OCCUPATIONAL EXPOSURES AND THE DEVELOPMENT OF LUNG DISEASE IN MINNESOTA MINERS

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Chapter 1 Introduction

Taconite Mining in Minnesota

Iron ore mining has taken place along the Mesabi Iron Range in northeastern Minnesota for over one hundred years. Mining started in the nineteenth century with hematite, an ore with a high concentration of iron. As hematite stores were exhausted during the twentieth century, especially following World War II, mining shifted to a second type of iron ore found in massive quantities along the Range called taconite. Taconite is considered a low-grade ore, as its natural concentration of iron is only about 30%, about half the iron concentration of hematite (1). In order for taconite to be commercially useful its iron is concentrated through extensive processing. After the taconite rock is mined, the rock is crushed and non-iron material removed through magnetic separation. The iron ore is formed into pellets, whose average iron concentration is approximately 63% (2). Pellets are fired in a kiln and shipped out for use in steel production. Today's taconite mines are an essential part of Minnesota's economy, having an annual impact of over three billion dollars and providing jobs for thousands of individuals (3).

There is the potential for harmful exposures in the taconite industry. The mining and processing of taconite rock releases respirable dust, respirable silica, and elongate mineral particles (EMPs) into the workplace. For years miners have wondered whether work in the taconite industry could lead to health issues later in life, and numerous miners have reported lung problems. With the discovery of mineral particles in Lake Superior drinking water in the 1970s (4), concerns about potentially hazardous exposures stemming from the taconite industry spread beyond workers into the community.

Previous Studies of Minnesota Iron Miners

A small number of epidemiologic studies in iron miners took place during the 1980s and 1990s. The effect of exposures such as crystalline silica (quartz) and EMPs was examined through several mortality studies. Higgins conducted a study of workers employed by the Reserve Mining Company, finding no excess causes of death (5). Cooper examined workers at the Erie and Minntac companies, and found no excess mortality from any malignant or non-malignant lung diseases (6,7). Clark (8) looked for radiographic abnormalities among men with and without exposure to taconite dust, finding several cases of silicosis but no pleural calcifications or mesothelioma.

In the early 1980s, the University of Minnesota collected all available work history records from the seven iron mines in existence at the time as part of the Mineral Resources Health Assessment Program (MRHAP). A cohort of approximately 72,000 workers was created from these records for use in future health studies. While no studies took place, the MRHAP cohort was periodically linked to the Minnesota Cancer Surveillance System, after its creation in 1988. It was through this linkage that an excess of mesothelioma was identified in Minnesota iron miners (9).

Exposures in Taconite Mining

The majority of mesothelioma cases are caused by asbestos exposure. Asbestos is a term for a collection of naturally occurring silicate minerals that occur in a particular fibrous form or habit. The six minerals regulated as asbestos include the serpentine chrysotile and the amphiboles amosite, crocidolite, anthophyllite, tremolite, and actinolite (10,11). As the link between asbestos and mesothelioma became understood (12), research on mineral particles has shifted to look at the nuances of asbestos exposure. Areas of scientific interest include looking for a potential threshold level and dose-response relationship (13) and determining the types and sizes of particles that are most pathogenic (14,15), specifically comparing chrysotile versus amphibole particle types and long versus short particle sizes. Additional research is trying to determine whether amphibole mineral particles chemically similar to asbestos, but with a different physical form are also capable of causing disease (11,16).

Many of the exposure conditions of interest to researchers are present in the taconite industry, including low-level exposures to various non-asbestos mineral particles. The predominant exposure is to short mineral particles less than five microns in length (17), mineral particles not included in current regulatory standards for asbestos and related EMPs (10,11). These shorter particles have not been the studied to the extent that regulated particles have been, and the effects of exposure to short mineral particles are not completely understood (18). The geology of the Mesabi Iron Range is variable along its length with four distinct geological zones containing different profiles of minerals (19). Starting at the western end of the Range and continuing through the majority of its length is Zone 1, which contains phyllosilicates such as talc and greenalite. Zone 2 is considered transitional with slight modifications of Zone 1 minerals. Zone 3 has greater transformations of Zone 1 minerals, but does not host any taconite mines. At the eastern edge of the Range in Zone 4, significant metamorphosis of minerals occurred following contact with the Duluth Complex approximately one billion years ago, creating amphibole minerals such as grunerite and hornblende (20). This heterogeneous geology creates the opportunity for exposure to multiple types of mineral particles. Amphiboles present in the eastern end of the Range occur in a non-asbestiform habit, a physical form about which less is known than the asbestiform habit of regulated asbestos.

Taconite Workers Health Study

The Taconite Workers Health Study is a study funded by the state of Minnesota whose goal is to understand the potential health effects from exposures present within the taconite industry. The Taconite study is conducted by researchers within the University of Minnesota School of Public Health, and researchers at the University of Minnesota Duluth's Natural Resources Research Institute. The study takes a comprehensive look at exposures and health outcomes within the taconite industry. Exposure assessments examine past and current exposures within the taconite mines and in the surrounding community. Study populations were drawn from the MRHAP cohort for a mortality study comparing causes of death in miners to causes of death among all Minnesotans, and for cancer incidence studies comparing miners who developed mesothelioma and lung cancer to miners who did not develop disease. Former and current miners and their spouses participated in the Respiratory Health Survey, answering questions on mining work history, potentially relevant exposures, and respiratory symptoms, as well as taking part in a clinical exam with pulmonary function testing and chest radiography. Exposures such as employment duration in taconite mining and EMPs have been looked at in relation to the outcomes of mesothelioma and non-malignant lung disease, and future studies will look at these exposures in relation to lung cancer, as well as the risks from exposure to respirable dust and respirable silica.

Research Objectives

This dissertation will focus on two exposures: duration of years spent in the taconite industry and EMPs. EMPs fitting four different dimension-based definitions will be included. These exposures will be examined in relation to the development of mesothelioma and non-malignant lung disease as evidenced by radiographic abnormalities. There are three research aims to this dissertation. Each aim is addressed in a chapter within the dissertation:

Aim 1: A Case-Control Study of Mesothelioma in Minnesota Iron Miners

Chapter 2 uses a nested case-control study to examine the association between duration of taconite employment, exposure to EMPs, and the risk of mesothelioma. EMPs are measured using the NIOSH 7400 phase contrast microscopy (PCM) method used as the basis for NIOSH's regulatory standard on exposure to airborne asbestos and related elongate mineral particles (21). The hypothesis of this study is that taconite miners with a longer employment duration and greater cumulative EMP exposure will be at a greater risk of developing mesothelioma.

Aim 2: Elongate Mineral Particle (EMP) Size and Risk of Mesothelioma

Chapter 3 is an extension of the mesothelioma case-control study, focusing on whether exposure to EMPs of different sizes leads to different mesothelioma risks. EMPs fitting three dimension-based exposure metrics are measured using the ISO method with TEM analysis. The hypothesis of this study is that taconite miners with a greater cumulative exposure of each particle type will be at a greater risk of developing mesothelioma.

Aim 3: Study of Radiographic Lung Abnormalities in Minnesota Taconite Miners

Chapter 4 uses a cross-sectional study of current and former taconite miners to examine the association between duration of taconite employment, exposure to NIOSH 7400 EMPs, and the development of parenchymal and pleural lung abnormalities as evidenced by chest radiography. The hypothesis of this study is that taconite miners with a longer employment duration and greater cumulative EMP exposure will be at a greater risk of developing radiographic lung abnormalities.

Significance

The Taconite Workers Health Study is the first industry wide study of multiple potential exposures and health risks for taconite miners. As part of the Taconite Study, this dissertation will describe three studies that examined whether the risk of developing mesothelioma and radiographic lung abnormalities is associated with the length of time spent working in the taconite industry, a crucial question for today's taconite workers, and a question long unanswered for former miners. While previous work has been done on the issues of mesothelioma and non-malignant lung disease in this population (8,22) this dissertation will be the first study to combine exposure, work history, and health data in an academic study of these health topics.

While the Taconite Workers Health Study is trying to address important health concerns for individuals living along the Iron Range, the study is in the unique position of being able to engage in a project that addresses multiple questions in mineral particle research. Exposure to EMPs within the taconite industry has not been studied previously, and this dissertation is the first study to look at quantitative EMP exposure in relationship to the proven excess of mesothelioma in iron miners. It is also the first quantitative study of EMPs in relation to the development of radiographic lung abnormalities within this group of workers. It is important to understand the potential effects of EMP exposure both within the context of taconite mining, and in the greater environment. This dissertation contributes to that understanding by analyzing EMPs of all sizes, being the first study to examine mesothelioma and non-malignant lung disease risk from non-asbestiform amphibole and non-amphibole EMPs of different sizes. Ultimately the work in this dissertation will provide insight into active questions within the field of mineral particle research, as well as helping to understand the potential health risks within Minnesota's taconite industry.

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Chapter 2 A Case-Control Study of Mesothelioma in Minnesota Iron Miners

INTRODUCTION

Mesothelioma is a rare cancer of the lining of body cavities such as the pleura and peritoneum. Starting in the mid-twentieth century, the occurrence of mesothelioma was linked to exposure to asbestos (1,2), a collection of silicate minerals from the amphibole and serpentine groups that occur in a fibrous, or asbestiform, form (3). Asbestos was widely used for industrial purposes during the twentieth century. Even though use of asbestos in the United States has decreased dramatically (4) asbestos remains in the environment within certain products, older buildings, and is still in active use in other parts of the world (5).

