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Primary liver cancer and exposure to solvents*

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Summary. A case-referent study was done on the possible association between primary liver cancer (ICD 155.0) and occupational exposures. In all, 374 cases were reported to the Finnish Cancer Registry in 1979 and 1980. After the exclusion of wrong diagnoses, nonrespondents and cases for whom the primary site was uncertain, 126 cases (64 men and 62 women) remained. Each case was matched for sex, age (± 5 years), vital status and geographical district with two cases of coronary infarction selected from hospital records without any knowledge of occupational history. Nonrespondence (38%) reduced the number to 175 referents (82 men and 92 women). A questionnaire on former employment and tasks was mailed to living subjects (6 + 6) and to the next of kin of deceased patients. An industrial hygienist then evaluated the exposure history blindly and, whenever necessary, contacted the workplace or the next of kin for more details. Only exposures commencing 10 years or more before diagnosis were considered. Altogether six female cases but no referent had been exposed to solvents. One had been exposed to chlorinated solvents in dry cleaning and two others had used both carbon tetrachloride and aromatic and aliphatic solvents. Three cases had been exposed to mixtures of aliphatic and aromatic solvents, but not chlorinated hydrocarbons. By contrast, the men did not differ with regard to exposure to solvents. Two cases and five referents were classified as having been exposed to solvent mixtures. The present results are hypothesis generating only, and the excess solvent exposure found for women must be confirmed in other studies before any conclusions can be drawn.

Key words: Case-referent study – Epidemiology – Organic solvents

Introduction

Although several chlorinated hydrocarbon solvents have had carcinogenic properties in animal experiments (IARC 1982), no convincing epidemiological evi-

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dence of human carcinogenicity has yet been published. The International Agency for Research on Cancer has recently classified the evidence available for the animal carcinogens carbon tetrachloride, chloroform, tetrachloroethylene and trichloroethylene as being inadequate to indicate human carcinogenicity (IARC 1982). Of the aromatic hydrocarbons, only benzene is considered a human carcinogen. Styrene has been suspected of carcinogenicity on the basis of short-term tests; however, no adequate epidemiological data exist, and the evidence provided from animal experiments is limited (IARC 1982).

The incidence of primary liver cancer has increased in several countries during the last decase. For example, in Finland the number of new cases reported to the Cancer Registry was 87 in 1970 but as high as 196 in 1979 (Finnish Cancer Registry 1982). In view of the hepatotoxicity and animal carcinogenicity of several chlorinated hydrocarbon solvents, we thought it worthwhile to examine the possible associations between primary liver cancer and exposure to organic solvents. When we began our study in 1978, we knew of no similar study on liver cancer, but in 1983 the results of a case-referent study done in the United States and addressing the same problem were published (Stemhagen et al. 1983). The American study revealed statistical associations between liver cancer and some occupational categories, e.g. work in laundries and dry cleaning establishments, which involve exposure to chlorinated solvents.

Material and methods

In all, 374 cases of primary liver cancer (ICD 155.0) were reported to the Finnish Cancer Registry in 1979 and 1980. After the cases had been identified, the hospital records were borrowed and consent to contact either the patient or his/her relatives was obtained from the chief medical officer of the hospital. At the same time the correctness of the diagnoses was preliminarily checked from the hospital records. This preliminary procedure resulted in a considerable loss of material. In nine cases, the hospital could not be located at all on the basis of the report to the Cancer Registry. The hospital refused patient contact in 38 cases, and the diagnosis was incorrect (usually metastatic tumor) in 83 cases. This left us with 244 cases. Their vital status was then checked and a questionnaire was mailed either to the patient or to the next of kin. Three deceased cases had no relatives, and in 79 instances the patient or the next of kin did not reply even though a reminder was sent. In all, 162 questionnaires (67%) were returned. One of us (U.A.) checked the diagnoses once more from hospital records and the original biopsy or autopsy slides. This check led to the discarding of an additional 36 cases whose tumors were metastatic rather than primary liver cancers. The final material was thus reduced to 126 cases, 64 of them men and 62 women. Table 1 shows how the diagnoses had

Table 1. Verification of diagnoses of liver cancer

	Men		Women	
	n	(%)	*n*	(%)
Thin needle biopsy	6	9.4	3	4.8
Coarse needle biopsy	10	15.6	7	11.3
Laparatomy biopsy	19	29.7	20	32.3
Autopsy specimen	29	45.3	32	51.6
Total	64	100.0	62	100.0

Table 2. Distribution of histological diagnoses

	Men		Women	
	n	(%)	*n*	(%)
1. Hepatocellular carcinoma	48	75.0	34	54.8
2. Cholangiocarcinoma	13	20.3	18	29.0
3. Anaplastic carcinoma	1	1.6	2	3.2
4. Angiosarcoma	–	–	1	1.6
5. Classification uncertain (either 1 or 2)	2	3.1	7	11.3
Total	64	100.0	62	100.0

