

ORIGINAL ARTICLE

Cancer risk in offspring of male pesticide applicators in agriculture in Sweden

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17 December 2002**Aims:** To explore cancer risk from date of birth until 1994 in children, born 1958 or later, of Swedish male pesticide applicators.**Methods:** Records of male pesticide applicators licensed 1965–76 were linked to the Multigeneration Register. The records of their offspring were then linked to the Swedish Cancer Registry and the Cause of Death Register.**Results:** In total 51 cases of cancer were observed, which is significantly lower than the expected 73.0 (standardised incidence ratio (SIR) 0.70, 95% CI 0.52 to 0.92). Tumours of the nervous system was most common, amounting to 20 cases, 39% of all cancer cases (SIR 1.01, 95% CI 0.62 to 1.56). A statistically significant reduced risk for leukaemia was found (SIR 0.43, 95% CI 0.19 to 0.86). For non-Hodgkin's lymphoma, three cases were observed and 4.8 expected (SIR 0.63, 95% CI 0.13 to 1.83). For Hodgkin's disease, five cases were observed versus 3.7 expected (SIR 1.36, 95% CI 0.44 to 3.17). Two cases of testicular cancer were observed and 1.7 expected (SIR 1.19, 95% CI 0.13 to 4.28).**Conclusions:** None of the a priori hypotheses of increased risk of tumours of the nervous system, kidney cancer, leukaemia, lymphoma, soft tissue sarcoma, and testicular cancer in children of male pesticide applicators could be confirmed.

In Sweden around 350 of the annual 45 000 new cases of primary cancer were diagnosed in persons under 20 years of age in 2000. Tumours in the nervous system (31%) and leukaemia (22%) are the most common diagnoses in this age group.¹

Current understanding of the aetiology of childhood cancer is limited and little is known about the role of environmental carcinogens.^{2–3} Ionising radiation, chemotherapeutic agents, and diethylstilboestrol are well established risk factors for childhood cancer.^{4–5} In the search for environmental factors that could cause cancer in children, attention has been focused on the role of parental exposures, particularly on occupational factors, but none has so far been established as a causal factor. Epidemiological studies have suggested increased risks of childhood cancers in children of workers, mainly fathers, exposed to magnetic fields, paints, solvents, petroleum products, metals, radiation, and agricultural chemicals.^{4–8} None of these studies have provided data to indicate how the occupational exposure might affect their offspring.

Parental exposures to pesticides have been suspected risk factors for kidney cancer, acute leukaemia, soft tissue sarcoma, non-Hodgkin's lymphoma, brain cancer, testicular cancer, colorectal cancer, and Ewings bone sarcoma.^{8–15} Residence on a farm, a proxy for pesticide exposure, has been associated with increased risk of a number of childhood cancers.^{9–14–16} An increased risk of leukaemia was found for children whose parents used pesticides at home.^{17–18} Pesticide use in the home has also been linked with childhood soft tissue sarcoma, brain tumours, and lymphoma.^{19–21} Indoor use of some insecticides and pesticide use in the garden and on interior plants was associated with increased risks of childhood leukaemia.¹⁸ The possibility of phenoxy acid herbicides being a cause of soft tissue sarcomas and lymphomas in adults is of interest, as these malignancies are relatively common in childhood and adolescence. In utero and childhood exposures to compounds with oestrogenic activity have been correlated with changes in male

reproductive health and fertility and might be related to the increased risk of testicular cancer.²² So far, however, the results are not consistent and an aetiological relation between pesticide exposure and specific childhood cancer is far from proven. One should bear in mind that childhood cancers are not aetiological homogeneous diseases, and from a biological perspective perhaps specific histology types of tumours should be studied.

Pesticides may enter the body by dermal absorption, inhalation, or oral absorption.^{10–23} Potential mechanisms by which pesticides may lead to cancer in humans remain speculative. Animal studies have shown that pesticides exert their carcinogenic effect through a variety of mechanisms: genotoxicity, tumour promotion, hormonal action, immunotoxicity, and peroxisome proliferation.^{10–24} Immunological mechanisms triggered by pesticides are suspected to be important for the development of leukaemia in adults.

