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Cancer health effects of pesticides

Systematic review

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Abstract

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OBJECTIVE

To review literature documenting associations between pesticide use and cancer.

DATA SOURCES

We searched MEDLINE, PreMedline, CancerLit, and LILACS to find studies published between 1992 and 2003 on non-Hodgkin lymphoma, leukemia, and 8 solid-tumour cancers: brain, breast, kidney, lung, ovarian, pancreatic, prostate, and stomach cancer.

STUDY SELECTION

Each title and abstract was assessed for relevance; disagreements among reviewers were resolved by consensus. Studies were assessed by a team of 2 trained reviewers and rated based on methodologic quality according to a 5-page assessment tool and a global assessment scale. Studies rated below a global score of 4 out of 7 were excluded.

SYNTHESIS

Most studies on non-Hodgkin lymphoma and leukemia showed positive associations with pesticide exposure. Some showed dose-response relationships, and a few were able to identify specific pesticides. Children's and

pregnant women's exposure to pesticides was positively associated with the cancers studied in some studies, as was parents' exposure to pesticides at work. Many studies showed positive associations between pesticide exposure and solid tumours. The most consistent associations were found for brain and prostate cancer. An association was also found between kidney cancer in children and their parents' exposure to pesticides at work. These associations were most consistent for high and prolonged exposures. Specific weaknesses and inherent limitations in epidemiologic studies were noted, particularly around ascertaining whether and how much exposure had taken place.

CONCLUSION

Our findings support attempts to reduce exposure to pesticides. Reductions are likely best achieved through decreasing pesticide use for cosmetic (non-commercial) purposes (where children might be exposed) and on the job.

RÉSUMÉ

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OBJECTIF

Faire une revue de la littérature portant sur l'association entre les pesticides et le cancer.

SOURCE DES DONNÉES

On a repéré dans MEDLINE, Premedicine, CancerLit et LILACS les études publiées entre 1992 et 2003 qui traitaient de lymphomes non hodgkiniens, de leucémies et de 8 tumeurs cancéreuses solides: cerveau, sein, rein, poumon, ovaire, pancréas, prostate et estomac.

CHOIX DES ÉTUDES

La pertinence de chacun des titres et résumés a été évaluée : toute discordance entre réviseurs a été résolue par consensus. Une équipe de 2 réviseurs expérimentés a évalué la qualité de la méthodologie à l'aide d'un outil d'évaluation de 5 pages et d'une échelle d'évaluation globale. Les études obtenant un score global inférieur à 4 sur 7 ont été exclues.

SYNTHÈSE

La plupart des études sur les lymphomes non hodgkiniens etsur les leucémies montraient une association positive avec l'exposition aux pesticides. Certaines montraient une relation dose-réponse et quelques-unes avaient pu identifier des pesticides spécifiques. Certaines études montraient que les cancers étudiés étaient plus fréquents chez les enfants et les femmes enceintes exposés à des pesticides, mais aussi chez les parents qui y étaient exposés au travail. Plusieurs travaux montraient une association positive entre l'exposition aux pesticides et certaines tumeurs solides. Les associations les plus fréquentes concernaient les cancers du cerveau et de la prostate. On a également observé une association entre le cancer rénal chez les enfants et l'exposition des parents aux pesticides au travail. Ces associations étaient plus fréquentes lors d'expositions fortes et prolongées. On a noté des faiblesses spécifiques et des limitations inhérentes dans les études épidémiologiques, en particulier dans la façon de déterminer s'il y avait eu exposition et à quel degré.

CONCLUSION

Nos observations viennent à l'appui des efforts pour réduire l'usage des pesticides. La meilleure façon d'y arriver est probablement en réduisant l'exposition professionnelle ainsi que l'usage à des fins cosmétiques (non commerciales), qui risque davantage d'exposer les enfants.

