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Uniform requirements for manuscripts submitted to biomedical journals: Writing and editing for biomedical publication

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INTERNATIONAL COMMITTEE OF MEDICAL JOURNAL EDITORS

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I. STATEMENT OF PURPOSE

I. A. About the uniform requirements

A small group of editors of general medical journals met informally in Vancouver, British Columbia, in 1978 to establish guidelines for the format of manuscripts submitted to their journals. This group became known as the Vancouver Group. Its requirements for manuscripts, including formats for bibliographic references developed by the National Library of Medicine (NLM), were first published in 1979. The Vancouver Group expanded and evolved into the International Committee of Medical Journal Editors (ICMJE), which meets annually. The ICMJE has gradually broadened its concerns to include ethical principles related to publication in biomedical journals. The ICJME has produced multiple editions of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals. Over the years, issues have

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arisen that go beyond manuscript preparation, resulting in the development of a number of Separate Statements on editorial policy. The entire Uniform Requirements document was revised in 1997; sections were updated in May 1999 and May 2000. In May 2001, the ICMJE revised the sections related to potential conflict of interest. In 2003, the committee revised and reorganized the entire document and incorporated the Separate Statements into the text. The committee prepared this revision in 2008.

The total content of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals may be reproduced for educational, not-for-profit purposes without regard for copyright; the committee encourages distribution of the material.

Journals that agree to use the Uniform Requirements are encouraged to state in their instructions to authors that their requirements are in accordance with the Uniform Requirements and to cite this version. Journals that wish to be listed on <u>www.ICMJE.org</u> as a publication that follows the Uniform Requirements should contact the ICMJE secretariat office.

The ICMJE is a small working group of general medical journals, not an open-membership organization. Ocasionally, the ICMJE will invite a new member or guest when the committee feels that the journal or organization will provide a new perspective. Open membership organizations for editors and others in biomedical publication include the World Association of Medical Editors <u>www.WAME.org</u> and the Council of Science Editors <u>www.councilofscienceeditors</u>.

I. B. Potential users of the uniform requirements

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The ICMJE created the Uniform Requirements primarily to help authors and editors in their mutual task of creating and distributing accurate, clear, easily accessible reports of biomedical studies. The initial sections address the ethical principles related to the process of evaluating, improving, and publishing manuscripts in biomedical journals and the relationships among editors and authors, peer reviewers, and the media. The latter sections address the more technical aspects of preparing and submitting manuscripts. The ICMJE believes that the entire document is relevant to the concerns of both authors and editors.

The Uniform Requirements can provide many other stakeholders—peer reviewers, publishers, the media, patients and their families, and general readers—with useful insights into the biomedical authoring and editing process.

I. C. How to use the uniform requirements

The Uniform Requirements state the ethical principles in the conduct and reporting of research and provide recommendations relating to specific elements of editing and writing. These recommendations are based largely on the shared experience of a moderate number of editors and authors, collected over many years, rather than on the results of methodical, planned investigation that aspires to be "evidence-based." Wherever possible, recommendations are accompanied by a rationale that justifies them; as such, the document serves an educational purpose.

Authors will find it helpful to follow the recommendations in this document whenever possible because, as described in the explanations, doing so improves the quality and clarity of reporting in manuscripts submitted to any journal, as well as the ease of editing. At the same time, every journal has editorial requirements uniquely suited to its purposes. Authors therefore need to become familiar with the Instructions to Authors specific to the journal they have chosen for their manuscript—for example, the topics suitable for that journal, and the types of papers that may be submitted (for example, original articles, reviews, or case reports)—and should follow those instructions.

II.Ethical Considerations in the Conduct and Reporting of Research

II. A. Authorship and contributorship

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II. A. 1. Byline authors An "author" is generally considered to be someone who has made substantive intellectual contributions to a published study, and biomedical authorship continues to have important academic, social, and financial implications (1). In the past, readers were rarely provided with information about contributions to studies from persons listed as authors and in Acknowledgments (2). Some journals now request and publish information about the contributions of each person named as having participated in a submitted study, at least for original research. Editors are strongly encouraged to develop and implement a contributorship policy, as well as a policy on identifying who is responsible for the integrity of the work as a whole.

While contributorship and guarantorship policies obviously remove much of the ambiguity surrounding contributions, they leave unresolved the question of the quantity and quality of contribution that qualify for authorship. The ICJME has recommended the following criteria for authorship; these criteria are still appropriate for journals that distinguish authors from other contributors.

- Authorship credit should be based on 1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published. Authors should meet conditions 1, 2, and 3.
- When a large, multicenter group has conducted the Uniform Requirements for Manuscripts Submitted to Biomedical Journals work, the group should identify the individuals who accept direct responsibility for the manuscript (3). These individuals should fully meet the criteria for authorship/contributorship defined above and editors will ask these individuals to complete journalspecific author and conflict-of-interest disclosure forms. When submitting a manuscript authored by a group, the corresponding author should clearly indicate the preferred citation and identify all individual authors as well as the group name. Journals generally list other members of the group in the Acknowledgments. The NLM indexes the group name and the names of individuals the group has identified as being directly responsible for the manuscript; it also lists the names of collaborators if they are listed in Acknowledgments.
- Acquisition of funding, collection of data, or general supervision of the research group alone does not constitute authorship.
- All persons designated as authors should qualify for authorship, and all those who qualify should be listed.
- Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

Some journals now also request that one or more authors, referred to as "guarantors," be identified as the persons who take responsibility for the integrity of the work as a whole, from inception to published article, and publish that information.

Increasingly, authorship of multicenter trials is attributed to a group. All members of the group who are named as authors should fully meet the above criteria for authorship/contributorship.

The group should jointly make decisions about contributors/ authors before submitting the manuscript for publication. The corresponding author/guarantor should be prepared to explain the presence and order of these individuals. It is not the role of editors to make authorship/contributorship decisions or to arbitrate conflicts related to authorship.

II. A. 2. Contributors listed in acknowledgments All contributors who do not meet the criteria for authorship should be listed in an acknowledgments section.

Examples of those who might be acknowledged include a person who provided purely technical help, writing assistance, or a department chairperson who provided only general support. Editors should ask corresponding authors to declare whether they had assistance with study design, data collection, data analysis, or manuscript preparation. If such assistance was available, the authors should disclose the identity of the individuals who provided this assistance and the entity that supported it in the published article. Financial and material support should also be acknowledged.

Groups of persons who have contributed materially to the paper but whose contributions do not justify authorship may be listed under such headings as "clinical investigators" or "participating investigators," and their function or contribution should be described-for example, "served as scientific advisors," "critically reviewed the study proposal," "collected data," or "provided and cared for study patients." Because readers may infer their endorsement of the data and conclusions, these persons must give written permission to be acknowledged.

II. B. Editorship

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II. B. 1. The role of the editor The editor of a journal is the person responsible for its entire content. Owners and editors of medical journals have a common endeavor—publication of a reliable, readable journal produced with due respect for the stated aims of the journal and for costs. Owners and editors, however, have different functions. Owners have the right to appoint and dismiss editors and to make important business decisions in which editors should be involved to the fullest extent possible. Editors must have full authority for determining the editorial content of the journal. The concept of editorial freedom should be resolutely defended by editors even to the extent of their placing their positions at stake. To secure this freedom in practice, the editor should have direct access to the highest level of ownership, not to a delegated manager.

Editors of medical journals should have a contract that clearly states his or her rights and duties, the general terms of the appointment, and the mechanisms for resolving conflict.

An independent editorial advisory board may be useful in helping the editor establish and maintain editorial policy.

II. B. 2. Editorial freedom The ICMJE adopts the World Association of Medical Editors' definition of editorial freedom. According to this definition, editorial freedom, or independence, is the concept that editors-in-chief have full authority over the editorial content of their journal and the timing of publication of that content. Journal owners should not interfere in the evaluation, selection, or editing of individual articles either directly or by creating an environment that strongly influences decisions. Editors should base decisions on the validity of the work and its importance to the journal's readers not on the commercial success of the journal. Editors should be free to express critical but responsible views about all aspects of medicine without fear of retribution, even if these views conflict with the concept of editorial freedom and to draw major transgressions of such freedom to the attention of the international medical, academic, and lay communities.

II. C. Peer review

Unbiased, independent, critical assessment is an intrinsic part of all scholarly work, including the scientific Uniform Requirements for Manuscripts Submitted to Biomedical Journals process. Peer review is the critical assessment of manuscripts submitted to journals by experts who are not part of the editorial staff. Peer review can therefore be viewed as an important extension of the scientific process. Although its actual value has been little studied and is widely debated (4), peer review helps editors decide which manuscripts are suitable for their journals and helps authors and editors to improve the quality of reporting. A peerreviewed journal submits most of its published research articles for outside review. The number and kinds of manuscripts sent for review, the number of reviewers, the reviewing procedures, and the use made of the reviewers' opinions may vary. In the interests of transparency, each journal should publicly disclose its policies in its Instructions to Authors.

