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Original article

Cancer incidence among Minnesota taconite mining industry workers

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ABSTRACT

Purpose: To evaluate cancer incidence among Minnesota taconite mining workers.
Methods: We evaluated cancer incidence between 1988 and 2010 in a cohort of 40,720 Minnesota taconite mining workers used between 1937 and 1983. Standardized incidence ratios (SIRs) with 95% confidence intervals (CIs) were estimated by comparing numbers of incident cancers with frequencies in the Minnesota Cancer Surveillance System. SIRs for lung cancer by histologic subtypes were also estimated. We adjusted for out-of-state migration and conducted a probabilistic bias analysis for smoking-related cancers.
Results: A total of 5700 cancers were identified, including 51 mesotheliomas and 973 lung cancers. The SIRs for lung cancer and mesothelioma were 1.3 (95% CI = 1.2–1.4) and 2.4 (95% CI = 1.8–3.2), respectively. Stomach, laryngeal, and bladder cancers were also elevated. However, adjusting for potential confounding by smoking attenuated the estimates for lung (SIR = 1.1, 95% CI = 1.0–1.3), laryngeal (SIR = 1.2, 95% CI = 0.8–1.6), oral (SIR = 0.9, 95% CI = 0.7–1.2), and bladder cancers (SIR = 1.0, 95% CI = 0.8–1.1).
Conclusions: Taconite workers may have an increased risk for certain cancers. Lifestyle and work-related factors may play a role in elevated morbidity. The extent to which mining-related exposures contribute to disease burden is being investigated.

Introduction

Minnesota's taconite mining industry began in the 1950s in northeastern Minnesota along the Mesabi Iron Range and has grown into an essential part of the states' economy. The industry directly contributes 1.8 billion dollars annually to Minnesota's economy and provides thousands of jobs. Today, Minnesota is the largest producer of taconite in the United States [1].

Taconite is a low-grade iron ore with a natural iron concentration of roughly 30%. For taconite to be commercially useful, its iron is concentrated through processing which involves blasting rock with explosives, crushing it into a powder, magnetically extracting the iron, and reforming the concentrated product into pellets [2]. This process generates a significant amount of dust that results in potential exposure to long and short nonasbestiform amphibole and nonamphibole elongate mineral particles (EMPs), respirable silica, and cleavage fragments [3]. The term "EMP" refers to any mineral particle with a minimum aspect ratio of 3:1 that is of inhalable size. Cleavage fragments are mineral EMPs that have broken along a cleavage plane during the crushing and fracturing process [4]. There have been long-standing concerns among workers and community members regarding the potential health risks associated with these exposures. Major concerns arose after the Minnesota Department of Health reported a 73% excess in cases of mesothelioma among men in northeastern Minnesota between 1988 and 1996 [5], suggestive of an occupational exposure. Given that the excess in mesothelioma cases occurred in proximity to the Mesabi Iron Range, this finding was concerning to the mining industry and contiguous communities.

The association between asbestiform EMP exposure and mesothelioma and lung cancer is well documented [4,6–8]; however, the

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carcinogenicity of nonasbestiform EMPs is not understood. The NIOSH has specifically identified nonasbestiform EMPs as a needed area of research [4]. The studies of occupational cohorts who experience exposures to nonasbestiform EMPs have been inconclusive. Talc miners in upstate New York and gold miners in South Dakota experience potential exposures to nonasbestiform EMPs. The studies of talc miners reported an excess in mortality from all cancers, lung cancer, ischemic heart disease, and nonmalignant respiratory disease (NMRD). Although an exposure-response relationship was seen for NMRD, none was observed for lung cancer [9–11]. Studies of the Homestake gold mine in South Dakota reported an excess of respiratory cancer and a small excess of lung cancer [12–14] with no observed exposure-response relationship, suggesting a weak association between dust exposure and lung cancer. Owing to the studies' limitations, NIOSH has concluded that the findings provide inconclusive evidence regarding the health effects associated with exposures to nonasbestiform EMPs [4].

