Lung cancer, stomach cancer, and smoking status among coal miners

A preliminary test of a hypothesis

by Richard G Ames, PhD, MPH, John F Gamble, PhD

AMES RG, GAMBLE JF. Lung cancer, stomach cancer, and smoking status among coal miners: A preliminary test of a hypothesis. Scand j work environ health 9 (1983) 443–448.

This paper presents an empirical test of the hypothesis of Meyer et al, who propose inhaled carcinogens to be a risk for both stomach and lung cancer, stomach cancer occurring in persons with nonimpaired lungs and lung cancer occurring in persons with impaired lungs. Based upon a case-referent study comparing 46 white male coal miners who died from stomach cancer in the United States with age-matched miners who died from lung cancer and with reference miners who died from other cancers or from non-cancer, nonaccident causes, the present study failed to confirm the Meyer hypothesis. The data suggest a reverse relationship than that postulated, namely, that airway obstruction may be a precondition for stomach cancer and normal pulmonary function a precondition for lung cancer. Different dust agents were found to be involved with cancers at the different sites. For coal miners with airway obstruction, greater years of coal mine dust exposure were found to pose a slightly elevated stomach cancer risk (odds ratio 3.64, not significant), while, for miners with normal ventilatory function, cigarette smoking posed a disproportionately elevated lung cancer risk (odds ratio 7.00, not significant).

Key terms: coal mine dust.

Meyer et al (6) present the hypothesis that inhaled atmospheric carcinogens and cocarcinogens play a major role in stomach carcinogenesis. This hypothesis is based in part upon reports of elevated stomach cancer risks among certain dusty trades, such as miners, wool and cotton workers, stone workers, and some agricultural laborers, and elevated risks in some dusty processes, such as those with exposure to carbon black, talc, iron dust, asbestos, grain dust, and inorganic dust with free silica. This positive association with dust exposure and the lack of a common factor associated with stomach cancer in food or diet led Meyer et al to suggest that inhaled carcinogens are more important in the etiology of stomach cancer than the ingestion of carcinogens in the diet. Meyer et al postulate:

...that those persons whose pulmonary clearance mechanisms are more susceptible to impairment by cigarette smoke retain carcinogens and other particulate matter in the lungs and are at increased risk for lung cancer if they are cancer-prone. Those whose clearance mechanisms are not damaged continue to clear these particles from their lungs, swallow the cleared particles, and receive more of these substances in the stomach. If cancer-prone, they are at risk for stomach cancer when exposed to various dusts, smokes, and particulates that are carcinogenic [p 887] (6).

Reprint requests to: Dr RG Ames, Appalachian Laboratory for Occupational Safety and Health, 944 Chestnut Ridge Road, Morgantown, WV 26505, USA.

This paper attempts a first tentative test of the hypothesis using data drawn from coal miner mortality records.
Our test of the hypothesis

We restate the Meyer et al hypothesis in a form testable using coal miner mortality data as:

Under the condition of airway obstruction or cigarette smoking, exposure to coal mine dust increases the risk of lung cancer. In the absence of airway obstruction or cigarette smoking, exposure to coal mine dust increases the risk of stomach cancer.

Our test of this hypothesis is based on the assumptions, proposed by Meyer et al, that (i) inhaled dusts, both cigarette smoke and coal mine dust, are carcinogenic agents (including coal mine dust increasing the risk of stomach cancer); that (ii) a dose-response cancer risk exists for both lung and stomach cancer; and that (iii) airway obstruction represents an operationalization of impaired pulmonary clearance.

