Pergamon

European Journal of Cancer Vol. 32A, No. 11, pp. 1943–1948, 1996

0959-8049/96 $15.00+0.00

PII: S0959-8049(96)00231-6

Original Paper

Childhood Leukaemia and Exposure to Pesticides: Results of a Case–control Study in Northern Germany

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The association between childhood leukaemia and exposure to pesticides was examined in a population-based case–control study conducted in Lower Saxony, Northern Germany. Between July 1988 and June 1992, 219 newly diagnosed cases were identified, of whom 173 participated in the study. Two sex- and age-matched control groups were recruited: local controls from the same communities as the newly diagnosed cases of leukaemia and state controls from other randomly selected communities in Lower Saxony. An additional study group consisted of 175 cases of solid tumours. When the leukaemia cases were compared with the local controls, positive associations with parental occupational exposure, particularly agriculture-related exposure, were observed, which were statistically non-significant. A significant association was found for pesticide use in gardens (odds ratio = 2.52, 95% confidence interval: 1.0–6.1). No positive associations were seen when the leukaemia cases were compared to the state controls, but this finding could be explained by a higher proportion of state controls living in rural areas. In communities with a significantly elevated standardised incidence ratio of childhood leukaemia over the last decade (1984–1993), the prevalence of pesticide use in the garden was 21%, compared with the 10% in other communities. None of the examined risk factors were more common among cases of solid tumours. Our findings add some evidence to the hypothesis that pesticides are a risk factor for childhood leukaemia, and there are good reasons to consider abundant pesticide use in rural areas as a possible cause for clustering of childhood leukaemia. Copyright © 1996 Elsevier Science Ltd

Key words: child, leukaemia, neoplasms, pesticides, adverse effects

Eur J Cancer, Vol. 32A, No. 11, pp. 1943–1948, 1996

INTRODUCTION

ASSOCIATIONS BETWEEN exposure to pesticides and childhood leukaemia have been observed in several case–control studies [1–7]. The relationship between pesticide exposure and other childhood malignancies [8–16], as well as associations between cancers in adults and occupational pesticide exposure, have been investigated [17, 18]. In a review of studies on parental occupational exposure and the risk of childhood cancer, O'Leary and colleagues concluded that the preponderance of evidence supports the hypothesis that occupational exposure of parents to chemicals increases the risk of cancer in their children [19]. Weisenburger concluded that the epidemiological data linking specific exposure to pesticides to cancer are strongest for haematopoietic cancers (i.e. non-Hodgkin's lymphoma, leukaemia and multiple myeloma) [20].

There are two possible sources of exposure to pesticides in childhood. The first possible source is an indirect contamination from parental occupational exposure to pesticides. Shu and colleagues reported an association between maternal exposure to pesticides during pregnancy and risk of acute lymphoblastic leukaemia (ALL) in children aged under 15 years [2]. Buckley and colleagues also found an association between duration of paternal exposure and the risk of childhood leukaemia (age <18 years) [3]. The second possible source is from a direct exposure to pesticide use on farms, in gardens or from extermination of insects with in the home. Lowengart and associates reported an odds ratio

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Received 11 Mar. 1996; revised 4 Jun. 1996; accepted 10 Jun. 1996.

EJC 32:11-E

(OR) of 6.5 for pesticide use in the garden among leukaemia cases (age <10 years) [1]. Environmental pollution with pesticides restricted to specific rural areas was also suspected to be a possible cause for a cluster of childhood leukaemia in The Netherlands [5].

This article presents data regarding the potential relationship between exposure to pesticides and childhood leukaemia from a population-based case–control study conducted in Lower Saxony. Lower Saxony is a predominantly rural state in Northern Germany, in which the use of pesticides is common practice. The stimulus for this study was the observation of two clusters of childhood leukaemia between 1985 and 1992 [21].

