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STUDIO CASO-CONTROLLO SUI SARCOMI DEI TESSUTI MOLLI
NELLE PROVINCE DI NOVARA ,VERCELLI E ALESSANDRIA

PROTOCOLLO PROVVISORIO

PROVISIONAL
PROTOCOL

Research Protocol.

I. Study design.

The choice of the proper epidemiologic study -to evaluate rapidly the association between herbicide exposures and occurrence of soft tissue sarcoma- is restricted to the retrospective cohort and case-control approaches. In fact a prospective cohort study would require large study populations and long periods of observation.

Retrospective cohort studies have been extensively carried out in occupational settings. In our case however assembling a cohort of workers exposed to Phenoxy herbicides during spraying in the past, would be a difficult, if not impossible task. Furthermore, since the incidence of soft tissue sarcoma is low, the cohort would need to be very large.

On the other hand case-control studies are generally considered to be inappropriate for investigation of a rare exposure. Nevertheless if the prevalence of exposure is sufficiently high in the population of the area selected for study, and the factor may be assumed to be related to a high population attributable risk, a case-control study is a suitable tool to evaluate the causal significance of a rare exposure⁽⁴⁵⁾.

On the basis of these arguments, a case-control study seems to be the proper epidemiologic technique to investigate the effects of herbicide exposures on

the development of soft tissue sarcoma.

II. Incidence of soft tissue sarcoma in Italy.

Nowadays only two Cancer Registries operate in Italy: the Cancer Registry of the Lombardy Region, operating in the Province of Varese and the Cancer Registry of the Piedmont Region, which has in late years limited its coverage to the population of the city of Turin.

Therefore no incidence data are available for the geographic area selected for study. Age-standardized incidence rates of soft tissue sarcoma in the Province of Varese were in 1976-77 2.4 per 100,000 per year in males and 1.3 in females⁽⁴⁶⁾.

Assuming that residents in the three provinces experienced the same incidence as in the Province of Varese, we would expect 16 new cases diagnosed with soft tissue sarcoma per year in males and 9 in females. A survey has been done in every hospital of the three provinces -where a department of Pathology operates- in order to obtain an initial rough estimate of the number of all cases diagnosed with soft tissue sarcoma. Thirty six cases (sixteen in males and twenty in females) of soft tissue sarcoma were histologically diagnosed in 1981 in the three provinces. Table V shows the histological diagnoses of soft tissue sarcoma and the places of residence (when recorded in the pathological logs).

Table V. Histological diagnoses of soft tissue sarcoma in 1981 (suspect cases included). From the Departments of Pathology of following hospitals: Novara, Vercelli, Biella, Casale and Borgomanero.

<u>Novara:</u>	No	<u>Place of residence</u>
Liposarcoma	3	(Cerano, Trecate, Trecate)
Malignant fibrous histiocy. 3	3	(Novara, Novara, Novara)
Dermatofibrosarcoma	1	(Santhia')
Pseudosarcoma fibromatosis	1	(Novara)
Fibrosarcoma	2	(Biella, Parona-PV)
Leiomyosarcoma	1	(Sozzago)
Tot.	11	
residents tot.	10 (4 males, 6 females)	
<u>Vercelli:</u>		
Fibrosarcoma	2	-
Liposarcoma	2	-
Embryonic sarcoma	1	-
Clear-cell sarcoma	1	-
Malignant fibrous histiocy. 1	1	-
Tot.	7 (2 males, 5 females)	
<u>Casale Monferrato:</u>		
Dermatofibrosarcoma	1	-
Fibrosarcoma	2	-
Malignant fibrous histiocy. 1	1	-
Retroperitoneal leiomyosarc. 1	1	-
Tot.	5 (3 males, 2 females)	
<u>Alessandria:</u>		
Rhabdomyosarcoma	2	(Alessandria, Alessandria)
Malignant synovioma	1	(Novi Ligure)
Liposarcoma	2	(Cassano, ?)
Leiomyosarcoma	1	(Lerma)
Malignant undifferentiated neoplasia of connect.tiss. 1	1	(?)
Tot.	7 (4 males, 3 females)	

Table V. cont'd

<u>Biella:</u>	No	<u>Place of residence</u>
Malignant fibrous histiocyoma	2	-
Leiomyosarcoma	2	-
Tot.	4	(2 males, 2 females)
<u>Borgomanero:</u>		
Malignant fibrous histiocyoma	1	(Borgoticino)
Neurofibrosarcoma	1	(Borgomanero)
Tot.	2	(1 male, 1 female)

This estimate may be biased since the actual residence was unknown in several cases and, on the other hand the possibility that some diagnoses have been made in other hospitals out of the area (i.e. in Turin and Milan) cannot be ruled out.

