

Angiosarcoma of the Liver: An Epidemiologic Survey^{1,2}

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ABSTRACT—Diagnosed from 1970 through 1975, the annual incidence rate for angiosarcoma of the liver among residents of New York State (excluding New York City) was 0.25 per million. A case-control study indicated that direct exposure to arsenic, vinyl chloride (VC), and thorium dioxide was a significantly important factor in the etiology of this disorder ($P < 0.02$). Direct exposure to these chemicals could not be demonstrated for 19 (73%) of the 26 study patients. The fact that 5 of these patients lived nearer to VC fabrication or polymerization plants than did their matched controls lent some support to the hypothesis that indirect modes of exposure, not specifically related to occupation, might be important in the etiology of this disorder. — *J Natl Cancer Inst* 59: 1383-1385, 1977.

ASL, a rare vascular tumor (1), has been associated with exposure to ThO_2 (2, 3), As [used both in pesticides (4, 5) and as a drug (Fowler's solution—potassium arsenite) (6-8)], and most recently, VC (9-13). Since most studies have centered around specific occupational groups, little is known about the actual incidence of ASL and the proportion of cases that can be attributed to exposure to the above chemicals. This report evaluates each of these issues in a geographic-based population.

METHODS

Incidence study.—All residents of New York State (excluding New York City),⁸ who had ASL diagnosed from 1970 through 1975 and reported to the Tumor Registry of the Cancer Control Bureau, New York State Department of Health, were used in the incidence study. This 6-year period was selected because during this time the Registry established a mechanism to improve reporting of cases through periodic examinations of the percent of cases accessioned into the State Cancer Registry by death certificate only from specific regions and by an ongoing survey of hospital records. In addition, as a check on ascertainment, a list of all reported cases was compared with a list of patients who developed ASL in the same study area and time period and were derived from: 1) an ongoing survey of all pathologists, epidemiologists, cancer-referral centers, and tumor registries in the United States conducted by the Center for Disease Control, Atlanta, Georgia, and 2) case records on VC disease obtained from the Bureau of Industrial Hygiene, New York State Department of Labor, Albany. An overall annual incidence rate for the 6-year period was calculated with the use of the 1970 census population. Male:female ratios for all patients were obtained and analyzed.

Case-control study.—All cases of ASL reported to the Tumor Registry among New York State residents 18 years of age or older and diagnosed from 1958 through 1975 were studied. For each patient, 1 matched control with an internal malignant tumor other than primary liver cancer was selected from the same registry by means of the following

criteria: same 5-year age group at diagnosis, race, sex, county of residence (when possible, the control was selected from the same minor civil division, as defined by the U.S. Bureau of the Census, Washington, D.C. or the one of most similar population density and size within the county), and alive or dead status. When more than 1 individual matched the above criteria, a table of random numbers was used to select a control. Using a prepared questionnaire, field investigators obtained information concerning various exposures (by occupations or hobbies) to hepatotoxic chemicals including VC, As, and ThO_2 for study patients and their matched controls. In addition, medical, familial, residential, and occupational histories of both groups were studied. Residential histories of all patients and controls up to the time of diagnosis were plotted on maps, indicating the geographic locations of all industrial complexes using VC and/or As. Inquiries were also made with the New York State Department of Environmental Conservation, Albany, concerning the ambient emissions of these chemicals associated with all pertinent companies. Additional documentation of exposure was obtained from medical records, industrial reports, and on-site visits to residences of patients and controls and the industrial complexes with which they were associated.

For statistical purposes, each subject and his/her matched control were dichotomized according to direct exposure (worked with or ingested VC, arsenicals, or ThO_2). The frequencies of the two cells that show dissimilar exposure histories were tested with the use of the binomial ($P = Q = \frac{1}{2}$) (14) in which Q equals probability of failures. All instances in which direct exposure to at least one of the above agents could not be documented for either a patient or control were excluded from statistical analyses.

