Mortality from asthma and chronic obstructive pulmonary disease among workers in a soft paper mill: a case-referent study

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ABSTRACT In a case-referent study encompassing 33 cases and 228 referents the potential risk for asthma and chronic obstructive pulmonary disease and respiratory cancer among workers in a soft paper mill was evaluated. The cases were selected from registers of deaths and burials in the parishes around the paper mill. Information on exposure was obtained from the personnel register of the mill but because of shortage of information the cases could only be classified as "exposed" or "non-exposed." At some places in the mill the concentrations of paper dust had previously been high, 10-30 mg/m³. Employment at the paper mill was found to be associated with an increased risk of bronchial asthma and chronic obstructive pulmonary disease (odds ratio = 3.8, $p < 0.05$).

Exposure to paper dust has been associated with impairment of pulmonary function. In a cross sectional study on workers exposed to soft paper dust Ericsson *et al* found significantly decreased FEV₁ and FVC among the most heavily exposed workers which could indicate both restrictive or obstructive pulmonary diseases.¹ In the studies by Ferris *et al*² and Deprez *et al*³ there were indications of an increased morbidity of asthma and chronic obstructive pulmonary disease (COPD) among paper and pulp mill workers. Järvholm *et al* have found an increased risk of mesothelioma among Swedish paper mill workers,⁴ and with this background it was decided to study further both the mortality from asthma and COPD and from respiratory cancer among paper mill workers.

For this purpose a case-referent study was undertaken in the parishes surrounding the mill where the previous investigation by Ericsson *et al* had been made.¹ This region is suitable for a case-referent study because the paper mill is the dominant industry in the area and the region has a convenient number of inhabitants, about 10 000.

Subjects and methods

SOURCE OF SUBJECTS

Subjects for the study, cases and referents, were obtained from the local registers of deaths and burials in three parishes surrounding the paper mill. The study

was restricted to men aged 40-75 who had died between 1965 and 1984. Men below the age of 40 were excluded because there were presumed to be few cases and the exposure times were likely to be short. Because among older men the reliability of the causes of death stated on the death certificates are not as good as among younger categories we excluded men over 75.

Based on the information from the registers of deaths and burials, a classification of causes of death was made according to the International Classification of Disease (ICD 8, 1967).⁵ Cases included in the study were men who had died of COPD (ICD 490-92), asthma (ICD 493), and respiratory cancers including mesothelioma (ICD 162-63). The referents, six for each case, were randomly selected without individual matching from the total population of men with non-malignant, non-respiratory diseases.

Thirty eight individuals were classified as cases and from the 281 available reference subjects 228 were selected.

The diagnosis of the cases was checked against hospital files or the Swedish Cancer Registry. Information was obtained for 33 cases (87%). Of the five cases lacking information, three died of asthma or COPD and two of lung cancer. As a result of the checking, five cases were excluded, four because of erroneous diagnoses on the death certificates (table 1). The fifth case was originally falsely selected because the birth date had been misread.

After these exclusions the study comprised 261 men, 33 cases and 228 referents. Twelve cases died of asthma

Table 1 Diagnoses of excluded cases

	Diagnosis in registers of deaths and burials	Diagnosis in hospital files
Case 1	Pleural tumour	Pleural metastases from fibrosarcoma
Case 2	Pulmonary bleeding	Wegener's granulomatosis
Case 3	Lung cancer	Renal cancer with pulmonary metastasis
Case 4	Emphysema	Cholangitis with empyaema

or COPD, 17 of lung cancer, and four of mesothelioma.

The 228 referents had many different diagnoses. To validate the analysis further it was decided to use more than one reference group. Therefore, a second reference group was selected from our original referents comprising all men with acute myocardial infarction (AMI). As a third reference group all men with cerebrovascular diseases (CVD) or AMI, or both, were selected. This gave 97 men with AMI and 124 men with CVD/AMI. The advantages of CVD and AMI are that they are common and well delineated and there is no known association with the exposures we were studying.