Despite community-wide health concerns and the lack of knowledge of the potential health effects, there is limited health research related to taconite mining industry workers. Small-scale mortality studies conducted in the early 1980s and 1990s produced null findings [15–17]. These early studies had small study populations, focused on single mining companies, and had relatively short follow-up periods. A larger mortality study of the population used for this analysis found an excess of death from lung cancer and mesothelioma [18]. This study aims to further characterize the overall health of Minnesota taconite mining workers by examining incident cancers in this population.

Methods

Study population

The study cohort was established in the 1980s by the University of Minnesota and the Iron Range Resources and Rehabilitation Board. Investigators assembled a database of 68,737 individuals who had ever worked in any of the mines in operation in 1983. Work history information was collected through 1983, although some individuals worked beyond this point. Funding was exhausted before data analysis could be completed.

In 2008, the University of Minnesota launched the Taconite Workers Health Study [19]. One objective was to assess the health of the 1983 cohort of 68,737 miners. The cohort included both taconite workers and those who had worked in earlier hematite mining operations. To capture the workers most likely to have been working after taconite mining began in the 1950s, the cohort was limited to those born in 1920 or later, reducing the cohort to 46,170 individuals. Additional workers were excluded because their only record on file was an application with no evidence of employment ($n = 477$), their vital status remained unknown after follow-up ($n = 679$), or their employment information was improbable, for example, began working at age 14 years or younger ($n = 535$). For this analysis, the cohort was further restricted to individuals living until at least 1988 when the Minnesota Cancer Surveillance System would capture the incident cases, which eliminated 3759 workers who died before 1988. The final study cohort included 40,720 individuals.

Cancer incidence

To identify incident cancers, the cohort was linked to the Minnesota Cancer Surveillance System (MCSS), the population-based cancer registry that collects histologic information of newly diagnosed cancers on Minnesota residents. The system was established in 1988 by state statute as a mandatory reporting system. Cancer incidence including date of diagnosis, primary cancer site, and histology was obtained for cohort members matched to the MCSS. Cancers in the registry are coded according to International Classification of Diseases for Oncology (ICD-O) current at the time of diagnosis. Estimated completeness of the MCSS is 99.7%, and overall accuracy is 96.5% [20].

Data analysis

The cancer incidence analysis covered the period from 1988 (when the MCSS began collecting data) through 2010. The cancer rate of the cohort was compared with that of the Minnesota population to estimate standardized cancer incidence ratios (SIRs) and 95% confidence intervals (CIs) adjusted for sex, 5-year age, and 5-year calendar period. Person-time at risk was accrued from January 1, 1988 until diagnosis date, date of death, or the end of the follow-up period (December 31, 2010). Individuals with more than one diagnosis of the same cancer were followed only to the date of first diagnosis. Those with multiple primary cancers were followed until each cancer diagnosis date. The expected number of cancers was calculated by applying age, calendar time, and sex-specific cancer rates of the Minnesota population to the person-year observations of the study population. The MCSS only reports cancer cases in Minnesota residents; thus, a valid estimation of incidence required adjusting for out-of-state migration. We used the age group specific proportions of out-of-state deaths ascertained in a previously published mortality study [18] as an estimate of out-of-state migration in the study population. The proportion of in-state deaths by age group was used as an estimate of the proportion of workers who stayed in Minnesota to directly adjust the person-years by age group for rate calculation.

SIRs were obtained by computing the ratio of the observed-to-expected number of cancers. The selected cancers, for which SIRs were computed, were mesothelioma, lung, esophageal, kidney, laryngeal, liver and bile duct, oral, pancreatic, stomach, and bladder cancers. These cancers were of interest to study investigators because of their established association with asbestos exposure [4,21,22]. All SIRs were computed using STATA 12.1 software (StataCorp LP, College Station, TX).