The environment on the farm is supposed to be contaminated, and young children who are likely to spend a large proportion of their time on the floor or ground, and who frequently put objects in their mouths could be exposed. Some children may accompany their parents to the fields. Children have a larger surface to volume ratio than adults, resulting in a larger proportion of skin surface across which absorption can occur.²⁵

Farmers have a lower overall cancer incidence than the general population in Sweden.²⁶ Most of the specific cancer diagnoses showed decreased risks, especially those associated with tobacco smoking. Increased risks were found for lip cancer, skin carcinoma, and malignant melanoma in the head-neck region, mainly due to sunlight exposure. The risks of multiple myeloma and stomach cancer were also increased. Swedish pesticide applicators have the same cancer pattern as farmers, except for prostate and testicular cancer, which is in excess among applicators.^{24–27–28} A large cohort study concerning cancer in offspring of parents engaged in agricultural activities conducted in Norway showed that use of pesticides was associated with cancer at

Main messages

- None of the findings in published studies of increased risk of tumours of the nervous system, kidney cancer, leukaemia, lymphoma, soft tissue sarcoma, and testicular cancer could be confirmed.
- Since this study is small we plan to extend the cohort by adding pesticide applicators licensed in the year 1977 and onwards by using information from The Swedish Board of Agriculture to further investigate a possible relation between paternal exposure to pesticide and cancer risk in their offspring.

an early age.⁹ A significantly increased risk of testicular cancer and non-significant increased risks of tumours of endocrine glands, bone tumours, and Hodgkin's disease were found. A dose-response relation was found between incidence of tumours of the nervous system and use of pesticides. In other studies risk estimates for children of farmers or agricultural workers have not deviated much from the null.²⁹⁻³²

In Sweden, applicators are the most appropriate occupational group for studying effects of pesticides on cancer, but also for investigating carcinogenic effects in their offspring. The aim of this retrospective cohort study was to explore cancer risk among children of male pesticide applicators in comparison with children in the general population.

METHODS

The present study included offspring to licensed pesticide applicators who were followed up for incident cancer in the Cancer Registry. Information was linked from several registers: pesticide applicators licensed 1965-76, Multi-generation Register, Cancer Registry, and Cause of Death Register. The linkage was possible since each register included the personal identification number. This number is unique to all citizens in Sweden and consists of 10 digits: two each for year, month, and day of birth; a three digit serial number; and a check digit.

The cohort of offspring of male pesticide applicators was created by linking the computerised cohort of 20 245 pesticide applicators licensed 1965-76 with the Multi-generation Register. In total 27 329 offspring born between 1958 and 1994 were identified.

Date of death was derived from the Cause of Death Register when an offspring was deceased. The offspring cohort was thereafter followed up in the Cancer Registry from date of birth until death or 31 December 1994. Notification to the Cancer Registry of all malignant and some benign tumours has been compulsory for all physicians and pathologists since the establishment in 1958. Each case is thus in general reported from two different sources.

The expected number of incident cases in the offspring cohort was calculated on the basis of annual cancer incidence in five-year age groups for the whole country. The standardised incidence ratio (SIR) was computed as the ratio between the observed and expected number of cases. The observed number of cases was assumed to be Poisson distributed, and a 95% confidence interval for SIR was derived by means of Poisson distribution tables.³³

A priori hypotheses based on previous studies were that this cohort had increased risk of tumours of the nervous system, kidney cancer, leukaemia, lymphoma, soft tissue sarcoma, and testicular cancer.

Since the number of statistical significant findings is directly related to the number of significance tests performed, the possibility of some findings being due to chance is likely

to be enhanced when testing several hypotheses. However, no correction for multiplicity has been performed in the calculations of confidence intervals.

RESULTS

Among the offspring, 51.5% were males and 48.5% were females. Table 1 presents the distributions of year of birth among the children and father's year of license for pesticide application. The mean age at diagnosis was 9.3 (SD 6.4). Table 2 shows the year of diagnosis distribution.