Data and methods

Forty-six white male coal miners who died from stomach cancer were matched with respect to age at death and year of birth, within each of four cohort series, to 46 cases who died from lung cancer and to a referent in each of two reference series (other cancer and noncancer, nonaccident mortality). By virtue of this matching, the cases and referents were linked in some dimensions and differed in others. They shared common occupations, age at death, social class, and some other characteristics. They differed as to cause of death, occupational exposure to coal mine dust, cigarette smoking, and ventilatory function. Age matching was attempted first with respect to exact age at death. If a match was not possible, the age range was expanded to ± one year. In no case did we go beyond ± three years. Matching by year of birth (± three years) was also performed to reduce any cohort effects. Mortality follow-up after baseline data collection for three of the four cohorts ranged between 10 and 17 years. All available stomach cancer deaths were used in order to aggregate sufficient numbers of cases for analysis. The cohorts used included two national (36 cases) and two regional (10 cases) samples of coal miners, all together almost 20,000. Baseline occupational history, spirometry, chest radiographs, and respiratory symptom data were obtained by the National Institute for Occupational Safety and Health (NIOSH). Periodic mortality follow-up is conducted on these cohorts by NIOSH. One cohort is an autopsy series for which no pulmonary function data are available.

Cause of death coding was performed from death certificates by certified nosologists according to the Eighth Revision of the International Classification of Diseases (9).

Since Meyer et al proposed that dust is carcinogenic, we have made the assumption that coal mine dust is a source of inhaled carcinogens. Included in coal mine dust are polynuclear aromatics and aerosol particulate (2). Exposure to coal mine dust is measured in this study through years of underground mining, a useful measure of coal mine dust exposure (8). Miners having less than 25 years underground have been defined as having low coal mine dust exposure and miners with 25 years or more underground have been defined as having high coal mine dust exposure.

The ventilatory function measures included the direct measures of forced vital capacity (FVC), forced expiratory volume in 1 s (FEV₁), and the ratio of the two (FEV₁/FVC %). Due to the inclusion of more than one cohort in the study, differences in administration, equipment, and personnel are likely to introduce some systematic, as well as random, error into this measurement, but this error is reduced somewhat as the referents were taken from the same cohort as the cases. Miners with an FEV₁/FVC ratio of less than 70 % have been defined as having airway obstruction, and miners with a ratio of 70 % or higher are defined as normal (4). The 23 autopsy cohort cases were missing ventilatory function data. No data on lung clearance were collected for any cohort.

Cigarette smoking status was measured by interview in terms of the following indicators: smoking status, number of years having smoked, and number of cigarettes. Smoking status was categorized as current smoker, exsmoker, and nonsmoker, as determined at the time the cohort was established. Miners with less than 30 years of cigarette smoking were defined as having "low years smoked," and miners with 30 or more years of smoking were...
defined as having "high years smoked." The number of cigarettes/d was reduced to the following two categories: 1 to 19, and > 20 cigarettes/d.

The analysis of risk was based upon the odds ratio (OR) as an index of relative risk, a common procedure in case-referent studies of risk exposure in rare diseases (5). The "other cancer" and "noncancer, nonaccident" series were combined for use as referents. The 95% confidence limits about the odds ratio were used to test for the statistical significance of the association between status on the risk exposure and case-referent status. The confidence intervals were calculated from logarithms of the odds ratios with formulas presented by Miettinen (7).

The basic data are presented in the appendix.

Results

High exposure to coal mine dust, measured by years underground, was not a statistically significant risk for either stomach cancer (OR 1.55, not significant) or lung cancer (OR 2.25, not significant) (table 1). When control was introduced for ventilatory function, as indexed by FEV_{1.6}; FCV %, it was found that the stomach cancer risk for coal mine dust exposure was concentrated among miners impaired by airway obstruction (OR 3.64, not significant) although the relationship did not reach statistical significance (table 1). No pattern was evident for the risk of coal mine dust exposure on lung cancer under control by ventilatory function. Although the test was inconclusive, these data were in opposition to the postulated relationship of obstruction reducing the risk of stomach cancer in comparison with lung cancer.

Current cigarette smoking, as contrasted with nonsmoking, was a statistically significant risk for lung cancer (OR 7.30, \( p < 0.05 \)), but not for stomach cancer (OR 0.67, not significant) (table 2). Neither years of smoking, nor cigarettes/d, nor ventilatory function impairment posed significant risks for either stomach or lung cancer (table 2).

