Gastric Cancer and Coal Mine Dust Exposure

A Case-Control Study

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Based on evidence that coal miners have elevated gastric cancer mortality rates, a case-control study was developed to assess the gastric cancer risk of coal mine dust exposure. Forty-six cases of US white male gastric cancer deaths from NIOSH coal miner cohorts were individually matched by age to controls. From these data we show that a statistically elevated gastric cancer risk exists for miners who have prolonged exposure to coal mine dust and prolonged exposure to cigarette smoke. Coal workers' pneumoconiosis, a disease defined in terms of coal dust deposition in the lungs, was not found to be a gastric cancer risk.

Cancer **52:1346-1350, 1983.**

An accumulating body of evidence suggests that US coal miners have an elevated risk of gastric cancer mortality. Elevated gastric cancer mortality rates have been reported for US coal miners by Enterline,[1,2] Matolo *et al.*,[3] Klauber and Lyon,[4] and Rockette.[5,6] Stomach cancer excesses did not, however, show up among miners in the Third National Cancer Survey.[7] Excess gastric cancer rates have also been reported for coal miners in England by Turner,[8] in England and Wales by Stocks,[9] and by Liddell[10] in England for underground workers with the exception of those at the coal face. Jacobsen[11] found an elevated gastric cancer death rate for English and Welsh miners who had simple coal workers' pneumoconiosis (CWP), but not among those having complicated CWP. He also found a dose-response relationship between CWP progression and gastric cancer mortality. Coal miner mortality rates have been reviewed by Enterline,[2] who concludes that US coal miner mortality excesses cannot be explained solely on the basis of accident and respiratory disease mortality; and by Rockette,[12] who concludes that elevated gastric cancer is the third most consistent mortality finding for coal miners behind accident and pneumoconiosis mortality. These findings and interpretations suggest the importance of questioning whether there is an occupational component to gastric cancer among coal miners, a step taken by this report.

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Accepted for publication July 6, 1982.

Overview of Gastric Cancer

Gastric cancer used to be the leading cause of cancer mortality in the US.[13] Since the 1930s, US gastric cancer mortality rates have declined remarkably.[14] No convincing explanation has yet been found for this temporal decline in gastric cancer mortality;[15] nor has any convincing explanation been offered for existing geographical and regional variations in gastric cancer mortality, either in the US or world-wide.[16] Finally, no specific causes for gastric cancer in humans have been identified.[17] It is safe to conclude that the etiology of gastric cancer remains enigmatic.

Gastric Cancer Risk Factors

While definitive causal associations between environmental or genetic risks and gastric cancer have remained elusive, consideration and speculation on the etiology of gastric cancer has been extensive. General reviews of gastric cancer risks have been undertaken by Wynder *et al.*,[16] Haas and Schottenfeld,[14] and Pfeiffer.[17] Hypotheses organized around answering the question of whether the observed gastric cancer excesses among coal miners are directly occupationally related, related through correlated life-style risks, or are the artifact of fortuitous aggregations of high risk persons in the mining industry are formalized by Ames.[18]

Given an identification of excess gastric cancer mortality among coal miners, high priority should be placed on assessing the risks associated with coal miners' occupational exposures. Coal mine dust exposure, a known major occupational exposure of coal miners, is of great potential importance, not only as a factor distinguishing coal miners from other occupational groups, but also

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in terms of carcinogenic potential. Coal mine dust is composed of the coal itself plus silica, metals such as iron and trace metals, and organic matter. Detailed analyses of coal mine dust are presented by Falk and Jurgelski[19] and by Green and Laqueur.[20] Concern for the carcinogenic potential of coal mine dust centers around polynuclear aromatic hydrocarbons (PNAs, also called polycyclic aromatic hydrocarbons or PAHs), N-nitrosamines, and some trace metals.[19] In addition to the carcinogenic potential of the raw coal mine dust *per se* to which coal miners might be exposed, additional carcinogenic compounds result from molecular rearrangement of the coal molecule as a consequence of heat, nitrogen dioxide (NO_2), or other activating agents. Therefore, there is sufficient basis for concern regarding the carcinogenic potential of coal mine dust.