PATIENTS AND METHODS

Data were collected in this case–control study in order to explore possible causes of childhood leukaemia in Lower Saxony. Lower Saxony is a state in Northwestern Germany with approximately 7.4 million inhabitants, of whom 1.25 million are children younger than 15 years. Cases were recruited from the German Children Cancer Registry (GCCR) [22]. Eligibility criteria for the study were: birth after 1 July 1975, age at time of diagnosis less than 15 years, leukaemia diagnosed between 1 July 1988 and 30 June 1993, and residence at diagnosis in the state of Lower Saxony. For each leukaemia case, 1 control was selected from the same place of residence (local controls) and a second one from another community in Lower Saxony by means of a population-weighted sampling scheme (state controls). Controls were matched by sex and date of birth (± 1 year). If a control family refused to collaborate, another control family was contacted. Hence, the number of contacted controls exceeded the number of selected leukaemia cases (Table 1).

As an additional group, cases of central nervous system (CNS) tumours, neuroblastomas, Wilms' tumours and rhabdomyosarcomas were checked for eligibility according to the same criteria as the leukaemia cases. The selection of these particular diagnostic groups was made to achieve a similar number and comparable sex and age distribution as the leukaemia group. The group with solid tumours was recruited not only as an additional study group, but also to enable the investigation of possible recall bias effects in the leukaemia group.

The questionnaire was a translated and adapted version of a questionnaire originally developed by the Childrens' Cancer Group [23]. Questionnaires were mailed by the physician responsible for the cancer treatment (cases) or by the study centre at the GCCR (controls) and were to be returned to the study centre. In addition, telephone interviews were made for validation and completion of the questionnaire and to obtain further information on rare exposures. Parents had to specify all occupations and the respective durations. The questionnaire also contained a list of possible occupationally related health hazards for each parent, among which one item was 'insecticides, herbicides or fungicides'. For all relevant health hazards, parents had to specify if these were present in the year before pregnancy, during pregnancy, and/or after the child's birth. In the telephone interview, information on extermination of insects at home and the use of pesticides on farms and in gardens was collected. It was asked whether extermination of insects had been performed by the parents themselves or by a professional pest controller. Parents who owned a garden or farm or had ever worked as farmers were asked whether they had come into contact with pesticides and, if so, when they had used pesticides. Farmers were also asked whether they worked the land [defined as agriculture (yes/no)] and/ or were cattle breeders.

Statistical analysis

Conditional logistic regression adjusted for social status (high versus other) was applied to compare leukaemia cases with their 1:1 matched local controls. Social status was defined as 'high' if the mother or father had a university degree or if the monthly family income was higher than DM 6000 (approximately £2700). For the state controls, there was no matching for place of residence and several case–control pairs were identical in sex and age. Hence, leukaemia cases and state controls were treated as having been frequency matched [24] and compared using a conditional logistic regression adjusted for degree of urbanisation (urban, mixed, rural) and social status. The group with solid tumours was simultaneously compared to the local and state controls using unconditional logistic regression adjusted for age (< 1, 1–4, 5–9, 10–14 years), sex, degree of urbanisation and social status. For all analyses presented in this paper, only exposures present within the time interval from 2 years prior to the child's birth up to the date of diagnosis (or corresponding reference date for controls) were considered as relevant. Furthermore, only occupations lasting for at least 1 year within this period were taken into account. All analyses were performed using the Statistical Analysis System SAS (Cary, North Carolina, U.S.A.).

RESULTS

The parents of 425 (90%) of 472 eligible children with leukaemia or solid tumours were contacted by the paediatric oncologists (Table 1). Forty-seven families were not contacted for several reasons (non-cooperation of the clinician, unavailability of current address, psychological reasons). The questionnaire was returned by 82% of the parents of children with cancer and by 71% of the contacted control families. Among families who returned the questionnaires, the participation rate for the telephone interviews was somewhat lower for the cancer cases (94%) than for the controls

Table 1. Results of case and control selection

	Number of cases			Number of controls		
	Leukaemia	Tumours	Total	Local	State	Total
Eligible	219	253	472	–	–	–
Contacted	204	221	425	305	308	613
Questionnaire	173 (85%)	175 (79%)	348 (82%)	220 (72%)	213 (69%)	433 (71%)
Telephone interview	160 (78%)	166 (75%)	326 (77%)	216 (71%)	206 (67%)	422 (69%)

