

Phenoxy herbicides and soft-tissue sarcomas in female rice weeders

A population-based case-referent study

by Paolo Vineis, MD,¹ Benedetto Terracini, MD,¹ Giovannino Ciccone, MD,¹ Alessandro Cignetti,² Eva Colombo,¹ Adalberto Donna, MD,³ Lidio Maffi,¹ Roberto Pisa, MD,⁴ Paolo Ricci, MD,⁵ Ermanno Zanini,³ Pietro Comba, DSc,⁶

VINEIS P, TERRACINI B, CICCONE G, CIGNETTI A, COLOMBO E, DONNA A, MAFFI L, PISA R, RICCI P, ZANINI E, COMBA P. Phenoxy herbicides and soft-tissue sarcomas in female rice weeders: A population-based case-referent study. *Scand J Work Environ Health* 13 (1987) 9–17. A population-based case-referent study was conducted in an area of northern Italy where rice growing is the predominant agricultural activity and phenoxy herbicides have been used since 1950. Manual rice weeding was formerly performed by a seasonal female working population; in the early 1950s these women were concurrently exposed to chemical herbicides. Sixty-eight persons representing incident and histologically revised cases (31 women) and 158 population referents (73 women) were interviewed. The cases were histologically confirmed independently by two blinded pathologists, and exposure to phenoxy herbicides was assessed by two blinded pesticide researchers. An age-adjusted odds ratio of 0.91 was found for the living men (with suspect exposures; no man diagnosed as a case had been exposed with certainty to phenoxy herbicides). Among the living women the relative risk was 2.7 (90 % confidence interval 0.59–12.37), and it further increased when attention was restricted to women exposed in the whole 1950–1955 period and to younger age groups.

Key terms: case-control study, occupational exposure, rice growing.

Chlorinated phenoxy acids, namely, 2,4,5-trichlorophenoxy acetic acid (2,4,5-T), 2,4-dichlorophenoxy acetic acid (2,4-D) and 2-methylchlorophenoxyacetic acid (MCPA), have been manufactured since the early 1940s and extensively used as herbicides in agriculture and forestry since the 1950s. A mixture of 2,4,5-T and 2,4-D (Agent Orange) was used as a defoliant during the Vietnam war.

An association between occupational exposure to phenoxy herbicides, both in their manufacture and use, and the subsequent occurrence of soft-tissue sarcomas has been suspected in some reports (2, 8, 9, 14, 18), but not confirmed by others (12, 27). A few studies

have not been sufficiently informative (10, 21, 24, 26). (See also the reviews in references 1 and 6). The International Agency for Research on Cancer, chiefly on the basis of reports by Eriksson et al (8) and Hardell & Sandström (14), evaluated the evidence on the carcinogenicity of phenoxy acid herbicides to humans as limited (15).

Most of the aforementioned authors emphasized the need for further knowledge. Therefore we decided to undertake an investigation in the provinces of Vercelli, Novara, and Alessandria (northern Italy), where rice growing is the predominant agricultural activity. The total population in this area is approximately 1.5 million. Phenoxy herbicides were introduced in large amounts in the early 1950s and have been extensively used up to now. According to official statistics (16, 17), more than 4.8 t of 2,4-D and 21.7 t of MCPA were used in the three provinces in 1959 (data not available for 2,4,5-T). The corresponding figures for 1969 were 24.5 t for 2,4-D, 29.4 t for MCPA and 125.1 t for 2,4,5-T. 2,4,5-T was officially banned in 1970. Before the introduction of chemical herbicides, a female working population was seasonally engaged in rice weeding. For a period around 1950–1955 rice weeding was still done manually although chemical weeding was being experimented with. It is therefore reasonable to assume that the rice weeders working during this period were exposed to phenoxy herbicides, mainly through skin contact.

¹ Unit of Cancer Epidemiology, University and Main Hospital, Torino, Italy.

² Institute of Agronomical Chemistry, University of Torino, Torino, Italy.

³ Department of Pathology, Main Hospital, Alessandria, Italy.

⁴ Department of Pathology, Ospedale Cervello, Palermo, Italy.

⁵ Institute of Pathology, University of Verona, Verona, Italy.

⁶ Istituto Superiore de Sanità, Roma, Italy.

Subjects and methods

Case identification and ascertainment

New cases of soft-tissue sarcoma with a proved or suspected histological diagnosis in 1981–1983 (age of person ≥ 20 years) were identified through all of the pathology departments of the three provinces (hospitals of Vercelli, Novara, Alessandria, Borgomanero, Biella, Casale Monferrato). The search was extended to six pathology departments in the city of Torino and to the National Cancer Institute in Milan, where residents in the three provinces could be referred for treatment. Overall, 135 potential cases were identified (116 in hospitals located in the three provinces and 19 in Torino or Milan). Visceral sarcomas were excluded.

