
Level 2	90,595 (11.2)	52.1 (37.6)
Level 3	38,461 (4.7)	53.4 (38.1)
Level 4	66,029 (8.1)	62.9 (42.1)
Level 5	36,240 (4.5)	54.3 (38.5)
Level 6	9,525 (1.2)	57.6 (39.0)

[a]Does not sum to total due to missing data.

years smoked squared (current and former smokers), age started smoking less than 18 years (current and former smokers), passive smoking (hours), quintiles of vegetable/fruit/fiber and fat intake, occupational exposures (asbestos, chemicals/acids/solvents, coal or stone dusts, coal tar/pitch/asphalt, formaldehyde, and diesel engine exhaust), as well as a previously developed "occupational dirtiness index" specifically designed for the CPS-II cohort (5, 17, 30). To adjust for potential confounding by geography, results were also adjusted for state of residence at enrollment. Potential confounding by previous lung disease, a related occupational "lung carcinogen index" (17, 30), and alternate adjustments for cigarette smoking status were examined. Further the potential confounding influence of various sociodemographic ecological variables and sulfate air pollution concentrations was also assessed. Because radon exposures experienced from 5 to 25 years in the past are thought to be most relevant for lung cancer (4), results were also examined in individuals who reported living in their same neighborhood for at least the past 5 years at enrollment. The functional form of the relationship between residential radon and lung cancer mortality was assessed by the supremum test (31).

Effect modification was assessed on both the additive and multiplicative scales. On the additive scale, estimates of the relative excess risk due to interaction, attributable proportion, and synergy index (and associated 95% CIs) were calculated according to the "MOVER" method for the analysis of 4 × 2 tables (32). On the multiplicative scale, interaction terms between radon and each risk factor were entered into proportional hazards models. Two-sided *P* values were calculated to assess the significance of the interaction term by using the likelihood ratio statistic. To assess the impact of attained age, time-dependent variables were constructed by allowing participants

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to be included in the risk set at each death time only if they met the attained age criteria for the model (<70, 70–79, or ≥80 years). The proportional hazards assumption was tested by assessing the significance of an interaction term between radon and follow-up time.

Finally, sensitivity analyses of the main findings were undertaken using generalized relative risk models for survival data (33), and using a random-effects Cox model originally developed for air pollution research in the CPS-II cohort (18, 34). General relative risk models for survival time data were fitted to compare relative risk estimates obtained from linear versus log-linear models using SAS PROC NLP (33). For each lung cancer death, a risk set consisting of all at-risk controls was constructed, and matched according to the stratification criteria of the North American combined analysis of residential radon case–control studies (10, 11): 5-year age groups, sex, cigarettes smoked per day (never smoker, 1–9, 10–19, 20–29, ≥30), duration of cigarette smoking (never smoker, 1–24, 25–34, 35–44, ≥45 years), and state of residence. Analyses were also repeated using the stratification criteria of the European combined analysis (8, 9): 5-year age groups, sex, smoking [never smokers, current smokers' age started smoking (<15, 15–17, 18–20, ≥21 years) and cigarettes per day (<15, 15–24, ≥25), former smokers' amount smoked (<15, 15–24, ≥25 cigarettes per day) and years smoked (<10, ≥10)], and state of residence.

All analyses were conducted by SAS version 9.2 (35) and our random-effects Cox regression program (18). Ethics approval was obtained from the Ottawa Hospital Research Ethics Board.

Results

Table 1 presents the distribution of mean county-level residential radon concentrations by region (LBL data). Overall, mean concentrations ranged from 6.3 to 265.7 Bq/m^3 (1 pCi/L = 37 Bq/m^3) with an average value (SD) of 53.5 (38.0) Bq/m^3. Mean county-level residential radon concentrations were higher in the Northeast and the Midwest with the lowest concentrations observed in the South. Mean radon concentrations exceeded the EPA guideline value in 3.1% of counties.

Table 2 presents the distribution of selected CPS-II participant characteristics at enrollment (1982). The majority of participants were between 40 and 69 years of age, had more than a high school education, and were never smokers. Mean county-level residential radon concentrations varied by participant characteristics including race and cigarette smoking status, where higher mean radon concentrations were observed in white participants and in never smokers as compared with black participants or ever smokers.

Table 3 presents adjusted HR (95% CI) for lung cancer mortality in relation to mean county-level residential radon concentrations. In the final fully adjusted model (2), lung cancer risk increased with increasing categorical radon concentrations. There was no significant departure from a linear relationship ($P = 0.23$), and a significant positive linear trend was observed ($P = 0.02$). A HR of 1.15 (95% CI, 1.01–1.31) was observed for lung cancer mortality per 100 Bq/m^3 increase in radon. Participants in counties with mean radon concentrations above the EPA guideline value (148 Bq/m^3) experienced a 34% (95% CI, 7–68) increase in risk for lung cancer death relative to those below the guideline value. Figure 1 shows adjusted HRs (95% CIs) for lung cancer mortality according to continuous and categorical indicators of radon concentrations. There was no evidence that the proportional hazards assumption was violated ($P > 0.05$).

Mean county-level residential radon concentrations were weakly correlated with sociodemographic ecological variables ($r = 0.12$ to -0.29). Results strengthened somewhat with the inclusion of 4 ecological variables in the model that were each independently associated with lung cancer mortality ($HR_{/100} = 1.18$; 95% CI, 1.04–1.35; Supplementary Table 1). Results were virtually unchanged with the inclusion of sulfate air pollution concentrations in the model in the 439,297 participants with data available on both radon and sulfate ($r = 0.06$; $HR_{/100} = 1.15$; 95% CI, 0.97–1.37).

Table 4 presents adjusted HRs for lung cancer mortality stratified according to selected participant characteristics at enrollment. There was no significant effect modification observed by cigarette smoking status, passive smoking, or sulfate air pollution concentrations on the additive (Supplementary Table 2) or multiplicative scale (Table 4). However, results did vary by geographic region ($P = 0.004$), with a significant positive association observed between radon and lung cancer mortality in the Northeast only ($HR_{/100} = 1.31$; 95% CI, 1.12–1.53; Table 4; Supplementary Figure 1). Results also strengthened

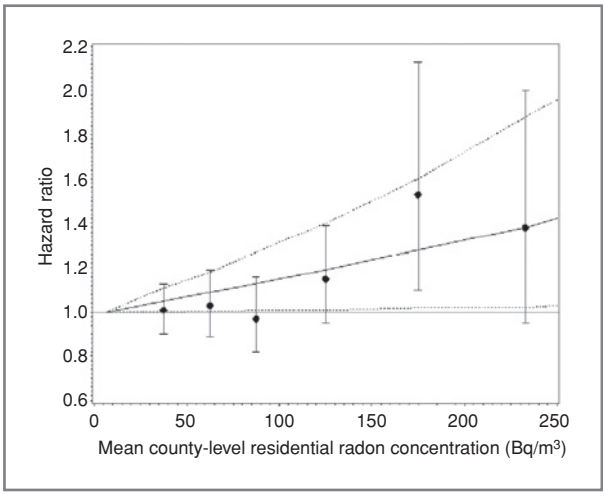

Figure 1. Adjusted HRs (95% CIs) for lung cancer mortality in relation to continuous (solid line, 95% CIs dashed lines) and categorical (reference category < 25 Bq/m^3) indicators of mean county-level residential radon concentrations (LBL) at enrollment (1982), follow-up (1982–1988), CPS-II cohort, United States.

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somewhat when restricting the analysis to individuals who reported living in the same neighborhood for at least the past 5 years at enrollment ($HR_{/100}$ = 1.19; 95% CI, 1.04–1.36).

Figure 2 presents a comparison of the exposure–response relationship using linear or log-linear general relative risk models. Little difference was observed. Results were also insensitive to the inclusion of clustering at the ZIP code–, county-, or state-level in the model with random effect variances being negligible ($\sim 10^{-6}$).

Mean county-level residential radon concentrations were strongly correlated between the LBL and Cohen [mean (SD) = 54.4 (32.5) Bq/m^3] data sources ($r = 0.89$), and similar findings were observed for lung cancer mortality (Supplementary Table 3). Using Cohen's data, in the final fully adjusted model (2), a HR of 1.22 (95% CI, 1.05–1.42) was observed per 100 Bq/m^3 increase in radon. Results were robust to the inclusion of various county-level sociodemographic risk factors compiled by Cohen (refs. 25, 26; results not shown). Results were also found to vary by geographic region ($P_{interaction} = 0.03$) with a significant positive association observed in the Northeast only ($HR_{/100}$ = 1.37; 95% CI, 1.13–1.67). On restriction of the analysis to participants who lived in 1,515 counties with data available from both the LBL and Cohen, overall HRs per 100 Bq/m^3 radon were 1.19 (95% CI, 1.04–1.36) and 1.22 (95% CI, 1.05–1.42), respectively.

Discussion

Overall, the findings of this large prospective study showed a positive association between residential radon and lung cancer mortality. A 15% increase in the risk of lung cancer mortality was observed per 100 Bq/m^3 increase in radon across the United States; in the Northeast the increase was 31%. Participants in counties with mean radon concentrations above the EPA guideline value (148 Bq/m^3) experienced a 34% increase in risk of lung cancer mortality relative to those below the guideline value. Findings were robust to adjustment of a variety of sociodemographic ecological risk factors and sulfate air pollution concentrations. Results showed no effect modification by cigarette smoking status or other risk factors on either the additive or multiplicative scales. Results were similar using either the radon data from the LBL (23, 24) or Cohen's data (25, 26, 27).

A major limitation of this study is the use of an area-based (county) indicator of residential radon concentrations. Previous studies using area-based indicators of residential radon have tended to follow an ecological design, linking mean county-level residential radon

Table 3. Adjusted HRs (95% CIs) for lung cancer mortality in relation to mean county-level residential radon concentrations (LBL; Bq/m^3) at enrollment (1982), follow-up 1982–1988, CPS-II cohort, United States

Radon concentration (Bq/m^3)	Lung cancer deaths	Person-years	Death rate[a]	Minimally adjusted HR (95% CI)[b]	Fully adjusted HR (1) (95% CI)[c]	Fully adjusted HR (2) (95% CI)[d]
Categorical						
<25	856	1,062,216.23	77.79	1.00	1.00	1.00
25-<50	1,312	1,767,001.74	75.59	0.97 (0.89–1.06)	0.96 (0.88–1.04)	1.01 (0.90–1.13)
50-<75	632	863,881.31	74.09	0.96 (0.86–1.06)	1.00 (0.90–1.10)	1.03 (0.89–1.19)
75-<100	274	428,430.94	64.47	0.82 (0.72–0.94)	0.90 (0.79–1.03)	0.97 (0.82–1.16)
100-<150	332	526,638.30	62.49	0.80 (0.70–0.90)	0.97 (0.85–1.10)	1.15 (0.95–1.39)
150-<200	53	62,903.34	83.53	1.07 (0.81–1.41)	1.27 (0.96–1.68)	1.53 (1.10–2.13)
≥200	34	42,084.48	82.20	1.07 (0.76–1.50)	1.24 (0.88–1.75)	1.38 (0.95–2.00)
P_{trend}[e]				*0.006*	*0.44*	*0.02*
EPA guideline value						
<148	3,396	4,631,071.50	73.31	1.00	1.00	1.00
≥148	97	122,084.84	80.82	1.10 (0.90–1.34)	1.24 (1.02–1.52)	1.34 (1.07–1.68)
Continuous						
per 100 Bq/m^3	3,493	4,753,156.34	73.49	0.88 (0.80–0.96)	1.03 (0.94–1.13)	1.15 (1.01–1.31)

[a]Per 100,000 person-years, age-standardized to the age distribution of the entire cohort.
[b]Age, race, gender stratified.
[c]Age, race, gender stratified and adjusted for education, marital status, BMI, BMI squared, cigarette smoking status, cigarettes per day, cigarettes per day squared, duration of smoking, duration of smoking squared, age started smoking, passive smoking, vegetable/fruit/fiber consumption, fat consumption, industrial exposures, occupation dirtiness index.
[d]As footnote c above, but also state stratified.
[e]Tests for linear trend used Wald χ^2 tests, with categorical medians modeled as ordinal variables.

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Table 4. Adjusted[a] HRs (95% CIs) for lung cancer mortality per 100 Bq/m^3 mean county-level residential radon concentrations (LBL) at enrollment (1982) stratified by selected risk factors, effect modification multiplicative scale, follow-up 1982–1988, CPS-II cohort, United States

Characteristic	*n*	Lung cancer deaths	Fully adjusted HR (2) (95% CI)	*P*
Age, y				
<65	633,932	1,922	1.12 (0.95–1.33)	
≥65	178,029	1,571	1.13 (0.93–1.38)	0.16
Attained age[b], y				
<70	615,247	2,228	1.18 (1.01–1.38)	
70–79	153,901	1,033	1.03 (0.80–1.32)	
≥80	42,813	232	0.88 (0.51–1.53)	0.56
Race				
White	770,352	3,332	1.14 (1.00–1.30)	
Other	41,609	161	1.77 (0.79–3.94)	0.10
Sex				
Male	362,600	2,423	1.14 (0.98–1.33)	
Female	449,361	1,070	1.17 (0.93–1.48)	0.59
Education				
<High school	106,668	946	1.20 (0.93–1.56)	
High school	262,853	1,115	0.95 (0.74–1.20)	
>High school	442,440	1,432	1.33 (1.09–1.64)	0.64
BMI, kg/m^2				
18.5–24.9	408,322	1,938	1.20 (1.00–1.43)	
25–29.9	302,762	1,208	1.12 (0.90–1.39)	
≥30	87,192	226	1.11 (0.67–1.84)	0.69
Marital Status				
Married	691,267	2,911	1.11 (0.96–1.27)	
Other	120,694	582	1.35 (0.96–1.90)	0.69
Cigarette Smoking				
Never Smoker	375,087	271	0.77 (0.47–1.25)	
Current	152,033	1,792	1.20 (1.00–1.44)	
Former	203,253	941	1.09 (0.84–1.41)	0.66
Cigarettes/day[c]				
1–19	128,212	479	1.14 (0.80–1.62)	
20–29	124,600	1,042	1.23 (0.97–1.57)	
≥30	102,474	1,212	1.15 (0.92–1.45)	0.67
Years smoked[c]				
1–34	250,099	723	1.11 (0.83–1.48)	
35–44	74,434	1,040	1.25 (0.99–1.59)	
≥45	30,753	970	1.21 (0.93–1.57)	0.59
Years since quitting[c]				
0	158,122	1,856	1.20 (1.01–1.44)	
1–9	57,601	434	1.06 (0.71–1.59)	
≥10	139,560	443	1.31 (0.90–1.91)	0.26
Age started smoking[c], y				
<18	140,360	1,397	1.26 (1.02–1.57)	
≥18	214,926	1,825	1.14 (0.93–1.40)	0.55
Passive smoking in home[d]				
Yes	54,532	24	1.20 (0.22–6.46)	
No	320,552	247	0.72 (0.43–1.21)	0.76
Vegetable/fruit/fiber consumption				
First tertile	313,799	1,766	1.08 (0.88–1.34)	
Second tertile	243,922	965	1.26 (0.98–1.60)	

(Continued on the following page)

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Table 4. Adjusted[a] HRs (95% CIs) for lung cancer mortality per 100 Bq/m^3 mean county-level residential radon concentrations (LBL) at enrollment (1982) stratified by selected risk factors, effect modification multiplicative scale, follow-up 1982–1988, CPS-II cohort, United States (Cont'd)

Characteristic	*n*	Lung cancer deaths	Fully adjusted HR (2) (95% CI)	*P*
Third tertile	254,240	762	1.03 (0.78–1.36)	0.55
Fat consumption				
First tertile	299,311	1,319	1.11 (0.87–1.42)	
Second tertile	258,329	1,005	1.12 (0.87–1.43)	
Third tertile	254,321	1,169	1.26 (1.00–1.59)	0.94
Industrial exposures				
Yes	166,660	920	1.05 (0.82–1.35)	
No	645,301	2,573	1.17 (1.01–1.37)	0.28
Occupational dirtiness				
Yes	351,027	1,915	1.04 (0.86–1.27)	
No	394,828	1,578	1.24 (1.02–1.50)	0.33
Asthma				
Yes	36,679	157	1.12 (0.43–2.93)	
No	775,282	3,336	1.15 (1.01–1.31)	0.40
Hay fever				
Yes	97,141	254	1.35 (0.79–2.32)	
No	714,820	3,239	1.12 (0.98–1.28)	0.56
Chronic bronchitis/emphysema				
Yes	39,016	611	0.99 (0.68-1.43)	
No	772,945	2,882	1.15 (1.00-1.33)	0.25
Region[e]				
Northeast	170,281	710	1.31 (1.12–1.53)	
South	257,243	1,246	0.95 (0.73–1.24)	
Midwest	234,952	954	1.07 (0.89–1.27)	
West	149,485	583	0.83 (0.65–1.04)	0.004
Sulfate air pollution[f]				
$<$6.4 μg/m^3	221,453	897	1.29 (0.94–1.77)	
$\geq$6.4 μg/m^3	217,844	946	1.08 (0.88–1.32)	0.57

[a]Age, race, gender, state stratified and adjusted for education, marital status, BMI, BMI squared, cigarette smoking status, cigarettes per day, cigarettes per day squared, duration of smoking, duration of smoking squared, age started smoking, passive smoking, vegetable/fruit/fiber consumption, fat consumption, industrial exposures, occupation dirtiness index where appropriate.

[b]Race, gender, state stratified and adjusted for cigarette smoking status, cigarettes per day, cigarettes per day squared, duration of smoking, duration of smoking squared, age started smoking only.

[c]Ever smokers. Additional participants with missing information were excluded for years since quitting. *P* values calculated with never and ever smokers.

[d]Never smokers.

[e]HRs and 95% CIs by region unadjusted for state.

[f]Participants with missing sulfate information excluded. Cutpoints were based on median participant sulfate value.

concentrations with county-level lung cancer death rates with conflicting results observed. In the ecological study of Cohen (25), a strong negative association between radon and lung cancer was reported. However, because there was a negative correlation between smoking prevalence and radon concentrations at the ecological level, such studies are subject to confounding by cigarette smoking (36, 37). There are also other potential limitations for the studies such as cross-level bias (36, 37). Here, mean county-level residential radon concentrations were linked to individuals in the CPS-II cohort and with detailed adjustment for a variety of individual-level risk factors, including cigarette smoking; positive associations between radon and lung cancer mortality were observed.

Mean county-level residential radon concentrations were linked to CPS-II participants as indicators of historic residential radon exposure. Radon data were estimated either on the basis of available short- and long-term monitoring data, as well as a variety of geological, meteor-

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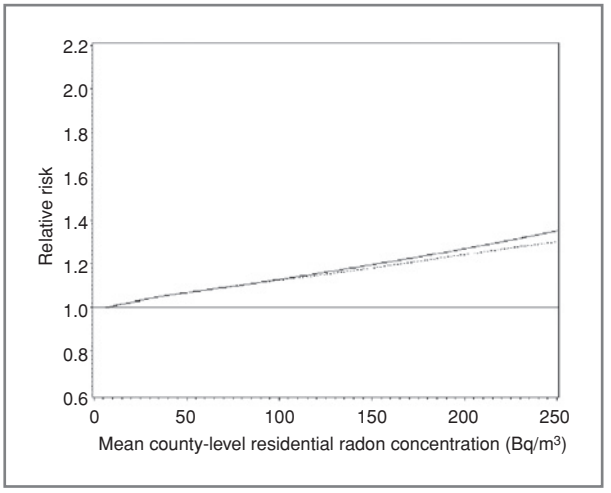

Figure 2. Comparison of linear and log-linear general relative risk models for the association between lung cancer mortality and mean county-level residential radon concentrations (LBL) at enrollment (1982), follow-up (1982–1988), CPS-II cohort, United States. According to the stratification criteria of Krewski and colleagues (10, 11) little difference in relative risk estimates obtained from either a linear (ERR = 1 + 0.00121 X; dotted line) or log-linear [Cox regression analysis; RR = exp(0.00119 X); solid line] model was observed. Relative risk estimates were also similar using the stratification criteria of Darby and colleagues [refs. 8, 9; ERR = 1 + 0.00108 X, RR = exp(0.00109 X)].

ologic, and housing data (LBL), or on the basis of a series of aggregated short-term screening measurements from several different sources normalized to the data of the U.S. NRRS (Cohen). Estimates of radon concentrations in individual homes are subject to a number of sources of uncertainty, including detector measurement error, variation due to detector placement, and changes in radon concentrations over time (seasonal and year-to-year variability; refs. 4, 38–43). However, these measurement errors are most likely to be nonsystematic. Mean county-level residential radon concentrations are also subject to sampling error (44). Residential radon concentrations can exhibit considerable variability due to individual housing characteristics (building materials, presence of a basement, age of construction, ventilation, water supply), soil permeability, and underlying geology (4, 7, 42, 45). The extent to which ecologic indicators of residential radon exposures are representative of the exposure experience of individuals in the CPS-II cohort is also not known.

Although it is difficult to predict the total potential cumulative impact of such errors on the results observed in the current study, the observed relative risk estimates may be subject to some degree of downward bias (38, 46, 47). Mallick and colleagues (48) examined the impact of adjusting for plausible levels of exposure measurement error associated with ecological measures of ambient air pollution under a cohort design and found the relative risk estimates were subject to downward bias. Jerrett and colleagues (49) observed that air pollution mortality relative risk estimates increased by nearly 3-fold in research in the CPS-II cohort examining within- as opposed to between-city contrasts in fine particulate matter concentrations.

Two studies (50, 51) have directly examined the impact of using either individual (measured in subject's homes) or ecological (aggregating individual-level measures) indicators of residential radon concentrations in case–control studies. Findings using ecological measures of radon resulted in notably less precise relative risk estimates, compared with those based on individual measures of radon. Results using ecological radon measures also required the inclusion of an additional indicator for geographical location, which takes into account broad spatial patterns in both radon concentrations and risk factors for lung cancer, for compatibility with results using individual data.

Despite these uncertainties, our findings are consistent with results obtained from combined analyses of residential case–control studies (8–11). In North America, ERR per 100 Bq/m^3 radon were found to range from 11% (95% CI, 0–28) overall to 21% (95% CI, 3–52) in subjects with complete historic radon data and limited residential mobility. In Europe, results ranged from 8% (95% CI, 3–16) overall to 16% (95% CI, 5–31) when adjusting for exposure measurement error. A pooled analysis of 2 residential radon case–control studies conducted in China reported an ERR of 13% (95% CI, 1–36) at 100 Bq/m^3 (52). A recent prospective study in Spain also reported elevated, although imprecisely determined, lung cancer risks for subjects with higher residential radon concentrations; however, only 5 lung cancer cases were observed in this cohort (12).

Results for the United States as a whole were largely due to a significant positive association between radon and lung cancer observed in the Northeast. Although this could conceivably be an artifact of the choice of administrative data boundaries, this finding may also be due to higher residential radon concentrations in the Northeast and other factors unaccounted for in the analysis including possible regional differences in time spent at home (53). Although there is no information on time-activity patterns for characterizing time spent at home for individuals in the CPS-II cohort, results from the U.S. National Human Activity Pattern Survey showed that time spent in a residence was consistent across all 10 regions of the United States (54). However, the Iowa Radon Lung Cancer Study reported that time spent at home varied by age from a low of 69.4% in women ages 50 to 59 years up to 81.6% in women ages 80 years or more (55); differences in time spent at home were also observed according to number of children in this study.