II. D. Conflicts of interest

Public trust in the peer-review process and the credibility of published articles depend in part on how well conflict of interest is handled during writing, peer review, and editorial decision making. Conflict of interest exists when an author (or the author's institution), reviewer, or editor has financial or personal relationships that inappropriately influence (bias) his or her actions (such relationships are also known as dual commitments, competing interests, or competing loyalties). These relationships vary from negligible to great potential for influencing judgment. Not all relationships represent true conflict of interest. On the other hand, the potential for conflict of interest can exist regardless of whether an individual believes that the relationship affects his or her scientific judgment. Financial relationships (such as employment, consultancies, stock ownership, honoraria, and paid expert testimony) are the most easily identifiable conflicts of interest and the most likely to undermine the credibility of the journal, the authors, and of science itself. However, conflicts can occur for other reasons, such as personal relationships, academic competition, and intellectual passion.

All participants in the peer-review and publication process must disclose all relationships that could be viewed as potential conflicts of interest. Disclosure of such relationships is also important in connection with editorials and review articles, because it can be more difficult to detect bias in these types of publications than in reports of original research. Editors may use information disclosed in conflict-of-interest and financial-interest statements as a basis for editorial decisions. Editors should publish this information if they believe it is important in judging the manuscript.

II. D. 1. Potential conflicts of interest related to individual authors' commitments When authors submit a manuscript, whether an article or a letter, they are responsible for disclosing all financial and personal relationships that might bias their work. To prevent ambiguity, authors must state explicitly whether potential conflicts do or do not exist. Authors should do so in the manuscript on a conflict-of-interest notification page that follows the title page, providing additional detail, if necessary, in a cover letter that accompanies the manuscript. (See Section IV. A. 3. Conflict-of-Interest Notification Page)

Authors should identify Individuals who provide writing or other assistance and disclose the funding source for this assistance.

Investigators must disclose potential conflicts to study participants and should state in the manuscript whether they have done so.

Editors also need to decide whether to publish information disclosed by authors about potential conflicts. If doubt exists, it is best to err on the side of publication.

II. D. 2. Potential conflicts of interest related to project support Increasingly, individual studies receive funding from commercial firms, private foundations, and government. The conditions of this funding have the potential to bias and otherwise discredit the research.

Scientists have an ethical obligation to submit creditable research results for publication. Moreover, as the persons directly responsible for their work, researchers should not enter into agreements that interfere with their access to the data and their ability to analyze them independently, and to prepare and publish manuscripts. Authors should describe the role of the study sponsor, if any, in study design; collection, analysis, and interpretation of data; writing the report; and the decision to submit the report for publication. If the supporting source had no such involvement, the authors should so state. Biases potentially introduced

when sponsors are directly involved in research are analogous to methodological biases. Some journals, therefore, choose to include information in the Methods section about the sponsor's involvement.

Editors may request that authors of a study funded by an agency with a proprietary or financial interest in the outcome sign a statement, such as "I had full access to all of the data in this study and I take complete responsibility for the integrity of the data and the accuracy of the data analysis." Editors should be encouraged to review copies of the protocol and/or contracts associated with project-specific studies before accepting such studies for publication. Editors may choose not to consider an article if a sponsor has asserted control over the authors' right to publish.

II. D. 3. Potential conflicts of interest related to commitments of editors, journal staff, or reviewers Ed itors should avoid selecting external peer reviewers with obvious potential conflicts of interest-for example, those who work in the same department or institution as any of the authors. Authors often provide editors with the names of persons they feel should not be asked to review a manuscript because of potential, usually professional, conflicts of interest. When possible, authors should be asked to explain or justify their concerns; that information is important to editors in deciding whether to honor such requests.

Reviewers must disclose to editors any conflicts of interest that could bias their opinions of the manuscript, and they should recuse themselves from reviewing specific manuscripts if the potential for bias exists. As in the case of authors, silence on the part of reviewers concerning potential conflicts may mean either that conflicts exist and the reviewer has failed to disclose them or conflicts do not exist. Reviewers must therefore also be asked to state explicitly whether conflicts do or do not exist. Reviewers must not use knowledge of the work, before its publication, to further their own interests.

Editors who make final decisions about manuscripts must have no personal, professional, or financial involvement in any of the issues they might judge. Other members of the editorial staff, if they participate in editorial decisions, must provide editors with a current description of their financial interests (as they might relate to editorial judgments) and recuse themselves from any decisions in which a conflict of interest exists. Editorial staff must not use information gained through working with manuscripts for private gain. Editors should publish regular disclosure statements about potential conflicts of interests related to the commitments of journal staff.

II. E. Privacy and confidentiality

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II. E. 1. Patients and study participants Patients have a right to privacy that should not be violated without informed consent. Identifying information, including names, initials, or hospital numbers, should not be published in written descriptions, photographs, or pedigrees unless the information is essential for scientific purposes and the patient (or parent or guardian) gives written informed consent for publication. Informed consent for this purpose requires that an identifiable patient be shown the manuscript to be published. Authors should disclose to these patients whether any potential identifiable material might be available via the Internet as well as in print after publication. Patient consent should be written and archived either with the journal, the authors, or both, as dictated by local regulations or laws. Applicable laws vary from locale to locale, and journals should establish their own policies with legal guidance.

Nonessential identifying details should be omitted. Informed consent should be obtained if there is any doubt that anonymity can be maintained. For example, masking the eye region in photographs of patients is inadequate protection of anonymity. If identifying characteristics are altered to protect anonymity, such as in genetic pedigrees, authors should provide assurance, and editors should so note, that such alterations do not distort scientific meaning.

The requirement for informed consent should be included in the journal's Instructions for Authors. When informed consent has been obtained, it should be indicated in the published article.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3142758/?report=printable

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II. E. 2. Authors and reviewers Manuscripts must be reviewed with due respect for authors' confidentiality. In submitting their manuscripts for review, authors entrust editors with the results of their scientific work and creative effort, on which their reputation and career may depend. Authors' rights may be violated by disclosure of the confidential details during review of their manuscript. Reviewers also have rights to confidentiality, which must be respected by the editor. Confidentiality may have to be breached if dishonesty or fraud is alleged but otherwise must be honored.

Editors must not disclose information about manuscripts (including their receipt, content, status in the reviewing process, criticism by reviewers, or ultimate fate) to anyone other than the authors and reviewers. This includes requests to use the materials for legal proceedings.

Editors must make clear to their reviewers that manuscripts sent for review are privileged communications and are the private property of the authors. Therefore, reviewers and members of the editorial staff must respect the authors' rights by not publicly discussing the authors' work or appropriating their ideas before the manuscript is published.

Reviewers must not be allowed to make copies of the manuscript for their files and must be prohibited from sharing it with others, except with the editor's permission. Reviewers should return or destroy copies of manuscripts after submitting reviews. Editors should not keep copies of rejected manuscripts.

Reviewer comments should not be published or otherwise publicized without permission of the reviewer, author, and editor.

Opinions differ on whether reviewers should remain anonymous. Authors should consult the Information for Authors of the journal to which they have chosen to submit a manuscript to determine whether reviews are anonymous. When comments are not signed, the reviewers' identity must not be revealed to the author or anyone else without the reviewers' permission.

Some journals publish reviewers' comments with the manuscript. No such procedure should be adopted without the consent of the authors and reviewers. However, reviewers' comments should be sent to other persons reviewing the same manuscript, which helps reviewers learn from the review process. Reviewers also may be notified of the editor's decision to accept or reject a manuscript.

II. F. Protection of human subjects and animals in research

When reporting experiments on human subjects, authors should indicate whether the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (5). If doubt exists whether the research was conducted in accordance with the Helsinki Declaration, the authors must explain the rationale for their approach and demonstrate that the institutional review body explicitly approved the doubtful aspects of the study. When reporting experiments on animals, authors should indicate whether the institutional and national guide for the care and use of laboratory animals was followed.

III. PUBLISHING AND EDITORIAL ISSUES RELATED TO PUBLICATION IN BIOMEDICAL JOURNALS

III. A. Obligation to publish negative studies

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Editors should consider seriously for publication any carefully done study of an important question, relevant to their readers, whether the results for the primary or any additional outcome are statistically significant. Failure to submit or publish findings because of lack of statistical significance is an important cause of publication bias.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3142758/?report=printable

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III. B. Corrections, retractions, and "expressions of concern"

Editors must assume initially that authors are reporting work based on honest observations. Nevertheless, two types of difficulty may arise.

First, errors may be noted in published articles that require the publication of a correction or erratum on part of the work. The corrections should appear on a numbered page, be listed in the Table of Contents, include the complete original citation, and link to the original article and vice versa if online. It is conceivable that an error could be so serious as to vitiate the entire body of the work, but this is unlikely and should be addressed by editors and authors on an individual basis. Such an error should not be confused with inadequacies exposed by the emergence of new scientific information in the normal course of research. The latter requires no corrections or withdrawals.

The second type of difficulty is scientific fraud. If substantial doubts arise about the honesty or integrity of work, either submitted or published, it is the editor's responsibility to ensure that the question is appropriately pursued, usually by the authors' sponsoring institution. Ordinarily it is not the responsibility of the editor to conduct a full investigation or to make a determination; that responsibility lies with the institution where the work was done or with the funding agency. The editor should be promptly informed of the final decision, and if a fraudulent paper has been published, the journal must print a retraction. If this method of investigation does not result in a satisfactory conclusion, the editor may choose to conduct his or her own investigation. As an alternative to retraction, the editor may choose to publish an expression of concern about aspects of the conduct or integrity of the work.

