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Cancer risk in a cohort of licensed pesticide users

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CORRAO G, CALLERI M, CARLE F, RUSSO R, BOSIA S, PICCIONI P. Cancer risk in a cohort of licensed pesticide users. *Scand J Work Environ Health* 1989;15:203–209. First admissions to the hospital among 25 945 men living in southern Piedmont and holding a license authorizing them to use pesticides were analyzed in a study of the cancer risk related to exposure to pesticides. Standardized incidence ratios significantly higher than one were encountered for malignant skin cancers and lymphomas. The risk of lymphoma was particularly high in predominantly arable areas. The standardized incidence ratios for tumors of the nervous system and hematopoietic tissue showed an interesting age-related pattern and a higher risk in areas primarily devoted to forest tree plantation, but did not reach significance. Certain hypotheses are advanced to explain these findings.

Key terms: cohort study, occupational exposure.

Several epidemiologic studies have investigated the relationship between pesticide exposure and the onset of cancer. A review of the literature reveals a complex and far from uniform picture. Blair et al (1) observed that rural populations have a different site distribution of cancer from other population groups. They reported a lower incidence of neoplasms causally associated with cigarette smoking and a higher risk for tumors at other sites, such as stomach, prostate, skin, lymphatic and hematopoietic tissues. A relationship between these tumor sites and chemical compounds used in agriculture has often been suggested (1–12).

Several authors have studied the relationship between exposure to phenoxyacids and chlorophenols and soft tissue sarcomas and lymphomas. However, while numerous reports have supported this hypothesis (13–17), the International Agency for Research on Cancer (IARC) maintains that “case-reports on cutaneous non-Hodgkin’s lymphoma and epidemiological results from three case-control studies from one country and from some relatively small cohorts in another country provide limited evidence for the carcinogenicity of phenoxyacids and chlorophenols, but do not allow unequivocal identification of the compounds involved (including those present as impurities in technical-grade compounds [p 50])” (18).

Several authors have suggested that exposure to insecticides such as organochlorine may cause leukemias and aplastic anemias (19), while others did not observe any such connection (20). As a result IARC (18) has stated that “the available data from case reports and from epidemiological studies provide inadequate evi-

dence to evaluate the carcinogenicity of organic pesticides as a broad class or as individual compounds [p 50].”

Furthermore, many studies suggest that there is a relationship between agricultural activities (and sometimes exposure to pesticides) and the onset of cancer of the bladder (12, 21), nasal sinus (5), brain (21, 22), ovarian mesothelium (23), and lung (24–28).

Thus, while several reports indicate a link between certain pesticides and certain tumor sites, this information is still insufficient, and additional data are needed. Research has to overcome several hurdles in this instance. First, it is not easy to assemble large enough cohorts of agricultural workers. Second, the real exposure history is not easily identified. Third, a matching reference group is difficult to find due to the peculiarities of rural populations.

The area examined in this paper is southern Piedmont (provinces of Asti, Alessandria and Cuneo), where 20 % of the occupationally active men are employed in agriculture and the land is cultivated with crops (30 % arable, 10 % woodland, 20 % pasture and 40 % other crops). Furthermore, in this area, the consumption of chlorophenoxyacetic herbicides was higher than the national average: 0.123 kg/ha in 1970 compared with a national average of 0.060 kg/ha.

Subjects and methods

Description of the cohort

The cohort consisted of 25 945 male farmers licensed between 1970 and 1974 to buy and use pesticides denominated by Italian law as toxicologic classes I and II. This period has been chosen because the Italian law on pesticide licenses came into force only in 1970. In that year the Inspectorate of Agriculture received applications for licenses from all farmers who were already using pesticides, and the licenses were issued over

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the next five years. Thus our cohort also included agricultural workers with a previous history of exposure to such products.

Region of the Piedmont Hospital Discharge File

The Piedmont Hospital Discharge File is a computerized file set up on 1 January 1976 and updated until 31 December 1983. The records are exhaustive, covering all admissions to public hospitals and private clinics in the Piedmont region.

Methods

The flow chart used for our study is shown in figure 1. The main features are the checking of the diagnoses reported in the discharge files, the transformation of the discharge file to a file of discharged patients, and the calculation of standardized incidence ratio (SIR) values.

Checking the diagnoses in the discharge file

From the discharge file we extracted reports on all male patients residing in the provinces of Cuneo, Asti, and Alessandria, born before 1952, and diagnosed as suffering from bone, connective tissue or skin tumors [International Classification of Diseases (ICD) 1700—1739]; tumors of the brain or other parts of the nervous system (ICD 1910—1929); lymphatic or hematopoietic tissue tumors (ICD 2000—2099).

