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Draft Research Protocol

A CASE-CONTROL STUDY OF SOFT-TISSUE SARCOMA

Environmental Studies Section
Environmental Epidemiology Branch
National Cancer Institute

and

Department of Soft Tissue Pathology
Armed Forces Institute of Pathology

May 5, 1982

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I. INTRODUCTION

The Environmental Epidemiology Branch of the National Cancer Institute (NCI) is collaborating with the Armed Forces Institute of Pathology (AFIP) in the conduct of an epidemiologic case-control study of soft tissue sarcoma (STS) among men. Cases will be selected from AFIP registries. Controls will be randomly selected from patient logs of referring pathologists, matching on age and race. Telephone interviews of cases and controls, or their next-of-kin will gather occupational histories, including military service, and other information that may be pertinent to the origins of these tumors. Particular attention will be paid to herbicide exposures.

II. OBJECTIVE

The objective of this study is to evaluate the effects of the following on the development of STS:

1) Occupational and non-occupational exposure to herbicides, especially phenoxyacetic acids and chlorophenols.

2) Exposure to phenoxyacetic acid-containing drugs, such as clofibrate, or related drugs, such as chloramphenicol.

3) Other host and environmental factors such as genetic syndromes, fa
immunologic deficiency, lymphedema, trauma, and exposure to ionizing radiation, arsenic, vinyl chloride, androgenic-anabolic steroids, allergenic extract injections, and animals susceptible to sarcoma-inducing viruses.

III. RATIONALE AND BACKGROUND

Recent speculation over the possible adverse health effects resulting from exposure to herbicides such as 2,4-D and 2,4,5-T and their contaminants has been widespread. Mounting evidence from animal studies and some epidemiology studies suggests associations of STS with exposures to phenoxy acetic acids and chlorophenols. Available data is far from complete, however, and there is need for additional epidemiologic evidence.

The AFIP offers a unique resource to contribute to this study. The AFIP routinely provides consultation services for pathologists throughout the United States, especially for conditions such as STS which present special diagnostic problems. One quarter to one third of the STS's occurring in the US are sent to AFIP for review. Approximately 6200 cases were reviewed in 1974-1980. Thus the AFIP is one of the largest single registries in the world for this group of tumors. The uniformity and high quality of diagnoses at AFIP give it an added advantage as a resource for epidemiologic studies of rare conditions.

This study will have a case-control design, in which environmental and occupational exposures of persons with soft tissue sarcomas (cases) will be compared with exposures of persons without this malignancy (controls). Exposure will be classified according to the likelihood and level of herbicide exposure, and exposures to other possible carcinogens. The underlying premise is that if herbicide exposure is unrelated to the development of soft-tissue sarcoma, then the proportion of individuals with past exposures to herbicides in the case and control group should be similar. On the other hand, if herbicides are human carcinogens, then a larger

proportion of STS cases should have evidence of past herbicide exposure than controls.

IV. LITERATURE REVIEW

Soft tissue sarcomas (STS) are a complex and diverse group of malignant neoplasms that originate in nonepithelial extraskeletal supporting structures of the body, excluding the hematopoietic-lymphatic system, the glia, and supporting tissues of specific organs and tissues (Enzinger, et al.,1969). Certain neuroectodermal tissues of the peripheral and autonomic nervous systems are, however, included in the group. The major well-defined sarcomas have features indicating differentiation toward cells such as adiposites (liposarcoma), smooth muscle (leiomyosarcoma), skeletal muscle (rhabdomyosarcoma), histiocytes (malignant fibrous histiocytoma), Schwann cells (malignant Schwannoma), vascular pericytes (hemangiopericytoma), endothelial cells (angiosarcoma, hemangiosarcoma), fibrocytes (fibrosarcoma, dermatofibrosarcoma protruberans), and synovial lining cells (synovial sarcoma). Some sarcomas show no morphologic features suggesting differentiation toward recognizable cell lines and are designated sarcoma, NOS (not otherwise specified), or sarcoma, poorly differentiated. Sarcomas with cells showing differentiation toward more than one cell line are usually classified according to the morphologic features of the predominent cell, or by a compound term, describing 2 or

if the proportions of cells of each line are equally prominent. An example is a neurofibrosarcoma in which component cells show characteristics of both nervous elements and fibrocytes or fibroblasts.

