Residential Exposure to Pesticide During Childhood and Childhood Cancers: A Meta-Analysis

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abstract

CONTEXT: There is an increasing concern about chronic low-level pesticide exposure during childhood and its influence on childhood cancers.

OBJECTIVE: In this meta-analysis, we aimed to examine associations between residential childhood pesticide exposures and childhood cancers.

DATA SOURCES: We searched all observational studies published in PubMed before February 2014 and reviewed reference sections of articles derived from searches.

STUDY SELECTION: The literature search yielded 277 studies that met inclusion criteria.

DATA EXTRACTION: Sixteen studies were included in the meta-analysis. We calculated effect sizes and 95% confidence intervals (CIs) by using a random effect model with inverse variance weights.

RESULTS: We found that childhood exposure to indoor but not outdoor residential insecticides was associated with a significant increase in risk of childhood leukemia (odds ratio [OR] = 1.47; 95% CI, 1.26–1.72; I² = 30%) and childhood lymphomas (OR = 1.43; 95% CI, 1.15–1.78; I² = 0%). A significant increase in risk of leukemia was also associated with herbicide exposure (OR = 1.26; 95% CI, 1.10–1.44; I² = 0%). Also observed was a positive but not statistically significant association between childhood home pesticide or herbicide exposure and childhood brain tumors.

LIMITATIONS: The small number of studies included in the analysis represents a major limitation of the current analysis.

CONCLUSIONS: Results from this meta-analysis indicated that children exposed to indoor insecticides would have a higher risk of childhood hematopoietic cancers. Additional research is needed to confirm the association between residential indoor pesticide exposures and childhood cancers. Meanwhile, preventive measures should be considered to reduce children’s exposure to pesticides at home.
Although pesticides are essential for eradication of pests in agriculture and for public health, they are toxic chemicals and can affect children’s health in a variety of settings, such as at home, in parks and gardens, and on school grounds. Children greatly increase their chances of pesticide exposure when they play on pesticide-treated surfaces such as a floor or lawn and then put their hands into their mouths. It is known that households with children commonly use and store pesticide products.1–3 The use of pesticides at child care facilities,4 on athletic fields,5 and on school grounds6 could all present potential exposures and health hazards to children.

Because children’s immune systems are still developing, they may provide less protection than adult immune systems. To be specific, their enzymatic and metabolic systems may be less able to detoxify and excrete pesticides than those of adults. Therefore, they are more vulnerable to pesticides. Epidemiologic studies also support the idea that pesticide exposure can have greater impact on children’s health than on adults’ health.7,8 Children exposed to pesticides at home or at school have experienced acute toxic effects on their respiratory, gastrointestinal, nervous, and endocrine systems, as well as other serious medical outcomes.6,9,10

Concern about the health effects of low-level exposure to pesticides in children has been increasing in recent years, generating a substantial number of epidemiologic studies demonstrating associations between pesticide exposures and childhood cancers.11–16 However, most of these studies focused on parental occupational exposure or agricultural exposure, not exposure in the home. We found a few systematic reviews examining the association between residential pesticide exposure and childhood cancers. But the association was not elucidated in these reviews, because authors included parental occupational exposure data or studies investigating multiple risk factors that increase chance findings through multiple statistical testing.12–14

The aim of our study was to perform a systematic review of the currently available epidemiologic evidence to estimate the relationship between residential (or nonoccupational and nonagricultural) childhood pesticide exposure and childhood cancers. We sought to provide scientific evidence for preventive actions and for making legislative decisions.

METHODS

Data Source and Study Selection

We conducted a literature search in PubMed for articles published before February 2014. We used combinations of the following keywords to identify relevant articles: [residential, urban, indoor, house, home, household, domestic or school] AND [pesticide, insecticide, herbicide, fungicide, organochlorine or organophosphorus] AND [children, childhood, youth, teenager, toddler, infant, neonate, prenatal or postnatal] AND [cancer; tumor; malignancy, neoplasm, neuroblastoma, lymphoma, leukemia, sarcoma, astrocytoma, glioma, craniofaryngioma, ependymoma, rhabdomyosarcoma or retinoblastoma]. The search was limited to human studies and written in English. All abstracts were screened to determine their suitability for review.