The lung cancer risk for cigarette smoking was reduced from an OR of 7.30 to an OR of 1.56 when we combined the former lung cancer (OR 1.42, not significant) and nonsmokers, a procedure we were forced to do in order to aggregate sufficient cases to allow control to be introduced for ventilatory function (see table 3). When control was introduced for ventilatory function, the risk of being a current cigarette smoker, in comparison to being an ex- or nonsmoker, was elevated disproportionally for lung cancer among

| Years underground by years of smoking (≥30 or < 30) | Stomach cancer | Lung cancer |
|--------------------------------------------------|----------------|-------------|
|                                                  | Odds ratio     | 95% confidence interval | Odds ratio     | 95% confidence interval |
| Years underground                                 | 1.55           | 0.76–3.17           | 1.42           | 0.70–2.89               |
| ≥ 30                                              | 3.52*          | 1.11–11.7           | 2.25           | 0.92–5.49               |
| < 30                                              | 0.55           | 0.15–1.99           | 0.27           | 0.00–1.29               |
| Years underground by ventilatory function\(^a\) (normal or impaired) | | | |
| Normal (≥ 70 %)                                   | 0.88           | 0.22–3.50           | 1.40           | 0.28–6.98               |
| Impaired (< 70 %)                                 | 3.64           | 0.62–21.38          | 1.21           | 0.31–4.72               |

\(^a\) Twenty-three cases were missing ventilatory function measurements.

\(^*\) \( p < 0.05 \) (test based on 95% confidence interval).
Table 2. Association (odds ratio) between cigarette smoking, ventilatory function, and stomach and lung cancer — Conventional case-referent (other cancer and noncancer, nonaccident reference) series.

| Risk factor                          | Stomach cancer | Lung cancer |
|--------------------------------------|----------------|-------------|
|                                      | Odds ratio     | 95% confidence interval | Odds ratio | 95% confidence interval |
| Current smokers versus nonsmokers    | 0.67           | 0.23–1.97    | 7.30*      | 1.11–59.22              |
| Years of smoking (smokers)           | 0.69           | 0.30–1.57    | 1.82       | 0.78–4.25               |
| Cigarettes/d (smokers)               | 0.55           | 0.25–1.21    | 1.39       | 0.65–2.99               |
| FEV₁₀ : FVC%ᵃ                        | 0.88           | 0.32–2.42    | 2.00       | 0.70–5.70               |

ᵃ Twenty-three cases were missing ventilatory function measurements (FEV₁₀ = forced expiratory volume in 1 s, FVC = forced vital capacity).

ᵇ p < 0.05 (test based on 95% confidence interval).

Table 3. Association (odds ratio) between current smoking, stomach cancer, and lung cancer by ventilatory function — Conventional case-referent (other cancer and noncancer, nonaccident reference) series.

| Risk factor                        | Stomach cancer | Lung cancer |
|------------------------------------|----------------|-------------|
|                                    | Odds ratio     | 95% confidence interval | Odds ratio | 95% confidence interval |
| Current smokers versus exsmokers   | 0.64           | 0.31–1.31    | 1.56       | 0.76–3.20               |
| and nonsmokers                     |                |              |            |                        |
| Smoking status by ventilatory      | 0.63           | 0.16–2.49    | 7.00       | 0.74–6.94               |
| function (normal or impaired)      |                |              |            |                        |
| Normal (≥ 70%)                     | 0.75           | 0.16–3.56    | 3.00       | 0.52–17.27              |
| Impaired (< 70%)                   |                |              |            |                        |

ᵃ Twenty-three cases were missing ventilatory function measurements.

Miners with normal ventilatory function (OR 7.00, not significant, vs OR 3.00, not significant), although the relationship did not meet the criterion of statistical significance (table 3). No pattern of relationship was evident for the stomach cancer risk of current cigarette smokers when examined under control by ventilatory function.

