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

Judith A. Bardin, BSN, MS,[1] Ellen A. Eisen, ScD,[1]* Paige E. Tolbert, PhD,[2] Marilyn F. Hallock, MS,[3] S. Katharine Hammond, PhD,[4] Susan R. Woskie, PhD,[1] Thomas J. Smith, PhD,[5] Richard R. Monson, MD, ScD[5]

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. Although a disproportionately high percent of the cases were 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 pancreatic cancer among blacks in this cohort remains unexplained. Am. J. Ind. Med. 32:240–247, 1997. © *1997 Wiley-Liss, Inc.*

KEY WORDS: cutting oils; metalworking fluid; synthetic fluid; gastro-intestinal cancer

INTRODUCTION

This investigation of pancreatic cancer is one of a series of nested case-control studies conducted to further elucidate the risks suggested in previous results from a cohort mortality study of autoworkers. The General Motors/ United Auto Workers (GM/UAW) cohort study was designed to investigate mortality patterns among a cohort of over 46,000 autoworkers exposed to metalworking fluids (MWF) at three separate plants in Michigan. Standardized mortality ratios (SMRs) were found to be elevated for various cancers, particularly digestive. An elevated risk for pancreatic 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 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.

In addition to the GM/UAW cohort study, others have suggested excess risk of pancreatic cancer in the metalworking industries. Sparks and Wegman [1980] reported an excess of pancreatic cancer among white jewelry workers (PMR = 1.8, $P < 0.05$). Vena et al. [1985] found that white males with more than 20 years employment in an engine

[1]Department of Work Environment, University of Massachusetts Lowell, Lowell, Massachusetts
[2]Environmental and Occupational Health Division, Rollins School of Public Health of Emory University, Atlanta, Georgia
[3]Environmental Medical Services, Massachusetts Institute of Technology, Cambridge, Massachusetts
[4]Environmental Health Science Division, School of Public Health, University of California, Berkeley, California
[5]Occupational Health Program, Harvard School of Public Health, Boston, Massachusetts

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*Correspondence to: Dr. Ellen A. Eisen, Department of Work Environment, University of Massachusetts Lowell, Lowell, MA 01854

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plant had increased pancreatic cancer mortality (PMR = 2.3, $P = 0.05$). Teta and Ott [1988] reported an excess of pancreatic cancer among hourly workers (SMR = 1.3, $P > 0.05$) in a research, engineering, and metal fabrications facility. Silverstein et al. [1988] studied bearing plant workers. Elevated ORs for pancreatic cancer were reported for both grinding and machining operations, and for straight as well as water-based fluids. Acquavella et al. [1993] reported an increased risk of pancreatic cancer in white factory workers at an Iowa facility manufacturing metal components. Those employed between 1950 and 1959 for at least ten years appeared to have the greatest risk (SMR 3.6, 95% CI: 1.2–8.3). Two studies have shown pancreatic cancer risks that were limited to black workers. Mallin et al. [1986] found elevated rates in black males employed for more than 20 years in an engine construction and equipment plant (PMR = 4.8, $P < 0.01$) and Rotimi et al. [1993] found increased mortality in black engine plant workers (SMR = 3.0, 95% CI: 1.2–6.2).

In most of these epidemiologic studies, MWF was treated as a single entity, instead of a complex mixture of many substances. In the GM/UAW cohort mortality study, MWF was classified into three types—straight, soluble, and synthetic—and components and additives were also assessed. Straight fluids include 80–100% petroleum oil. Soluble fluids are water emulsions of 3–10% petroleum oil. Synthetic fluids contain no mineral oil at all and include synthetic lubricants such as glycols in large dilutions of water with additives such as nitrites, ethanolamines, and biocides.

The goal of the present study was to further investigate the risk of pancreatic cancer associated with the water-based fluids in the GM/UAW 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, with a high control-to-case ratio, was chosen because it afforded a flexible statistical modeling approach while still maintaining most of the power of the full cohort.

MATERIALS AND METHODS

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

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. Date of hire ranged from 1917, when Plant I started operations, to 1981. MWFs were used extensively at all three plants, referred to as Plants I, II, and III. Follow-up ended in 1984, at which time 10,159 (22%) were deceased. Of the deceased subjects, 64% had worked in Plant I, 28% in Plant II, and 8% in Plant III. The cohort was comprised mainly of white males, but also included 7,750 blacks and 4,680 females.

