CASE-CONTROL STUDIES OF SOFT TISSUE NEOPLASMS IN RELATION TO EXPOSURE TO ENVIRONMENTAL CARCINOGENS

Hardell, et al (1) and Eriksson, et al (2) have reported that patients with soft tissue sarcomas have a greater frequency of exposure to phenoxy compounds and related chemicals than matched controls without neoplasms. These reports were results of case-control studies of histologically confirmed neoplasms identified in an oncology clinic.

Phenoxy herbicides were first manufactured in 1944 in the U.S. and since that time have been widely used in the U.S. and in many countries of the world. During wartime, particularly in Vietnam where most of the fighting involved guerilla warfare, the phenoxy acids 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) in a 50-50 mixture known as "Herbicide Orange", or later as "Agent Orange", and other herbicides, were used to destroy enemy cover in forests and also to destroy food crops (3,4). 2,4,5-T was contaminated with a potent, toxic compound, tetrachlorodibenzodioxin (TCDD). This compound known as "dioxin" (although there are many other "dioxins"), is carcinogenic in rats producing neoplasms of several organs including liver, hard palate, tongue and nasal turbinates (5). So far, neoplasms of soft tissues have not been reported in test animals but results of National Cancer Institute (NCI) studies are incomplete. (The two phenoxy acids are not in themselves known to be carcinogenic). Reports of carcinogenicity of TCDD in animals and its possible carcinogencity in man are of considerable concern to the Veterans Administration (VA) because of the high risk of exposure to many soldiers and airmen in Vietnam during the years 1962-1971.

The civilian population in the U.S. and throughout the world has also been exposed to unknown amounts of herbicides, including the widely used 2,4,5-T with its TCDD contaminant. Therefore it is important to determine the health effects of these materials on both civilian and military populations. Some servicemen who were in Vietnam had opportunity for contact with relatively high concentrations of herbicides. Because of the large amounts of herbicides used by civilians in the U.S., Vietnam veterans also had considerable opportunity for exposure before and after military service. Workers who manufacture herbicides and their precursors or related compounds, foresters, farmers, railroad right-of-way workers and those in many other occupations are also potential risks of phenoxy acid-related neoplasms.

Several groups of men having experienced heavy occupational exposure to TCDD and/or phenoxy acids have been under medical surveillance for as long as 30 years (6,7,8). To date, none of these occupational groups has shown an excessive number of neoplasms, but these cohorts of exposed people are small and many more individuals and years of follow-up will be required before sufficient numbers of neoplasms develop to permit statistical analyses. Because neoplasia is a relatively rare event and latent periods can be very long, cohort studies require that large numbers of individuals be followed for long periods of time before significant numbers of neoplasms develop in either exposed or control populations. Case-control studies on the other hand, have the advantage over cohort studies in that relatively fewer patients and controls are required to permit statistical analyses because all members of the study group are selected because they have a neoplasm and the controls do not (9).

The Armed Forces Institute of Pathology (AFIP) offers an ideal opportunity for case-control studies of soft tissue neoplasms because of the large number accessioned each year and the diagnostic expertise of the staff of the Soft Tissue Pathology Department assures consistent and correct histopathological diagnoses. Because there are relatively large numbers of neoplasms of different histologic types in the collection, neoplasms of individual cell types and/or anatomic locations can be analyzed separately with the possibility of relating neoplasms of unusual histologic types or sites of origin to service in Vietnam, or other environmental exposure. Most Vietnam verterans were ages 19-20 at the time they served in Vietnam. These men are now at least 28 years of age, and most would be older. The earliest exposure to phenoxy acids would have been in 1962, some 18 years ago; the last in 1971 or 1972. Veterans who were age 19 in 1962 would be 37 years old now and exposure would have been 18 years ago; those who were aged 19 in 1971 would be 28 years now and the exposure would have been 9 years ago. These time periods are within the latent periods of many occupational cancers. The duration of time between exposure to phenoxy herbicides and development of neoplasia in the Hardell report ranged from 9 to 27 years. Thus if exposure to herbicides in Vietnam causes neoplasia, sufficient time has elapsed for such neoplasia to occur in some of the exposed men. Because of the role of the AFIP in performing consultative services to pathologists of civilian, military and veterans hospitals, the AFIP routinely receives a large volume of material from biopsies and/or autopsies of men in military service and veterans. If the study reveals that a disproportionate number of patients with soft tissue neoplasms have served in Vietnam, compared to controls, evidence incriminating herbicides will be strengthened but a cause-effect relationship will not be proven. If, on the other hand, the results of the statistical analyses reveal no significant differences with regard to service in Vietnam, or other exposures to herbicides between "cases" and "controls", it might be concluded either that sufficient time had not elapsed for neoplasia to occur or that soft tissue neoplasia was not a result of exposure to herbicides or other chemicals in Vietnam. In the latter instance it might be desirable to repeat the study later using new cases accessioned after 1980 allowing a longer latent period to elapse.