Updated information on neither cigarette smoking status nor residential mobility from enrollment was available for individuals in the full CPS-II cohort. In an attempt to control for changes in cigarette smoking over time, a major risk factor for lung cancer, it was decided *a priori* to restrict the follow-up time period for the analysis

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to the first 6 years of follow-up only (19). There was no detailed information on address history prior to enrollment; however, study participants did report living in their current neighborhood at enrollment for a mean (SD) of 19.4 (14.1) years. Radon–lung cancer associations strengthened somewhat when restricting the analysis to individuals who reported living in the same neighborhood for at least the past 5 years ($HR_{/100} = 1.19$; 95% CI, 1.04–1.36). No information was available on lung cancer histologic subtype.

Mean county-level residential radon concentrations for black individuals in the CPS-II cohort (mean = 40.2 Bq/m^3) tended to be lower than those for white individuals (mean = 54.2 Bq/m^3). This could be because of the tendency for black individuals in the cohort to live in ZIP codes that were more highly urbanized, where radon concentrations tend to be lower (8, 9). Urban areas also tend to have higher smoking rates (8, 9).

Few studies have examined potential interrelationships between residential radon and other inhalable environmental agents. Lagarde and colleagues (56) reported that residential radon may be a more important risk factor for lung cancer in never smokers with a smoking spouse. However, in the combined analysis of European case–control studies, lung cancer risk did not vary according to spousal smoking status (8, 9). In China, increased lung cancer risk associated with radon did not vary according to level of indoor smokiness (52). Brauner and colleagues (57) reported that the association between residential radon and childhood leukemia in Denmark strengthened in the presence of exposure to traffic-related air pollution, although further research is needed to clarify this finding. Here the association between county-level residential radon concentrations and lung cancer mortality did not vary according to exposure to passive cigarette smoke or ambient sulfate concentrations.

In conclusion, this large prospective study showed positive associations between ecological indicators of residential radon and lung cancer mortality. Current data suggest that residential radon is the second leading cause of lung cancer after tobacco smoking (3). The results of this study further support the need for continued efforts to reduce radon concentrations in homes to the lowest possible level (58).

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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SUPPLEMENTARY MATERIAL

Supplementary Table 1. Correlation between mean county-level residential radon concentrations (LBL) and 1980 zip code-level ecological covariates and adjusted[*] HRs (95% CIs) for lung cancer mortality per 100 Bq/m^3 radon at enrollment (1982) adjusting for each ecological covariates individually or in combination, follow-up 1982-1988, CPS-II cohort, US (n=811,373).

Ecological covariate	Correlation coefficient	Fully-adjusted HR (2) (95% CI)[*]
Fully-adjusted HR, individual level covariates only	-	1.15 (1.01-1.31)
+ Median household income	-0.06	1.14 (1.01-1.30)
+ % Air conditioning	-0.11	1.15 (1.01-1.31)
+ % Non-white	-0.27	1.15 (1.01-1.31)
+ % Non-white (incl. hisp)	-0.29	1.15 (1.01-1.31)
+ % Black	-0.23	1.15 (1.01-1.32)
+ % Non-hispanic black	-0.23	1.15 (1.01-1.32)
+ % Hispanic	-0.15	1.15 (1.01-1.31)
+ % Population with post-secondary education	-0.11	1.15 (1.01-1.31)
+ % Adults with post-secondary education	-0.10	1.15 (1.01-1.31)
+ % Unemployment	-0.02	1.17 (1.03-1.33)
+ % Poverty	-0.07	1.15 (1.01-1.31)
+ % Urban	-0.15	1.15 (1.01-1.31)
+ % Mover	-0.07	1.16 (1.02-1.33)
+ % Mover (outside county)	-0.07	1.17 (1.03-1.33)
+ % Well	0.12	1.14 (1.01-1.30)
+ adjusting for all ecological covariates independently associated with lung cancer mortality[†]	-	1.18 (1.04-1.35)
+ adjusting for six ecological covariates selected *a priori*[‡]	-	1.16 (1.01-1.32)

[*] Age, race, gender, state stratified and adjusted for education, marital status, body mass index, body mass index squared, cigarette smoking status, cigarettes per day, cigarettes per day squared, duration of smoking, duration of smoking squared, age started smoking, passive smoking, vegetable/fruit/fiber consumption, fat consumption, industrial exposures, occupation dirtiness index.

[†] Ecological variables included here were: % population with post-secondary education, % unemployment, % poverty, and % mover (outside county).

[‡] Ecological variables included here were: median household income, % air conditioning, % non-white, % population with post-secondary education, % poverty, and % unemployment.

Supplementary Table 2. Three measures of additive interaction* (95% CIs) between mean county-level residential radon concentration (LBL), cigarette smoking, and other inhalable environmental agents for lung cancer mortality, follow-up 1982-1988†, CPS-II cohort, US.

	RERI (95% CI)	AP (95% CI)	S (95% CI)
Overall			
Cigarette Smoking	1.26 (-0.24, 3.03)	0.12 (-0.03, 0.24)	1.15 (0.97, 1.36)
SO_4	0.15 (-0.46, 0.66)	0.13 (-0.49, 0.45)	-
Industrial Exposures	-0.06 (-0.34, 0.24)	-0.05 (-0.35, 0.14)	0.78 (0.25, 2.47)
Northeast Region			
Cigarette Smoking	2.41 (-0.42, 6.34)	0.23 (-0.06, 0.41)	1.33 (0.96, 1.86)
SO_4	-0.68 (-4.22, 0.68)	-0.53 (-3.50, 0.45)	0.30 (0.02, 4.09)
Industrial Exposures	-0.26 (-0.87, 0.43)	-0.23 (-1.19, 0.14)	0.33 (0.01, 17.03)
Never Smokers			
SO_4	1.64 (-0.11, 5.70)	0.74 (-0.36, 1.42)	-
Industrial Exposures	-0.41 (-1.52, 1.17)	-0.38 (-3.28, 0.13)	-
Passive Smoking in Home	-0.30 (-1.27, 1.93)	-0.42 (-8.56, 2.12)	-

* Relative excess risk due to interaction (RERI), attributable proportion (AP), synergy index (S)

† Exposures categorized as: mean county-level residential radon concentrations: <100 Bq/m^3, ≥100 Bq/m^3; cigarette smoking: never, ever; sulfate air pollution concentration: <6.4 μg/m^3, ≥6.4 μg/m^3, industrial exposures: yes, no; passive smoking in home: none, any. Results were repeated with mean county-level residential radon concentrations dichotomized as: <150 Bq/m^3, ≥150 Bq/m^3 with similar results found. Cox regression models were fitted with the baseline hazard stratified by age, race, gender, and state, and adjusted for education, marital status, body mass index, body mass index squared, cigarette smoking status, cigarettes per day, cigarettes per day squared, duration of smoking, duration of smoking squared, age started smoking, passive smoking, vegetable/fruit/fiber consumption, fat consumption, industrial exposures, occupation dirtiness index where appropriate.

Supplementary Table 3. Adjusted HRs (95% CIs) for lung cancer mortality in relation to mean county-level residential radon concentrations (Cohen) (Bq/m^3) at enrollment (1982), follow-up 1982-1988, CPS-II cohort, US (n = 610,577).

Radon concentration (Bq/m^3)	No. lung cancer deaths	Person-years	Death rate*	Minimally-adjusted HR (95% CI)†	Fully-adjusted HR (1) (95% CI)‡	Fully-adjusted HR (2) (95% CI)§
Categorical						
<25	360	470,403.25	77.79	1.00	1.00	1.00
25-<50	1,074	1,515,618.14	71.57	0.91 (0.81-1.02)	0.94 (0.84-1.06)	0.99 (0.86-1.14)
50-<75	617	884,695.21	68.98	0.88 (0.77-1.00)	0.98 (0.86-1.11)	1.04 (0.89-1.23)
75-<100	276	383,341.29	70.31	0.89 (0.76-1.04)	1.02 (0.87-1.19)	1.13 (0.93-1.38)
100-<150	173	248,351.27	69.40	0.88 (0.74-1.06)	1.01 (0.84-1.21)	1.22 (0.99-1.52)
150-<200	55	66,199.23	81.59	1.04 (0.78-1.38)	1.25 (0.94-1.66)	1.43 (1.04-1.96)
≥200	6	7,844.24	71.35	0.89 (0.40-2.00)	1.16 (0.52-2.61)	1.22 (0.53-2.78)
p for trend‖				*0.56*	*0.08*	*0.002*
EPA Guideline Value						
<148	2,498	3,498,031.58	71.45	1.00	1.00	1.00
≥148	63	78,421.04	75.67	1.10 (0.86-1.41)	1.25 (0.97-1.60)	1.27 (0.97-1.66)
Continuous**						
per 100 Bq/m^3	2,561	3,576,452.62	71.61	0.95 (0.84-1.07)	1.09 (0.97-1.23)	1.22 (1.05-1.42)

* per 100 000 person-years, age-standardized to the age distribution of the entire cohort.

† Age, race, gender stratified.

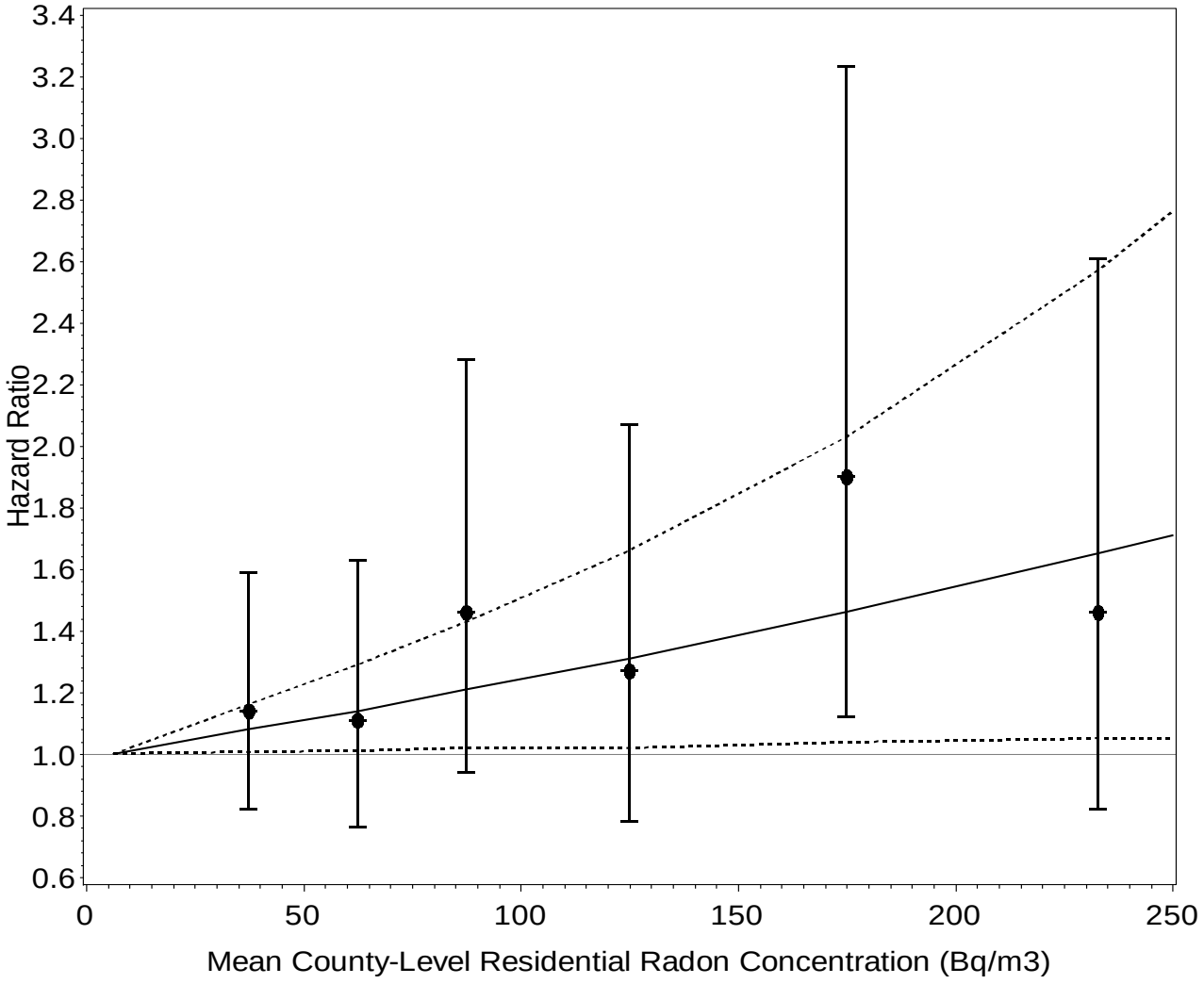
‡ Age, race, gender stratified and adjusted for education, marital status, body mass index, body mass index squared, cigarette smoking status, cigarettes per day, cigarettes per day squared, duration of smoking, duration of smoking squared, age started smoking, passive smoking, vegetable/fruit/fiber consumption, fat consumption, industrial exposures, occupation dirtiness index.

§ As (1) above, but also including stratification by state.

‖ tests for linear trend used Wald chi-square tests, with categorical medians modeled as ordinal variables.

** HRs varied by region (*p* value for interaction = 0.03). HRs per 100 Bq/m^3 for the Northeast, South, Midwest, and West of 1.37 (95% CI 1.13-1.67), 0.96 (95% CI 0.72-1.29), 1.07 (95% CI 0.87-1.31), and 0.80 (95% CI 0.54-1.20) were observed respectively.

Supplementary Figure 1. Adjusted HRs (95% CIs) for lung cancer mortality in relation to continuous (solid line, 95% CIs dashed lines) and categorical (reference category < 25 Bq/m^3) indicators of mean county-level residential radon concentrations (LBL) at enrollment (1982), follow-up 1982-1988, Northeast region, CPS-II cohort, US.


Hazard Ratio
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0
50
100
150
200
250
Mean County-Level Residential Radon Concentration (Bq/m3)

4. ARTICLE 2

Turner MC, Krewski D, Chen Y, Pope CA III, Gapstur SM, Thun MJ. Radon and COPD mortality in the American Cancer Society cohort [published online ahead of print October 17, 2011]. Eur Resp J 2011;erj00582-2011; doi:10.1183/09031936.0005811.

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5. ARTICLE 3

Turner MC, Krewski D, Chen Y, Pope CA III, Gapstur SM, Thun MJ. Radon and non-respiratory mortality in the American Cancer Society cohort. Unpublished manuscript, 2011.

Radon and Non-Respiratory Mortality in the American Cancer Society Cohort

Michelle C. Turner, Daniel Krewski, Yue Chen, C. Arden Pope III, Susan M. Gapstur, Michael J. Thun

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ABBREVIATIONS

Body mass index (BMI)

Cancer Prevention Study-II (CPS-II)

Chronic obstructive pulmonary disease (COPD)

Confidence interval (CI)

Environmental Protection Agency (EPA)

Hazard ratio (HR)

Lawrence Berkeley National Laboratory (LBL)

National Death Index (NDI)

ABSTRACT

Radon is a known cause of human lung cancer. Previously, we observed a significant positive association between mean county-level residential radon concentrations and lung cancer mortality in the Cancer Prevention Study-II (CPS-II), a large prospective study of nearly 1.2 million participants recruited in 1982 by the American Cancer Society. There was also a significant positive association with mortality from chronic obstructive pulmonary disease (COPD). Since it is unclear whether radon is associated with mortality from other malignant or non-malignant disease, we examined the association between radon and non-respiratory mortality in the CPS-II. Mean county-level residential radon concentrations (mean (SD) = 53.5 (38.0) Bq/m^3) were linked to participants based on their ZIP code at enrollment. Cox proportional hazards regression models were used to estimate adjusted hazard ratios and 95% confidence intervals for all cause (excluding respiratory mortality) and cause-specific mortality associated with radon concentrations. A total of 811,961 participants in 2,754 counties were analyzed, including 265,477 deaths through 2006. There were no clear associations between radon and non-respiratory mortality in the CPS-II. These findings suggest that residential radon is not associated with any other mortality beyond lung cancer or COPD.

Key words: radon; neoplasms; cardiovascular diseases; cohort studies; United States

Radon is a naturally occurring gas formed during the radioactive decay of uranium-238. Radon further decays into a series of daughters, some of which emit alpha-particles capable of damaging cellular DNA (1). Radon is found in the indoor and outdoor air, soil, and water, and accumulates in confined spaces, including in underground mines as well as in the basement and lower living areas of homes (2). In 1988, radon and its decay products were designated a human lung carcinogen, based on experimental evidence as well as on studies of underground miners exposed to high levels of radon gas before effective ventilation of mines (3). Recent combined analyses of data from residential radon case-control studies conducted in North America and Europe have strengthened the epidemiological evidence linking residential radon exposure and lung cancer (4-8).

Although there have been a number of residential radon case-control studies, there have been few prospective studies in the general population. We recently observed a significant positive association between mean county-level residential radon concentrations and lung cancer mortality in the American Cancer Society Cancer Prevention Study-II (CPS-II) (9). Each 100 Bq/m^3 increase in radon was associated with a 15% (95% confidence interval (CI): 1, 31) increase in risk for lung cancer death. Participants with mean radon concentrations above the guideline value of the US Environmental Protection Agency (EPA) (4 pCi/L) (equivalent to 148 Bq/m^3) experienced a 34% (95% CI 7, 68) increased risk of lung cancer death relative to those below the guideline value.

While it is conceivable that radon may affect other malignant or non-malignant diseases besides lung cancer, the epidemiological evidence in this regard is sparse (10, 11). A pooled analysis of data from 11 cohorts of underground miners reported excess mortality from stomach cancer, liver cancer, and leukemia that were unrelated to radon exposure (12). A French cohort study showed an increased mortality from lung and kidney cancer in uranium miners that was not associated with cumulative radon exposure (13). There was also a significant positive association between radon and mortality

from cerebrovascular disease in this study; however, potential confounding by circulatory system disease risk factors could not be assessed (14). Mortality from multiple myeloma and non-Hodgkin's lymphoma was not related to cumulative radon exposure in the Colorado Plateau cohort (15). There was no strong evidence for an association between radon and death from all extrapulmonary cancers in the German uranium miners cohort (16). However, radon was positively associated with incident chronic lymphocytic leukemia (relative risk = 1.98, 95% CI 1.10, 3.59) in Czech uranium miners (17).

Although ecologic analyses have reported positive associations between residential radon and leukemia, case-control studies have not supported a link (18). Excesses in total and site-specific (colorectal, breast, kidney, and prostate) cancer incidence were observed in census tracts with elevated groundwater uranium concentrations in a South Carolina study; however there were no individual-level risk factor data (19). No association between radon or other drinking water radionuclides and leukemia, stomach, bladder, or kidney cancer was observed in Finland (20-22). In the CPS-II, we recently observed a significant positive association between mean county-level residential radon concentrations and chronic obstructive pulmonary disease (COPD) mortality (hazard ratio (HR) per each 100 Bq/m^3 = 1.13, 95% CI 1.05, 1.21) (23).

This paper examines the association between residential radon and non-respiratory mortality in the CPS-II. CPS-II is a large, well-established, prospective study, with detailed individual-level risk factor data collected at enrollment. It provides a unique resource to evaluate whether residential exposure to radon is associated with other causes of death. Some of the results presented in this report were previously reported in an abstract (24).

MATERIALS AND METHODS

Study Population

CPS-II is a prospective study of nearly 1.2 million participants enrolled in 1982. Participants, largely friends and family members of volunteer recruiters, were recruited in all 50 US states, the District of Columbia, and Puerto Rico. Participants were at least 30 years of age and had at least one family member aged 45 years or older. A four-page self-administered questionnaire was completed at enrollment that captured data on a range of demographic, lifestyle, and medical factors, including ZIP code of residence at enrollment.

Follow-up for vital status is conducted every two years. In 1984, 1986, and 1988, vital status was obtained from volunteer recruiters and death certificate information. From 1989, follow-up is conducted through computerized linkage to the National Death Index (NDI) (25). In September of 1988, follow-up was terminated for 2,840 (0.2%) participants due to insufficient information to link to the NDI. Over 99% of all known deaths have been assigned a cause. Deaths were classified by the underlying cause according to the International Classification of Disease 9 and 10 (26, 27).

Of the total 1,184,881 participants, participants with missing vital status (419), prevalent cancer (except non-melanoma skin cancer) at enrollment (82,329), missing ZIP code (99,479) or county data (22,872), or missing data on radon (below) (5,836), or any other individual-level covariates of interest (161,985) were excluded. A total of 811,961 participants residing in 2,754 counties were retained for analysis. Through 2006, a total of 314,311 deaths in 16,554,617 person-years of follow-up were observed, of which 265,477 were due to causes other than respiratory mortality.

Ecological Measures of Residential Radon

Participants were assigned to a primary county of residence based on the five-digit ZIP code provided at enrollment, according to the boundaries (STF3B) of the 1980 US Census (28). Two different ecological measures of residential radon concentrations were linked to study participants as indicators of historical radon exposure. A detailed description is provided elsewhere (9). In brief, researchers at the Lawrence Berkeley National Laboratory (LBL) used a variety of short- and long-term indoor radon monitoring data (mid to late 1980's) along with a variety of geological, soil, meteorological, and housing data, to predict the annual average radon concentrations in the main living areas of homes in 3,079 US counties using an empirical statistical model (29, 30). Cohen (31-33) compiled a series of screening measurements in a nonrandom sample of homes in 1,601 US counties made by researchers at the University of Pittsburgh, the US EPA, and other state-level sources (mid 1980s to the early 1990s). Counties with less than 10 measurements or states with high rates of migration (Florida, California, Arizona) were excluded and data were normalized to the long-term US National Residential Radon Survey (2). County-level residential radon concentrations (LBL) ranged from 6.3 to 265.7 Bq/m^3 (1 pCi/L = 37 Bq/m^3), with a mean value (SD) of 53.5 (38.0) Bq/m^3.

Statistical Analysis

Cox proportional hazards regression models were used to examine the independent effects of radon on all cause (excluding respiratory mortality) and cause-specific mortality (34). The baseline hazard in the proportional hazards model was stratified by one-year age categories, sex, race (white, black, other), and state of residence. Follow-up time since enrollment (1982) was used as the time axis. The survival times of those still alive at the end of follow-up were censored.

Estimated HRs and 95% CIs were adjusted for a range of individual-level risk factors including education, marital status, body mass index (BMI), BMI squared, cigarette smoking status and intensity (each of cigarettes per day, cigarettes per day squared, years smoked, and years smoked squared), age started smoking less than 18 years, passive smoking (home, work, other), quintiles of vegetable/fruit/fiber and fat intake, occupational exposures (asbestos, chemicals/acids/solvents, coal or stone dusts, coal tar/pitch/asphalt, formaldehyde, diesel engine exhaust), and an 'occupational dirtiness index' (9, 23, 35).