While asbestos has been the focus of many health studies, less is known about similar mineral particles. In 1990 the National Institute for Occupational Safety and Health (NIOSH) revised its recommended exposure limit for elongate mineral particles (EMPs) to include any mineral particle with an aspect ratio of at least three and a minimum length of five μm. This definition encompasses the asbestos minerals chrysotile, amosite, actinolite, anthophyllite, tremolite, and crocidolite, but also includes the non-asbestiform analogs of these minerals, along with amphibole minerals from certain mineral series, and the non-asbestiform cleavage fragments of select serpentine minerals (6).

Research focused on exposure to non-asbestiform mineral particles has consisted largely of mortality studies within a few mining industries. Previous work in New York talc miners (7,8), South Dakota gold miners (9,10), and Minnesota taconite miners (11,12) has shown inconclusive evidence of an association between non-asbestiform amphibole exposure and malignant lung disease, yet these studies focused primarily on lung cancer mortality. Few cases of mesothelioma were identified, and efforts to look at mesothelioma specifically were hampered by the lack of an ICD code for mesothelioma until 1999.

In 2003, an excess of mesothelioma was identified in iron ore miners in northeastern Minnesota (13). Mining of iron ore along the Mesabi Iron Range began with hematite ore mining in the 19th century, and in the latter half of the twentieth century switched to the mining of taconite ore, a lean ore that requires extensive processing of the rock unlike the high grade hematite. Minnesota's taconite mines are crucial both for domestic steel production and for Minnesota's economy, with a direct contribution 1.8 billion dollars each year (14). Concerns about exposures within the mining industry grew into the Taconite Workers Health Study, a state funded study tasked with examining the potential health effects of exposure within the taconite industry.

The Taconite Workers Health Study addresses important health concerns in the taconite industry, but it is also a unique opportunity to examine some of the key questions in mineral particle research. Taconite miners are exposed to a variety of substances, including respirable dust, respirable silica, and EMPs. These EMPs can vary in mineral type, including non-asbestiform amphiboles and non-amphiboles, and in particle size with particles of regulatory length as well as smaller cleavage fragments (15,16).

Characterizing EMP exposures is complicated by the geology of the Mesabi Iron Range, which varies along its length creating four geological zones, including one zone that contains amphibole minerals (17).

The purpose of this study was twofold; first to examine the association between length of work in the taconite mines and the risk of mesothelioma. The second is to examine the association between exposure to EMPs in taconite mining and the risk of mesothelioma, looking at all EMP exposure and EMP exposure within each geological zone to see if geological differences along the Mesabi Range impact mesothelioma risk.

METHODS

Study Design and Population

We conducted a nested case-control study of mesothelioma in a cohort of iron mining workers. The cohort was enumerated by the University of Minnesota in 1983 and included 68,737 individuals who worked in the iron ore mining industry sometime before 1982. The cohort was followed for vital status through 2010 and causes of death were obtained through 2007. Vital status was ascertained using the Social Security Administration, the National Death Index, the Minnesota Department of Health, and state death certificates. All deaths were coded to the International Classification of Disease (ICD) codes in effect at the time of death.

Selection of Cases and Controls

All cases and controls were nested within the MRHAP cohort, and had to have evidence of employment in the mining industry. Mesothelioma cases were identified using two sources, the Minnesota Cancer Surveillance System (MCSS) and death certificate records. MCSS has pathologically confirmed cancer information dating back to 1988 on cancer cases diagnosed within the state of Minnesota. Linkage of the MRHAP cohort to MCSS identified 63 cases of mesothelioma. Mesothelioma was coded using ICD-O-3 histology codes 9050-9053. Death certificates identified 53 mesothelioma cases using the ICD 10th revision code C45. While MCSS cases were in state only, death certificates identified 13 cases of mesothelioma that occurred in ten states outside of Minnesota. Thirty-six individuals were identified by both MCSS and death certificates records. In total there were 80 mesothelioma cases. Four controls were selected for each case using an incidence density sampling approach. For each case controls were selected from risk sets of cohort members of similar age (years of birth +/- two years) and who were alive and without a diagnosis of mesothelioma on the date of diagnosis or death of the case. Five controls were eliminated from the study due to lack of employment in mining, giving 315 controls and a total study population of 395 miners.

Exposure Assessment

The details of the exposure assessment have been described elsewhere (18). Briefly, a database of mining job titles was created that split up jobs by tasks and processes. Job titles were collected from the Mining Safety and Health Administration (MSHA), a 1986 University of Minnesota study by Sheehy (19), and the internal industrial hygiene databases of three current taconite companies. In collaboration with company industrial hygienists, jobs were used to create 28 Similarly Exposed Groups (SEGs). Historical exposure data was collected from MSHA and taconite mining companies. Using all sources, historical data on EMPs was available for the period 1978 to 2009.

From 2010 to 2011, measurements of personal and area exposure levels were taken at the six active taconite mines. At each mine personal sampling was conducted for SEGs in existence at that mine. Volunteer miners wore a personal air-sampling pump for two three-hour periods. Each SEG was sampled approximately six to eight times. All personal EMP samples were analyzed using the NIOSH 7400 PCM method that counted

EMPs with a length greater than five µm and an aspect ratio of three or greater. Personal exposure data for the years 1978-2009 was collected from MSHA and two of the currently operating taconite mines. This historical data was combined with current exposure data and served as the basis for a time-varying linear regression model that imputed EMP exposure values for each of the 28 SEGs within each of seven different mines for the period of 1955 to 2010.

Work History and Exposure Matrix

Work history information for cases and controls, including all job titles and dates, was abstracted from available mining company work records. Work history ended in 1982 at the time the cohort was enumerated. Mining job titles varied greatly across companies, and were standardized to the greatest extent possible. All jobs were assigned to an SEG and departmental information was used to assign SEGs when the job title did not provide enough information. Additional SEGs were created for jobs where some idea of job task was possible that categorized jobs into departmental level classifications. Missing or vague job titles were assigned to an “Unknown” SEG. Exposure values for department level SEGs were based on the average of other SEGs in that department. Exposures for the Unknown SEG at each mine were an average of all SEGs at that mine.

A portion of MRHAP members worked in the earlier hematite industry. Hematite does not require the extensive processing and concentrating techniques of taconite and does not have the same exposures, therefore hematite and taconite work histories were separated. Historical data on mining operations and yearly taconite production totals was used to determine a taconite start date for each company. Jobs held before the taconite start dates were assigned to a Hematite SEG.

An exposure data matrix was created to calculate the cumulative EMP exposure value for each individual. Each SEG had a daily EMP concentration that differed depending on the company and year of employment. The concentration for an SEG was multiplied by the length of time spent working in the SEG, and the values for all SEGs summed to give the cumulative exposure for a worker, measured in EMP/cc-years.

Data Analysis

Descriptive analyses compared cases and controls by demographic and occupational factors. Employment duration in taconite mining and exposure to EMPs was examined using conditional logistic regression, with estimation of odds ratios and 95% confidence intervals. The overall effect of years of taconite employment and EMP/cc-years was examined, as well separate models looking at years of taconite employment and EMP/cc-years within each Iron Range Zone. Zones 1, 2, and 4 hosted taconite mines. Primary models were run with no latency and with a twenty-year latency. All models were run using SAS Version 9.2.

The main focus of the exposure models was EMP exposure received during employment in taconite mining, but workers had additional exposures such as dust from hematite operations that needed to be taken into account. A second possible exposure was commercial asbestos, which was used throughout the iron ore mines for maintenance and building purposes. For each SEG a commercial asbestos score of low, medium, or high was generated based on the combined likelihood and frequency of exposure to commercial asbestos in that SEG. Industrial hygiene experts within the taconite industry reviewed commercial asbestos scores. Exposure models accounted for length of time spent in an SEG where there was a high probability of exposure to commercial asbestos. Length of time employed in hematite mining was used in the models, as no exposure data was available for hematite.

RESULTS

Characteristics of Cases and Controls

A total of 80 cases and 315 controls were included in the study (Table 1). All cases were male and 5% of controls female. A greater percentage of cases worked in taconite and a greater percentage of controls worked in hematite, with mean length of employment in hematite similar for both groups. The largest percentage of cases occurred in taconite workers who had ever worked in Zone 2, and the largest percentage of controls in taconite workers who had ever worked in Zone 1. Both mean years of taconite employment and mean EMP/cc-years were greater for cases across all Zones and within Zone 1 and Zone 2. The mean years spent in SEGs assigned a medium commercial asbestos score was slightly greater in controls, while the mean years spent in SEGs with a high commercial asbestos score was greater in cases.

Taconite Employment Duration

The risk of mesothelioma was associated with increasing duration of employment in taconite mining (Table 2). A model divided workers into low and high duration groups based on median length of employment in cases, with the high group showing a 15% increase in risk. The risk of mesothelioma is elevated for each additional year of employment in Zone 1 and significantly elevated for each additional year of employment in Zone 2, with no elevation seen in Zone 4. The risk estimates were adjusted for age and length of employment in hematite. The zone specific models were also adjusted for duration of employment in other zones. Measures did not alter greatly with a twenty-year lag in the data or with exclusion of female controls.