Cases

A total of 97 cases of pancreatic cancer were found among deceased subjects. 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.'' Data on race, date of birth, sex, and social security number were obtained from employment records. Classification of race was either white, black, or unknown.

Controls

Incidence density sampling was used to select controls from within the cohort [Checkoway et al., 1989]. This sampling design ensures that controls have lived at least as long as the case and that any exposure incurred after this date is not included in cumulative exposure. Additional matching factors included: race, sex, plant, and date of birth (± 5 years). For each case, an attempt was made to choose 20 controls, but for some fewer were available. In total, 1,825 controls were selected.

Exposure Assessment

MWFs were classified in this study as either straight, soluble, or synthetic fluids. Both soluble and synthetic fluids are water-based. Solubles contain petroleum oil emulsified in water and synthetics contain only synthetic lubricants. Semi-synthetic MWF contains a combination of mineral oils in water and the chemicals found in synthetics, and were classified with soluble fluids in this study. Common additives to MWFs include ethanolamines, nitrites, biocides, and sulfur. Ethanolamines are added to synthetic or soluble MWF to inhibit corrosion or to adjust pH. Nitrite compounds were frequently included in synthetic MWF formulations and act as corrosion inhibitors. The interaction of ethanolamines and nitrites can form nitrosamines, specifically N-nitrosodiethanolamine (NDELA) [Lijinsky et al., 1972; Zingmark and Rappe, 1977]. For the purposes of this study, nitrosamines were classified as the co-presence of nitrite and ethanolamine in the same MWF. Biocides are used to decrease microbial contamination and are frequently added to synthetic MWF and sometimes to solubles. In addition to additives, MWF aerosols may contain metal

particulate. Exposures to aluminum, chromium, iron, and steel were also evaluated.

Exposures were estimated for each unique plant, department, job, and calendar period in an exposure matrix. For each cell in the matrix, quantitative assessments (mg/m^3) were made for MWF and classified by type of MWF and metal-working operation. Operations were classified as either machining or grinding. Air samples were collected to estimate gravimetric concentration of aerosol in the subjects' breathing zone using a two-stage Marple Personal Cascade Impactor. In this analysis of pancreatic cancer, exposure was measured by inhalable particulate, since larger particles deposited in the upper airways can reach the digestive tract.

Scale factors based on statistical models of historical measurements were defined for combinations of MWF/operation/plant. Estimation of past exposures were calculated by using scale factors as multipliers for current air samples. By combining the exposure matrix with employment records, total cumulative exposure to each type of MWF was determined for each subject (mg/m^3-years). The presence of each component was also determined in each unique plant, department, job, and year. Summing these qualitative indices over time, duration (years) of exposure was estimated for each specific component.

Latency Analysis

Many cancers are known to have a latency period of up to 20 years. Specific latency periods for pancreatic cancer have not been ascertained. For all exposure variables, lagged exposures were defined to account for two possible latency periods, 10 and 20 years. These variables ignore exposures occurring 10 or 20 years immediately prior to the year of death of the case (and prior to the same year for all controls matched to that case).

Statistical Analysis

Egret software (Statistics and Epidemiology Research Corporation (SERC), 1985–91) was used to fit conditional logistic regression models. The odds ratios (ORs) were estimated by exponentiating model parameters. Years since hire was added to all models as a covariate in order to minimize confounding due to the healthy-worker effect, which tends to wear off with increased time since hire [Monson, 1986]. Model fit was compared between nested models by examining model deviances and their associated *P*-values.

Models were fit with both continuous and categorical exposure variables to obtain a more complete understanding of the patterns of risk. When exposure is treated as a continuous variable, the change in the odds ratio (OR) per unit change in exposure is estimated. This model assumes an exponentially shaped dose–response curve. In the regression models based on categorical exposure variables, the categories were defined as dummy variables and the odds in each category of exposure were compared to that of an internal group of nonexposed subjects.

Two criteria were used to define the exposure categories. First, cut-offs were chosen to equalize the number of cases in each non-zero exposure group. Second, whenever there were a sufficient number of unexposed cases, the reference group was defined as those subjects with zero exposure to a particular agent. In stratified analyses, new cut-points were defined using the same criteria.

Risk estimates were first computed in models including only a single exposure variable. Further modeling was done to evaluate relationships between variables with the higher risk estimates. Exposures were often moderately correlated, raising concern of confounding relationships existing between exposures. To address this possibility, models were fit with several exposure variables included simultaneously. An appreciable change in the 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.