The histology slides for all patients included in the incidence and case-control studies were reassessed and

ABBREVIATIONS USED: ASL = angiosarcoma of the liver; ThO_2 = thorium dioxide; As = arsenic; VC = vinyl chloride.

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⁸ New York City was excluded from the incidence study because reporting from this area was not required until 1975.

diagnosed as ASL by our panel of pathologists (Dr. J. N. P. Davies, Dr. M. Bishop) or by Dr. L. Thomas (National Cancer Institute, National Institutes of Health, Bethesda, Md.) and by Dr. H. Popper, (Mount Sinai Hospital, New York, N.Y.). Autopsy material on 12 patients in the incidence study and on 19 in the case-control study was also examined.

RESULTS

Incidence Study

All 16 study patients with histologically confirmed ASL included in the incidence study were found in the Tumor Registry of the Cancer Control Bureau, when they were compared with lists of patients from the other two sources. The annual incidence rate for these patients (8 males and 8 females), whose ASL was diagnosed from 1970 through 1975, was 0.25 per million. The median age of all patients was 51 years (males, 61.5 yr; females, 38 yr), with a range from 4 months to 77 years; the male:female ratio was 1:1. All the males were over 40 years of age, whereas half the females were under 40 years of age. Of the study patients, 14 were Caucasian; 1 was Oriental; and 1, Negro.

Case-Control Study

In the study area from 1958 to 1975, 27 patients with confirmed ASL were identified in the Tumor Registry. One patient, a 65-year-old male Caucasian with a documented history of chronic exposure to As pesticides, was excluded because histologic reassessment suggested a diagnosis of pericytoma of the liver. Table 1 summarizes the demographic data and occupational and possible residential exposure histories of the 26 patients in this study. Seven patients (#1-7) had documented exposure to VC, As, or ThO₂ for 16-60 years prior to diagnosis. There were 6 pairs of patients who were exposed and controls who were not exposed; however, no patients or controls had reverse exposure ($P < 0.02$).

Statistical analysis was limited to patients with documented direct exposure; however, for 6-62 years before diagnosis of their disease, 5 patients (#8-12) lived in the industrialized areas no more than 4,500 feet from a fabrication or polymerization factories (table 1). Of importance is the fact that the ambient emission of VC monomer for the factory located approximately 1,700 feet from the residence of patient #10 were as high as 85,000

TABLE 1.—Demographic data and exposure history of 26 New York State residents with ASL: 1958 through 1975

Patient No.	Age at diagnosis, yr	Race*	Sex	Yr of diagnosis	Direct exposure agent	Duration of exposure, before diagnosis, yr	Exposure history
1	64	C	♀	1973	As	≈60	Direct: Dairy farmer—frequently worked with arsenical pesticides
2	32	C	♂	1958	As	≈30	Commercial gardener—used arsenical pesticides daily
3	54	C	♂	1968	VC	18	Chemical operator—VC monomer and polymerization procedures
4	60	C	♂	1970	VC	30	Chemical operator—supervisor of VC monomer and polymerization procedures
5	40	C	♂	1951	VC	16	Chemical operator—polymerization procedure (chained reactor tank)
6	47	C	♂	1973	ThO ₂	28	Given injections of ThO ₂ —ventriculography
7	52	C	♂	1958	ThO ₂	29	Given injections of ThO ₂ —arteriography
8	45	C	♀	1970		22	Possible (estimated distance from residence to VC or PVC* factory): 4,500 feet
9	31	C	♀	1974		27	507 feet
10	62	C	♀	1973		62	1,700 feet
11	31	O	♀	1972		6	1,500 feet
12	49	C	♀	1955		15	4,500 feet
13	47	N	♂	1973			
14	45	C	♂	1974			
15	52	C	♂	1950			
16	40	C	♂	1959			
17	65	C	♂	1975			
18	55	C	♀	1971			
19	67	C	♀	1967			
20	77	C	♂	1972			
21	18	C	♀	1974			
22	45	C	♂	1970			
23	68	C	♂	1971			
24	63	C	♂	1973			
25	18	N	♀	1970			
26	60	C	♂	1969			

* C=Caucasian; N=Negro; O=Oriental.