EMP/cc-years of Exposure

The risk of mesothelioma was imprecisely associated with cumulative EMP/cc-years of exposure. Similar to the results for years of exposure, the mesothelioma risk was greater for each additional EMP/cc-year within Zone 1 and Zone 2 but not Zone 4. When workers were split into low and high exposure groups, using the median EMP/cc-year value in cases, the high exposure group showed a 93% increase in risk. Models of average exposure and average exposure by zone showed similar results to the models of cumulative exposure. Risk estimates were adjusted for age, length of employment in hematite, and years of employment with high probability of exposure to commercial asbestos. The results for the zone specific models were also adjusting for EMP/cc-years in other zones. Measures did not alter greatly when the data was lagged by twenty years or with the exclusion of female controls.

DISCUSSION

In this study examining the health effects of employment and EMP exposure in the taconite industry, we observed an association between employment duration in taconite mining and the risk of mesothelioma, and a similar finding for cumulative exposure to EMPs. The strongest associations were observed in geological Zones 1 and 2. Zone 1 makes up the majority of the Range and contains minerals such as quartz and talc. Zone 2 is a transitional area consisting largely of Zone 1 minerals with some mineral transformations. The risk estimate for EMP exposure was highest in Zone 1, the area of the Range with the lowest mean exposure values. Unlike Zones 2 and 4, Zone 1 contains multiple mines and has the widest range of exposure values, including four individuals with very high exposures who likely drive this result.

At the eastern edge of the Range in Zone 4, metamorphosis of mineral occurred with the creation of amphibole minerals such as grunerite and hornblende. The amount of amphibole mineral particles in this area of the Iron Range is quite small at less than one percent of the rock mass (20) and does not appear to be associated with the excess of mesothelioma seen in Minnesota iron ore miners. Zone 4 was the only zone where mean years of taconite employment and mean EMP/cc-years were greater in controls than cases, and no increase in mesothelioma risk was observed. A possible explanation for these results is the health worker survivor effect. In general, EMP exposures in Zone 4 tended to be higher than in Zones 1 and 2 (18), and it is possible Zone 4 workers experienced greater mortality, leaving fewer to be alive at the time case identification and control selection.

Risk estimates for employment duration reflect the risk from a variety of exposures in addition to EMPs such as respirable silica and respirable dust. Risk estimates for EMP/cc-years focus on EMP exposure, specifically the longer particles that are counted using the NIOSH 7400 PCM method (21). The risk of mesothelioma with increasing cumulative EMP exposure is less than that seen in studies focusing specifically on occupational asbestos exposure (22,23). Two case-control studies that estimated occupational asbestos exposure using participant interviews and using a similar cumulative exposure measure of fibers/ml-years, found higher odds ratios for similar exposure levels. This could suggest the potency of EMPs found in the taconite industry is not as great as commercial asbestos particles.

This study does have several key limitations. The small amount of data on historical EMP levels made the reconstruction of EMP exposures challenging. No data were available for multiple years in the study period, leading to the use of imputation and regression modeling to estimate historical exposure levels. Multiple approaches were tried in estimating historical EMP levels, and regression models were estimated using both a time trend and no trend. These variations on exposure reconstruction did not alter the overall interpretation of the results.

The NIOSH 7400 PCM method was chosen because it is the basis for regulatory standards widely used, but it does have limitations. Studies have suggested analyses of mineral particles are more accurate when using transmission electron microscopy (TEM) methods in comparison to PCM (24) as TEM allows for the examination of particles less than 5 µm in length (25). Short mineral particles, including cleavage fragments, make up the majority of mineral particle exposures for taconite miners (19). Evidence remains mixed on whether short particles and cleavage fragments play an important role in the development of lung disease (26-30), and the question of particle length and mesothelioma risk in taconite miners is examined in a separate study. An additional limitation is that PCM cannot differentiate between asbestiform and non-asbestiform EMPs. The EMPs generated from the liberation and crushing of bedrock along the Mesabi Range are non-asbestiform (15), but there is the potential for asbestiform EMP exposure from commercial asbestos within the mining facilities.

Commercial asbestos is a known cause of mesothelioma, and was used in the building and maintenance of the taconite plants. There is limited information on its use, and no quantitative data on asbestos type or levels that could be used to model exposure. We cannot rule out the involvement of commercial asbestos in our elevated risk estimates, but have tried to control for the effects of commercial asbestos exposure, in order to focus specifically on the risks of exposure to non-asbestiform EMPs. Our models accounted for commercial asbestos by looking at the probability of exposure by SEG, and the final models included the number of years of work in an SEG with high probability of asbestos exposure. Cases did have a higher mean employment duration in high commercial asbestos SEGs, but in total only thirteen cases ever worked in one of the high commercial asbestos SEGs, which included crusher maintenance, furnace operator, electrician, carpenter, pipefitter/plumber, lubricate technician, and auto mechanic. Commercial asbestos was also modeled using maximum asbestos SEG, ever working in high or medium asbestos SEG, and a time weighted average of all commercial asbestos scores. All commercial asbestos variables used yielded similar measures of risk for mesothelioma. As with many occupational studies, our work history data is limited to work within the iron mining industry only, and we do not have information on military service or additional occupations where workers could have been exposed to asbestos.

As with all case-control studies there is the potential for exposure misclassification. Work history records were obtained through MRHAP, so any exposure misclassification would occur primarily through assignment to the incorrect SEG. It is likely this misclassification is non-differential as all abstraction of work history and assignment of jobs to SEGs was performed blind to case-control status. Finally this study is limited by its small size, making it impossible to examine certain subgroups within the population.

This study does have a number of strengths. We performed an extensive exposure assessment, the most comprehensive in the taconite industry to date, and used direct measurements of EMPs for our analyses. MRHAP was extremely thorough in gathering records, and we expect the cohort to include almost all workers employed in the iron mining industry during the later half of the twentieth century. As our work history information came directly from mining company records and did not rely upon individual workers, there was no possibility of recall bias.

The study period of 1950-1982 also covers the times when dangers from EMP exposures could have been the greatest. Taconite mining began on a large scale in the 1950s, with its peak in the 1970s. It is reasonable to believe that EMP exposures could have been the highest during these periods, due to the newness of the taconite process and industrial controls in the 1950s, and the high rate of production in the 1970s. Though our work history data ends in 1982, the exposure assessment shows that in general exposure levels in the mines have been decreasing over time. Improved industrial controls, stricter exposure regulations, and increased use of personal protective equipment have all combined to lower the EMP exposures in taconite mining.

The case-control design allows for a more comprehensive examination of mesothelioma than has been possible in previous mortality studies of iron ore, talc, and gold miners. MCSS captures all mesothelioma diagnosed within the state of Minnesota since the start of MCSS in 1988, an advantage over previous studies of Minnesota taconite miners that had to exclusively on mortality data. Most work in the taconite industry began in the 1950s and 1960s, and almost seventy percent of the study population first started work in 1950 or later. Therefore it is unlikely that a lot of mesothelioma cases would have been missed before 1988, as there would not have been enough of a latency period. Not all miners continued to live in Minnesota after completing work in the mines, and these workers would not be captured by MCSS, but the development of a mesothelioma code in ICD-10 enabled us to include those miners who died of mesothelioma in a state outside Minnesota starting in 1999. It is possible that some out-of-state deaths were not included. Based on the percent of miners predicted to be living out of state and the number of MCSS cases diagnosed between 1988 and 1999 the number of out of state mesothelioma deaths during that period is likely to be between three and ten. Disease follow-up for both MCSS and death certificates lasted until 2010, giving a minimum latency of twenty-eight years for those workers employed at the end of the study period in 1982.

CONCLUSIONS

Our results show an association between employment duration in taconite mining and the risk of mesothelioma. We also see and association between cumulative EMP exposure and mesothelioma risk. These associations are seen as a slight elevation of the odds ratio when looking at mesothelioma risk across the Iron Range, with the strongest associations seen when looking at risk within geological Zones 1 and 2. An association with mesothelioma was not seen for either employment duration or cumulative EMP exposure in Zone 4. Based on these findings it does not appear that exposure to naturally occurring non-asbestiform amphibole minerals found in the eastern edge of the Mesabi Iron Range is driving the excess of mesothelioma seen in Minnesota iron ore miners. The exact role that EMP exposure plays in the elevation of mesothelioma rates in this population is not entirely clear, nor can the involvement of commercial asbestos exposure in the taconite mines or outside of the mines be ruled out.

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Table 2-1: Characteristics of all cases and controls in study population, and cases and controls who worked in taconite

	Cases (n=80)	**Controls (n=315)**
Gender (%)		
Female	0 (0.0)	17 (5.4)
Male	80 (100.0)	298 (94.6)
Type of Ore Mining (%)		
Hematite Only	23 (28.7)	131 (41.6)
Taconite & Hematite	25 (31.3)	81 (25.7)
Taconite Only	32 (40)	103 (32.7)
Mean years of hematite employment	4.7	4.6
TACONITE WORKERS	**Cases (n=57)**	**Controls (n=184)**
Taconite Zone Ever Worked (%)		
Zone 1	18 (31.6)	74 (40.2)
Zone 2	31 (54.4)	58 31.5)
Zone 4	12 (21.1)	66 (35.9)
Mean years of taconite employment		
Overall	10.9	9.4
Zone 1	11.1	7.8
Zone 2	10.6	7.9
Zone 4	7.6	10.4
Mean EMP/cc-years		
Overall	2.2	1.7
Zone 1	1.5	0.3
Zone 2	2.5	1.7
Zone 4	1.9	2.9
Mean years in SEGs with medium commercial asbestos score[ϕ]	4.1	5.0
Mean years in SEGs with high commercial asbestos score*	7.1	4.0

[ϕ] SEGs with a medium asbestos score are operating technician, concentrator maintenance, maintenance technician, and repairman