The precise classification of neoplasms of the STS group is frequently difficult, requiring the use of electron microscopy or other special techniques usually not available in the average pathology diagnostic laboratory. The AFIP is therefore frequently consulted to assist in the diagnosis of STS because specialized facilities and pathologists with experience in the diagnosis of these relatively infrequent neoplasms are available there. As mentioned, the AFIP receives, in consultation, material from one quarter to one third of all STS diagnosed in the United States. Although patterns of use of the AFIP for consultation by practicing pathologists is subject to a number of varying factors, certain patterns are suggested by the tabulations of the AFIP STS by age and sex.

In the AFIP records of STS accessioned during the 6-year-period 1975-1981, in individuals aged 20 to 79 years, rhabdomyosarcomas were more frequent in younger individuals whereas most of the sarcomas of specific diagnostic categories occurred in older people. Hemangiopericytoma was the only extravisceral sarcoma that predominated in women. The higher number of leiomyosarcomas in women can be accounted for by the fact that a large proportion of these sarcomas originate in the uterus. All of the other diagnostic categories show a slight to moderate excess in males, probably in part, because of the large proportion of cases originating in hospital of the Veterans Administration which use the facilities of the relatively more frequently than most other institutions. Sarcomas designated "NOS' or "undifferentiated" are relatively more

frequent in younger individuals, whereas most of the better-differentiated sarcomas are observed in older patients. It is not yet known whether differences in histopathologic types of sarcomas imply different etiologies. One of the major purposes of this study is to attempt to answer this question.

The overall incidence of STS was 2.4 per 100,000 in 1973-77 in areas covered by a network tumor registries sponsored by NCI (1981). The incidence of STS among adults increases with age, but not as rapidly as most carcinomas. The age-specific male STS rate for ages 75-79 was approximately 5 times the rate in the 40-44 age group, whereas the ratio of rates for lung, colon, or rectal cancers in the 75-79 age group relative to those 40-44 fell in the range 20-35 (NCI, 1981).

The etiology of STS is largely unknown. A small proportion of cases are related to Mendelian syndromes and familial multiple-cancer syndromes (Tucker and Fraumeni, 1981; Li and Fraumeni, 1969; Blattner et al., 1979). Some cases are associated with genetically determined immunodeficiency syndromes and iatrogenic immunosuppressed states (Hoover and Fraumeni, 1973; Kinlen et al., 1979; Spector et al., 1978). Chronic lymphedema has been linked to sarcomas in case reports (Dubin et al., 1974).

The best known examples of associations between specific chemical compounds and sarcomas of specific cell types and anatomic locations are vinyl chloride and inorganic arsenicals, both of which have been associated with a rather characteristic type of angiosarcoma of the liver and, in the case of vinyl chloride, of other organs. No other associations between a characteristic type of STS, organ site and chemical compound has been reported

External radiation therapy and radioisotopes have also been associated with the development of sarcomas (Kim et al., 1978). Thorotrast, used for radiographic studies of blood vessels in the liver, resulted in angiosarcomas of the liver and sarcomas at the site of injection (da Motta et al., 1979; Falk et al., 1979a). Use of the radioisotope, I-125, for treatment of thyrotoxicosis was followed eight years later by the development of a sarcoma of the larynx (McKillop et al., 1978). Other agents used medicinally and occupationally and suspected of being associated with development of STS include: arsenic, vinyl chloride, androgenic-anabolic steroids, iron-dextran injections, and aluminum compounds (Falk et al., 1979b, McIllmurray and Langman, 1978; Weinbren et al.,1978). Viruses appear to be responsible for the induction of sarcomas in chickens, cats, and mice and may play a role in the causation of human sarcoma (Kufe et al., 1972), although there is no epidemiologic evidence to date.