Our interest was focused on these diseases in view of the fact that one of our earlier surveys revealed a high incidence of tumors at these sites (29). Using a stratified sampling system (in which each stratum was represented by groups of hospitals homogeneous in size and degree of specialization), we sampled a group of hospitals where we were able to find clinical reports on patients affected by the diseases in question. Two doctors unaware of the purpose of our investigation recoded the original diagnoses, and their recodings were subsequently compared with the original codings listed in the file.

Figure 1. Flow chart of the study.

This procedure enabled us to calculate the proportion of conflicting diagnoses for each disease and to assess whether the discrepancy was uniformly distributed among the subjects exposed and not exposed to pesticides.

Transformation of the discharge file to a file of patients for the present study

From the discharge file we extracted all reports on patients admitted between 1976 and 1983 with the tumors in question, the only difference being that in this case we were interested in all malignant tumors that were diagnosed (ICD 1400–2099). We set up an automatic linkage computer program able to recognize multiple admissions for the same patient on the basis of the first three letters of his/her surname, date of birth, and code of place of birth. In this way we were able to transform the discharge files consisting of 44 494 records to a patient file consisting of 19 494 records.

Calculation of the standardized incidence ratios

We then matched the patient file to the license-holder file and were able to calculate the numerator of admission rates for the persons in this file and the corresponding value for the unlicensed referents, represented by the number of first admissions occurring between 1976 and 1983. We obtained the denominator of the admission rates for the license-holders by calculating the person-years estimated from the sur-

vival rate in each year from 1976 to 1983 on the basis of current mortality rates according to age.

The denominator of the admission rates for the reference group was represented by the difference between the sum of the resident populations in the eight years under examination and the person-years of the cohort. SIR values were then calculated for the diseases considered and for all tumors. An indirect standardization according to age was used, with reference to incidence rates for each disease in the unlicensed population. The confidence intervals for the SIR values were calculated on the basis of a Poisson distribution (30).

The SIR values were calculated for the total cohort, for various age groups, and for groups of villages with the same kind of agricultural activity. The villages in question were identified with a cluster analysis performed on the 560 villages in the three provinces under study on the basis of the distribution of the proportion of farm land devoted to arable crops and woodland in each village.

Results

Table 1 shows the results for the quality control study conducted on each disease under investigation. The results of the study indicate that the records are far from reliable and that the extent of this unreliability varies according to the type of tumor.

Table 1. Results of the quality control checks.

Malignant neoplasm ^a	Records checked (N)	Correct fourth digit ^b (N)	Correct third digit ^b (N)	Other cancer ^c (N)	Non-cancer ^c (N)	Error (%)
Bone (1700–1709)	294	203	220	63	11	25.17
Connective and other soft tissue (1710–1719)	144	86	108	30	6	25.00
Melanoma of skin (1720–1729)	209	171	189	18	2	9.57
Other malignant neoplasm of skin (1730–1739)	581	468	553	24	4	4.82
Brain (1910–1919)	227	206	212	11	4	6.61
Other and unspecified parts of the nervous system (1920–1929)	43	24	25	15	3	41.86
Lymphosarcoma and reticulosarcoma (2000–2008)	190	147	166	21	3	12.63
Hodgkin's disease (2010–2019)	357	302	304	49	4	14.85
Other malignant neoplasm of lymphoid tissue (2020–2029)	357	183	215	133	9	39.78
Multiple myeloma (2030–2038)	246	229	237	3	6	4.88
Lymphoid leukemia (2040–2049)	292	233	259	30	3	11.30
Myeloid leukemia (2050–2059)	176	126	145	29	2	18.18
Monocytic leukemia (2060–2069)	22	11	11	10	1	50.00
Other and unspecified leukemias (2070–2078)	93	51	65	19	9	30.11
Polycythemia vera (2080–2089)	40	38	38	1	1	5.00
Myelofibrosis (2090–2099)	36	28	28	3	5	22.22
Total	3 307	2 500	2 775	459	73	16.09

^a Code of the International Classification of Diseases (ICD), eighth revision, in parentheses.

^b Of the ICD.

^c Incorrectly diagnosed as the cancer in column 1.

Table 2. Results of the quality control after aggregation by pathology.

Site of malignant neoplasm ^a	Records checked (N)	Correct by category (N)	Other cancer ^b (N)	Non-cancer ^b (N)	Error by category (%)
Skin (1720—1739)	790	768	16	6	2.79
Nervous system (1910—1929)	270	253	10	6	6.30
Lymphatic tissue (2000—2029)	904	870	18	16	3.76
Hematopoietic tissue (2030—2099)	905	866	12	27	4.31

^a Code of the International Classification of Diseases, eighth revision, in parentheses.

^b Incorrectly diagnosed as the cancer in column 1.