* SEGs with a high asbestos score are crusher maintenance, furnace operator, electrician, carpenter, auto mechanic, pipefitter/plumber, and lubricate technician

Table 2-2: Risk of mesothelioma for duration of taconite employment (years) and duration of taconite employment in each Iron Range Zone

Exposure	Cases/Controls	OR	95% CI
Overall Employment*			
Employment duration	57/184	1.03	1.00-1.06
Hematite	48/212	0.99	0.94-1.04
High vs Low			
Low Employment	28/97	1.00	---
High Employment	29/87	1.15	0.62-2.11
Zone Analysisǂ			
Employment duration-Zone 1	18/74	1.05	1.00-1.11
Employment duration-Zone 2	31/58	1.06	1.02-1.09
Employment duration-Zone 4	12/66	0.97	0.92-1.02
Hematite	48/212	0.97	0.92-1.03

*Results adjusted for age and employment in hematite

ǂ Results adjusted for age, employment in hematite, and duration in other zones

Table 2-3: Risk of mesothelioma for cumulative EMP/cc-years and cumulative EMP/cc-years in each Iron Range Zone

Exposure	Cases/Controls	OR	95% CI
Overall Exposure*			
EMP/cc-year	57/184	1.10	0.97-1.24
Hematite	48/212	1.00	0.95-1.05
High vs Low			
Low Exposure	29/125	1.00	---
High Exposure	28/59	1.93	1.00-3.72
Zone Analysisǂ			
EMP/cc-year -Zone 1	18/74	1.96	1.15-3.34
EMP/cc-year -Zone 2	31/58	1.31	1.12-1.54
EMP/cc-year -Zone 4	12/66	0.88	0.71-1.09
Hematite	48/212	0.99	0.94-1.04

*Results adjusted for age, employment in hematite, and commercial asbestos

ǂ Results adjusted for age, employment in hematite, commercial asbestos, and exposure in other zones

Chapter 3 Elongate mineral particle (EMP) size and risk of mesothelioma

Introduction

Mesothelioma is a rare cancer of the mesothelial cells lining the surfaces of body cavities, and most often seen in the pleura and peritoneum. The majority of mesothelioma cases result from exposure to asbestos (1, 2), a generic term for a collection of silicate minerals from the amphibole and serpentine mineral groups that occurring in an fibrous asbestiform habit (3). During the twentieth century asbestos was mined and incorporated into a variety of commercial products due to its tensile strength and low conductivity of heat and electricity (4). As the dangers of asbestos exposure became known, asbestos production dropped dramatically in the 1970s, and today is banned in fifty countries, though its use continues, especially in developing countries (5).

A key area of current asbestos research is identifying the physical characteristics, such as particle length and diameter that contribute to disease pathogenesis. The National Institute for Occupational Safety and Health (NIOSH) has included this topic in their strategic research agenda (6), and particle dimension continues to be the subject of debate in scientific literature. Multiple studies have suggested the development of mesothelioma and lung cancer is most strongly associated with exposure to asbestos particles at least 5-10 μm in length (7-9). While long particles may show the strongest disease associations, particles in a variety of sizes have demonstrated an association with lung and pleural tumors (9,10), and multiple studies stress the importance of including short particles, defined here as particles whose length is < 5 μm, in any health assessment of mineral particle exposure (11-13).

Long particles are hard for the body to clear as they can be too big for proper phagocytosis by macrophages, often leading to frustrated phagocytosis and other damaging reactions within the lungs (14,15**)**. Short particles, while easier to clear, constitute the majority of mineral particle exposure within most occupational settings (13,16,17). The lung and mesothelial tissues of individuals with asbestos-related disease contain short particles in greater amounts than long particles (11,13), as clearance mechanisms are likely not fast enough to deal with chronic exposure (18). Understanding the potential health effects of short particle exposures takes on a greater importance in light of asbestos regulatory standards. Both NIOSH and the Occupational Safety and Health Administration (OSHA) limit their regulations to particles with lengths of 5 μm or greater, as these are the only particles that can be consistently identified and counted using current analysis techniques (19,20). Thus exposure to short particles is not typically monitored.

Previous studies of occupational exposure to different particle lengths in people have focused on exposure to the serpentine chrysotile (9,17,21) or matched data on chrysotile and amphibole dimension distributions to existing cohorts (8). There is little research looking at non-asbestiform amphibole and non-amphibole exposures, and specifically at exposures to different particle sizes of these minerals. One industry with known exposure to a variety of amphibole and non-amphibole minerals is the taconite industry in northeastern Minnesota (22).

Taconite is a type of iron ore, mined along the Mesabi Iron Range. Minnesota produces the majority of domestic iron ore, accounting for over seventy-six percent of usable iron ore in the United States in 2007 (23). Taconite requires extensive processing to concentrate the iron content, with crushing and separating techniques that break down the taconite rock, producing cleavage fragments and mineral particles of various sizes. The characteristics of the mineral particles vary across the Iron Range due to geological variations of four distinct geological zones (24).

The risk of mesothelioma has been associated with duration of employment (25) and potentially with exposure to elongate mineral particles (EMPs) from taconite operations (26). Here we examine the association between mesothelioma incidence and exposure to EMPs of different sizes using three dimension-based exposure metrics.

METHODS

Study Population

The methods for this study have been described in detail elsewhere (26). Briefly, all cases and controls were nested within a cohort of 68,737 iron ore miners enumerated in 1983 by the University of Minnesota. Cases were identified using both the Minnesota Cancer Surveillance System (MCSS) and death certificates. MCSS was established in 1988 and captures all pathology confirmed cancer cases in the state of Minnesota. Death certificate data on mesothelioma was available starting in 1999, when a code specifically for mesothelioma was introduced as part of ICD-10. Linkage of the cohort to MCSS identified 63 in-state incident cases and an additional 17 cases were identified through death certificates. For each case, up to four controls were sampled from risk sets of cohort members of similar age (birth year +/- two years) who had not been diagnosed or died of mesothelioma at the time of case diagnosis or death. In total there were 80 cases and 315 controls. Five controls were excluded due to lack of documented employment in mining.

Exposure Assessment

Exposure to EMPs of various size was estimated using job-based personal sampling to characterize respirable dust exposure and area sampling to determine relative concentrations of EMPs of various sizes. Details of the exposure assessment have been described by Hwang et al. 2013 (22,27). Briefly, 28 Similarly Exposed Groups (SEGs) were created from a database of mining jobs, in collaboration with company industrial hygienists. Personal sampling was conducted at the six currently operating mines. At each mine for each SEG a volunteer miner wore an air-sampling pump for two three-hour periods. In total across all mines each SEG was sampled six to eight times. All personal EMP samples were analyzed using the NIOSH 7400 PCM method that counted EMPs with a length of at least five μm and an aspect ratio of three or greater. Current personal sampling data was combined with historical personal exposure data for the years 1978-2009, collected from the Mining Safety and Health Administration and two of the currently operating taconite mines. The combined exposure data served as the basis for a time-varying linear regression model that imputed EMP exposure values for each of the 28 SEGs within each of seven different mines for the period of 1955 to 2010.

Area samples were obtained in one or two representative locations per SEG during normal operating conditions, using a Nano-Micro Orifice Uniform Deposit Impactor (Nano-MOUDI) Model 125B, and analyzed with the ISO 13794 Indirect-Transfer TEM method. EMPs with an aspect ratio greater than three and a length greater than 0.3μm were counted and classified as chrysotile, amphibole, or non-amphibole. Only five chrysotile EMPs were identified and these were excluded from the analysis. Three dimension-based exposure metrics were used, Chatfield for long EMPs (28), and Suzuki and Cleavage for short EMPs (28,29). The dimensions for each of the three different EMP exposure metrics are given in Table 1 alongside the dimensions for NIOSH 7400 EMPs.

An SEG specific TWA concentration for each of the EMP size categories was estimated as a function of the fraction of the size-specific EMP and the total EMP concentration from the 7400 personal exposure measurement (27). The equations used for this conversion are shown in Figure 1. Two equations were used, one for exposures in the eastern Iron Range, employing linear regression (Equation 1), and one for exposures in the western Iron Range, which included a term for the ratio of NIOSH EMPs to each of the three dimension-based metrics, Chatfield, Suzuki, and Cleavage (Equation 2). The ratio of NIOSH EMPs to EMPs of each dimension could differ depending on the location within the mine that an area sample was collected. Equation 3 was used to compare the ratio of NIOSH to dimension-based EMPs at different locations in the mine to see how much the ratio varied from location to location. The location specific ratios were found to be comparable, showing that one overall ratio term could be used for Equation 2.

Work History and Exposure Matrix

Work history for cases and controls was abstracted in detail through 1982 at the time the cohort was enumerated. Job titles were standardized and assigned to the SEGs developed for the exposure assessment. If job titles were not sufficiently specific to assign SEGs departmental information was used to assign these jobs to departmental SEGs. Work in the earlier hematite industry was assigned to a Hematite SEG. An individual's cumulative exposure to Chatfield, Suzuki, and Cleavage particles was calculated separately using three different exposure data matrixes. The daily exposure concentration for an SEG depended on the mine, year, and particle type (Chatfield, Suzuki, or

Cleavage), and this concentration was multiplied by the length of time spent working in the SEG giving an EMP/cc-years value for each SEG. The EMP/cc-years values for all SEGs were added to give the lifetime cumulative exposure for a worker. Cumulative exposure was calculated for each EMP type, giving an individual three separate cumulative measures: Chatfield EMP/cc-years, Suzuki EMP/cc-years, and Cleavage EMP/cc-years.

