Mortality Studies of Metalworking Fluid Exposure in the Automobile Industry V: A Case-Control Study of Pancreatic Cancer

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ABSTRACT

Results are presented from a case-control study of 97 cases of pancreatic cancer nested in a cohort of workers from three automobile manufacturing plants. Risk was examined for lifetime exposure to straight, soluble and synthetic metalworking fluids, as used in specific machining or grinding operations, as well as for constituents of the fluids. Pancreatic cancer was associated with exposure to synthetic fluids in grinding operations, with an odds ratio of 3.0 (95% CI: 1.2 - 7.5) among those with more than 1.4 mg/m^3-years of exposure. We were unable to examine synthetic exposure in the absence of grinding, because there was virtually no exposure to synthetics in machining operations in this study population. Despite a disproportionately high percent of the cases being black, no black workers had any exposure to synthetic fluids, and no other measured exposure was found to be related to risk. Thus, the previously documented excess risk of pancreas cancer among blacks in this cohort remains unexplained.

INTRODUCTION

This investigation of pancreas cancer is one of a series of nested case-control studies conducted to further elucidate the risks suggested in previous results from the General Motors/United Autoworkers (GM/UAW) cohort mortality study of autoworkers. Standardized mortality ratios (SMRs) were found to be elevated for various cancers, particularly digestive. An elevated risk for pancreas cancer was observed only among blacks (SMR=1.7, 95% CI: 1.1-2.6) [Eisen et al., 1992]. When pancreatic cancer risk was examined in relation to specific fluid types, an SMR of 1.6 (1.0-2.5) was found for blacks exposed to soluble metalworking fluid (MWF) [Tolbert et al., 1992]. When cancer risk was estimated in relation to duration of exposure, a rate ratio of 2.0 (0.9 - 4.7) for pancreatic cancer was found among all workers exposed to synthetics for more than eight years.

The goal of the present study was to further investigate the risk of pancreatic cancer associated with the water-based fluids in the cohort. Special attention was focused on sorting out exposure-response relationships in the presence of multiple exposures to different types of fluids and operations—with a variety of additives and contaminants—over many years of employment. A nested case-control design was chosen because it afforded a flexible statistical modeling approach.

METHODS

The definition of the cohort and exposure assessment methods have been described in detail in previous articles [Eisen et al., 1992; Eisen et al.,1994; Woskie et al., 1994; Hallock et al., 1994].

The Cohort

The cohort consisted of 46,384 hourly employees who had worked at least three years prior to January 1, 1985, at three auto parts manufacturing facilities in Michigan. Follow-up ended in 1984, at which time 10,159 (22%) were deceased.

Cases: Cases were defined as those subjects for whom pancreatic cancer was listed as the underlying cause of death on the death certificate or as an "other significant condition."

Controls: Incidence density sampling was used to select controls from within the cohort [Checkoway et al., 1989]. Additional matching factors included: race, sex, plant, and date of birth (± 5 years). For each case an attempt was made to choose twenty controls. In total, 1825 controls were selected.

Exposure Assessment

MWF were classified into three types: straight, soluble, and synthetic. The components and additives of the MWF were also assessed. Measures of cumulative

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exposure (mg/m^3-years) were classified for each type of fluid, in accordance to the type of operation in which the exposure occurred (i.e. grinding versus machining). Information on components and additives were qualitatively measured in years.

Statistical Analysis

Egret software [Statistics and Epidemiology Research Corporation (SERC), 1985-91] was used to fit conditional logistic regression models. Categorical exposure variables were based on cumulative exposure. Cut-offs for the exposure categories were chosen to equalize the number of cases in each non-zero exposure group. Risk estimates were first computed in models including only a single exposure variable. To address the possibility of confounding, models were fit with several exposure variables included simultaneously. An appreciable change in the odds ratio (OR) for the first variable in the model with the addition of a second was considered evidence of confounding. Interaction terms were also added to discover any potential effect modification. Model deviances and their associated p-values were used to evaluate the best fitting model.