In recent years, few environmental issues have aroused public concern as much as use of and exposure to pesticides, especially with respect to children's health. Despite many published studies on the relationships between exposure to pesticides and human health, deep controversy surrounds these associations. Since the Supreme Court ruling in 2001 allowing the municipality of Hudson, Que, to pass a bylaw restricting use of pesticides for cosmetic purposes (non-commercial use), many municipalities across the country have passed similar bylaws. Cosmetic use of pesticides remains a complex issue involving arguments about the rights of lawn-care companies and property owners, and increasingly, the effects of pesticides on health. Because randomized controlled trials on the health effects of potentially harmful chemicals cannot be conducted and because of the difficulty of measuring exposure to pesticides and the limitations innate in observational studies, we are still unsure about the effects of pesticides on human health.

As family physicians, cancer specialists, and epidemiologists, we initiated a systematic review of the literature on the effects of pesticide use on chronic health outcomes in order to assess the evidence currently available.

DATA SOURCES

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Primary peer-reviewed studies were found by searching PreMedline, MEDLINE, CancerLit, and LILACS (Spanish- and Portuguese-language articles) databases. These databases were selected as we considered them to be the most comprehensive for studies of causes of cancer among humans. The references lists of all studies were checked to identify papers not captured in our search. We included studies that were systematic in their approach; peer reviewed; and published in English, French, Spanish, or Portuguese. Decisions regarding language restrictions were based on the language capabilities of the reviewers. Studies on organochlorines were excluded, as most of these chemicals are no longer used as pesticides in Canada. Studies were collected and organized according to health effect (Table 1) rather than specific pesticide exposure, because most of the literature considers mixed pesticide exposures.

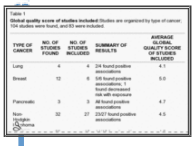

Table 1

Global quality score of studies included: Studies are organized by type of cancer; 104 studies were found, and 83 were included.

Study selection

Our search strategy was designed to be comprehensive. To ensure this, all searches included the key MeSH heading "pesticides" and the MeSH headings for the cancers of interest. Our inclusion criteria were that studies be peer reviewed, that they looked at a cancer with an important burden in Canada, and that they were published between 1992 and 2003. The Canadian Cancer Statistics webpage[1] lists cancers in terms of greatest incidence and associated morbidity and mortality. From this list, 8 categories of solid tumours were selected for inclusion. No studies of acceptable quality were found for testicular cancer or colorectal cancer. We chose 1992 as the starting point for our search because a previous review had covered the period to 1991.[2]

A list of abstracts was produced from each search and distributed to reviewers for evaluation. Reviewer pairs read the abstracts and selected articles that met the inclusion criteria. When articles lacked abstracts or contained too little information on which to make a selection, the original primary studies were obtained for evaluation. Disagreements between reviewers concerning selection of articles for inclusion were resolved by discussion and input from a third reviewer. After abstract selections were agreed upon, the primary studies were collected and distributed back to the reviewer teams for evaluation.

Each study was evaluated by 2 independent reviewers using a quality-assessment and data-extraction tool designed to assess the methodologic quality of each study and developed through consultation with colleagues with experience in systematic reviews. All members of the reviewer team participated in a pilot exercise to test the tool, which was revised until we achieved high interrater reliability (κ> 0.8 on global assessment scores). A global assessment scale that integrated reviewers' judgment of various methodologic components was used to decide which studies would be included in the final report. This scale used a 7-point response format; all studies ranked below 4 were considered of insufficient methodologic quality to provide valid data to the review and were excluded.

Data extraction and synthesis

Data from the 104 studies included were transferred to tables by cancer type and study type. Reviewers tabulated the number of studies and calculated mean quality scores. Synthesis was based on number and quality of studies and aspects of heterogeneity relevant to the studies included. Tables by cancer type are available in the full report on the Ontario College of Family Physicians' website.[3]

SYNTHESIS

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Non-Hodgkin lymphoma

We reviewed 32 papers on non-Hodgkin lymphoma (NHL)[4–35]; 27 met the quality criteria for inclusion.[4–6,8,11–30,32,34,35] Cohort studies looked at exposure to a variety of pesticides. Subjects were usually adult white males in occupational groups such as farmers, pesticide applicators, workers in pesticide factories, landscapers, lumberjacks, and golf course superintendents.