An important potential confounder is exposure to commercial asbestos. Commercial asbestos was used in the processing operations in buildings as well as some of the processes. No quantitative data exists on asbestos exposure in these operations so a qualitative scale was established to estimate exposures by job title. The same SEGs used in the EMP exposure reconstruction were evaluated by the study team and company industrial hygienists to estimate the probability and frequency of exposure to commercial asbestos. Each SEG was assigned a commercial asbestos score of low, medium, or high based on these estimates. Several metrics were evaluated, but the number of years at high exposure was ultimately used as a metric to control for the potential effects of asbestos exposure.

Data Analysis

The risk of mesothelioma associated with the three EMP metrics was estimated with conditional logistic regression models and the precision of the estimates was characterized with 95% confidence intervals. Models were fit to examine cumulative exposure across the Iron Range, and cumulative exposure within each of the geological zones of the Iron Range where taconite mining occurred (zones 1,2, and 4). In addition to the exposure variables, models included a term for the number of years employed in hematite mining, as well as a term number of years spent working in SEGs with a high commercial asbestos score. All analyses were conducted in SAS Version 9.2.

RESULTS

Characteristics of Study Population

Of the 80 cases and 315 controls, 57 of the cases and 184 controls worked in taconite operations (Table 2). All cases and 95 percent of the controls were male. Cases more frequently worked in Zone 2 while the greatest percentage of controls worked at some point in Zone 1. The mean years worked in SEGs with high commercial asbestos scores was greater for cases. Mean Chatfield EMP/cc-years across all Zones were greater for cases, as were mean Chatfield EMP/cc-years within Zones 1 and 2. Mean Suzuki and Cleavage EMP/cc-years were greater for controls across all Zones, and greater for cases in Zones 1 and 2.

Dimension based exposure metrics

The risk of mesothelioma was increased, with increasing cumulative exposure to Chatfield EMPs for the entire range and within Zone 1 and 2 (Table 3). No elevation of risk is seen across Zones for additional Suzuki EMP/cc-years of exposure, though the risk is still elevated significantly when looking at exposure within Zone 1 and Zone 2 (Table 4). The risks for Cleavage EMP/cc-years are significantly elevated in Zone 1 and Zone 2 but not across all Zones (Table 5). There was no elevation in mesothelioma risk from work within hematite mining in any of the models. The risk estimates were adjusted for age, length of employment in hematite, and years of employment with high probability of exposure to commercial asbestos. The results for the zone specific models were also adjusted for EMP/cc-years in other zones.

DISCUSSION

In this study examining the health effects of exposure to EMPs of different sizes within the taconite industry, we observed an association between cumulative exposure to Chatfield EMPs and the risk of mesothelioma. An association was also seen with cumulative exposure to Suzuki and Cleavage EMPs within specific geological zones of the Mesabi Iron Range. The mesothelioma risks seen with Chatfield EMPs are comparable to those found for NIOSH EMPs (26), while the mesothelioma risks for Suzuki and Cleavage EMPs are comparable, showing the risk of mesothelioma differs depending on EMP length.

As with previous studies (9,10) the longer particles, Chatfield and NIOSH, showed the strongest associations with the disease outcome. This was true when looking across all the geological zones of the Iron Range, and within Zones 1 and 2. Also in line with previous work (9,10), associations were still seen for the shorter particles, Suzuki and Cleavage, at a smaller level and in this study only when looking at cumulative exposure within Zone 1 and Zone 2.

The risk of mesothelioma was elevated in Zones 1 and 2 for all EMP types, including NIOSH EMPs (26). Geological events over one billion years ago at the eastern end of the Iron Range led to changes in mineral composition. Zone 1, the westernmost zone, was not affected by these events and contains minerals such as magnetite, iron-silicates, and quartz. Zone 2 is a transitional zone with some alterations in mineral composition, while the easternmost Zone 4 contains minerals that went through metamorphosis to form amphiboles such as grunerite and hornblende (24,30). Zones 2 and 4 each have one mine whereas multiple taconite mines are located in Zone 1, giving it the largest variation in cumulative exposure values, including a few cases with extremely high exposures. The studies by Stanton, et al. 1981 and Loomis et al. 2010 (10,17) noted high correlations between the different sizes of mineral particles, an effect also seen in the taconite EMP exposure data used for this study (27). The elevated mesothelioma risks seen in Zones 1 and 2 for Suzuki and Cleavage particles could be due to the correlation of these shorter particles with the longer Chatfield and NIOSH particles.

This study does have several limitations. There are no historical area measurements, thus we assume the ratio of NIOSH 7400 EMPs to each of the other EMPs is the same over time. Given that the taconite process has not changed significantly since its inception the main factor in changing the relative amounts of each particle type would likely be improvements made in industrial controls and ventilation systems. No historical EMP data were available for multiple years of the 1955-1982 study period necessitating the use of imputation and regression modeling to estimate exposures. Multiple models were tried, assuming either a trend for exposures over time or no trend. These differences in the exposure reconstruction models did not alter the interpretation of the results.

Commercial asbestos products were used in the building and or maintenance of the mines and mining machinery. There is no quantitative data on how asbestos was used in the mines, or in what amount. In order to account for the possible exposure to asbestos that workers might have experienced we created qualitative asbestos categories, low, medium, and high, for each SEG based on the probability of asbestos exposure within the SEG. Asbestos score assignments were reviewed by experts, and the length of time spent in SEGs with high commercial asbestos scores included in the model. While we have tried to control for asbestos exposure, we can't rule out the possibility that exposure to asbestos, either in the mines or outside in another occupation or military service, plays a role in the elevated mesothelioma risks we have identified. The mean years of work in an SEG with a high commercial asbestos score was greater for cases; however this result is based on only thirteen cases. Commercial asbestos was modeled in a variety of ways, including a time-weighted average of all commercial asbestos scores, ever working in a medium or high asbestos SEG, and highest asbestos SEG score. The use of different commercial asbestos variables did not change the interpretation of the results.

There are a number of strengths in this study. The exposure assessment performed for this study is the most comprehensive study of exposures in the taconite industry to date. The study period of 1955-1982 includes several key points for the industry, including its build-up in the 1950s and 1960s, as well as the peak in the 1970s, both times when exposures were likely to be higher. Though we have no work history after 1982, historical and our current data sources show that EMP exposures decreased over time (22), and any recent exposures would not be relevant to the development of mesothelioma as there would not have been an adequate latency period.

Our mesothelioma cases were identified between 1988 and 2010, giving at minimum a twenty-eight year latency after the end of the study period. We confident that almost all mesothelioma cases within the cohort were identified as MCSS provides data on all mesothelioma cases diagnosed in Minnesota after 1988, and death information is available for out of state deaths after 1999. It is doubtful that many cases were diagnosed before 1988 due to mesothelioma's latency of thirty years or more, and what cases might have occurred would likely be in hematite workers. Some individuals could have died of mesothelioma out of state before 1999. Based on the number of MCSS cases diagnosed between 1988 and 1999 and the percent of miners predicted to be living outside Minnesota, the number of out of state deaths during that time is estimated to be between three and ten.

CONCLUSIONS

Our results show the risk of mesothelioma is associated with EMP size, with higher risks identified after exposure to long EMPs, and slight risks identified for short EMPs within specific locations along the Mesabi Iron Range. Our study offers some support to the hypothesis that long mineral particles have the greatest bearing on the development of mesothelioma, and extends this argument to non-asbestiform amphibole and non-amphibole particles. The role of short EMPs remains unclear, but their involvement in disease pathogenesis should not be completely discounted, especially as they make up the majority of mineral particle exposures in most occupational settings.

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Table 3-1: EMP dimensions for NIOSH, Chatfield, Suzuki, and Cleavage exposure metrics

EMP type	**Length (µm)**	**Width (µm)**	**Aspect Ratio**
NIOSH	> 5	---	≥ 3
Chatfield	---	$0.04 < W < 1.5$	$20 < AR < 1{,}000$
Suzuki et al.	≤ 5	≤ 0.25	---
Cleavage	---	---	≤ 20

Table 3-2: Characteristics of all cases and controls in study population, and mean exposures for cases and controls who worked in taconite

	Cases (n=80)	**Controls (n=315)**
Type of Ore Mining (%)		
Hematite Only	23 (28.7)	131 (41.6)
Taconite & Hematite	25 (31.3)	81 (25.7)
Taconite Only	32 (40)	103 (32.7)
TACONITE WORKERS	**Cases (n=57)**	**Controls (n=184)**
Gender (%)		
Female	0 (0.0)	9 (4.9)
Male	57 (100.0)	175 (95.1)
Taconite Zone Ever Worked (%)		
Zone 1	18 (31.6)	74 (40.2)
Zone 2	31 (54.4)	58 31.5)
Zone 4	12 (21.1)	66 (35.9)
Mean years in SEGs with high commercial asbestos score*	7.1	4.0
Mean Chatfield EMP/cc-years		
Overall	1.5	1.3
Zone 1	1.2	0.3
Zone 2	1.4	0.9
Zone 4	1.6	2.4
Mean Suzuki EMP/cc-years		
Overall	16.8	23.2
Zone 1	20.0	1.9
Zone 2	7.5	5.0
Zone 4	34.8	58.3
Mean Cleavage EMP/cc-years		
Overall	10.8	16.6
Zone 1	10.2	1.2
Zone 2	4.9	3.2
Zone 4	23.5	42.0