In table 2 the same results are grouped into tumor site classes. Bone and soft tissue tumors have not been considered due to the high error levels encountered (25.2 and 25.0 %, respectively). In contrast, in other tumor site groups (skin, central nervous system, lymphatic and hematopoietic tissues), the error level was low (2.8—6.3 %) and also uniformly distributed between the records of licensed and unlicensed patients. The degree of occupational risk was therefore calculated only for these diseases.

Table 3 shows the SIR values calculated for these diseases and reveals an SIR significantly greater than one for skin tumors and malignant lymphomas. In contrast, despite a slightly higher degree of risk, the SIR for tumors of the hematopoietic tissue was not significantly increased. With regard to tumors of the nervous system, the number of cases expected was slightly but not significantly higher than the number observed. The SIR for total tumors was significantly lower than one.

The SIR values were also divided into birth groups (births after 1934; between 1914 and 1933 and before 1913) (table 4). Although statistical significance was found only for skin and nervous system tumors among the older subjects, for all tumors but lymphomas the risk tended to increase with age.

Table 5 shows the SIR values for the license-holders in the three clusters of villages grouped according to agricultural activity. In cluster I, where 92.4 % of the agricultural land is devoted to arable farming, the figures revealed a high risk for malignant lymphomas (SIR 1.8, $P < 0.01$). In cluster II, where 68.8 % of the land is devoted to woodland, only skin tumors had an SIR significantly greater than one (SIR 1.7, $P < 0.05$), though it should be pointed out that the number of person-years was much smaller than in the other two clusters. For this reason, the increased risk of tumors of the nervous system (SIR 1.6) and hematopoietic tissue (SIR 1.6) could be of relevance. We also observed that the SIR for lymphomas was less than one. Finally, in cluster III, where land is devoted to mixed farming (58.0 % arable, 42.0 % woodland), all the SIR values fell between those of the other two clusters.

Discussion

The objective of this study was to discover whether the incidence of certain malignant tumors was higher

among pesticide users than among a reference population in an intensively agricultural area. We therefore examined the first hospital admissions of the men living in three provinces of south Piedmont and authorized to buy and use pesticides in Italy's toxicologic classes I and II. We compared our findings with those on the entire male population residing in the same area but not authorized to use pesticides.

The first limitation of our study stems from the exposure criterion adopted (possession or not of a license to buy and use pesticides), which inevitably resulted in the misclassification of those who were effectively exposed to potentially carcinogenic pesticides despite their not being license holders. The license authorizes holders to buy and use pesticides known to be highly toxic (on the basis of their median lethal dose), whereas our interest was in the carcinogenicity of the pesticides. In fact, the question is irrelevant as far as the potential misclassification of exposure among the cohort under study was concerned. Sampling conducted on the farmers in the area under study revealed that those authorized to buy and use pesticides in classes I and II also employed other products for which no license is required (31). At the same time, a proportion of the reference group considered not exposed in our research was actually occupationally exposed to potentially carcinogenic products that do not require a license, due to their low acute toxicity.

Given the causal association between exposure and tumor onset, the bias described has led us to underestimate the degree of risk (SIR), since the design of our research involved a comparison between a group of the occupationally exposed persons and a population of which at least part, though possibly only a small part, was in some danger of occupational exposure.

The second potential limitation is related to the information source employed in our search for tumor cases among the pesticide license-holders and the reference group. Our quality control study showed that coding errors were irrelevant and in any event uniformly distributed between the subjects "exposed" and those "not exposed." However, we estimated the errors due only to false positives (patients admitted to the hospital with noncancerous diseases or tumors at sites not considered in this study, but wrongly coded as a study site tumor). We did not consider false negatives (patients admitted to the hospital with a tumor at one of

the study sites wrongly coded as a tumor at another site or a noncancerous disease). Though we may assume such errors to be evenly distributed between the two groups compared, any interpretation of the results must necessarily take into account this potential source of bias — since the incidence of the diseases considered is already low, the omission of only a few cases could significantly alter incidence rates that are already unstable.

Another problem arising from the source of information used is that the discharge file covered the whole of Piedmont but did not include admissions to hospitals outside this region. In this context, an investigation was conducted in a cancer hospital of a nearby region that attracts most Piedmont residents. It was found that not only was admission to this hospital always preceded by a period in a Piedmontese hospital, but also that the proportion of emigrations outside our region was evenly distributed between the subjects “exposed” and those “not exposed.” In this instance the check on a single hospital outside the region offered no guarantee that some cases had not been missed.