RESULTS

In the cohort there were a total of 97 cases of pancreatic cancer. On average, cases started work in 1942 and were 64 years of age in the year of their death. The largest number of cases occurred in Plant I, which is the oldest of the three plants and includes the largest proportion of black workers. Black workers made up 17% of the cohort as a whole, and 22% of the pancreatic cancer cases.

The vast majority of the cohort was exposed to soluble fluids (92.7%), and more than half were exposed to straight fluids (55.4%). Only 16.2% of the cohort had any exposure to synthetic MWF, and almost all of this exposure occurred in grinding operations (15.8%) rather than machining (0.6%). A limited number of subjects were exposed to nitrosamines, defined as the copresence of ethanolamines and nitrites (16.2 %) or biocides (15.2%), which were found almost exclusively in grinding/synthetic fluids. Steel (91%) and iron (73.6%) contamination were common, aluminum (9.7%) was less common, and chromium was so rare that it was excluded from this analysis.

The strongest associations were seen with variables that measured exposure to synthetic MWF. A significantly elevated risk of 2.8 was observed in the highest category of synthetic MWF (Table 1). The average exposure in this category was 5.5 mg/m^3 (median 2.3). A slightly stronger association was seen with grinding/synthetic where the OR rose to 3.0 (1.2 - 7.5) in the highest category. When grinding/synthetic exposure was reclassified into four (rather than three) categories with six cases per exposed group, the ORs were 1.0, 0.9, 2.0, and 2.9. No clear risk patterns were seen for exposure to straight MWF or soluble MWF, whether in machining or grinding operations. When grinding with soluble MWF was examined (Table 1) there was a slight elevation of risk; however, a dose-response relationship was not observed.

Turning to the component exposures, some evidence of a dose-response relationship was seen for nitrosamines and for aluminum. Neither result had a confidence interval that excluded 1.0. The odds ratios were 2.1 for nitrosamine and 2.2 for aluminum in the highest exposure categories (Table 1). Although no elevation in risk is presented for biocides, when a fourth category was added, the OR was 4.5 (1.3 - 16) in the highest exposure group.

Further modeling was done to examine the risk associated with grinding/synthetics by adding other exposure variables to assess confounding. The only exposures that altered the risk estimate for grinding/synthetic were nitrosamine and biocides. The addition of nitrosamine dropped the OR in the highest category from 3.0 to 1.5. The addition of biocides raised the OR for grinding/synthetic MWF from 3.0 to 5.5. However, the confidence intervals widen dramatically with the addition of either component, reflecting the high degree of collinearity between these exposures which prohibits meaningful interpretation—97% of the grinding/synthetic exposures included nitrosamines, and 91% included biocides.

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Table 1. Adjusted ORs for Pancreatic Cancer in a Separate Conditional Logistic Regression Model for Selected MWF Exposures and Components (All Plants Combined).

Exposure	Cut Points	# Cases	OR	95% CI
Synthetic MWF (mg/m^3-years)	0	79	1.0	
	>0-1.4	9	1.0	0.4-2.4
	>1.4	9	2.8	1.1-6.9
Grinding Synthetic MWF (mg/m^3-years)	0	79	1.0	
	>0-1.4	9	1.0	0.4-2.5
	>1.4	9	3.0	1.2-7.5
Grinding Soluble MWF (mg/m^3-years)	0	20	1.0	
	>0-1.8	20	0.9	0.5-1.8
	>1.8-5.0	19	1.7	0.9-3.3
	>5.0-21	19	1.2	0.6-2.4
	>21	19	1.4	0.7-2.7
Biocides (Years)	0	82	1.0	
	>0-2.4	7	1.1	0.4-2.7
	>2.4	8	1.2	0.5-3.1
Nitrosamines (Years)	0	78	1.0	
	>0-3.6	10	1.5	0.6-3.5
	>3.6	9	2.1	0.8-5.4
Aluminum (Years)	0	88	1.0	
	>0-4.5	5	0.7	0.3-1.9
	>4.5	4	2.2	0.6-7.3

Stratified Analyses

Stratified analyses were conducted to examine whether risks seen for synthetics were consistent across plants and races.