Histological specimens (with the exception of the cases diagnosed in Torino and Milan and four other cases) were independently reviewed by two pathologists (AD, RP), blindly with respect to the exposure status and to previous diagnosis. The classification of the World Health Organization (WHO) was adopted for the soft-tissue sarcomas (7).

Of the 135 identified cases, 18 were excluded because the person's town of residence was unknown or the person was not traced after five attempts (table 1). After the histological review, 26 cases were discarded. For five others the two pathologists agreed on the diagnosis of soft-tissue sarcoma but did not agree on the histological type. After a check of the clinical records, four cases turned out to be visceral sarcomas and were excluded. For nine histologically confirmed cases, we met with refusal to participate, and for two in which the subject was deceased no relative could be traced. Of the remaining 75 cases, 68 were incident (ie, newly diagnosed in 1981–1983), and seven turned out to be prevalent (ie, diagnosed prior to 1981) during a check of the clinical records. The seven prevalent cases were

not included in the analyses. Of the 68 subjects remaining, 44 were living and 24 were deceased.

The age-standardized annual incidence rate (including interviewed and noninterviewed subjects and excluding prevalent and visceral cases) was 2.8/100 000 [95 % confidence limits (CL) 1.3–4.2] for the men and 2.0 (95 % CL 0.8–3.1) for the women (age ≥ 20 years). These rates do not take into account the histological revision in order to be comparable to the rates reported in 1976–1977 by the Cancer Registry of the Province of Varese (an area close to the study area). The latter rates (per 100 000, age ≥ 20 years) were 2.3 (95 % CL 0.4–4.1) for the men and 1.5 (95 % CL 0.06–2.9) for the women (23). (All the rates have been age-standardized on the basis of the world population.)

Living referents

A random sample of eligible referents (30 living men and 30 living women aged ≥ 20 years from each province) with a distribution, by municipality, representative of the population of each province was drawn from electoral rosters. The overall number of referents was approximately twice the expected number of eligible cases. In fact, a total of 168 individuals from 65 municipalities were identified versus 180 expected. (Four electoral offices did not respond at all, and a few offices provided a lower than required number of individuals, for a total of 12 losses.)

Deceased referents

Thirty-seven of the 135 persons originally enrolled as cases were deceased at the time of the interview. Therefore, for each of these 37 persons, two deceased individuals, to be matched to the deceased subject by age (± 4 years), sex, and year of death, were identified as referents from the same municipality as the deceased subject through the demographic offices of the municipalities. There was no selection of the cause of death, with the exception of the exclusion of one suicide (for ethical reasons).

Seventeen deceased subjects with soft-tissue sarcoma had two matched referents. Only one referent met the matching criteria for six cases. No individual with the corresponding requirements was found for five cases. The municipalities did not respond for eight referents. And, finally, no referent was sought for five persons with soft-tissue sarcoma because they were enrolled in the National Cancer Institute in Milan after the scheduled end of the study. A total of 40 deceased referents were therefore known for interview purposes, and in fact the relatives of 36 were interviewed.

Interviews

Each enrolled subject was given a code number unrelated to the nature of their case-referent status. All subsequent procedures until the final stage of the analysis were blind. Each living subject was mailed an invi-

Table 1. Distribution of cases and referents by categories of inclusion/exclusion.

	Cases	Referents
Originally enrolled	135	208
Excluded or lost		
Residence unknown	10	•
Untraced individual	8	20
Refusal ^a	9	26
Relative not traced ^b	2	—
Change of residence ^c	1	4
Histologic diagnosis not confirmed	26	•
Visceral sarcoma ^d	4	•
Prevalent case ^d	7	•
Histologically confirmed and interviewed nonvisceral cases	68	•
Interviewed referents	•	158

^a Including individuals not available for interview due to illness, deafness or mental disorders.

^b Relatives of deceased individuals were not available.

^c Moved to other provinces; in strict sense not eligible.

^d The four visceral and seven prevalent sarcomas were identified as such after a check of the clinical records after the cases had been enrolled. (See the text.)

tation to be interviewed, with no mention of the precise purpose of the study. Whenever possible, the invitation was followed by telephone calls in an attempt to schedule an interview date. Otherwise, additional letters inviting the individual to suggest a possible date for the interview were sent with a prepaid envelope inside. For each individual, at least five attempts (either by telephone or by a home visit by the interviewer) were made before the individual was considered untraceable. For deceased persons the next-of-kin was identified, and the same procedure was followed.