**Discussion**

Obtaining an adequate data base upon which to test the Meyer hypothesis is a difficult task. This attempt at hypothesis testing is based on an aggregation of all the NIOSH data that can be brought to bear on the issue. In recognition of the limitations of the data, such as small sample size, missing ventilatory function data in some cases, data aggregation over four different cohorts, etc, our test should be viewed as suggestive only.

The Meyer et al hypothesis proposes that smokers with airway obstruction and exposure to dust are at high risk for lung cancer, if susceptible, while persons with normal ventilatory function and exposure to dust remain at a high risk for stomach cancer. Our data tend not to confirm the Meyer et al hypothesis. Rather these data show a trend for the stomach cancer risk of coal mine dust exposure to be concentrated in miners with normal ventilatory function, and a very slight trend for the lung cancer risk of coal mine dust exposure to be concentrated in miners with normal ventilatory function. We suggest that, for both stomach and lung cancer, ventilatory function (as a surrogate measure of clearance) simply sets a condition under which inhaled...
carcinogenic agents may be effective in carcinogenesis. In the present study population, long tenure underground among miners with a long history of smoking cigarettes posed a significant stomach cancer risk (OR 3.52, p < 0.05). The risk ratio was virtually the same (OR 3.64) for miners with long underground tenure and airway obstruction, but it was not statistically significant due to the number of cases with missing pulmonary function data. Airway obstruction is often a consequence of long-term smoking. If coal mine dust is a stomach carcinogen, these data suggest the importance of additional dimensions such as particle size and site of impaction (3). Cigarette smoking could act synergistically to increase further the stomach cancer risk by elevating the level of salivary thiocyanate (10), a potential catalyst for the intragastric nitrosation (1) of coal mine dust. In a laboratory study Whong et al (11) showed that coal dust and nitrite produced mutagenic reaction products in an acidic condition.

In the present study there was no significantly increased risk of lung cancer with prolonged underground exposure (OR 1.42, not significant). A similar elevated, but not statistically significant, relationship between airway obstruction and lung cancer risk was observed. This finding does not support the idea that airway obstruction by itself presents a lung cancer risk, as might be assumed from a literal interpretation of the Meyer et al hypothesis. Since elutriation of polynuclear aromatics from particles may vary with the biochemical environment, the lungs may not provide an appropriate environment for the elutriation of carcinogens from particles.

Current cigarette smoking was found to be a significant lung cancer risk factor (OR 7.30, p < 0.05) with some evidence that normal pulmonary function is a condition. Normal pulmonary function could allow deeper penetration of the small particles in cigarette smoke, and deeper penetration would result in a longer residency of the particulate. An alternative perspective is that cigarette smokers who suffer no pulmonary impairment may feel no urgency to quit smoking and, as a result, continue to place themselves at a high risk for lung cancer.

Conclusions

A preliminary and tentative empirical test of the Meyer et al hypothesis was attempted with the use of NIOSH coal miner mortality data. Our findings suggest that the identified variables are in fact interrelated, but in a different pattern than that anticipated by Meyer et al. Rather than impaired ventilatory function (airway obstruction) predisposing persons to lung cancer and normal ventilatory function predisposing persons to stomach cancer, our data suggest that obstruction may set a condition for stomach cancer and normal ventilatory function may set a condition for lung cancer and that the inhaled carcinogen or type of carcinogenic agent is different for each type of cancer. For miners with airway obstruction or long-term cigarette smoking, coal mine dust exposure poses a stomach cancer risk. For miners with normal ventilatory function, current cigarette smoking poses a disproportionately elevated lung cancer risk.