Table 2. Distribution of selected demographic characteristics

	Cases (%)		Controls (%)		Matched pairs (%)	
	Leukaemia ($n = 173$)	Solid tumours ($n = 175$)	Local ($n = 220$)	State ($n = 213$)	Leukaemia ($n = 161$)	Local controls ($n = 161$)
Gender						
Male	53.8	48.6	50.9	52.6	52.8	52.8
Female	46.2	51.4	49.1	47.4	47.2	47.2
Age (years)						
< 1	4.6	17.7	5.5	6.1	4.4	3.7
1–4	50.9	45.2	47.7	47.4	50.3	51.6
5–9	31.8	24.6	31.8	33.3	31.7	30.4
10–14	12.7	12.6	15.0	13.2	13.7	14.3
Living in						
Urban area	19.1	15.4	17.7	12.7	18.0	18.0
Mixed area	43.9	46.9	43.6	42.7	43.5	43.5
Rural area	37.0	37.7	38.6	44.6	38.5	38.5
Social status						
Other	74.0	76.0	68.6	75.1	72.7	67.1
High*	26.0	24.0	31.4	24.9	27.3	32.9

* Father or mother with university degree or monthly family income >6000 DM (approximately £2700).

(97%). Among the 173 cases of leukaemia were 145 children with ALL and 28 children with acute non-lymphoblastic leukaemia (ANLL). The group of 175 solid cancers consisted of 75 CNS tumours, 30 neuroblastomas, 43 Wilms' tumours and 27 rhabdomyosarcomas. For the 1:1 matched analyses comparing cases of leukaemia with local controls, 161 matched pairs were available.

Demographic characteristics for the cases and controls are shown in Table 2. As expected, leukaemia cases were similar to both control groups regarding the respective matching factors. More parents of the local controls enjoyed a high social status than parents of children with leukaemia. State controls seemed to be comparable to the leukaemia cases with respect to social status, but the proportion of state controls living in rural areas was higher than in the leukaemia group (44.6% versus 37.0%, two-sided P value = 0.057 from conditional logistic regression analysis).

Parental occupational exposures

The occupations of 'farmer', 'gardener' and 'florist' were regarded as occupations with potential exposure to pesticides. There were only three gardeners (fathers) and five florists (mothers) among all parents of the cases and controls, and no predominance of these professions among case parents was obvious (Table 3). The occupation of 'farmer' was more common among parents of the state controls than among parents of the leukaemia cases, but less common among parents of the local controls. None of these differences were statistically significant. A direct contact with pesticides was reported by 49 fathers (25 of whom were farmers) and 13 mothers (Table 4). Again, the prevalence was highest among the state controls and lowest among the local controls. Correspondingly, ORs were increased (not significantly) in comparisons between leukaemia cases and locals controls, although slightly decreased for comparisons between leukaemia cases and state controls. Regarding the group of solid tumours, the highest risk estimate was observed for maternal exposure to pesticides during pregnancy (OR = 3.01).

Farming, gardening and indoor extermination of insects

Of 748 families with whom telephone interviews could be performed, 78 had been living on farms (Table 5). On these farms, cattle breeding was more common ($n = 75$) than agriculture ($n = 42$). Regarding the comparison between the leukaemia cases and the local controls, a higher risk esti-

Table 3. Parental occupations with potential exposure to pesticides. Occupation lasting at least 1 year and occurring within the time interval 2 years prior to the child's birth and the diagnosis or reference date

	Cases				Controls				OR for leukaemia cases versus local controls	OR for leukaemia cases versus state controls	OR for solid tumours versus all controls
	Leukaemia		Tumours		Local		State				
	%	(n)	%	(n)	%	(n)	%	(n)			
Father											
Farmer	3.7	(6)	4.2	(7)	3.2	(7)	8.2	(17)	1.64	0.50	0.64
Gardener	0.6	(1)	0.0	(0)	0.5	(1)	0.5	(1)	–	–	–
Florist	0.0	(0)	0.0	(0)	0.0	(0)	0.0	(0)	–	–	–
Total	4.4	(7)	4.2	(7)	3.7	(8)	8.6	(18)	1.23	0.55	0.59
Mother											
Farmer	2.4	(4)	1.7	(3)	1.4	(3)	4.3	(9)	3.20	0.55	0.53
Gardener	0.0	(0)	0.0	(0)	0.0	(0)	0.0	(0)	–	–	–
Florist	0.6	(1)	0.0	(0)	0.9	(2)	1.0	(2)	–	–	–
Total	3.0	(5)	1.7	(3)	2.3	(5)	5.2	(11)	1.93	0.63	0.43

Odds ratios (OR) are adjusted for sex, age, social status and degree of urbanisation.