A simplified postal questionnaire was sent to subjects who, for any reason, refused a direct interview but agreed to provide information by mail. Overall, information on 16 cases and 37 referents was obtained in this way. The postal questionnaire was suitable for an exposure assessment identical to that provided by the direct interviews.

All the interviews were carried out by a trained interviewer (LM). The questionnaires collected (i) demographic information, (ii) a life-long smoking history, (iii) a life-long occupational history (including job titles, addresses of the plants or farms, and types of products or crops), (iv) a history of radiological therapeutic treatment, and (v) a history of residence changes, including a specific question on periods spent in rice-growing areas. In addition the questionnaire included a list of job titles potentially involving exposure to phenoxy herbicides or chlorophenols (including jobs in sawmills, the paper and leather industries, highway and railway maintenance, and flower and market gardening). Two additional sheets were filled out for those who had worked in agriculture, one for rice growing and one for other crops. In these sheets information was collected on the involvement in jobs entailing the handling, transportation, and distribution of herbicides; herbicide spraying procedures; other specific jobs involving (or not) herbicide exposure (ie, weeding and water regulation in rice growing); knowledge of exposure to herbicides (and more specifically to phenoxy acids or chlorophenols) or insecticides. This part of the questionnaire was prepared in cooperation with pesticide researchers.

Demographic information (including current occupation and educational level) for nonrespondents was collected from demographic offices of the municipalities of residence.

Assessment of exposure

Two experts with experience in chemical aspects of agriculture (EZ, AC) were asked to assess the exposure to phenoxy acids for each job recorded in the interviews. This assessment was done independently by the two and in a blind manner. The following criteria were used for reading and interpreting the questionnaires: category 1 = not exposed, category 2 = exposure could not be ruled out, and category 3 = certainly exposed. Attempts to distinguish between skin contact

and other paths of exposure and between low and high levels of exposure proved not to be feasible. Rice weeders were considered to be exposed to phenoxy herbicides when they worked after 1950 and did not work exclusively in a small rice allotment of their own. Category 2 was used particularly for people engaged after 1950 in corn, wheat and pasture growing. As a first step, a separate exposure assessment was performed by each of the two experts. Subsequently, a joint assessment was made, in which they reached a common evaluation for each recorded job. The latter assessment was used in the analyses.

Herbicide spraying in the area has been chiefly done by tractor.

Coding of occupational histories

In addition to the aforementioned exposure assessment, all occupational histories were coded according to the classification for job titles of the International Labour Organization (4) and the United Nations classification for economic activities of plants or farms (22). All coding work was done by a single person (GC) in a blind manner.

Analyses

The analyses were performed with an HP-61 calculator using programs for epidemiology (25). Age-adjusted relative risks were computed according to Mantel-Haenszel's estimator (19); 90 % confidence intervals were obtained with Miettinen's approximate procedure (20) (the lower limit of each interval corresponding to a 95 % one-tailed confidence limit). In addition to age (in four groups), therapeutic X rays and smoking were included as potential confounders. The X-ray exposure represents a known risk factor for soft-tissue sarcoma (3), but there is no evidence of association with herbicide exposure. Smoking is not known to be a risk factor for this kind of tumor, but it was conservatively included as a potential confounder.

Results

Response and characteristics of the subjects

Table 2 reports the educational levels represented by the persons with soft-tissue sarcoma broken down into respondents and nonrespondents. The presented educational levels are those of the persons scheduled for interview (ie, the next-of-kin of deceased subjects). Responding men showed an unbalanced distribution for the cases and referents in the different educational categories (<6 years: 26 cases and 37 referents, ≥6 years: 10 cases and 43 referents; unknown: 1 case and 5 referents); the distribution of the women was more balanced (<6 years: 17 cases and 42 referents; ≥6 years: 12 cases and 30 referents; unknown: 2 cases and 1 referent).

Table 2. Educational levels (years of schooling) for the responding and nonresponding living subjects or the next-of-kin of deceased subjects. Nonresponding individuals include refusals, untraced individuals, individuals whose relatives were not identified, and individuals who had changed residence.

Years of schooling	Living subjects				Next-of-kin of deceased subjects			
	Nonrespondents		Respondents		Nonrespondents		Respondents	
	Cases	Referents	Cases	Referents	Cases	Referents	Cases	Referents
<6	10	18	28	56	4	3	15	23
≥6	1	11	14	65	—	1	8	8
Unknown	5	13	2	1	—	4	1	5

Table 3. Distribution of the living subjects by age group and exposure level (1 = not exposed, 2 = exposure could not be ruled out, 3 = exposed). Exposure refers to any calendar period. The number of subjects for whom information came from postal questionnaires is presented in parentheses.