ASSESSMENT OF EXPOSURES

In the mill the production of soft paper began in 1942. Soft paper is used in the production of toilet paper, paper towels, and napkins. Compared with the production of "ordinary" paper the workers in a soft paper mill are more exposed to paper dust.

In the mill both stationary and personal sampling of total dust have been performed since 1976. Workers at the paper machines were intermittently exposed to about 20–40 mg/m³ and workers in the converting departments where the soft paper is processed to other products were constantly exposed to 5–20 mg/m³. More details about exposure in the mill are described by Ericsson *et al.*¹

The intention was to classify all the subjects into different exposure categories with regard to paper dust based on their occupation in the mill, but as the personnel registers were incomplete with regard to occupational titles and periods of employment it was only possible to classify the men into "exposed" or "not exposed" categories. Thus exposed implies that the man was employed in the paper mill whereas not exposed implies that the man was not found in the personnel files. The information from the personnel files was supplemented with information from two old employees (employed more than 40 years each) who were unaware of the causes of death of the men. From

their statements four more men, three referents and one case, were classified as exposed.

STATISTICAL METHODS

Statistical analysis of the data was based on Mantel-Haenszel procedures⁶ and the principles outlined by Axelson⁷; confidence intervals were calculated according to Miettinen.⁸ The fourfold table with asthma and COPD was also analysed with Fisher's exact test.

Results

ASTHMA AND COPD

Six of the 12 cases with asthma or COPD were exposed, which implies a significantly increased risk (odds ratio 3.8, $p < 0.05$) (table 2); the crude odds ratio, SMR, and the Mantel-Haenszel odds ratio were almost equal, 3.9 and 3.8 respectively. Hence, there is little or no negative confounding by age. The Mantel-Haenszel procedure is probably somewhat suboptimal with regard to the small numbers affected in the different strata, but when the unstratified material was analysed with Fisher's exact test the difference was still significant ($p < 0.05$).

Among the exposed were four cases with bronchial asthma and two with COPD. Among the unexposed were three cases with bronchial asthma and three with COPD. Hospital files were obtained for nine of the cases, four exposed and five unexposed. The exposed cases are presented in greater detail in table 3.

RESPIRATORY CANCER

There was no significantly increased risk for res-

Table 2 Distribution of cases with COPD and asthma (ICD 490–93) and referents by exposure

Age group	Unexposed	Exposed
40–49:		
Case	0	1
Referent	10	3
50–59:		
Case	1	0
Referent	33	5
60–69:		
Case	2	3
Referent	66	23
70–75:		
Case	3	2
Referent	72	16
Total:		
Case	6	6
Referent	181	47
Crude odds ratio	(1.0)	3.9
SMR	(1.0)	3.9
SRR	(1.0)	3.5
Mantel-Haenszel odds ratio:		
Point estimate	(1.0)	3.8
95% Confidence interval		1.2–12.0

Table 3 Exposed cases with asthma or COPD

Case	Diagnosis	Age at disease onset	Age from beginning to end of employment	Age at death	Smoking habits
A*	Asthma	44	39–54	60	?
B*	Asthma	?	50–?	61	?
C*	Asthma	46	36–62	62	?
D*	COPD	66	44–68	72	Ex-smoker
E	Asthma?	?	24–43	43	?
F	COPD?	?	?–65	75	?

*Hospital files were available.

Table 4 Distribution of cases with respiratory cancers (ICD 162–63) and referents by exposure

Age group	Unexposed	Exposed
40–49:		
Case	0	1
Referent	10	3
50–59:		
Case	4	1
Referent	33	5
60–69:		
Case	5	4
Referent	66	23
70–75:		
Case	6	0
Referent	72	16
Total:		
Case	15	6
Referent	181	47
Crude odds ratio	(1.0)	1.5
SMR		1.6
SRR		1.4
Mantel-Haenszel odds ratio:		
Point estimate	(1.0)	1.6
95% Confidence interval		0.7–3.2

Table 5 Odds ratios, SMR, and SRR among 12 cases with asthma or COPD and 97 referents with AMI and 124 referents with AMI/CVD

	Referents	
	AMI	AMI/CVD
Crude odds ratio	4.1	4.3
Point estimate	4.0	4.4
95% Confidence interval	1.2–12.2	2.7–7.1
SMR	4.0	4.3
SRR	4.4	4.5

piratory cancer among the exposed men (table 4). Four mesotheliomas were found among the cases; three were unexposed.