Certain herbicides and herbicide-contaminants have been associated with teratogenesis, mutagenesis, and carcinogenesis in animal and bacterial experiments (Young et al., 1978; National Toxicology Program, 1982a; National Toxicology Program, 1982b). Recent epidemiologic studies from Sweden suggest that persons exposed to herbicides may be at excess risk of cancer. A retrospective cohort study of railroad workers exposed to amitrole (3-amino-1,2,4-triazole) and phenoxyacetic acids (2,4-dichlorophenoxyactic acid and 2,4,5-trichlorophenoxyacetic acid) showed elevated rates of cancer incidence and mortality (Axelson and Sundell, 1974; Axelson et al., 1980). Case-control studies revealed associations between exposure to phenoxyacetic acids and chlorophenols and STS (Hardell L and Sandstrom A, 1979; Eriksson M et al., 1979; Hardell L et al., 1981). Risks were increased five- to six- fold, regardless of whether exposures were contaminated by

polychlorinated dibenzodioxins (PCDDs) and dibenzofurans (PCDFs). Honchar et al. (1981) noted 3 deaths attributed to soft tissue sarcoma (0.07 expected) among 105 reported deaths from four cohorts industrially exposed to chlorophenols or phenoxy herbicides (Zack and Suskind, 1980; Cook et al., 1980; Ott et al., 1980; Zack, unpublished, cited by Honchar et al.,1981).

There is widespread potential for exposure to phenoxy-acetic acids and chlorophenols. In addition to herbicide formulations these chemicals appear in blue stain fungicides used in sawmills, slime control preparations in paper and pulp manufacturing, cutting oils and fluids, wood preservatives, waterproofing agents for leather and textiles, and in medications. Clofibrate, a plasma lipid-lowering drug, is a phenoxyacetic acid-derivative and has induced hepatocellular carcinomas and sarcomas in rats (Svoboda and Azarnoff, 1979). If the reported epidemiologic associations are causal and as strong as suggested by the Swedish research, these agents could be responsible for a large proportion of the cases of STS in the United States. Many factors have been suggested as contributing to the development of STS, but need to be further evaluated and quantified. In particular, the heavy use of herbicides and the high cancer risk possibly associated with their exposure underscore the urgent need to conduct an independent epidemiologic investigation of persons with this tu

V. THE STUDY POPULATION

A. The following specific histopathologic types of soft tissue sarcoma, as , will be eligible for inclusion in the study. Noted in the

Noted in the

list are the approximate numbers of male cases, and their relative

their relative proportions among all male STS cases accessioned by AFIP in

January 1, 1975 through XXXXXXXXXXX.

Type of Soft Tissue Sarcoma	N	Percentage
Malignant fibrous histiocytoma	1114	25.2%
Leiomyosarcoma	592	13.4
Liposarcoma	485	11.0
Fibrosarcoma	288	6.5
Malignant Schwannoma	250	5.7
Atypical fibroxanthoma	290	6.6
Hemangiopericytoma	144	3.3
Dermatofibrosarcoma protruberans	170	3.8
Angiosarcomas	139	3.1
Synovial sarcomas	134	3.0
Rhabdomyosarcomas	88	2.0
Poorly differentiated sarcomas, sarcomas NOS, and other	729	16.5
TOTAL	4423	99.9%

B. Cases will be drawn from accession lists of the AFIP. Selection will be restricted to white men, aged 20-79, who were diagnosed after January 1, 1976. Geographic limits for eligibility will be established to enhance the probability of exposure to agricultural chemicals, especially herbicides, while ensuring that an adequate number of cases are included. Selection will therefore be focussed in geographic areas in which wheat, rice, or corn is grown. One or

more areas with an active forest-products industry may also be selected. Selection of geographic areas will also be guided by a goal of identifying at least 400 cases for the study. Cases and controls will not be drawn from regions of the United States where NCI or other research groups are anticipating or already conducting epidemiologic studies of STS. These places include the states of Kansas and New York, and the counties of Washington State covered by the Seattle tumor registry.

C. Controls will be selected from the logs of referring pathologists. Excluded from consideration as controls will be diagnoses of STS, non-Hodgkin's lymphoma, and Hodgkin's disease. The latter two conditions have been associated with exposure to phenoxyacetic acids, chlorophenols, or their contaminants. A contact person in each referring pathology unit, usually a medical assistant or nurse, will be asked to select the next two sequential patients in the log book following the STS case who matches the case on sex and 5-year age group. This approach to control selection has not yet been tried by AFIP, so there is a need to test its feasibility. It is likely that this approach will prove feasible, but if not, siblings of cases will be used as controls.

