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Registry-based case–control studies of liver cancer and cancers of the biliary tract nested in a cohort of autoworkers exposed to metalworking fluids

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Objective Results are presented for a registry-based study of hepatobiliary cancer (liver and biliary tract) nested in a cohort of workers from three automobile manufacturing plants with potential exposure to metalworking fluids.

Methods Altogether 63 cases of hepatobiliary cancer were identified from the cohort by the Michigan cancer registries. Each case was matched to 10 controls. Odds ratios (OR) were estimated in conditional logistic regression models for lifetime exposure to straight, soluble, and synthetic metalworking fluid and fluid components.

Results Overall, hepatobiliary cancer was not associated with exposure to metalworking fluids. However, when the cases were stratified into liver cancer (N=39) and biliary tract cancer (N=24) the risk was nonhomogeneous across the two categories. While liver cancer was not associated with exposure to metalworking fluids, the results suggested a possible excess risk of biliary tract cancer with more than 1.0 mg/m^3-years of exposure to straight metalworking fluids [OR 2.7, 95% confidence interval (95% CI) 0.9–7.6], as well as any exposure to chlorinated paraffins (OR 3.9, 95% CI 0.9–17). When exposures to straight metalworking fluids were separated into 10-year exposure periods, the odds ratio increased to 6.24 (95% CI 1.62–24.16) for exposures occurring >20 years prior to the risk date.

Conclusions There is limited evidence that exposure to straight metalworking fluids is associated with biliary tract cancer. The small numbers of cases of these rare cancers were reflected in the wide confidence intervals, and these findings need to be examined further in other exposed populations.

Key terms biliary tract cancer; gall bladder cancer; occupational health.

Hepatobiliary cancers are highly malignant tumors accounting for 3% of cancer deaths annually in the United States. These fatal cancers have a 5-year survival rate of only 5–10% (1–4). Other than exposures to hepatitis B and C in health care settings, vinyl chloride, and arsenic (3, 4–7), little is known about the occupational risk factors for these cancers.

In an updated cohort mortality study of 46 400 autoworkers exposed to metalworking fluids (MWF), elevated hepatobiliary cancer risk was found for both white [standardized mortality ratios (SMR) 1.4, 95% confidence interval (95% CI) 1.1–1.8] and African American males (SMR 1.3, 95% CI 0.8–2.1) (8). To understand the relations between MWF and hepatobiliary cancer, we conducted a nested case–control study within the cohort. The registry-based study of hepatobiliary cancer was followed by separate case–control studies of the component cancers, liver cancer and cancers of the biliary tract. The ninth revision of the International Classification of Diseases (ICD) classifies liver cancer (ICD code 155) as primary liver and intrahepatic bile duct cancers. Cancers of the biliary tract (ICD code 156) groups gallbladder, extrahepatic bile duct, and ampulla of Vater cancer under the same rubric (9).

Liver cancer and biliary tract cancer arise from a common embryonic origin and share a close anatomic and physiological relationship with the epithelial tissue of these cancers, all exposed to bile and its constituents (1, 10). Previous studies have suggested risks for both of these cancers among workers employed in jobs with

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potential exposure to MWF (11–14). It was unclear, however, whether the elevated standardized mortality ratios observed for hepatobiliary cancer in our cohort study of autoworkers were the result of an elevated risk of liver cancer, biliary tract cancer, or both because the software used to calculate the ratios (15) combines these cancers into hepatobiliary cancer to handle the mixed coding system created by changes in the ICD codes over time (4, 9, 16).

Study population and methods

Study population

The study population was comprised of all hourly workers at three auto parts plants in Michigan who were employed for at least 3 years prior to 1984. Follow-up began in 1941 and ended in 1994, at which time approximately one-third (15 613) of the 46 400 cohort members were deceased. The cohort consisted predominantly of white male workers, but also included African Americans (17%) and females (10%). The cohort selection and the exposure assessment have been described in detail previously (17–19).

Cases

To prevent the misclassification of tumors, only registry-determined cases of incident cancer occurring in the Michigan cancer registries between 1973 and 1997 were used in this analysis. Liver cancer is a site for which metastases from a variety of primary sites frequently occur, and it is not unusual for secondary tumors to be listed on death certificates as primary liver cancer (3, 20). The mixed coding system from the seventh to the ninth revision of the ICD codes made the assignment of cancer by ICD codes alone inaccurate (9, 16). Although we had information on the underlying cause of death from our earlier follow-up of the cohort, this information was obtained from company and union computer tapes in the form of an electronic record, but the capability of examining the text was not available. Therefore these records were not used, and the cases were defined as incident cases from the Michigan cancer registries.