Plant: Exposures to synthetics occurred predominantly in Plant II, and to a lesser extent in Plant III, but were virtually nonexistent in Plant I. Plants II and III were combined because only nine cases occurred in Plant III. The odds ratios for both synthetics and grinding/synthetic in Plants II/III were similar to risk estimates in the model for all plants combined.

Race: Plant I permitted stratification by race, since 20 of the 21 black cases of pancreatic cancer had worked at that facility. In blacks, a risk was seen for those working in grinding operations; however, a dose response relationship was not observed, and ORs had wide confidence intervals (Table 2). None of the black cases had ever been exposed to synthetics. Among whites, none of the exposures were found to be associated with pancreatic cancer.

Characteristics of white and black cases of pancreatic cancer in Plant I were examined in more detail. Mean exposures to all types of fluids and operations were uniformly lower among blacks, and duration of employment was shorter for blacks than whites, 18.4 versus 25.3 years. The mean age of pancreatic cancer death was younger for blacks, 59.3 verses 70.0.

Table 2. Adjusted ORs for Pancreatic Cancer and MWF Exposures in Separate Conditional Logistic Regression Models for Blacks in Plant I.

Exposure (mg/m^3-years)	Cases	OR	95% CI
Straight MWF			
0	11	1.0	
0-0.6	4	1.4	0.4-4.5
>0.6	5	0.8	0.3-2.6
Soluble MWF			
<6.1	5	1.0	
>6.1-27	8	1.1	0.3-3.3
>27	7	0.9	0.3-3.1
Synthetic MWF			
0	20	NA	
Grinding			
<1.3	5	1.0	
>1.3-8.6	7	2.1	0.6-6.9
>8.6	8	2.1	0.6-6.8

Up-dated Standardized Mortality Analysis

A 10-year update (1985-1994) of the mortality study is currently underway. A total of 193 cases of pancreatic cancer have now been identified. The updated SMR for pancreatic cancer among black males in Plant I is 1.5 (95% CI: 1.00-2.1). Limited evidence of elevated risk can also be seen among black females in all three plants; based on four cases, the SMR is 5.1 (95% CI: 1.4-13.1).

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CONCLUSION

In summary, data presented suggest a moderately strong association between pancreatic cancer and exposure to synthetic MWF in grinding operations. While nitrosamine and biocides were of particular interest *a priori*, the collinearity between grinding/synthetics and these two constituents prohibited the attribution of risk. Further investigation of pancreatic cancer in our extended follow-up as well as in other exposed populations is needed to corroborate the risk observed in this study.

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The reader will notice a variety of nomenclature differences among authors when referring to these fluids which were the subject of the Symposium and of this volume. Indeed, even the Symposium title reflected some of this variation: "*Metalworking* Fluids Symposium II," and "The Industrial Metalworking Environment: Assessment and Control of *Metal Removal* Fluids." Lest we add to the confusion, our use of the term *metalworking* in the title "Metalworking Fluids Symposium II" was a conscious decision based on nothing more than to maintain continuity with the title from the first Symposium. It was for that reason that "Assessment and Control of Metal Removal Fluids" was added in recognition of, and to call attention to the fact that the vast majority of research and data to date has been generated on a subset or class of metalworking fluids known as **metal removal fluids**. In addition to metal removal fluids, the very general term 'metalworking' fluids also encompasses the large and general classes of *metal protecting* fluids, *metal forming* fluids, and *metal treating* fluids. Besides functional differences between metalworking fluid classes, there are substantial compositional differences both between and within classes. So while it is somewhat sloppy though quite common and generally harmless to use generic terms such as metalworking fluids, or machining fluids, or coolants, the reader should be well aware of these important distinctions and that in virtually all instances where there is a connection with purported health effects, the person is really referring to that subclass of metalworking fluids known as *metal removal fluids.*

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