A test for linear trend was conducted when a significantly elevated risk was observed together with a pattern of rising risk across increasing categories of exposure. To test for trend, a linear regression model was fit with the odds ratio as the dependent variable and the median exposure in each category as the independent variable. The independent variable was weighted by the inverse of the number of subjects in each category [Rothman, 1986].

RESULTS

In the cohort, there were a total of 97 cases of pancreatic cancer. The largest number of cases occurred in Plant I, the oldest of the three plants. All but one of the 21 black cases worked in Plant I. The majority of subjects in Plant II were of unknown race, since race was not routinely recorded in this plant until the early 1970s. On average, cases started work in 1942 and were 64 years old in the year of their death (Table I).

There were no significant differences between mean exposures of cases and controls, although exposures were generally higher for cases (Table II). The largest differences were observed for synthetic MWF, grinding/synthetic, and for three components: biocides, nitrosamines, and aluminum. The vast majority of the cohort was exposed to soluble fluids. 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%). (Because machining/synthetic was so uncommon, it was excluded from further analysis.) A limited number of

TABLE I. Characteristics of Pancreatic Cancer Cases and Controls with Potential Exposure to Metalworking Fluids (MWF) in the Automobile Industry (All Plants Combined)

	Cases n = 97	Controls n = 1,825
Number of subjects		
Plant*		
I	62	1169
II	26	502
III	9	154
Race*		
White and other (%)	48.4	48.3
Black (%)	21.7	21.7
Unknown (%)	29.9	30.0
Gender*		
Male (%)	96.9	96.9
Age started work	33 (9.4)**	34 (9.8)
Year started work	1942 (11.8)	1943 (12.0)
Year of birth*	1909 (12.2)	1909 (11.9)
Age in risk year*	64 (10.6)	64 (10.4)
Years worked	19 (11.0)	17 (10.5)

*Matching factor.
**Mean (SD).

TABLE II. Exposure Characteristics of Pancreatic Cancer Cases and Controls with Potential Exposure to MWF in the Automobile Industry (All Plants Combined)

Exposure type	Average exposure		Percent subjects exposed
	Cases	Controls	
MWF and MWF/Operation	mg/m^3-years		
Straight MWF	3.73	4.66	55.4
Soluble MWF	33.74	29.56	92.7
Synthetic MWF	0.47	0.29	16.2
Grinding MWF	16.59	16.27	77.2
Grinding synthetic MWF	0.47	0.29	15.8
Grinding soluble MWF	15.61	14.45	75.7
Machining synthetic MWF	0	0.01	0.6
Machining soluble MWF	18.13	15.10	90.6
Components	Years		
Biocides	1.17	0.68	15.2
Nitrosamines	1.28	0.70	16.2
Steel	10.82	9.91	91.0
Iron	6.35	5.35	73.6
Aluminum	0.44	0.27	9.7
Sulfur	1.78	1.58	28.7

subjects were exposed to nitrosamines (16.2%) or biocides (15.2%), which were found almost exclusively in grinding/synthetic fluids. Steel and iron contamination were common, aluminum was less common, and chromium so rare that it was excluded from this analysis.

TABLE III. Adjusted Odds Ratios (ORs) for Pancreatic Cancer in a Separate Conditional Logistic Regression Model for Each Continuous MWF Exposure Variable (All Plants Combined)

	No lag		10-Year lag		20-Year lag	
Exposure	OR	95% CI	OR	95% CI	OR	95% CI
Straight MWF						
mg/m^3-years	0.99	0.98–1.01	1.00	1.00–1.01	1.00	0.98–1.02
Years	1.01	0.98–1.04	1.01	0.97–1.04	1.00	0.94–1.05
Soluble MWF						
mg/m^3-years	1.00	1.00–1.01	1.00	1.00–1.01	1.00	0.99–1.01
Years	1.02	1.00–1.04	1.02	1.00–1.05	1.01	0.98–1.05
Synthetic MWF						
mg/m^3-years	1.03	0.96–1.11	1.05	0.97–1.14	1.21	0.98–1.48
Years	1.07	1.01–1.14	1.10	1.01–1.20	1.05	0.84–1.30
Grinding						
mg/m^3-years	1.00	0.99–1.01	1.00	0.99–1.01	1.00	0.99–1.01
Years	1.02	0.99–1.04	1.02	1.00–1.05	1.01	0.98–1.05
Grinding synthetic						
mg/m^3-years	1.03	0.96–1.11	1.05	0.97–1.14	1.21	0.99–1.48
Years	1.07	1.01–1.14	1.10	1.01–1.20	1.05	0.84–1.31
Grinding soluble						
mg/m^3-years	1.00	1.00–1.01	1.00	1.00–1.01	1.00	1.00–1.01
Years	1.02	1.00–1.04	1.02	1.00–1.05	1.01	0.98–1.05
Machining soluble						
mg/m^3-years	1.01	1.01–1.02	1.02	1.00–1.05	1.01	1.00–1.02
Years	1.02	1.00–1.04	1.03	1.00–1.06	1.02	0.98–1.06
Biocide years	1.07	1.00–1.15	1.09	1.00–1.20	0.95	0.72–1.27
Nitrosamine years	1.08	1.01–1.15	1.10	1.01–1.20	1.06	0.86–1.31
Steel years	1.01	0.99–1.03	1.02	0.99–1.04	1.01	0.97–1.05
Iron years	1.02	0.99–1.04	1.02	0.99–1.05	1.03	0.98–1.07
Aluminum years	1.09	0.96–1.24	1.15	0.96–1.38	1.64	1.06–2.54
Sulfur years	1.01	0.96–1.06	1.02	0.96–1.08	0.99	0.88–1.10