Exposure level	Age group (years)							
	<55		55–64		65–74		≥75	
	Men	Women	Men	Women	Men	Women	Men	Women
Category 1								
Cases	7 (3)	5 (2)	6 ^a (1)	1	1	6 (3)	7 (1)	4 (2)
Referents	36 (8)	36 (10)	12 (2)	6 (2)	5	9 (5)	1 (1)	2 (1)
Category 2								
Cases	1 (1)	—	1	—	—	—	—	1 (1)
Referents	4	1	2	1	—	—	—	—
Category 3								
Cases	—	—	—	1	—	3 (1)	—	—
Referents	2	2	—	2	—	1	—	—

Table 4. Distribution of the living female subjects by age group and exposure level (1 = not exposed, 2 = exposure could not be ruled out, 3 = exposed). Only women exposed continuously during 1950–1955 have been included.

Exposure level	Age group (years)			
	<55	55–64	65–74	≥75
Category 1				
Cases	5	1	6	4
Referents	36	6	9	2
Category 2				
Cases	—	—	—	—
Referents	—	—	—	—
Category 3				
Cases	—	1	2	—
Referents	—	1	—	—

Among the men 26 (30.5 %) of 85 referents and 15 (40.5 %) of 37 subjects with soft-tissue sarcoma had worked in agriculture during at least some period of their worklife. The women with such occupations were 21 (28.5 %) of 73 referents and 14 (45.5 %) of 31 women with soft-tissue sarcoma. Two male referents and no men with soft-tissue sarcoma were assigned a job title code of rice grower. The respective numbers for the women were three and three (crude odds ratio 2.5). This code was the only job title code mentioning rice growing, and it was assigned when rice growing was the only activity performed in a given work period.

Living subjects

Table 3 reports the absolute numbers of living subjects with soft-tissue sarcoma and their referents by expo-

sure levels and age groups for the two sexes. No men with soft-tissue sarcoma were definitely exposed, and exposure could not be ruled out for only two, the age-adjusted odds ratio being 0.91 (90 % CL 0.21–3.91).

Among the alive women, four subjects with soft-tissue sarcoma and five of their referents were certainly exposed, and one and two, respectively, belonged to exposure category 2. This distribution corresponds to an odds ratio of 2.42 (90 % CL 0.56–10.34) when exposure categories 2 and 3 are combined and an odds ratio of 2.70 (90 % CL 0.59–12.37) for category 3 alone. The odds ratios were age-adjusted in the four age groups.

Table 4 shows the distribution of the living female subjects who were engaged in relevant jobs in the whole 1950–1955 period. Three with soft-tissue sarcoma and one referent met these criteria, all from exposure category 3. Unexposed were 16 women with soft-tissue sarcoma and 53 female referents, as shown in table 3.

Deceased subjects

Table 5 reports the age and exposure distribution for the deceased subjects. There were 24 next-of-kin of persons with soft-tissue sarcoma interviewed and 36 next-of-kin of referents. Three women and no men with soft-tissue sarcoma belonged to exposure category 3, and one woman and one man with soft-tissue sarcoma were classified into category 2. The odds ratio (age-adjusted in two age groups) for the women in exposure categories 2 and 3 was 1.05 (90 % CL 0.21–5.1). When matched pairs or triplets were considered, there

Table 5. Distribution of deceased subjects by age group and exposure status. The number of subjects for whom information came from postal questionnaires is presented in parentheses.

Exposure status	Age group (years)							
	<55		55–64		65–74		≥75	
	Men	Women	Men	Women	Men	Women	Men	Women
Unexposed								
Cases	5	1	5	1	2 (1)	1	1	3
Referents	5 (4)	—	6	2	5 (2)	1	1	4
Exposed ^a								
Cases	—	—	—	—	—	1	1	3
Referents	1	—	2	—	—	—	3 (1)	6 (1)

^a Categories 2 (exposure could not be ruled out) and 3 (exposed) have been combined under this heading.

were only two: One was a triplet in which the subject with soft-tissue sarcoma and the two referents had been definitely exposed to phenoxy herbicides (category 3), and the second was a triplet in which one of the two referents (but not the sarcoma subject) belonged to category 3. Therefore a matched analysis of deceased female subjects was uninformative.