The proportional hazards assumption was tested by assessing the significance of an interaction term between radon and follow-up time. Analyses were conducted using SAS version 9.2 (36). Ethics approval was obtained from the Ottawa Hospital Research Ethics Board.

RESULTS

The distribution of participant characteristics at enrollment is presented in Table 1. The majority of participants were between 40 and 69 years of age, had more than a high school education, and were never smokers. There was a tendency for higher radon concentrations to be observed among participants who were white, had a lower level of educational attainment, a higher BMI, or were never smokers. The highest radon concentrations were observed in the Northeast and the lowest in the South.

Table 2 presents adjusted HRs (95% CIs) for all cause (excluding respiratory mortality) and cause-specific mortality in relation to each 100 Bq/m^3 increase in radon concentrations (LBL). There was no association between radon and all non-respiratory mortality (HR per each 100 Bq/m^3 = 0.98, 95% CI 0.97, 1.00). There was also no association between radon and any other specific cause of death

category, with the exception of mortality from salivary gland tumors where a significant inverse association was observed (HR per each 100 Bq/m^3 = 0.24, 95% CI 0.07, 0.85). There was no evidence that the proportional hazards assumption was violated for any specific cause of death category ($p \geq 0.05$), with the exception of ischemic heart disease (IHD) with HRs of 0.91 (95% CI 0.85, 0.97) (1982-1989), 0.95 (95% CI 0.90, 1.00) (1990-1999), and 1.04 (95% CI 0.99, 1.09) (2000-2006) observed per each 100 Bq/m^3 radon.

Results using Cohen's data are presented in Supplementary Table 1. There was no association between radon and all cause mortality (excluding lung cancer and respiratory mortality) (HR per each 100 Bq/m^3 = 0.99, 95% CI 0.97, 1.01). However, significant positive associations were observed between radon and mortality from cerebrovascular disease (HR per each 100 Bq/m^3 = 1.07, 95% CI 1.01, 1.14) and benign neoplasms (HR per each 100 Bq/m^3 = 1.69, 95% CI 1.05, 2.75). There were also significant inverse associations observed for mortality from hypertensive disease (HR per each 100 Bq/m^3 = 0.78, 95% CI 0.66, 0.91) and stomach cancer (HR per each 100 Bq/m^3 = 0.74, 95% CI 0.59, 0.93).

DISCUSSION

We previously observed significant positive associations between mean county-level residential radon concentrations and mortality from both lung cancer and COPD in the CPS-II (9, 23). Results from the present study provided no clear evidence of associations between radon and all other non-respiratory mortality. Although there was a significant inverse association between radon and mortality from cancer of the salivary gland (LBL), this finding was based on a small number of deaths, has little biological plausibility, and may be due to chance. Some significant increases in

mortality (cerebrovascular disease, benign neoplasms) with radon exposure were observed with Cohen's data; however they were not replicated in the larger LBL cohort.

Strengths of this study include its large prospective design, the ability to examine multiple endpoints other than lung cancer, and detailed individual-level risk factor data collected at enrollment. Limitations include its mortality-based design and the use of ecological measures of radon concentrations. Radon data were estimated in a statistical model (LBL) or were based on a nonrandom series of short-term measurements (Cohen). There may be errors in radon measurements, seasonal and yearly variability, as well as within-county variation in residential radon concentrations (37-39). There were also no time-activity data (6, 7, 40). However, estimates of increased lung cancer mortality in the CPS-II were compatible with estimates obtained in combined analyses of residential case-control studies (9). There were also no updated data on cigarette smoking or residential mobility available beyond enrollment. However, with a mean age of 57 years at enrollment, it is unlikely that participants would begin smoking during follow-up. Radon concentrations and cigarette smoking are also inversely related (4, 5, 9, 41).

These findings suggest residential radon is not associated with mortality beyond lung cancer or COPD. Although the lung and respiratory tract experience the highest doses of ionizing radiation from the inhalation of radon and its decay products, the kidney, bone, bone marrow, and breast are also exposed, however to a substantially lesser degree, through the entrance of radon decay products into the blood stream (10, 42). There are also exposures to the stomach (ingestion) and skin (external radiation). However, any effect of radon on non-respiratory endpoints is likely small. Further research examining associations between radon and non-respiratory disease incidence may be useful to further confirm these mortality-based findings.

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Author affiliations: Faculty of Graduate and Postdoctoral Studies, University of Ottawa, Ottawa, Ontario, Canada (Michelle C. Turner); McLaughlin Center for Population Health Risk Assessment, Institute of Population Health, University of Ottawa, Ottawa, Ontario, Canada (Michelle C. Turner, Daniel Krewski); Department of Epidemiology and Community Medicine, Faculty of Medicine, University of Ottawa, Ottawa, Ontario, Canada (Daniel Krewski, Yue Chen); Risk Sciences International, Ottawa, Ontario, Canada (Daniel Krewski); Department of Economics, Brigham Young University, Provo, Utah, United States (C. Arden Pope III); Epidemiology Research Program, American Cancer Society, Atlanta, Georgia, United States (Susan M. Gapstur, Michael J. Thun)

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Table 1. Distribution (%) of Selected Participant Characteristics at Enrollment (1982), CPS-II Cohort, US.

Characteristic	No. (%)	Mean (SD) radon (Bq/m^3) (LBL)
Overall	811,961 (100)	53.5 (38.0)
Age at Enrollment (years)		
<40	37,262 (4.6)	50.1 (35.4)
40-49	173,768 (21.4)	54.0 (37.9)
50-59	297,108 (36.6)	54.2 (38.5)
60-69	213,231 (26.3)	53.1 (38.0)
70-79	76,633 (9.4)	52.4 (37.5)
80+	13,959 (1.7)	51.9 (36.9)
Race		
White	770,352 (94.9)	54.2 (38.2)
Black	29,832 (3.7)	40.2 (28.3)
Other	11,777 (1.5)	39.3 (32.1)
Sex		
Male	362,600 (44.7)	53.8 (38.2)
Female	449,361 (55.3)	53.2 (37.8)
Education		
Less than high school	106,668 (13.1)	55.2 (38.9)
High school	262,853 (32.4)	56.8 (39.5)
More than high school	442,440 (54.5)	51.1 (36.6)
BMI (kg/m^2)		
<18.5	13,685 (1.7)	50.3 (36.1)
18.5-24.9	402,003 (49.5)	52.2 (37.2)
25-29.9	299,755 (36.9)	54.6 (38.6)
30+	96,518 (11.9)	55.6 (39.1)
Marital Status		
Single	25,564 (3.2)	51.7 (36.7)
Married	691,267 (85.1)	54.1 (38.2)
Other	95,130 (11.7)	49.7 (36.0)
Cigarette Smoking Status		
Never	375,087 (46.2)	55.5 (39.0)
Current	152,033 (18.7)	51.5 (36.4)
Former	203,253 (25.0)	51.2 (36.9)
Pipe/cigar only	81,588 (10.1)	53.4 (37.9)
Region		
Northeast	170,281 (21.0)	58.3 (42.3)
South	257,243 (31.7)	35.6 (21.7)
Midwest	234,952 (28.9)	73.7 (36.6)
West	149,485 (18.4)	46.9 (40.3)

Table 2. Adjusted HRs (95% CIs) for All Cause (Excluding Respiratory Mortality) and Cause Specific Mortality per Each 100 Bq/m^3 Increase in Mean County-Level Residential Radon Concentrations (LBL), Follow-Up 1982-2006, CPS-II Cohort, US.

Cause of Death	ICD 9; 10	No. of Deaths	Fully-adjusted HR (95% CI)[a]
All cause (excluding respiratory mortality)	All cause minus 162; C33-C34 and 460-519; J00-J98	265,477	0.98 (0.97-1.00)
Diseases of the circulatory system (plus diabetes)	390-459, 250; I00-I99, E10-E14	142,272	0.98 (0.96-1.00)
Ischemic heart disease	410-414; I20-I25	61,790	0.97 (0.94-1.01)
Dysrhythmias, heart failure, cardiac arrest	420-429; I30-I51	25,172	0.97 (0.92-1.02)
Hypertensive disease	401-405; I10-I13	4,213	0.89 (0.78-1.02)
Other atherosclerosis and aortic aneurysms	440-441; I70-I71	4,964	0.90 (0.80-1.01)
Cerebrovascular disease	430-438; I60-I69	23,344	1.05 (0.99-1.10)
Diabetes	250; I10-E14	6,954	1.02 (0.93-1.12)
All other cardiovascular diseases	all not specified	15,835	0.96 (0.90-1.02)
All cancer (excluding lung)	140-208; C00-C75, C80, C97 minus 162; C33-C34	62,309	0.97 (0.94-1.00)
Malignant neoplasms of lymphatic and hematopoietic tissue	200-208; C81-C96	10,142	0.97 (0.89-1.04)
Non-Hodgkin's lymphoma	200,202; C82-C85	4,053	1.02 (0.90-1.14)
Hodgkin's disease	201; C81	172	0.95 (0.54-1.68)
Multiple myeloma	203; C88, C90	2,075	0.93 (0.78-1.11)
Leukemia	204-208; C91-C95	3,835	0.93 (0.82-1.05)
Malignant neoplasms of lip, oral cavity, and pharynx	140-149; C00-C14	834	0.80 (0.59-1.08)
Tongue and mouth	141, 143-145; C01-C06	370	0.86 (0.57-1.30)
Salivary gland	142; C07-C08	85	0.24 (0.07-0.85)
Pharynx	146-149; C09-C14	352	0.99 (0.62-1.60)
Malignant neoplasms of digestive organs and peritoneum	150-159; C15-C26, C48	20,854	0.96 (0.91-1.02)
Esophagus	150; C15	1,625	1.08 (0.89-1.30)
Stomach	151; C16	1,880	0.85 (0.70-1.03)
Colorectal	153-154; C18-C21	9,165	0.94 (0.87-1.02)
Liver	155; C22	1,526	0.89 (0.73-1.10)
Gallbladder	156; C23-C24	530	1.07 (0.77-1.50)
Pancreas	157; C25	5,441	1.03 (0.92-1.14)
Malignant neoplasms of respiratory and intrathoracic organs (excluding lung)	160-165; C30-C39 minus 162; C33-C34	740	0.95 (0.73-1.24)
Nose	160; C30-C31	67	1.47 (0.69-3.17)
Larynx	161; C32	314	1.06 (0.69-1.62)
Malignant neoplasms of bone, connective tissue, skin, and breast	170-175; C40-C44, C46-C47, C49-C50	7,733	0.95 (0.87-1.04)
Bone	170; C40-C41	104	1.19 (0.60-2.38)
Connective tissue	171; C47, C49	538	1.10 (0.80-1.51)
Melanoma	172; C43	1,247	1.08 (0.88-1.33)
Other skin	173; C44, C46	313	0.70 (0.42-1.19)
Breast (female)[b]	174-175; C50	5,479	0.91 (0.82-1.01)
Malignant neoplasms of genitourinary organs	179-189; C51-C68	-	-
Uterus[b,c]	179, 182; C54-C55	906	1.16 (0.90-1.48)
Cervix[b,c]	180; C53	184	0.70 (0.37-1.31)
Ovary[b,c,d]	183; C56	1,316	0.91 (0.74-1.13)
Prostate[b]	185; C61	1,374	0.99 (0.79-1.23)
Bladder	188; C67	1,933	1.11 (0.94-1.32)
Kidney	189; C64-C66, C68	1,251	0.94 (0.76-1.16)
Malignant neoplasms of other and unspecified sites	190-199; C69-C80, C97	7,803	0.94 (0.86-1.02)
Eye	190; C69	46	0.65 (0.19-2.25)
Brain	191; C71	2,232	0.98 (0.83-1.15)
Thyroid	193; C73	55	1.10 (0.34-3.53)

Benign neoplasms	210-229; D10-D36	284	1.18 (0.77-1.82)
All other causes	all other not specified	60,612	0.99 (0.96-1.03)

[a] Age, race, gender, state stratified and adjusted for education, marital status, body mass index, body mass index squared, cigarette smoking status, cigarettes per day, cigarettes per day squared, duration of smoking, duration of smoking squared, age started smoking, passive smoking, vegetable/fruit/fiber consumption, fat consumption, industrial exposures, occupation dirtiness index.

[b] As above but not gender stratified.

[c] Females reporting a previous hysterectomy or an artificial menopause (143,991) excluded here.

[d] Females reporting having undergone an ovarian surgery (9,232) also excluded here.

Supplementary Material

Radon and Non-Respiratory Mortality in the American Cancer Society Cohort

Michelle C. Turner, Daniel Krewski, Yue Chen, C. Arden Pope III, Susan M. Gapstur, Michael J. Thun

Supplementary Table 1. Adjusted HRs (95% CIs) for all cause (excluding respiratory mortality) and cause specific mortality per each 100 Bq/m^3 increase in mean county-level residential radon concentrations (Cohen), follow-up 1982-2006, CPS-II cohort, US.

Cause of Death	ICD 9; 10	No. of Deaths	Fully-adjusted HR (95% CI)[a]
All cause (excluding respiratory mortality)	All cause minus 162; C33-C34 and 460-519; J00-J98	195,672	0.99 (0.97-1.01)
Diseases of the circulatory system (plus diabetes)	390-459, 250; I00-I99, E10-E14	104,092	0.99 (0.97-1.02)
Ischemic heart disease	410-414; I20-I25	45,011	0.98 (0.95-1.02)
Dysrhythmias, heart failure, cardiac arrest	420-429; I30-I51	18,820	0.98 (0.92-1.04)
Hypertensive disease	401-405; I10-I13	3,011	0.78 (0.66-0.91)
Other atherosclerosis and aortic aneurysms	440-441; I70-I71	3,619	0.89 (0.78-1.01)
Cerebrovascular disease	430-438; I60-I69	16,721	1.07 (1.01-1.14)
Diabetes	250; I10-E14	5,224	1.06 (0.95-1.17)
All other cardiovascular diseases	all not specified	11,686	1.01 (0.94-1.08)
All cancer (excluding lung cancer)	140-208; C00-C75, C80, C97 minus 162; C33-C34	46,511	0.98 (0.94-1.01)
Malignant neoplasms of lymphatic and hematopoietic tissue	200-208; C81-C96	7,616	0.96 (0.88-1.05)
Non-Hodgkin's lymphoma	200,202; C82-C85	3,040	1.00 (0.87-1.14)
Hodgkin's disease	201; C81	126	0.80 (0.40-1.56)
Multiple myeloma	203; C88, C90	1,566	0.92 (0.75-1.13)
Leukemia	204-208; C91-C95	2,878	0.96 (0.83-1.11)
Malignant neoplasms of lip, oral cavity, and pharynx	140-149; C00-C14	587	0.83 (0.59-1.17)
Tongue and mouth	141, 143-145; C01-C06	265	0.82 (0.50-1.35)
Salivary gland	142; C07-C08	59	0.40 (0.11-1.42)
Pharynx	146-149; C09-C14	243	1.13 (0.66-1.92)
Malignant neoplasms of digestive organs and peritoneum	150-159; C15-C26, C48	15,527	0.97 (0.91-1.04)
Esophagus	150; C15	1,220	1.01 (0.81-1.27)
Stomach	151; C16	1,389	0.74 (0.59-0.93)
Colorectal	153-154; C18-C21	6,798	0.97 (0.89-1.07)
Liver	155; C22	1,121	0.94 (0.74-1.19)
Gallbladder	156; C23-C24	411	1.34 (0.94-1.92)
Pancreas	157; C25	4,061	1.00 (0.88-1.13)
Malignant neoplasms of respiratory and intrathoracic organs (excluding lung cancer)	160-165; C30-C39 minus 162; C33-C34	557	0.86 (0.62-1.19)
Nose	160; C30-C31	48	2.05 (0.75-5.66)
Larynx	161; C32	237	0.91 (0.55-1.51)
Malignant neoplasms of bone, connective tissue, skin, and breast	170-175; C40-C44, C46-C47, C49-C50	5,816	1.01 (0.91-1.11)
Bone	170; C40-C41	74	1.48 (0.63-3.44)
Connective tissue	171; C47, C49	430	0.99 (0.69-1.43)
Melanoma	172; C43	943	1.07 (0.84-1.38)
Other skin	173; C44, C46	208	0.82 (0.46-1.47)
Breast (female)[b]	174-175; C50	4,122	1.00 (0.88-1.12)
Malignant neoplasms of genitourinary organs	179-189; C51-C68	-	-
Uterus[b,c]	179, 182; C54-C55	691	1.05 (0.78-1.40)
Cervix[b,c]	180; C53	137	0.64 (0.30-1.36)
Ovary[b,c,d]	183; C56	982	0.89 (0.69-1.14)
Prostate[b]	185; C61	1,019	0.94 (0.74-1.21)
Bladder	188; C67	1,434	1.07 (0.87-1.30)
Kidney	189; C64-C66, C68	938	0.91 (0.70-1.17)
Malignant neoplasms of other and unspecified sites	190-199; C69-C80, C97	5,850	0.94 (0.85-1.05)
Eye	190; C69	32	0.55 (0.11-2.73)

Brain	191; C71	1,696	0.97 (0.81-1.18)
Thyroid	193; C73	46	1.54 (0.49-4.86)
Benign neoplasms	210-229; D10-D36	206	1.69 (1.05-2.75)
All other causes	all other not specified	44,863	1.00 (0.96-1.03)

[a] Age, race, gender, state stratified and adjusted for education, marital status, body mass index, body mass index squared, cigarette smoking status, cigarettes per day, cigarettes per day squared, duration of smoking, duration of smoking squared, age started smoking, passive smoking, vegetable/fruit/fiber consumption, fat consumption, industrial exposures, occupation dirtiness index.

[b] As above but not gender stratified.

[c] Females reporting a previous hysterectomy or an artificial menopause (104,677) excluded here.

[d] Females reporting having undergone an ovarian surgery (7,100) also excluded here.

6. ARTICLE 4

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Long-term Ambient Fine Particulate Matter Air Pollution and Lung Cancer in a Large Cohort of Never-Smokers

Michelle C. Turner[1,2], Daniel Krewski[2,3,4], C. Arden Pope, III[5], Yue Chen[3], Susan M. Gapstur[6], and Michael J. Thun[6]

[1]Faculty of Graduate and Postdoctoral Studies, [2]McLaughlin Centre for Population Health Risk Assessment, Institute of Population Health, and [3]Department of Epidemiology and Community Medicine, Faculty of Medicine, University of Ottawa, Ottawa, Ontario, Canada; [4]Risk Sciences International, Ottawa, Ontario, Canada; [5]Department of Economics, Brigham Young University, Provo, Utah; and [6]Epidemiology Research Program, American Cancer Society, Atlanta, Georgia

***Rationale*: There is compelling evidence that acute and chronic exposure to ambient fine particulate matter ($PM_{2.5}$) air pollution increases cardiopulmonary mortality. However, the role of $PM_{2.5}$ in the etiology of lung cancer is less clear, particularly at concentrations that prevail in developed countries and in never-smokers.**

***Objectives*: This study examined the association between mean long-term ambient $PM_{2.5}$ concentrations and lung cancer mortality among 188,699 lifelong never-smokers drawn from the nearly 1.2 million Cancer Prevention Study–II participants enrolled by the American Cancer Society in 1982 and followed prospectively through 2008.**

***Methods*: Mean metropolitan statistical area $PM_{2.5}$ concentrations were determined for each participant based on central monitoring data. Cox proportional hazards regression models were used to estimate multivariate adjusted hazard ratios and 95% confidence intervals for lung cancer mortality in relation to $PM_{2.5}$.**

***Measurements and Main Results*: A total of 1,100 lung cancer deaths were observed during the 26-year follow-up period. Each 10 $\mu g/m^3$ increase in $PM_{2.5}$ concentrations was associated with a 15–27% increase in lung cancer mortality. The association between $PM_{2.5}$ and lung cancer mortality was similar in men and women and across categories of attained age and educational attainment, but was stronger in those with a normal body mass index and a history of chronic lung disease at enrollment ($P < 0.05$).**

***Conclusions*: The present findings strengthen the evidence that ambient concentrations of $PM_{2.5}$ measured in recent decades are associated with small but measurable increases in lung cancer mortality.**

Keywords: fine particulate matter air pollution; lung neoplasms; never-smokers; asthma; pulmonary disease, chronic obstructive

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

There is compelling evidence that acute and chronic exposure to ambient fine particulate matter ($PM_{2.5}$) air pollution increases cardiopulmonary mortality. However, the role of $PM_{2.5}$ in the etiology of lung cancer is less clear.

What This Study Adds to the Field

This study examined the association between mean long-term ambient $PM_{2.5}$ concentrations and lung cancer mortality in a 26-year prospective study of a large cohort of lifelong never-smokers. Each 10 $\mu g/m^3$ increase in $PM_{2.5}$ concentrations was associated with a 15–27% increase in lung cancer mortality. These results strengthen the evidence that ambient concentrations of $PM_{2.5}$ are associated with small but measurable increases in lung cancer mortality.

Time-series and prospective studies provide compelling evidence that acute and chronic exposure to ambient fine particulate matter ($PM_{2.5}$) air pollution is associated with increased cardiopulmonary mortality (1). However, the role of $PM_{2.5}$ in the etiology of lung cancer is less clear, particularly at concentrations that prevail in developed countries ($\sim$ 5–35 $\mu g/m^3$) and in never-smokers (2). In China, high levels of indoor air pollution caused by coal and biomass burning contribute to high lung cancer rates observed even among nonsmoking women (3). There are also high background concentrations (>100 $\mu g/m^3$) of outdoor air pollution in some industrial regions of the country (2).

Given the strong relationship between cigarette smoking and lung cancer risk, evidence of an association between $PM_{2.5}$ and lung cancer is more convincing when observed among never-smokers, compared with current or former smokers, because of possible residual confounding by cigarette smoking (4, 5). A previous analysis of the American Cancer Society Cancer Prevention Study-II (CPS-II), based on 16 years of follow-up data of approximately 500,000 included participants controlling for measured parameters of active smoking, found an 8% (95% confidence interval [CI], 1–16%) increase in lung cancer mortality for each 10 $\mu g/m^3$ increase in $PM_{2.5}$ concentrations (6). The risk was somewhat higher, although statistically insignificant, when restricted to the subgroup of never-smokers. An extended analysis of the Harvard Six Cities Study (n = 8,096) found a positive association between $PM_{2.5}$ and lung cancer mortality (hazard ratio [HR] per each 10 $\mu g/m^3$ = 1.27; 95% CI, 0.96–1.69) controlling for active smoking (7). Naess and coworkers (8) observed significant positive associations between $PM_{2.5}$ and lung cancer mortality among Oslo women in a recent register-based study; however, no data on smoking history were available in this study.

Despite this, the World Health Organization has estimated that long-term $PM_{2.5}$ exposure is responsible for approximately 5% of all cancers of the trachea, bronchus, and lung (9). To address the potential for residual confounding by cigarette smoking status, the present study examined associations between mean long-

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Correspondence and requests for reprints should be addressed to Michelle C. Turner, M.Sc., McLaughlin Centre for Population Health Risk Assessment, Institute of Population Health, University of Ottawa, One Stewart Street, Room 313, Ottawa, ON, K1N 6N5 Canada. E-mail: mturner@uottawa.ca

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term ambient $PM_{2.5}$ concentrations and lung cancer mortality in a 26-year (1982–2008) prospective follow-up of 188,699 lifelong never-smoking CPS-II participants.