We included original epidemiologic studies reporting on nonoccupational pesticide exposure and children’s health. We used the following criteria to exclude articles from the meta-analysis. We excluded those not reporting original results (eg, review articles, ecologic studies, or case reports); toxicological studies; studies conducted in occupational settings, on hazardous waste sites, on farms, or in proximity to agricultural pesticides; studies involving only adults or children with Down syndrome or without reporting children’s health outcomes; studies with only pesticides in general (no specific pesticide groups) or studies with a list of chemicals including pesticides; studies without specific windows of exposure; or duplicate studies that included subjects already included in a more complete or more recent study examining a greater number of subjects.

Two authors of this article (M.C. and C.L.) independently retrieved and screened all the titles and abstracts of studies according to the predetermined selection criteria. We also manually screened references in the selected articles for additional relevant studies. The full texts of the studies with potential eligibility were obtained and assessed independently by the 2 authors (M.C. and C.L.) for final inclusion. Any discrepancies were resolved by consensus.

Data Extraction

From each eligible study, 2 authors (M.C. and C.C.) extracted information about the study design, location, study period, study population and control characteristics, exposure assessment method, outcomes, and key findings. The same 2 authors independently extracted and tabulated the most relevant estimators, namely odds ratios (ORs) and 95% confidence intervals (CIs). ORs and CIs are 2 commonly used estimators in most meta-analyses dealing with health risks associated with environmental chemical exposures.12,13,15,17–21 The results were compared and consensus was obtained before the meta-analysis.

After classification of the studies, the data were subgrouped and calculated by pesticide categories, exposure locations, and type of cancer in the following stratified meta-analyses:

- Pesticide category and exposure locations:
  - Indoor pesticide exposure
  - Indoor insecticide exposure
• Outdoor pesticide exposure
• Herbicide exposure
• Outdoor insecticide exposure

Cancer types: acute leukemia, leukemia, lymphoma, hematopoietic cancers (leukemia and lymphoma), childhood brain tumor, and all childhood cancers (including neuroblastoma, Wilms tumor, and soft tissue sarcoma)

We analyzed data from professional home treatment (ie, the work done by licensed pest control professionals) by performing a meta-analysis on data with professional home treatment together with parental home treatment or by using data for professional home treatments alone (if number of studies was ≥2). We calculated dose effect by performing a separate meta-analysis on data of the highest frequency of pesticide uses.

Data Analysis

We performed the meta-analysis by using the Comprehensive Meta Analysis version 2 (Biostat, Inc, Englewood, NJ) in accordance with Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines.22 The random effects model was used in this analysis. The random effects summary of ORs and 95% CIs was estimated to provide an indicator of the overall strength of association between childhood pesticide exposure and childhood cancers. These associations are illustrated in the forest plots. In the plots, the CI for each study is represented by a horizontal line and the estimate of summary OR by a box square. The box area is proportional to the weight, which is the inverse of the variance of the effect estimate from each individual study in the meta-analysis. The diamond and broken vertical line for type of cancer represent the subtotal summary estimate, with CI indicated by its width. The null hypothesis is 1 and is represented by the central vertical dashed line from top to bottom of the plot. All statistical tests were 2 sided, and a P value of <.05 was considered statistically significant.

Assessment of Heterogeneity

Because the current review includes a limited number of studies, and the conventional statistical approach to evaluating heterogeneity using a χ² test (Cochran’s Q) has low power when there are few studies,23 we used the I² statistic to quantify the amount of variation in results across studies that is due to heterogeneity. I² can be interpreted as a measure of the percentage of the total variation that cannot be explained by chance.23 An I² value of 25%, 50%, or 75% can be taken to mean low, moderate, or high degrees of heterogeneity,23 A value of 0% indicates no observed heterogeneity, and estimations from either the fixed effects model or random effects model would be the same. The P values for heterogeneity are based on the Q statistic.