All Plants Combined

ORs were elevated for all continuous variables which characterized exposure to synthetics (Table III). In general, risks for MWF types were slightly higher for duration of exposure than for cumulative exposure. The OR for years of grinding with synthetic (and for synthetic) was 1.07 (1.01–1.14). Lagging years of exposure did not substantially change the ORs; however, when cumulative exposures were lagged the associations with grinding/synthetic increased from 1.03 to 1.05 to 1.21 with 0-, 10-, and 20-year lags, respectively. Elevations were also seen for two components of synthetic fluids: nitrosamines, with an OR of 1.08 (1.01–1.15), and biocides, with an OR of 1.07 (1.00–1.15).

TABLE IV. Adjusted ORs for Pancreatic Cancer in a Separate Conditional Logistic Regression Model for Each MFW Exposure (All Plants Combined)

Exposure (mg/m^3-years)	Cut points	# Cases	OR	95% CI
Straight MWF	0	43	1.0	
	>0–0.8	18	1.0	0.5–1.7
	>0.8–2.1	18	1.1	0.6–2.1
	>2.1	18	0.9	0.5–1.6
Soluble MWF	0	8	1.0	
	>0–6.3	23	0.8	0.4–1.9
	>6.3–21	22	0.7	0.3–1.5
	>21–51	22	1.1	0.4–2.5
	>51	22	1.1	0.5–2.7
Synthetic MWF	0	79	1.0	
	>0–1.4	9	1.0	0.4–2.4
	>1.4	9	2.8	1.1–6.9
Grinding	0	18	1.0	
	>0–2.2	20	1.0	0.5–1.9
	>2.2–5.3	20	2.1	1.1–4.0
	>5.3–23	20	1.2	0.6–2.4
	>23	19	1.3	0.7–2.5
Grinding synthetic	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	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
Machining soluble	0	9	1.0	
	>0–3.7	22	0.9	0.4–2.0
	>3.7–9.5	22	1.1	0.5–2.5
	>9.5–28	22	0.9	0.4–2.0
	>28	22	1.3	0.6–3.1

TABLE V. Adjusted ORs for Pancreatic Cancer in a Separate Conditional Logistic Regression Model for Each MWF Component (All Plants Combined)

Exposure (years)	Cut points	# Cases	OR	95% CI
Biocides	0	82	1.0	
	>0–2.4	7	1.1	0.4–2.7
	>2.4	8	1.2	0.5–3.1
Nitrosamines	0	78	1.0	
	>0–3.6	10	1.5	0.6–3.5
	>3.6	9	2.1	0.8–5.4
Steel	0	8	1.0	
	>0–3.0	23	1.4	0.6–3.2
	>3.0–8.7	22	0.8	0.3–1.8
	>8.7–20	22	1.3	0.4–2.4
	>20	22	1.0	0.6–3.3
Iron	0	32	1.0	
	>0–2.8	22	0.6	0.4–1.1
	>2.8–12	21	0.6	0.3–1.0
	>12	22	1.1	0.6–1.9
Aluminum	0	88	1.0	
	>0–4.5	5	0.7	0.3–1.9
	>4.5	4	2.2	0.6–7.3
Sulfur	0	69	1.0	
	>0–1.9	10	0.9	0.4–1.8
	>1.9–5.4	9	1.5	0.6–3.7
	>5.4	9	0.9	0.4–2.3

In addition, when duration of exposure to aluminum was lagged 20 years, the OR was 1.64 (1.06–2.54).