METHODS

Study Population

The CPS-II is a prospective study of nearly 1.2 million participants enrolled by over 77,000 volunteers in 1982. Ethics approval for the CPS-II was obtained from the Emory University School of Medicine Human Investigations Committee. Participants were recruited in all 50 states and the District of Columbia and Puerto Rico. Participants were largely friends and family members of the volunteers. For inclusion in CPS-II, participants had to be at least 30 years of age and have at least one family member aged 45 years or older. A four-page self-administered questionnaire completed at enrollment captured data on a range of demographic, lifestyle, medical, and other factors, including ZIP code of residence.

Follow-up for vital status has been conducted every 2 years. In 1984, 1986, and 1988, vital status was obtained from the study volunteers, and confirmed by obtaining the corresponding death certificate. Since 1989, computerized linkage to the National Death Index has been used for follow-up (10). Through 2008, a total of 637,033 (53.8%) participants were alive; 544,545 (46%) had died; and 2,840 (0.2%) had follow-up terminated in September of 1988 because of insufficient information to link to the National Death Index. Over 99% of all known deaths have been assigned a cause. Lung cancer deaths were classified according to the underlying cause of death using the International Classification of Disease-9 (162) and -10 (C33, C34) coding system (11, 12).

Of the 1,184,881 CPS-II participants, we excluded current or former cigarette smokers (702,427); individuals with missing data on vital status (46); prevalent cancer (except nonmelanoma skin cancer) at enrollment (33,852); missing ZIP code (39,093) or county (9,552) data; or missing data on any individual-level covariates of interest (24,828). A total of 375,083 lifelong never-smokers were retained for the present analysis, of which 188,699 resided in a Metropolitan Statistical Area (MSA) with available $PM_{2.5}$ monitoring data (*see below*). A total of 1,100 lung cancer deaths were observed in 4,225,436 person-years of follow-up.

Ecologic Measures of $PM_{2.5}$

Study participants were assigned to a primary MSA of residence using five-digit ZIP code information provided at enrollment according to the ZIP code boundaries (STF3B) of the 1980 United States Census (13). Three different ecologic measures of $PM_{2.5}$ were used as indicators of historical $PM_{2.5}$ exposure. Average ambient $PM_{2.5}$ concentrations for the 4-year period (1979–1983) encompassing the year of enrollment were obtained for 131,864 participants residing in 61 MSAs from the Inhalable Particle Monitoring Network, as compiled by the Health Effects Institute reanalysis team (14). Average ambient $PM_{2.5}$ concentrations were also available in 1999 and in the first three quarters of 2000 for 177,752 participants residing in 117 MSAs from the Aerometric Information Retrieval System, implemented in response to the 1997 United States Environmental Protection Agency $PM_{2.5}$ standard. Quarterly mean $PM_{2.5}$ concentrations were determined by site and MSA and averaged when there were at least 50% of sixth-day samples and at least 45 total sampling days in one of the two corresponding quarters. Because there was no systematic monitoring of $PM_{2.5}$ in the United States in the period spanning the early 1980s to the late 1990s, a third measure representing the average of $PM_{2.5}$ concentrations in the two time periods (1979–1983 and 1999–2000) was also constructed for 120,917 participants in 53 MSAs. These indicators of ambient $PM_{2.5}$ concentrations have been extensively examined in relation to mortality health effects in the CPS-II (6, 14, 15).

Ecologic Measures of Residential Radon

Mean county-level residential radon concentrations were obtained from the Lawrence Berkeley National Laboratory (16). Because long-term residential radon monitoring data in the United States are sparse, researchers at the Lawrence Berkeley National Laboratory used a variety of short- and long-term indoor radon monitoring data, along with a variety of geologic, soil, meteorologic, and housing data, to estimate the annual average radon concentrations in the main living areas of homes using an empirically constructed statistical model. Short-term screening data from the United States Environmental Protection Agency State Residential Radon Survey (mid- to late 1980s) were combined with geologic data, including estimated radium concentrations, and location of screening measurements within the home, along with a short- to long-term radon monitoring data conversion factor, to predict annual average radon concentrations in homes in 3,079 United States counties. We recently observed a significant positive association between mean county-level residential radon concentrations and lung cancer mortality in the CPS-II (17).

Sociodemographic Ecologic Covariates

Data on a range of social and demographic ecologic-level covariates were compiled for 18,731, 17,096, and 17,508 participant ZIP codes or zip code tabulation areas from the 1980, 1990, and 2000 United States Census, respectively (13, 18, 19). Variables included median household income, and percent air conditioning (1980 only), nonwhite, black, Hispanic, postsecondary education, unemployment, poverty, urban, moving, and homes with a well (1980 and 1990 only).

Statistical Analysis

Cox proportional hazards regression models were used to examine the independent effects of $PM_{2.5}$ concentrations on lung cancer mortality in lifelong never-smokers. The proportional hazards models were stratified by 1-year age categories; sex; and race (white, black, or other). Follow-up time since enrollment (1982) was used as the time axis. The survival times of those still alive at the end of follow-up were treated as censored observations.

Estimated HRs and 95% CIs were adjusted for the following individual-level risk factors: education; marital status; body mass index (BMI); BMI squared; passive smoking (hours); quintiles of vegetable, fruit, and fiber and fat intake; occupational exposures (asbestos, chemicals-acids-solvents, coal or stone dusts, coal tar-pitch-asphalt, formaldehyde, and diesel engine exhaust); a previously developed occupational dirtiness index specifically designed for the CPS-II (14, 20); and mean county-level residential radon concentrations (17). Adjustment for prevalent chronic lung disease (CLD) (asthma, chronic bronchitis, or emphysema) or hay fever at enrollment produced virtually no change in the results.

Potential effect modification was assessed by including multiplicative interaction terms between $PM_{2.5}$ concentrations and each risk factor in the proportional hazards models. Two-sided P values were calculated to assess the significance of the interaction term using the likelihood ratio statistic. To assess the impact of attained age, time-dependent variables were constructed by allowing participants to be included in the risk set at each death time only if they met the attained age criteria for the model (<70, 70–79, or ≥ 80 yr). The significance of an interaction term between $PM_{2.5}$ and follow-up time was used to assess the plausibility of the proportional hazards assumption.

All analyses were conducted using SAS version 9.2 (SAS Institute Inc., Cary, NC) (21). Ethics approval was obtained from the Ottawa Hospital Research Ethics Board.

RESULTS

Mean (SD) $PM_{2.5}$ concentrations ranged from 21.1 (4.7) $\mu g/m^3$ in 1979–1983 to 14 (3) $\mu g/m^3$ in 1999–2000 with an average of 17.6 (3.7) $\mu g/m^3$ observed for the two time periods (Table 1). The three $PM_{2.5}$ measures were strongly correlated ($r = 0.72$–0.96), whereas weak inverse correlations were observed between $PM_{2.5}$ and radon (Table 2).

Table 3 presents the distribution of selected participant characteristics overall and in relation to $PM_{2.5}$ (1999–2000) concentrations. Most participants were between 50 and 69 years of age, were female, and had some postsecondary education. There was a tendency for higher $PM_{2.5}$ concentrations to be observed in participants who were nonwhite, had a lower level of educational

TABLE 1. DISTRIBUTION OF MEAN AMBIENT FINE PARTICULATE MATTER AIR POLLUTION AND RESIDENTIAL RADON CONCENTRATIONS, NEVER-SMOKERS, FOLLOW-UP 1982–2008, CPS-II COHORT, UNITED STATES

$PM_{2.5}$/Radon Concentration	Participants	MSAs	Mean (*SD*)	Minimum	1st Quartile	2nd Quartile	3rd Quartile	Maximum
$PM_{2.5}$ (1979–1983), $\mu g/m^3$	131,864	61	21.1 (4.7)	10.3	17.5	21.7	24.1	37.8
$PM_{2.5}$ (1999–2000), $\mu g/m^3$	177,752	117	14 (3)	5.8	11.8	14.3	16	22.2
$PM_{2.5}$ (1979–1983) and (1999–2000) average, $\mu g/m^3$	120,917	53	17.6 (3.7)	9	14.4	18.2	20.2	27.7
Radon, Bq/m^3	375,083	—	55.5 (39)	6.3	27.4	43.3	74	265.7

Definition of abbreviations: CPS-II = American Cancer Society Cancer Prevention Study-II; MSA = Metropolitan Statistical Area; $PM_{2.5}$ = ambient fine particulate matter.

attainment, had a higher BMI, were nonmarried, and had a lower intake of vegetables, fruit, and fiber.

Adjusted HRs (95% CIs) for lung cancer mortality in relation to mean $PM_{2.5}$ concentrations are presented in Table 4. In the partially adjusted model, each 10 $\mu g/m^3$ increase in $PM_{2.5}$ was associated with a significant 19–30% increase in the risk of lung cancer death, depending on the specific $PM_{2.5}$ measure used. Results were similar although slightly attenuated in the fully adjusted model, which included an additional term for mean county-level residential radon concentrations. In the fully adjusted model, a HR of 1.15 (95% CI, 0.99–1.35) was observed for lung cancer mortality associated with each 10 $\mu g/m^3$ increase in $PM_{2.5}$ (1979–1983) concentrations. A significant positive association (HR per each 10 $\mu g/m^3 = 1.27$; 95% CI, 1.03–1.56) was observed for $PM_{2.5}$ (1999–2000). Figure 1 presents adjusted HRs (95% CIs) for lung cancer mortality according to categorical indicators of $PM_{2.5}$ (1999–2000) concentrations. No association was observed between $PM_{2.5}$ and mortality from nonmalignant respiratory disease overall (*see* Table E1 in the online supplement). There was no evidence that the proportional hazards assumption was violated ($P > 0.05$).

Mean $PM_{2.5}$ (1999–2000) concentrations were weakly correlated with sociodemographic ecologic covariates (*r* ranged from −0.22 to 0.22) (*see* Table E2). There was little change in results observed with the inclusion of ecologic covariates from any time period in the model.

Table 5 presents adjusted HRs (95% CIs) for lung cancer mortality in relation to mean $PM_{2.5}$ (1999–2000) concentrations stratified according to selected participant characteristics at enrollment. Similar results were observed in men and women and across categories of attained age and educational attainment. However, results varied across categories of BMI, with a stronger association observed in participants with a normal BMI (18.5–24.9 kg/m^2) (HR per each 10 $\mu g/m^3 = 1.42$; 95% CI, 1.07–1.88) compared with other BMI groups ($P < 0.05$). Results were also found to vary by a history of self-reported physician-diagnosed asthma, or any CLD, at enrollment with stronger associations observed in those with a positive history of asthma (HR per each 10 $\mu g/m^3 = 5.18$; 95% CI, 1.96–13.71) or any CLD (HR per each 10 $\mu g/m^3 = 3.78$; 95% CI, 1.69–8.43) compared with those without ($P < 0.05$).

DISCUSSION

This large prospective study showed positive associations between mean long-term ambient fine particulate matter air pollution concentrations and lung cancer mortality in lifelong never-smokers. Each 10 $\mu g/m^3$ increase in $PM_{2.5}$ concentrations was associated with a 15–27% increase in the relative risk of lung cancer death after detailed adjustment for a number of potential confounders including passive smoking, occupational exposures, and radon. The association was similar in men and women and across categories of attained age and educational attainment but was stronger in those with a normal BMI or a history of asthma or any CLD at enrollment. Findings were robust to the adjustment of a variety of sociodemographic ecologic covariates at different time points in the model.

Strengths of this study include the examination of lung cancer mortality in a large cohort of 188,699 lifelong never-smokers to eliminate potential residual confounding by cigarette smoking status; an extended 26-year follow-up time period (1982–2008) with a total of 1,100 observed lung cancer deaths; detailed prospectively collected individual-level lung cancer risk factor data; and the availability of ecologic measures of residential radon concentrations and sociodemographic characteristics to examine potential confounding by radon and community-level factors.

Although previous studies examining associations between $PM_{2.5}$ and lung cancer adjusting for cigarette smoking history have generally reported positive findings (6, 7, 15), there remains concern regarding potential residual confounding by cigarette smoking status; previous studies of nonsmokers were also limited by the small numbers of lung cancer cases. Results from a prospective investigation of 3,769 participants from the Adventist Health Study of Smog, a cohort of nonsmoking California Seventh-Day Adventists followed-up from 1977–1992, reported a positive, although imprecise, association between estimated $PM_{2.5}$ concentrations and lung cancer mortality in males (HR per each 24.3 $\mu g/m^3 = 2.23$; 95% CI, 0.56–8.94); however only 13 lung cancer deaths were observed (22). A previous 16-year follow-up of never-smoking CPS-II participants reported a positive, although statistically insignificant, association between $PM_{2.5}$ and lung cancer death (6).

Several European studies have examined associations between measures of traffic air pollution and lung cancer incidence

TABLE 2. CORRELATION BETWEEN MEAN AMBIENT FINE PARTICULATE MATTER AIR POLLUTION AND RESIDENTIAL RADON CONCENTRATIONS, NEVER-SMOKERS, FOLLOW-UP 1982–2008, CPS-II COHORT, UNITED STATES

$PM_{2.5}$/Radon Concentration	$PM_{2.5}$ (*1979–1983*)	$PM_{2.5}$ (*1999–2000*)	$PM_{2.5}$ (*1979–1983*) and (*1999–2000*) Average	Radon
$PM_{2.5}$ (1979–1983)	—	0.72	0.96	−0.22
$PM_{2.5}$ (1999–2000)		—	0.89	−0.26
$PM_{2.5}$ (1979–1983) and (1999–2000) average			—	−0.31
Radon				—

Definition of abbreviations: CPS-II = American Cancer Society Cancer Prevention Study-II; $PM_{2.5}$ = ambient fine particulate matter.

TABLE 3. DISTRIBUTION (%) OF SELECTED PARTICIPANT CHARACTERISTICS AT ENROLLMENT (1982), NEVER-SMOKERS, CPS-II COHORT, UNITED STATES

		Quartiles of $PM_{2.5}$ (*1999–2000*) Concentration ($\mu g/m^3$)			
Characteristic	No. (%)	Q1 (*5.8 to <11.8*)	Q2 (*11.8 to <14.3*)	Q3 (*14.3 to <16*)	Q4 (*⩾16*)
Overall	177,752 (100)	42,397 (100)	46,478 (100)	42,258 (100)	46,619 (100)
Age at enrollment, yr					
<40	9,510 (5.4)	2,069 (4.9)	2,512 (5.4)	2,563 (6.1)	2,366 (5.1)
40–49	38,438 (21.6)	9,125 (21.5)	10,012 (21.5)	9,606 (22.7)	9,695 (20.8)
50–59	61,553 (34.6)	14,314 (33.8)	16,148 (34.7)	14,714 (34.8)	16,377 (35.1)
60–69	45,028 (25.3)	11,087 (26.2)	11,675 (25.1)	10,231 (24.2)	12,035 (25.8)
70–79	18,618 (10.5)	4,680 (11)	4,920 (10.6)	4,106 (9.7)	4,912 (10.5)
80+	4,605 (2.6)	1,122 (2.7)	1,211 (2.6)	1,038 (2.5)	1,234 (2.7)
Race					
White	166,222 (93.5)	40,844 (96.3)	43,447 (93.5)	38,573 (91.3)	43,358 (93)
Black	7,315 (4.1)	754 (1.8)	1,840 (4)	2,732 (6.5)	1,989 (4.3)
Other	4,215 (2.4)	799 (1.9)	1,191 (2.6)	953 (2.3)	1,272 (2.7)
Sex					
Male	50,805 (28.6)	12,538 (29.6)	13,281 (28.6)	12,156 (28.8)	12,830 (27.5)
Female	126,947 (71.4)	29,859 (70.4)	33,197 (71.4)	30,102 (71.2)	33,789 (72.5)
Education					
Less than high school	19,934 (11.2)	4,230 (10)	5,183 (11.2)	4,733 (11.2)	5,788 (12.4)
High school	57,345 (32.3)	13,813 (32.6)	15,216 (32.7)	12,945 (30.6)	15,371 (33)
More than high school	100,473 (56.5)	24,354 (57.4)	26,079 (56.1)	24,580 (58.2)	25,460 (54.6)
Marital status					
Single	8,172 (4.6)	1,761 (4.2)	2,006 (4.3)	2,042 (4.8)	2,363 (5.1)
Married	144,111 (81.1)	35,185 (83)	37,762 (81.3)	33,955 (80.4)	37,209 (79.8)
Other	25,469 (14.3)	5,451 (12.9)	6,710 (14.4)	6,261 (14.8)	7,047 (15.1)
Body mass index, kg/m^2					
<18.5	2,989 (1.7)	681 (1.6)	816 (1.8)	713 (1.7)	779 (1.7)
18.5–24.9	93,163 (52.4)	22,364 (52.8)	24,591 (52.9)	22,244 (52.6)	23,964 (51.4)
25–29.9	59,546 (33.5)	14,387 (33.9)	15,415 (33.2)	13,954 (33)	15,790 (33.9)
30+	22,054 (12.4)	4,965 (11.7)	5,656 (12.2)	5,347 (12.7)	6,086 (13.1)
Exposure to smoking, hr/d (SD)	1.9 (3.1)	1.7 (2.9)	2 (3.1)	2.1 (3.2)	2 (3.2)
Vegetable, fruit, fiber consumption					
1st quintile	25,002 (14.1)	5,334 (12.6)	6,392 (13.8)	6,058 (14.3)	7,218 (15.5)
2nd quintile	29,611 (16.7)	6,716 (15.8)	7,700 (16.6)	7,153 (16.9)	8,042 (17.3)
3rd quintile	32,986 (18.6)	7,922 (18.7)	8,646 (18.6)	7,866 (18.6)	8,552 (18.3)
4th quintile	36,865 (20.7)	9,098 (21.5)	9,647 (20.8)	8,772 (20.8)	9,348 (20.1)
5th quintile	38,001 (21.4)	9,855 (23.2)	9,995 (21.5)	8,730 (20.7)	9,421 (20.2)
Fat consumption					
1st quintile	32,980 (18.6)	6,874 (16.2)	8,806 (19)	8,192 (19.4)	9,108 (19.5)
2nd quintile	35,075 (19.7)	8,201 (19.3)	9,155 (19.7)	8,450 (20)	9,269 (19.9)
3rd quintile	34,790 (19.6)	8,644 (20.4)	9,100 (19.6)	8,101 (19.2)	8,945 (19.2)
4th quintile	32,787 (18.5)	8,377 (19.8)	8,477 (18.2)	7,631 (18.1)	8,302 (17.8)
5th quintile	26,833 (15.1)	6,829 (16.1)	6,842 (14.7)	6,205 (14.7)	6,957 (14.9)
Unclassifiable diet	15,287 (8.6)	3,472 (8.2)	4,098 (8.8)	3,679 (8.7)	4,038 (8.7)
Industrial exposures (%)	26,746 (15.1)	6,680 (15.8)	7,037 (15.1)	6,337 (15)	6,692 (14.4)
Occupational Dirtiness Index					
Level 0	94,866 (53.4)	22,241 (52.5)	24,776 (53.3)	22,444 (53.1)	25,405 (54.5)
Level 1	27,771 (15.6)	6,715 (15.8)	7,347 (15.8)	6,793 (16.1)	6,916 (14.8)
Level 2	18,268 (10.3)	4,581 (10.8)	4,745 (10.2)	4,383 (10.4)	4,559 (9.8)
Level 3	6,977 (3.9)	1,788 (4.2)	1,897 (4.1)	1,606 (3.8)	1,686 (3.6)
Level 4	9,531 (5.4)	2,498 (5.9)	2,588 (5.6)	2,167 (5.1)	2,278 (4.9)
Level 5	4,756 (2.7)	1,215 (2.9)	1,284 (2.8)	1,065 (2.5)	1,192 (2.6)
Level 6	1,272 (0.7)	318 (0.8)	323 (0.7)	258 (0.6)	373 (0.8)
Not able to ascertain	14,311 (8.1)	3,041 (7.2)	3,518 (7.6)	3,542 (8.4)	4,210 (9)
Radon concentrations, Bq/m^3 (mean SD)	53.8 (39.9)	75.4 (44.9)	48.9 (37.9)	43.3 (33.7)	48.3 (34.4)
Asthma, %	8,158 (4.6)	2,049 (4.8)	2,242 (4.8)	1,914 (4.5)	1,953 (4.2)
Hay fever, %	25,621 (14.4)	7,064 (16.7)	6,895 (14.8)	5,858 (13.9)	5,804 (12.5)
Chronic obstructive pulmonary disease, %	5,318 (3)	1,242 (2.9)	1,368 (2.9)	1,273 (3)	1,435 (3.1)
Region					
Northeast	42,925 (24.2)	9,212 (21.7)	16,528 (35.6)	11,802 (27.9)	5,383 (11.6)
South	35,479 (20)	3,195 (7.5)	10,288 (22.1)	14,602 (34.6)	7,394 (15.9)
Midwest	54,342 (30.6)	10,590 (25)	9,143 (19.7)	11,531 (27.3)	23,078 (49.5)
West	45,006 (25.3)	19,400 (45.8)	10,519 (22.6)	4,323 (10.2)	10,764 (23.1)

Definition of abbreviations: CPS-II = American Cancer Society Cancer Prevention Study-II; $PM_{2.5}$ = ambient fine particulate matter.

or mortality (8, 23–33). Beelen and coworkers (23) observed positive associations between measures of black smoke concentrations and traffic intensity and lung cancer incidence in 40,114 never-smoking participants in the Netherlands Cohort Study on Diet and Cancer. A total of 252 lung cancer cases were observed in the 11-year follow-up time period. Vineis and coworkers (32) reported a significant positive association between NO_2 concentrations (upper vs. lowest and intermediate tertiles combined) and lung cancer incidence (odds ratio = 1.37; 95% CI, 1.06–1.75), but not PM_{10} or SO_2, in a case-control study of 271

TABLE 4. ADJUSTED HR (95% CI) FOR LUNG CANCER MORTALITY IN RELATION TO EACH 10 μg/m³ INCREASE IN MEAN AMBIENT FINE PARTICULATE MATTER AIR POLLUTION CONCENTRATIONS, FOLLOW-UP 1982–2008, NEVER-SMOKERS, CPS-II COHORT, UNITED STATES

$PM_{2.5}$ Concentration	No. of Subjects (*deaths*)	Minimally Adjusted HR (*1*) (*95% CI*)*	Partially Adjusted HR (*2*) (*95% CI*)*	Fully Adjusted HR (*3*) (*95% CI*)*
$PM_{2.5}$ (1979–1983)	131,864 (772)	1.21 (1.04–1.41)	1.19 (1.02–1.38)	1.15 (0.99–1.35)
$PM_{2.5}$ (1999–2000)	177,752 (1,042)	1.31 (1.07–1.60)	1.30 (1.06–1.59)	1.27 (1.03–1.56)
$PM_{2.5}$ (1979–1983) and (1999–2000) average	120,917 (714)	1.29 (1.06–1.57)	1.26 (1.03–1.54)	1.19 (0.97–1.47)

Definition of abbreviations: CI = confidence interval; CPS-II = American Cancer Society Cancer Prevention Study-II; HR = hazard ratio; $PM_{2.5}$ = ambient fine particulate matter.