The retraction or expression of concern, so labeled, should appear on a numbered page in a prominent section of the print journal as well as in the online version, be listed in the Table of Contents page, and include in its heading the title of the original article. It should not simply be a letter to the editor. Ideally, the first author of the retraction should be the same as that of the article, although under certain circumstances the editor may accept retractions by other responsible persons. The text of the retraction should explain why the article is being retracted and include a complete citation reference to that article.

The validity of previous work by the author of a fraudulent paper cannot be assumed. Editors may ask the author's institution to assure them of the validity of earlier work published in their journals or to retract it. If this is not done, editors may choose to publish an announcement expressing concern that the validity of previously published work is uncertain.

Editors who have questions related to editorial or scientific misconduct may find it useful to consult the excellent flow charts that the Committee on Publication Ethics (COPE) has developed (<u>www.publicationethics.org.uk</u>). COPE, which was formed in 1997, is a forum in which editors of peer-reviewed journals can discuss issues related to the integrity of the scientific record; it supports and encourages editors to report, catalogue, and instigate investigations into ethical problems in the publication process. COPE's major objective is to provide a sounding board for editors struggling with how best to deal with possible breaches in research and publication ethics.

III. C. Copyright

Many biomedical journals ask authors to transfer copyright to the journal. However, an increasing number of "open-access" journals do not require transfer of copyright. Editors should make their position on copyright transfer clear to authors and to others who might be interested in using editorial content from their journals. The copyright status of articles in a given journal can vary: Some content cannot be copyrighted (for example, articles written by employees of the U.S. and some other governments in the course of their work); editors may agree to waive copyright on others; and still others may be protected under serial rights (that is, use in publications other than journals, including electronic publications, is permitted).

III. D. Overlapping publications

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III. D. 1. Duplicate submission Most biomedical journals will not consider manuscripts that are simultaneously being considered by other journals. Among the principal considerations that have led to this policy are: 1) the potential for disagreement when two (or more) journals claim the right to publish a manuscript that has been submitted simultaneously to more than one; and 2) the possibility that two or more journals will unknowingly and unnecessarily undertake the work of peer review, edit the same manuscript, and publish the same article.

However, editors of different journals may decide to Uniform simultaneously or jointly publish an article if they believe that doing so would be in the best interest of public health.

III. D. 2. Redundant publication Redundant (or duplicate) publication is publication of a paper that overlaps substantially with one already published in print or electronic media.

Readers of primary source periodicals, whether print or electronic, deserve to be able to trust that what they are reading is original unless there is a clear statement that the author and editor are intentionally republishing an article.

The bases of this position are international copyright laws, ethical conduct, and cost-effective use of resources. Duplicate publication of original research is particularly problematic, since it can result in inadvertent double counting or inappropriate weighting of the results of a single study, which distorts the available evidence.

Most journals do not wish to receive papers on work that has already been reported in large part in a published article or is contained in another paper that has been submitted or accepted for publication elsewhere, in print or in electronic media. This policy does not preclude the journal considering a paper that has been rejected by another journal, or a complete report that follows publication of a preliminary report, such as an abstract or poster displayed at a professional meeting. It also does not prevent journals from considering a paper that has been presented at a scientific meeting but was not published in full or that is being considered for publication in a proceedings or similar format. Brief press reports of scheduled meetings are not usually regarded as breaches of this rule, but they may be if additional data or copies of tables and figures amplify such reports. The ICMJE does not consider results posted in clinical trial registration of trial methods occurred and if the results are posted in the form of a brief structured abstract or table. The ICMJE also believes that the results registry should either cite full publications of the results when available or include a statement that indicates that the results have not yet been published in a peer-reviewed journal.

When submitting a paper, the author must always make a complete statement to the editor about all submissions and previous reports (including meeting presentations and posting of results in registries) that might be regarded as redundant or duplicate publication. The author must alert the editor if the manuscript includes subjects about which the authors have published a previous report or have submitted a related report to another publication. Any such report must be referred to and referenced in the new paper. Copies of such material should be included with the submitted manuscript to help the editor decide how to handle the matter.

If redundant or duplicate publication is attempted or occurs without such notification, authors should expect editorial action to be taken. At the least, prompt rejection of the submitted manuscript should be expected. If the editor was not aware of the violations and the article has already been published, then a notice of redundant or duplicate publication will probably be published with or without the author's explanation or approval.

Preliminary reporting to public media, governmental agencies, or manufacturers of scientific information described in a paper or a letter to the editor that has been accepted but not yet published violates the policies of many journals. Such reporting may be warranted when the paper or letter describes major therapeutic advances or public health hazards, such as serious adverse effects of drugs, vaccines, other biological products, or medicinal devices, or reportable diseases. This reporting should not jeopardize publication, but should be discussed with and agreed upon by the editor in advance.

III. D. 3. Acceptable secondary publication Certain types of articles, such as guidelines produced by governmental agencies and professional organizations, may need to reach the widest possible audience. In such instances, editors sometimes deliberately publish material that is also being published in other journals, with the agreement of the authors and the editors of those journals. Secondary publication for various other reasons, in the same or another language, especially in other countries, is justifiable and can be beneficial provided that the following conditions are met.

- 1. The authors have received approval from the editors of both journals; the editor concerned with secondary publication must have a photocopy, reprint, or manuscript of the primary version.
- The priority of the primary publication is respected by a publication interval of at least 1 week (unless specifically negotiated otherwise by both editors).
- 3. The paper for secondary publication is intended for a different group of readers; an abbreviated version could be sufficient.
- 4. The secondary version faithfully reflects the data and interpretations of the primary version.
- 5. The footnote on the title page of the secondary version informs readers, peers, and documenting agencies that the paper has been published in whole or in part and states the primary reference. A suitable footnote might read: "This article is based on a study first reported in the [title of journal, with full reference],"

Permission for such secondary publication should be free of charge.

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- 6. The title of the secondary publication should indicate that it is a secondary publication (complete republication, abridged republication, complete translation, or abridged translation) of a primary publication. Of note, the NLM does not consider translations to be "republications" and does not cite or index translations when the original article was published in a journal that is indexed in MEDLINE.
- 7. Editors of journals that simultaneously publish in multiple languages should understand that NLM indexes the primary language version. When the full text of an article appears in more than one language in a journal issue (such as Canadian journals with the article in both English and French), both languages are indicated in the MEDLINE citation (for example, Mercer K. The relentless challenge in health care. Healthc Manage Forum. 2008 Summer; 21(2):4-5. English, French. No abstract available, PMID:18795553.)

III. D. 4. Competing mnanuscripts based on the same study Publication of manuscripts to air the disputes of coinvestigators may waste journal space and confuse readers. On the other hand, if editors knowingly publish a manuscript written by only some of a collaborating team, they could be denying the rest of the team their legitimate coauthorship rights and journal readers access to legitimate differences of opinion about the interpretation of a study.

Two kinds of competing submissions are considered: submissions by coworkers who disagree on the analysis and interpretation of their study, and submissions by coworkers who disagree on what the facts are and which data should be reported.

Setting aside the unresolved question of ownership of the data, the following general observations may help editors and others address such problems.

III. D. 4. a. Differences in analysis or interpretation: If the dispute centers on the analysis or interpretation of data, the authors should submit a manuscript that clearly presents both versions. The difference of opinion should be explained in a cover letter. The normal process of peer and editorial review may help the authors to resolve their disagreement regarding analysis or interpretation.

If the dispute cannot be resolved and the study merits publication, both versions should be published. Options include publishing two papers on the same study, or a single paper with two analyses or interpretations. In such cases, it would be appropriate for the editor to publish a statement outlining the disagreement and the journal's involvement in attempts to resolve it.

III. D, 4, b. Differences in reported methods or results: If the dispute centers on differing opinions of what was actually done or observed during the study, the journal editor should refuse publication until the disagreement is resolved. Peer review cannot be expected to resolve such problems. If there are allegations of dishonesty or fraud, editors should inform the appropriate authorities; authors should be notified of an editor's intention to report a suspicion of research misconduct.

III. D. 5. Competing manuscripts based on the same database: Editors sometimes receive manuscripts from separate research groups that have analyzed the same data set (for example, from a public database). The manuscripts may differ in their analytic methods, conclusions, or both. Each manuscript should be considered separately. If interpretation of the data is very similar, it is reasonable but not mandatory for editors to give preference to the manuscript that was received first. However, editorial consideration of multiple submissions may be justified under these circumstances, and there may even be a good reason to publish more than one manuscript because different analytical approaches may be complementary and equally valid.

III. E. Correspondence

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The corresponding author/guarantor has primary responsibility for correspondence with the journal, but the ICMJE recommends that editors send a copy of any correspondence to all listed authors.

Biomedical journals should provide the readership with a mechanism for submitting comments, questions, or criticisms about published articles, as well as brief reports and commentary unrelated to previously published articles.