When the towns of residence of the deceased referents were compared with those of the living referents, important differences appeared. Six of the 23 deceased male referents lived in four towns of rice-growing areas versus 3 of 62 living referents. Among the women, 6 of 13 deceased referents lived in two towns with the same characteristics, versus 2 of 60 living referents. This comparison strongly suggests that overmatching of deceased subjects was introduced into the study by the inclusion of residence as a matching factor.

Confounding

Therapeutic X rays and smoking were considered as potential confounders. Overall, only two men and one woman with soft-tissue sarcoma, and one male and no female referents had been exposed to therapeutic radiation before 1981. Confounding by this variable, therefore, can be ruled out.

As for smoking, 24 (65 %) of 37 men and 3 (11 %) of 28 women with soft-tissue sarcoma and 54 (65 %) of 83 male referents and 21 (40 %) of 52 female referents were smokers or exsmokers. (For two male referents information on smoking was not available.) These findings indicate a clear deficit of smokers among the women with soft-tissue sarcoma. Such a pattern can be interpreted as a consequence of the greater proportion of agricultural workers among the persons with soft-tissue sarcoma.

Histology and site of the sarcomas

Table 6 reports the distribution of the cases by histological type according to the WHO classification. Table 7 gives the histological type and site of the tumors for the exposed cases. Among the exposed women with soft-tissue sarcoma (categories 2 and 3 of exposure), there were two chondrosarcomas, two Kaposi sarcomas, two malignant fibrous histiocytomas, one chor-

Table 6. Distribution of the interviewed incident histologically revised cases by histological type, according to the classification of the World Health Organization.

Histological type	Men	Women
Dermatofibrosarcoma protuberans	1	—
Liposarcoma	2	1
Myxoid liposarcoma	3	3
Leiomyosarcoma	4	2
Rhabdomyosarcoma	1	1
Angiosarcoma	1	—
Malignant hemangio pericytoma	1	—
Other vascular malignant tumors	—	1
Synovial sarcoma	1	1
Malignant schwannoma	3	1
Other malignant tumors of the peripheral nerves	2	—
Malignant tumors of nonchromaffin tissue	—	1
Chordoma	—	1
Chondrosarcoma of soft parts	2	3
Malignant giant cell tumor of soft parts	1	—
Malignant fibroxanthoma (malignant histiocytoma)	3	5
Kaposi sarcoma	7	6
Uncertain	1	4
Total ^a	33	30

^a The original diagnosis of the five interviewed incident cases which were not reviewed were one dermatofibrosarcoma protuberans, one angiosarcoma, one malignant histiocytoma, and one Kaposi sarcoma among the men and one malignant schwannoma among the women. These cases were included in the analyses because of the confidence of the high level of the histological diagnosis. One of the men belonged to exposure category 2, while the others were unexposed.

doma, and one leiomyosarcoma. (One case was uncertain with respect to histological type.) No gross differences were noticed between the exposed and unexposed women with respect to the sites of the tumors. Their locations were as follows: head and neck (0 exposed/3 unexposed), retroperitoneal (1 exposed/2 unexposed), upper limbs (1 exposed/4 unexposed), lower limbs (3 exposed/7 unexposed), thorax (1 exposed/3 unexposed), abdomen (1 exposed/1 unexposed), pelvis (2 exposed/1 unexposed), site not specified (0 exposed/1 unexposed).

Table 7. Sex, age, exposure category, job title, years of exposure, and histology and site of tumor (if a case) for the exposed subjects with soft-tissue sarcoma (cases) and the exposed referents.