Processes thought to be implicated in gastric cancer carcinogenesis for coal miners include the lung clearance function,[20] the P-450 mixed function oxidase enzyme system,[21] and the nitrosation process.[19] Lung clearance is postulated to be involved in gastric cancer because the mucociliary action moves inhaled particles, some of which have been engulfed by macrophages, to the pharynx, where they are often swallowed. These particles may be important in themselves, or they could act as vehicles of transport to convey adsorbed gases to the stomach environment. The P-450 enzyme system is thought to be important to gastric cancer because these enzymes have the potential to activate precarcinogens in the lung or stomach. Nitrosation is potentially important to gastric cancer becuse it is the process through which nitrosamine precursors are converted to carcinogenic nitrosamines.

Cigarette smoking, an almost mandatory variable to include in any occupational epidemiology inquiry due to confounding effects with other variables, is an especially important covariable for consideration in an investigation of gastric cancer because cigarette smoking affects both the lung clearance function and the nitrosation process. Lung clearance is increased by light smoking and decreased by heavy smoking.[22] Smoking facilitates the nitrosation process through elevation of salivary thiocyanate, a catalyst of nitrosation.[23,24] In addition, cigarette smoke has also been identified as a possible gastric cancer carcinogen or cocarcinogen.[25]

Case-control Study

Data and Methods

A case–control study using 46 cases of gastric cancer deaths matched by age with 138 controls was developed. Cases and controls were drawn from four National Institute for Occupational Safety and Health (NIOSH) coal miner cohorts. The Lainhart and the National Coal Study cohorts were designed as representative samples of the US coal mining population; the Charleston-Beckley and National Coalworkers' Autopsy cohorts have restricted geographic focus and voluntary inclusion respectively. Coal miners for whom gastric cancer, ICD code 151, was recorded on their death certificates are compared with miners who died from other causes. The rationale for considering as similar miners for whom gastric cancer was a primary cause of death and miners for whom gastric cancer was a contributing or other cause of death is that gastric cancer is usually a rapidly fatal disease. Therefore, the decision to augment the number of cases available for analysis in this way appears justified.

Three series of age-matched miners were developed for each gastric cancer case: (1) miners who died from lung cancer; lung cancer was selected as a series due to a postulated antithesis between lung and gastric cancer,[20] (2) miners who died of cancer other than gastric or lung cancer; and (3) miners who died from noncancer, nonaccident causes. In this article, the "other cancer" and "noncancer, nonaccident" series are combined for use as controls.

The Odds Ratio (OR) is used in this study as an estimate of relative risk (RR).[26] Two parallel modes of analysis are employed. The first is a conventional case–control study which allows more straightforward control on smoking status. The second analysis is a matched-case analysis using both 2-for-1 and 1-for-1 matching. The latter analysis takes better advantage of the fact that each gastric cancer case is matched by age and date of birth (±3 years) to a miner who died from other causes. Procedures presented by Rothman and Boice[27] for use on the HP-67 calculator are employed for the matched-case analysis. For both modes of analysis, 95% confidence limits are used to test statistical significance of the association between status on the risk exposure and case–control status. Ninety percent confidence limits about the OR are presented for descriptive purposes. Summary tables are provided in the text.

Coal mine dust exposure is indexed through a surrogate measure of number of years of underground coal mining. NIOSH experience has been that this simple index is useful to measure exposure to coal mine dust.[28]

Cigarette smoking is measured in terms of current smoking status, years smoked, and cigarettes per day. The designation "current smoker" refers to miners who were current smokers at the time the cohort was established.