There are two working registries in Michigan. As far back as 1973, the Statistical and Epidemiologic End Reports (SEER) registry covered Detroit and the surrounding area. The Michigan Cancer Registry was instituted in 1985 and encompassed the entire state. Despite this excellent registry coverage, cases diagnosed prior to 1973 could not be determined, and the ascertainment of cases diagnosed in 1973–1984 was incomplete since two of the three study plants were outside the Detroit area.

In 1998, a search of the two registries was conducted for all persons in the cohort known to be alive as of 1973. We requested all incident cases for ICD-O codes C22.0 through C24.9 (21). Altogether, 67 cases of hepatobiliary cancer, 43 cases of liver cancer, and 24 cases of biliary tract cancer (12 gallbladder, 7 extrahepatic bile duct, 3 ampulla of Vater, and 2 biliary tumors not otherwise specified) were determined from the registry matches. Four of the liver cancer cases were missing more than 25% of their exposure history and were excluded from the analyses, leaving 39 remaining liver cancer cases. Nine cases were diagnosed after the end of the follow-up, and, to maximize the statistical power for studying these rare cancers, we included these cases with appropriate adjustment in the selection of their controls (see below).

Controls

Using incidence density sampling, we defined risk sets for each case, including all persons who lived to be at least as old as the case at the age of diagnosis (risk age). We then randomly selected 10 controls matched for race, gender, plant of work, and year of birth (±5 years). To ensure an adequate pool of controls for the cases who were diagnosed within the 3 years after the end of the follow-up, we assumed that the controls who were still alive at the end of the follow-up lived the additional 1 to 3 years until the diagnosis of the case. Altogether a total of 569 controls were chosen (349 liver and 220 biliary tract cancer controls).

Exposures

Exposures in the cohort spanned a period of 75 years (1920–1994). A job-exposure matrix was used to derive exposure estimates. Aerosol samples of MWF in different operations were collected in the mid-1980s (18). Scale factors were constructed that served as multipliers of current air samples to estimate past levels. For each person, annualized exposures were summed to form an estimate of cumulative exposure. In this analysis, exposure was measured by inhalable particulate, since larger particles deposited in the upper airways can reach the digestive tract. Cumulative exposures to specific fluids used in specific operations were quantified in milligrams per cubic meter -years (19).

MWF can be divided into the following four main classes: straight, soluble, synthetic, and semisynthetic. Straight MWF, the earliest type of MWF, is primarily a mineral oil-based fluid from either napthenic or paraffinic lube oil refinery streams. Soluble oils are based on mineral oils emulsified in water, combined with other additives to improve product characteristics. Synthetic MWF consist of a wide variety of chemicals and lubricants in water, but contain no mineral oil, whereas semisyntheics also contain some mineral oil. Synthetic, semisynthetic, and soluble MWF are often characterized together as water-based fluids. There was only a small number of semisynthetic fluids, and for this study they were grouped with soluble oils. In these work environments, straight and soluble MWF had been in widespread use since the 1920s, and synthetics since the mid-1970s.

Several specific MWF additives were also evaluated in the exposure assessment. These included the chlorinated paraffins used in extreme pressure operations with straight oils, biocides that are utilized in water-based fluid to minimize microbial contamination, nitrite added to prevent corrosion in synthetic MWF, and ethanolamine also used in synthetic MWF to stabilize pH and inhibit corrosion. The co-presence of nitrite and ethanolamine can lead to the formation of nitrosamines (22). Exposure to metal particulate can occur when particulate from the tool or part is aerosolized or when metal becomes entrained in MWF itself and is aerosolized with the fluid. Exposures to additives and two metals, aluminum and iron, were quantified as years of exposure.

All the exposures were accumulated for the controls until the risk age (age of diagnosis of the matching case). To compensate for the extra 3 years of follow-up for cases identified after 1994, exposures were lagged in the analysis by 3 years for all the participants. Missing exposures were estimated by averaging the exposures in the years just before and after the missing data.