Publication Bias

Publication bias was tested with funnel plots and Egger’s test.24 The funnel plot was made by the natural logarithm of the estimate of ORs versus the SE from all included individual studies in a meta-analysis. We tested funnel plot asymmetry, which can result from unpublished small studies without statistically significant effects, by using the linear regression method.24

Sensitivity Analysis

To measure the robustness and determine whether some of the factors (or possible biases) have a major effect on the results of this meta-analysis, we conducted several sensitivity analyses by

• Removing the study with highest weight
• Removing the studies reporting extreme ORs (the highest and the lowest)
• Removing hospital-based studies (or performing a meta-analysis including only population-based studies)
• Removing extended exposure windows or ill-defined pesticide categories

RESULTS

Study Identification and Characteristics

Figure 1 describes this study’s identification, screening, and selection process. From the initial 277 articles identified from PubMed search, 239 were excluded based on their titles or abstracts, and 17 were excluded based on the full text. We excluded 3 other studies from the analysis. One had a duplicated population, another had a study population located in a region with high agricultural pesticide use, and a third had insufficient data to permit the calculation.25–27 No additional articles were identified from the references cited in the included articles. A total of 16 articles met the full inclusion criteria and were eventually included in the meta-analysis.28–43

The characteristics of the studies used in the meta-analysis are shown in Table 1. All 16 studies are case-controlled studies published between 1993 and 2012. The participation rates for most studies ranged between 65% and 96% for case groups and between 61% and 99% for control groups. The sample sizes ranged from 4532 to 1184 cases,38 and the upper age limits of case groups were between 9 and 19 years. Among these studies, 10 focused on hematopoietic malignancies, 5 on childhood brain tumor (CBT), and 2 on Wilms tumor and neuroblastoma. Four other studies reported data on >1 malignancy.36–38,41

The current meta-analysis was run separately for the 2 windows of exposure: before and after birth to diagnosis, and after birth to diagnosis. Because the outcomes from either window of exposure were similar (as shown in Supplemental Table 3), the
following results and discussion focus on the window from prenatal and after birth until diagnosis.

Publication Bias

We examined the main findings from all studies and included them in an inverse funnel plot of log-transformed odds ratio versus SE. Although we were limited by the small number of studies included, we saw no clear trend of publication bias (or asymmetry) from visual inspection of the plot, with Egger’s test P values at .92, .10, and .14 for indoor pesticides, herbicides, and outdoor pesticide exposures, respectively.

Study Synthesis

Table 2 summarizes the results of the subgroup meta-analyses and the assessment of heterogeneity. The results of 13 studies on home pesticide exposure, grouped by types of childhood cancer and listed by years of publication, are shown in Fig 2. Exposure to indoor insecticides during childhood was associated with a significant increase in risk of childhood leukemia (OR = 1.47; 95% CI, 1.26–1.72; $I^2 = 30\%$) and childhood lymphomas (OR = 1.43; 95% CI, 1.15–1.78; $I^2 = 0\%$).

Additional subgroup analysis combining studies on acute leukemia (AL) yielded elevated risks for exposure to both home pesticides (OR = 1.55; 95% CI, 1.38–1.75) and indoor insecticides (OR = 1.59; 95% CI, 1.39–1.81) with significantly lower heterogeneities ($I^2$ of 0%). When we combined studies on leukemia and lymphoma, we observed a statistically significant association between childhood hematopoietic malignancies and home pesticide exposure during childhood (11 out of 12 data were from indoor insecticides). There was low heterogeneity (OR = 1.46; 95% CI, 1.32–1.60; $I^2 = 5\%$). A positive but not statistically significant association between home pesticide exposure during childhood and CBT was observed (OR = 1.22; 95% CI, 0.83–1.81; $I^2 = 23\%$) and this association decreased after data were combined with those for professional home treatment (OR = 1.11; 95% CI, 0.87–1.42; $I^2 = 5\%$).