Table 4. Parents with direct occupational exposure to insecticides, herbicides or fungicides

	Cases				Controls				OR for	OR for	OR for
	Leukaemia		Tumours		Local		State		leukaemia cases	leukaemia cases	solid tumours
	%	(*n*)	%	(*n*)	%	(*n*)	%	(*n*)	versus local controls	versus state controls	versus all controls
Father											
Year before pregnancy	5.2	(9)	5.2	(9)	4.1	(9)	9.5	(20)	1.19	0.56	0.79
During pregnancy	5.2	(9)	4.1	(7)	3.2	(7)	8.1	(17)	1.76	0.68	0.71
After pregnancy	2.9	(5)	3.5	(6)	2.8	(6)	7.6	(16)	1.33	0.38	0.65
Ever	5.2	(9)	5.2	(9)	4.1	(9)	10.4	(22)	1.19	0.50	0.73
Mother											
Year before pregnancy	2.3	(4)	1.7	(3)	0.9	(2)	1.4	(3)	1.58	1.62	1.74
During pregnancy	1.2	(2)	1.5	(2)	0.0	(0)	0.9	(2)	–	1.22	3.01
After pregnancy	1.2	(2)	0.0	(0)	0.0	(0)	0.9	(2)	–	1.16	–
Ever	2.3	(4)	1.7	(3)	0.9	(2)	1.9	(4)	1.58	1.16	1.47
Father or mother											
Year before pregnancy	6.9	(12)	6.9	(12)	4.6	(10)	9.9	(21)	1.53	0.73	1.01
During pregnancy	6.4	(11)	5.2	(9)	3.2	(7)	8.5	(18)	2.22	0.79	0.91
After pregnancy	4.1	(7)	3.5	(6)	2.7	(6)	8.0	(17)	1.95	0.51	0.63
Ever	6.9	(12)	6.9	(12)	4.6	(10)	11.3	(24)	1.53	0.62	0.92

Odds ratios (OR) are adjusted for sex, age, social status and degree of urbanisation.

mate was found for agriculture (OR = 2.55) than for cattle breeding (OR = 1.3). Since the state controls more frequently lived in rural areas than the leukaemia cases, a reverse association was observed if the leukaemia cases were compared with the state controls. Accordingly, the use of pesticides in gardens or on farms was most frequent among state control families (21.8%). However, a significant effect for pesticide use was found if the leukaemia cases were compared with the local controls (OR = 2.47, 95% confidence interval (CI): 1.13–5.38), particularly in garden use (OR = 2.52, 95% CI: 1.03–6.14). Regarding the indoor extermination of insects, almost identical prevalences of approximately 25% were found in both cancer groups as well as in both control groups. The numbers of families who engaged a professional pest controller to exterminate insects were very low and hardly differed between groups.

Analyses of subgroups

As some studies have reported weak positive associations between exposure to pesticides and the risk of brain cancer [8, 11, 15], we repeated all analyses for the group of 75 CNS tumours. However, none of the factors examined were found to be significantly more frequent among cases of CNS tumour cases than in the combined group of controls.

In a further step, 11 municipalities ('cluster areas'), which had been identified from the GCCR as having a significantly ($P < 0.05$) elevated standardised incidence ratio of childhood leukaemia over the last decade (1984–1993), were separately investigated. In three of these municipalities, either no case was observed during the study period or the parents refused to participate in the study. From the eight remaining cluster areas, 17 leukaemia cases and 15 corresponding local controls were exploratively studied. For 1 leukaemia case and 2 controls, no telephone interview could be made. The only noteworthy finding was a prevalance of pesticide use in the garden of 21% (6 families out of 29) in the cluster areas, compared with the 10% in other areas. Of the six families living in cluster areas and having used pesticides in the garden, five had a child with leukaemia.