To explore lung cancer incidence by histologic type, lung cancers were grouped into one of five subtypes: adenocarcinoma, squamous cell, small cell, other and/or rare (including large cell), and nonspecified carcinomas. The histology code groupings were determined by study investigators (Appendix Table A). SIRs and 95% CIs were estimated for each of the five histologic subtypes.

No information on tobacco smoking was available for cohort members; however, because some of the cancers of interest (lung, oral, laryngeal, and bladder) are strongly associated with smoking [23,24], we conducted a probabilistic bias analysis to adjust for smoking as an unmeasured confounder. As part of the Taconite Workers Health Study, a subset of 1313 taconite mining industry workers participated in a cross-sectional survey which included a questionnaire with smoking history. Roughly, 75% of these individuals were also in the study cohort. Details of this study can be found elsewhere [25]. The smoking prevalence in this subset was used as an estimate of the smoking prevalence in the target population. We used Minnesota Behavioral Risk Factor Surveillance System [26] data weighted by age and sex to resemble the taconite survey participants to estimate smoking prevalence in the reference population. Based on the probabilistic bias analysis outlined by Lash et al., 2009 [26], we assigned a trapezoidal distribution for each of the three bias parameters: smoking prevalence among taconite workers, smoking prevalence among the Minnesota population, and cancer rates in smokers versus nonsmokers. We centered the modes approximately on the values identified for each bias

parameter; chose a reasonable range for the mode, then extended the distribution such that the width of the trapezoid was approximately twice the range between modes. Using the software accompanying Lash et al., 2009 [27], we randomly sampled from the distribution of each bias parameter and used those values to create corrected effect estimates. We repeated this simulation 1000 times and summarized the results. This approach considers the variability in smoking prevalence with a final adjusted estimate to compare to the unadjusted estimate. We conducted this bias analysis for four of the smoking-related cancers (lung, laryngeal, oral, and bladder cancers). The bias parameter distributions are summarized in Table 1.

Results

The study cohort was predominantly male (93%) and worked an average of 6.5 years. Among the 40,720 workers, 5700 cancers were identified by MCSS (5408 for men and 292 for women). Of those, 973 lung cancers and 51 mesotheliomas were identified. Characteristics of the study cohort are described in Table 2.

Adjusting for age, sex, calendar period, and out-of-state migration, the cohort members experienced elevated rates of mesothelioma (SIR = 2.4, 95% CI = 1.8–3.2), lung (SIR = 1.3, 95% CI = 1.2–1.4), laryngeal (SIR = 1.4, 95% CI = 1.1–1.7), stomach (SIR = 1.4, 95% CI = 1.1–1.6), and bladder (SIR = 1.1, 95% CI = 1.0–1.2) cancers. SIRs and 95% CIs for selected cancers are summarized in Table 3.

Among the 973 incident lung cancers, there were 313 adenocarcinomas, 260 squamous cell carcinomas, 138 small cell carcinomas, 201 nonspecified lung cancers, and 61 other or rare types of lung cancer. SIRs were elevated for adenocarcinoma (SIR = 1.2, 95% CI = 1.1–1.4), squamous cell (SIR = 1.3, 95% CI = 1.2–1.5), nonspecified (SIR = 1.6, 95% CI = 1.3–1.8), and rare cancers (SIR = 1.3, 95% CI = 1.0–1.7) after adjusting for age, sex, calendar period, and out-of-state migration (Table 4).

Questionnaire data taken from the subset of miners who participated in the survey study were summarized into ever and never smokers. Among the 1313 current and former taconite workers, 38.2% were considered never smokers compared to 50.1% of the reference population. Cancer rates in smokers versus nonsmokers obtained from World Health Organization estimates were: 10 for lung cancer, 27 for oral cancer, 12 for laryngeal cancer, and 3 for bladder cancer [23]. After probabilistic adjustment for smoking, rates of laryngeal, oral, and bladder cancers in the taconite population were similar to what is expected in Minnesota (laryngeal SIR = 1.2, 95% CI = 0.8–1.6; oral SIR = 0.9, 95% CI = 0.7–1.2; bladder SIR = 1.0, 95% CI = 0.8–1.1). SIR for lung cancer was also attenuated but still elevated (lung SIR = 1.1, 95% CI = 1.0–1.3). Although the effect of smoking on lung cancer risk varies by histologic subtype, squamous and small cell carcinomas are found to be the most strongly associated [28]. After probabilistic adjustment, the SIRs were attenuated to what would be expected in Minnesota for both squamous (SIR = 1.1, 95% CI = 0.9–1.2) and small cell carcinoma (SIR = 0.9, 95% CI = 0.8–1.1). These results are summarized in Table 5.

