Reprinted from *Banbury Report 9: Quantification of Occupational Cancer*

VC
health
info

Hepatic Angiosarcoma Registries: Implications for Rare-tumor Studies

HENRY FALK AND PETER J. BAXTER*
Chronic Diseases Division
Centers for Disease Control
Atlanta, Georgia 30333

In this paper we describe the nationwide case-finding efforts for hepatic angiosarcoma (HAS) in the United States for the years 1964-1974 (conducted by the Centers for Disease Control [CDC]) and in the United Kingdom for the years 1963-1977 (conducted by the Employment Medical Advisory Service [EMAS]). A summary of our results is included, along with a discussion of the role of rare-tumor registries, the methodologic difficulties involved, and possible future approaches.

BACKGROUND

The stimulus for starting these studies was the discovery by Creech and Johnson in early 1974 that polyvinyl chloride (PVC) polymerization workers exposed to vinyl chloride monomer (VCM) appeared to have a markedly increased relative risk for the development of the rare HAS (Creech and Johnson 1974). The HAS registries were intended to complement the retrospective occupational cohort studies that were initiated at about the same time and to identify any other modes of exposure to VCM leading to HAS (e.g., PVC fabrication, where exposures had been much lower than in PVC polymerization plants). Furthermore, because HAS at that time was considered to have three apparent causative agents with widely differing chemical and physical properties (VCM, Thorotrast, and inorganic arsenic) (Roth 1957; Horta et al. 1974), it was thought that additional causative agents might be related to the development of HAS. Additional reasons for establishing the registries were to obtain precise incidence data, to study the pathogenesis of HAS in greater detail, and to compare the VCM-induced cases with those of unknown etiology. Underlying our thinking for studying this marker tumor was the concern that other illnesses

*On leave of absence from: Health and Safety Executive, Employment Advisory Service, London NW1 5DT, England

(such as other tumor types and nonmalignant hepatic disease) were probably much more common than HAS in populations exposed to these causative agents.

METHODS

Detailed reviews of both the British and American studies have been published (Baxter et al. 1980a; Falk et al. 1981c). The methods are summarized here to compare the main features of the studies.

In the United States, information relating to cases of HAS occurring from 1964 through 1974 was solicited in a variety of ways, including: (1) announcements in medical journals; (2) a single mailing to all pathologists in the country; (3) additional mailings to tumor registries, tumor referral centers, and state epidemiologists; (4) a review of cases on file at the Armed Forces Institute of Pathology (AFIP); and (5) a review of death certificates in code 197.8 (liver tumors, unspecified primary or secondary), International Classification of Diseases (ICD), eighth revision, for 1966-1973. For each identified case, appropriate pathologic specimens were requested for review and were obtained in about 95% of the cases. After confirmation of the diagnosis, and with permission of the local physician, the next of kin was identified and contacted. Consent was obtained to review medical records, and a questionnaire was administered by telephone to obtain detailed occupational, residential, and chemical exposure histories. A total of 168 confirmed deaths from HAS was identified during this 11-year period (mean = 15.3/yr).

The approach in Britain was slightly different. The EMAS of the Health and Safety Executive, in cooperation with the Office for Population Censuses and Surveys (England and Wales) and the General Register Office (Scotland), reviewed death certificates for all hepatic neoplasm-related codes (including eighth revision ICD Nos. 155.0, 155.1, 197.7, 197.8, 211.5, 227 and 230.5) for the 15-year period, 1963-1977. It should be noted that in the United States it would have been prohibitively expensive and impractical to obtain death certificates for all liver neoplasm codes from all 50 states. Other sources of identification of cases (such as hospital pathologists, tumor registries, factory medical departments, and published reports) were also used in the United Kingdom. The U.K. pathology review process also included control cases of liver neoplasms certified as other than angiosarcoma. After pathologic confirmation of the diagnosis, full medical records were sought. Interviews of next of kin for exposure information were conducted in person by an employment medical or nursing advisor using a standardized questionnaire. In all, 35 confirmed cases were identified (mean = 2.3/yr).