DISCUSSION

The interpretation of our results is made somewhat difficult by the recruitment of two different comparison groups (local and state controls). Local controls were recruited to investigate specific individual factors (e.g. indoor extermina-

Table 5. Farming, use of pesticides and extermination of insects from 2 years before child's birth to date of diagnosis or reference date

	Cases				Controls				OR for	OR for	OR for
	Leukaemia		Tumours		Local		State		leukaemia cases	leukaemia cases	solid tumours
	%	(*n*)	%	(*n*)	%	(*n*)	%	(*n*)	versus local controls	versus state controls	versus all controls
Farming ('yes')	10.0	(16)	7.2	(12)	9.7	(21)	14.1	(29)	1.30	0.73	0.59
Agriculture	5.6	(9)	2.4	(4)	4.6	(10)	9.2	(19)	2.55	0.65	0.35
Cattle breeding	10.0	(16)	6.6	(11)	9.7	(21)	13.1	(27)	1.30	0.79	0.56
Pesticide use ('yes')	17.8	(27)	10.4	(16)	8.8	(17)	21.8	(42)	2.47*	0.81	0.67
In garden	12.9	(20)	7.1	(11)	5.1	(10)	15.4	(30)	2.52*	0.83	0.71
On farm	4.5	(7)	3.7	(6)	4.3	(9)	9.0	(18)	1.64	0.55	0.53
Extermination of insects ('yes')	24.3	(37)	26.8	(42)	27.0	(54)	24.4	(49)	0.83	1.01	1.12
By pest controller	1.9	(3)	3.1	(5)	1.9	(4)	1.5	(3)	1.03	1.20	2.00

Odds ratios (OR) are adjusted for sex, age, social status and degree or urbanisation.
* $P < 0.05$ (two-sided).

Table 6. Prevalences (%) of potential risk factors stratified for degree of urbanisation

	Degree of urbanisation			
	Urban	Mixed	Rural	*P* value*
Profession with potential exposure to pesticides				
Father	2.5	5.1	4.2	0.124
Mother	1.6	2.6	6.6	0.095
Any direct occupational exposure				
Father	1.6	7.3	7.2	0.078
Mother	0.8	2.0	1.6	0.720
Farming	4.2	8.1	15.5	< 0.001
Pesticide use in garden or on farm	7.8	13.0	19.6	0.001

* Mantel extension test for trend.

tion of insects), thereby ruling out a possible confounding of factors related to the place of residence (e.g. pollution caused by local industries). It was thought that because of a possible overmatching, local controls might be less useful for investigating factors related to the region, and state controls were therefore also recruited.

A possible relationship between case–control status and factors such as farming and the use of pesticides might have been confounded by the degree of urbanisation if the latter varied among the cases and controls. Although we used a population-weighted random sampling scheme, in our study, the proportion of children living in rural areas was clearly higher among the state controls than among the leukaemia cases (Table 2). A somewhat higher incidence of childhood leukaemia in urban than in rural areas has been observed in Germany since 1980, when the GCCR was installed [22]. Therefore it is not likely that, compared to state controls, the lower proportion of leukaemia cases living in rural municipalities solely occurred by change. However, results from the comparison of the leukaemia cases with local controls are remarkably different from the results of comparisons with state controls. While, for all factors investigated, ORs are consistently higher than 1 if leukaemia cases are compared to local controls, ORs are less than 1 for most comparisons incorporating state controls (Tables 3–5). Table 6 shows that several of the potential risk factors investigated are related to the degree of urbanisation. As the state controls more frequently lived in rural areas, a plausible explanation for the observation that results depend on the choice of the control group might be that the comparison between leukaemia cases and state controls is negatively confounded by geographic factors, which cannot sufficiently be ruled out by adjusting for degree of urbanisation in the regression models. Hence, for the examination of a possible relationship between exposure to pesticides and case–control status, the local controls might be a better comparison group than the state controls.

In addition to degree of urbanisation, social status could be a possible negative confounder. The proportion of families with high social status was somewhat higher among local control families than among families with leukaemia cases (Table 2). Agriculture, in particular, was a less common source of income among families enjoying a high social status (3.0%) than among those having another social status (6.6%).