* SEGs with a high asbestos score are crusher maintenance, furnace operator, electrician, carpenter, auto mechanic, pipefitter/plumber, and lubricate technician

Table 3-3: Risk of mesothelioma for cumulative Chatfield EMP/cc-years and cumulative Chatfield EMP/cc-years in each Iron Range Zone

Exposure	Cases/Controls	OR	95% CI
EMP/cc-year*	57/184	1.05	0.89-1.25
Hematite	48/212	0.99	0.95-1.04
EMP/cc-year – Zone 1ǂ	18/74	1.73	1.06-2.83
EMP/cc-year – Zone 2	31/58	1.56	1.16-2.09
EMP/cc-year – Zone 4	12/66	0.84	0.64-1.09
Hematite	48/212	1.00	0.95-1.05

*Results adjusted for age, employment in hematite, and commercial asbestos

ǂ Results adjusted for age, employment in hematite, commercial asbestos, and exposures in other zones

Table 3-4: Risk of mesothelioma for cumulative Suzuki EMP/cc-years and cumulative Suzuki EMP/cc-years in each Iron Range Zone

Exposure	Cases/Controls	OR	95% CI
EMP/cc-year*	57/184	0.99	0.98-1.00
Hematite	48/212	0.99	0.94-1.03
EMP/cc-year – Zone 1ǂ	18/74	1.07	1.01-1.14
EMP/cc-year – Zone 2	31/58	1.15	1.06-1.25
EMP/cc-year – Zone 4	12/66	0.99	0.97-1.00
Hematite	48/212	1.00	0.95-1.05

*Results adjusted for age, employment in hematite, and commercial asbestos

ǂ Results adjusted for age, employment in hematite, commercial asbestos, and exposures in other zones

Table 3-5: Risk of mesothelioma for cumulative Cleavage EMP/cc-years and cumulative Cleavage EMP/cc-years in each Iron Range Zone

Exposure	Cases/Controls	OR	95% CI
EMP/cc-year*	57/184	0.99	0.99-1.00
Hematite	48/212	0.99	0.94-1.04
EMP/cc-year – Zone 1ǂ	18/74	1.05	1.01-1.10
EMP/cc-year – Zone 2	31/58	1.10	1.04-1.16
EMP/cc-year – Zone 4	12/66	0.99	0.98-1.00
Hematite	48/212	1.00	0.95-1.05

*Results adjusted for age, employment in hematite, and commercial asbestos

ǂ Results adjusted for age, employment in hematite, commercial asbestos, and exposures in other zones

Figure 3-1: Equations used in the conversion of Chatfield, Suzuki, and Cleavage area measurements into personal measurements

Equation 1: $C_{Definition}=a_1 (C_{NIOSH\ EMP})^b$ for total and amphibole EMP in the eastern zone

Equation 2: $C_{Definition}=a_2 (C_{NIOSH\ EMP})$ for total EMP in the western zone

Equation 3: $C_{Definition} = a_i C_{NIOSH\ EMP}$ of the i^{th} location

$C_{Definition}$ = concentration of total EMP that meet a specific size definition, either Chatfield, Suzuki, or Cleavage

$C_{NIOSH\ EMP}$ = concentration of total EMP that meet NIOSH 7400 definition

a_1= intercept based on linear regression between log-transformed concentrations $C_{Definition}$ and $C_{NIOSH\ EMP}$

b = linear regression slope

a_2 = concentration ratio for each size EMP definition to NIOSH 7400 definition based on linear regression

Chapter 4 Study of Radiographic Lung Abnormalities in Minnesota Taconite Miners

INTRODUCTION

The term asbestos describes a collection of six fibrous minerals, five from the amphibole and one from serpentine mineral groups. The properties of these minerals have long made them desirous for use in insulation, friction products, and roofing (1). Asbestos is present in a variety of occupational settings, and is actively used in multiple parts of the world (1).

Chest radiography has long been used as a screening tool to identify signs of pneumoconiosis from asbestos and other occupational exposures, and specific radiographic abnormalities are recognized as signs of asbestos exposure (2). Asbestosis occurs when there is interstitial fibrosis of the lung due to asbestos fibers (3). Radiography is the most common method of identifying asbestos related benign pleural disease (4), and the most common manifestation of asbestos exposure is the presence of localized areas of thickening on the surface of the parietal pleura, known as pleural plaques (3). Diffuse pleural thickening involves fibrosis and thickening of the visceral pleura with obliteration of the costophrenic angle (5).

The prevalence of radiographic abnormalities consistent with asbestos exposure has been reported for a large number of industries (6-10). The studies focused on occupational asbestos exposure, though exposure to asbestos as well as other fibrous minerals such as erionite has been examined in environmental studies (11,12). The effects of non-asbestiform amphiboles, minerals with chemical similarity to asbestos but without the fibrous habit, and non-amphiboles are not well understood (13). Previous studies of these minerals have focused primarily upon lung cancer and mesothelioma mortality with some attention on non-malignant respiratory disease (14,15).

Iron mining has taken place along the Mesabi Iron Range in northeastern Minnesota for over 100 years, but there have been a limited number of studies looking at occupational exposures and health outcomes in this population (16-18). Recently it has been shown that workers in the Minnesota iron mining industry are at greater risk of mesothelioma (19**)** and lung cancer. There is the potential for non-malignant respiratory disease consistent with pneumoconiosis as the miners are exposed to a variety of substances including crystalline silica and a variety of elongate mineral particles (EMPs) including non-asbestiform amphiboles and cleavage fragments. By definition EMPs are mineral particles with a minimum aspect ratio of 3:1, a definition that incorporates mineral particles of a variety of types and sizes. The pathogenicity of EMPs is thought to be related to both their mineral composition and size, but this remains an area of research. The geological make-up of the Mesabi Range is characterized by four distinct geological zones (20), which may impose variable EMP exposures.

In this study we evaluate potential associations between working in the taconite iron mining industry and attendant exposure to EMPs and radiographic evidence of pleural or parenchymal abnormalities.

METHODS

Study Population and Recruitment

Rosters of current and former workers were obtained for four mining companies, encompassing the six currently operating taconite mines and one former mine. An age-stratified sample of 1,200 was selected from16,990 workers. Workers were recruited for study participation by letter. Non-respondents were sent a reminder postcard and follow-up letter followed by a telephone call to ensure receipt. A final letter was sent to non-respondents approximately 6 months later when the clinic was relocated to be more convenient for some workers. Interested workers were informed of study requirements, and eligible workers were sent a consent form and study questionnaire to fill out before their scheduled clinic appointment. All study and recruitment protocols and materials were approved by the Institutional Review Boards at the University of Minnesota and the two clinic sites.

Clinical Data Collection and Chest Radiography

A total of 1,188 workers completed a clinical exam. Clinical exams consisted of a review of the study questionnaire, check of vital signs, pulmonary function test, blood draw, chest exam, and X-ray. A single posteroanterior chest film was taken using International Labor Organization (ILO) criteria (21). All X-rays were performed by radiologic technologists trained to administer B-read x-rays. All films were read independently by two NIOSH certified B Readers using ILO guidelines and standard images (21). For the purposes of this study, parenchymal abnormalities were defined as the presence of small opacities of profusion ILO category 1/0 or above, and pleural abnormalities defined as any pleural abnormalities consistent with pneumoconiosis. When necessary a third certified reader performed an arbitration read. For parenchymal abnormalities a third read took place when the two initial readers disagreed on the presence of parenchymal abnormalities with an ILO classification of 1/0 of the extent of profusion of more than two categories. If there were discrepancies between two initial readers regarding pleural abnormalities, the radiographs were reviewed by a third certified B-reader.

Exposure Assessment

The details of the exposure assessment have been described previously (22). Briefly a database of mining job titles was created using mining company records, data from the Mining Safety and Health Administration (MSHA), and a previous University of Minnesota study (23). The job database was used to create twenty-eight Similarly Exposed Groups (SEGs), each SEG containing jobs with similar tasks and processes. Personal exposure sampling was carried out at all six currently active taconite mines, with each SEG sampled six to eight times. Volunteer miners wore a personal air-sampling pump for two three-hour periods during their work shift. All personal samples were analyzed using the NIOSH 7400 PCM method, which counts EMPs with a length greater than five µm and an aspect ratio of at least three. Historical EMP exposures were reconstructed using current exposure data in combination with personal exposure data for the years 1978-2009 that was collected from MSHA and two of the currently operating taconite mines. For years when no EMP data was available, imputation was used to estimate EMP levels. Regression models were created for each SEG within each mine, and used to calculate EMP exposure values for all years between 1955 and 2010. 1955 exposure levels were used for any jobs that occurred in 1954 or earlier.

Commercial asbestos was used in the maintenance and building of the mines, but no quantitative data exists of asbestos levels within the mines. To account for potential asbestos exposure in the mines, each SEG was assigned an asbestos score of low, medium, or high based on the combined likelihood and frequency of asbestos exposure. Industrial hygiene experts reviewed the asbestos scores, and the number of years in SEGs with a high asbestos score was included in the exposure models. Potential occupational asbestos exposure outside the mines was assessed in the questionnaire, and a variable included in the models that indicated whether an individual had ever been employed in an occupation with a high potential for asbestos exposure.

Work History and Exposure Matrix

Work history information was collected from study questionnaires, and included job title, major job activities, start and stop years, and company of employment. Reported work history covered the period from 1941 to 2010. Job titles were standardized and assigned to SEGs. Additional departmental level SEGs were created for jobs that were too vague to assign to a specific SEG. Missing or unknown jobs were assigned to an “Unknown” SEG. Exposures for departmental SEGs were based on an average of all SEGs in that department and exposures for the Unknown SEG at each mine were based on an average of all SEGs at that mine.