* Minimally adjusted HR (1): age, race, and sex stratified. Partially adjusted HR (2): age, race, and sex stratified and adjusted for education, marital status, body mass index, body mass index squared, passive smoking, vegetable/fruit/fiber consumption, fat consumption, industrial exposures, and occupation dirtiness index. Fully adjusted HR (3): age, race, and sex stratified and adjusted for education, marital status, body mass index, body mass index squared, passive smoking, vegetable/fruit/fiber consumption, fat consumption, industrial exposures, occupation dirtiness index, and mean county-level residential radon concentrations.

nonsmoking lung cancer cases nested within the European Prospective Investigation on Cancer and Nutrition. There was also some evidence for higher air pollution relative risk estimates in nonsmokers compared with current or former smokers in other recent work (30, 31, 33).

Ambient fine particulate matter comprises a diverse group of air pollutants that may be deposited and retained in the deep branches of the respiratory system, the chemical composition of which varies widely and may include a variety of adsorbed organic compounds, transition metals, ions, and minerals capable of inducing toxic biologic effects (34). Long-term exposure to fine particulate air pollution may lead to increased lung cancer risk through inflammatory injury, reactive oxygen species production, and oxidative damage to DNA (35). Genotoxic and mutagenic effects have also been demonstrated in laboratory studies (34, 36). In 1989, the International Agency for Research on Cancer identified diesel engine exhaust as a probable human carcinogen, based largely on findings from animal-based studies (37). Studies of occupational diesel exposure have also reported positive associations with lung cancer, although uncertainties with respect to exposure-response and residual confounding by cigarette smoking status remain (38).

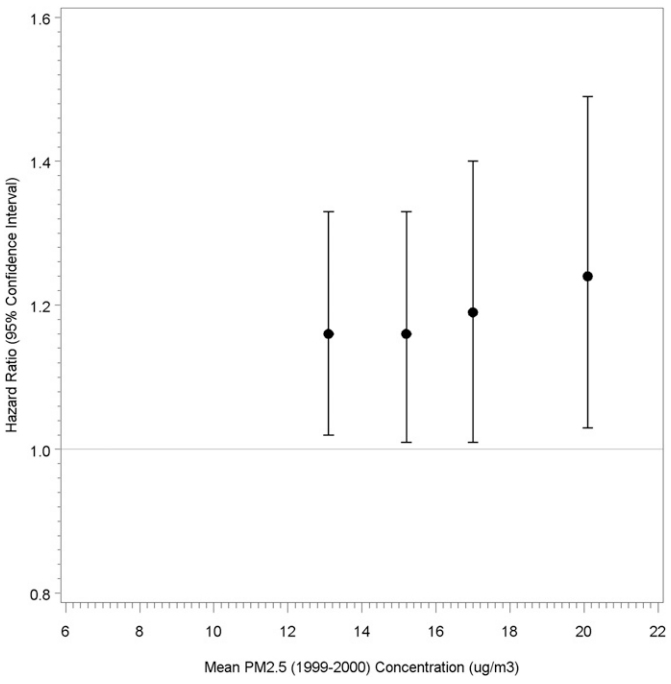

Figure 1. Fully adjusted hazard ratios (95% confidence interval) for lung cancer mortality in relation to categoric indicators of mean ambient fine particulate matter ($PM_{2.5}$) (1999–2000) concentrations, follow-up 1982–2008, never-smokers, Cancer Prevention Study–II (CPS-II) cohort, United States. The cutpoints between exposure categories were based on the 25th (11.8 μg/m³), 50th (14.3 μg/m³), 75th (16 μg/m³), and 90th (17.9 μg/m³) percentiles. The reference category was less than 11.8 μg/m³. Fully adjusted hazard ratios (95% confidence interval) were plotted at the category midpoint.

Although potential mechanisms surrounding the stronger $PM_{2.5}$-lung cancer mortality association observed in those with a normal BMI are unclear, there may be other more important influences on the mortality experience of overweight and obese individuals that may compete with lung cancer, including elevated underlying cardiovascular disease risk factors (39). Stronger associations were also observed in individuals with a history of asthma or any CLD at enrollment. Although these results should be interpreted cautiously because of the small number of participants with CLD in the present study, findings may be caused by an increased susceptibility to the carcinogenic effects of fine particulate air pollution in those with underlying respiratory disease, possibly as a result of impaired clearance or defense mechanisms (35, 40), or some form of common underlying exposure that may be independently associated with both CLD and lung cancer. Impaired pulmonary function and CLDs have been associated with ambient air pollution (4, 41–43). CLDs may also be independently associated with lung cancer because of local mechanisms of inflammation and repair (44–46). No information was available on CLD from enrollment. Although some studies have also suggested potential modifying effects of educational attainment and fruit and vegetable consumption on air pollution–mortality associations (6, 14, 15, 23, 26, 30, 31), this was not observed in the present study.

Limitations include the assignment of $PM_{2.5}$ data to study participants at a coarse geographic scale, at the level of the MSA of residence at enrollment, rather than at the individual- or household-level. Previous research in the CPS-II examining mortality health effects at the intraurban scale in Los Angeles, California, revealed relative risk estimates approximately threefold greater than those estimated using between-city contrasts (47). There was also limited historical $PM_{2.5}$ monitoring data, with widespread systematic $PM_{2.5}$ monitoring occurring only in the late 1990s, nearly two decades after cohort enrollment. Air pollution exposures experienced over an extended historical time period are likely more relevant to the etiology of lung cancer than air pollution exposures experienced in the more recent past (7, 29). Although $PM_{2.5}$ concentrations have declined in recent decades, with an approximate in 33% decline in mean $PM_{2.5}$ concentrations observed from 1979–1983 to 1999–2000 in the 53 MSAs with data available on both time periods, $PM_{2.5}$ data from both historical monitoring time periods were strongly correlated ($r > 0.7$) and the relative ranking of MSAs in terms of $PM_{2.5}$ concentrations was generally retained

TABLE 5. FULLY ADJUSTED HR (95% CI) FOR LUNG CANCER MORTALITY IN RELATION TO EACH 10 μg/m³ INCREASE IN $PM_{2.5}$ (1999–2000) CONCENTRATIONS ACCORDING TO SELECTED RISK FACTORS, NEVER-SMOKERS, MULTIPLICATIVE SCALE, FOLLOW-UP 1982–2008, CPS-II COHORT, UNITED STATES

Characteristic	No. of Deaths	Fully Adjusted HR (*95% CI*)*	*P* Value
Age at enrollment			
<65 yr	674	1.30 (1.00–1.69)	
≥65 yr	368	1.22 (0.87–1.73)	1.00
Attained age			
<70 yr	516	1.37 (0.91–2.07)	
70–79 yr	640	1.14 (0.80–1.63)	
≥80 yr	849	1.33 (0.96–1.84)	0.77
Race			
White	965	1.26 (1.01–1.56)	
Other	77	1.63 (0.77–3.45)	0.72
Sex			
Male	334	1.19 (0.83–1.73)	
Female	708	1.30 (1.01–1.68)	0.84
Education			
Less than high school	164	1.50 (0.86–2.62)	
High school	361	1.29 (0.90–1.85)	
More than high school	517	1.21 (0.90–1.61)	0.96
Marital status			
Married	814	1.24 (0.98–1.57)	
Other	228	1.44 (0.91–2.26)	0.51
Body mass index			
18.5–24.9 kg/m²	536	1.42 (1.07–1.88)	
25–29.9 kg/m²	362	1.28 (0.89–1.83)	
≥30 kg/m²	121	0.54 (0.27–1.07)	0.01
Passive smoking (any)			
None	499	1.39 (1.03–1.87)	
Any	543	1.17 (0.88–1.57)	0.67
Vegetable, fruit, fiber consumption			
1st Tertile	378	1.15 (0.76–1.74)	
2nd Tertile	288	1.70 (1.13–2.54)	
3rd Tertile	376	1.03 (0.73–1.44)	0.27
Fat consumption			
1st Tertile	441	1.29 (0.91–1.82)	
2nd Tertile	337	1.31 (0.90–1.90)	
3rd Tertile	264	1.06 (0.69–1.62)	0.59
Industrial exposures			
Yes	143	1.17 (0.66–2.09)	
No	899	1.29 (1.03–1.61)	0.79
Residential radon concentrations			
<148 Bq/m³	1,005	1.26 (1.03–1.55)	
148+ Bq/m³	37	3.97 (1.14–13.83)	0.11
Asthma			
No	995	1.18 (0.96–1.47)	
Yes	47	5.18 (1.96–13.71)	0.005
Hay fever			
No	912	1.30 (1.04–1.62)	
Yes	130	1.07 (0.60–1.90)	0.66
Chronic obstructive pulmonary disease			
No	1,014	1.24 (1.01–1.54)	
Yes	28	2.08 (0.55–7.90)	0.16
Any chronic lung disease			
No	972	1.17 (0.94–1.45)	
Yes	70	3.78 (1.69–8.43)	0.003
Region			
Northeast	256	2.08 (0.98–4.43)	
South	221	0.96 (0.48–1.92)	
Midwest	316	1.18 (0.72–1.93)	
West	249	1.24 (0.89–1.73)	0.23

Definition of abbreviations: CI = confidence interval; CPS-II = American Cancer Society Cancer Prevention Study-II; HR = hazard ratio; $PM_{2.5}$ = ambient fine particulate matter.

* Fully adjusted model: age, race, and sex stratified and adjusted for education, marital status, body mass index, body mass index squared, passive smoking, vegetable/fruit/fiber consumption, fat consumption, industrial exposures, occupation dirtiness index, and mean county-level residential radon concentrations where appropriate.

over time. Similar findings for lung cancer mortality were also observed using either $PM_{2.5}$ (1979–1983) or $PM_{2.5}$ (1999–2000) among participants residing in one of the 53 MSAs common to both measures (fully adjusted HR per each 10 μg/m³ $PM_{2.5}$ [1979–1983] = 1.16, 95% CI 0.99–1.35; $PM_{2.5}$ [1999–2000] = 1.15, 95% CI 0.89–1.48).

The present results provide no information as to whether there may be a critical exposure time window that may be most relevant for lung cancer etiology. However, previous work in a subset of the CPS-II using estimated yearly $PM_{2.5}$ (1972–2000) concentrations, derived from concentrations of PM_{10} and total suspended particulates, examining the relative importance of different exposure time windows for all-cause and cause-specific mortality, including lung cancer, was largely uninformative because of limitations in study design and modest spatiotemporal variation in $PM_{2.5}$ concentrations over time (15).

There was no information on residential mobility after enrollment; however, never-smoking participants reported living in their current neighborhood at enrollment for a mean number (SD) of 20.7 (14.9) years. Misclassification because of residential mobility would also likely be nondifferential, biasing estimated RR estimates toward unity. No updated data on cigarette smoking or other individual-level covariates of interest were collected from enrollment in the full CPS-II; however, it is unlikely that lifelong never-smokers in the cohort with an average age at enrollment of 57 years would begin smoking during follow-up. There may also have been changes in other sociodemographic ecologic-level factors over time; however, little change in results was observed on the inclusion of sociodemographic ecologic covariates in the model from any three of the time periods considered (1980s, 1990s, or 2000s).

Although the present study was based on mortality, inferences about the incidence of highly fatal diseases, such as lung cancer, may be reasonably approximated using mortality-based data. Similar associations between ambient air pollution and lung cancer incidence and mortality were also observed in other recent work (23, 24, 28, 29). There was no information available on the histologic subtype of lung cancer. Results from a Danish study reported stronger associations between estimated NO_x concentrations and incident small-cell carcinoma and squamous cell carcinoma than adenocarcinoma (30).

Finally, this study used ecologic measures of residential radon to adjust for the potential confounding effects of residential radon exposure, rather than residential radon concentrations measured in individual homes. However, in previous work, estimates of increased lung cancer mortality caused by environmental radon observed in the CPS-II were compatible with estimates obtained in combined analyses of residential case-control studies (17). Mean radon concentrations were also weakly (and inversely) correlated with $PM_{2.5}$, suggesting that any potential confounding effect of residential radon concentrations on $PM_{2.5}$–lung cancer associations is likely small.

In conclusion, results from this large prospective study showed positive associations between mean long-term ambient $PM_{2.5}$ concentrations and lung cancer mortality in lifelong never-smokers, further strengthening the evidence that ambient concentrations of $PM_{2.5}$ measured in recent decades are associated with small but measurable increases in lung cancer mortality. Results also demonstrate that the magnitude of lung cancer risk associated with exposure to $PM_{2.5}$ is notably smaller than that caused by active smoking (48).

Author Disclosures are available with the text of this article at www.atsjournals.org.

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Long-Term Ambient Fine Particulate Matter Air Pollution and Lung Cancer in a Large Cohort of Never Smokers

Michelle C. Turner, Daniel Krewski, C. Arden Pope III, Yue Chen, Susan M. Gapstur, Michael J. Thun

ONLINE DATA SUPPLEMENT

Table E1. Adjusted HRs (95% CIs) for non-malignant respiratory disease mortality (ICD 9 460-519; ICD 10 J00-J98) in relation to each 10 μg/m^3 increase in mean ambient fine particulate matter air pollution concentrations, follow-up 1982-2008, never smokers, CPS-II cohort, US.

$PM_{2.5}$ Concentration	No. of subjects (deaths)	Minimally-adjusted HR (1) (95% CI)*	Partially-adjusted HR (2) (95% CI)*	Fully-adjusted HR (3) (95% CI)*
$PM_{2.5}$ (1979-1983)	131,864 (3,309)	1.03 (0.96-1.11)	1.01 (0.94-1.09)	1.02 (0.95-1.10)
$PM_{2.5}$ (1999-2000)	177,752 (4,313)	1.04 (0.94-1.14)	1.03 (0.93-1.13)	1.04 (0.94-1.16)
$PM_{2.5}$ (1979-1983) and (1999-2000) Average	120,917 (3,014)	1.01 (0.91-1.11)	0.99 (0.90-1.09)	1.01 (0.91-1.12)

* Minimally-adjusted HR (1): age, race, gender stratified.

Partially-adjusted HR (2): age, race, gender stratified and adjusted for education, marital status, body mass index, body mass index squared, passive smoking, vegetable/fruit/fiber consumption, fat consumption, industrial exposures, occupation dirtiness index.

Fully-adjusted HR (3): age, race, gender stratified and adjusted for education, marital status, body mass index, body mass index squared, passive smoking, vegetable/fruit/fiber consumption, fat consumption, industrial exposures, occupation dirtiness index, and mean county-level residential radon concentrations.

Table E2. Correlation between mean $PM_{2.5}$ (1999-2000) concentrations and 1980, 1990, and 2000 zip code-level ecological covariates and adjusted HRs (95% CIs) for lung cancer mortality per 10 $\mu g/m^3$ increase in mean $PM_{2.5}$ (1999-2000) concentrations adjusting for each ecological covariates individually or in combination, never smokers, follow-up 1982-2008, CPS-II cohort, US.

Ecological Covariate	1980 (n=374,798)		1990 (n=365,210)		2000 (n=364,001)	
	Correlation (*r*)	Fully-adjusted HR (95% CI)*	Correlation (*r*)	Fully-adjusted HR (95% CI)*	Correlation (*r*)	Fully-adjusted HR (95% CI)*
Fully-adjusted HR, individual level covariates only	-	1.27 (1.03-1.56)	-	1.25 (1.01-1.55)	-	1.27 (1.02-1.56)
+ Median household income	0.10	1.27 (1.03-1.56)	0.12	1.25 (1.01-1.54)	0.06	1.27 (1.02-1.56)
+ % Air conditioning	0.16	1.25 (1.01-1.54)	-	-	-	-
+ % Non-white	0.16	1.27 (1.03-1.57)	0.21	1.25 (1.01-1.55)	0.22	1.25 (1.01-1.55)
+ % Non-white (incl. hisp)	0.16	1.28 (1.04-1.58)	0.20	1.26 (1.02-1.55)	0.20	1.25 (1.01-1.55)
+ % Black	0.13	1.26 (1.03-1.56)	0.15	1.24 (1.00-1.53)	0.16	1.25 (1.01-1.55)
+ % Non-hispanic black	0.13	1.26 (1.03-1.56)	0.15	1.24 (1.00-1.53)	0.16	1.25 (1.01-1.55)
+ % Hispanic	0.09	1.29 (1.05-1.59)	0.11	1.27 (1.03-1.57)	0.09	1.27 (1.03-1.57)
+ % Adults with post-secondary education (25)	-	-	-0.09	1.25 (1.01-1.54)	-0.09	1.26 (1.02-1.56)
+ % Population with post-secondary education (25)	-	-	-0.06	1.26 (1.02-1.56)	-0.07	1.27 (1.03-1.57)
+ % Adults with post-secondary education (18)	-0.06	1.26 (1.03-1.56)	-0.08	1.25 (1.01-1.54)	-	-
+ % Population with post-secondary education (18)	-0.04	1.27 (1.03-1.56)	-0.06	1.25 (1.01-1.55)	-	-
+ % Unemployment	0.05	1.27 (1.03-1.56)	0.05	1.26 (1.02-1.55)	0.08	1.27 (1.02-1.57)
+ % Poverty	-0.0006	1.26 (1.03-1.56)	0.004	1.25 (1.01-1.54)	0.06	1.27 (1.02-1.56)
+ % Urban	0.01	1.27 (1.03-1.56)	0.009	1.25 (1.01-1.54)	0.03	1.27 (1.02-1.56)
+ % Highly urban	-	-	0.02	1.25 (1.01-1.55)	0.03	1.26 (1.02-1.56)
+ % Mover	-0.11	1.25 (1.01-1.54)	-0.05	1.24 (1.01-1.54)	-0.12	1.25 (1.01-1.55)
+ % Mover (outside county)	-0.20	1.24 (1.00-1.53)	-0.14	1.23 (1.00-1.53)	-0.22	1.27 (1.02-1.58)
+ % Well	-0.004	1.26 (1.03-1.56)	-0.01	1.25 (1.01-1.54)	-	-
+ adjusting for six ecological covariates selected *a priori*†	-	1.27 (1.02-1.58)	-	1.24 (1.00-1.55)	-	1.26 (1.01-1.57)

* Age, race, gender, stratified and adjusted for education, marital status, body mass index, body mass index squared, passive smoking, vegetable/fruit/fiber consumption, fat consumption, industrial exposures, occupation dirtiness index, and mean county-level residential radon concentrations.

† Ecological variables included here were: 1980: median household income, % air conditioning, % non-white, % population with post-secondary education at 18 years, % poverty, and % unemployment; 1990: median household income, % non-hispanic black, % hispanic, % population with post-secondary education at 18 years, % poverty, and % unemployment; 2000: median household income, % non-hispanic black, % hispanic, % population with post-secondary education at 25 years, % poverty, and % unemployment.

7. DISCUSSION

Summary of Findings

This thesis examined associations between ecological indicators of residential radon and fine particulate matter air pollution and lung cancer mortality in the CPS-II. Findings indicated significant positive associations between radon and both malignant and non-malignant respiratory disease mortality but no clear associations with other cause of death categories. More specifically, each 100 Bq/m^3 of radon was associated with a 15% (95% CI 1-31%) increase in the risk of lung cancer mortality. Among participants with radon concentrations above the guideline value of the US EPA (148 Bq/m^3) a HR of 1.34 (95% CI 1.07-1.68) was observed relative to those below the guideline value. Radon was also associated with COPD mortality. Each 100 Bq/m^3 of radon was associated with a 13% (95% 5-21%) increase in the risk of COPD death. Although it remains uncertain whether radon may lead to the induction of COPD, in addition to its exacerbation, airway dysfunction may represent an earlier indicator of the radon effect. Findings were robust to the inclusion of socio-demographic ecological risk factors and ambient air pollution concentrations in the model. There was no significant effect modification observed by cigarette smoking status or other individual or ecological-level risk factors; however, results for both mortality endpoints varied according to geographic region. Results for COPD also varied according to age at enrollment with stronger findings observed in those aged at least 65 years. Similar findings were observed using either the estimated radon data from the Lawrence Berkeley National Laboratory or measured data from Cohen.

Positive associations between mean ambient $PM_{2.5}$ concentrations and lung cancer mortality in never smokers were also observed. Each 10 µg/m^3 of $PM_{2.5}$ was associated with a 15-27% increase in risk of lung cancer death adjusting for radon concentrations and other lung cancer risk factors. The

association was similar in men and women and across categories of attained age and educational attainment but was stronger in those with a normal BMI and a history self-reported physician-diagnosed asthma or any chronic lung disease (asthma, chronic bronchitis, or emphysema) at enrollment. No association was observed between $PM_{2.5}$ and non-malignant respiratory disease mortality overall. Although it is unclear whether the stronger associations observed in participants with CLD may be due to increased susceptibility, chance, or some form of common underlying exposure, CLD may also lie on the lung cancer pathway. Figure 2 summarizes observed and hypothesized associations between radon/$PM_{2.5}$, chronic lung disease, and lung cancer.

Strengths and Limitations

Strengths of this thesis include the examination of environmental risk factors for lung cancer mortality in a large, national, prospective study; the availability of detailed individual-level lung cancer risk factor data collected at enrollment including demographic, cigarette smoking, passive smoking, diet, and occupational exposures as well as various socio-demographic ecological-level variables available at three points in time (1980, 1990, 2000)[44]; extended follow-up time data with large numbers of lung cancer deaths and near complete mortality follow-up; the ability to examine the potential mutual confounding and/or modifying effects of radon and air pollution for lung cancer; and the ability to take into account potential spatial clustering in the mortality experience of CPS-II participants. Detailed adjustment for cigarette smoking history is particularly relevant as residential radon concentrations and cigarette smoking rates are inversely correlated with lower residential radon concentrations in urban areas due to apartment-living and geology as well as higher rates of cigarette smoking[10;11;133].

Another strength is the availability of an occupational dirtiness index previously designed for the CPS-II in order to address potential limitations in the reporting of occupational exposures[268]. The

index was constructed based on expert assessment of reported job titles, assigning participants to a seven point dirtiness scale ranging from 0 (clean occupational environment) to 6 (very dirty occupational environment). However variability in occupational exposures is not considered or cumulative occupational history, as only the dirtiest job was included based on either the current, last, or longest occupation.

Potential limitations include the use of ecological indicators of residential radon and $PM_{2.5}$; limited historical residential radon and $PM_{2.5}$ data; the use of mortality-data for outcome ascertainment, particularly for less fatal outcomes, since both disease incidence and survival influence outcome status; no information on residential history prior to or from enrollment in the full CPS-II; the self-reported nature of individual-level covariate data collected at enrollment including BMI[269]; and no updated individual-level covariate data, including possible changes in passive smoking or cigarette smoking (usually quitting) over follow-up time (below). Although adjustment for both passive smoking as well as socio-demographic ecological factors was attempted using either self-reported passive smoking data collected at enrollment or socio-demographic ecological covariates compiled from the US Census, it is possible that changes in passive smoking or other socio-demographic ecological-level factors may have occurred over follow-up time that may vary according to radon or $PM_{2.5}$ levels, thereby confounding associations observed. There may also be some unrecognized confounders that may impact study findings.