D. (Cases currently alive, cases dead - how to handle?)

E. Statistical power of the study. Assuming a p level of 0.05 and 10% of the controls exposed to herbicides, a study of 200 cases with a 2:1 matching ratio would be able to detect an odds ratio of at least &&&& with 90% power.

VI. Interview

The cases and controls, or their next-of-kin, will be interviewed by telephone concerning the following items:

- Date of birth
- Place of birth
- Marital status
- Religion
- Ethnicity
- Height/Weight
- Education
- Occupation (emphasis on exposure to phenoxyacetic acids, chlorophenols, ionizing radiation, arsenic compounds, vinyl chloride, cattle, poultry, other fowl, and cats)
- Non-occupational use of herbicides
- Military experience (emphasis on theatre of operations, time period, direct or indirect exposure to phenoxyacetic acids, and chlorophenols)
- Smoking
- Familial cancer
- Trauma
- Present or past medical conditions (allergies, chloracne, immunodeficiency syndromes)
- Medical treatments (phenoxyacetic acid-containing drugs, ionizing radiation, chemotherapy, immuno-suppressive therapy, allergy shots, vaccines, iron-dextran injections, androgenic-anabolic steroids, Fowler's solution)

VI. PROPOSED STUDY STEPS

1. Tabulate the age and geographic distribution of all male STS cases, by specific diagnosis, that AFIP has registered since January 1, 1975.

2. Obtain information on the agricultural and demographic characteristics of the geographic areas from which the cases and controls are likely to be selected.

3. Using data from steps 1 and 2, select two or more geographic regions of the United States in which at least 5% of the male population is likely to have been exposed to herbicides and which can provide adequate numbers of cases (400) and controls (800) for this study.

4. Develop an interview schedule. Conduct a pretest and make necessary revisions.

5. Prepare introductory and informed consent letters and obtain consent of cases and controls, or their next-of-kin, prior to conducting interviews, in accordance with existing federal, state, and local regulations.

6. Obtain necessary clearance for the interview schedule and project protocol from the NCI Environmental Epidemiology Branch Technical Evaluation of Projects and Questionnaires Committee, the Office of Management and Budget, state vital records offices, and participating hospitals.

7. Identify from AFIP records the white men, aged 20-79 who were diagnosed with STS and who resided in the geographic area(s) selected for study. Select cases from the five most recent years.

8. Select controls from pathology log books with the assistance of referring pathologists. Controls will be randomly selected from among all diagnoses except non-Hodgkin's lymphoma and Hodgkin's disease, matching to cases on 5-year age group and sex. A 2:1 case:control matching ratio will be used.

sex, 5-year age group, and year of diagnosis. Controls non-Hodgkin's lymphoma, and Hodgkin's disease.

9. Obtain copies of death certificates for deceased cases and controls.

10. Develop training and procedure manuals for supervisors, interviewers, abstractors, and coders.

11. AFIP receives most referrals from pathologists. The first step in locating cases and in identifying controls will be to contact the referring pathologist. The physician or surgeon will then be contacted to help locate the patient or next-of-kin, and to obtain permission to contact the subject. When this procedure was used by AFIP in another study, they were successful in locating and interviewing ZZZ of XXXX nasal cancer cases from their registry.

12. Hire and train supervisors, interviewers, abstractors, and coders.

13. Conduct telephone interviews of the cases and controls, or their next-of-kin.

14. Review, edit, and code all completed interviews.

15. Analyze the data.

16. Write a final report.

17. Document each step of the study.

CONFIDENTIALITY

Confidentiality of all records pertaining to individuals in this study will be carefully protected. Names of individuals will be used solely to locate persons for the purpose of interviewing, or to locate their death certificates, if they are deceased. Personal identifiers will not be retained on any data record used for analysis, nor will they be included in any publication or other presentation of study results. Records with personal identifiers will be under the control of NCI and AFIP investigators or their agents and will not be accessible to other individuals or groups.

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