Some of the workers were employed in the hematite mining industry. Hematite is a higher-grade ore that did not require significant processing. Hematite deposits were depleted by the mid 1960's. Historical mining data were used to determine the transition point from hematite to taconite for each mine. As no exposure data were available for hematite jobs they were treated as a separate SEG.

Cumulative EMP exposures were calculated using an exposure data matrix. SEGs were given a daily EMP concentration based on the mine and year of employment, with the SEG concentration multiplied by the length of time spent in the SEG. In cases where multiple jobs were reported for the same years, all jobs in the period were given an equal portion of time. Exposure values for all SEGs were summed to give the cumulative EMP exposure for each worker, expressed as EMP/cc-years.

Data Analysis

Descriptive analyses examined the characteristics of workers who completed the questionnaire and clinic visit. Separate analyses examined the characteristics of study responders versus non-responders, and the details of these analyses are described elsewhere (24). Multivariable logistic regression models were used to estimate prevalence odds ratios and 95% confidence intervals to describe the association between radiographic abnormalities and employment in the taconite industry and cumulative EMP exposure. Employment duration models examined the effect of years worked in taconite across the entire Iron Range, with a separate model examining the effect of years worked within each Iron Range Zone. Cumulative EMP models examined EMP exposure across all zones, with a second model examining cumulative exposure within each zone. SAS Version 9.2 was used to run all statistical models.

Models included several additional variables including age, BMI, number of years in an SEG with a high probability for asbestos exposure, and outside occupation with a high probability of asbestos exposure. As hematite mining does not require the processing steps needed for taconite, hematite and taconite mining exposures are different. No exposure data was available for the Hematite SEG so models included the number of years spent in the Hematite SEG. Four individuals did not undergo chest radiography and six individuals were excluded who did not have BMI information, giving a total of 1,178 workers in the final analyses.

RESULTS

Study Responders and Non-Responders

A total of 1,188 miners took part in the questionnaire and clinic visit (Table 1). Non-respondents (N=1,988) included 1,210 who declined participation and 778 who were not successfully contacted. The study participants were more likely to be older and live closer to the clinic.

Radiographic Abnormalities

The prevalence of a parenchymal abnormality identified by any of the B-Readers was 7.5% and 5.3% when the abnormality was a consensus of two readers (Table 2). Pleural abnormalities had a prevalence of 23.1% when identified by any of the B-Readers, and 16.8 when identified by a consensus of two readers. The prevalence of diffuse pleural thickening was 1.0%, and 2.5% of workers had both consensus parenchymal and consensus pleural abnormalities.

Characteristics of Study Population

The study population was predominantly male former workers (Table 3). Workers with pleural and parenchymal abnormalities tended to be older and had a higher BMI. Former smokers made up the largest percentage of all groups, and the percentage of never smokers was greater among workers without abnormalities. The percentage of workers who worked in an outside occupation with the potential for asbestos exposure was similar for all groups. The greatest percentage of workers spent time in Zone 1 followed by Zone 2. Mean years of taconite employment were greater in workers with abnormalities. Mean cumulative EMP/cc-years were greater in workers with abnormalities. Zone 4 workers had greater cumulative exposure in comparison to workers in Zones 1 and 2.

Parenchymal Abnormalities

No clear association was observed between employment duration and risk of parenchymal abnormalities (Table 4), though some elevation of risk was seen for workers with longer employment duration and workers within Zones 1 and 2. Similar findings were seen for cumulative EMP exposure, with an elevation of risk for workers with higher cumulative exposure, and exposure within Zone 1 and Zone 2 (Table 5). All parenchymal models were adjusted for age, BMI, years in hematite, and ever being employed in an outside occupation with the high potential for asbestos exposure. Exposure models were also adjusted for years of taconite employment with a high probability of exposure to commercial asbestos, and Zone specific models were adjusted for the duration or exposure experience in other zones. Associations with parenchymal abnormalities did not alter appreciably when adjusted for smoking status (current, former, never), or adjusted for gender.

Pleural Abnormalities

The risk of pleural abnormalities was associated with duration of taconite employment (Table 6). There is evidence of an exposure-response relationship as workers with increasing employment duration had greater levels of risk. The association with length of employment was greatest for employment in Zone 2 and Zone 1. The risk of radiographic pleural abnormalities was also associated with cumulative EMP/cc-years of exposure (Table 7). Similar to the results for employment duration, workers with increasing levels of EMP exposure had higher risks of pleural abnormalities. Zone specific analyses showed higher risks for workers in Zone 1 and Zone 2. Pleural models were all adjusted for age, BMI, years in hematite, and ever being employed in an outside occupation with the high potential for asbestos exposure. Exposure models were also adjusted for years of taconite employment with a high probability of exposure to commercial asbestos, and Zone specific models were adjusted for the duration or exposure experience in other zones. Pleural measures did not alter greatly when the data was adjusted gender.

DISCUSSION

In this study examining the effects of length of employment and cumulative EMP exposure within the taconite industry, we observed an association between employment duration and the risk of pleural lung abnormalities. A similar association was seen for cumulative EMP exposure. The risk of radiographic parenchymal abnormalities was increased in workers with longer periods of employment and greater exposure levels, though the risks were lower than those observed for pleural abnormalities.

We observed variability in the association across the zones with greater risks for pleural than parenchymal abnormalities, in Zone 2 and Zone 1. These zone results are similar to those found in a mesothelioma case-control in this population, where mesothelioma risk was elevated in Zones 1 and 2 (25). Zone 1 comprises the majority of the Mesabi Range, and is the location for almost all the taconite mines in operation today. Zone 1 contains minerals such as talc, quartz, and magnetite. Zone 2, a small area with one former taconite mine is a geological transition zone where Zone 1 minerals such as quartz and magnetite have started to undergo recrystallization (20). Zone 4 minerals underwent a metamorphosis, creating amphibole minerals such as hornblende and grunerite (26). While EMP exposures were highest in Zone 4, no associations with radiographic abnormalities were observed.

Prevalence of consensus parenchymal abnormalities was 5.3% and 16.8% for pleural abnormalities. The greater prevalence of pleural abnormalities is consistent with previous assessments of workers exposed to mineral fibers including asbestos (27). The prevalence observed in this population is higher than that seen in unexposed workers and the general population (28,29). While the exposures to EMPs in this population were relatively low compared to many asbestos exposed populations there have been associations between pleural abnormalities and short employment duration and very low cumulative EMP levels previously reported (9).

It can be difficult to make comparisons between the level of radiographic abnormalities seen in different industries, as each industry has unique exposure conditions and the study methods, latency, and population demographics can be quite variable. The level of abnormalities seen in taconite workers is slightly less than that in other industries such as plumbing/pipefitting where the prevalence of parenchymal and pleural abnormalities was 7.8% and 26.1% respectively (8), and sheet metal work with 6.6% and 18.8% prevalence for parenchymal and pleural abnormalities (7). The prevalence in workers with potentially heavy asbestos exposure is much higher, with 18% and 27% parenchymal and pleural prevalence in construction/shipyard workers (6). The lower level of disease in taconite miners could be due to a variety of factors including shorter latency, smaller exposures, or evidence that EMP exposure is not as potent as the asbestos exposure examined in other studies. Mean exposures were fairly low, and few workers displayed signs of more serious disease such as diffuse pleural thickening (1.0%) or parenchymal disease at a level of 2/1 or greater (0.8%).

The risks seen in this study were lower for parenchymal than pleural abnormalities, and less than those observed with higher exposures (9). A study of workers in various trades at Department of Energy (DOE) nuclear sites reported risks for increasing employment duration that were similar for pleural disease, but greater for parenchymal disease. The types of trades present in the DOE study are similar to those present in taconite mines, and the prevalence of radiographic abnormalities is similar to that observed in the current study with 5.4% and 23.1% of DOE workers having parenchymal and pleural abnormalities. The increased prevalence of parenchymal abnormalities in this study despite no clear association with taconite employment or EMP exposure could be because the abnormalities seen are the result of silica and not EMP exposure. Levels of respirable silica in taconite mines are far greater than EMP levels (30), and radiographic findings could be evidence of silicosis.

There are limitations to this study. As with many cross-sectional studies a key concern is selection bias. Ultimately 40% of selected workers took part in the study. A comparison of study responders and non-responders shows that non-responders tended to be younger and live farther from the study clinic. Based on these characteristics it is possible that this study over estimates the prevalence of disease, as older workers are more likely to have radiographic findings than younger workers. But it is also possible that out study underestimates disease level, as sick workers are less likely to travel to the clinic especially across longer distances.

In order to examine potential biases to the results, we compared respiratory symptoms in the 134 workers who took part in the questionnaire only to the 1,188 workers who took part in the questionnaire and clinic visit (24). Our assumptions were that respiratory symptoms were a surrogate marker for exposure, and that questionnaire only workers were similar to non-responders. Comparisons of the two groups showed no significant differences in the presence of respiratory symptoms, suggesting non-responders could be similar to the study population. In the future we will examine non-responders using iron mining work records to see how their length of employment compares to workers in this study.

The work history data used for this study was collected from worker questionnaires so there is the potential for recall bias. We tried to minimize bias by assigning all reported jobs to exposure groups that were standardized to the greatest extent possible, and had been used in a previous study of this population (25). Assignment of jobs to exposure groups was performed blind to radiographic status.

