American Journal of Industrial Medicine 18:19–24 (1990)

Liver and Biliary Tract Cancer Among Chemical Workers

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A recent cohort mortality study of male, hourly wage employees of a large Michigan chemical production and research facility had found a greater than expected number of deaths coded to liver and biliary tract cancer. In response, an additional investigation was then undertaken of the 44 liver and biliary tract cancer deaths observed between 1940 and 1982. A random sample (N = 1,888) of subjects was selected from the total cohort (N = 21,437) to serve as referents. Company work history records were used to classify cases and referents by work area assignment and potential for exposure to 11 selected chemical agents which have been shown to produce cancer of the liver or biliary passages in experimental animals. Statistically significant associations in both positive and negative directions were found for several work areas within the facility. A suggestive association was found for vinyl chloride monomer, based on five cases with presumed exposure.

Key words: carbon tetrachloride, epidemiology, methylene chloride, retrospective studies, vinyl chloride

INTRODUCTION

A recently conducted cohort study of the more than 37,000 male employees from Dow Chemical's Midland/Bay City, Michigan, production, research, and headquarters units showed more deaths than expected from cancer of the liver and biliary passages (SMR = 140, 95% CI = 99–191) among hourly workers [Bond et al., 1987]. No data relating to personal or occupational exposures were collected as a part of the original study. This was by design since it was not feasible to collect such comprehensive information on all workers. This paper describes the results of a follow-up investigation which used a hybrid study design involving a modification of the traditional case-control method [Kupper et al., 1975].

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Accepted for publication February 7, 1990.

METHODS AND MATERIALS

Death certificates of all male, hourly employees who died during 1940–1982 (N = 6,259) were reviewed for a statement of primary liver cancer, cancer of the liver not specified as primary or secondary, or cancer of the gallbladder or bile ducts (ICDA-8 codes 155–156 and 197.8) mentioned anywhere on the document. This identified 44 cases, of which 11 were coded to primary liver cancer, 14 to cancer of gallbladder or bile ducts, and the remaining 19 to cancer of the liver not specified as primary or secondary. From the cohort of male, hourly employees (N = 21,437) who composed the original study population [Bond et al., 1987], a random sample (N = 1,888) was chosen to serve as referents.

Company work history records were used to classify employee exposures by work area assignment [Bond et al., 1985, 1986] as well as by potential for exposure to 11 chemical agents chosen because they had been shown to produce cancer of the liver or biliary passages under experimental conditions in animals [Chu et al., 1984; Haseman et al., 1984; NTP, 1985; Wilbourn et al., 1986]. Visits to the Medical Department by the cases were reviewed by a nurse co-investigator (E.A.M.) to ascertain a history of excessive alcohol use or hepatitis, as they are established risk factors for primary liver cancer [Falk, 1982]. This exercise was of limited usefulness, however, owing to: 1) the unavailability of medical records for those subjects who terminated their employment prior to 1947 (N = 24); and 2) a lack of information concerning any post-employment illnesses among the workers.

Risk ratios were computed adjusted for birthyear by using the Mantel-Haenszel (1959) procedure. Analyses which additionally controlled for period of hire showed similar results to those which controlled only for birthyear and are not presented. Likewise, analyses of the primary liver cancers separate from the gall bladder/bile duct cancers did not reveal additional information and are not shown. Ninety-five per cent test-based confidence intervals were calculated about the risk ratio estimates [Miettinen, 1976].

RESULTS

Analyses by work area assignments (Table I) showed the cases were significantly less likely to have held assignments in electrochemicals or organic chemical production, but were more likely to have held assignments in office maintenance (RR = 3.6; 95% CI = 1.4–9.1). A positive association with assignment to polyvinyl-polyvinylidene chloride production did not reach statistical significance (RR = 2.0; 95% CI = 0.9–4.6).