Conditional logistic regression analysis was then extended to categorical variables for both duration and cumulative exposure. Again, the strongest associations were seen with variables that measured exposure to synthetic MWF. Synthetic variables had the highest risk estimates and models with the lowest deviances and smallest *P*-values. However, unlike in models with continuous exposure variables, relationships were strongest for the unlagged measures of cumulative exposure. Therefore, only cumulative exposure models are presented in Table IV and subsequent presentation of results concentrate on unlagged cumulative exposure.

A significantly elevated risk of 2.8 was observed in the highest category of synthetic MWF (Table IV). 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 synthetic/grinding 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 ($P < .05$ in test for linear trend). No clear risk patterns were seen for exposure to straight MWF or soluble MWF, whether in machining or grinding operations. For grinding operations, which include both synthetic and soluble grinding, the OR rose slightly to 2.1 (1.1–4.0) and then fell back to 1.3 in the highest exposure category. This slight elevation of risk in the middle category (2.2–5.3 mg/m^3) is consistent with elevated risks observed for grinding/synthetic, since less than 1% of synthetic exposures in grinding were higher than 5.3.

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 which excluded 1.0. The odds ratios were 2.1 for nitrosamine and 2.2 for aluminum in the highest exposure categories (Table V). Although no elevation in risk is presented for

TABLE VI. Adjusted ORs for Pancreatic Cancer in Three Separate Conditional Logistic Regression Models (All Plants Combined)

		Model 1		Model 2		Model 3	
Exposure	**Cases**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
Grinding synthetic (mg/m^3-years)							
<0	79	1.0		1.0		1.0	
>0–1.4	9	1.0	0.4–2.5	0.5	0.1–3.0	1.9	0.4–9.2
>1.4	9	3.0	1.2–7.5	1.5	0.2–9.3	5.5	1.3–22
Nitrosamine (years)							
<0	78			1.0			
>0–3.6	10			2.1	0.4–12		
>3.6	9			2.2	0.3–15		
Biocide (years)							
<0	82					1.0	
0–2.4	7					0.6	0.1–3.2
>2.4	8					0.4	0.1–2.1
Goodness-of-Fit		LRS* = 6.1		LRS = 6.8		LRS = 7.4	
		$P = 0.11$		$P = 0.24$		$P = 0.20$	

Model 1—grinding/synthetic.
Model 2—grinding/synthetic and nitrosamines.
Model 3—grinding/synthetic and biocides.
*LRS = likelihood ratio statistic.

TABLE VII. Adjusted ORs for Pancreatic Cancer and MWF Exposure 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

biocides, when exposure was split into four categories (with five cases per exposed group), the ORs were 1.0, 1.1, 0.7, and 4.5 (1.3–16.0).

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 (Model 2 in Table VI). The addition of biocides raised the OR for synthetic/grinding from 3.0 to 5.5 (Model 3). 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. Interaction terms were then added to models including main effects variables. No evidence of effect modification was seen for any variables; however, interaction terms could not be fit between grinding/synthetics, biocides, and nitrosamines due to their collinearity—97% of the grinding/synthetic exposure included nitrosamines, and 91% included biocides.

Stratified Analyses

Stratified analyses were conducted to examine whether risks seen for synthetics were consistent across plants and races. Exposures to synthetics, biocides, and nitrosamine 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 ORs for synthetics, grinding/synthetic, biocides, and nitrosamines in Plants II/III were similar to risk estimates in the model for all plants combined.

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 VII). 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 than whites. The majority of white cases worked between 1930–1960, while the majority of blacks were hired later, between 1950–1970, when exposures had been somewhat reduced. Duration of employment was shorter for blacks than whites, 18.4 vs. 25.3 years. The mean age of pancreatic cancer death was lower for blacks, 59.3 vs. 70.0.

DISCUSSION

Pancreatic cancer is estimated to cause 25,000 deaths in the United States annually [Fernandez et al., 1994], and is the ninth most common malignancy [Murr et al., 1994]. Mortality and morbidity rates for pancreatic cancer are almost identical, with an estimated 90% [Zheng et al., 1993]

of all cases dying within a year of diagnosis and only a 3–4% five-year survival rate [Friedman and Van Den Eeden, 1993]. Despite a doubling of the incidence of pancreatic cancer between 1930 and 1980, little progress has been made in prevention or treatment [Murr et al., 1994].