A further potential bias could be the misclassification of exposure due to crude exposure assessment. As pesticides were not the exposure of primary interest but just one factor among others that were investigated in this study [21], assessment of exposure to pesticides was solely based on questionnaires and telephone interviews. We do not have any information on the amount and concentration of exposure, nor do we know which particular chemical agents were used. Furthermore, from the occupations of the parents, it was not always obvious why they could have been exposed to pesticides, which suggests that parents sometimes did not know for sure whether a specific substance was a pesticide or not. As the degree of such misclassification might be similar for the cases and the controls, this phenomenon would result in bias towards unity.

The statistical power of an analysis depends on the number of individuals, the prevalence of the risk factor of interest, and the relative risk associated with the risk factor. Given the number of 161 matched pairs, the power of detecting risk factor associated with a relative risk of 2 and having prevalences of 5%, 15% and 25% would have been 46%, 80% and 90%, respectively. This means that the study might have lacked the power to detect a risk factor associated with a small relative risk or with a prevalence of below 15%. Alternatively, the power would have been sufficient to identify a possible risk associated with a factor having a prevalence of approximately 25%, such as the indoor extermination of insects.

The results of our study add little evidence to the hypothesis that parental occupational exposure to pesticides is a risk factor for childhood leukaemia. Only a small number of the parents had occupations in which contact with pesticides was likely. Among those who had been exposed to pesticides, farming was the most common occupation. Regarding the comparison between leukaemia cases and local controls, it seems that if farming was a risk factor for childhood leukaemia, this risk would be more likely to be related to agriculture (OR = 2.55) than to cattle breeding (OR = 1.30). However, in contrast to pesticide use in gardens, pesticide use on farms was not significantly associated with leukaemia. One explanation for this observation could be the lack of statistical power due to the low prevalence of pesticide use on farms (5.5%). A further explanation might be that children probably spent much more time in gardens treated with pesticides than in fields treated with pesticides. The only statistically significant finding was a more frequent use of pesticides in the garden when leukaemia cases were compared with local controls (OR = 2.52). It will be possible to check this finding using data from a nationwide study that is currently being conducted in West Germany.

Similar but more pronounced findings were reported by Lowengart and associates from a matched case–control study of 123 cases of leukaemia in children under 10 years of age [1]. They found an OR of 6.5 associated with garden sprays used at least once per month which remained statistically significant after adjusting for relevant occupational exposures of the father. In addition, the use of pesticides in the household ($\geq$ once/week) was significantly related to case-control status (OR = 3.8). In a population-based case-control study of 309 leukaemia cases (age <15 years) and 618 controls in Shanghai, maternal occupational pesticide exposure during pregnancy was significantly related to ALL (OR = 3.5) and to a lower extent to ANLL (OR = 2.4) [2]. A study in 204 children with ANLL and under 18 years of age conducted by the Childrens' Cancer Group found not only significant effects of maternal occupational pesticide exposure, but also showed a dose–response relationship (higher OR for longer duration of exposure) and a higher risk for younger children [3]. Based on a small number of individuals, Leiss and Savitz found consistently increased ORs for use of pest strips inside the home, but not for home extermination of insects or the treatment of yards with insecticides or herbicides [7]. Weak positive findings were also observed in a study conducted in Mexico City [4]. Buckley and colleagues tried to investigate risk factors for four ALL subtypes [6]. Their results do not suggest that exposure to pesticides is a risk factor only for certain subtypes of ALL. We observed a high prevalence of pesticide use within cluster areas and a predominance of exposure to pesticides among case families in such areas. This notion is in accordance with findings by Mulder and colleagues, who speculated that a locally increased incidence of haematopoietic malignancies in Aalsmeer, The Netherlands, could have been associated with specific local environmental factors, one of which was intensive pesticide use due to flower cultivation [5].

The relationship between the risk of childhood leukaemia and exposure to pesticides is still uncertain, but evidence from several studies suggests a possible link. Nevertheless, further research is necessary and, as realised by Leiss and Savitz, better methods of measuring exposure are needed [7]. Indirect exposure from parental occupation seems to be less important than direct exposure from the use of pesticides in homes and gardens. While in most occupations, there are security regulations restricting human exposure to hazardous substances, safety recommendations for the private use of pesticides are less regulated and might often be disregarded by non-professionals. The possibility of abundant use of pesticides in rural areas should also be taken into consideration in future studies investigating clusters of childhood leukaemia.

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Acknowledgement—The study was supported by the State of Lower Saxony.