Analyses also only considered residential exposures and there was no data on time-activity patterns such as time spent at home that may vary by region. Results from an Iowa study revealed that attempts to minimize misclassification through restricting participant selection to individuals who had lived in their home for at least the past 20 years and compiling detailed retrospective mobility assessments with measurements of radon in multiple locations both within and outside of the home resulted in an improved ability to detect associations between radon and lung cancer[144;270]. However,

the association between radon and lung cancer mortality, strengthened upon restriction of the analysis to individuals who had lived in their same neighbourhood at enrollment for at least 5 years (HR = 1.19, 95% CI 1.04-1.36).

CPS-II participants are also generally more educated compared to the US population as a whole due to the volunteer-based recruitment strategy. Although this may affect the generalizability of disease rates or exposures levels, the internal validity of the study is unlikely compromised due to the enhanced socio-economic status of the cohort overall[271]. There was also no evidence for effect modification by educational attainment.

Ecological Indicators of Residential Radon and $PM_{2.5}$

This study used ecological indicators of residential radon (county) and $PM_{2.5}$ (MSA) that were assigned to individuals in the CPS-II in a type of semi-ecological design. Ecological radon data were estimated in a statistical model based on available short- and long-term monitoring, geological, meteorological, and housing data (LBL), or were based on a non-random series of short-term screening measurements normalized to the data of the US National Residential Radon Survey (Cohen). Long-term ecological $PM_{2.5}$ data were obtained from central monitoring data. Although the potential impact of exposure measurement error on the results observed in the present study is complex and difficult to predict, the use of ecological indicators of residential radon and $PM_{2.5}$ likely result in some degree of reduced precision and downwards bias in mortality RR estimates[272-274]. Lagarde and Pershagen[143] noted the use of aggregated, ecological-level residential radon concentrations (county), as opposed to individual household-level estimates of radon in a case-control study resulted in a reduced precision of RR estimates, likely due to greater within- as opposed to between-area variability in radon concentrations. Jerrett et al.[275] noted that taking into account within-area gradients in $PM_{2.5}$ concentrations among CPS-II participants residing in Los Angeles resulted in mortality RR estimates that were up to three-fold greater compared to those based on

between-area comparisons. However, such findings were not replicated in the city of New York[203]. There may also be errors in the measurement of residential radon and $PM_{2.5}$ concentrations that are likely non-differential with respect to mortality status as well as errors associated with the use of measures of radon or $PM_{2.5}$ concentrations at one point in time to represent cumulative or historical levels of exposure as well as errors do to the use of sample data[138].

Analytic Approach

The analytic approach was informed by previous studies of the CPS-II cohort including extensive research examining the mortality health effects of ambient air pollution[5;202]. Detailed adjustment for a variety of individual- and ecological- level covariates was performed including both linear and squared terms for cigarette smoking amount and duration and BMI in order to account for potential non-linear mortality effects. One exception is the exclusion of variables representing alcohol (beer, wine, liquor) consumption here since the reported relationship between alcohol consumption and lung cancer is likely due to residual confounding[253]. Although other potential confounders were also examined, including physical activity, family history of lung cancer, chronic lung disease, reproductive and hormonal variables, as well as substitution of the occupational dirtiness index for a related lung carcinogen index, they exerted a negligible effect on associations observed. Participants were also excluded with prevalent cancer, except non-melanoma skin cancer, at enrollment to avoid secondary lung cancers in analysis. Results (not presented here) were also virtually identical upon exclusion of the 40,359 included CPS-II participants who reported a non-melanoma skin cancer at enrollment.

Although a similar analytic approach was used throughout this thesis, including inclusion/exclusion criteria, modeling approach, and covariate construction, there were some differences in follow-up time and included covariates among the different analyses (Table 3). To address potential concerns

regarding control for cigarette smoking in analysis of associations between residential radon and lung cancer mortality due to possible changes in cigarette smoking over time (usually quitting), analysis in the first article was restricted *a priori* to the first six years of follow-up only (1982-1988). In contrast, in an attempt to maximize statistical power to detect possible associations between residential radon and other mortality (articles two and three) an extended follow-up time period (1982-2006) was used. Residential radon concentrations and cigarette smoking are also inversely correlated[10;11;140;276] and negative confounding of radon associated lung cancer and COPD mortality by cigarette smoking was observed. With the exception of ischemic heart disease mortality, results for other specific non-lung cancer mortality did not vary with follow-up time. Since the fourth article examined associations between $PM_{2.5}$ and lung cancer mortality in never smokers only, a further extended follow-up time period (1982-2008) was used as updated mortality follow-up data became available over the course of the analysis. Figure 3 and 4 present a comparison of HRs for cigarette smoking (current smokers at enrollment) over follow-up time for lung cancer and non-malignant respiratory disease mortality in men and women in the CPS-II. Due to different follow-up time periods, there were also some differences in ecological covariates examined. Results from all four manuscripts were robust to their adjustment.

Results examining mortality associations with radon were adjusted for a variety of individual-level covariates as well as state of residence at enrollment in order to control for complex underlying spatial patterns in residential radon concentrations and lung cancer risk factors. In analyses adjusting for state of residence, a significant positive linear trend was observed between residential radon and lung cancer mortality whereas there was no evidence for a linear trend in analyses unadjusted for state. Although a similar state of residence adjustment was attempted in analysis examining associations between $PM_{2.5}$ and lung cancer mortality, this lead to a type of overadjustment (or unnecessary adjustment[277]), with HR point estimates remaining unchanged with a simultaneous

decrease in their precision, likely due to the coarser level of geographic scale of $PM_{2.5}$ exposure (MSA) compared to residential radon concentrations (county).

Regional Differences

Results for residential radon varied by region with the strongest associations with lung cancer mortality observed in the Northeast (HR = 1.31, 95% CI 1.12-1.53). For COPD mortality, significant positive associations ranging from 12-21% were observed in all US regions, with the exception of the South, where no association was observed (HR = 0.94, 95% CI 0.81-1.08). Although reasons for regional differences in results are unclear, they may be due to a variety of factors including, differences in residential radon concentrations (Figure 5), underlying participant characteristics (Table 4), radon exposure measurement error, housing stock, or behavior, including possible regional differences in time spent at home, or other factors unaccounted for in the analysis that may vary by region. Regional differences in results may also be a function of the particular administrative data boundaries used in analysis.

Interactions

A unique aspect of this thesis was the ability to examine the potential mutual confounding and/or modifying effects of residential radon and ambient air pollution for lung cancer since little of such information exists. Boffetta and Trichopoulos[278] describe how such exposures may interact, either externally – thereby influencing lung penetration, or internally – accelerating carcinogenic mechanisms. The question remains as to whether such agents may interact, thereby producing additive or multiplicative effects on lung cancer risk.

Greenland and Rothman[279] point out the distinction between statistical interaction, biologic interaction, and public health interaction. Ahlbom and Alfredsson[280] define a statistical interaction as

"*the necessity for a product term in a linear model*" whereas a biological interaction occurs "*where two risk factors are involved in the same sufficient cause of disease…*" (p. 563). Rothman and Greenland[281] further point out that two risk factors do not need to act simultaneously, but rather they may occur at different points in time, as part of a sequence of component causes leading to disease. Accordingly, it is suggested that biological interactions are best assessed as a departure from additivity, and not multiplicativity, in disease rates[279;280]. Although theoretical predictions of the effect of two carcinogens based on an approximate form of the two-stage clonal expansion model of carcinogenesis reported interactive effects ranging from additive interactions in the case of two initiators to supra-multiplicative effects in the case of an initiator and a promoter or two promoters[282], further work using an exact form of the model revealed supra-multiplicative through supra-additive effects in the case of two promoters in both younger and older age groups respectively[283;284].

However, no significant interactions were observed between radon and ambient air pollution for lung cancer mortality on either the additive or multiplicative scales (see Table 5 for three measures of additive interaction between $PM_{2.5}$ and other inhalable agents for lung cancer mortality in never smokers), indicating that the two risk factors may act independently; although there may also have been limited power to detect second order effects here. There was also little evidence for potential mutual confounding of radon and ambient air pollution for lung cancer mortality and correlations between the two ecological exposures were weak.

There was also no significant interaction between radon and cigarette smoking. Results from miners studies, with high levels of radon exposure, have indicated some evidence for supra-additive but sub-multiplicative effects[4]. Results from combined analyses of case-control studies with lower radon levels indicated little evidence that the association between radon and lung cancer varied by cigarette smoking status on either scale[10-13]. Cigarette smokers may experience higher radon doses due to changes in lung physiology and breathing rates[285]. There may also be differences in dose and lung

deposition characteristics due to the attachment of radon progeny to aerosols present in the indoor environment, however it is difficult to predict their cumulative impact on lung cancer risk[286;287].

Radon in Canada

This thesis observed significant positive associations between ecological indicators of residential radon and mortality from malignant and non-malignant respiratory disease. In Canada, mean residential radon concentrations were estimated to range from 33.8 Bq/m^3 in Newfoundland and Labrador to 143 Bq/m^3 in Manitoba with an overall population-weighted mean value of 45.5 Bq/m^3, corresponding to a mean annual effective dose of approximately 1.15 mSv[288]. In Canada, the guideline value for radon concentrations in homes was recently lowered by Health Canada and the Federal/Provincial/Territorial Radiation Protection Committee from 800 Bq/m^3 to 200 Bq/m^3 due to increasing scientific evidence of adverse human health effects and the cost-effectiveness of radon mitigation strategies[289;290]. Currently, it is estimated that 3.3% of homes exceed the revised guideline value increasing to 8.8, 10, and 19% in Saskatchewan, Nova Scotia, and Manitoba respectively[288]. Estimates of residential radon concentrations worldwide are provided by Chambers and Zielinski[291]. Interestingly, a recent report of the Independent Advisory Group on Ionizing Radiation in the UK recommended that the concept of a radon affected area should be reviewed since it has lead to beliefs that there exist areas unaffected by radon[292].

Results of an evaluation examining the impact of residential radon in Canada reported that 7.8% (95% CI 4.1-13.8%) of the lung cancer burden, or 1,400 lung cancer deaths, can be attributed to residential radon each year, translating to 0.10 (95% CI 0.05-0.17) of one year of life-years lost [293]. In terms of compliance with the revised Canadian guideline value, it was estimated that there would still be over 1,200 radon-induced deaths annually if radon concentrations in all homes met the revised

guideline, since the majority of lung cancer cases will occur among those in homes below the guideline value [294].

Radon Mitigation

Although radon mitigation in homes can be achieved using a variety of active and passive techniques including sub-slab depressurization, block wall or baseboard ventilation, foundation drain suction, heat recovery ventilation, house pressurization, crawl space sealing and ventilation, or sealing or plugging of cracks, joints or holes, it can also be associated with significant cost[15;295]. Radon mitigation techniques in North America and Europe were summarized by Rahman and Tracy[295]. A recent economic analysis of the cost-effectiveness of radon mitigation in the UK revealed that extending basic radon prevention measures to all new homes would be cost-effective but that the identification and remediation of existing homes would only be so if the current Action Level was reduced from 200 Bq/m^3 and only in high radon regions[296]. In a recent Quebec analysis, radon screening in primary and secondary schools was found to represent the most effective screening scenario for reducing radon associated lung cancer deaths in the province[297].

Results from several US surveys have revealed that few homeowners have measured radon concentrations in their homes. Results from the National Health Interview Survey (1990, 1993-1994) revealed that only 3-7% of homeowners had their homes tested for radon[298;299]. Results varied according to smoking status, education, income, and geographic region. However awareness of radon was relatively high with 69.1% of respondents (1990 survey) reporting that they had ever heard of the gas[299]. Similar results were observed in more recent surveys[300;301]. Results from 4,501 participants in the US Women Physicians' Health Study revealed somewhat higher rates of residential radon testing compared to the general population, however rates overall were still low (18%)[302]. Results from a UK study revealed higher levels of radon concern, acceptability, and trust in

authorities among participants in high compared to low radon areas possibly due to impact of recent radon risk communications on public perception[303].

There are also studies assessing barriers to radon mitigation. In a telephone survey of 1,209 New York residents (1995-1997), 82% reported that they had ever heard of radon with 15% reporting that they had tested their home[304]. Barriers to testing included beliefs that there was no radon in their own particular home, radon was not a problem in their area, and that radon risk is exaggerated. An optimistic bias regarding radon associated health risks has also been reported as a barrier to mitigation[305]. A follow-up study of 62 participants in an Iowa study with high (20 pCi/L ~ 740 Bq/m^3) radon screening measurements revealed that only 39% planned further radon testing due to reasons of unconcern, belief that radon concentrations were low, and either too busy or planning to move[306]. In a survey of 179 Vermont households who had elevated levels of radon in their home, only 43% indicated that they had mitigated. Factors associated with mitigation included a high level of educational attainment, concern over property values, and a home aged 10 years or less[307]. Results from other studies have also revealed low levels of recognition that lung cancer was specifically associated with exposure to radon gas[300;306;307]. Results from a Manitoba study revealed that respondents were willing to mitigate radon concentrations in their homes only at very high concentrations (>1,100 Bq/m^3)[308]. In 2010, the National Building Code in Canada was revised to require basic radon prevention measures in new homes as well as a rough-in requirement for a sub-slab depressurization device should further radon remediation be required in the future[309].

It should also be noted that although the relative risk of lung cancer was similar per unit increase in radon concentrations between smokers and never smokers both here and in combined analysis of residential radon case control studies, Darby et al.[10;11] noted that since higher rates of lung cancer are observed in smokers, radon results in greater increases in the cumulative absolute risk of lung cancer death in smokers. Additionally, in smokers with low residential radon concentrations, greater

reductions in the cumulative absolute risk of lung cancer death would be achieved by reductions in cigarette smoking than reductions in residential radon[11].

The WHO International Radon Project recently published a Handbook on Indoor Radon, providing guidance on radon prevention, mitigation and risk communication[15]. A reference level of 100 Bq/m^3 was proposed for the maximum allowable level of radon concentrations in homes. Multi-level, multi-stakeholder participation in national radon programs was recommended including research scientists, radiation protection and construction standard agencies, measurement laboratories, training providers, and media groups. It was also recommended to link radon policy with tobacco and indoor air quality programs.

Air Pollution in Canada

This thesis also observed significant positive associations between ecological indicators of $PM_{2.5}$ and lung cancer mortality in never smokers, providing further evidence that ambient concentrations of $PM_{2.5}$ measured in recent decades are associated with small but measurable increases in lung cancer mortality. In Canada, mean $PM_{2.5}$ concentrations range from approximately 15 $\mu g/m^3$ to 20 $\mu g/m^3$ in most major centres (2001-2005) according to monitoring data collected as part of the National Air Pollution Surveillance network[310]. However $PM_{2.5}$ concentrations in some areas of Southern Ontario and British Columbia were either near or exceeded the 2010 Canada-Wide Standard (CWS) of 30 $\mu g/m^3$ (24 hour averaging) largely due to transboundary air pollution and forest fire sources respectively[310]. In setting the CWS, the Canadian Council of Ministers of the Environment, an intergovernmental group consisting of Federal/Provincial/Territorial environment ministers, attempted to balance between health protection, feasibility and associated costs[310;311]. The CWS also aims to support continuous improvement in $PM_{2.5}$ concentrations even in areas where concentrations are currently below the standard. In contrast the 2005 WHO Air Quality Guideline for long-term

$PM_{2.5}$ is 10 μg/m^3 representing the lowest concentrations where long-term mortality health effects have been observed.

Hystad et al.[312] using LUR modeling techniques, recently predicted a mean 2006 national population weighted average $PM_{2.5}$ concentration in Canada of 8.39 μg/m^3. In contrast, mean population weighted $PM_{2.5}$ concentrations worldwide were estimated to range from 7 μg/m^3 in South America to 44 μg/m^3 in Eastern Asia with a worldwide mean of 27 μg/m^3 using a satellite-based approach[18]. However concentrations exceeding 100 μg/m^3 are observed in some areas of Eastern China.

Worldwide, the WHO has estimated that fine particulate matter air pollution is responsible for approximately 5% of all cancers of the trachea, bronchus, and lung[22]. In Canada, 7.4% (95% CI 2.8-11.6%) of lung cancers in major cities can be attributed to $PM_{2.5}$[313]. Coyle et al.[314] estimated that each unit reduction in sulfate air pollution concentrations in Canada would yield an overall mean increase of 20,960 quality-adjusted life years per year.

Air Pollution Interventions

An overview of air quality management in Canada is provided by Craig et al.[311]. Air quality management is complex, including multiple and transboundary sources, complex mixtures, and various science and policy challenges including links with climate change[311;315]. Although air quality management has traditionally followed a single-pollutant, emissions-based approach, there is increasing interest in multi-level, multipollutant air quality management strategies[316;317]. Giles et al.[318] explored interventions for air pollution at the individual- and community-level including source substitution, technology upgrades, urban planning initiatives, opportunities to reduce individual susceptibility (including reducing underlying cardiovascular risk factors and control of underlying illness), as well as individual behavioural interventions to aid in the avoidance of outdoor and indoor air pollution sources. There may be synergies in urban transport policy for health, behavior, and

environmental quality[319]. There are also community-based participatory approaches for air pollution research and policy[320;321].

A large (n = 1,503) 2004 national general risk perception survey revealed that air pollution was perceived as posing a high risk to the health of Canadians[322]. A total of 48.5% of respondents reported that air pollution posed a 'high health risk'. Differences in air pollution risk perceptions were observed by age, gender, education, and region. Results from a companion project revealed greater air pollution risk perceptions from members of the general public compared with expert groups (toxicologists and medical doctors)[323]. Results from a US study revealed gender and population group differences in outdoor air pollution risk perceptions as well as different reactions to outdoor air pollution risk communications[324]. A UK case-study reported that respondents predominantly attributed respiratory concerns to traffic-related air pollution whereas cancer and heart disease were identified to a lesser extent[325].

Stieb et al.[326] described a recent multipollutant, no-threshold air quality health index (AQHI) for Canada. The AQHI was designed as a risk communication tool, providing hourly information on integrated air pollution levels and associated health messages (such as avoiding outdoor exercise) for the general public, including vulnerable groups. The AQHI was based on short-term mortality associations with NO_2, O_3, and $PM_{2.5}$ observed in twelve major Canadian cities. Limitations include the fact that there is little evidence supporting the health messages provided as part of the AQHI or the effectiveness of the AQHI in achieving intended behavioral modifications. The relevance of the AQHI, or related indices, for lung cancer is also unclear.

Conclusions and Future Research

In conclusion, this thesis has observed positive associations between ecological indicators of residential radon and fine particulate matter air pollution and malignant and non-malignant

respiratory disease mortality. Results both support previous associations observed between residential radon and lung cancer in combined analyses of residential radon case-control studies as well as suggestions of increased lung cancer risk associated with $PM_{2.5}$ in studies of both smokers and non-smokers combined. Results also suggest a possible association between residential exposure to radon and mortality from COPD which requires confirmation in further studies. No clear associations were observed between residential radon and non-respiratory mortality.

Further research is required in order to better understand potential adverse population health impacts of residential radon and ambient air pollution including: examination of associations between residential radon and $PM_{2.5}$ and the incidence of malignant and non-malignant disease; further examination of associations using indicators of exposure at finer geographic levels of scale, novel approaches including the assessment of glass-based residential radon concentrations as well as LUR or satellite-based estimates of $PM_{2.5}$ concentrations may be particularly useful in this regard; examination of associations between specific components of $PM_{2.5}$ or specific $PM_{2.5}$ sources with lung cancer; further work to disentangle possible complex inter-relationships between environmental radon and air pollution with chronic lung disease and lung cancer; further work to examine potential interrelationships between inhalable environmental exposures for lung cancer, and further work assessing genetic susceptibility to the adverse health effects of radon and $PM_{2.5}$.

STATEMENT OF CONTRIBUTIONS OF COLLABORATORS AND/OR CO-AUTHORS

I (MCT) conceived of this thesis project, conducted all statistical analyses, compiled ecological covariates from the 1980, 1990, and 2000 US Census, and drafted all thesis chapters and manuscripts. Thesis co-directors (DK, YC), committee members (CAP, MJT), and other co-authors (SMG), provided input into the design of the project, the analysis and interpretation of results, and participated in the drafting of thesis manuscripts by providing critical comments on initial versions of each manuscript. MJT and SMG also provided access to the CPS-II dataset.

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TABLES

Table 1. Risk factors for lung cancer.

Genetics and Biology	Environment and Occupation	Social and Behavioural
Family history	Radon	Cigarette smoking
Specific genetic polymorphisms	Air pollution	β-carotene supplements
Chronic lung disease	Environmental tobacco smoke	Low dietary carotenoid, fruit,
Infection	Indoor air pollution (coal, biomass)	cruciferous vegetable consumption
	Arsenic in drinking water	Low physical activity
	Occupational and medical radiation	Hormonal replacement therapy
	Occupational carcinogens and carcinogenic circumstances	

Table 2. Previous case-control and cohort studies examining the association between air pollution and lung cancer.