RESULTS

A major feature of both the American and British studies was the difficulty in finding cases. There is no ICD code for HAS, and as a result, even when

Table 1
Classification by Pathology Review Panels of Cases Identified Through Death Certificate Search with Recorded Diagnosis of HAS (1964-1974 in U.S.; 1963-1977 in U.K.)

	United States	United Kingdom
Confirmed HAS	31 (42%)	18 (26%)
Confirmed not HAS	37 (50%)	27 (40%)
No pathology available	6 (8%)	15 (22%)
Doubtful or unclassifiable	–	8 (12%)
Total	74	68

cases were identified as HAS or one of its commonly used synonyms (e.g., malignant hemangioendothelioma or Kupffer cell sarcoma), they were distributed over a number of ICD codes, the most common being 197.8 (Baxter et al. 1980a). (In the U.S., only code 197.8 was reviewed in the death certificate search.)

Because of the rarity of the tumor, and because many cases were diagnosed only at autopsy, it had been anticipated that the death certificate review would miss a large number of cases. About 50% of the cases in Britain and about 80% of the cases in the United States were identified by sources other than the death certificate search. What was not so readily anticipated was that even when a death certificate recorded HAS, the diagnosis agreed upon by the pathology review panel was not HAS in the majority of cases where specimens were available for review (Table 1). The pathologic review in the British study had an obvious effect on conclusions regarding time trends of this rare disease (Baxter et al. 1980a).

In the United States, the best source of case material was the single mailing to all pathologists; the second best was the large case series already in the files of the AFIP. The utility of collections such as the latter in epidemiologic studies should always be kept in mind, as for example in the large case-control study of benign hepatic adenoma and oral contraceptive use (Rooks et al. 1979).

On the basis of the U.S. death certificate review, we were also able to note a number of differences between HAS and other sarcomas of the liver. HAS has a striking preponderance in males (4:1 in the U.K. and 3:1 in the U.S.) that persists even when cases of known etiology are excluded (Table 2); this is not seen in the other hepatic sarcomas (leiomyosarcoma, fibrosarcoma, undifferentiated sarcoma, and miscellaneous sarcomas). Further, HAS appears to occur at an earlier age than do other sarcomas of the liver (Falk et al. 1981c).

In the United Kingdom, the incidence of HAS may well be increasing, although the numbers are very small. In the United States, time trends for HAS occurrence were not striking, but were particularly revealing when looked at in terms of causative agents. Four main causative agents were identified and

Table 2
Sex Ratios for Confirmed HAS Cases by Etiologic Categories (1964-1974 in U.S.; 1963-1977 in U.K.)

	Male	Female	Ratio
United States			
VCM	12	0	12:0
Thorotrast	15	5	3:1
Arsenic	4	2	2:1
Androgenic-anabolic steroids	3	1	3:1
Idiopathic	93	33	2.8:1
Total	127	41	3.1:1
United Kingdom			
VCM	2	0	2:0
Thorotrast	7	1	7:1
Idiopathic	19	6	3.2:1
Total	28	7	4:1
Combined			
VCM	14	0	14:0
Thorotrast	22	6	3.7:1
Arsenic	4	2	2:1
Androgenic-anabolic steroids	3	1	3:1
Idiopathic	112	39	2.9:1
Total	155	48	3.2:1

they have been discussed in detail for both the British and American studies (Berk et al. 1976; Baxter et al. 1977, 1980a, b; Falk et al. 1979a, b, 1981a, b, c). VCM, Thorotrast, and arsenic had been reported previously; androgenic-anabolic steroids were implicated as a fourth cause of HAS (Table 2). In the United States, the distribution of cases occurring during the 11-year period 1964-1974 reflects the patterns of use of these causative agents. Arsenic-associated cases occurred primarily in the early years of the study, since the use of Fowler's solution (potassium arsenite) for therapeutic purposes was discontinued in the 1940s and early 1950s. VCM- and androgenic-anabolic steroid-associated cases occurred primarily in the second half of the study period, due to the relatively recent introduction and use of these substances.

Most surprising was the recent increase in the numbers of Thorotrast cases that was prominent in both studies. This increase appears to be related to the increasing cumulative dose in the dwindling population of survivors. The Thorotrast data in the United States also suggest that the most recent cases had relatively low-dose exposures compared with the earlier cases; a longer latent period in recent cases also was noted (Falk et al. 1979). The latent period as

calculated from the earliest cases lengthened as the cohort matured. Therefore, one should not discount the possibility of increased numbers of VCM-associated HAS cases in the future in individuals with low exposure from occupational or environmental sources.