The etiology of pancreatic cancer has largely eluded epidemiologists. Cigarette smoking is the only clearly documented risk factor with this disease [Silverman et al., 1994; Siemiatycki et al., 1995]. The roles of race, socioeconomic status, diet, and alcohol are unclear. Black Americans have one of the highest incidence rates for pancreatic cancer both in the United States and worldwide. Yet, in Iabadam, Nigeria (a predominantly black country), incidence rates are among the lowest. Socioeconomic patterns are not well defined, though the highest incidence rates occur in Western industrialized nations [Fontham, 1982]. Diet may play a role in pancreatic carcinogenesis. Recent studies have linked high meat intake [Zheng et al., 1993] and high serum levels of iron [Friedman and Van Den Eeden, 1995] to pancreatic cancer. The link between alcohol consumption and pancreatic cancer remains equivocal [Zheng et al., 1993; Kalapothaki et al., 1993; Friedman and Van Den Eeden, 1995; Murr et al., 1994].

As information on smoking and alcohol was not available for this cohort, it is possible that some of the association observed between synthetic MWF and pancreatic cancer is due to confounding. To address this possibility, lung/laryngeal cancer and cirrhosis mortality were treated as surrogate measures of smoking and alcohol consumption. With regard to lung cancer, an inverse dose–response association was recently reported for synthetic exposure in a nested case-control study in this cohort [Schroeder et al., 1997]. With regard to laryngeal cancer and cirrhosis, there was no evidence of increasing mortality with increasing duration of exposure to synthetic fluids in the Tolbert et al. [1992] analysis of the full cohort. Thus, it appears unlikely that either cigarette smoking or alcohol consumption explains the observed elevation in the risk of pancreatic cancer among subjects exposed to synthetics.

Synthetic fluids have been used since the mid- to late-1950s [Vena et al., 1985]. In 1977, the nitrosamine N-nitrosodiethanolamine (NDELA) was discovered to be a frequent contaminant of synthetic MWF [Fan et al., 1977]. The International Agency for Research on Cancer (IARC) has classified NDELA as a group 2B carcinogen, ''possibly carcinogenic to humans'' [IARC, 1987]. Since nitroso products are formed by the interaction of ethanolamines and nitrite, the EPA prohibited the addition of nitrosating agents to machining fluids in 1984 [US EPA, 1984 49 Fed. Reg.]. Despite the EPA's prohibition, persistent NDELA contamination has been found in 14 of 18 samples of commercial MWF more recently collected [Keefer et al., 1990], although the concentrations Keefer reported were well below those typically found in the past [Järvholm et al., 1991].

Biocides were used in the majority of synthetic fluids in this study. One class of biocides are the formaldehyde condensate products [Rossmoore, 1981]. Material Safety Data Sheets (MSDS) of metalworking fluids and components used at the plants have documented the use of this class of biocide in the cohort. Formaldehyde may act as a catalyst in nitrosamine formation [Keefer, et al., 1973]. Although formaldehyde is regulated by OSHA as a carcinogen [OSHA, 1987 52 Fed. Reg.], it has not been associated with pancreatic cancer in any of the large cohort mortality studies of occupationally exposed workers [Acheson et al., 1984; Bertazzi et al., 1986; Blair et al., 1986].

Black workers make up 17% of the cohort as a whole, and 22% of the pancreatic cancer cases. Stratification by race did not identify an MWF-related risk factor among blacks. None of the black cases had ever been exposed to synthetics. Moreover, blacks worked for shorter periods than whites and appeared to have generally lower cumulative exposures. Thus, no explanation has been found in this case-control study for the elevated SMR previously reported for pancreatic cancer among blacks in this cohort. In light of the two previous reports of excess pancreatic cancer mortality among blacks in other metalworking populations [Mallin et al., 1986; Rotimi et al., 1993], these findings deserve further examination.

CONCLUSION

In summary, data presented suggest a moderately strong association between pancreatic cancer and exposure to synthetic MWF in grinding operations. This conclusion is unlikely to be confounded by cigarette smoking or alcohol consumption, but could be confounded by unmeasured risk factors. Although there was some evidence that contamination of synthetics by nitrosamine or the addition of biocides might explain some of the risk, the results were inconclusive. Synthetic MWF are currently regarded as safer than the mineral-based oils and are increasingly used in the metalworking industry. Further investigation of pancreatic cancer in other exposed populations is needed to corroborate the risk observed in this study.

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