Case/referent status	Sex	Age (years)	Exposure category ^a	Job title	Years of exposure	Histology and site of tumor
Living case	Female	84	2	Rice weeder	Unknown	Uncertain histology, lower limb
Living case	Female	71	3	Rice weeder	1950–1963	Kaposi, upper limb
Deceased referent	Female	77	3	Rice weeder	1950–1958	·
Living case	Male	55	2	Rice weeder	1950–1984	Dermatofibrosarcoma protuberans, site unknown
Deceased referent	Male	62	2	Farm laborer in rice growing	1950–1952	·
Deceased referent	Female	82	3	Rice weeder	1950–1960	·
Deceased referent	Female	84	3	Rice weeder	1958–1971	·
Deceased referent	Male	86	2	Wheat, corn and pasture grower	1950–1974	·
Deceased referent	Male	43	3	Water regulator in rice fields	1954–1966	·
Living case	Female	74	3	Rice weeder	1950–1967	Chondrosarcoma, lower limb
Deceased referent	Male	79	2	Wheat and corn grower	1950–1971	·
Deceased referent	Female	77	3	Rice weeder	1950–1960	·
Deceased referent	Female	79	3	Rice weeder	1950–1970	·
Deceased referent	Female	81	2	Corn and wheat grower	1950–1967	·
Deceased referent	Male	62	2	Wheat, pasture and corn grower	1950–1970	·
Living referent	Male	54	2	Flower gardener	1950–1984	·
Living referent	Female	56	2	Corn and pasture grower	1952–1984	·
Deceased case	Female	79	2	Wheat and corn grower	1950–1980	Chordoma, pelvis
Living referent	Male	47	3	Rice grower	1960–1984	·
Living referent	Female	52	3	Rice weeder	1963–1968	·
Living referent	Female	64	3	Rice weeder	1960–1971	·
Living referent	Male	44	3	Rice weeder	1955–1968	·
Deceased case	Male	88	2	Wheat and corn grower	1950–1980	Leiomyosarcoma, upper limb
Living referent	Female	69	3	Rice weeder	1955–1970	·
Deceased case	Female	77	3	Rice weeder	1950–1966	Malignant fibrous histiocytoma, pelvis
Living case	Female	73	3	Rice weeder	1961–1963	Chondrosarcoma, thorax
Deceased case	Female	84	3	Rice weeder	1950–1960	Kaposi, lower limb
Living case	Male	64	2	Wheat and corn grower	1960–1970	Liposarcoma, head-neck
Living referent	Female	62	3	Rice weeder	1950–1978	·
Deceased case	Female	75	3	Rice weeder	1950–1970	Malignant histiocytoma, retroperitoneal
Living case	Female	60	3	Rice weeder	1950–1963	Leiomyosarcoma, abdomen
Living referent	Female	47	2	Market gardener	1974–1984	·
Living referent	Female	50	3	Wheat, corn and pasture grower	1970–1984	·
Living referent	Male	65	2	Wheat, corn and pasture grower	1975–1983	·
Living referent	Male	47	2	Wheat, corn and pasture grower	1978–1983	·

(continued)

Table 7. Continued.

Case/referent status	Sex	Age (years)	Exposure category ^a	Job title	Years of exposure	Histology and site of tumor
Living referent	Male	30	2	Wheat, corn and pasture grower	1967–1984	·
Living referent	Male	47	2	Corn and pasture grower	1953–1957 1970–1982	· ·
Living referent	Male	63	2	Wheat and corn grower ^b	1959–1984	·
Deceased referent	Male	77	3	Farm laborer in rice growing	1950–1968	·

^a 2 = exposure could not be ruled out; 3 = exposed.

^b Also engaged in railway maintenance (1953–1978).

Table 7 reports the ages at the time of the interview, vital status, job titles, years of start and cessation of exposure, and the level of exposure (as assessed by experts) for the exposed subjects, in addition to the histological types and tumor sites of those with soft-tissue sarcoma.

Exposure of persons with prevalent cases of soft-tissue sarcoma and those with visceral sarcomas

Of the five women interviewed who were considered to have prevalent cases of soft-tissue sarcoma, four were unexposed and one was definitely exposed, and they belonged to the 55- to 64-year age group. Two persons with visceral sarcoma were interviewed; they were both unexposed.

Discussion

Testing the hypothesis of an association between exposure to phenoxy acids in agricultural practice and soft-tissue sarcomas required a study to be carried out (i) on a population basis and (ii) in an area where phenoxy acids have been widely used. The present study meets both these requirements.

The most important exposures took place in the early 1950s, due to the concurrent presence of manual weeding and chemical spraying. Indeed, an increased risk of soft-tissue sarcoma was shown among the female rice weeders who had been employed in the early 1950s. Exposure among the men was negligible.

Although the present study is limited by a low power, on qualitative grounds our findings are consistent with both those obtained by Hardell & Sandström (14) and Eriksson et al (8) in similar population-based studies and with those of reports on small series of cases among workers exposed to chlorophenols and/or their derivatives in the chemical industry (9, 18).

Studies failing to suggest an association either (i) selected referents from cancer patient files (2) or adopted an approach involving proportional mortality ratios, which implied some loss in sensitivity (10, 21), or

(ii) used a crude categorization of exposures, in terms of occupation at the time of diagnosis (2) or at the time of death (21). A misclassification of exposure may lead to an underestimation of the relative risk, if not a systematic bias (28).

Intensity and duration of exposure should also be kept in mind when different studies are compared, although no clear picture of the levels of exposure in different jobs and different countries is available.

The statistical power of the present study is low since we had planned a sample size suitable for increases in risk of the same order of magnitude of those reported by Swedish authors (8, 14). This outcome is reflected by the large confidence intervals around the relative risks. The one-tailed lower confidence limit was, in most instances, lower than one. Indeed, the target population (female rice weeders affected by soft-tissue sarcomas) was inherently limited in size.