This probably but not necessarily takes the form of a correspondence section or column. The authors of articles discussed in correspondence should be given an opportunity to respond, preferably in the same issue in which the original correspondence appears. Authors of correspondence should be asked to declare any competing or conflicting interests.

Published correspondence may be edited for length, grammatical correctness, and journal style. Alternatively, editors may choose to publish unedited correspondence, for example in rapid-response sections on the Internet. The journal should declare its editorial practices in this regard. Authors should approve editorial changes that alter the substance or tone of a letter or response. In all instances, editors must make an effort to screen out discourteous, inaccurate, or libelous statements and should not allow ad hominem arguments intended to discredit opinions or findings.

Although editors have the prerogative to reject correspondence that is irrelevant, uninteresting, or lacking cogency, they have a responsibility to allow a range of opinions to be expressed. The correspondence column should not be used merely to promote the journal's or the editors' point of view.

In the interests of fairness and to keep correspondence within manageable proportions, journals may want to set time limits for responding to published material and for debate on a given topic. Journals should also decide whether they would notify authors when correspondence bearing on their published work is going to appear in standard or rapid-response sections. Journals should also set policy with regard to the archiving of unedited correspondence that appears online. These policies should be published both in print and electronic versions of the journal.

III. F. Supplements, theme issues, and special series

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Supplements are collections of papers that deal with related issues or topics, are published as a separate issue of the journal or as part of a regular issue, and are usually funded by sources other than the journal's publisher. Supplements can serve useful purposes: education, exchange of research information, ease of access to focused content, and improved cooperation between academic and corporate entities. Because funding sources can bias the content of supplements through the choice of topics and viewpoints, journals should consider adopting the following principles.

These same principles apply to theme issues or special series that have external funding and/or guest editors.

- The journal editor must take full responsibility for the policies, practices, and content of supplements, including complete control of the decision to publish all portions of the supplement. Editing by the funding organization should not be permitted.
- The journal editor must retain the authority to send supplement manuscripts for external peer review and to reject manuscripts submitted for the supplement. These conditions should be made known to authors and external supplement editors before beginning editorial work on the supplement.
- 3. The journal editor must approve the appointment of any external editor of the supplement and take responsibility for the work of the external editor.
- 4. The sources of funding for the research, publication, and products of the funding source that are considered in the supplement should be clearly stated and prominently located in the supplement, preferably on each page. Whenever possible, supplements should be funded by more than one sponsor.
- 5. Advertising in supplements should follow the same policies as those of the rest of the journal.
- Journal editors must enable readers to distinguish readily between ordinary editorial pages and supplement pages.
- Journal editors and supplement editors must not accept personal favors or remuneration from sponsors of supplements.
- 8. Secondary publication in supplements (republication of papers published elsewhere) should be clearly identified by the citation of the original paper. Supplements should avoid redundant or duplicate publication. Supplements should not republish research results, but republication of guidelines or other material in the public interest might be appropriate.
- The principles of authorship and disclosure of potential conflicts of interest discussed elsewhere in this document should be applied to supplements.

III. G. Electronic publishing

Most biomedical journals are now published in electronic as well as print versions, and some are published only in electronic form. Because electronic publishing (which includes the Internet) is the same as publishing in print, in the interests of clarity and consistency the recommendations of this document should be applied to electronically published medical and health information.

The nature of electronic publication requires some special considerations, both within and beyond this document. At a minimum, Web sites should indicate the following: Names, appropriate credentials, affiliations, and relevant conflicts of interest of editors, authors, and contributors; documentation and attribution of references and sources for all content; information about copyright; disclosure of site ownership; and disclosure of sponsorship, advertising, and commercial funding.

Linking from one health or medical Internet site to another may be perceived as an implicit recommendation of the quality of the second site. Journals thus should exercise caution in linking to other sites; when users are linking to another site, it may be helpful to provide an explicit statement that they are leaving the journal's site. Links to other sites posted as a result of financial considerations should be clearly indicated as such. All dates of content posting and updating should be indicated. In electronic layout as in print, advertising and promotional messages should not be juxtaposed with editorial content, and commercial content should be clearly identified as such.

Electronic publication is in flux. Editors should develop, make available to authors, and implement policies on issues unique to electronic publishing. These issues include archiving, error correction, version control, choice of the electronic or print version of the journal as the journal of record, and publication of ancillary material. Under no circumstances should a journal remove an article from its Web site or archive. If a correction or retraction becomes necessary, the explanation must be labeled appropriately and communicated as soon as possible on a citable page in a subsequent issue of the journal.

Preservation of electronic articles in a permanent archive is essential for the historical record. Access to the archive should be immediate and should be controlled by a third party, such as a library, instead of the publisher. Deposition in multiple archives is encouraged.

III. H. Advertising

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Most medical journals carry advertising, which generates income for their publishers, but advertising must not be allowed to influence editorial decisions. Journals should have formal, explicit, written policies for advertising in both print and electronic versions; Web site advertising policy should parallel that for the print version to the extent possible. Editors must have full and final authority for approving advertisements and enforcing advertising policy.

When possible, editors should make use of the judgments of independent bodies for reviewing advertising.Readers should be able to distinguish readily between advertising and editorial material. The juxtaposition of editorial and advertising material on the same products or subjects should be avoided. Interleafing advertising pages within articles interrupts the flow of editorial content and should be discouraged. Advertising should not be sold on the condition that it will appear in the same issue as a particular article.

Journals should not be dominated by advertising, but editors should be careful about publishing advertisements from only one or two advertisers, as readers may perceive that these advertisers have influenced the editor. Journals should not carry advertisements for products that have proved to be seriously harmful to health—for example, tobacco. Editors should ensure that existing regulatory or industry standards for advertisements specific to their country are enforced, or develop their own standards. The interests of organizations or agencies should not control classified and other nondisplay advertising, except where required by law. Finally, editors should consider all criticisms of advertisements for publication.

III. I. Medical journals and the general media

The public's interest in news of medical research has led the popular media to compete vigorously for information about research. Researchers and institutions sometimes encourage reporting research in the nonmedical media before full publication in a scientific journal by holding a press conference or giving interviews. The public is entitled to important medical information within a reasonable amount of time, and editors have a responsibility to facilitate the process. Biomedical journals are published primarily for their readers, but the general public has a legitimate interest in their content: An appropriate balance between

these considerations should guide the journal's interaction with the media. Doctors in practice need to have reports available in full detail before they can advise their patients about the reports* conclusions.

Moreover, media reports of scientific research before the work has been peer reviewed and fully vetted may lead to dissemination of inaccurate or premature conclusions.

An embargo system has been established in some countries to prevent publication of stories in the general media before publication of the original research in the journal. The embargo creates a "level playing field," which most reporters appreciate since it minimizes the pressure on them to publish stories which they have not had time to prepare carefully. Consistency in the timing of public release of biomedical information is also important in minimizing economic chaos, since some articles contain information that has great potential to influence financial markets. On the other hand, the embargo system has been challenged as being self-serving of journals' interests and an impediment to rapid dissemination of scientific information.

Editors may find the following recommendations useful as they seek to establish policies on these issues.

- Editors can foster the orderly transmission of medical information from researchers, through peerreviewed journals, to the public. This can be accomplished by an agreement with authors that they will not publicize their work while their manuscript is under consideration or awaiting publication and an agreement with the media that they will not release stories before publication of the original research in the journal, in return for which the journal will cooperate with them in preparing accurate stories.
- Editors need to keep in mind that an embargo system works on the honor system; no formal
 enforcement or policing mechanism exists. The decision of a significant number of media outlets or
 biomedical journals not to respect the embargo system would lead to its rapid dissolution.
- Very little medical research has such clear and urgently important clinical implications for the
 public's health that the news must be released before full publication in a journal. However, if such
 exceptional circumstances occur, the appropriate authorities responsible for public health should
 decide whether to disseminate information to physicians and the media in advance and should be
 responsible for this decision. If the author and the appropriate authorities wish to have a manuscript
 considered by a particular journal, the editor should be consulted before any public release. If editors
 acknowledge the need for immediate release, they should waive their policies limiting prepublication
 publicity.
- Policies designed to limit prepublication publicity should not apply to accounts in the media of
 presentations at scientific meetings or to the abstracts from these meetings (see Redundant
 Publication). Researchers who present their work at a scientific meeting should feel free to discuss
 their presentations with reporters, but they should be discouraged from offering more detail about
 their study than was presented in the talk.
- When an article is soon to be published, editors should help the media prepare accurate reports by
 providing news releases, answering questions, supplying advance copies of the journal, or referring
 reporters to the appropriate experts. This assistance should be contingent on the media's cooperation
 in timing the release of a story to coincide with publication of the article.
- Editors, authors, and the media should apply the above-stated principles to material released early in electronic versions of journals.

III. J. Obligation to register clinical trials

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The ICMJE believes that it is important to foster a comprehensive, publicly available database of clinical trials. The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or concurrent comparison or control groups to study the cause-and-effect relationship

between a medical intervention and a health outcome. Medical interventions include drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like. The ICMJE member journals will require, as a condition of consideration for publication in their journals, registration in a public trials registry. The details of this policy are contained in a series of editorials (see Editorials, under Frequently Asked Questions). The ICMJE encourages editors of other biomedical journals to adopt similar policy.