There were no statistically significant trends apparent when analyses were made of duration of assignment within work areas; however, the odds ratio for an assignment of five or more years to polyvinyl-polyvinylidene chloride production was 3.7 (95% CI = 0.[illegible] 4.6) based on the contribution of two cases.

Assignment to polyvinyl-polyvinylidene chloride production areas was explored further in Figure 1 via a plot of the "attributable fraction" [Goldsmith et al., 1980] for each year during the period 1940–1980. The peak "attributable fraction" occurred in 1952, a year in which four of the seven cases assigned to these areas were all employed, no two in the same plant, however.

None of the chemical agent comparisons revealed statistically significant dif-

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TABLE I. Age-Adjusted Risk Ratios for Analyses by Major and Minor Work Areas: Study of Liver and Biliary Tract Cancer Among Chemical Workers, Midland, Michigan, 1940–1982*

Major/minor work areas	Exposure frequencies (%) Cases (N = 44)	Referents (N = 1,888)	RR	95% CI
Administration	0.0	5.8	—	0.0–1.5
Manufacturing	68.2	75.7	0.7	0.4–1.3
Agricultural chemicals	9.1	26.2	0.4	0.1–1.0
Herbicides	6.8	17.1	0.5	0.2–1.6
Insecticides	4.6	9.7	0.6	0.1–2.4
Inorganic chemicals	47.7	40.0	1.1	0.6–2.0
Ammonia	0.0	1.0	—	0.0–8.4
Brine	6.8	4.6	0.9	0.3–3.0
Brominated products	4.6	5.9	0.9	0.2–3.7
Calcium/magnesium	9.1	12.5	0.7	0.2–1.8
Caustic	4.6	1.9	2.1	0.5–9.5
Cellulose products	2.3	7.6	0.4	0.1–2.5
Electrochemicals	0.0	10.2	—	0.0–0.8
Metal fabrication	22.7	16.8	1.1	0.6–2.2
Organic chemicals	36.4	56.8	0.5	0.3–0.9
Acrylamide	0.0	2.1	—	0.0–4.0
Alkyl benzenes	0.0	3.9	—	0.0–2.2
Chlorinated benzenes	0.0	3.6	—	0.0–2.3
Dyes	6.8	6.1	0.7	0.2–2.3
Fabricated plastics	6.8	16.5	0.6	0.2–1.9
Glycols	0.0	1.8	—	0.0–4.7
Halogenated hydrocarbons	4.6	7.7	0.4	0.1–1.6
Ion exchange resins	2.3	2.0	1.2	0.2–8.7
Latex	2.3	2.7	0.8	0.1–6.2
Olefins	4.6	2.5	1.5	0.3–6.7
Phenol derivatives	6.8	13.0	0.4	0.1–1.4
Polystyrene	6.8	15.0	0.5	0.1–2.0
Polyvinyl-polyvinylidene chloride	15.9	10.1	2.0	0.9–4.6
Unknown manufacturing	0.0	1.0	—	0.0–8.4
Research	15.9	22.8	0.8	0.3–1.8
Service	65.9	59.8	1.1	0.6–2.0
Animal handling	0.0	0.6	—	0.0–14.0
Boiler shop	4.6	3.4	1.0	0.2–4.1
Construction	13.6	13.6	0.7	0.3–1.7
Electric shop	2.3	2.8	0.9	0.1–6.4
Engineering	2.3	1.6	1.7	0.2–12.5
Garage	0.0	2.5	—	0.0–3.4
Lead shop	0.0	0.3	—	0.0–28.0
Lubrication	0.0	0.4	—	0.0–21.0
Machine shop	4.6	4.2	0.9	0.2–3.5
Maintenance	4.6	8.6	0.4	0.1–1.6
Material handling	11.4	8.1	1.4	0.5–3.7
Office maintenance	11.4	3.3	3.6	1.4–9.1
Paint shop	4.6	7.9	0.6	0.1–2.5
Pipe shop	9.1	10.3	0.8	0.3–2.3
Plant protection	9.1	5.6	1.1	0.4–3.2
Power	2.3	7.1	0.2	0.0–1.3
Road and yard mtc.	4.6	2.0	2.2	0.5–9.6
Shops-steel & instrument	6.9	2.3	2.2	0.7–7.5
Waste management	0.0	1.2	—	0.0–7.0
Well services	0.0	0.1	—	0.0–83.8

*Workers may have been assigned to more than one work area during their employment and thus may be counted more than once in the table.