We conducted sensitivity analysis on the results to test whether these results were influenced by 1 or 2 studies (Supplemental Table 3). Sensitivity analysis conducted by removing highest weights, excluding extreme ORs, or deleting hospital and friends controls did not change the associations between home pesticide (or indoor insecticide) exposure and childhood AL, leukemia, lymphoma, and childhood hematopoietic malignancies (shown in Supplemental Table 3), and statistical significance remained. Heterogeneities were significantly lower (most $I^2$ were 0%) after extreme ORs were removed in the sensitivity analyses. When we replaced the indoor pesticide data of Ma et al with insecticide data in the rerun meta-analysis, the result was very similar. This finding was consistent with the statement by those authors that “there was a considerable overlap between the definition as well as the results between indoor pesticides and insecticides.”

Subgroup analysis on dose and multiple-agent effect yielded a statistically significant higher risk for childhood leukemia (OR = 1.92; 95% CI, 1.27–2.89) and hematopoietic malignancies (OR = 2.04; 95% CI, 1.40–2.97). However, when the studies on professional home treatment were grouped together, the seemingly significant increase in risk for childhood leukemia became not statistically significant.
<table>
<thead>
<tr>
<th>Study</th>
<th>Sample Size (case/control)</th>
<th>Age (y)</th>
<th>Study Population, Location, and Period</th>
<th>Exposure Assessment</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Davis et al (1993), USA</td>
<td>45/85</td>
<td>≤10</td>
<td>Patients in Missouri, diagnosed 1985–1993</td>
<td>Maternal phone interview</td>
<td>CBT</td>
</tr>
<tr>
<td>Infante-Rivard et al (1999), Canada</td>
<td>491/491</td>
<td>≤9</td>
<td>Patients from metropolitan Montreal, diagnosed 1990–1993</td>
<td>Parental phone interview</td>
<td>ALL</td>
</tr>
<tr>
<td>Meinert et al (2000), Germany</td>
<td>1184,234, 940/2588</td>
<td>≤15</td>
<td>Patients from West Germany, diagnosed 1992–1994</td>
<td>Mail and parental phone interview</td>
<td>Leu, NHL</td>
</tr>
<tr>
<td>Ma et al (2002), USA</td>
<td>162/162</td>
<td>≤14</td>
<td>Hospital patients in northern California, 1995–1999</td>
<td>Maternal in-home personal interview</td>
<td>ALL, Leu</td>
</tr>
<tr>
<td>Urayama et al (2007), USA</td>
<td>294/389</td>
<td>&lt;15</td>
<td>Patients from northern and central California, diagnosed since 1995</td>
<td>In-home interviews with caretaker</td>
<td>ALL</td>
</tr>
</tbody>
</table>

ALL, acute lymphoblastic leukemia; HL, Hodgkin lymphoma; Leu, leukemia; Lym, lymphoma; NHL, non-Hodgkin lymphoma; STS, soft tissue sarcoma.
Part of the reason could be the small number of studies included.

Combining all studies reporting childhood cancers (including neuroblastoma and Wilms tumor) with childhood home pesticide exposure yielded a meta-rate summary OR of 1.40 (95% CI, 1.28–1.52) with a low degree of heterogeneity ($I^2$ of 5%). Therefore, the results show that there is a statistically significant risk of childhood cancers associated with exposures to home pesticides, especially indoor insecticides, during childhood.