The ICMJE does not advocate one particular registry, but its member journals will require authors to register their trial in a registry that meets several criteria. The registry must be accessible to the public at no charge. It must be open to all prospective registrants and managed by a not-for-profit organization. There must be a mechanism to ensure the validity of the registration data, and the registry should be electronically searchable. An acceptable registry must include at minimum the data elements listed in Table 1. Trial registration with missing fields or fields that contain uninformative terminology is inadequate.

It is important to note that the ICMJE requires registration of trial methodology but does not require registration of trial results; it recognizes the potential problems that could arise from the posting of research results that have not been subjected to an independent peer-review process. However, the ICMJE understands that the U.S. Food and Drug Administration Amendments Act of 2007 (FDAAA) does require researchers to register results. The ICMJE will not consider to be previous publication results posted in the same primary clinical trial registry as the initial registration if the results are posted in the tabular form dictated by the FDAAA. Researchers should be aware that editors of journals that follow the ICMJE recommendations may consider more detailed description of trial results and results published in registries other than the primary registry (in the case of FDAAA, ClinicalTrials.gov) to be prior publication. The ICMJE anticipates that the climate for results registration will change dramatically over coming years and the ICMJE may need to amend these recommendations as additional agencies institute other mandates related to results registration.

The ICMJE recommends that journals publish the trial registration number at the end of the abstract. The ICMJE also recommends that, whenever a registration number is available, authors list the registration number the first time they use a trial acronym to refer to either the trial they are reporting or to other trials that they mention in the manuscript.

IV. MANUSCRIPT PREPARATION AND SUBMISSION

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IV. A. Preparing a manuscript for submission to a biomedical journal

Editors and reviewers spend many hours reading manuscripts, and therefore appreciate receiving manuscripts that are easy to read and edit. Much of the information in a journal's Instructions to Authors is designed to accomplish that goal in ways that meet each journal's particular editorial needs. The following information provides guidance in preparing manuscripts for any journal.

IV. A. 1. a. General principles The text of observational and experimental articles is usually (but not necessarily) divided into the following sections: Introduction, Methods, Results, and Discussion. This so-called "IMRAD" structure is not an arbitrary publication format but rather a direct reflection of the process of scientific discovery. Long articles may need subheadings within some sections (especially Results and Discussion) to clarify their content. Other types of articles, such as case reports, reviews, and editorials, probably need to be formatted differently.

Electronic formats have created opportunities for adding details or whole sections, layering information, crosslinking or extracting portions of articles, and the like only in the electronic version. Authors need to work closely with editors in developing or using such new publication formats and should submit supplementary electronic material for peer review.

Double spacing all portions of the manuscript— including the title page, abstract, text, acknowledgments, references, individual tables, and legends—and generous margins make it possible for editors and reviewers to edit the text line by line and add comments and queries directly on the paper copy. If manuscripts are submitted electronically, the files should be double-spaced to facilitate printing for reviewing and editing.

Authors should number all of the pages of the manuscript consecutively, beginning with the title page, to facilitate the editorial process.

IV. A. 1. b. Reporting guidelines for specific study designs Research reports frequently omit important information. Reporting guidelines [Table 2] have been developed for a number of study designs that some journals may ask authors to follow. Authors should consult the Information for Authors of the journal they have chosen. The general requirements listed in the next section relate to reporting essential elements for all study designs. Authors are encouraged also to consult reporting guidelines relevant to their specific research design. For reports of randomized, controlled trials, authors should refer to the CONSORT statement. This guideline provides a set of recommendations comprising a list of items to report and a patient flow diagram.

IV. A .2. Title page The title page should have the following information:

- Article title. Concise titles are easier to read than long, convoluted ones. Titles that are too short may, however, lack important information, such as study design (which is particularly important in identifying randomized, controlled trials). Authors should include all information in the title that will make electronic retrieval of the article both sensitive and specific.
- 2. Authors' names and institutional affiliations. Some journals publish each author's highest academic degree(s), while others do not.
- 3. The name of the department(s) and institution(s) to which the work should be attributed.
- 4. Disclaimers, if any.

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- 5. Contact information for corresponding authors. The name, mailing address, telephone and fax numbers, and e-mail address of the author responsible for correspondence about the manuscript (the "corresponding author;" this author may or may not be the "guarantor" for the integrity of the study). The corresponding author should indicate clearly whether his or her e-mail address can be published.
- The name and address of the author to whom requests for reprints should be addressed or a statement that reprints are not available from the authors.
- 7. Source(s) of support in the form of grants, equipment, drugs, or all of these.
- 8. A running head. Some journals request a short running head or footline, usually no more than 40 characters (including letters and spaces) at the foot of the title page. Running heads are published in most journals, but are also sometimes used within the editorial office for filing and locating manuscripts.
- 9. Word counts. A word count for the text only (excluding abstract, acknowledgments, figure legends, and references) allows editors and reviewers to assess whether the information contained in the paper warrants the amount of space devoted to it, and whether the submitted manuscript fits within the journal's word limits. A separate word count for the Abstract is useful for the same reason.
- 10. The number of figures and tables. It is difficult for editorial staff and reviewers to determine whether the figures and tables that should have accompanied a manuscript were actually included unless the numbers of figures and tables are noted on the title page.

IV. A. 3. Conflict-of-interest notification page To prevent the information on potential conflicts of interest from being overlooked or misplaced, it needs to be part of the manuscript. However, it should also be included on a separate page or pages immediately following the title page. Individual journals may differ in

where they include this information, and some journals do not send information on conflicts of interest to reviewers. (See Section II. D. Conflicts of Interest.)

IV. A. 4. Abstract The abstract (requirements for length and format vary) should follow the title page. It should provide the context or background for the study and should state the study's purpose, basic procedures (selection of study subjects or laboratory animals, observational and analytical methods), main findings (giving specific effect sizes and their statistical significance, if possible), and principal conclusions. It should emphasize new and important aspects of the study or observations.

Articles on clinical trials should contain abstracts that include the items that the CONSORT group has identified as essential (<u>www.consort-statement.org/?1190</u>).

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Because abstracts are the only substantive portion of the article indexed in many electronic databases, and the only portion many readers read, authors need to be careful that they accurately reflect the content of the article. Unfortunately, the information contained in many abstracts differs from that in the text (6). The format required for structured abstracts differs from journal to journal, and some journals use more than one format; authors need to prepare their abstracts in the format specified by the journal they have chosen. The ICMJE recommends that journals publish the trial registration number at the end of the abstract. The ICMJE also recommends that, whenever a registration number is available, authors list that number the first time they use a trial acronym to refer to either the trial they are reporting or to other trials that they mention in the manuscript.

IV. A. 5. Introduction Provide a context or background for the study (that is, the nature of the problem and its significance). State the specific purpose or research objective of, or hypothesis tested by, the study or observation; the research objective is often more sharply focused when stated as a question. Both the main and secondary objectives should be clear, and any prespecified subgroup analyses should be described. Provide only directly pertinent references, and do not include data or conclusions from the work being reported.

IV. A. 6. Methods The Methods section should include only information that was available at the time the plan or protocol for the study was being written; all information obtained during the study belongs in the Results section.

IV. A. 6. a. Selection and description of participants Describe your selection of the observational or experimental participants (patients or laboratory animals, including controls) clearly, including eligibility and exclusion criteria and a description of the source population. Because the relevance of such variables as age and sex to the object of research is not always clear, authors should explain their use when they are included in a study report-for example, authors should explain why only participants of certain ages were included or why women were excluded. The guiding principle should be clarity about how and why a study was done in a particular way. When authors use such variables as race or ethnicity, they should define how they measured these variables and justify their relevance.

IV. A. 6. b. Technical information: Identify the methods, apparatus (give the manufacturer's name and address in parentheses), and procedures in sufficient detail to allow others to reproduce the results. Give references to established methods, including statistical methods (see below); provide references and brief descriptions for methods that have been published but are not well-known; describe new or substantially modified methods, give the reasons for using them, and evaluate their limitations. Identify precisely all drugs and chemicals used, including generic name(s), dose(s), and route(s) of administration.

Authors submitting review manuscripts should include a section describing the methods used for locating, selecting, extracting, and synthesizing data. These methods should also be summarized in the abstract.

IV. A. 6. c. Statistics: Describe statistical methods with enough detail to enable a knowledgeable reader with access to the original data to verify the reported results. When possible, quantify findings and present

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3142758/?report=printable

them with appropriate indicators of measurement error or uncertainty (such as confidence intervals). Avoid relying solely on statistical hypothesis testing, such as P values, which fail to convey important information about effect size. References for the design of the study and statistical methods should be to standard works when possible (with pages stated). Define statistical terms, abbreviations, and most symbols. Specify the computer software used.

IV. A. 7. Results: Present your results in logical sequence in the text, tables, and illustrations, giving the main or most important findings first. Do not repeat all the data in the tables or illustrations in the text; emphasize or summarize only the most important observations. Extra or supplementary materials and technical detail can be placed in an appendix where they will be accessible but will not interrupt the flow of the text, or they can be published solely in the electronic version of the journal.