Table 1
Parameter distributions for probabilistic bias analysis of taconite exposures and cancer stratified by smoking as an unmeasured confounder

Bias parameter	Minimum	Lower mode	Upper mode	Maximum
Smoking prevalence among taconite workers*	0.52	0.57	0.67	0.72
Smoking prevalence among Minnesota population†	0.40	0.45	0.55	0.60
Cancer rate in smokers versus nonsmokers‡				
Lung	8	9	11	12
Larynx	10	11	13	14
Oral	25	26	28	29
Bladder	1.1	2	4	5

* Estimated from Taconite Workers Health Study survey [19].
† Estimated from Minnesota Behavioral Risk Factor Surveillance System data [22].
‡ Estimated from World Health Organization [25].

Table 2
Characteristics of taconite workers study cohort

	Study cohort	
	n	%
Employment duration (y)		
<1	11,994	29.45
1–5	14,206	34.89
6–14	8445	20.74
15 or more	6075	14.92
Sex		
Male	37,755	92.72
Female	2953	7.25
Unknown	12	0.03
Age at hire		
<20 y	14,899	36.56
20–29 y	21,708	53.31
30–39 y	3417	8.39
40 or more	706	1.73
Decade of hire		
<1950	5190	12.75
1950–1959	12,075	29.65
1960–1969	9407	23.10
1970–1979	13,384	32.87
>1980	664	1.63
Decade of birth		
<1930	9976	24.50
1930–1939	9961	24.46
1940–1949	9332	22.92
1959–1959	10,759	26.42
>1959	692	1.70
Total	40,720	100.0

Discussion

In this analysis, there were higher than expected rates of certain cancers as compared to the Minnesota population, specifically for mesothelioma, lung, laryngeal, stomach, and bladder cancers. Lung cancer by histologic subtype showed an increased SIR. A sensitivity analysis to account for differences in smoking rates between the study and reference populations suggested that an association between taconite work and lung, laryngeal, bladder, and oral cancers as well as squamous cell and small cell carcinomas of the lung is small if not absent. Restricting the cohort to those with at least 1 year of employment did not substantially change the results.

Table 3
Selected standardized incidence ratios of cancer in Minnesota taconite workers

Cancer	Observed	Expected	SIR*	95% CI
Mesothelioma	51	21.1	2.4	1.8–3.2
Lung	973	750.9	1.3	1.2–1.4
Esophagus	87	76.9	1.1	0.9–1.4
Kidney	170	178.2	1.0	0.8–1.1
Larynx	94	68.6	1.4	1.1–1.7
Liver and bile duct	52	49.4	1.1	0.8–1.4
Oral	172	162.5	1.1	0.9–1.2
Pancreas	120	105.9	1.1	0.9–1.4
Stomach	105	77.7	1.4	1.1–1.6
Bladder	363	338.5	1.1	1.0–1.2

*Adjusted for age, sex, calendar period, and out-of-state migration.

Table 4
SIRs of cancer for lung cancer by histologic subtype

Lung cancer histological subtype	*n*	SIR*	95% CI
Adenocarcinoma	313	1.2	1.1–1.4
Squamous cell	260	1.3	1.2–1.5
Small cell	138	1.1	1.0–1.3
Nonspecified	201	1.6	1.3–1.8
Rare or other (including large cell)	61	1.3	1.0–1.7
Total	973	1.3	1.2–1.4

*Adjusted for age, sex, calendar period, and out-of-state migration.