Outdoor pesticides include outdoor insecticides, herbicides, and fungicides. Table 2 and Fig 3 show the cancer risks from exposure to residential herbicides during childhood. A statistically significant association between childhood leukemia and exposure to herbicides (OR = 1.26; 95% CI, 1.10–1.44; $I^2$ = 0%) was observed, and the sensitivity analysis confirmed the robustness of this association. The greatest risk estimates were observed in the association between childhood exposure to herbicides and the risk of leukemia. The observed association with increase in risk of childhood lymphoma became not statistically significant during the sensitivity analyses. No association appeared between herbicide exposure and CBT. When studies on all types of childhood cancers were combined, including neuroblastoma and Wilms tumor, a statistically significant association with residential herbicide exposure was observed (OR = 1.35; 95% CI, 1.16–1.55; $I^2$ = 23%). We did not find any statistically significant association between exposure to outdoor pesticides or outdoor insecticides and any types of childhood cancers (Fig 4). Because only a few studies were available on exposure to residential fungicides and childhood cancers, we did not include exposure to fungicides in the current analysis.

**DISCUSSION**

In this meta-analysis, we examined 16 epidemiologic studies on the possible association between residential pesticide exposure during childhood and childhood cancers. Overall, the results suggest that cancer risks are related to the type of pesticide and where it was used. Exposure to indoor insecticides but not outdoor insecticides during childhood was significantly associated with an

### TABLE 2 Meta-Analysis Using Random Effects Model for the Relationship Between Childhood Cancer and Exposure to Residential Pesticides During Childhood