Major biases were prevented.

The similarity of the incidence rates of soft-tissue sarcoma in the study area and in the near province of Varese suggests that case ascertainment was likely to be complete. The analysis was restricted to histologically revised incident cases. Population referents were selected from electoral rosters. Response was reasonable. (Nonrespondents were 9 of 80 for the confirmed incident cases and 26 of 208 referents.) Selection bias is therefore a remote explanation of the findings. As table 8 suggests, almost all of the exposed living females were in fact in the lowest educational level (relative risk in the category $<6 = 3.86$, 90% CL 0.87–17.15). The interviewer was thoroughly trained, all questionnaires were coded blindly with respect to caseness, and exposures were blindly assessed by expert pesticide researchers.

However, the relative risks may have been underestimated because of the following three types of problems:

1. A median latency time of 15 years has been estimated for soft-tissue sarcomas after exposure to chemical agents (13); Fingerhut et al (9) reported figures in the range 9–29 years. Thus a proportion of the cases induced in rice weeders by exposures in the

Table 8. Distribution of living female subjects by age group, exposure category, and educational level.^a

Length of schooling	Age group (years)							
	<55		55–64		65–74		≥75	
	Unexposed	Exposed ^b	Unexposed	Exposed ^b	Unexposed	Exposed ^b	Unexposed	Exposed ^b
<6 years ^c								
Cases	1	—	1	1	3	3	1	1
Referents	12	2	5	3	7	1	2	—
≥6 years								
Cases	4	—	—	—	3	—	1	—
Referents	24	1	1	—	2	—	—	—

^a There are two values missing.

^b Categories 2 (exposure could not be ruled out) and 3 (exposed) are combined under this heading.

^c Age-adjusted odds ratio: 3.86 (90 % confidence limits 0.87–17.15).

early 1950s may have been diagnosed before 1981, when our study started.

2. Elderly women (≥75 years) were less likely to be engaged in highly-exposing jobs in the 1950s, since they were already 45 years of age or older in that period. Their inclusion in the study may have introduced an underestimation of the risks.

3. The procedure of matching deceased referents to the deceased persons with soft-tissue sarcoma with respect to town of residence may have artifactually raised the proportion of exposed referents. The proportion of definitely exposed women was similar among the deceased (3 of 10) and living (4 of 21) women with soft-tissue sarcoma but quite different among the deceased (5 of 13) and living (5 of 60) referents. The choice of a group of living referents, extracted from the general population, for comparison with the deceased subjects inducted as cases is considered to be the best option in case-referent studies; the only flaw is the quality of the interview, obtained from the next-of-kin of deceased subjects (5, 11). If we compare all of the female subjects with soft-tissue sarcoma (living + deceased) with the living referents only, the age-adjusted odds ratio is 2.71 (90 % CL 0.51–14.17). We intend, in any case, to select another reference group of deceased individuals, unmatched to the subjects with soft-tissue sarcoma in respect to town of residence.

In conclusion, our study showed an odds ratio of 2.7 for living women who were exposed to phenoxy herbicides in any period of their life. When we restricted our attention to living women less than 75 years of age and exposed in the 1950–1955 period, an age-adjusted odds ratio of 15.5 (90 % CL 1.3–180.3) was determined (table 4). When exposure to phenoxy herbicides among living females who had a regular job in agriculture (ie, excluding unexposed nonagricultural workers) was analyzed, the age-adjusted odds ratio (Mantel-Haenszel) for exposure category 3 was 3.0.

The number of definitely exposed subjects with soft-tissue sarcoma and referents was negligible among the men. There is no specialized job such as pesticide ap-

plicator in rice growing in Piedmont, and annual herbicide spraying is performed, among numerous other jobs, by unspecialized rice growers or farm laborers.

No dose-response relationship could be considered because we were not able to distinguish between high and low levels of exposure in the exposure assessment (with the exception of the a priori hypothesis concerning the 1950–1955 period). Most of the exposed subjects (both those with soft-tissue sarcoma and the referents) had been employed in rice weeding for more than 10 years (table 7).

Acknowledgments

This research was supported by Regione Piemonte (Ricerca biomedica finalizzata) and by CSI-Piemonte. In addition G Ciccone received a fellowship from the Associazione Italiana per la Ricerca sul Cancro.