Coal workers' pneumoconiosis (CWP) is measured through standard posteroanterior (PA) chest roentgenograms evaluated by NIOSH-certified "B-readers" and scored on a standard NIOSH roentgenographic inter-

TABLE 1. Association between Years of Underground Mining, Gastric Cancer, and Smoking Status: Conventional Case–Control

Subpopulation, controls, and Smoking status	OR for gastric cancer risk of years of underground mining	(90% confidence int)
Both control series		
All cases	1.55	(0.85–2.83)
By current smoking status		
Current smokers	3.10	(1.15–8.37)
Non- and exsmokers	1.00	(NA)
By years smoked		
30+ years smoked	3.52*	(1.34–9.28)
Under 30 years smoked	0.55	(0.19–1.62)
By cigarettes per day		
20+ cigarettes per day	1.82	(0.68–4.84)
10 to 19 cigarettes per day	1.17	(0.37–3.70)
1 to 9 cigarettes per day	1.39	(0.29–6.62)

* $P < 0.05$.
NA: not applicable/not ascertainable.

pretation form using ILO U/C 1971 criteria.[29] Simple CWP is based upon profusion of small opacities and is scored as 0 = not present, or progressively higher categories of 1, 2, or 3 simple pneumoconiosis. Complicated CWP, also called progressive massive fibrosis (PMF), is based on the presence of large opacities and is scored 0 = not present, or progressively higher categories A, B, and C of complicated CWP. Complicated CWP may be a different disease entity than simple CWP, and progressively higher categories may not indicate additional coal dust deposition in the lungs.

While many other risks, both direct occupational exposures as well as correlated life-style risks, are potentially important, only a few can be included in a retrospective study of this type due to the simple fact that others are not available.

Results

Coal mine dust exposure is a slightly elevated gastric cancer risk. In the conventional case–control analysis, the odds ratio (OR) is 1.55 (Table 1). Using 2-for-1 matching, the maximum likelihood estimate of the OR is 1.79, and in 1-for-1 matchings, the OR is 2.40 against other cancer and 1.50 against noncancer, nonaccident controls (Table 2).

When the coal mine dust exposure risk is examined under control by cigarette smoking status, the risk is statistically elevated in miners with prolonged exposure to cigarette smoke. The elevated risk shows up in the conventional case–control analysis as an OR for current smokers of 3.10, and an OR for 30+ years smoked of 3.52 ($P < 0.05$; Table 1). In the 1-for-1 matched-case analysis, the OR for 30+ years smoked is 6.00 against other cancer and 3.00 against noncancer, nonaccident controls (Table 2). These elevated ORs do not attain statistical significance at the 0.05 P level due to the small sample sizes involved. Smoking intensity, as measured by cigarettes per day, does not modify the gastric cancer risk of exposure to coal mine dust (Tables 1 and 2).

Coal workers' pneumoconiosis (CWP) was not found to be a gastric cancer risk. In the conventional case-control analysis, the OR is 0.43 (Table 3). No distinction is apparent in terms of gastric cancer risk between simple CWP and complicated CWP. (These data are not

TABLE 2. Association between Years of Underground Mining, Gastric Cancer, and Smoking Status: Matched Case–Control

Subpopulation, controls, and smoking status	OR for gastric cancer risk of years of underground mining	(90% confidence int)
Both control series: 2-for-1 match		
All cases	1.79	(0.90–3.58)
Other cancer control: 1-for-1 match		
All cases	2.40	(1.03–5.61)
By current smoking status		
Both case and control current smokers	NA	
Both case and control nonsmokers	NA	
Other smoking combinations	1.40	(0.54–3.65)
By years smoked		
Both case and control 30+ yrs smoked	6.00	(1.26–28.54)
Both case and control less than 30	NA	
Other combinations of years smoked	2.00	(0.64–6.26)
By cigarettes per day		
Both case and control 20+ cigs/day	1.00	(NA)
Both case and control less than 20	1.00	(NA)
Other combination of cigs/day	4.50*	(1.39–14.53)
Noncancer, nonaccident controls: 1-For-1 matching		
All cases	1.50	(0.63–3.55)
By current smoking status		
Both case and control current smokers	NA	
Both case and control nonsmokers	NA	
Other smoking combinations	1.33	
By years smoked		
Both case and control 30+ yrs smoked	3.00	(0.49–18.28)
Both case and control less than 30	NA	
Other combinations of years smoked	1.50	(0.52–4.31)
By cigarettes per day		
Both case and control 20+ cigs/day	NA	
Both case and control less than 20	1.00	(NA)
Other combinations of cigs/day	1.20	(0.44–3.25)