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Study N</th>
<th>Summary OR 95% CI</th>
<th>Heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indoor pesticides</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(A) AL</td>
<td>6</td>
<td>1.59 (1.40–1.80)</td>
<td>.839 0</td>
</tr>
<tr>
<td>Add professional home treatment</td>
<td>7</td>
<td>1.55 (1.38–1.75)</td>
<td>.794 0</td>
</tr>
<tr>
<td>Indoor insecticides</td>
<td>5</td>
<td>1.59 (1.39–1.81)</td>
<td>.725 0</td>
</tr>
<tr>
<td>(B) Leukemia</td>
<td>8</td>
<td>1.48 (1.29–1.70)</td>
<td>.267 20</td>
</tr>
<tr>
<td>Add professional home treatment</td>
<td>9</td>
<td>1.46 (1.29–1.65)</td>
<td>.327 13</td>
</tr>
<tr>
<td>Dose and multiple agents effects</td>
<td>3</td>
<td>1.92 (1.27–2.89)</td>
<td>.859 0</td>
</tr>
<tr>
<td>Professional treatment only</td>
<td>3</td>
<td>2.04* (1.03–3.95)</td>
<td>.061 64</td>
</tr>
<tr>
<td>Indoor insecticides</td>
<td>7</td>
<td>1.47 (1.28–1.72)</td>
<td>.197 30</td>
</tr>
<tr>
<td>(C) Lymphoma</td>
<td>4</td>
<td>1.43 (1.15–1.78)</td>
<td>.578 0</td>
</tr>
<tr>
<td>Indoor insecticides</td>
<td>4</td>
<td>1.43 (1.15–1.78)</td>
<td>.578 0</td>
</tr>
<tr>
<td>(D) Hematopoietic cancers</td>
<td>12</td>
<td>1.47 (1.33–1.62)</td>
<td>.457 0</td>
</tr>
<tr>
<td>Add professional home treatment</td>
<td>13</td>
<td>1.46 (1.32–1.60)</td>
<td>.513 0</td>
</tr>
<tr>
<td>Indoor insecticides</td>
<td>11</td>
<td>1.46 (1.31–1.63)</td>
<td>.388 5</td>
</tr>
<tr>
<td>Dose and multiple agents effects</td>
<td>4</td>
<td>2.04 (1.40–2.97)</td>
<td>.894 0</td>
</tr>
<tr>
<td>(E) CBTs</td>
<td>10</td>
<td>1.12 (1.08–1.16)</td>
<td>.012 8</td>
</tr>
<tr>
<td>Add professional home treatment</td>
<td>5</td>
<td>1.11 (1.07–1.15)</td>
<td>.030 5</td>
</tr>
<tr>
<td>(F) All cancers</td>
<td>10</td>
<td>1.40 (1.28–1.52)</td>
<td>.390 5</td>
</tr>
<tr>
<td><strong>Outdoor pesticide</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(A) Leukemia</td>
<td>6</td>
<td>1.15 (0.95–1.38)</td>
<td>.190 33</td>
</tr>
<tr>
<td>Herbicide</td>
<td>5</td>
<td>1.26 (1.10–1.44)</td>
<td>.762 0</td>
</tr>
<tr>
<td>Yard insecticides</td>
<td>3</td>
<td>1.11 (0.80–2.05)</td>
<td>.002 84</td>
</tr>
<tr>
<td>(B) Lymphoma</td>
<td>4</td>
<td>0.86 (0.82–1.19)</td>
<td>.131 47</td>
</tr>
<tr>
<td>Herbicide</td>
<td>3</td>
<td>1.52* (1.02–2.27)</td>
<td>.060 58</td>
</tr>
<tr>
<td>Yard insecticides</td>
<td>2</td>
<td>1.12 (0.78–1.50)</td>
<td>.314 2</td>
</tr>
<tr>
<td>(C) Hematopoietic cancers</td>
<td>10</td>
<td>1.04 (1.20–1.33)</td>
<td>.660 41</td>
</tr>
<tr>
<td>Herbicide</td>
<td>8</td>
<td>1.33 (1.16–1.52)</td>
<td>.350 10</td>
</tr>
<tr>
<td>Yard insecticides</td>
<td>5</td>
<td>0.75 (0.58–1.09)</td>
<td>.007 71</td>
</tr>
<tr>
<td>(D) CBTs</td>
<td>3</td>
<td>0.95 (0.47–1.89)</td>
<td>.012 77</td>
</tr>
<tr>
<td>Herbicide</td>
<td>2</td>
<td>1.98 (0.94–4.14)</td>
<td>.409 0</td>
</tr>
<tr>
<td>Yard insecticides</td>
<td>2</td>
<td>0.75 (0.48–1.29)</td>
<td>.548 0</td>
</tr>
<tr>
<td>(E) All cancers</td>
<td>16</td>
<td>1.10 (0.93–1.32)</td>
<td>.001 62</td>
</tr>
<tr>
<td>Herbicide</td>
<td>12</td>
<td>1.35 (1.16–1.55)</td>
<td>.221 23</td>
</tr>
<tr>
<td>Yard insecticides</td>
<td>8</td>
<td>1.14 (0.89–1.45)</td>
<td>.028 55</td>
</tr>
</tbody>
</table>

*The summary ORs became not statistically significant in the sensitivity analysis when we removed ill-defined herbicide or highest weight or extreme ORs. Study N: number of studies included. Hematopoietic cancers include leukemia and lymphoma. All cancers include neuroblastoma and Wilms tumor and soft tissue sarcomas in outdoor pesticides. Study results with case numbers <3 are not included in the summary.

a In the study where insecticides against different types of nuisance were reported, data with the highest OR were used.

b In the study where results of different exposure windows in the same study were reported, the windows away from birth were used.

c The data of >10 per year were used in the study, and the data of >5 per year were used in the study.

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increasing risk of childhood cancers including leukemia, AL, and lymphoma but not CBT. Among the 5 studies reporting CBT outcomes in the analyses, 4 studies did not provide specific exposure locations, although the applications were probably indoors. This ambiguity about where pesticides were used could dilute the true effects of residential pesticides and therefore result in the association toward the null. Similarly, the fact that adding professional home treatment in hematopoietic cancers and CBT lowers the summary ORs could also result from the ambiguity of exposure location. The greatest risk estimates were observed in the association between childhood exposure to indoor insecticides and the risk of AL. The risk of childhood hematopoietic malignancies increased with the frequency of use. These observations provide additional support to the positive exposure–response relationship between indoor insecticide use and the increased risk of childhood hematopoietic malignancies.