* PVC=polyvinyl chloride.

parts per million in 1975.⁹ No pertinent exposure or residential history was obtained for 14 patients (#13-26, table 1) with ASL, despite interviews with all available relatives and employers. Although each patient and control lived within the same minor civil division, all controls resided more than 1 mile from all relevant plants. The distributions were similar for subjects and controls with regard to religion, marital status, years of education, occupation of spouse, travel history, prior liver disease, social history, exposure to drugs (including birth control pills), and familial history of cancer or liver disease. One patient (#14) and his matched control were alive and both were interviewed. In the other 25 instances, both the patient and control were deceased. In 18 instances, the spouses of both the subject and matched control were interviewed, whereas in the other 7 pairs, another first degree relative (sib, parent, or offspring) was contacted. Thus we made every effort to achieve comparable quality of information for patients and controls.

Twenty-two (84.6%) of the 26 study patients lived in nine urban counties containing 52% of the State's population. Six of the 8 patients exposed to VC (#3, 4, 5, 8, 9, and 10) resided in two urban counties, whereas both documented exposures to As occurred in rural areas.

DISCUSSION

Our results suggest that the rate for ASL in New York State, excluding New York City, might be greater than the expected annual incidence of 0.14 per million in the United States (13). Of greater importance is the observation that 19 of the 26 patients studied (73%) had no documented direct exposure to any of the three chemicals implicated in the etiology of this disorder. This finding raises the possibility that other toxic substances are involved and/or more indirect modes of exposure, not specifically related to occupation, play a major role. If one considers the first alternative, it might be important to evaluate other chemicals that cause fibrosis involving the liver and other organs and are hepatotoxic, features shared by As (6, 7), Thorotrast (3), and VC (1). Certain chlorinated hydrocarbons such as chloropropene, which are structurally similar to VC and are hepatotoxic, should also be examined. Interestingly, this and a previous study (15) suggest that alcoholism and prior liver disease do not predispose one to ASL.

Although no proved cases of ASL have been found among workers not exposed to gaseous VC (16), Block (12) suggested that this disorder results from chronic, low-level exposure to this chemical. One way of evaluating this possibility is to determine whether subjects with ASL with no pertinent occupational history lived nearer to VC factories prior to the diagnosis of the disease than did their matched controls. Although this finding is particularly true for polymerization plants, varying amounts of trapped gaseous VC are released upon heating⁹ in the fabrication process. In this study, 5 people with ASL lived nearer to polymerization (patient #10) and fabrication plants (patients #8, 9, 11, 12) than did their matched controls. In addition, all 5 patients resided in these locations for long periods (8-62 yr) prior to ASL being diagnosed. These observations lend some in-

direct support to the hypothesis that exposure outside the industrial setting is an important factor, but the few patients involved and the lack of information concerning the air levels of monomer around their residences severely limit interpretation. Accordingly, this issue must be considered unresolved at present.

Future studies should also evaluate the possibility that residents close to certain smelter-related industries and farms have an increased risk of developing ASL due to arsenical contamination of the air and soil. In a study of 10 patients with ASL in Wisconsin (17), 1 patient lived near a chemical company that made plastics and resin, and 7 patients lived on farms during their lifetimes. The marked male preponderance observed in this (17) and previous investigations (1, 11) has suggested the potential importance of occupational exposure. In our incidence study we observed a sex ratio of unity, largely due to the high frequency of ASL in young adult females. This observation, if verified, can be interpreted as being consistent with the hypothesis that the hazards associated with certain occupations extend beyond the industrial plant.

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⁹ Information obtained from the New York State Department of Environmental Conservation.