Table 3. Age distribution of the cases and the referents

Age group	Males		Females	
	Cases	Referents	Cases	Referents
20-24	2	2	–	–
25-29	1	–	–	–
30-34	–	1	1	2
35-39	–	–	1	–
40-44	–	–	–	2
45-49	1	–	1	–
50-54	2	5	2	2
55-59	6	6	4	3
60-64	7	18	8	7
65-69	24	27	10	20
70-74	12	14	13	26
75-79	5	3	14	16
80-84	1	4	4	7
85-89	3	2	3	6
90-94	–	–	1	1
20-94	64	82	62	92

been verified and Table 2 the distribution of histological diagnoses. Table 3 shows the age distribution of the material. The mean age (± SD) of the male cases was 65 years (± 12) and that of the female cases 70 years (± 11).

Each of the 162 cases whose questionnaire had been returned was matched for sex, vital status, central hospital district, and age (± 5 years) with two referents whose diagnosis was coronary infarction (ICD 410) and in whose death certificates cancer was not mentioned. Living referents were selected from the hospital registers and dead referents from the autopsy material of the hospital in question. In 22 instances no relatives could be located. The questionnaire was mailed to the remaining 307 referents or their next of kin. Altogether 190 questionnaires (62%) were returned. It turned out that eight referents had also had cancer and the replies of another eight referents were incomplete. When the data for these referents

Respondent	Cases		Referents	
	n	(%)	*n*	(%)
Patient	6	4.8	12	6.9
Spouse	65	51.6	95	54.6
Child/Parent	39	31.0	40	23.0
Sibling	7	5.6	20	11.5
Others	9	7.1	7	4.0
Total	126	100	174	100

Table 4. Response to the questionnaire

	Cases		Referents	
	n	(%)	*n*	(%)
First	100	79.4	152	87.4
Second	26	20.6	22	12.6
Total	126	100	174	100

Table 5. Response to first or second query

were omitted, the final material had shrunk to 174 referents, 82 men and 92 women (Table 3). The mean age of the male referents was 65 years (± 11) and that of the female referents 71 years (± 11).

The questionnaire comprised questions on dietary habits, the use of alcohol and tobacco, previous gastrointestinal diseases, the use of medicines (e.g. steroid hormones), leisure activities, and occupational history. In this context only occupational exposures will be reported, but the somewhat surprising finding that there were rather slight differences in drinking habits between the cases and the referents deserves mentioning. For example, 85% of the female cases (or their next of kin) and 82% of the female referents (or their next of kin) reported that they never used large quantities (feeling of drunkenness) of alcohol. Table 4 shows who answered the questionnaires and Table 5 the proportion of cases and referents responding to the first and second letters.

An industrial hygienist (R.R.) went through each questionnaire without knowing whether a case or a referent was concerned. The occupations, tasks or firms where exposures to chemicals could have occurred were further checked by telephone contact with either the workplace in question or the next of kin. To maintain blinding, the hygienist was not allowed to ask questions that could reveal the patient's diagnosis. Exposure was classified according to duration, calendar time and estimated intensity. No exposure that occurred ten years or less before diagnosis was taken into account in order to allow for a latency period. At least one year of exposure was required, and "moderate" exposure, estimated to be at least half of the American Conference of Governmental Industrial Hygienists' threshold limit values (TLV) as of 1980, but not above them, and "heavy" (above the TLV) exposure were combined in the dichotomous data analysis. The exposure classification, of course, had to be based on estimates, as many exposures had taken place decades ago. For the same reason no hygienic measurements were considered meaningful.

Results

Altogether eight cases had had either heavy (2) or moderate (6) exposure to solvents. Of the referents, 5 had been exposed, 1 heavily and 4 moderately. These

Table 6. Histological diagnosis and exposure data for the 6 female cases of liver cancer

Case no.	Histology	Period	Duration (years)	Intensity	Type
1.	C	1964–1968	4	Moderate	Chlorinated hydrocarbons in a laundry
2.	A	1959–1972	11 before 1970	Moderate	Solvent mixtures in carpentry, glues, lacquers, paints
3.	H	1933–1969	15	Heavy	Exposed to thinners in spray painting, possibly also to trichloroethylene
4.	H	1935–1952	17	Moderate	Mixture of solvents in spray painting
5.	H	1927–1971	44	Moderate	Variety of hydrocarbon mixtures, toluene, and possibly carbon tetrachloride and benzene in a shoe factory
6.	H	1939–1972	33	Heavy	Same as case 5, but not the same factory, exposure to carbon tetrachloride certain

A = Angiosarcoma
C = Cholangiocarcinoma
H = Hepatocellular carcinoma

data yielded an odds ratio of 2.3 (95% confidence limits 0.8 to 7.0). However, the excess of exposure among the cases was confined entirely to the women, among whom 6 cases, but not a single referent, had been exposed. The exact Fisher's two sided *p*-value for the female cases versus their referents was 0.007. The odds ratio for the two male cases and the five male referents was 0.5, a result not significantly different from unity. No other frequency of occupational exposure differed between the cases and the referents, but this finding is not informative because of the low number of exposed cases (1–3) in each exposure category.