Statistical analysis

Conditional logistic regression models were fit using the PHREG procedure, with SAS software (23). Odds ratios were estimated by exponentiating model parameters. In regression models, levels of exposure were characterized by dummy variables, and the odds in each exposure category contrasted to the odds for an internal reference group of assembly workers exposed to very low levels of MWF of unspecified type. Exposure categories were defined by case percentiles, evenly distributing cases among the exposure groups. To test for a trend in risk across exposure categories, we used weighted linear regression (24). The dependent variable was defined as the odds ratio, and the independent variable for exposure was defined by the median value for all subjects in each exposure category weighted by the inverse of the number of cases in each exposure category. Time periods of exposure were constructed for both continuous and categorical variables in 10-year periods: the most recent 10 years, >10–20 years, and >20 years prior to the date of the risk age (risk date). The models were fit with the three exposure periods in the same model, to control for potential confounding of one exposure window by another.

Data were managed and analyzed using SAS software (23). The exposure variables were not normally distributed, and correlations were estimated by Spearman's nonparametric rank correlation coefficient.

Results

Most of those with hepatobiliary cancer were of white race, but 25% were African American. Only 6% of the cases were female. On the average, the cases were born in 1923, started work at 30 years of age, in 1953, and died at 64 years of age (table 1).

Two contaminants were highly correlated with exposure to synthetic MWF, nitrosamines (r=0.91) and biocides (r=0.86). These component exposures were dropped from further analysis. Straight MWF and chlorinated paraffins were moderately correlated (r=0.20). Correlations between cumulative exposure to the three MWF were positive and low to moderate: straight and soluble MWF (r=0.10), soluble and synthetic MWF (r=0.16), and straight and synthetic MWF (r=0.29).

Table 1. Characteristics of the cases of hepatobiliary, liver, and biliary tract cancers and their controls with potential exposure to metalworking fluids in the automobile industry.

Group	N	Race [a]			Gender [a, b] (%)	Age started work (years)		Year started work		Year of birth [a]		Age in risk year (years)		Years worked	
		White and others (%)	African-American (%)	Unknown (%)		Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Cases															
Hepatobiliary	63	49.2	25.4	25.4	93.7	30	9.6	1954	14.6	1923	14.9	64	12.4	18.3	12.1
Liver	39	48.7	30.8	20.5	100.0	31	9.4	1955	12.6	1924	14.0	64	12.0	16.9	10.6
Biliary tract	24	50.0	16.7	33.3	83.3	30	10.2	1952	17.4	1922	16.4	65	13.1	20.5	14.2
Controls	569	49.7	25.0	25.3	94.4	30	9.1	1953	12.2	1923	14.9	64	12.5	20.6	11.0

[a] Matching factor.
[b] Male.

Table 2. Exposure characteristics of the cases of liver and biliary tract cancer and their controls with potential exposure to metalworking (MWF) fluids in the automobile industry (limited to exposed workers).

	Straight MWF		Soluble MWF		Synthetic MWF		MWF component					
							Aluminum		Chlorinated paraffins		Iron	
	Exposed (%)	Mean exposure (mg/m³-years)	Exposed (%)	Mean exposure (mg/m³-years)	Exposed (%)	Mean exposure (mg/m³-years)	Exposed (%)	Mean exposure (years)	Exposed (%)	Mean exposure (years)	Exposed (%)	Mean exposure (years)
Cases [a]												
Liver cancer (N=24)	40	5.8	95	13.2	21	1.8	15	4.5	03	0.6	62	3.8
Biliary tract cancer (N=39)	67	8.0	99	24.2	25	0.5	38	3.2	21	1.3	70	5.1
Controls [b] combined (N=569)	54	4.4	93	23.4	25	1.7	24	4.1	13	2.2	68	5.4

[a] Mean exposures based on all cases exposed.
[b] Mean exposures based on all controls exposed.

Table 3. Adjusted odds ratios (OR) and 95% confidence intervals (95% CI) for liver and biliary tract cancer in separate conditional logistic regression models for the total cumulative exposure to metalworking fluid (MWF) types and components.