* $P < 0.05$.

shown). Smoking status did not modify the gastric cancer risk of CWP (Table 3).

TABLE 3. Association between Coal Workers' Pneumoconiosis, Gastric Cancer, and Smoking Status: Conventional Case–Control

Subpopulation, controls, and smoking status	OR for gastric cancer risk of CWP (90% confidence int)	
Both control series		
All cases	0.43	(0.18–1.05)
By current smoking status		
Current smokers	0.28	(0.07–1.14)
Exsmokers	0.71	(0.20–2.60)
Nonsmokers	NA	

Discussion

The elevated gastric cancer risk for coal mine dust exposure is limited to coal miners who smoke cigarettes. Duration of cigarette smoking and continuance of smoking appear to be more important than the number of cigarettes smoked per day.

In relating this interaction between cigarette smoking and exposure to coal mine dust as a risk factor for gastric cancer, it should be noted that the lung clearance hypothesis implies a curvilinear relationship between smoking intensity and lung clearance: light smoking increases lung clearance, whereas heavy smoking reduces lung clearance. These data do not suggest such a curvilinear relationship between intensity of smoking and coal mine dust exposure as a risk for gastric cancer; at the same time the data are not inconsistent with the general notion of lung clearance involvement in gastric carcinogenesis.

There is a possibility that cigarette smoking and prolonged exposure to coal mine dust together, over time, overwhelm the lungs' protective defenses or some other defense mechanism resulting in an as yet unspecified state which allows the gastric carcinogenesis process to proceed. An alternative explanation might be that while neither cigarette smoking nor coal mine dust separately constitute gastric cancer risk, in conjunction they produce an undesirable carcinogenic side effect. For example, miners exposed to ammonium nitrate during blasting operations might be additionally exposed to the production of carcinogenic nitrosamines in the stomach due to cigarette smoking which enhances nitrosation or perhaps both enhanced nitrosation and activation of PNAs by the P-450 enzyme system, and, following prolonged exposure, develop gastric cancer.

The relationship between CWP and gastric cancer needs further exploration. Our data do not confirm the earlier finding by Jacobsen that simple CWP is a gastric cancer risk. If CWP is an index of exposure to coal mine dust, and exposure to coal mine dust is a gastric cancer risk, at least under the condition of prolonged exposure to cigarette smoke or cigarette smoking, then lack of a CWP risk relationship is unexpected and inconsistent with our previous findings regarding exposure to coal mine dust.

The mechanism producing the interactive effect between coal mine dust exposure, cigarette smoking, and gastric cancer requires further study. Two previously identified mechanisms, the lung clearance function and the nitrosation process, appear to deserve intensive investigation. The findings from this study are basically consistent with both the lung clearance hypothesis and the nitrosation hypothesis as possible explanations for gastric carcinogenesis. A coordinated effort of laboratory, clinical, and epidemiological investigation may be required to answer the question of mechanisms of operation.

Conclusion

In conclusion, this study demonstrates that among US white male coal miners, an occupational gastric cancer risk posed by exposure to coal mine dust exists, but only when a life-style feature, cigarette smoking, is also present. When prolonged coal mine dust exposure is conjunctive with prolonged cigarette smoking, a statistically significant gastric cancer risk occurs.

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