Closer scrutiny of the exposed female cases showed that one had been exposed to chlorinated hydrocarbon solvents in dry cleaning, and two others had used both carbon tetrachloride and aromatic and aliphatic solvents. Three cases had been exposed to mixtures of aliphatic and aromatic solvents, but not to chlorinated hydrocarbons. Table 6 summarizes the pertinent data on the exposure of the 6 female cases. Also the 2 male cases had beeen exposed for several decades, but since 5 male referents showed similar exposure patterns, no significance can be ascribed to this finding.

Altogether 28 cases (20 men, 8 women) had verified cirrhosis of the liver, and an additional 5 men and 2 women had a suspicion of cirrhosis. Of the verified cases with cirrhosis, 5 were ascribed to alcohol and one to biliary etiology, while the rest were of unknown etiology. None of the solvent-exposed cases had cirrhosis.

Discussion

The main finding of this study was a statistical association between primary liver cancer and exposure to solvents among women, an association that was absent for men. This association must be interpreted with great caution because of the inconsistency and because there are very few earlier epidemiological studies to support the causality of such an association. In fact, only three prior studies have suggested an occupational etiology for primary liver cancer. Blair et al. (1979) found 4 cases of liver cancer against 1.7 expected in a cohort of laundry and dry cleaning workers, but the result was not statistically significant. Houten and Sonnesso (1980), in a clinical study without control groups, suspected an association between liver cancer and work in the non-electrical machinery and primary metal industries. A recent case-referent study by Stemhagen et al. (1983) gave an odds ratio of 2.5 for laundering, cleaning, and other garment services. Their finding was significant at the 5% level. Other significantly elevated odds ratios were found for farming occupations, gasoline service station work and restaurant work. Inconclusive or negative studies have also been published (e.g. Malek et al. 1979; Tola et al. 1980; Katz and Jowett 1981). Of all the solvents scrutinized by the International Agency for Research on Cancer, only benzene has been listed as a human carcinogen due to the lack of reliable data (IARC 1982).

The identification of human carcinogens by epidemiological methods is subject to several major difficulties (Hernberg 1982). Because primary liver cancer is a rare tumor, cohort studies are usually not powerful enough to detect an excess risk of moderate magnitude. Case-referent studies are hampered by difficulties in obtaining detailed and valid exposure data, by confounding due to multiple exposures, by recall bias and by errors in classification. In this study we tried to sharpen and validate the exposure history by including an experienced industrial hygienist in our team. This inclusion made it possible to rely rather little on the exposure data given by the patient or the next of kin, who in general reported only the name of the workplace and the patient's task and occupational title. Requests for additional details, especially from the employer whenever possible, or the application of informed judgment (e.g. thousands of workplaces have been surveyed by hygienists from our institute during the last two decades), considerably improved the reliability of the data on exposure. The fact that the hygienist was never aware of the case or referent status of the patient should be sufficient to eliminate observer bias. A problem which in spite of this could not be helped was the multiple exposure pattern of most patients. Histological rechecking of the diagnoses—without any knowledge of exposure status—should also have increased the sensitivity of the study. In fact, both in our study and in that published by Stemhagen et al. (1983), this procedure reduced the number of cases by more than half. Without such scrutiny, more than 50% of the "case"-series would have been misclassified.

Confounding non-occupational and occupational exposures must also be considered. No asymmetry between occupational exposures to other toxic agents was found. We also could not detect any significant difference in alcohol consumption between cases and referents, and none of the exposed cases had cirrhosis. The old age distribution of the female cases renders possible con-

founding by steroid hormone therapy, especially anticonceptive drugs, highly unlikely. A more detailed report dealing with nonoccupational factors will be published elsewhere (Asikainen, in preparation).

If these considerations are thought sufficient to exclude any major bias, the question remains as to how the association between primary liver cancer and exposure to solvents can be explained. Despite the low p-value, a chance association is always possible. Another explanation, of course, would be that the association indeed is causal, and that, for some reason, women are more vulnerable than men. The female liver, for example, is known to be more sensitive to the toxic effects of ethyl alcohol (e.g. Wyngaarden and Smith 1982). Could differences in sensitivity explain the sex difference found in our study? This and other unanswered questions render the interpretation of our findings very difficult, and at most they can be considered as hypothesis generating. A new study on another series is needed to test this hypothesis.

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