Exposure	Liver cancer			Biliary tract cancer		
	Cases (N= 39)	OR	95% CI	Cases (N= 24)	OR	95% CI
Straight MWF						
0 mg/m³-years	24	1.00	..	8	1.00	..
0–1.0 mg/m³-years	8	0.58	0.24–1.43	8	1.21	0.42–3.51
>1.0 mg/m³-years	7	0.47	0.19–1.16	8	2.65	0.93–7.54
Soluble MWF						
<1.4 mg/m³-years	8	1.00	..	6	1.00	..
>1.4–12.6 mg/m³-years	18	0.95	0.40–2.29	9	0.62	0.20–1.91
>12.6 mg/m³-years	13	0.57	0.21–1.53	9	0.66	0.14–3.05
Synthetic MWF						
0 mg/m³-years	31	1.00	..	18	1.00	..
>0 mg/m³-years	8	1.16	0.35–3.81	6	0.71	0.20–2.56
MWF component						
Aluminum						
0 years	33	1.00	..	15	1.00	..
>0 years	6	0.71	0.17–2.91	9	2.12	0.48–9.40
Chlorinated paraffins						
0 years	38	..	..	19	1.00	..
>0 years	1	..	..	5	3.88	0.88–19.96
Iron						
0 years	15	1.00	..	7	1.00	..
0–2.5 years	13	1.07	0.48–2.30	8	1.04	0.36–3.02
> 2.5 years	11	0.68	0.28–1.64	9	0.73	0.24–2.11

These low correlations suggested minimal potential confounding of one fluid type by another.

Odds ratios were initially estimated for all the hepatobiliary cancers combined. A flat dose–response curve was found for all three types of MWF (straight, soluble, and synthetic) and components (models not shown). To ascertain if the patterns of risk might differ for the liver and biliary tract cancers, the two diseases were then examined separately.

The mean cumulative exposure was calculated for each fluid, component, and metal for the exposed. Almost all persons had some exposure to soluble MWF, and cumulative exposure was lower for the liver cancer cases than for the controls, 13.2 versus 23.4 mg/m³-years. A little over half of all the participants were exposed to straight MWF, and no significant differences were observed, although exposures were higher in both of the case groups than among the controls. Synthetic MWF exposure was the least common, and the controls had higher exposure (1.7 mg/m³-years) than the cases of biliary tract cancer (0.5 mg/m³-years). In terms of components, most of the workers were exposed to iron, but exposures to aluminum and chlorinated paraffins were more limited (table 2).

Stratified exposure response models for liver cancer and biliary tract cancer are presented in table 3. No associations were found with liver cancer and fluids or components (table 3). A possible association between biliary tract cancer and straight MWF was suggested by the increasing odds ratio (OR), up to 2.65 in the highest exposure category (the P-value for the test of linear trend being 0.004) although the confidence intervals were wide. Elevated risk was also suggested for any exposure to chlorinated paraffins (OR 3.9, 95% CI 0.9–17.0), although again the confidence interval was wide. Positive confounding was found between straight MWF and chlorinated paraffins. When these two variables were included in the same model, the risk estimates for both diminished. The odds ratio for straight MWF in the highest exposure group decreased from 2.7 to 2.3, while for chlorinated paraffins the odds ratio for any exposure decreased from 3.9 to 3.2 (P-value for the test of linear trend=0.002) (not shown).

To better understand the patterns of risk associated with exposure to straight MWF and biliary tract cancer, we then divided cumulative exposure to straight MWF into three time periods of exposure prior to the risk date. Risks were estimated for both continuous and categorical variables. The highest risks were found for exposures occurring more than 20 years prior to the risk date: OR of 1.09 (95% CI 0.97–1.22) in the models with continuous exposures (model 1, table 4), OR of 2.55 for the low-exposure group in the models with categorical exposures (model II, table 4), increasing to an OR of 6.24 (95% CI 1.62–24.16) with exposure >1 mg/m^3-years more than 20 years prior to the diagnosis.

Discussion

Our results provide limited evidence for a possible association between cancers of the biliary tract and exposure to straight MWF. A 2.5-fold risk was found for workers with cumulative exposure to straight MWF above 1 mg/m^3-years. The confidence interval for this odds ratio was fairly wide and included 1.0, but there was an increasing trend in risk with cumulative exposure. A close to fourfold risk was found (also with a wide confidence interval) for exposure to chlorinated paraffins, but this risk was based on only five exposed cases (table 3). When exposures to straight MWF were divided into 10-year time periods of exposure, the risk estimates increased to 6.24 (with an even wider confidence interval) in the high-exposure group for exposures occurring >20 years prior to the risk date (table 4).