Reference, Country	Subjects	Follow-up	% Non-smokers	Air Pollution	No. lung cancer cases/deaths	Unit of analysis	RR (95% CI)	Comments
CASE-CONTROL STUDIES								
Vena[178], USA	417 prevalent white male lung cancer cases and 752 non-cancer/infectious disease/respiratory disease controls from Erie County, New York admitted to Roswell Park Memorial Institute 1957-1965 aged 30 years or older	-	?	High/medium, low air pollution zones based on TSP monitoring data (1961-63) and historical stack emissions inventory	417 prevalent lung cancer cases	>= 50 years in high/medium air pollution area vs < 50 years or low air pollution	1.09 (0.66-2.20)	Age adjusted Possible evidence for synergy between air pollution, smoking, occupation
Jedrychowski et al.[181], Poland	1,099 lung cancer deaths and 1,073 age, sex matched non-respiratory deaths in Cracow Poland 1980-1985	-	5-25% never smoker males 39-84% never smoker females	High, medium, low air pollution zones based on TSP and SO_2 monitoring data (1973-1980)	1,099 lung cancer deaths	High (TSP > 150 and SO_2 > 104 µg/m3), medium (TSP > 150 or SO_2 > 104 µg/m^3 but not both), low (TSP < 150 and SO_2 < 104 µg/m^3)	Males 1.46 (1.06-1.99) high vs low overall 1.45 (0.74-2.87) high vs low non-smokers Females 1.17 (0.70-1.96) medium/high vs low 1.16 (0.48-2.80) high vs low non-smokers	Age adjusted Proxy completed questionnaire Possible evidence for synergy between air pollution, smoking, occupation
Katsouyanni et al.[179], Greece	101 prevalent female lung cancer cases and 89 orthopedic controls from Athens hospitals aged 35 years or greater who were permanent Athens residents 1987-1989	-	48-75% non smokers	Air pollution quartiles for each borough based on smoke and NO_2 monitoring data (1983-85)	101 prevalent lung cancer cases	Quartiles	1.22 (0.91-1.63) upper 2 vs lower 2 quartiles 0.81 in non-smokers, highest vs lowest quartile	Possible evidence for synergy between air pollution and smoking
Jockel et al.[180], Germany	194 incident lung cancer cases from 7 hospitals and 194 hospital (diagnosis unrelated to smoking) and 194 population (residence registry) age-gender matched controls	-	2-14% non smoker	Estimated SO_2 emissions by county (1955-1980), semiquantitative index based on BaP, TSP, SO_2 emissions, coal, and urbanization by county (1895-1984)	194 lung cancer cases	High vs low	1.01 (0.53-1.91) emission index 1.16 (0.34-2.13) semiquantitative index	Age, smoking, occupation adjusted

Barbone et al.[165], Italy	755 male lung cancer deaths from Trieste Cancer Registry (1979-1981/1985-1986) and 755 age-matched controls who had died during similar time period from other chronic diseases excluding lung diseases or cancers of the upper aerodigestive tract, urinary tract, pancreas, liver, gastrointestinal system	-	3-26% non smokers	Average value of total particulate from nearest monitoring station from 1972-1977 at last residence	755 lung cancer deaths	Highest vs lowest tertile	1.2 (0.8-1.7) squamous cell 1.7 (1.1-2.5) small cell 1.7 (0.9-3.0) large cell 1.3 (0.8-2.0) adenocarcinoma 1.4 (1.1-1.8) all lung cancer 3.7 (1.0-15) all lung cancer, non-smokers	Age, smoking, occupational exposure, social level adjusted Proxy completed questionnaire Examined histologic subtypes of lung cancer
Nyberg et al.[185], Sweden	1,042 incident male lung cancer cases and 2,364 age-matched population-based controls (1,274 from population register, 1,090 from cause of death registry) aged 40-75 years, and stable residents of Stockholm County 1985-1990	-	3-30% never smokers	NO_x, NO_2, SO_2, indicators of air pollution using dispersion modeling at residential addresses (1950-1990)	1,042 lung cancer cases	per 10 $\mu g/m^3$	30 year average 1.05 (0.93-1.18) NO_2 1.00 (0.96-1.05) SO_2 10 year average, lagged 20 years 1.10 (0.97-1.23) NO_2 1.01 (0.98-1.03) SO_2 1.68 (0.67-4.19) NO_2 never smokers 90^{th} percentile	Age, selection year, smoking, radon, socioeconomic group, occupational exposure adjusted Time-weighted average air pollution exposure Multipollutant models
Chiu et al.[182], Taiwan	972 female lung cancer deaths and 972 age, year of death matched non-cancer/respiratory death controls 1994-2003, Taiwan, aged 50-69, housewives	-	No smoking data, but very low prevalence overall	Municipality-based aggregate index of long-term exposure to air pollution by dividing annual average values for each pollutant (PM_{10}, O_3, CO, NO_2, SO_2) by national standard for the pollutant, and averaged together (1994-2003)	972 lung cancer deaths	highest vs lowest tertile	1.28 (1.02-1.61)	Urbanization adjusted
Pisani et al.[184], Thailand	211 prevalent lung cancer cases diagnosed from 1993-1995 and 211 hospital controls (admitted for non-tobacco related disease) recruited from Lampang Provincial Hospital and 202 age, sex matched	-	7-33% never smokers	Air pollution index calculated for each village/township based on linear distance from electrical generating plants, SO_2, NO_2, TSP, and wind (1978-1994)	211 lung cancer cases	highest vs lowest tertile	1.2 (0.7-2.0) cumulative SO_2 or NO_2 exposure 1.1 (0.7-1.8) cumulative TSP exposure 3.4 (0.7-23.3)	Age, sex, smoking adjusted Using population controls only

	population controls						cumulative SO_2 or NO_2 exposure non smokers	
Liu et al.[183], Taiwan	1,676 female lung cancer deaths and 1,676 age, year of death matched non-cancer/respiratory death controls from 1995-2005, Taiwan, aged 50-69, housewives	-	No smoking data, but very low prevalence overall	Measured levels of PM_{10}, O_3, CO, NO_2, SO_2 (1995-2005)	1,676 lung cancer deaths	highest vs lowest tertile	1.34 (1.12-1.60) NO_2 1.38 (1.16-1.66) CO 1.05 (0.88-1.25) SO_2 0.95 (0.80-1.13) PM_{10} 0.78 (0.65-0.92) O_3	
COHORT STUDIES								
Mills et al.[327]; Abbey et al.[328], USA	6,340 nonsmoking California Seventh-Day Adventists (AHSMOG) aged atleast 25 years, non-Hispanic white, lived at least 10 years at current residence, residents of San Francisco, Los Angeles, or San Diego primarily	1977-1982	100% nonsmokers (14-36% former smokers)	Average annual TSP, O_3 (1973-1977) concentrations at zip code centroid	17 incident lung cancers	Exceedance frequencies (each 1000 h/y TSP > 200 mg/m^3, each 500 h/y in excess of 10 pphm ozone)	1.72 (0.81-3.65) TSP 2.25 (0.96-5.31) O_3	Gender, education, smoking, occupation adjusted
Dockery et al.[191]; Krewski et al.[202], USA	8,111 randomly selected white subjects, aged 25-74, spirometric tested, from six US cities 1974-1977	1974-1991	35-42% never smokers	Total particles, SO_2, NO_2, ozone (1977-1985), inhalable fine particles (1979-1985), SO_4 (1979-1984), aerosol acidity (1985-1988), from study-specific central monitors	120 lung cancer deaths	Most polluted to least polluted city (18.6 $\mu g/m^3$)	1.37 (0.81-2.31) fine particles	Age, sex, smoking, education, BMI adjusted
Pope et al.[201]; Krewski et al.[202], USA	552,138 CPS-II participants in 151 US metropolitan areas, atleast 30 years of age and at least one individual in the household of atleast 45 years of age	1982-1989	49% never smokers	$PM_{2.5}$ (1979-1983) and SO_4 (1980) from central monitors at the MSA level	2,001 lung cancer deaths (see Krewski et al. 2009)	Most polluted to least polluted city (19.9 $\mu g/m^3$ SO_4, 24.5 $\mu g/m^3$ $PM_{2.5}$)	1.36 (1.11-1.66) SO_4 1.03 (0.80-1.33) PM2.5	Age, sex, race, smoking, passive smoking, BMI, alcohol, education, occupational exposure adjusted
Beeson et al.[187],	6,338 nonsmoking California Seventh-Day Adventists	1977-1992	100% nonsmokers (14-	Mean monthly PM_{10}, TSP, SO_2, O_3, NO_2,	36 incident lung cancer	IQR	Males 1.65 (0.72-3.80) O_3	Age, smoking, education, alcohol

USA	(AHSMOG) aged atleast 25 years, non-Hispanic white, lived at least 10 years at current residence, residents of San Francisco, Los Angeles, or San Diego primarily		36% former smokers)	and SO_4 (1973-1992) from central monitors interpolated to participant zip codes at work and at home	cases		5.21 (1.94-13.99) PM_{10} 2.66 (1.62-4.39) SO_2 1.45 (0.67-3.14) NO_2 4.48 (1.25-16.04) O_3(100) never smokers 2.90 (1.49-5.62) PM_{10}(100) never smokers Females 2.14 (1.36-3.37) SO_2	adjusted 3 year lag in average annual exposure Multipollutant models also explored
Abbey et al.[186], USA	6,338 nonsmoking California Seventh-Day Adventists (AHSMOG) aged atleast 25 years, non-Hispanic white, lived at least 10 years at current residence, residents of San Francisco, Los Angeles, or San Diego primarily	1977-1992	100% nonsmokers (14-36% former smokers)	Mean monthly PM_{10}, TSP, SO_2, O_3, NO_2, and SO_4 for the years 1973-1992 from central monitors interpolated to participant zip codes at work and at home	30 lung cancer deaths	IQR	Males 3.36 (1.57-7.19) PM_{10} 1.99 (1.24-3.20) SO_2 2.10 (0.99-4.44) O_3 6.94 (1.12-43.08) O_3 never smokers 1.82 (0.93-3.57) NO_2 Females 1.33 (0.60-2.96) PM_{10} 3.01 (1.88-4.84) SO_2 2.99 (1.66-5.40) SO_2 never smokers 0.77 (0.37-1.61) O_3 2.81 (1.15-6.89) NO_2	Age, smoking, education, alcohol adjusted 3 year lag in average annual exposure Multipollutant models also explored
McDonnell et al.[188], USA	3,769 California Seventh-Day Adventists (AHSMOG) aged 27-95 years who lived near an airport	1977-1992	100% nonsmokers (14-37% former smokers)	Mean monthly fine ($PM_{2.5}$) and coarse ($PM_{2.5\text{-}10}$) PM_{10} fractions estimated from airport visibility for the years 1973-1977 and mean monthly PM_{10}, SO_2, O_3, NO_2, and SO_4 from central monitors	24 lung cancer deaths	IQR	Males 2.23 (0.56-8.94) $PM_{2.5}$ 1.84 (0.59-5.67) PM_{10} 1.25 (0.63-2.49) $PM_{2.5\text{-}10}$	Age, smoking, education, alcohol adjusted Multipollutant models also explored
Hoek et al.[189], Netherlands	4,492 participants from the NLCS aged 55-69 years	1986-1994	23-38% never smokers	BS, NO_2 estimated at home address (1987-1990) as a function of regional, urban, and local sources	60 lung cancer deaths	5-95 percentile (10 µg/m^3 BS, 30 µg/m^3 NO_2)	1.06 (0.43-2.63) BS 1.25 (0.42-3.72) NO_2	Age, sex, education, Quetelet-index, occupation, active and passive smoking, neighbourhood socioeconomic score,

								fat and vegetable consumption adjusted
Pope et al.[5], USA	~500,000 CPS-II participants in 116 US metropolitan areas ($PM_{2.5}$), atleast 30 years of age and at least one individual in the household of atleast 45 years of age	1982-1998	not provided	$PM_{2.5}$ (1979-1983), $PM_{2.5}$ (2000) as well as data on PM_{10}, PM_{15}, TSP, SO_4, SO_2, NO_2, CO, O_3 from central monitors at the MSA level at different time periods	8,754 lung cancer deaths (see Krewski et al. 2009)	10 μg/m^3 ($PM_{2.5}$)	1.08 (1.01-1.16) $PM_{2.5}$ (1979-1983) 1.13 (1.04-1.22) $PM_{2.5}$ (1999-2000) 1.14 (1.04-1.23) Average	Age, sex, race, smoking, education, marital status, BMI, alcohol, occupational exposure, diet adjusted Numerical HRs for other pollutants not provided
Nafstad et al.[192], Norway	16,209 Olso men aged 40-49 from cardiovascular disease study	1972-1998	19% nonsmoker	Individual mean SO_2 and NO_x exposures from GIS (1974-1998)	418 incident lung cancer cases	10 μg/m^3	1.08 (1.02-1.15) NO_x (1974-1978) 1.20 (0.70-2.03) NO_x (1974-1978) in non-smokers 1.01 (0.94-1.08) SO_2	Age, smoking, education adjusted Also computed HRs from two pollutant models
Nafstad et al.[193], Norway	16,209 Olso men aged 40-49 from cardiovascular disease study	1972-1998	19% nonsmoker	Individual mean SO_2 and NO_x exposures from GIS (1974-1998)	382 lung cancer deaths	10 μg/m^3	1.11 (1.03-1.19) NO_x 1.00 (0.93-1.08) SO_2	Education, occupation, smoking, physical activity, cardiovascular risk group, age adjusted
Filleul et al.[194], France	14,284 adults (25-59 years) in 24 areas from 7 French towns, PAARC study, lived in area for 3 years or more, excluded if head of family was manual worker	1974-1998	50.4% non or passive smoker	Mean SO_2, TSP, BS, NO_2, NO from central monitors (1974-1976)	178 lung cancer deaths	10 μg/m^3	1.00 (0.91-1.11) SO_2 0.95 (0.88-1.02) Acidimetric method 1.00 (0.92-1.10) TSP 1.03 (0.92-1.15) BS 1.48 (1.05-2.05) NO_2 1.06 (0.87-1.29) NO	Age, smoking, BMI, education, occupation, sex adjusted
Jerrett et al.[275], USA	22,905 Los Angeles CPS-II participants, atleast 30 years of age and at least one individual in the household of atleast 45 years of age	1982-2000	not provided	$PM_{2.5}$ interpolated (kriged) from 23 central monitors, O_3 from 42 central monitors	434 lung cancer deaths	10 μg/m^3	1.44 (0.98-2.11)	Age, sex, race, smoking, education, marital status, BMI, alcohol, occupational exposure, diet adjusted
Laden et al.[20], USA	8,096 randomly selected white subjects, aged 25-74, spirometric tested, from six US cities 1974-1977	1974-1998	35-42% never smokers	$PM_{2.5}$ from central monitors (1979-1987) and estimated via regression equation (1985-1998)	226 lung cancer deaths	10 μg/m^3	1.27 (0.96-1.69)	Age, sex, smoking, education, BMI adjusted

Vineis et al.[195],	Nested in EPIC, aged 35-74, former (past 10 years) and never smokers, recruited 1993-1998, 271 incident cases and 737 gender, age, smoking, country, time period matched controls	-	53-55% never smokers 45-47% former smokers	Proximity to heavy traffic roads and NO_2, PM_{10}, SO_2 from central monitors (1980-1999) at residence at enrollment	271 lung cancer cases	10 $\mu g/m^3$	1.46 (0.89-2.40) heavy traffic roads 1.14 (0.78-1.67) NO_2 0.91 (0.70-1.18) PM_{10} 1.08 (0.89-1.30) SO_2	Age, gender, smoking, time since recruitment, country, BMI, education, fruit, vegetable, meat, alcohol consumption, physical activity adjusted
Naess et al.[21], Norway	All (143,842) inhabitants of Olso, 51-90 years of age, from population and death register	1992-1998	Smoking status unknown	NO_2, $PM_{2.5}$, PM_{10} from air dispersion model (1992-1995) for 470 neighborhoods	1,453 lung cancer deaths	IQR	Men, 51-70 years 1.07 (0.97-1.18) NO_2 1.07 (0.97-1.18) $PM_{2.5}$ 1.07 (0.97-1.18) PM_{10} Women, 51-70 years 1.23 (1.10-1.38) NO_2 1.27 (1.13-1.43) $PM_{2.5}$ 1.27 (1.13-1.43) PM_{10} Men, 71-90 years 1.09 (0.98-1.20) NO_2 1.07 (0.97-1.18) $PM_{2.5}$ 1.08 (0.98-1.20) PM_{10} Women, 71-90 years 1.12 (0.98-1.27) NO_2 1.16 (1.02-1.32) $PM_{2.5}$ 1.17 (1.03-1.33) PM_{10}	Occupational class and education adjusted
Beelen et al.[196], Brunekreef et al.[329], Netherlands	114,378 in the NLCS aged 55 to 69 years, without prevalent cancer at baseline	1986-1997	13.5-41.1% never smokers	Sum of regional, urban, and local air pollution for 1987-1996 (BS, $PM_{2.5}$, NO_2, SO_2, traffic intensity) estimated at home address (1976-1985/1986-1996)	1,940 incident lung cancer cases	5-95 percentiles (30 $\mu g/m^3$ NO_2, 10 $\mu g/m^3$ BS, 20 $\mu g/m^3$ SO_2, 10 $\mu g/m^3$ $PM_{2.5}$)	0.96 (0.83-1.11) BS 0.86 (0.70-1.07) NO_2 0.81 (0.63-1.04) $PM_{2.5}$ 0.90 (0.72-1.11) SO_2 1.05 (0.94-1.16) traffic nearest road 1.05 (0.9-1.19) traffic in a 100m buffer 1.11 (0.91-1.34) live near major road Never smokers 1.47 (1.01-2.16) BS 1.11 (0.88-1.41) traffic nearest road 1.36 (0.99-1.87) traffic 100m 1.55 (0.98-2.43) live	Age, sex, smoking, area socioeconomic status adjusted

							near major road	
Beelen et al.[197], Brunekreef et al.[329], Netherlands	117,582 in the NLCS aged 55 to 69 years	1987-1996	30-43% never smokers	Sum of regional, urban, and local air pollution for 1987-1996 (BS, $PM_{2.5}$, NO_2, SO_2, traffic intensity) estimated at home address (1976-1985/1986-1996)	1,888 lung cancer deaths	5-95 percentiles (30 μg/m^3 NO_2, 10 μg/m^3 BS, 20 μg/m^3 SO_2, 10 μg/m^3 $PM_{2.5}$)	1.03 (0.88-1.20) BS 1.48 (0.97-2.25) BS never smokers 1.06 (0.82-1.38) $PM_{2.5}$ 0.91 (0.72-1.15) NO_2 1.00 (0.79-1.26) SO_2 1.07 (0.96-1.19) traffic nearest road 1.07 (0.93-1.23) traffic 100m buffer 1.20 (0.98-1.47) major road	Age, sex, smoking, area socioeconomic status adjusted
Krewski et al.[203], USA	~500,000 CPS-II participants in 116 US metropolitan areas ($PM_{2.5}$), atleast 30 years of age and at least one individual in the household of atleast 45 years of age	1982-2000	48% never smokers	$PM_{2.5}$ (1979-1983), $PM_{2.5}$ (2000) as well as data on SO_4, SO_2, PM_{15}, TSP, O_3, NO_2, CO from central monitors at the MSA level at different time periods	9,788 lung cancer deaths	10 μg/m^3 ($PM_{2.5}$)	1.08 (1.03-1.14) $PM_{2.5}$ (1979-1983) 1.11 (1.04-1.18) $PM_{2.5}$ (1999-2000) 1.05 (1.02-1.09) SO_4 (1980)	Age, sex, race, smoking, education, marital status, BMI, alcohol, occupational exposure, diet adjusted No significant association with other pollutants
Raaschou-Nielsen et al.[198], Denmark	679 incident lung cancer cases from Danish Cancer Registry in the Diet Cancer Health Cohort, the Copenhagen City Heart Study, and the Copenhagen Male Study and 3,481 controls weighted on cohort, gender, smoking duration, and year of birth (1971-2001)	-	2.4-3.1% never smokers	NO_x at residence from dispersion models (1971-2001)	679 lung cancer cases	100 μg/m^3	1.37 (1.06-1.76) 2.58 (0.39-17.20) in never smokers 1.53 (1.02-2.28) small cell 2.01 (1.27-3.43) squamous cell 0.95 (0.57-1.58) adenocarcinoma 1.18 (0.68-2.03) other	Cohort, gender, smoking, period of birth, education, BMI, intake adjusted
Yorifuji et al.[190], Japan	14,001 participants from the Shizuoka elderly cohort, aged 65-84 years	1999-2006	68% never smokers	Individual mean NO_2 exposures from LUR model for the years 2000-2006 at baseline home address	86 lung cancer deaths	10 μg/m^3	0.95 (0.78-1.17) NO_2 1.30 (0.85-1.93) never smokers	Age, sex, smoking, BMI, hypertension, diabetes, financial capability adjusted
Hart et al.[199], USA	53,814 men employed in 1985 in four US trucking companies, mean age 42 years	1985-2000	Smoking status unknown	Individual mean PM_{10}, NO_2, and SO_2 (1985-2000) concentrations	800 lung cancer deaths	IQR	1.00 (0.92-1.08) PM_{10} 1.09 (0.98-1.21) SO_2 1.06 (0.97-1.15) NO_2	Results attenuated in multipollutant models with the exception of

				at last known home address from spatial smoothing and LUR, $PM_{2.5}$ (2000) from nearest monitor			1.02 (0.95-1.10) $PM_{2.5}$	NO_2
Raaschou-Nielsen et al.[200], Denmark	52,907 members of the Diet Cancer and Health Cohort (1993-1997), aged 50-64 years in Copenhagen and Aarhus	1993-2006	64% non-smokers	Individual mean NO_x and NO_2 concentrations at home address using traffic data and dispersion model (1971-2006), presence of a major road, and traffic load	592 incident lung cancer cases	100 μg/m^3 NO_x 10^4 vehicle km/day traffic load	1.09 (0.79-1.51) NO_x 1.51 (0.72-3.16) NO_x non smoker 1.21 (0.95-1.55) major road 1.83 (1.04-3.23) major road non smoker 1.03 (0.90-1.19) traffic load 1.21 (0.88-1.67) traffic load non smoker	Age, smoking, environmental tobacco smoke, education, fruit intake, occupation adjusted

Note: benzo(a)pyrene (BaP), interquartile range (IQR), particulate matter of ≤ 15 microns in diameter (PM_{15}).

Table 3. Comparison of main features of thesis manuscripts.

	Article 1	Article 2	Article 3	Article 4
Study population	Entire CPS-II	Entire CPS-II	Entire CPS-II	CPS-II never smokers
Follow-up time	1982-1988	1982-2006	1982-2006	1982-2008
Number of subjects	811,961	811,961	811,961	188,699
Exposure of interest, scale	Radon, county-level	Radon, county-level	Radon, county-level	$PM_{2.5}$, MSA level
Outcome of interest	Lung cancer	Non-malignant respiratory	Non-respiratory (excluding lung cancer and non-malignant respiratory)	Lung cancer
Number of deaths	3,493	28,300	265,477	1,100
Covariate adjustment, final fully-adjusted model	Age, race, gender, state stratified and adjusted for education, marital status, BMI, BMI squared, cigarette smoking status, cigarettes per day (and squared), duration of smoking (and squared), age started smoking, passive smoking, vegetable/fruit/fiber consumption, fat consumption, industrial exposures, occupation dirtiness index	Age, race, gender, state stratified and adjusted for education, marital status, BMI, BMI squared, cigarette smoking status, cigarettes per day (and squared), duration of smoking (and squared), age started smoking, passive smoking, vegetable/fruit/fiber consumption, fat consumption, industrial exposures, occupation dirtiness index	Age, race, gender, state stratified and adjusted for education, marital status, BMI, BMI squared, cigarette smoking status, cigarettes per day (and squared), duration of smoking (and squared), age started smoking, passive smoking, vegetable/fruit/fiber consumption, fat consumption, industrial exposures, occupation dirtiness index	Age, race, gender stratified and adjusted for education, marital status, BMI, BMI squared, passive smoking, vegetable/fruit/fiber consumption, fat consumption, industrial exposures, occupation dirtiness index, mean county-level residential radon concentrations
Ecological covariates	1980	1990	-	1980, 1990, 2000

Table 4. Selected participant characteristics at enrollment (1982) by region, CPS-II cohort.