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When data are summarized in the Results section, give numeric results not only as derivatives (for example, percentages) but also as the absolute numbers from which the derivatives were calculated, and specify the statistical methods used to analyze them. Restrict tables and figures to those needed to explain the argument of the paper and to assess supporting data. Use graphs as an alternative to tables with many entries; do not duplicate data in graphs and tables. Avoid nontechnical uses of technical terms in statistics, such as "random" (which implies a randomizing device), "normal," "significant," "correlations," and "sample." Where scientifically appropriate, analyses of the data by such variables as age and sex should be included.

IV. A. 8. Discussion Emphasize the new and important aspects of the study and the conclusions that follow from them. Do not repeat in detail data or other information given in the Introduction or the Results section. For experimental studies, it is useful to begin the discussion by summarizing briefly the main findings, then explore possible mechanisms or explanations for these findings, compare and contrast the results with other relevant studies, state the limitations of the study, and explore the implications of the findings for future research and for clinical practice.

Link the conclusions with the goals of the study but avoid unqualified statements and conclusions not adequately supported by the data. In particular, avoid making statements on economic benefits and costs unless the manuscript includes the appropriate economic data and analyses. Avoid claiming priority or alluding to work that has not been completed. State new hypotheses when warranted, but label them clearly as such.

IV. A. 9. References IV. A. 9. a. General considerations related to references: Although references to review articles can be an efficient way to guide readers to a body of literature, review articles do not always reflect original work accurately. Readers should therefore be provided with direct references to original research sources whenever possible. On the other hand, extensive lists of references to original work on a topic can use excessive space on the printed page. Small numbers of references to key original papers often serve as well as more exhaustive lists, particularly since references can now be added to the electronic version of published papers, and since electronic literature searching allows readers to retrieve published literature efficiently. Avoid using abstracts as references. References to papers accepted but not yet published should be designated as "in press" or "forthcoming"; authors should obtain written permission to cite such papers as well as verification that they have been accepted for publication. Information from manuscripts submitted but not accepted should be cited in the text as "unpublished observations" with written permission from the source.

Avoid citing a "personal communication" unless it provides essential information not available from a public source, in which case the name of the person and date of communication should be cited in parentheses in the text. For scientific articles, obtain written permission and confirmation of accuracy from the source of a personal communication.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3142758/?report=printable

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Some but not all journals check the accuracy of all reference citations; thus, citation errors sometimes appear in the published version of articles. To minimize such errors, verify references against the original documents. Authors are responsible for checking that none of the references cite retracted articles except in the context of referring to the retraction. For articles published in journals indexed in MEDLINE, the ICMJE considers PubMed the authoritative source for information about retractions.

Authors can identify retracted articles in MEDLINE by using the following search term, where pt in square brackets stands for publication type: Retracted publication [pt] in PubMed.

IV. A. 9. b. Reference style and format: The Uniform Requirements style for references is based largely on an American National Standards Institute style adapted by the NLM for its databases. Authors should consult NLM's Citing Medicine for information on its recommended formats for a variety of reference types.

References should be numbered consecutively in the order in which they are first mentioned in the text. Identify references in text, tables, and legends by Arabic numerals in parentheses. References cited only in tables or figure legends should be numbered in accordance with the sequence established by the first identification in the text of the particular table or figure. The titles of journals should be abbreviated according to the style used in the list of Journals Indexed for MEDLINE, posted by the NLM on the Library's Web site. Journals vary on whether they ask authors to cite electronic references within parentheses in the text or in numbered references following the text. Authors should consult with the journal to which they plan to submit their work.

IV. A. 10. Tables Tables capture information concisely and display it efficiently; they also provide information at any desired level of detail and precision. Including data in tables rather than text frequently makes it possible to reduce the length of the text.

Type or print each table with double spacing on a separate sheet of paper. Number tables consecutively in the order of their first citation in the text and supply a brief title for each. Do not use internal horizontal or vertical lines. Give each column a short or an abbreviated heading. Authors should place explanatory matter in footnotes, not in the heading. Explain all nonstandard abbreviations in footnotes, and use the following symbols, in sequence:

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Identify statistical measures of variations, such as standard deviation and standard error of the mean.

Be sure that each table is cited in the text.

If you use data from another published or unpublished source, obtain permission and acknowledge that source fully.

Additional tables containing backup data too extensive to publish in print may be appropriate for publication in the electronic version of the journal, deposited with an archival service, or made available to readers directly by the authors. An appropriate statement should be added to the text to inform readers that this additional information is available and where it is located. Submit such tables for consideration with the paper so that they will be available to the peer reviewers.

IV. A. 11. Illustrations (Figures) Figures should be either professionally drawn and photographed, or submitted as photographic-quality digital prints. In addition to requiring a version of the figures suitable for printing, some journals now ask authors for electronic files of figures in a format (for example, JPEG or GIF) that will produce high-quality images in the Web version of the journal; authors should review the images of such files on a computer screen before submitting them to be sure they meet their own quality standards.

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For X-ray films, scans, and other diagnostic images, as well as pictures of pathology specimens or photomicrographs, send sharp, glossy, black-and-white or color photographic prints, usually 127×173 mm (5 × 7 inches). Although some journals redraw figures, many do not. Letters, numbers, and symbols on figures should therefore be clear and consistent throughout, and large enough to remain legible when the figure is reduced for publication. Figures should be made as self-explanatory as possible, since many will be used directly in slide presentations. Titles and detailed explanations belong in the legends–not on the illustrations themselves.

Photomicrographs should have internal scale markets. Symbols, arrows, or letters used in photomicrographs should contrast with the background. Photographs of potentially identifiable people must be accompanied by written permission to use the photograph.

Figures should be numbered consecutively according to the order in which they have been cited in the text. If a figure has been published previously, acknowledge the original source and submit written permission from the copyright holder to reproduce the figure. Permission is required irrespective of authorship or publisher except for documents in the public domain.

For illustrations in color, ascertain whether the journal requires color negatives, positive transparencies, or color prints. Accompanying drawings marked to indicate the region to be reproduced might be useful to the editor. Some journals publish illustrations in color only if the author pays the additional cost. Authors should consult the journal about requirements for figures submitted in electronic formats.

IV. A. 12. Legends for illustrations (figures) Type or print out legends for illustrations using double spacing, starting on a separate page, with Arabic numerals corresponding to the illustrations. When symbols, arrows, numbers, or letters are used to identify parts of the illustrations, identify and explain each one clearly in the legend. Explain the internal scale and identify the method of staining in photomicrographs.

IV. A. 13. Units of measurement Measurements of length, height, weight, and volume should be reported in metric units (meter, kilogram, or liter) or their decimal multiples.

Temperatures should be in degrees Celsius. Blood pressures should be in millimeters of mercury, unless other units are specifically required by the journal. Journals vary in the units they use for reporting hematologic, clinical chemistry, and other measurements. Authors must consult the Information for Authors of the particular journal and should report laboratory information in both local and International System of Units (S1). Editors may request that authors add alternative or non-SI units, since SI units are not universally used. Drug concentrations may be reported in either SI or mass units, but the alternative should be provided in parentheses where appropriate.

IV. A. 14. Abbreviations and symbols Use only standard abbreviations; use of nonstandard abbreviations can be confusing to readers. Avoid abbreviations in the title of the manuscript. The spelled-out abbreviation followed by the abbreviation in parenthesis should be used on first mention unless the abbreviation is a standard unit of measurement.

IV. B. Sending the manuscript to the Journal

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An increasing number of journals now accept electronic submission of manuscripts, whether on disk, as an e-mail attachment, or by downloading directly onto the journal's Web site. Electronic submission saves time and money and allows the manuscript to be handled in electronic form throughout the editorial process (for example, when it is sent out for review). For specific instructions on electronic submission, authors should consult the journal's Instructions for Authors.

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If a paper version of the manuscript is submitted, send the required number of copies of the manuscript and figures; they are all needed for peer review and editing, and the editorial office staff cannot be expected to make the required copies.

Manuscripts must be accompanied by a cover letter, which should include the following information.

- A full statement to the editor about all submissions and previous reports that might be regarded as redundant publication of the same or very similar work. Any such work should be referred to specifically and referenced in the new paper. Copies of such material should be included with the submitted paper to help the editor address the situation.
- A statement of financial or other relationships that might lead to a conflict of interest, if that information is not included in the manuscript itself or in an authors' form.
- A statement that the manuscript has been read and approved by all the authors, that the requirements
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V.REFERENCES

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V.A. References cited in this document

- 1. Davidoff F, for the CSE Task Force on Authorship. Who's the author? Problems with biomedical authorship, and some possible solutions. Science Editor. 2000; 23:111-9.
- Yank V, Rennie D. Disclosure of researcher contributions: A study of original research articles in The Lancet. Ann Intern Med. 1999;130:661-70.
- Flanagin A, Fontanarosa PB, DeAngelis CD. Authorship for research groups. JAMA. 2002;288:3166-8.
- 4. Godlee F, Jefferson T. Peer Review in Health Sciences. London: BMJ Books; 1999.
- World Medical Association Declaration of Helsinki. Ethical principles for medical research involving human subjects. JAMA. 2000;284:3043-5.
- Pitkin RM, Branagan MA, Burmeister LF. Accuracy of data in abstracts of published research articles. JAMA. 1999;281:1110-1.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3142758/?report=printable

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Monitoring and Treatment

Minimum Latency & Types or Categories of Cancer

John Howard, M.D., Administrator World Trade Center Health Program

Revision: May 1, 2013

(Replaces Administrator's White Paper on Minimum Latency & Types of Cancer dated October 17, 2012)

Note for May 1, 2013 Revision: As new scientific information becomes available to the World Trade Center (WTC) Program Administrator on minimum latencies for the types or categories of cancers on the List of WTC-Related Health Conditions found at 42 C.F.R. § 88.1, minimum latencies may be modified. The Administrator's May 1, 2013 revision to the White Paper on Minimum Latency & Types or Categories of Cancer changes minimum latencies for mesothelioma and the category of lymphoproliferative and hematopoietic cancers.