Geographic clusters of cases in rare-tumor studies are readily identifiable because of the low background rates. In the United States, clusters of VCM-associated cases were seen near some of the PVC polymerization plants and Thorotrast cases clustered in the northeastern cities (e.g., Philadelphia, New York, and Washington, D.C.) where Thorotrast was first introduced. A particularly good example is the cluster of six Thorotrast-induced cases seen in and around Edinburgh, where Thorotrast was first and most widely used in the United Kingdom (Baxter et al. 1980b).

DISCUSSION

Completeness of case finding is particularly important in a rare-tumor registry such as this, where even a few cases might identify an affected plant, a different means of exposure, or a new causative agent. Because of diagnostic and classification limitations (and despite an intensive search), it is likely that a sizeable fraction of cases was missed, particularly in the United States. These studies confirmed that death certificate reviews alone clearly are inadequate for the study of rare tumors and that rigorous pathologic review is needed.

In addition to the four causative agents discussed above, individual cases related to a variety of factors, including chloroprene, radiotherapy, radium implants, acrylonitrile, hemochromatosis, diethylstilbestrol, echinococcosis, copper, phenelzine, and urethane chemotherapy, were seen in these studies or have been reported elsewhere (Ross 1932; Baghirzade et al. 1971; Sussman et al. 1974; Pimentel and Menezes 1977; Hoch-Ligeti 1978; Daneshmend et al. 1979; Pollice 1979). A number of experimental carcinogens (in addition to VCM and some of its structural analogs) also are known to cause HAS; these include nitrosamines, urethane, hydrazines, azoxymethane, and lasiocarpine (Deringer 1962; Herrold 1967; Toth 1972, 1973; Maltoni and Lefemine 1974; Narisawa et al. 1976; Rao and Reddy 1978; Infante and Marlow 1980). The pathology panels were not able to distinguish morphologically between idiopathic HAS and the cases related to the various causative agents (Popper et al. 1978). It appears that the agents that cause HAS differ from traditional hepatocarcinogens in that they affect both hepatocellular and sinusoidal cell lines in the liver and represent, in a sense, a new class of hepatotoxins capable of causing both angiosarcoma and other liver lesions (Falk et al. 1979a). It would not be surprising, therefore, for other causative agents to be identified in the future, and time trends will continue to reflect the introduction, use, and discontinuation of the various causative agents. The potential to identify a new causative agent, even with only a handful of cases, makes the rare-tumor registry an attractive option.

The major limitations of these studies included: (1) the long start-up time and the considerable effort required to find and confirm cases; (2) the difficulty of getting detailed, accurate information from the widely dispersed family members in this retrospective setting; (3) the lack of adequate control groups in the United States (although the small number of cases limited the usefulness of control groups in the U.K.); and (4) the absence or limitations of past occupational exposure records.

A number of other rare marker tumors have been identified and studied in great detail. In addition to HAS, these include mesothelioma (related to asbestos), osteosarcoma (radium), vaginal adenocarcinoma (diethylstilbestrol), and hepatic adenoma (oral contraceptives). For these tumors, the associations with known causative agents and the concern about other agents that may be identified in the future (e.g., other fibers in mesothelioma, a variety of other halogenated hydrocarbons in HAS, and other internal alpha-emitters such as thorium or plutonium in osteosarcoma) make continuation of rare-tumor registries valuable. Registries covering a prolonged period of time may also be useful in evaluating dose-response relationships and latent periods.

Perhaps the most economical use of limited resources would be to develop the means of canvassing pathologists and others in a more systematic way for a variety of these tumors, either by computerizing and consolidating pathology (biopsy and autopsy) records or by querying pathologists from a centralized source at a single time for information on a variety of tumor types.

In addition to studying the above known marker tumors, a systematic approach also would allow study of other rare tumors that are of interest because of epidemiologic or experimental data. HAS, for example, would have been of interest even before the association with VCM was known for the following reasons: (1) the higher male:female ratio and earlier age of appearance than that for all other hepatic sarcomas; (2) the previously noted human causative agents (Thorotrast and arsenic); and (3) the large number of experimental chemicals that induce HAS in animals.