Table 3 presents observed and expected numbers of cases and SIR for selected cancer sites. In total 51 cases of cancer were observed in the follow up of 472 461 person-years, significantly lower than the expected 73.0 (SIR 0.70, 95% CI 0.52 to 0.92).

Tumours of the nervous system

This site was the most common, amounting to 39% of all cases of cancer in the cohort. The observed number of tumours was close to the number expected, 20 cases; SIR was 1.01 (95% CI 0.62 to 1.56). The majority of the tumours were localised in the brain and the meninges.

Leukaemia

A statistically significant reduced risk for leukaemia was found (SIR 0.43, 95% CI 0.19 to 0.86). Seven of the eight observed cases were acute lymphatic leukaemia; the other was a blast and stem cell leukaemia.

Lymphoma

With regard to non-Hodgkin's lymphoma, three cases were observed as against 4.8 expected (SIR 0.63, 95% CI 0.13 to 1.83). For Hodgkin's disease, there were five cases observed versus 3.7 expected (SIR 1.36, 95% CI 0.44 to 3.17).

Testicular cancer

With regard to testicular cancer, two cases were observed and 1.7 expected (SIR 1.19, 95% CI 0.13 to 4.28).

Table 1 Distribution of gender, year of birth, and father's year of license for pesticide application among offspring to pesticide applicators born 1958-94

	%
Gender	
Males	51.5
Females	48.5
Year of birth	
1958-59	7.0
1960-64	18.0
1965-69	18.9
1970-74	19.1
1975-79	15.9
1980-84	11.4
1985-89	7.1
1990-94	2.7
Year of license	
1965	26.3
1966	10.0
1967	7.2
1968	7.3
1969	6.1
1970	7.3
1971	5.0
1972	7.2
1973	6.8
1974	5.3
1975	6.3
1976	5.2

Table 2 Year of diagnosis distribution of cancer diagnosed 1958–94 among offspring of pesticide applicators born 1958–94

Year of diagnosis	%
1965–69	5.9
1970–74	7.8
1975–79	23.5
1980–84	29.4
1985–89	11.8
1990–94	21.6

Kidney cancer

An SIR of 0.27 (95% CI 0.00 to 1.52) was found, based on one observed versus 3.7 expected cases.

Soft tissue sarcoma

Only one case was found versus 2.7 expected (SIR 0.38, 95% CI 0.00 to 2.09).

Cancer sites not included in the a priori hypotheses

Noteworthy are two non-significant results; an increased SIR for endocrine glands of 1.62 (95% CI 0.33 to 4.73) and a decreased SIR for bone tumours of 0.54 (95% CI 0.06 to 1.93).

DISCUSSION

Offspring of male pesticide applicators, who have used the most acutely toxic pesticides in agriculture, were in this study found to have a statistically significant decreased overall risk of cancer compared with the whole population. None of the a priori hypotheses could be confirmed. For leukaemia a significantly decreased risk was found.

An explanation of the decreased cancer risk could be that the offspring were brought up on farms and have had a healthier environment with regard to air pollution, exhausts, smoking, diet, drinking water, less stress, more physical activity, etc. There could, however, be a number of potentially hazardous agents on a farm, such as pesticides, solvents, motor vehicle fuels, lubricants, dusts, manure gases, infectious agents, mould, antibiotics, fungi, etc., some of which are known or suspected carcinogens. The fact that a blood relationship exists does not guarantee that a child has shared the environment with the father. However, farmers have the lowest rate of divorces in Sweden; for example, in 1960 the

rate was 0.5% among farmers compared to 2.5% in the general population (personal communication with Gunilla Ringbäck, The National Board of Health and Welfare). Parental cancer has been shown to modify the risk of cancer in the offspring.³⁴ Decreased risks in both pesticide applicators and their offspring suggest environmental and/or hereditary factors.

Children born 1958–60 and who have died before 1961 are not included in the offspring cohort. This will have the effect of underestimating the risk of cancer. However, a very conservative estimate is that 0.3 offspring would have been diagnosed with any type of cancer and died during these years.