Assuming that all cases were living in the area and that the survey was exhaustive, the crude incidence rates of soft tissue sarcoma are 2.4 per 100,000 per year in males and 2.6 in females.
The total number of inhabitants of the three provinces is 1,386,100 (668,600 males and 717,500 females).

III. Sample size.

Estimates of the relative risk likely to be detected, of the prevalence of exposure in the control group, together with the level of significance and the power, are necessary to determine the size of a case-control study.

A relative risk of about 5-6 has been detected in the Swedish case-control studies.

A guess on the prevalence of exposure among controls runs the risk to be very imprecise.

The National Institute of Statistics (ISTAT) publishes the number of workers employed in the different branches of economic activities. These figures are drawn from the National Census.

Table VI shows the data referring to agricultural workers in the three provinces in 1961⁽⁴⁷⁾.

Table VI.

Working population

in agriculture

% to all workers

Province	M	F	M	F
Alessandria	70,000	52,000	56	52
Novara	43,000	25,000	31	21
Vercelli	36,000	22,000	22	21

Assuming an level of 0.05 and 20% of the population exposed to herbicides, a study of 30 cases and 30 controls would be able to detect an odds ratio of 5 with 90% power⁽⁴⁸⁾. The same relative risk is detected (with the same level and power) with 75 cases and 75 controls (or 43 cases and 129 controls) if only 5% of the population are exposed. An estimate of 5% of the population exposed to herbicides may be considered to be realistic in the three provinces.

On these assumptions the study will consist of 100 cases and 300 controls, since a larger study may permit an evaluation of the dose-response relationship.

IV. Study subjects.

1) Cases.

The case group will consist of all cases of soft tissue sarcoma, who were residents in the Provinces of Novara, Vercelli and Alessandria, aged 21 or over at time of diagnosis.

Both sexes will be included, given the large number of women working in rice-growing, mostly in the past.

The case list will contain both live and deceased cases.

Enrollment of cases into the study will cover the period 1981-1983.

Pathology blocks, slides and medical records will be obtained and reviewed for confirmation of the diagnosis of soft tissue sarcoma.

Specimens will be reviewed by a panel of pathologists, ad hoc set up after the interviews have been conducted.

The goal is to select 100 cases.

2) Controls.

Ideally the controls should be representative of the population from which the cases derived.

In this study the controls will be selected from different sources.

Each case will be matched on sex, age (\pm 3 years) and province of residence to two controls, identified from pathological logs, choosing the first diagnosis filed immediately before the case and the first filed immedia-

tely after which match. The diagnoses of malignant tumours will be excluded.

The second group will consist of population controls randomly drawn from the general population only in the largest towns (Novara, Vercelli, Alessandria, Biella). They will be compared to the cases living in the same towns. This limitation is due to difficulties in drawing a sample from the Registry Office's files of hundreds of little towns. The case:control ratio for population controls of larger towns will be at least of 1:4.

The choice of two series of controls is suggested by the need of assuring a high comparability of cases and controls. Since a population-based series of cases will be assembled, population controls will be especially comparable to cases.

For cases who have died the controls could be selected from the mortality files of the three provinces. In addition to age of death these controls could be matched to the cases on year of death. The next of kin will be interviewed.

V. Interview.

Interviews will be conducted by trained interviewers, using a field-tested questionnaire. The questionnaire is being designed to elicit a complete occupational history with emphasis on occupational exposure to Phenoxy and Chlorophenols herbicides.

Information will be collected on the following items: demographic characteristics, smoking habits and the long life occupational history. For each job of cases and controls the job title, the activity of the plant or farm, name and address of the plant or farm, the specific workplace of the subject and the relevant dates will be collected. For people having worked in rice-growing a detailed form will be filled; this will deepen information on jobs entailing exposure to herbicides. The form is being established with the cooperation of agronomists.