One must also be very specific when considering rare tumors. Epidemiologically, HAS is very different from angiosarcoma of the breast, limb, skin, and other sites (McBride et al. 1969; Girard et al. 1970; Chen et al. 1979, 1980), although, experimentally, some nonhepatic angiosarcomas also are induced by VCM, and their possible appearance in humans cannot be dismissed (Maltoni and Lefemine 1974). Recent reports have suggested an increased risk of soft-tissue sarcomas in groups exposed to chlorophenols and phenoxy acetic acids (Hardell and Sandstrom 1979); our experience suggests that it would be very important to consider carefully the various histologic types and sites that might be involved when addressing this issue.

In summary, although the absolute numbers of cases are small, registries for rare marker tumors provide unique opportunities for epidemiologic and pathogenetic studies of occupational and environmental carcinogens. A

systematic or centralized approach to case finding would greatly facilitate such studies.

ACKNOWLEDGMENTS

Dr. Peter Baxter worked on the British angiosarcoma registry while with EMAS in the United Kingdom. We are both greatly indebted to the highly skilled and motivated pathologists (H. Popper, K.G. Ishak, L.B. Thomas, P.P. Anthony, R.N.M. MacSween, and P.J. Scheuer) who worked with us on the U.S. and British studies. We also thank all the individuals who worked on and supported these studies.

Use of trade names is for identification only and does not constitute endorsement by the Public Health Service or by the U.S. Department of Health and Human Services.

REFERENCES

Baghirzade, M.F., E.U. Hertel, and P. Schumacher. 1971. Hamangioendotheliom (reticulosarcoma angioplasticum) der leber und alte echinokokkusinfektion. *Acta Hepato-splenologica* 18:224.

Baxter, P.J., P.P. Anthony, R.N.M. MacSween, and P.J. Scheuer. 1977. Angiosarcoma of the liver in Great Britain, 1963-73. *Br. Med. J.* 2:919.

_____. 1980a. Angiosarcoma of the liver: annual occurrence and aetiology in Great Britain. *Br. J. Ind. Med.* 37:213.

Baxter, P.J., A.O. Langlands, P.P. Anthony, R.N.M. MacSween, and P.J. Scheuer. 1980b. Angiosarcoma of the liver: A marker tumour for the late effects of Thorotrast in Great Britain. *Br. J. Cancer* 41:446.

Berk, P.D., J.F. Martin, R.S. Young, J. Creech, I.J. Selikoff, H. Falk, P. Watanabe, H. Popper, and L. Thomas. 1976. Vinyl chloride-associated liver disease. *Ann. Intern. Med.* 84:717.

Chen, K.T.K., J.C. Bolles, and E.F. Gilbert. 1979. Angiosarcoma of the spleen—A report of two cases and review of the literature. *Arch. Pathol. Lab. Med.* 103:122.

Chen, K.T.K., D.D. Kirkegaard, and J.J. Bocian. 1980. Angiosarcoma of the breast. *Cancer* 46:368.

Creech, J.L. Jr. and M.N. Johnson. 1974. Angiosarcoma of liver in the manufacture of polyvinyl chloride. *J. Occup. Med.* 16:150.

Daneshmend, T.K., G.L. Scott, and J.W.B. Bradfield. 1979. Angiosarcoma of liver associated with phenelzine. *Br. Med. J.* 1:1679.

Deringer, M.K. 1962. Response of strain HR/De mice to painting with urethan. *J. Natl. Cancer Inst.* 29:1107.

Falk, H., L.B. Thomas, H. Popper, and K.G. Ishak. 1979a. Hepatic angiosarcoma associated with androgenic-anabolic steroids. *Lancet* ii:1120.

Falk, H., G.G. Caldwell, K.G. Ishak, L.B. Thomas, and H. Popper. 1981a. Arsenic-related hepatic angiosarcoma. *Am. J. Ind. Med.* (in press).