Applicators smoke less than the general population and this has been used as an explanation for their lower incidence of cancer compared to the general population. Less passive smoking could contribute to the lower risk of cancer in their offspring.

Another question is whether the children are exposed enough to increase the cancer risk and whether it is feasible to use "license for pesticide application in agriculture" as a proxy for pesticide exposure, since neither the applicators nor their children have an increased cancer risk. There is no individual information of pesticide use in the pesticide applicator cohort. A random sample of 268 applicators was studied with reference to pesticide trade name, application days per year and years, application method, wearing protective clothing, tobacco habits, and occupational history during the 1950s, 1960s, and 1970s.²⁸ That study showed that few of the applicators worked full time applying pesticides. The most common occupations were in agriculture and/or forestry (70%), and in horticulture (10%). The remainder worked in a variety of occupations. The majority had used pesticides, some already during the 1950s. Wearing protective clothing has, despite the special education, been only slightly more frequent than among farmers in general, and as late as in the 1970s about 50% never or seldom wore mask, glasses, or dress when applying pesticides.

In Sweden, the sales of phenoxy acid herbicides and other pesticides increased steeply from the introduction in the late 1940s until the middle of the 1970s.^{35–36} Licensed pesticide applicators and farmers are the occupational groups most exposed to pesticides. Since 1965 it has been mandatory to have a licence for handling the most acutely toxic pesticides in Sweden. A cohort of 20 245 pesticide applicators with licences issued between 1965 and 1976 was established

Table 3 Observed and expected number of cases 1958–94, by cancer site among offspring of pesticide applicators born 1958–94

Site (ICD7)	Diagnosis	Obs	Exp	SIR (95% CI)
178	Testis	2	1.7	1.19 (0.13 to 4.28)
180	Kidney	1	3.7	0.27 (0.00 to 1.52)
190	Malignant melanoma	1	1.7	0.58 (0.01 to 3.24)
192	Eye	2	2.6	0.76 (0.09 to 2.75)
193	Nervous system	20	19.8	1.01 (0.62 to 1.56)
193.0	Brain (incl. meninges)	17*	16.4	1.03 (0.60 to 1.65)
194	Thyroid gland	1	1.3	0.78 (0.01 to 4.34)
195	Endocrine glands	3	1.8	1.62 (0.33 to 4.73)
196	Bone	2	3.7	0.54 (0.06 to 1.93)
197	Connective tissue, muscle	1	2.7	0.38 (0.00 to 2.09)
200	Non-Hodgkin's lymphoma	3	4.8	0.63 (0.13 to 1.83)
201	Hodgkin's disease	5	3.7	1.36 (0.44 to 3.17)
204	Leukaemia	8	18.4	0.43 (0.19 to 0.86)
	Other	2†	7.0	
All		51	73.0	0.70 (0.52 to 0.92)

*Cases included in ICD 193.

†Cancer site: 153 (colon) and 205 (mycosis fungoides).

earlier. Cancer risks in the cohort have been studied and reported in several papers.^{26–28 37 38} Around 70% of the pesticide applicators were occupied in agriculture and the majority had used pesticides, some as early as in the 1950s.

There are some advantageous features specific for this study. The large cohort of pesticide applicators is unique and consists of the occupational group most exposed to pesticides in Sweden. Another advantage is that the Swedish Cancer Registry is population based, with high quality and coverage.^{1 39 40}

Another advantage of this cohort study is that it is free from recall bias. Many studies of childhood cancer and pesticide use suffer from methodological limitations. Most of the previous epidemiological investigations have been case-control studies with few exposed cases and the possibility of recall bias.

A disadvantage of the study is that individual confounding factors and detailed pesticide exposure are not available, either for the pesticide applicators or their offspring.

“License for pesticide application in agriculture” was used as surrogate for pesticide exposure. However, the cancer risks associated with pesticide exposure in the general population would not be higher than among pesticide applicators and their offspring.

To further investigate a possible relation between paternal exposure to pesticide and cancer risk in their offspring, we plan to extend the cohort by adding pesticide applicators licensed in year 1977 and onwards by using information from The Swedish Board of Agriculture.

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