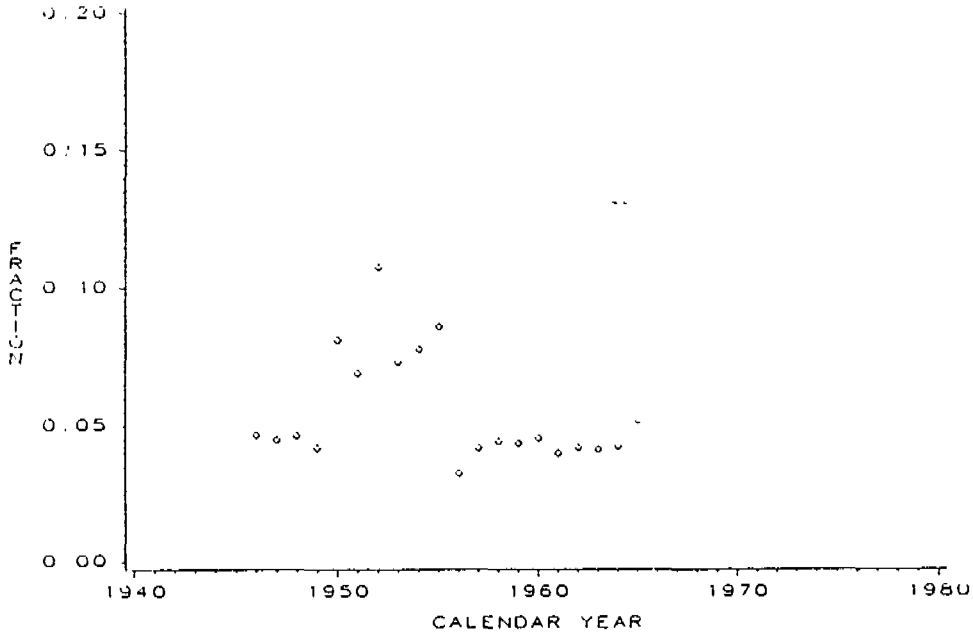

Fig. 1. Study of liver and biliary tract cancer. Attributable fraction for assignment to polyvinyl-polyvinylidene chloride areas in each year during 1940–1980.

ferences (Table II). The highest risk ratio (RR = 2.2; 95% CI = 0.9–5.8) was for presumed exposure to vinyl chloride based on the contribution of five cases. There were no statistically significant trends for analysis by duration of exposure to any of the 11 agents, although in many instances there were too few exposed cases to permit meaningful conclusions. Likewise, there were no statistically significant trends apparent when analyses were made by estimated dose of exposure.

DISCUSSION

The present investigation revealed a statistically significant positive association with assignment to office maintenance, and some marginal associations with polyvinyl-polyvinylidene chloride production. The association with an assignment in office maintenance is curious, since this type of work is not generally considered hazardous. In fact, it was a common practice to assign to that department any workers who were not considered medically fit to work in more strenuous jobs. Company medical records were available to review for four of the five cases assigned to office maintenance, and revealed that two of the men had been hospitalized for chronic alcoholism, suggesting that this finding may have resulted from confounding.