Mineral oils, the major component of straight MWF, and chlorinated paraffins are both recognized carcinogens. Using animal studies, the Environmental Protection Agency determined that short-chain chlorinated paraffins are potential carcinogens and listed them according to the Emergency Planning and Community Right-to-Know Act (25). The International Agency for Research on Cancer (IARC) has classified untreated or mildly treated mineral oils as group 1 human carcinogens (26). These oils have significant amounts of polyaromatic hydrocarbons (PAH), which themselves are associated with carcinogenicity. Until recently, mineral oil containing MWF in the United States were formulated with oil stocks that had undergone little (only hydrofinishing) or no treatment to reduce the polyaromatic content of the oil base stock. Severe hydrotreatment or solvent refinement can remove most of the PAH content. And many manufacturers voluntarily switched to these processes after 1985 when the Occupational Safety and Health Administration (OSHA) required only oils with mild hydrotreatment or mild solvent refining to be listed as carcinogenic on material safety data sheets (27). Manufacturers also switched to other linear hydrochlorocarbons as alternative sources for chlorinated paraffins to avoid the carcinogen label. Despite these trends, the production of PAH has still been shown to occur during MWF use (28, 29). The greatest risk for biliary tract cancer was determined with exposure to straight MWF occurring >20 years prior to the risk age. This finding suggests a relatively long latency period between straight MWF exposure and cancer development. In addition, straight MWF in this earlier time period was more likely to have a higher PAH content.

Other registry-based studies have found an elevated risk of biliary tract cancer in occupations in which potential exposures to mineral oils or PAH occur. Krain (13) found an excess risk for biliary tract cancer among California automotive workers and also an excess risk for gallbladder cancer among California workers in the metal fabricating industries. Malker (30) found an elevated risk for gallbladder cancer among men employed in Swedish petroleum refining [standardized incidence ratio (SIR) 3.8, $P<0.05$] and sheet and plate metal fabrication (SIR 2.3, $P<0.05$).

Nonoccupational risk factors for biliary tract cancer are better understood for gallbladder cancer than for other biliary tract cancers. A history of gallstones is the most well established risk factor for gallbladder cancer. Females have the highest risk for both gallbladder cancer and gallstones (2, 3, 31). In this cohort, 12 of the 24 cases of biliary tract cancer were gallbladder in origin, but only 3 occurred among females. Dietary factors such as an excess body mass index or increased sugar intake have been found to increase the risk of the various biliary tract cancers (31, 32). The association between smoking and biliary tract cancer is inconsistent (10, 31, 33). Both heavy alcohol consumption and previous

Table 4. Adjusted odds ratios (OR) for biliary tract cancer from model 1 with continuous exposure to straight metalworking fluids (MWF) and model 2 with categorical exposure to straight MWF, each for the total cumulative exposure and the time periods of exposure.

Straight MWF	Total cumulative exposure (no lag)		Time periods of exposure (years prior to diagnosis)					
			>0 to 10 years		>10 to 20 years		> 20 years	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Model 1 (continuous; mg/m^3-years)	1.03	1.00–1.06	NA	..	0.86	0.60–1.24	1.09	0.97–1.22
Model 2 (categorical)								
0 mg/m^3-years	1.00	..	1.00	..	1.00	..	1.00	..
0–1 mg/m^3-years	1.21	0.42–3.51	1.42	0.09–21.41	0.22	0.03–1.77	2.55	0.74–8.83
>1 mg/m^3-years	2.65	0.93–7.54	NA	..	0.64	0.10–4.14	6.24	1.62–24.16

infection with hepatitis B or C have been associated with liver cancer (3).

Our positive findings may have been due to confounding, if, for example, smoking or obesity were more common among the exposed workers. On the other hand, our negative findings for liver cancer may have been due to higher alcohol consumption or a higher rate of previous infection with hepatitis B or C among the unexposed workers.

Cases previously identified from death certificates but not found in the Michigan cancer registries were excluded from this analysis. This exclusion included cases that died out of state or before the start-up of the registries. The exposures of these excluded out-of-state cases were probably similar to those of workers diagnosed in Michigan. However, the cases that died prior to the registry start-up would have been employed during the earlier time period when exposure to MWF was highest and this occurence may have biased the results to the null.

Our findings may also have been due to chance because the number of cases was small, particularly after the subdivision of the hepatobiliary cancers into liver and biliary tract cancer. The width of the confidence intervals for the risk estimates underscores this uncertainty. However, the results do have biological plausibility. The two major routes of excretion of systemic carcinogens are the urinary tract and the hepatobiliary system. Biliary contents are both stored and concentrated in the tract prior to their release into the large intestine (34). Thus the longer residence time of carcinogens in the biliary system may explain the difference in risk for the two cancers.

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