Chest radiography, while the most widely used screening method, has some limitations. The sensitivity in of chest radiographs in comparison to CT or histology at autopsy is 50 to 80% for pleural plaques (3). One study of parenchymal fibrosis at autopsy found no radiographic evidence of disease in 18% of cases with histological fibrosis (31). Specificity is also an issue, as other conditions can manifest similarly to benign pleural disease and asbestosis. Pleural plaques can be especially hard to distinguish from extrapleural fat pads (4, 32) particularly in overweight individuals. In this study BMI was associated with pleural abnormalities, a finding of other radiographic studies (11). Among the participants in this study, mean BMI was highest in workers with pleural abnormalities, making it plausible that some pleural findings were due to pleural fat.

EMP data was not available for all years of the study period, causing the use of imputation and regression modeling to help estimate historical exposure levels. Multiple modeling approaches were tried incorporating different methods and assumptions on whether or not there was an exposure time trend. Models included variables for commercial asbestos exposure both within taconite mines and in non-mining occupations but we cannot rule out the possibility that these exposures played a role in our results.

CONCLUSIONS

Our results show an association between duration of employment in taconite mining and the risk of radiographic pleural abnormalities. We also see an association between cumulative EMP exposure and pleural abnormality risk. Stronger risks were observed in geological Zones 1 and 2, while no clear association was seen for parenchymal abnormalities. The prevalence of abnormalities in taconite workers is similar to that seen in other occupational studies. This study suggests that non-malignant lung disease can occur after mineral particle exposure within the taconite industry.

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Table 4-1: Characteristics of Responders and Non-Responders in Study Population

Characteristic	Responders N=1,888	Non-Responders N= 1,988
Sampling Age group %		
35-44	7.7	21.0
46-55	18.3	26.1
55-65	35.3	24.5
66-75	25.3	15.4
75+	13.5	13.0
Distance from clinic %		
0-15.1	15.8	15.6
15.2-30.1	21.8	18.4
30.2-60.1	34.5	29.9
60.2-120.1	15.8	16.0
120.1+	12.0	20.1

Table 4-2: Summary of Radiographic Abnormalities in Taconite Workers who obtained chest X-ray

Radiographic Interpretation	N (%)
Any parenchymal abnormality[Φ]	88 (7.5)
Consensus parenchymal abnormality	63 (5.3)
Any pleural abnormality[¤]	272 (23.1)
Consensus pleural abnormality	198 (16.8)
Consensus diffuse pleural thickening[€]	12 (1.0)
Consensus pleural and parenchymal abnormality	29 (2.5)

[Φ] Parenchymal abnormality=Profusion 1/0 or greater
[¤] Pleural abnormality=Pleural abnormality consistent with pneumoconiosis
[€] Diffuse pleural thickening defined as costophrenic angle obliteration

Table 4-3: Demographics and exposure levels of taconite workers who obtained chest X-ray by radiographic abnormality status

Characteristic	Parenchymal Abnormality		Pleural Abnormality	
	Yes=63	No=1115	Yes=198	No=980
Working Status %				
Former	93.6	69.9	84.9	68.4
Current	6.4	30.1	15.1	31.6
Gender %				
Female	1.6	9.6	2.0	10.6
Male	98.4	90.4	98.0	89.4
Mean Age	67.9	60.1	65.6	59.5
Mean BMI	30.5	31.4	34.3	30.8
Smoking Status %				
Current	15.9	11.7	8.1	12.7
Former	61.9	48.3	66.7	45.5
Never	22.2	40.0	25.2	41.8
Outside Asbestos Occupation %				
No	76.2	77.9	74.2	78.5
Yes	23.8	22.1	25.8	21.5
Zone ever worked %				
Zone 1	57.1	61.5	58.6	61.8
Zone 2	38.1	34.8	36.9	34.6
Zone 4	22.2	25.0	22.7	25.3
Mean years of taconite employment				
Overall	29.0	25.3	28.5	24.9
Zone 1	25.9	20.8	22.7	20.7
Zone 2	22.7	19.2	24.9	18.2
Zone 4	24.1	21.2	24.5	20.8
Mean EMP/cc-years				
Overall	3.8	2.9	3.9	2.8
Zone 1	2.3	1.5	2.0	1.5
Zone 2	3.1	2.4	3.7	2.2
Zone 4	5.7	4.6	5.9	4.5

Table 4-4: Risk of parenchymal abnormalities[Φ] for duration of taconite employment (years) and duration of taconite employment in each Iron Range Zone

Exposure	Abnormalities Yes	Abnormalities No	OR	95%CI
Overall Employment*				
Employment duration	63	1115	1.02	0.99-1.04
Hematite	7	51	1.01	0.94-1.08
Duration Category*ɤ				
0 < years < 22	15	425	1.00	---
22+ years	48	690	1.38	0.75-2.56
Zone Analysis‡				
Employment duration-Zone 1	36	686	1.03	1.00-1.06
Employment duration-Zone 2	24	388	1.03	1.00-1.06
Employment duration-Zone 4	14	279	1.01	0.98-1.04

[Φ] Parenchymal abnormality defined as profusion 1/0 or greater

* Results adjusted for age, BMI, hematite years, and outside occupation with high probability of asbestos exposure

‡ Results adjusted for age, BMI, hematite years, outside occupation with high probability of asbestos exposure, and duration in other zones

ɤ Duration category comparison is duration quartile 1 vs duration quartiles 2-4

Table 4-5: Risk of parenchymal[Φ] abnormalities[¤] for cumulative EMP/cc-years and cumulative EMP/cc-years in each Iron Range Zone

Exposure	Abnormalities Yes	Abnormalities No	OR	95%CI
Overall Employment◊				
EMP/cc-year	63	1115	1.01	0.92-1.10
Hematite	7	51	1.00	0.93-1.07
Exposure Category◊ ꭓ				
0 < EMP/cc-years < 0.96	15	380	1.00	---
0.96+ EMP/cc-years	48	735	1.28	0.69-2.36
Zone Analysis§				
EMP/cc-year -Zone 1	36	686	1.06	0.92-1.23
EMP/cc-year -Zone 2	24	388	1.04	0.91-1.19
EMP/cc-year -Zone 4	14	279	0.99	0.90-1.09

[Φ] Parenchymal abnormality defined as profusion 1/0 or greater

◊ Results adjusted for age, BMI, hematite years, commercial asbestos, and outside occupation with high probability of asbestos exposure

§ Results adjusted for age, BMI, hematite years, commercial asbestos, outside occupation with high probability of asbestos exposure, and exposure in other zones

ꭓ Exposure category comparison is exposure quartile 1 vs exposure quartiles 2-4

Table 4-6: Risk of pleural abnormalities[¤] for duration of taconite employment (years) and duration of taconite employment in each Iron Range Zone

Exposure	Abnormalities Yes	Abnormalities No	OR	95%CI
Overall Employment*				
Employment duration	198	980	1.02	1.00-1.04
Hematite	15	43	1.01	0.95-1.07
Duration Category* ϫ				
0 < years < 21	40	342	1.00	---
21+ years	158	638	1.59	1.06-2.40
Duration Quartile*				
0 < years < 21	40	342	1.00	---
21 < years < 30	50	248	1.39	0.86-2.26
30 < years < 35	57	218	1.65	1.02-2.65
35+ years	51	172	1.84	1.11-3.07
Zone Analysisǂ				
Employment duration-Zone 1	116	606	1.02	1.00-1.04
Employment duration-Zone 2	73	339	1.03	1.01-1.05
Employment duration-Zone 4	45	248	1.01	0.99-1.03

[¤] Pleural abnormality defined as abnormality consistent with pneumoconiosis

* Results adjusted for age, BMI, hematite years, and outside occupation with high probability of asbestos exposure

ǂ Results adjusted for age, BMI, hematite years, outside occupation with high probability of asbestos exposure, and duration in other zones

ϫ Duration category comparison is duration quartile 1 vs duration quartiles 2-4

Table 4-7: Risk of pleural abnormalities[¤] for cumulative EMP/cc-years and cumulative EMP/cc-years in each Iron Range Zone

Exposure	Abnormalities Yes	Abnormalities No	OR	95%CI
Overall Employment*				
EMP/cc-year	198	980	1.06	1.00-1.12
Hematite	15	43	1.01	0.96-1.07
Exposure Category◊ ϫ				
0 < EMP/cc-years < 1.16	48	415	1.00	---
1.16 + EMP/cc-years	150	565	1.93	1.32-2.83
Exposure Quartile◊				
0 < EMP/cc-years < 1.16	48	415	1.00	---
1.16 < EMP/cc-years < 3.29	51	238	1.84	1.18-2.94
3.29 < EMP/cc-years < 5.89	49	176	2.22	1.42-3.63
5.89 + EMP/cc-years	50	151	1.78	1.11-2.98
Zone Analysis§				
EMP/cc-year -Zone 1	116	606	1.09	0.99-1.21
EMP/cc-year -Zone 2	73	339	1.16	1.06-1.27
EMP/cc-year -Zone 4	45	248	1.04	0.97-1.10

[¤] Pleural abnormality defined as abnormality consistent with pneumoconiosis

◊ Results adjusted for age, BMI, hematite years, commercial asbestos, and outside occupation with high probability of asbestos exposure

§ Results adjusted for age, BMI, hematite years, commercial asbestos, outside occupation with high probability of asbestos exposure, and exposure in other zones

ϫ Exposure category comparison is exposure quartile 1 vs exposure quartiles 2-4

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