Falk, H., N.C. Telles, K.G. Ishak, L.B. Thomas, and H. Popper. 1979b. Epidemiology of Thorotrast-induced hepatic angiosarcoma in the United States. *Environ. Res.* 18:65.

Falk, H., J.T. Herbert, L. Edmonds, C.W. Heath, Jr., L.B. Thomas, and H. Popper. 1981b. Review of four cases of childhood hepatic angiosarcoma–Elevated environmental arsenic exposure in one case. *Cancer* 47: 382.

Falk, H., J.T. Herbert, S. Crowley, K.G. Ishak, L.B. Thomas, H. Popper, and G.G. Caldwell. 1981c. Epidemiology of hepatic angiosarcoma in the United States 1964-1974. *Environ. Health Perspect.* (in press).

Girard, C., W.C. Johnson, and J. H. Graham. 1970. Cutaneous angiosarcoma. *Cancer* 26:868.

Hardell, L., and A. Sandstrom. 1979. Case-control study: Soft-tissue sarcomas and exposure to phenoxyacetic acids or chlorophenols. *Br. J. Cancer* 39:711.

Herrold, K.M. 1967. Histogenesis of malignant liver tumors induced by dimethylnitrosamine. An experimental study in Syrian hamsters. *J. Natl. Cancer Inst.* 39:1099.

Hoch-Ligeti, C. 1978. Angiosarcoma of the liver associated with diethylstilbestrol. *J. Am. Med. Assoc.* 240:1510.

Horta, J. Da Silva, L.C. Da Motta, and M.H. Tavares. 1974. Thorium dioxide effects in man–epidemiological, clinical, and pathological studies (experience in Portugal). *Environ. Res.* 8:131.

Infante, P.F. and P.B. Marlow. 1980. Evidence for carcinogenicity of selected halogenated hydrocarbons including ethylene dichloride. *Banbury Rep.* 5:287.

Maltoni, C. and G. Lefemine. 1974. Carcinogenicity bioassays of vinyl chloride. 1. Research plan and early results. *Environ. Res.* 7:387.

McBride, C.M., J.W. Reeder, and J.L. Smith. 1969. Angiosarcoma in the lymphedematous limb. *South Med. J.* 62:378.

Narisawa, T., C.Q. Wong, and J.H. Weisburger. 1976. Azoxymethane-induced liver hemangiosarcomas in inbred strain-2 guinea pigs. *J. Natl. Cancer Inst.* 56:653.

Pimental, J.C. and A.P. Menezes. 1977. Liver disease in vineyard sprayers. *Gastroenterology* 72:275.

Pollice, L. 1979. Primary vascular tumors of the liver. *Pathol. Res. Pract.* 165:145.

Popper, H., L.B. Thomas, N.C. Telles, H. Falk, and I.J. Selikoff. 1978. Development of hepatic angiosarcoma in man induced by vinyl chloride, Thorotrast, and arsenic–Comparison with cases of unknown etiology. *Am. J. Pathol.* 92:349.

Rao, M.S. and J.K. Reddy. 1978. Malignant neoplasms in rats fed lasiocarpine. *Br. J. Cancer* 37:289.

Rooks, J.B., H. W. Ory, K.G. Ishak, L.T. Strauss, J.R. Greenspan, A.P. Hill, and C.W. Tyler, Jr. 1979. Epidemiology of hepatocellular adenoma–the role of oral contraceptive use. *J. Am. Med. Assoc.* 242:644.

Ross, J.M. 1932. A case illustrating the effects of prolonged action of radium. *J. Pathol.* 35:898.

Roth, F. 1957. Arsen leber tumoren (hemangioendotheliom). *Z. Krebsforsch.* 61:468.

Sussman, E.B., I. Nydick, and G.F. Gray. 1974. Hemangioendothelial sarcoma of the liver and hemochromatosis. *Arch. Pathol.* 97:39.

Toth, B. 1972. Morphological studies of angiosarcomas induced by 1,2-dimethylhydrazine dihydrochloride in Syrian golden hamsters. *Cancer Res.* 32:2818.

———. 1973. 1,1-dimethylhydrazine (unsymmetrical) carcinogenesis in mice. Light microscopic and ultrastructural studies on neoplastic blood vessels. *J. Natl. Cancer Inst.* 50:181.