We did not observe any significant childhood cancer risk associated with exposure to outdoor pesticides. However, when we looked into the different categories of outdoor pesticides, we found that exposure to herbicides was associated with a slightly higher risk of childhood cancers in general, which include leukemia, lymphoma, and CBT, although statistical significance appeared only in association with leukemia. No significant association between outdoor insecticides and childhood cancers was observed. This result emphasizes how important it is to specify the type and location of the pesticide when analyzing pesticide exposure and childhood cancer. Because of the small number of studies included in the current meta-analysis, more studies are needed to confirm these associations.

Results from the current analysis are in agreement with the main findings of 2 previously published studies on residential pesticide exposure and childhood leukemia. Both observed significant associations between insecticide exposure and childhood leukemia. Although these results were based on a small number of studies, the consistency of the main findings suggests that there probably is a higher risk of childhood leukemia with indoor insecticide exposure during childhood. We have observed a slightly elevated risk of childhood leukemia associated with exposure to herbicides, with no evidence of heterogeneity. This finding is also consistent with that reported by Van Maele-Fabry et al but not by Turner et al, and both reported a high degree of heterogeneity ($I^2$ of 61% and 72%, respectively). Neither our study nor the study of Turner et al observed any association between childhood leukemia and exposure to outdoor insecticides during childhood. Like Van Maele-Fabry et al, we also did not observe any association between childhood leukemia and outdoor pesticide exposure.

We also found a positive association between childhood lymphoma and indoor insecticide exposure. Furthermore, the overall childhood cancer risk is elevated with childhood home pesticide exposure. There was a third study reporting that pesticide use at home or in the garden was statistically associated with the elevated risk of lymphoma, leukemia, and CBT. However, Vinson et al did not provide information on specific categories of pesticides or locations of use in their analysis; most of their study results were related to occupational exposure. Therefore, we
could not directly compare our results with those reported by Vinson et al.\textsuperscript{20}
Although most of our findings are consistent with those of the earlier meta-analyses, there are some differences. One main difference is that several studies included in the previous 2 meta-analyses were excluded from the current analysis. These were studies that either were conducted in occupational settings, involved only adults, reported only pesticides in general (not specifying pesticide groups), or included other chemicals with pesticides. Therefore, we eliminate the effects from these studies in the summary ORs.

Although previous meta-analyses took into account exposure locations and pesticide categories when performing stratification analysis, Van Maele-Fabry et al.\textsuperscript{14} reported indoor and outdoor exposures but gave no information about pesticide category. Stratification analyses based on categories of pesticide exposure were run in the study by Van Maele-Fabry et al.,\textsuperscript{14} but no analysis was done on the exposure location for each category of pesticide; therefore, the true risk factors could be diluted. There were also no results from sensitivity analyses provided by Van Maele-Fabry et al.\textsuperscript{14}

Unlike Van Maele-Fabry et al.’s \textsuperscript{14} report and our observation, Turner et al.\textsuperscript{13} reported a statistically significant positive association between childhood leukemia and exposure to residential outdoor pesticides but not outdoor insecticides nor herbicides. However, these results were inconsistent with each other because outdoor pesticides were most likely to be outdoor insecticides or herbicides.

In the current meta-analysis, we divided studies into 3 subgroups based on the pesticide use pattern, such as indoor pesticides and insecticides, outdoor pesticides and herbicides, and outdoor pesticides and insecticides. We used a random effects model to estimate the summary ORs for each subgroup. In the home pesticide (mostly indoor insecticides) category, although some subgroup analyses were conducted on only a limited number of studies (<5), the observed heterogeneity was low ($I^2 \leq 13\%$) in these analyses. We also pooled studies to increase the accuracy of estimated summary ORs for hematopoietic malignancy and all cancers, and we observed zero or low levels of heterogeneity. Similarly, there was no observed heterogeneity in the herbicide category, including estimated summary ORs for hematopoietic malignancy and all cancers. These results of zero or low heterogeneity for indoor pesticides and herbicide exposure indicated the consistency of studies included and suggest that combining data is appropriate. However, the heterogeneity for outdoor pesticide or outdoor insecticide exposure was high. Because these studies included in the current meta-analysis differed in study design, study population, and the exposure and timing of exposure, the heterogeneity of the associations should be interpreted with caution.