Executive Summary

The WTC Program Administrator has determined minimum latencies for the following five types or categories of cancer eligible for coverage in the WTC Health Program:

(1) Mesothelioma—11 years, based on direct observation after exposure to mixed forms of asbestos, which represents a change from the October 17, 2012 version of the Administrator's *White Paper on Minimum Latency & Types or Categories of Cancer;*

(2) All solid cancers (other than mesothelioma, lymphoproliferative, thyroid, and childhood cancers)—4 years, based on low estimates used for lifetime risk modeling of low-level ionizing radiation studies;

(3) Lymphoproliferative and hematopoietic cancers (including all types of leukemia and lymphoma)—0.4 years (equivalent to 146 days), based on low estimates used for lifetime risk modeling of low-level ionizing radiation studies, which represents a change for lymphoproliferative cancers only from the October 17, 2012 version of the Administrator's White Paper on Minimum Latency & Types of Categories of Cancer;

(4) Thyroid cancer—2.5 years, based on low estimates used for lifetime risk modeling of lowlevel ionizing radiation studies; and

(5) Childhood cancers (other than lymphoproliferative and hematopoietic cancers)—1 year, based on the National Academy of Sciences findings.

I. Introduction

According to the James Zadroga 9/11 Health and Compensation Act of 2010 ("Act") (42 U.S.C. §§ 300mm to 300mm-61), a determination that an individual's 9/11 exposure is substantially likely to be a significant factor in aggravating, contributing to, or causing an individual's health condition must be made based on an assessment of the following: (1) the individual's exposure to airborne toxins, any other hazard, or any other adverse condition resulting from the terrorist attacks; and (2) the type of symptoms and temporal sequence of symptoms (42 U.S.C. § 300mm-22(a)(2)). With regard to the temporal sequence of symptoms, cancers do not occur immediately after exposure to a causative agent and they usually take many years up to several decades to manifest clinically. The formation of a tumor is a complex process, and tumor progression occurs by a sequence of randomly occurring changes in genetic material that alter cell functions such as proliferation, survival, and growth inhibition, as well as other cellular changes needed to overcome the normal barriers to becoming malignant. Based on the requirement in the Act to consider the temporal sequence of symptoms, the Administrator determined that a minimum time period (i.e., latency) must have elapsed between the initial date of the individual's 9/11 exposure and the date of the initial diagnosis of the individual's cancer for the cancer to be certified.

The assessment of minimum latency periods for various types or categories of cancer is straightforward when exposures occur at a single point in time or regularly. However, most human exposures to carcinogens vary significantly over time, making a precise determination of minimum latency periods difficult.

The basis for selecting minimum latencies to specific types or categories of cancer is described in the sections below. However, at the outset it is important to understand that the scientific literature assessing minimum latency periods for specific types of cancer is scarce. Estimates of minimum latencies are available in the scientific literature for only a small number of the covered cancers associated with exposure to carcinogenic agents present in the aftermath of the 9/11 attacks (also referred to as "9/11 agents"). Similarly, observations of minimum latencies are available for only a few of the cancers that the Administrator added to the List of WTC—Related Health Conditions ("List") eligible for coverage under the WTC Health Program associated with other agents.

Therefore, the Administrator derived minimum latency estimates using several methods based on the best available scientific evidence for each type or category of cancer considered.

II. Methods Used to Determine Minimum Latency Estimates (Latency Methods)

The four specific methods used by the Administrator to select minimum latency estimates for types or categories of cancer are described below in order of the best available science, as judged by the Administrator. The methods are as follows:

Latency Method 1: Studies reporting minimum latency estimates for cancer from a 9/11 agent based on direct observation of latencies.

In this approach, the population studied must be large enough to develop a reasonable estimate of the lower bound of the distribution of latencies, which is the estimate of the minimum latency.

Latency Method 2: Authoritative Recommendations

When estimates of minimum latency are not available using *Latency Method 1*, the Administrator reviewed available recommendations on minimum latency from authoritative bodies, such as the National Academy of Sciences, and selected the shortest latency period.

Latency Method 3: Studies reporting observed latencies for a cancer from another agent, with preference given to agents chemically analogous to a 9/11 agent.

In this approach, the population studied must be large enough to develop a reasonable estimate of the lower bound of the distribution of latencies, which is the estimate of the minimum latency.

Latency Method 4: Statistical Modeling

When estimates of minimum latency are not available from studies with direct observations of minimum latencies [Latency Methods 1 and 3], or from authoritative recommendations [Latency Method 2], the Administrator looks to estimates of the minimum latency periods used in statistical models and published in the scientific literature. The two modeling approaches are described below.

4A: Estimates of cancer latency obtained by statistical modeling in epidemiologic studies of the association between exposure to an agent and a type of cancer.

Using this method, an investigator excludes exposure for some period of time (e.g., 10 or 20 years) before diagnosis is made. Exposure time is excluded because any exposure that occurs *after* a cancer develops in an individual does not contribute to the developmental time for that cancer. Several time periods may be tested, and the time period that yields the strongest association between exposure and the cancer is used as the estimate of the minimum latency period.¹*

4B: Estimates of cancer latency obtained from statistical models used to estimate the lifetime risk of low-level ionizing radiation-related cancers.

The use of a radiation-induced cancer latency estimate is supported by scientific literature indicating shared mechanisms of carcinogenesis that apply to most solid tumors.² Furthermore, cancers that may develop as a result of radiation exposure are indistinguishable from those that occur as a result of exposure to other carcinogens.³

If multiple estimates of minimum latency based on statistical modeling in epidemiologic studies were available in the scientific literature, the Administrator's policy is to resolve any uncertainties inherent in this method [Latency Method 4] in favor of the WTC Health Program member by selecting the shortest latency period.

^{*} This procedure is referred to as "lagging" in epidemiologic studies.

The strength of the available scientific evidence for estimates of minimum latency for each type of cancer or category of cancer was evaluated. The Administrator selected minimum latencies for use in the evaluation of a case of cancer for certification in the WTC Health Program based on that evaluation.

III. Basis for Selecting Minimum Latencies

A. Mesothelioma

The basis for adding mesothelioma to the List was exposure to chrysotile asbestos, which was the only form of asbestos identified in any of the settled surface dust samples in the New York City disaster area.⁴ However, a literature search did not identify any studies which reported a minimum latency that was specific for chrysotile exposure [*Latency Method 1*] for more than a few individuals. All reported latencies in these studies were greater than 20 years. Also, the Administrator was unable to find recommendations on minimum latency from other authoritative sources [*Latency Method 2*]. Therefore, the Administrator has decided to rely on estimates of latency in the scientific literature for exposures to mixed forms of asbestos [*Latency Method 3*].

A review of 21 studies by Lanphear and Buncher covered a large variety of occupations, and identified 1,105 cases of asbestos-related mesothelioma.⁵ The studies reported a median latency period of 32 years, with 96% of cases diagnosed at least 20 years following initial exposure and 33% of cases diagnosed 40 years after initial exposure. Lanphear and Buncher reported a minimum latency of 11 years. The minimum latencies of malignant mesothelioma reported in other studies of exposures to mixed forms of asbestos ranged from 13 to 15 years.⁶⁻¹⁰

Therefore, based on the best available scientific evidence and following the methodology presented in this revised *White Paper on Minimum Latency and Types or Categories of Cancer*, the Administrator selected a minimum latency of 11 years for use in the evaluation of a case of mesothelioma for certification in the WTC Health Program. For a cancer occurring in a person less than 20 years of age, see Section III, E.

B. Solid Cancers (other than mesothelioma, lymphoproliferative, thyroid, and childhood cancers)

Latency estimates based on a small number of individuals in direct observational studies have been reported for a few of the solid cancers included on the List. Those latency estimates are as follows:

- The minimum interval between the onset of gastro-esophageal reflux disease (GERD) and diagnosis of esophageal cancer (latency) has been reported to be 20 years.¹¹ However, in individuals with GERD who have also been exposed to 9/11 agents acting as cancer initiators or promoters, the Administrator notes that the minimum latency may be significantly shortened;
- The minimum latency of 12 years has been reported for liver cancer associated with vinyl chloride exposure.¹² Additional 9/11 agents are known to cause liver cancer, however direct observations of latency [Latency Methods 1 and 3] or authoritative recommendations [Latency Method 2] are not available for those agents.