We thank also Professor B Giau (Istituto di Economia Agraria, Università di Torino) for his skilled advice and the heads of the pathology departments of the hospitals of Biella, Novara, Vercelli, Borgomanero, Casale Monferrato and of the National Cancer Institute in Milan for access to their files and the submission of histological slides.

References

1. Axelson O. The health effects of phenoxy acid herbicides. In: Harrington JM, ed. Recent advances in occupational health. Churchill Livingstone, Edinburgh 1984, pp 253–266.
2. Balarajan R, Acheson ED. Soft tissue sarcomas in agriculture and forestry workers. *J Epidemiol Community Health* 38 (1984) 113–116.
3. Boice JD. Cancer following medical irradiation. *Cancer* 47 (1981) 1081–1090.
4. Bureau International du Travail. Classification internationale type des professions. Atar SA, Genève 1969.
5. Calle EE. Criteria for selection of decedent versus living controls in a mortality case-control study. *Am J Epidemiol* 120 (1984) 635–642.
6. Coggon D, Acheson ED. Do phenoxy herbicides cause cancer in man? *Lancet* 1 (1982) 1057–1059.

7. Enzinger FR, Lattes R, Torloni R, ed. Histological typing of soft-tissue tumours: International classification of tumours 3. World Health Organization, Geneva 1969.
8. Eriksson M, Hardell L, Berg NO, Möller T, Axelsson O. Soft-tissue sarcomas and exposure to chemical substances: A case-referent study. *Br J Ind Med* 38 (1981) 27–33.
9. Fingerhut MA, Halperin WE, Honchar PA, Smith AB, Groth DM, Russell WO. An evaluation of reports of dioxin exposure and soft tissue sarcoma pathology among chemical workers in the United States. *Scand J Work Environ Health* 10 (1984) 299–303.
10. Gallagher RP, Threlfall WJ. Cancer and occupational exposure to chlorophenols. *Lancet* 2 (1982) 48.
11. Gordis L. Should dead cases be matched to dead controls? *Am J Epidemiol* 115 (1982) 1–5.
12. Greenwald P, Kovasznay B, Collins DN, Theriault G. Sarcomas of soft tissues after Vietnam service. *J Natl Cancer Inst* 73 (1984) 1107–1109.
13. Hardell L. Epidemiological studies on soft-tissue sarcoma and malignant lymphoma and their relation to phenoxy acid or chlorophenol exposure. Umeå University, Umeå 1981. (Doctoral dissertation).
14. Hardell L, Sandström, A. Case-control study: Soft-tissue sarcomas and exposure to phenoxyacetic acids or chlorophenols. *Br J Cancer* 39 (1979) 711–717.
15. International Agency for Research on Cancer. Chemicals and industrial processes associated with cancer in humans. Lyon 1979. (IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans, supplement 4).
16. Istituto Centrale di Statistica. Annuario di statistica agraria. Roma 1959.
17. Istituto Centrale di Statistica. Annuario di statistica agraria. Roma 1969.
18. Lynge E. *Ukrudtsmidler og Kræft*. Arbejdsmiljøfondet, Copenhagen 1984.
19. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. *J Natl Cancer Inst* 22 (1959) 719–748.
20. Miettinen OS. Estimability and estimation in case-referent studies. *Am J Epidemiol* 103 (1976) 226–235.
21. Milham S. Herbicides, occupation and cancer. *Lancet* 1 (1982) 1464–1465.
22. Nations Unies. Index de la classification internationale type, par industrie, de toutes les branches d'activité économique. New York, NY 1975.
23. Regione Lombardia. Epidemiologia dei tumori maligni: Incidenza e mortalità in provincia di Varese: 1976–77. Milano 1981.
24. Riihimäki V, Asp S, Hernberg S. Mortality of 2,4-dichlorophenoxyacetic acid and 2,4,5-trichlorophenoxyacetic acid herbicide applicators in Finland. *Scand J Work Environ Health* 8 (1982) 37–42.
25. Rothman K, Boice UD. Epidemiologic analysis with a programmable calculator. US Department of Health, Education and Welfare, Washington, DC 1979.
26. Sarma PR, Jacobs J. Thoracic soft-tissue sarcoma in Vietnam veterans exposed to Agent Orange. *N Engl J Med* 306 (1982) 1109.
27. Smith AH, Pearce NE, Fisher DO, Giles HJ, Teague CA, Howard JK. Soft-tissue sarcomas and exposure to phenoxy-herbicides and chlorophenols in New Zealand. *J Natl Cancer Inst* 73 (1984) 1111–1117.
28. Tockman MS. Epidemiology in the workplace: The problem of misclassification. *J Occup Med* 24 (1982) 21–24.

Received for publication: 21 January 1986