High levels of vinyl chloride exposure have produced a specific hazard of angiosarcoma of the liver in some work forces [Doll, 1988]. In the present study, five of the seven cases of liver and biliary tract cancer who held assignments in the polyvinyl-polyvinylidene work area were considered to have had the opportunity for exposure to vinyl chloride monomer. There was no evidence that any of the five cases experienced angiosarcoma; however, pathology reports and/or medical records were

TABLE II. Age-Adjusted Risk Ratios for Analyses by Selected Chemical Agent Exposures: Study of Liver and Biliary Tract Cancer Among Chemical Workers, Midland, Michigan, 1940–1982*

	Exposure frequencies (%)			
Agent	Cases (N = 44)	Referents (N = 1,888)	RR	95% CI
Carbon tetrachloride	11.4	20.0	0.5	0.2–1.4
Chlorodibenzo-(p)-dioxins	2.3	9.1	0.2	0.4–1.4
Chloroform	4.6	6.7	0.6	0.2–2.7
Ethylene dibromide	2.3	7.3	0.4	0.1–3.0
Ethylene dichloride	6.8	14.6	0.4	0.1–1.3
Methylene chloride	4.6	8.9	0.8	0.2–3.6
Perchloroethylene	13.6	11.3	1.8	0.8–4.3
Polychlorinated biphenyls	0.0	1.2	—	0.0–7.0
1,1,2-Trichloroethane	0.0	0.5	—	0.0–16.8
2,4,6-Trichlorophenol	0.0	0.9	—	0.0–9.3
Vinyl chloride	11.4	7.8	2.2	0.9–5.8

*Workers may have been exposed to more than one agent during their employment and thus may be counted more than once in the table.

available to confirm the diagnosis for only two of them. Table III presents some descriptive information concerning these cases. By virtue of the time period in which they worked and the nature of their jobs, each of the men was considered to have had the opportunity for high levels of exposure to vinyl chloride monomer, with peak exposures probably exceeding 1,000 ppm. Although two of the cases had spent more than 20 years each in areas of potential vinyl chloride monomer exposure, the other three had very brief exposures on the order of one to several months.

Of interest, none of the other chemical agents suspected a priori as potential risk factors was shown to be statistically significantly associated with liver or biliary tract cancer. It may be that some of the agents are weak carcinogens, but this study could not explore that hypothesis. An examination of the upper limits of the 95% confidence intervals about the risk ratios presented in Table II shows that the study apparently had sufficient power to rule-out modest increases in risk for several chemicals (i.e., carbon tetrachloride and ethylene dichloride), but only relatively large increases in risk could be excluded for others.

Some misclassification of exposure may have occurred; however, the availability of industrial hygiene data from the distant past for many of the plants at this production site should have reduced this possibility considerably. If misclassification did occur, and was non-differential, the tendency would be to diminish the strength of the associations.

ACKNOWLEDGMENTS

The authors gratefully acknowledge technical assistance from Tom Bradley, Wendy Dahar, Mike Dupuis, Stan Gorgacz, Harold Hoyle, Bruce Houtman, Carl Mueller, Gordon Roush, Dan Schmidt, Belinda Scortichini, Tricia Stirrett, and Mike Strieter. They also thank Diana Diamond for help with preparation of the manuscript.

TABLE III. Descriptive Data on Five Cases Presumed to Have Been Exposed to Vinyl Chloride Monomer: Study of Liver and Biliary Tract Cancer Among Chemical Workers, Midland, Michigan, 1940–1982

Case no.	Year first exposed	Year last exposed	Duration of exposure (yr: mo)	Year of death	Job classification	Best diagnosis (source)[a]
1	1943	1943	0; <1	1960	Assistant operator	Adenocarcinoma of common bile duct (DC)
2	1943	1943	0; 3	1964	Janitor	Carcinoma of liver (DC)
3	1950	1970	20; 0	1976	Operator	Hepatocellular carcinoma (PR)
4	1946	1967	20; 8	1980	Operator	Intrahepatic bile duct cancer (MR and PR)
5	1952	1952	0; 2	1972	Handyman/ packager	Cancer of liver (DC)

[a]DC = death certificate, MR = medical record, PR = pathology report.

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