The number of tumor cases encountered in the cohort of our study was significantly lower than expected. This finding confirms reports in the literature (1, 32) and has been attributed to a lower incidence of smokers (3) and the healthier environment enjoyed by rural dwellers (32). In this context, the sample survey that we mentioned earlier (31) showed a lower incidence of smoking (40 %) than that found among industrial workers in the same area (60 %). While we accept that part of the low tumor incidence is attributable to these factors, it is also possible that the low incidence of tumors among the subjects exposed to the pesticides in question is due to the “healthy worker effect,” a

term used to indicate a series of situations that, as a result of the cohort selection process, leads researchers to underestimate occupational risk. In this specific case, our selection of the cohort was influenced by the fact that the subjects selected had actively requested authorization to buy and use pesticides so that, at least when they presented the request, none of them was suffering from clinically evident cancer. In contrast, during the years in which the cohort was recruited, a certain number of referents had tumors. As a result, due to the short duration of follow-up, the number of prevalent cases recorded is likely to have been higher among the reference group than among the exposed group, especially for diseases with a longer life expectancy. This source of bias also leads to an underestimation of the degree of risk.

The higher incidence of skin tumors might be indicative of exposure to ultraviolet rays typical of farm workers (1). Though this finding does not allow us to hypothesize a chemical etiology for the diseases in question, it does confirm the validity of our research design and the adequate size of our sample.

The higher incidences of nervous and hematopoietic tissue tumors, though not significantly increased for the cohort as a whole, did reveal a clear-cut age-related trend and a greater risk in villages primarily devoted

Table 3. Standardized incidence ratios (SIR) for the overall cohort. (95 % CI = 95 % confidence interval)

Malignant neoplasm	Observed	Expected	SIR	95 % CI
All malignant neoplasms	631	877.81	0.7	0.6—0.8
Skin	58	41.29	1.4	1.0—1.8
Nervous system	25	25.62	1.0	0.6—1.4
Lymphatic tissue	45	31.79	1.4	1.0—1.9
Hematopoietic tissue	49	43.01	1.1	0.8—1.5

Table 4. Standardized incidence ratios (SIR) by birth cohorts. (95 % CI = 95 % confidence interval)

Malignant neoplasm	Birth cohorts								
	1934 and later			1933—1914			1913 and earlier		
	Observed	SIR	95 % CI	Observed	SIR	95 % CI	Observed	SIR	95 % CI
Skin	5	1.1	0.4—2.6	29	1.3	0.9—1.9	24	1.6	1.0—2.4
Nervous system	2	0.4	0.0—1.4	14	0.9	0.5—1.4	9	2.1	1.0—4.0
Lymphatic tissue	10	1.6	0.8—2.9	24	1.3	0.8—1.9	11	1.5	0.8—2.7
Hematopoietic tissue	2	0.4	0.1—1.6	23	1.0	0.6—1.5	24	1.6	0.9—2.2

Table 5. Standardized incidence ratios (SIR) by cluster of villages with homogeneous main crop. (95 % CI = 95 % confidence interval)

Malignant neoplasm	First cluster (arable land)			Second cluster (woodland)			Third cluster (mixed)		
	Observed	SIR	95 % CI	Observed	SIR	95 % CI	Observed	SIR	95 % CI
Skin	22	1.0	0.7—1.6	14	1.7	1.0—2.9	22	1.7	1.1—2.6
Nervous system	10	0.7	0.3—1.3	5	1.6	0.5—3.8	10	1.6	0.8—2.9
Lymphatic tissue	31	1.8	1.2—2.5	4	0.9	0.3—2.3	10	1.0	0.5—1.9
Hematopoietic tissue	24	1.0	0.7—1.7	8	1.6	0.7—3.1	16	1.3	0.8—2.1
Person-years	99 284			29 159			55 393		

to woodland crops. These findings may be related to the widespread use of chlororganic insecticides in the area under study up to the early 1970s (3, 5—7, 10, 19).

Malignant lymphomas showed an SIR significantly higher than one for the total cohort. There are at least two reasons for believing that this finding may be attributable to exposure to chlorophenoxyacetic herbicides, as it has been suggested by many authors (13—17). First, the higher incidence was only found in predominantly arable areas, where greater use is made of herbicides. Second, the use of chlorophenoxyacid products has increased in recent years. Data available in the three provinces under study show that annual consumption rose from 73 659 kg in 1965 to 125 495 kg in 1978. In line with this hypothesis, the absence of an age-related SIR trend suggests that the quantitatively different exposures in the age ranges considered make up for a higher risk among the younger subjects.

Our results do not allow us to reject the hypothesis of an association between occupational exposure to pesticides and the onset of certain tumors. Indeed, they seem to support it, especially in view of their similarity to reports in the literature (external consistency) and their being justified and explained by the geographic and age distribution (internal consistency). Nevertheless, the potential sources of bias described suggest that we should be extremely cautious in interpreting the results of this study. They will only be validated by the monitoring of mortality in the cohort of pesticide users, and this procedure would thus solve the problems raised by the case source employed.

If the results of such a study confirm our present findings, we will carry out a case-referent study on our cohort in order to identify the nature and degree of the association shown in the present study.

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