Cancer incidence has not been previously examined in this population. Early studies of taconite mining exposures focused on ingestion and showed no association between cancers and EMP ingestion [29,30]. These were followed by mortality assessments [15–17]. Although these mortality studies did not show an excess in respiratory cancers, they had small study populations, short follow-up periods and thus limited statistical power. The most recent study of this population reported an excess in mortality from mesothelioma and lung cancer [18]. In 2007, the Minnesota Department of Health reported a 73% excess in cases of mesothelioma for men in northeastern Minnesota between 1988 and 1996 [5], consistent with the elevated SIR reported here. The cause of this excess remains unknown.

Several studies have examined the risk of exposure to nonasbestiform EMPs [9,10,12–14], but the toxicity of these exposures is uncertain [4]. A limited number of animal studies in this field suggested that nonasbestiform amphiboles might pose different risks than asbestos [31–33], but that risk remains unclear [4]. Crystalline silica is classified as a known human lung carcinogen by the International Agency for Research on Cancer [34]. In a 2010 subset analysis of approximately 1200 workers, 5% to 6% had a chest X-rays consistent with pneumoconiosis [35].

As in most occupational epidemiology studies that use historical employment records, we did not have data on personal risk factors that might confound the results. In this case, we had no information on smoking habits of the study population, the major risk factor for lung cancer and many other cancers in our analysis. A difference in smoking habit between the taconite workers and the general Minnesota population is likely given the documented higher rates of smoking in working cohorts [36]. However, subject-specific data on confounders are not necessarily needed to evaluate potential confounding [37]. Without direct measures of smoking information for cohort members, we conducted an indirect adjustment, a method shown to be effective in estimating bias associated with unmeasured confounders in occupational studies [37,38]. One such method is to estimate hypothetical smoking habits using available records from a subset or similar population [39]. Using a probabilistic bias analysis, we adjusted our point estimates to account for smoking as an unmeasured confounder, a method that incorporates systematic and random error and uncertainty in the adjustment [27].

Table 5
SIRs of cancer for smoking-related cancers before and after probabilistic bias adjustment for smoking

Cancer	SIR*	95% CI	Adjusted SIR*,†	95% CI
Lung	1.3	1.2–1.4	1.1	1.0–1.3
Squamous cell	1.3	1.2–1.5	1.1	0.9–1.3
Small cell	1.1	1.0–1.3	1.0	0.7–1.2
Larynx	1.4	1.1–1.7	1.2	0.8–1.6
Oral	1.1	0.9–1.2	0.9	0.7–1.2
Bladder	1.1	1.0–1.2	1.0	0.8–1.1

* Adjusted for age, sex, calendar period, and out-of-state migration.
† Adjusted for smoking using probabilistic bias adjustment for unmeasured confounder.

Some limitations should be considered when interpreting these results. Using the Minnesota state cancer registry data requires cohort members to remain in Minnesota to capture newly diagnosed cancers. Because it was not feasible to identify if an individual was diagnosed with cancer outside Minnesota, adjustments in person-years were required to correct for potential underestimation of SIRs. We used out-of-state deaths by age group as an estimate of the proportion of individuals in each age group who left Minnesota. The MCSS was not in operation before 1988; thus, the analysis was based on the cohort members who survived until that year. Among those who died before 1988 and thus, were excluded from this analysis, we observed 747 deaths from cancer, including cancer of the lung ($n = 261$), esophagus ($n = 22$), kidney ($n = 25$), larynx ($n = 10$), liver and bile duct ($n = 13$), pancreas ($n = 40$), stomach ($n = 24$), and bladder ($n = 12$). Before 1988, mesothelioma did not have a specific ICD code and was thus not identified. To the extent, these cases were related to mining exposures, the estimated SIRs could have been biased toward the null, analogous to the healthy worker effect which can result in attenuated estimates [40].