Results were positive in 10 of the 12 studies; results reached statistical significance in 4 studies. A large study of 155 000 farmers found an increased risk of NHL with exposure to pesticides (relative risk [RR] 2.11, 95% confidence interval [CI] 1.1 to 3.9) that increased with the number of acres sprayed.[25] Another study found an increased rate of NHL (proportionate mortality ratio 237, range 137 to 410) among golf course superintendents who had been exposed to pesticides as well as other chemicals, such as diesel fumes and fertilizers.[20]

Results of 12 of the 14 case-control studies were positive; 8 reached statistical significance. The 1 study of children found elevated odds ratios (ORs) in children from homes where pesticides were used most days (OR 7.3, $P < .05$), where pesticides were used for professional home exterminations (OR 3.0, $P = .002$), when children had had direct postnatal exposure (OR 2.4, $P = .001$), and when parents had had occupational exposure (OR 1.74) (not statistically significant).[8]

Most studies revealed an elevated risk of NHL with several classes of pesticides. A well-designed Canadian study assessed risk, first with major classes of pesticides and then with individual compounds within these classes, including dicamba, mecoprop (both commonly used weed-killers available in hardware stores) and carbamate (an insecticide).[24] One pooled study found elevated ORs for NHL and hairy cell leukemia, a rare form of NHL, for men exposed to herbicides, insecticides, fungicides, and impregnating agents (chemicals added to assist in applying pesticides). Elevated risk was also seen with some individual compounds, such as the herbicides glyphosate and MCPA (2-methyl-4-chlorophenoxyacetic acid). A dose-response effect was found with certain other pesticides and classes.[16]

Leukemia

This review assessed 23 studies on leukemia,[36–58] 16 of which met the quality criteria for inclusion.[36–39,43–50,52–54,58] Most of the 6 cohort studies looked at occupationally exposed adult white males. Exposure histories in

most of the studies were estimated indirectly from information such as amount of money spent on pesticides, location of farm, type of crop, number of acres treated, and duration of employment. Two studies showed elevated rates of leukemia associated with livestock farming.[45,46] A study of golf course superintendents found an increased rate of leukemia, but it was not statistically significant.[20]

Results of all 8 case-control studies were statistically significantly positive. One of the few studies that included women found an elevated OR of 4.4 (95% CI, 1.7 to 11.5) for chronic myelocytic leukemia and acute myelocytic leukemia, though specific pesticides were not named or quantified.[37]

Several case-control studies analyzed rates of leukemia among children exposed to pesticides. Increased rates of all types of leukemia were found in children whose parents used insecticides in the garden and on indoor plants and whose mothers had been exposed while pregnant.[44] A case-only cytogenetic study within this study found that the presence of 1 of 3 “poor metabolizer” mutations increased the risk of all types of leukemia when subjects had been exposed to pesticides.[44]

An excellent study showed increased rates of childhood leukemia with exposure to insecticides. Timing of exposure seemed to be critical (preconception, and both prenatal and postnatal periods).[48] The most crucial exposure period for later development of leukemia was during pregnancy.

An interesting laboratory study found a different pattern of chromosomal aberrations, cytologic features, peripheral blood and bone marrow indices, prognosis, and resistance to treatment in leukemia patients who were exposed to pesticides compared with patients who were not.[39] This pattern resembled the pattern found in patients with secondary leukemia, usually caused by radiation, chemotherapy, or other chemical exposure, suggesting that exposure to pesticides might be a precipitant to development of leukemia.