REFERENCES

1. Hardell, L. and Sandstrom, A: Case-Control Study: Soft-Tissue Sarcomas and Exposure to Phenoxyacetic Acids or Chlorophenols. Br. J. Cancer 39: 711-717, 1979.

2. Eriksson, M. et al: Case-Control Study of Malignant Mesenchymal Tumors of the Soft Tissue and Exposure to Chemical Substances. Lakartidningen 76: 3872-3875, 1979.

3. Young Al, et al: The Toxicology, Environmental Fate and Human Risk of Herbicide Orange and its Associated Dioxin. USAF OEHL TR-78-92.

4. WHO, International Agency for Research on Cancer. IARC Monographs on Evaluation of the Carcinogenic Risk of Chemicals to Man. Some Fumigants, The Herbicides 2,4-D and 2,4,5-T, Chlorinated Dibenzodioxins and Miscellaneous Industrial Chemicals. Vol 15, Lyon, 1977, pp 41-102, 111-138, 273-300.

5. Kociba, R.J., et al: Results of a Two-Year Chronic Toxicity and Oncogenicity Study of 2,3,7,8-Tetrachlorodibenzo-p-dioxin in Rats. Tox. Appl. Pharm. 46: 279-303, 1978.

6. Zack, J.A, Suskind, R.R: The Mortality Experience of Workers Exposed to Tetrachlorodibenzodioxin in a Trichlorophenol Process Accident. J. Occup. Med. 22: 11-14, 1980.

7. Axelson, O., et al: Herbicide Exposure and Tumor Mortality: An updated Epidemiological Investigation on Swedish Railroad Workers. (Unpublished manuscript).

8. Thiess, A.M., et al: Mortality Study of persons Exposed to Dioxin following an Accident which occurred in BASF on 13 November, 1953. (In press).

9. Cole, P.: The Evolving Case-Control Study. J. Chron. Dis. 32: 15-27, 1979.

STUDY DESIGN

1. The Central Computer Data Branch of the AFIP will be requested to prepare a printout of all or selected histopathologic types of soft tissue neoplasms in males and females age 25 years and over, accessioned to the AFIP between January 1, 1975 and December 31, 1980.

2. Four controls for each case, matched for age, sex, race, state of residence, and year of diagnosis, will be randomly selected from computer records of non-neoplastic diseases accessioned during the same period.

3. Environmental questionnaires and cover letters to patients or surviving relatives will be sent to contributing pathologists with instructions for forwarding to primary care physicians who will in turn be requested to contact patients or relatives. The questionnaire will be carefully prepared in consultation with members of the VA Advisory Committee on Health-Related Effects of Herbicides, and will include questions about military service, occupation and other sources of exposure to chemicals in the environment. The questionnaire will be designed to be self-administered. As required by law, all patients or relatives will be furnished a printed statement concerning their rights under the Privacy Act. Information about military service will be confirmed by checking official DOD records. Other types of occupational exposure will also be checked, where possible. The questions concerning both military service and occupational exposure will be worded in such a way so as not to suggest that these specific exposures were associated with the neoplasms.

4. The data from completed questionnaires will be analyzed according to standard statistical methods to determine differences between cases and controls with regard to civilian and military exposure to herbicides, service in Vietnam, other environmental and occupational exposures, and medical history. Relative risks will be estimated by odds ratios, calculated by Mantel-Haenszel procedures for combining 2x2 tables, and by logistic regression techniques. Standard risks of statistical significance will be used to calculate p-values and confidence limits of relative risk estimates. Other statistical procedures will be used, as warranted.

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