Overall, our study has shown that childhood cancer risks are related to the type of pesticide use and its application locations during childhood. Childhood exposure to residential indoor insecticides was associated with an increasing risk of childhood cancers but not outdoor insecticides.

Although meta-analysis is a useful tool to assess causal relationships by combining results from different studies, outcomes can be constrained...
by the limitations of the original studies. In the current analysis, the small number of studies is a major limitation. Very few studies have assessed pesticide exposures and childhood cancers. In addition, other limitations such as selection bias, recall bias, misclassification, and publication bias might limit the applicability of the findings to the general population. To deal with the potential selection bias associated with hospital or friend controls, we performed a sensitivity analysis by excluding Davis et al.32 and Menegaux et al.39 from each pesticide category to reinforce the associations.

To reduce recall bias and misclassification, the studies we included used several strategies to reduce confounding factors and biases, such as restriction of entry to study of subjects with confounding factors, matching controls to have equal distribution of confounders, using standardized questionnaires, identical interviewing procedures for both cases and controls, and adjustment of the results. Publication bias refers to the fact that studies with less significant findings may be less publishable than those with positive outcomes; therefore, they would be unavailable for meta-analyses. For example, one of the studies from the current analysis stated that “neither residential use of insecticides nor use of pesticides in the garden was found to be significantly more frequent in any group of cases with solid tumors compared with controls, therefore no quantitative data were provided.”38 Although the results from the current meta-analysis do not seem to be significantly influenced by publication bias, this bias cannot be completely excluded. Note that when Van Maele-Fabry et al.14 assessed the impact of exclusion of nonpublished data and studies in languages other than English, they found that rerunning the meta-analysis and including nonpublished and non–English-language studies did not substantially modify the results.

A positive exposure–response relationship between residential indoor insecticide use and occurrence of childhood cancers was observed in the current study. Some studies have also shown that maternal pesticide exposure during pregnancy was associated with childhood cancers.35,37,39 Although current data do not establish the most critical exposure period for the occurrence of childhood cancers, their development is probably multifactorial and probably includes gene–environment interactions.11,44–46 Some studies assert a possible association between pesticide exposure with genetic predisposition and defined subtypes of childhood cancers.26,42,43 Additional studies are needed to examine the potential mechanisms by which childhood exposure to pesticides could lead to the development of childhood cancers.

CONCLUSIONS

The current meta-analysis has revealed positive associations between exposure to home pesticides and childhood cancers, with the strongest association observed between indoor insecticide exposure and acute childhood leukemia. Although epidemiologic research is limited in identifying the association between the adverse health outcomes in young children and pesticide uses in residential areas, the findings from the present meta-analysis and those previously published have consistently demonstrated...
associations between pesticide exposure and childhood cancers. While the research community is working toward a better understanding of the causality of pesticides in various childhood diseases, more and more pesticides are being used in farming, in landscape maintenance, and in the home. Therefore, public health policies should be developed to minimize childhood exposure to pesticides in the home. States and local authorities can establish programs, such as integrated pest management, to minimize residential pesticide uses, especially indoor uses. In the meantime, parents, school and daycare teachers, and health care providers can learn about common pesticide types and labeling information and can stay aware of the short- and long-term effects of these chemicals. Every effort should be made to limit children’s exposure to pesticides.

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ABBREVIATIONS
AL: acute leukemia
CBT: childhood brain tumor
CI: confidence interval
OR: odds ratio


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