References

1. Boyland E, Walker SA. Effect of thiocyanate on nitrosation of amines. Nature 248 (1974) 601.
2. Falk HL, Jurgelski W. Health effects of coal mining and combustion: Carcinogens and cofactors. Environ health perspect 33 (1979) 203–226.
3. Gamble JF, Ames RG. The role of the lung in stomach carcinogenesis: A revision of the Meyer et al hypothesis. Med hypotheses 11 (1983) 355–364.
4. Kanner RE, Morris AE, ed. Clinical pulmonary function testing. Intermountain Thoracic Society, Salt Lake City, UT 1975, pp 1–11.
5. Mausner JS, Bahn AK. Epidemiology. WB Saunders, Philadelphia, PA 1974, pp 307–340.
6. Meyer MB, Luk GD, Sotelo JM, Cohen BH, Menkes HA. Hypothesis: The role of the lung in stomach carcinogenesis. Am rev respir dis 121 (1980) 887–892.
7. Miettinen OS. Estimation of relative risk from individually matched series. Biometrics March (1970) 75–86.
8. Morgan WKC, Burgess DB, Jacobson G, O'Brien RJ, Pendergrass EP, Reger RB, Shoub EP. The prevalence of coal workers' pneumoconiosis in U.S. coal miners. Arch environ health 27 (1973) 221–226.
9. US Department of Health Education, and Welfare. Eighth Revision International Classification of Diseases. Washington,
Appendix

Basic data by dust exposure, ventilatory (vent) function, smoking status, and case-referent status

| Correlated variables                  | Cases               |       | Referents (Other cancer & noncancer, nonaccident) |
|---------------------------------------|---------------------|-------|---------------------------------------------------|
|                                       | Stomach cancer      | Lung cancer |                                               |
| Ventilatory function by dust          |                     |       |                                                   |
|                                       | ≥ 25 years exposure | < 25 years exposure | Data not available | ≥ 25 years exposure | < 25 years exposure | Data not available | ≥ 25 years exposure | < 25 years exposure | Data not available |
| Impaired vent function                | 8                   | 2     | 0                                               | 11                   | 10                  | 0                     |
| Normal vent function                  | 5                   | 8     | 0                                               | 4                    | 4                   | 0                     | 10                   | 14                  | 0                     |
| Data not available                    | 14                  | 9     | 0                                               | 14                   | 10                  | 0                     | 23                   | 24                  | 0                     |
| Smoking status by ventilatory function|                     |       |                                                   |
|                                       | Impaired vent function | Normal vent function | Data not available | Impaired vent function | Normal vent function | Data not available | Impaired vent function | Normal vent function | Data not available |
| Current smokers                       | 6                   | 5     | 7                                               | 12                   | 7                   | 9                     | 14                   | 12                  | 20                    |
| Nonsmokers + exsmokers                | 4                   | 8     | 16                                              | 2                    | 1                   | 15                    | 7                    | 12                  | 27                    |
| Smoking status by dust exposure       |                     |       |                                                   |
|                                       | ≥ 25 years exposure | < 25 years exposure | Data not available | ≥ 25 years exposure | < 25 years exposure | Data not available | ≥ 25 years exposure | < 25 years exposure | Data not available |
| Current smokers                       | 13                  | 5     | 0                                               | 15                   | 13                  | 0                     | 21                   | 25                  | 0                     |
| Nonsmokers + exsmokers                | 14                  | 14    | 0                                               | 11                   | 7                   | 0                     | 23                   | 23                  | 0                     |
| Years of smoking by dust exposure     |                     |       |                                                   |
|                                       | ≥ 25 years exposure | < 25 years exposure | Data not available | ≥ 25 years exposure | < 25 years exposure | Data not available | ≥ 25 years exposure | < 25 years exposure | Data not available |
| ≥ 30 years of smoking                 | 15                  | 5     | 0                                               | 23                   | 12                  | 0                     | 23                   | 27                  | 0                     |
| < 30 years of smoking                 | 7                   | 8     | 0                                               | 3                    | 7                   | 0                     | 16                   | 10                  | 0                     |

Received for publication: 18 July 1983