ALTERNATIVE REFERENTS

When referents with AMI were used the odds ratios for all cases and the cases with asthma or COPD were almost the same as the earlier calculations based on 228 men (table 5). When men with AMI or CVD, or

both, are used together as a reference entity the odds ratios were higher; the crude odds ratio was for the cases with asthma or COPD—4, 3, with Mantel-Haenszel the point estimate was 4.4.

Discussion

The present study suggests an excess mortality from asthma and COPD among workers in a soft paper mill. There are, however, possible sources of bias in the study.

The diagnoses of the cases and referents obtained from the parish registers may be incomplete. These registers are based on the diagnosis from the death certificates. In the present study the causes of death stated for the cases were compared with information from medical files and from the Swedish Cancer Registry. In accordance with that information four cases were excluded as having erroneous causes of death.

In the present study asthma and COPD were analysed together although they are probably separate diseases. The reason is that asthma and COPD are often difficult to separate with information obtained from death certificates and hospital files that are often incomplete.

Selection bias is not relevant because the subjects were selected with no knowledge of their earlier exposure status. In the selection of referents those who had died from malignant diseases were excluded to avoid a possible confounding effect of asbestos. Järvholm *et al* have described an excess of mesothelioma among mainly maintenance personnel in Swedish paper mills.⁴

The selection of referents is important to the results, as is shown by the analyses with alternative referents. When AMI is used as a reference entity the result is about the same but when CVD is also included among the referents the odds ratios increased.

It is unlikely that there was an observation bias in the exposure classifications because they were made with no knowledge of the diagnosis of the subjects. In addition, the estimation of exposure is based on presence in the personnel register, which is not influenced by recall bias.

Another possible confounding factor is smoking. The smoking habits of the cases and referents cannot be ascertained. Instead the actual smoking habits were studied in a random sample of 400 men aged 20–75 in the parishes around the paper mill. In a mailed questionnaire they were asked about their smoking habits and if they were working or had worked in the paper mill. The results are presented in table 6. The response rate, about 80%, was acceptable and the results indicate that smokers are equally prevalent in both groups. Ex-smokers are more prevalent among

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Table 6 Smoking habits among a random sample of 400 men from the parishes surrounding the paper mill

History of employment in the paper mill	Smoking habits		
	Non-smokers	Ex-smokers	Smokers
Yes (n = 81)	28%	45%	27%
No (n = 243)	40%	34%	26%

the paper mill workers, however, indicating that the paper mill workers have smoked somewhat more often than other people in the region in the past. The confounding effect of this small difference in smoking habits is probably weak. Odds ratios exceeding three can scarcely be explained by different smoking habits.⁹

The increased mortality from asthma and COPD among paper mill workers is supported by other studies. Ferris *et al* have, in a study from the United States in 1963, observed a proportionate mortality of 15% from asthma and COPD and respiratory insufficiency among paper and pulp mill workers.² This is not discussed further in the paper but, compared with Sweden, it seems a rather high death rate. In a study from Finland Niemelä *et al* found a significantly increased prevalence of confirmed diagnosis of bronchial asthma among debarkers in a paper mill.¹⁰ Another study from the United States by Deprez *et al* showed that hospital admission rates for COPD and asthma were positively correlated with the proportion of the workforce of a town employed at a pulp or paper mill.³ It is not clear from that study, however, whether they have studied paper mill workers, pulp mill workers, or both.

By contrast, Chan-Yeung *et al* found no signs of increased prevalence of respiratory diseases and abnormal lung function among workers in a paper mill

where the dust concentrations were low, beneath 5 mg/m¹¹.

In conclusion despite the presence of smoking as a potential confounding factor, the present study provides evidence of a possible association between employment in a Swedish soft paper mill and increased mortality in asthma and COPD.

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