Although the bias analysis used is an accepted method for adjusting for unmeasured confounding in occupational studies, there are potential limitations using the subset of miners as an estimate of smoking habits in our study population. Differences in past smoking habits, at a point in time before disease incidence, are most critical; however, the subset analysis from which smoking data were collected was done in 2010, the end of the follow-up period. Those who participated in the subset analysis thus may have very different smoking habits than their historic counterparts because of generational differences in smoking patterns. Furthermore, comparing recent smoking prevalence data in the exposed cohort with smoking prevalence in the nonexposed referent group excludes most of cohort members who died during the follow-up period. Focusing on survivors runs the risk of underestimating the cohort's smoking prevalence, given that decedents are likely to have smoked more than survivors [41]. However, because smoking habits for the reference population were taken from Behavioral Risk Factor Surveillance System 2010 data, the relative differences in smoking between the two groups were taken at the same time. We assumed that population and cohort smoking rates changed at the same rate. Thus, the bias factor analysis accounted for this relative difference in smoking and adjusted the SIRs accordingly. We were unable to examine an interaction with smoking using this bias analysis. The sensitivity analysis also required knowing the cancer rate in smokers versus nonsmokers. This estimation can vary among different sources [23,38]; however, changing this variable in the probabilistic bias calculation did not substantially change the results of the sensitivity analysis.

One of the main strengths of this study is the large size of the cohort. The study population included all taconite mining industry workers with any work experience across the entire Mesabi Iron Range with very few workers (4%) excluded from the analysis because of data quality problems. Having mortality data including state of death for the study population allowed for an estimation of out-of-state migration which can be challenging for other cancer incidence studies of this nature.

Conclusions

This analysis provides some evidence that Minnesota taconite mining workers are at higher risk for mesothelioma and other cancers. The sensitivity analysis we conducted indicates the elevated risk of some cancers may be a consequence of smoking and other unmeasured confounders. However, because confounding variables were not measured in the study population and

workplace exposures include known carcinogens, it is possible that workplace exposures contribute to the excess in cancer incidence.

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Appendix

Table A
Lung cancer major histology groupings

Histology	ICD-O code	count
Adenocarcinoma		313
Acinic cell adenocarcinoma	85503	1
Adenocarcinoma NOS	81403	263
Bronchioloalveolar adenocarcinoma	82503	23
Bronchioloalveolar mucinous	82533	1
Bronchioloalveolar nonmucinous	82523	4
Mixed cell adenocarcinoma	83233	1
Mucin-producing adenocarcinoma	84813	11
Clear cell adenocarcinoma	83103	1
Mucinous adenocarcinoma	84803	5
Papillary adenocarcinoma NOS	82603	3
Small cell carcinoma		139
Combined small cell carcinoma	80453	2
Intermediate cell small cell carcinoma	80443	5
Neuroendocrine carcinoma	82463	9
Oat cell carcinoma	80423	4
Small cell tumor	80023	1
Small cell carcinoma NOS	80413	118
Squamous cell carcinoma		258
Basaloid squamous cell carcinoma	80833	1
Squamous cell carcinoma spindle cell	80743	1
Squamous cell carcinoma keratinizing	80713	9
Squamous cell carcinoma nonkeratinizing	80723	10
Squamous cell carcinoma	80703	237
Nonspecified		202
Neoplasm malignant	80003	19
Nonsmall cell carcinoma	80463	97
Carcinoma NOS	80103	68
Undifferentiated carcinoma	80203	11
Carcinoid tumor	82403	4
Atypical carcinoid tumor	82493	1
Tumor cells malignant	80013	2
Rare/other		61
Anaplastic carcinoma	80213	2
Spindle cell carcinoma	80323	1
Large cell carcinoma NOS	80123	38
Large cell carcinoma rhabdoid phenotype	80143	1
Adenosquamous carcinoma	85603	12
Fibrous histiocytoma	88303	1
Large cell neuroendocrine carcinoma	80133	5
Sarcome NOS	88003	1