Solid tumours

Brain cancer All 11 studies from the United States, Canada, and Europe examining the association between pesticide exposure and brain cancer showed increased risk.[20,45,59–67] A large European study also found this relationship in the children of parents exposed to pesticides at work, particularly for non-astrocytic neuroepithelial tumours.[45] A strong association was also found for exposure to pesticides indoors at home.[63]

Breast cancer Six studies analyzed the association between pesticide exposure and breast cancer.[68–73] Most of them supported an association. One exception was a study that found that women who farmed had a decreased risk of breast cancer.[69] This might have been due to the protective effect of physical activity against breast cancer, or exposure to sunlight, which might reduce risk by increasing vitamin D levels. Even within this group of farmers, however, those who reported being in the field during or shortly after pesticide application and those who reported not using protective clothing while applying pesticides had an increased risk of breast cancer. A study of female greenhouse workers in Crete found that exposure to pesticides for more than 4 hours daily for at least 10 years increased the risk of benign breast disease (as seen on mammography).[70]

Although most of these studies considered a mix of pesticides, 1 study looked at exposure to triazine herbicides and atrazine (a corn herbicide) as a specific example. While the results did not support a positive association between atrazine and breast cancer, there was an increased risk of breast cancer with medium and high levels of exposure to triazine herbicides as a class.[73]

Kidney cancer Six papers evaluated the relationship between pesticide exposure and kidney cancer, and all found positive associations.[74–79] The association was found not only in directly exposed populations, but also in children of exposed parents, and was most consistent when people had had prolonged exposure.

Lung cancer Four studies examined the association between lung cancer and pesticide exposure.[20,61,80,81] Results of these studies are somewhat difficult to interpret as only 2 collected information regarding smoking status. One of these studies[80] found an elevated risk of lung cancer among women exposed to pesticides at work, and the other found an increased risk in a cohort of Florida pest-control workers who had been exposed to specifically named pesticides. The confidence intervals were extremely broad, however, making interpretation difficult.

Ovarian cancer Few studies were found on pesticide exposure and ovarian cancer. One paper included ovarian cancer as a health effect of interest and evaluated its association with exposure to atrazine. No association was found.[72]

Pancreatic cancer Three studies evaluated the relationship between pancreatic cancer and pesticide exposure, and all 3 found positive associations.[82–84]

Prostate cancer Eight papers examined the association between prostate cancer and pesticide exposure and consistently showed positive associations.[20,85–91] One well-designed US study investigated more than 55 000 men who applied pesticides and found an increased risk of prostate cancer, especially among those with a family history of prostate cancer, and particularly with use of methyl bromide, a fumigant.[85]

Stomach cancer One study investigated the relationship between stomach cancer and nitrates and atrazine.[92] A higher rate of stomach cancer was found in areas with high levels of atrazine contamination in the water.

DISCUSSION

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The preponderance of evidence uncovered in our systematic review indicated a positive relationship between exposure to pesticides and development of some cancers, particularly brain, prostate, and kidney cancers, as well as NHL and leukemia. A number of the studies on children found increased risk of cancer associated with critical periods of exposure, both prenatal and postnatal, and with parental exposure at work. Most studies showed increased risk, and many showed dose-response relationships. Other reviews have suggested a possible link between pesticide exposure and certain cancers, and further studies have been recommended due to limitations innate in the design of cohort and case-control studies.[2,93] The studies varied in terms of number and types of subjects, types of pesticides studied, ways of measuring exposure, covariates examined, and follow-up times.

Limitations

In studying any potentially harmful substances, such as pesticides, where randomized controlled trials are not ethically possible to do, researchers rely mostly on cohort and case-control studies. Each of these designs have limitations, given the difficulty of measuring pesticide exposure. Cohort studies typically rely on indirect measures of exposure, such as type of occupation, duration of employment, and agricultural census data. Usually, specific pesticides are not named or quantified. Covariates, such as family history, smoking, and race, are not always available. Follow-up timesare sometimes too short to account for the long latency period between exposure and onset of illness. Recall bias (relying on subjects' memories) is a limitation to case-control studies, as are low response rates and use of proxy respondents. Publication bias (lack of publication of negative studies) is also a potential limitation, as is incomplete collection of all relevant studies in any particular systematic review.