Characteristic	Northeast n = 170,281	South n = 257,243	Midwest n = 234,952	West n = 149,485
Radon				
(Mean, Range)	58.3 (17.8-265.7)	35.6 (6.3-143.9)	73.7 (18.9-221.6)	46.9 (9.6-232.0)
Person Years				
1982-1988	996,028.9	1,504,669.6	1,377,243.7	875,214.2
1982-2006	3,478,618.7	5,213,160.7	4,827,357.2	3,035,480.2
Age at Enrollment				
(Years)	55.9	56.6	56.3	57.3
Sex				
Male (%)	44.8	43.7	45.2	45.2
Race				
White (%)	97.1	92.2	96.8	93.9
Education				
> High School (%)	50.9	55.8	49.9	63.6
BMI (kg/m^2)	25.4	25.0	25.5	24.9
Married (%)	84.0	84.1	87.0	85.2
Smoking Status (%)				
Never	42.3	46.5	47.1	48.8
Current	19.8	19.6	18.8	15.9
Former	26.6	24.4	23.7	26.4
Pipe/Cigar	11.3	9.6	10.4	8.8
Passive Smoke (Mean Hours/Day)	3.3	3.1	3.1	2.5
Industrial Exposures (%)	21.6	18.4	21.5	21.6
Fat Consumption				
Upper quartile (%)	15.1	20.5	20.7	16.8
Vegetable, Fruit, Fiber Consumption				
Upper quartile (%)	18.1	16.5	17.9	23.7
Asthma (%)	4.0	4.6	4.1	5.7
COPD (%)	4.4	5.4	4.4	4.9
No. All Cause Deaths				
1982-1988	9,537	14,418	12,180	8,188
1982-2006	64,493	101,578	88,589	59,651
All Cause Death Rate				
1982-1988	957.5	958.2	884.4	935.5
1982-2006	1,854.0	1,948.5	1,835.1	1,965.1
Age at Death				
1982-1988	70.0	70.0	69.8	71.5
1982-2006	77.1	77.6	77.3	78.7
No. Lung Cancer Deaths				
1982-1988	710	1,246	954	583
1982-2006	4,314	7,041	5,867	3,312
Lung Cancer Death Rate				
1982-1988	71.3	82.8	69.3	66.6
1982-2006	124.0	135.1	121.5	109.1
Age at Lung Cancer Death				
1982-1988	66.6	67.3	66.4	67.0
1982-2006	72.3	72.7	72.3	73.3
No. COPD Deaths				
1982-1988	324	512	398	347
1982-2006	2,646	4,359	3,695	2,841
COPD Death Rate				
1982-1988	32.5	31.11	28.9	39.6
1982-2006	76.1	83.6	76.5	93.6
Age at COPD Death				
1982-1988	71.7	72.4	71.7	72.6
1982-2006	77.6	77.9	77.7	78.4

Table 5. Three measures of additive interaction[*] (95% CIs) between mean $PM_{2.5}$ concentrations, residential radon, passive smoking, and industrial exposures for lung cancer mortality, follow-up 1982-2008[†], never-smokers, CPS-II cohort, US.

	RERI (95% CI)	AP (95% CI)	S (95% CI)
Radon	0.64 (-0.13, 1.59)	0.41 (-0.21, 0.63)	-7.00
Passive Smoke	-0.25 (-0.68, 0.16)	-0.23 (-0.77, 0.08)	0.25 (0.01, 7.18)
Industrial Exposures	-0.20 (-0.56, 0.16)	-0.22 (-0.80, 0.10)	-1.12

[*] Relative excess risk due to interaction (RERI), attributable proportion (AP), synergy index (S).

[†] Exposures categorized as: mean $PM_{2.5}$ concentrations: <14.8 $\mu g/m^3$, ≥ 14.8 $\mu g/m^3$; mean county-level residential radon concentrations: <148 Bq/m^3, ≥ 148 Bq/m^3; passive smoking in home: none, any; industrial exposures: no, yes. Cox proportional hazards regression models were fitted with the baseline hazard stratified by age, race, gender and adjusted for education, marital status, body mass index, body mass index squared, passive smoking, vegetable/fruit/fiber consumption, fat consumption, industrial exposures, occupation dirtiness index, and mean county-level residential radon concentrations where appropriate.

FIGURES

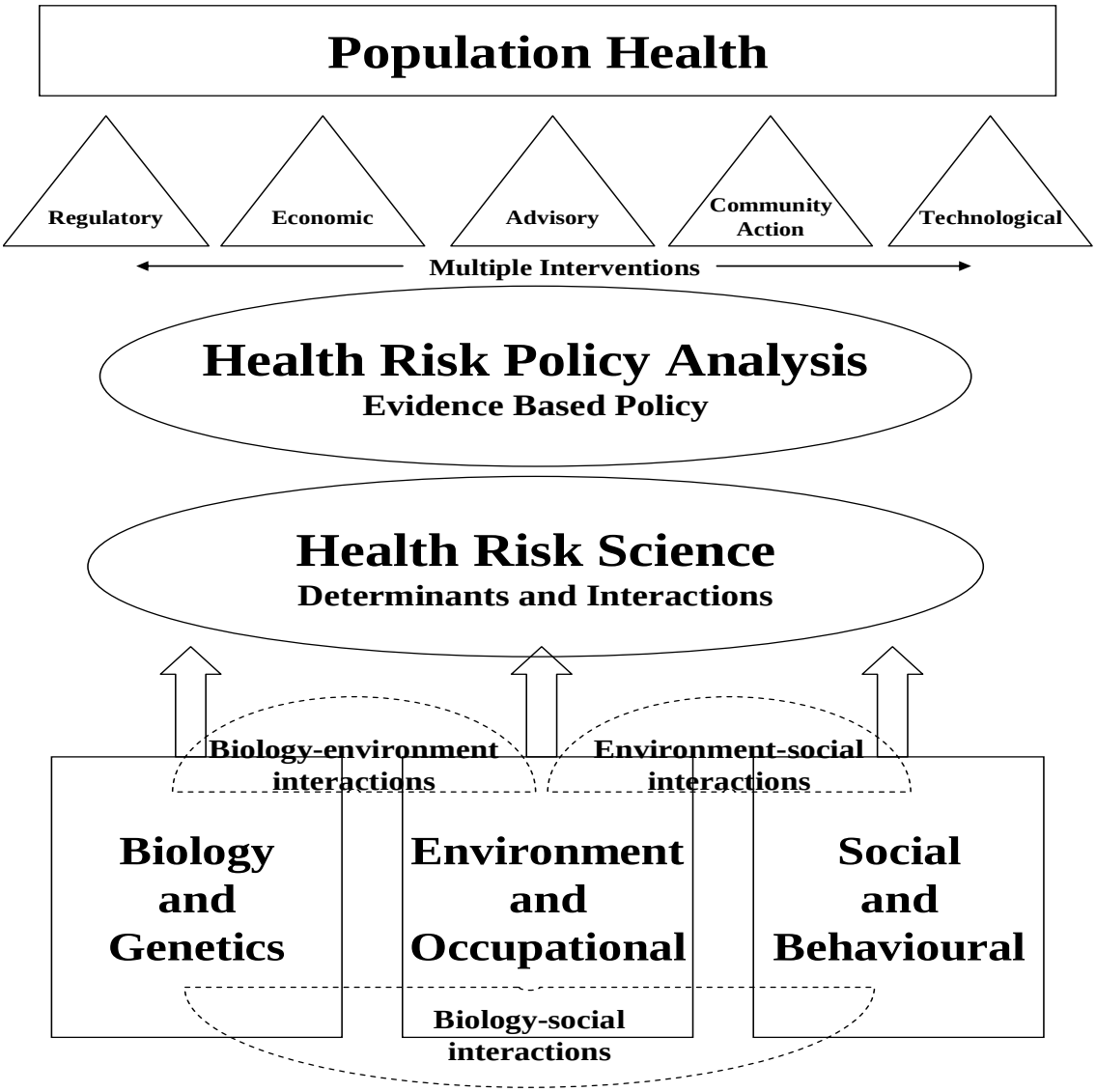

Figure 1. An integrated framework for risk management and population health

Source: Krewski D, Hogan V, Turner MC, Zeman P, McDowell I, Edwards N, Losos J. An integrated framework for risk management and population health. Hum Ecol Risk Assess 2007;13:1288-312. Reprinted by permission of the publisher (Taylor & Francis Ltd, www.taylorandfrancis.com).

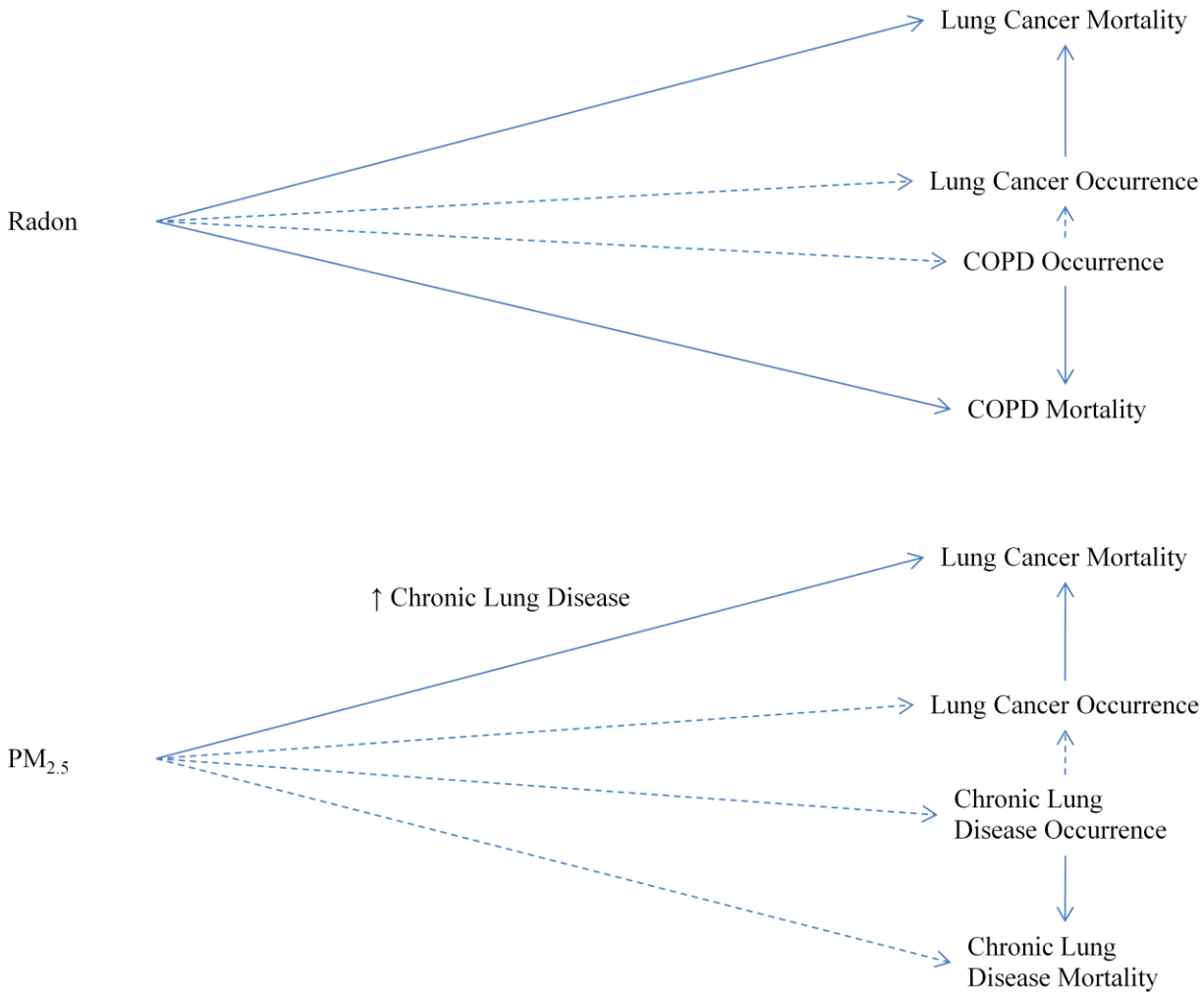

Figure 2. Observed (solid line) and hypothesized (dotted line) associations between radon/$PM_{2.5}$, chronic lung disease, and lung cancer.

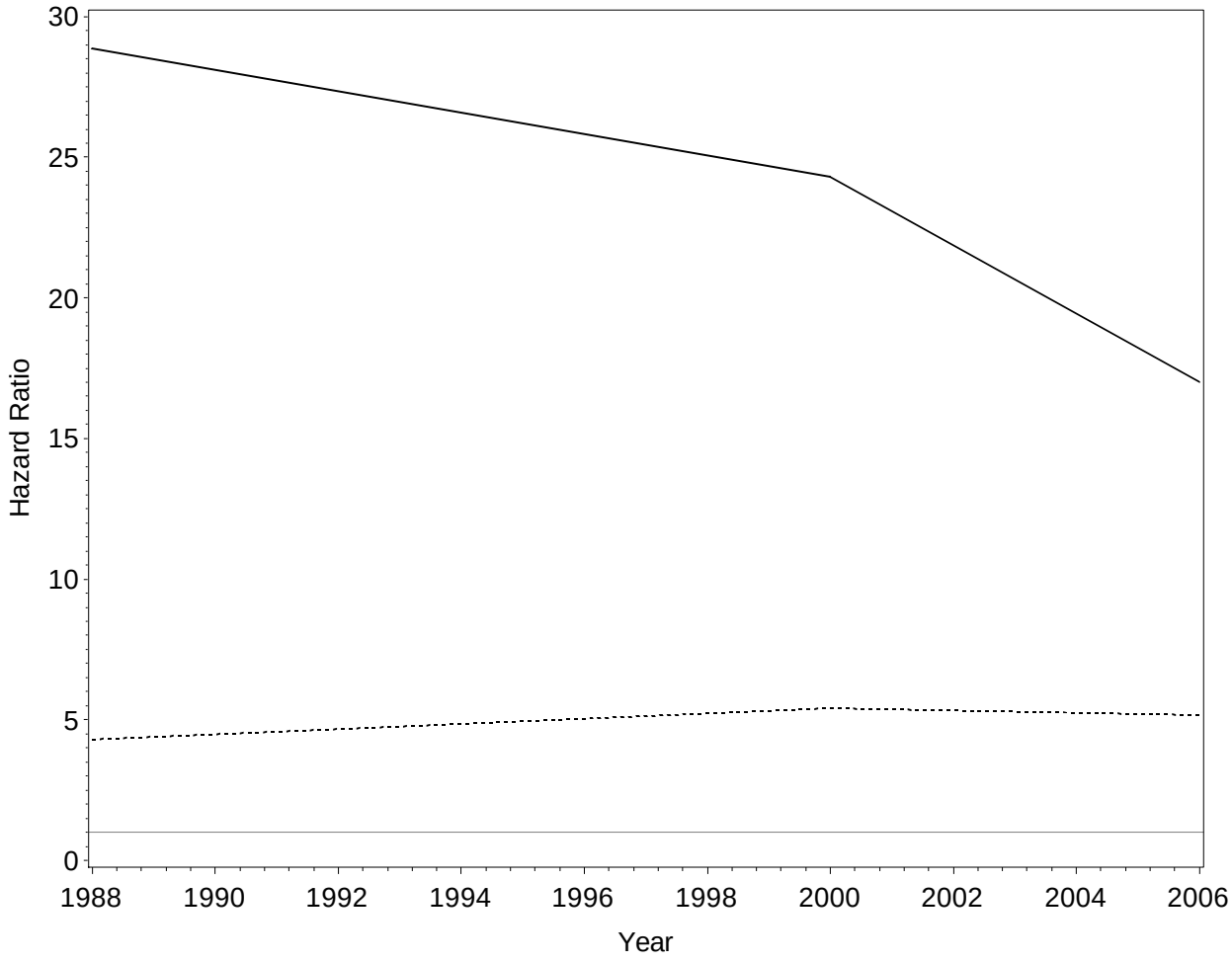

Figure 3. HRs for cigarette smoking (current smokers at enrollment) with increasing follow-up time for lung cancer mortality (solid line) and non-malignant respiratory disease mortality (dotted line) in men, CPS-II cohort.

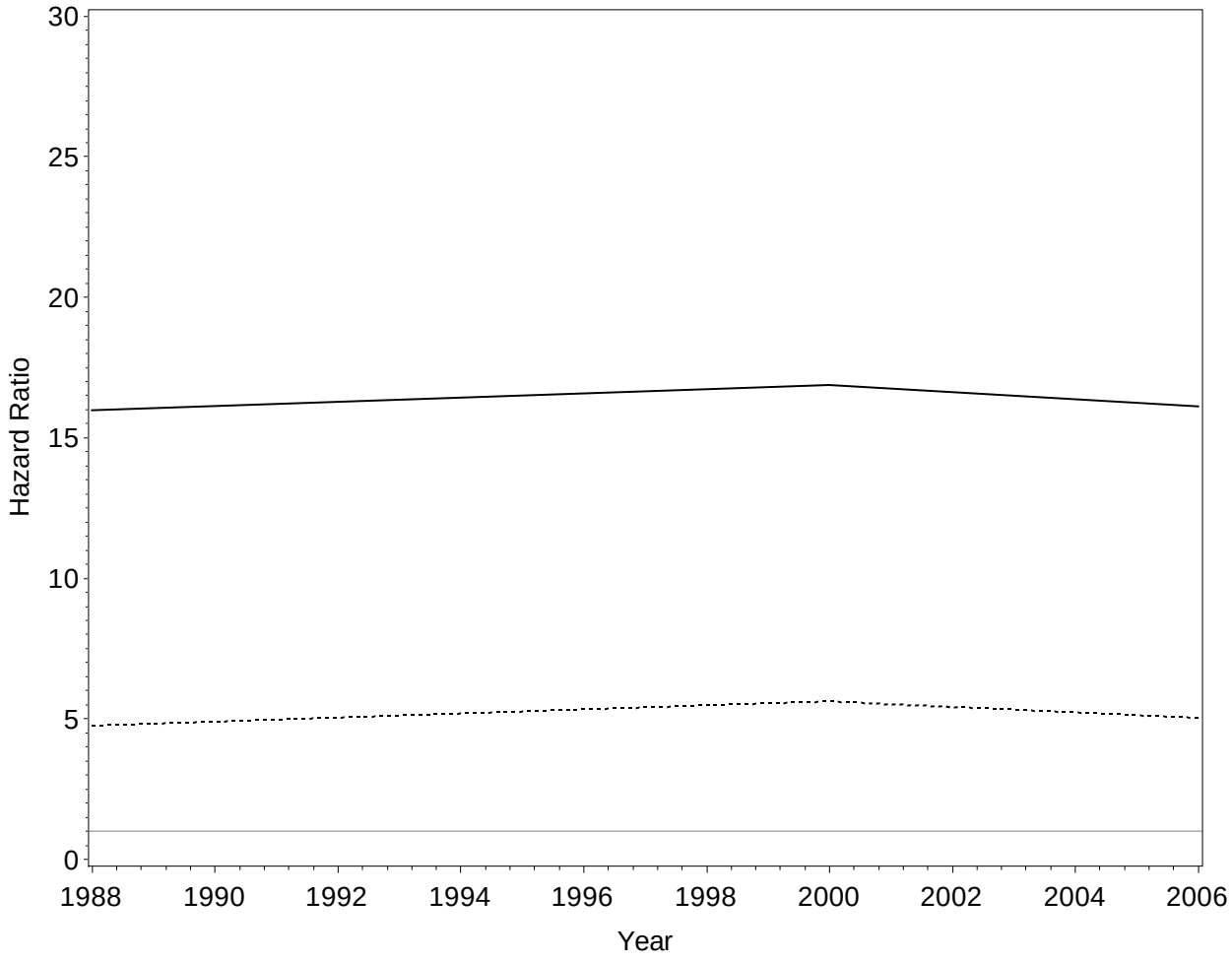

Figure 4. HRs for cigarette smoking (current smokers at enrollment) with increasing follow-up time for lung cancer mortality (solid line) and non-malignant respiratory disease mortality (dotted line) in women, CPS-II cohort.

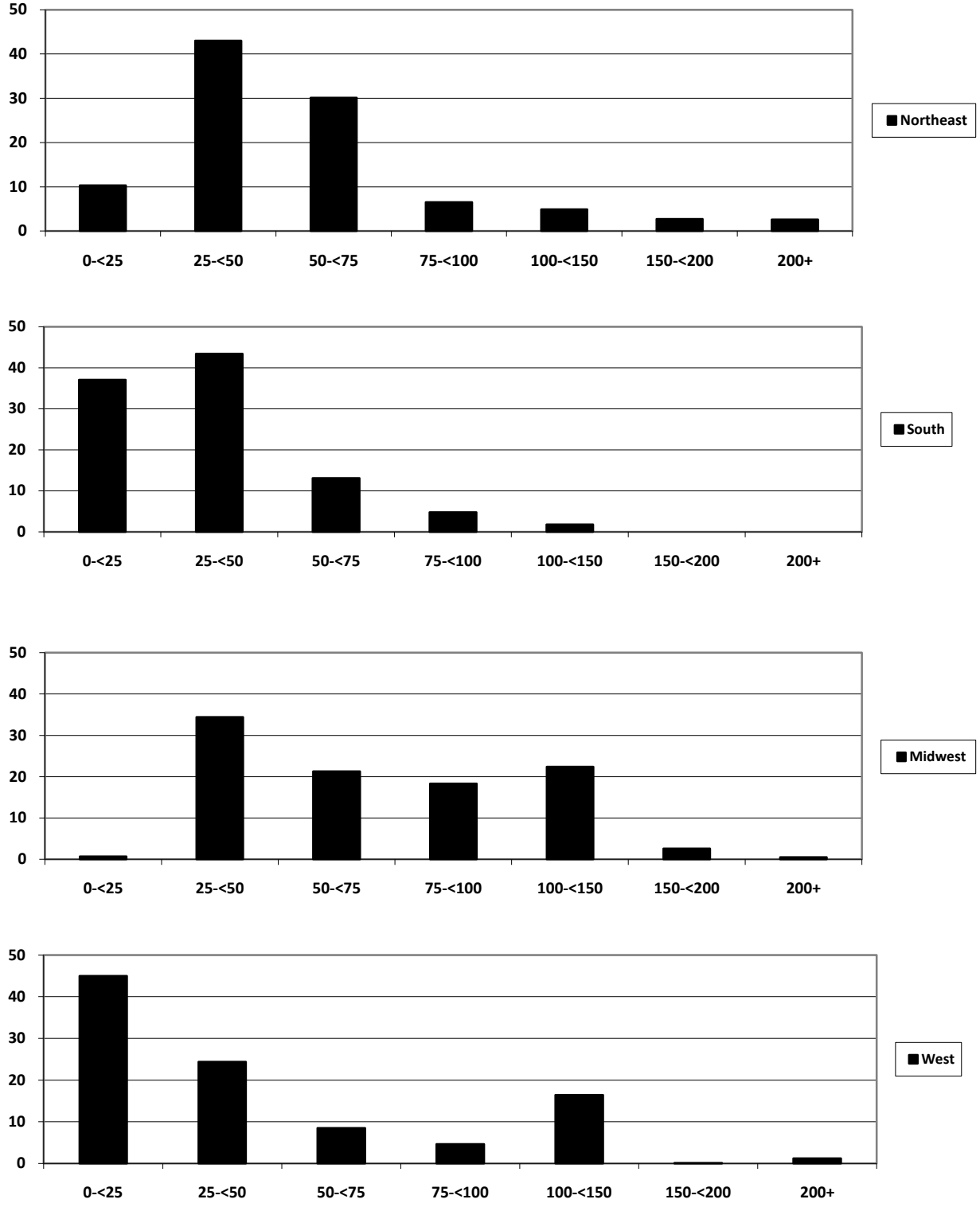

Figure 5. Distribution (%) of residential radon concentrations by region, CPS-II cohort.