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Item ID Number	01771
Author	Blair, Aaron
Corporate Author	
Report/Article Title	Typescript: Research Protocol, a Case-Control Study of Lymphoma and Soft-Tissue Sarcoma: Association with Herbicide Exposures, [nd]
Journal/Book Title	
Year	0000
Month/Day	
Color	☐
Number of Images	16
Description Notes	

Research Protocol

A CASE-CONTROL STUDY OF LYMPHOMA AND SOFT-TISSUE SARCOMA: ASSOCIATION WITH HERBICIDE EXPOSURES

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A Case-Control Study of Lymphoma and Soft-Tissue Sarcoma: Association with Herbicide Exposures

I. Introduction

The Environmental Epidemiology Branch of the National Cancer Institute is planning to conduct an epidemiologic case-control investigation of soft-tissue sarcoma (STS), non-Hodgkin's lymphoma (NHL), and Hodgkin's disease (HD). The cases and controls, or their next-of-kin, will be interviewed by telephone to obtain occupational histories and other information pertinent to the origins of these cancers. Particular attention will be paid to herbicide exposures.

II. Objective

The objective of this study is to evaluate the effects of the following factors on the development of STS, NHL, and HD:

1) Occupational and non-occupational exposure to herbicides, in particular phenoxyacetic acids and chlorophenols.
2) Exposure to phenoxyacetic acid-containing drugs, eg. clofibrate.
3) Other factors such as genetic syndromes, familial clustering, immunologic deficiency, lymphedema, trauma, and exposure to radiation, arsenic, vinyl chloride, androgenic-anabolic steroids, allergenic extract injections, and animals susceptible to

sarcoma-inducing viruses.

III. Literature Review

Certain herbicides and herbicide-contaminants have been associated with teratogenesis, mutagenesis, and carcinogenesis in animal and bacterial experiments (Young AL et al., 1978). 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 O and Sundell L, 1974; Axelson O et al., 1980). Case-control studies revealed associations between exposure to phenoxyacetic acids and chlorophenols and STS, NHL, and HD (Hardell L and Sandstrom A, 1979; Eriksson M et al., 1979; Hardell L et al., 1981). For all three cancers, risks were increased five- to six- fold, regardless of whether exposures were contaminated by polychlorinated dibenzodioxins (PCDDs) and dibenzofurans (PCDFs).

There is widespread potential for exposure to phenoxy-acetic acids and chlorophenols. In addition to herbicide formulations these chemicals appear in blue stain retardants 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, NHL, and HD in the United States.

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).

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, McIlmurray 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.

Epidemiologic studies have also suggested possible links between these diseases and selected occupations (Grufferman et al., 1976, Tucker and Fraumeni, 1981). Woodworkers, clerical workers, accountants, engineers, lawyers, judges, physicians, and textile workers reportedly have an increased risk of HD. Several, but not all, cohort studies of chemists have demonstrated excess mortality from HD and NHL (Li et al., 1969; Olin, 1976; Olin, 1978; Searle et al., 1978; Hoar and Pell, 1981).

Non-occupational factors associated with HD and NHL include age, race, sex, geographical location (Cole and MacMahon, 1968), socioeconomic status, marital status, ethnicity, religion, obesity, smoking history, coffee drinking habits (Paffenbarger et al., 1977; Paffenbarger et al., 1978), familial cancer history, diabetes (Kalant and Seemayer, 1979), systemic lupus erythematosus (Green et al., 1978), infectious mononucleosis (Carter et al., 1977), celiac disease (Douglas, 1977), immunodeficiency syndromes (Filipovich et al., 1980), tonsillectomy (Gutensohn et al., 1975), ionizing radiation, chemotherapy (Krikorian et al., 1979), immunosuppressive drugs (Hoover and Fraumeni, 1973), and other exposures.

Many factors have been suggested as contributing to the development of STS, NHL, and HD 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 underscores the urgent need to conduct an independent epidemiologic investigation of persons exposed to these pesticides.

IV. Study Subjects

1) The case group will consist of white men, aged 21 and older, diagnosed with STS, NHL, or HD, from a region where at least 10% of the working white population has been engaged in occupational activities that involve contact with herbicides. Kansas has been selected since it is a wheat-producing area where herbicide use is great but use of insecticides and fungicides is considerably less.

The goal is to select 200 cases of each cancer, however because the study region is sparsely populated and these are rare tumors, a minimum of 100 cases of each cancer will be acceptable. Cases from the last five years will be drawn from the University of Kansas Medical Center Cancer Data Service, a population-based cancer registry. Next-of-kin will serve as respondents for those cases who have died.

2) The controls will be white men from the general population of the geographic area selected for study. Three controls will be matched to each case on age (+/- 2 years), vital status, and area of residence (probably a

multi-county unit).

For cases who are currently alive, controls aged 65 years or older will be selected from the Health Care Financing Administration file, to be provided by NCI; whereas, controls aged 64 years or younger could be selected by telephone through a random digit dialing technique.

For cases who have died before the initiation of the study, the controls could be selected from Kansas state mortality files. In addition to age at death (+/- 2 years), these controls would be matched to the cases on year of death. Persons whose cause of death is STS, NHL, HD, or a malignancy of an ill-defined site (ICDA code 195) would be excluded. The next-of-kin will be interviewed.

The same controls should be used for the three case series whenever possible. The goal is that each case have three suitably matched controls for comparison. We anticipate that 700 to 1000 controls will be necessary to meet this requirement.

Assuming an level of .05 and 10% of the population exposed to herbicides, a study of 100 cases with a 3:1 matching ratio would be able to detect a minimum odds ratio of 2.7 with 90% power.

V. Pathology Review

Pathology blocks, slides, and/or medical records will be obtained for confirmation of the diagnosis of STS, NHL, or HD. Specimens will be reviewed by NCI pathologists.

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, arsenic compounds, vinyl chloride, poultry, other birds, and cats)

Non-occupational use of herbicides

Smoking

Coffee drinking

Familial cancer

Trauma

Present or past medical conditions (diabetes, eczema, allergies, chloracne, varicella [chicken pox], systemic lupus erythematosus, infectious mononucleosis, celiac disease, immunodeficiency syndromes)

Medical treatments (phenoxyacetic acid-containing drugs, tonsillectomy, ionizing radiation, chemotherapy, immunosuppressive therapy, allergy shots,

vaccines, iron-dextran injections, androgenic-anabolic steroids, Fowler's solution, amphetamines, diphenylhydantoin, etc.)

VI. Proposed Study Steps

1. Obtain demographic, agricultural, and industrial characteristics of the geographic area from which the cases and controls will be selected.

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

3. 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.

4. Identify the white men, aged 21 years or older, who were diagnosed with STS, NHL, or HD, and who resided in the geographic area selected for study. Select the cases from the five most recent years.

5. Select three controls per case, matching on age (+/- 2 years), vital status, year of diagnosis or death, and area of residence (probably a multi-county unit). Draw population controls using HCFA files, random digit dialing, and Kansas state mortality files. Use the

same controls for the three case series whenever possible.

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

7. Obtain and review pathology blocks, slides, and/or medical records for confirmation of the diagnosis.

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

9. Locate cases and controls, or their next-of-kin.

10. 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.

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

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

13. Obtain corroborative evidence of herbicide exposure from resources, such as employers, employees, or agricultural agencies, for study subjects suspected of having such exposure. This important step will reduce potential observer bias introduced by interviewers aware of the

study hypothesis.

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

15. Analyze the data.

16. Write a final report.

17. Document each step of the study.

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