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

Y Rodvall, J Dich, K Wiklund

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 toal 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.2–4 Ionising radiation, chemotherapeutic agents, and diethylstilboestrol are well established risk factors for childhood cancer.4–7 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.8–11 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 Ewing’s bone sarcoma.12–15 Residence on a farm, a proxy for pesticide exposure, has been associated with increased risk of a number of childhood cancers.12–17 An increased risk of leukaemia was found for children whose parents used pesticides at home.18–20 Pesticide use in the home has also been linked with childhood soft tissue sarcoma, brain tumours, and lymphoma.12–18 Indoor use of some insecticides and pesticide use in the garden and on interior plants was associated with increased risks of childhood leukaemia.12 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.21 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 aetio logically 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.22–24 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, immuno toxicity, and peroxisome proliferation.24–26 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 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.

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 3.7 expected (SIR 1.36, 95% CI 0.44 to 3.17). 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

<table>
<thead>
<tr>
<th>Year of license</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1965</td>
<td>26.3</td>
</tr>
<tr>
<td>1966</td>
<td>10.0</td>
</tr>
<tr>
<td>1967</td>
<td>7.2</td>
</tr>
<tr>
<td>1968</td>
<td>7.3</td>
</tr>
<tr>
<td>1969</td>
<td>6.1</td>
</tr>
<tr>
<td>1970</td>
<td>7.3</td>
</tr>
<tr>
<td>1971</td>
<td>5.0</td>
</tr>
<tr>
<td>1972</td>
<td>7.2</td>
</tr>
<tr>
<td>1973</td>
<td>6.8</td>
</tr>
<tr>
<td>1974</td>
<td>5.3</td>
</tr>
<tr>
<td>1975</td>
<td>6.3</td>
</tr>
<tr>
<td>1976</td>
<td>5.2</td>
</tr>
</tbody>
</table>

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.

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<table>
<thead>
<tr>
<th>Gender</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>51.5</td>
</tr>
<tr>
<td>Females</td>
<td>48.5</td>
</tr>
</tbody>
</table>

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. 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.
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 decreased SIR for bone tumours of 0.54 (95% CI 0.06 to 1.93).

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).

Table 2

<table>
<thead>
<tr>
<th>Year of diagnosis</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1965–69</td>
<td>5.9</td>
</tr>
<tr>
<td>1970–74</td>
<td>7.8</td>
</tr>
<tr>
<td>1975–79</td>
<td>23.5</td>
</tr>
<tr>
<td>1980–84</td>
<td>29.4</td>
</tr>
<tr>
<td>1985–89</td>
<td>11.8</td>
</tr>
<tr>
<td>1990–94</td>
<td>21.6</td>
</tr>
</tbody>
</table>

Table 3

<table>
<thead>
<tr>
<th>Site (ICD7)</th>
<th>Diagnosis</th>
<th>Obs</th>
<th>Exp</th>
<th>SIR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>178</td>
<td>Testis</td>
<td>2</td>
<td>1.7</td>
<td>1.19 (0.13 to 4.28)</td>
</tr>
<tr>
<td>180</td>
<td>Kidney</td>
<td>1</td>
<td>3.7</td>
<td>0.27 (0.00 to 1.52)</td>
</tr>
<tr>
<td>190</td>
<td>Malignant melanoma</td>
<td>1</td>
<td>1.7</td>
<td>0.58 (0.01 to 3.24)</td>
</tr>
<tr>
<td>192</td>
<td>Eye</td>
<td>2</td>
<td>2.6</td>
<td>0.76 (0.09 to 2.75)</td>
</tr>
<tr>
<td>193</td>
<td>Nervous system</td>
<td>20</td>
<td>19.8</td>
<td>1.01 (0.62 to 1.56)</td>
</tr>
<tr>
<td>193.0</td>
<td>Brain (incl. meninges)</td>
<td>1</td>
<td>1.3</td>
<td>1.03 (0.60 to 1.65)</td>
</tr>
<tr>
<td>194</td>
<td>Thyroid gland</td>
<td>1</td>
<td>1.3</td>
<td>0.78 (0.01 to 3.34)</td>
</tr>
<tr>
<td>195</td>
<td>Endocrine glands</td>
<td>3</td>
<td>1.8</td>
<td>1.62 (0.33 to 4.73)</td>
</tr>
<tr>
<td>196</td>
<td>Bone</td>
<td>2</td>
<td>3.7</td>
<td>0.54 (0.06 to 1.93)</td>
</tr>
<tr>
<td>197</td>
<td>Connective tissue, muscle</td>
<td>1</td>
<td>2.8</td>
<td>0.38 (0.00 to 2.09)</td>
</tr>
<tr>
<td>200</td>
<td>Non-Hodgkin’s lymphoma</td>
<td>3</td>
<td>4.8</td>
<td>0.63 (0.13 to 1.83)</td>
</tr>
<tr>
<td>201</td>
<td>Hodgkin’s disease</td>
<td>5</td>
<td>3.7</td>
<td>1.36 (0.44 to 3.17)</td>
</tr>
<tr>
<td>204</td>
<td>Leukaemia</td>
<td>8</td>
<td>18.4</td>
<td>0.43 (0.19 to 0.86)</td>
</tr>
<tr>
<td>Other</td>
<td>2†</td>
<td></td>
<td>7.0</td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>51</td>
<td>73.0</td>
<td>0.70 (0.52 to 0.92)</td>
<td></td>
</tr>
</tbody>
</table>

*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. 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. 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.

ACKNOWLEDGEMENTS

We thank the staff at The Centre for Epidemiology, The National Board of Health and Welfare for valuable help with the matching procedures and for fruitful discussions.

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Financial support: Swedish Council for Social Research

REFERENCES