A promising newer method of studying the effects of pesticides is to examine chromosomal aberrations, and, therefore, future cancer risk,[94] in people exposed to pesticides. Looking at gene polymorphisms (the genetically

determined ability to metabolize substances slowly or quickly) will also be a very exciting method of studying the health effects of pesticides.

Conclusion

We believe that there is enough evidence to recommend that patients reduce use of pesticides. Because most studies analyzed exposure to multiple rather than individual pesticides, our recommendation is to reduce exposure to all pesticides. The results of this systematic review have prompted the Ontario College of Family Physicians to recommend that everyone, especially children and pregnant women, reduce exposure to pesticides whenever possible, both at home and in the workplace. Bans on the cosmetic use of pesticides (used only for appearance and not for major infestations and risks to human health) are also supported by the Ontario College of Family Physicians, the Canadian Paediatric Society, the Canadian Cancer Society, the Canadian Nurses Association, the Registered Nurses' Association of Ontario, the Toronto Board of Health, both the Canadian and the Ontario Public Health Associations, and many other physician and health professional associations.

The public has expressed concern about the issue of pesticides, especially regarding the risk to children. More than 100 municipalities across the country have implemented bylaws restricting and banning cosmetic use of pesticides, including Toronto, Vancouver, Montreal, and Halifax, and these bylaws havebeen supported by the public.

Family doctors should consider asking about pesticide exposure during periodic health examinations and make recommendations about minimizing exposure. They should also encourage use of protective clothing and masks for patients who use pesticides on the job and encourage them to be attentive to the timing of re-entry into recently sprayed areas. Family doctors can also advocate for reductions in pesticide use in communities, schools, and hospitals, and to governments, and can educate patients about the potentially harmful effects of pesticides on health.

Notes

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EDITOR'S KEY POINTS

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- There is increasing controversy over the use of pesticides in the community. Studies looking at pesticide use and cancer have shown a positive relationship between exposure to pesticides and the development of some cancers, particularly in children.
- Because most studies assessed use of multiple pesticides, the authors recommend that exposure to all pesticides be reduced.
- The quality of studies looking at the association between pesticide use and cancer is variable, consisting mainly of cohort and case-control methodologies.

POINTS DE REPÈRE DU RÉDACTEUR

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- L'utilisation de pesticides dans la communauté est de plus en plus remise en question. Certaines études ont montré une relation positive entre l'exposition aux pesticides et le développement de certains cancers, notamment chez les enfants.

- Comme la plupart de ces études portaient sur l'utilisation de plusieurs pesticides, les auteurs recommandent qu'on réduise l'exposition à tous les pesticides.
- Les études examinant l'association entre les pesticides et le cancer sont de qualité variable, reposant surtout des cohortes ou des castémoins.

Footnotes

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This article has been peer reviewed.

Competing interests

The systematic review was completed with funding from the Laidlaw Foundation and the Ontario College of Family Physicians. **Dr Vakil** has received teaching honoraria from the Ontario College of Family Physicians and the International Joint Commission Health Professional Task Force. **Dr Sanborn** received honoraria for working on this project. **Dr Cole** has received funding from the International Development Research Centre and the Canadian Institutes for Health Research. **Dr Kerr** has received honoraria from the Ontario College of Family Physicians and from the Foundation for Science and Education.

Contributors

Ms Bassil, **Dr Vakil**, **Dr Sanborn**, **Dr Cole**, **Dr Kaur**, and **Dr Kerr** contributed to concept and design of the study, data analysis and interpretation, and preparing the article for submission.

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