Minimum latency estimates have been reported in the literature for lung cancer associated with exposure to asbestos (19 years),^{7, 13, 14} to chromium (5 years),¹⁴ and to soot (9 years).¹⁵
 Additional 9/11 agents are known to cause lung cancer, however direct observations of latency [Latency Methods 1 and 3] or authoritative recommendations [Latency Method 2] are not available.

Latency estimates are available in the scientific literature for other covered solid cancers associated with exposures to agents not known to be present at the sites of the 9/11 terrorist attacks. For example, a minimum latency of 20 years has been reported for chlorinated biphenyl-related melanoma ¹⁶ and a minimum latency of 4 years has been reported for urinary bladder cancer associated with aromatic amine exposure.¹⁷ Specific 9/11 agents are known to cause melanoma and bladder cancer, however direct observations of latency [Latency Methods 1 and 3] or authoritative recommendations [Latency Method 2] are not available.

For some types of solid cancers on the List, estimates of minimum latency were found in the scientific literature based on statistical modeling in epidemiologic studies of associations between an exposure and cancer [*Latency Method 4A*]. Estimates of latency using this method have been reported for nasopharyngeal cancer associated with formaldehyde exposure (15 years)¹⁸ and for asbestos-related cancer of the pleura (30 years).¹³

For solid cancers as a group, an estimate of minimum latency of 4 years is available from statistical modeling of risk between exposure to low-level ionizing radiation and solid cancers [Latency Method 4B].^{19, 20}

Therefore, based on the best available scientific evidence and following the methodology presented in this revised *White Paper on Minimum Latency and Types or Categories of Cancer*, the Administrator selected a minimum latency of 4 years for use in the evaluation of all types and categories of solid cancers other than mesothelioma, lymphoproliferative, thyroid, and childhood cancers) for certification in the WTC Health Program. For a cancer occurring in a person less than 20 years of age, see Section III, E.

C. Lymphoproliferative and Hematopoietic Cancers

Latency estimates vary widely for different lymphoproliferative and hematopoietic malignancies. For leukemia and lymphoma, direct observations of latency are not available in the literature for 9/11 agents [*Latency Method 1*]. Also, the Administrator was unable to find recommendations on minimum latency from other authoritative sources [*Latency Method 2*]. The only estimates of minimum latency found in the scientific literature were based on statistical modeling in epidemiologic studies of associations between an exposure and cancer [*Latency Methods 4A and 4B*]. The reported minimum latency estimate using statistical modeling in epidemiologic studies for acute non-lymphocytic leukemia and benzene exposure is 1.5 years,^{21, 22} and for lymphoproliferative and hematopoletic malignancies resulting from formaldehyde exposure is 2 years [*Latency Method 4A*].²³ For chronic lymphocytic leukemia, a minimum latency estimate of 15 years has been reported for ionizing radiation exposure [*Latency Method 4B*].²⁴ A minimum latency period of 2 years has been reported for non-Hodgkin lymphoma²⁵ following treatment of Hodgkin disease with chemotherapy and radiotherapy, which is similar to the latency for secondary acute leukemia [*Latency Method 3*].²⁶ Evaluation of the latencies of leukemias, including chronic lymphocytic leukemia, and lymphomas from exposures to occupational and environmental agents is difficult for a number of reasons. First, the nomenclature used in the histological classification of these diseases is in flux. Second, a particular lymphoid neoplasm may manifest both lymphoid and leukemic features. Third, there is substantial overlap in the estimates of latency periods for lymphomas, which range from 2 to 10 years, and leukemias, which range from 1.5 to 15 years. This similarity in estimates of the minimum latencies for lymphoproliferative and hematopoietic malignancies is demonstrated as noted above and in risk models for radiation-induced leukemia and for chemotherapy-related acute myelocytic leukemia,¹⁹ as well as acute non-lymphocytic leukemia from benzene exposure.²¹ Moreover, leukemia that develops after exposure to benzene is similar to atomic bomb irradiation or therapy-induced leukemia.²⁷

Although latencies based on direct observations for some types of lymphomas and leukemias have been reported in the scientific literature, the nomenclature, classification, and latency overlap issues discussed above cast doubt on the reliability of these observations for use in the WTC Health Program. For these reasons, the Administrator has decided to rely on the estimate of minimum latency for all lymphoproliferative and hematopoietic malignancies of 0.4 years based on low estimates used for lifetime risk modeling of low-level ionizing radiation studies for lymphomas and leukemias.²⁰

Therefore, based on the best available scientific evidence and following the methods presented in this revised *White Paper on Minimum Latency and Types or Categories of Cancer*, the Administrator has selected a minimum latency of 0.4 years or 146 days for use in the evaluation of cases of lymphoproliferative and hematopoietic cancers for certification in the WTC Health Program. For a lymphoproliferative or hematopoietic cancer occurring in a person less than 20 years of age, the Administrator has also selected this minimum latency of 0.4 years, see Section III,E.

D. Thyroid Cancer

For thyroid cancer, direct observations or estimates of latency for 9/11 agents (*Latency Method* 1) or other agents (*Latency Method* 3) are not available in the literature. Also, the Administrator was unable to find recommendations on minimum latency from other authoritative sources [*Latency Method* 2]. Therefore, the Administrator has decided to rely on estimates of minimum latency based on the statistical modeling of risk for associations between exposure to low-level ionizing radiation and thyroid cancer of 2.5 years [*Latency Method* 4B].²⁰

Therefore, based on the best available scientific evidence and following the methodology presented in this revised *White Paper on Minimum Latency and Types or Categories of Cancer*, the Administrator selected a minimum latency of 2.5 years for use in the evaluation of a case of thyroid cancer for certification in the WTC Health Program. For a cancer occurring in a person less than 20 years of age, see Section III,E.

E. Childhood Cancers

The most common cancers in children are leukemia (34%), brain and nervous system tumors (34%), lymphomas (8%), Wilms tumor of the kidney (5%), bone cancers (4%), rhabdomyosarcoma (3%), and retinoblastoma (3%).²⁸ One of the differences between childhood cancers and adult cancers is that

childhood cancers typically have a shorter latency period. After reviewing the scientific literature, the Administrator has determined that estimates of minimum latency by *Latency Methods 1, 3, and 4* are not available for this broad category of cancer types. However, the National Academy of Sciences has reported that childhood cancers have a latency period of 1 to 10 years [*Latency Method 2*].²⁹

Therefore, based on the best available scientific evidence and following the methodology presented in this revised *White Paper on Minimum Latency and Types or Categories of Cancer*, the Administrator selected a minimum latency of 1 year for use in the evaluation of cases of childhood cancer for certification in the WTC Health Program (excluding lymphoproliferative and hematopoietic cancers in children, for which the Administrator selected the minimum latency of 0.4 years). For purposes of the WTC Health Program, a childhood cancer means all types of cancer occurring in a person less than 20 years of age (42 C.F.R. §88.1).

IV. Summary

The Administrator has selected minimum latencies for the following five types or categories of cancer:

(1) Mesothelioma-11 years;

(2) All solid cancers (other than mesothelioma, lymphoproliferative, thyroid, and childhood cancers) — 4 years;

(3) Lymphoproliferative and hematopoietic cancers (including all types of leukemia and lymphoma) — 0.4 years (146 days);

- (4) Thyroid cancer 2.5 years; and
- (5) Childhood cancers (other than lymphoproliferative and hematopoietic cancers)-1 year.

List of References

- 1. Rothman KJ, Greenland S. Modern Epidemiology. 2nd ed. Philadelphia: Lippincott-Raven; 1998.
- 2. Baba Al, Câtoi C. Comparative Oncology. Bucharest: The Publishing House of the Romanian Academy; 2007.
- 3. United States Nuclear Regulatory Commission. Fact Sheet on Biological Effects of Radiation. Available at: <u>http://www.nrc.gov/reading-rm/doc-collections/fact-sheets/bio-effects-radiation.html;</u> 2011.
- 4. New York City Department of Health and Mental Hygiene, Agency for Toxic Substances and Disease Registry. Final technical report of the public health investigation to assess potential exposures to airborne and settled surface dust in residential areas of lower Manhattan; 2002.
- Lanphear BP, Buncher CR. Latent period for malignant mesothelioma of occupational origin. J Occup Med. 1992;34:718-721.
- 6. Kamp DW. Asbestos-induced lung diseases: an update. *Translational research : the journal of laboratory and clinical medicine*. 2009;153:143-152.
- 7. Selikoff IJ, Hammond EC, Seidman H. Latency of asbestos disease among insulation workers in the United States and Canad. ACancer. 1980;46:2736-2740.
- Linton A, Vardy J, Clarke S, van Zandwijk N. The ticking time-bomb of asbestos: its insidious role in the development of malignant mesotheliom. ACritical reviews in oncology/hematology. 2012;84:200-212.
- 9. Bianchi C, Bianchi T. Malignant pleural mesothelioma in Italy. *Indian journal of occupational and environmental medicine*, 2009;13:80-83.
- 10. Bianchi C, Giarelli L, Grandi G, Brollo A, Ramani L, Zuch C. Latency periods in asbestos-related mesothelioma of the pleur. A*Eur J Cancer Prev.* 1997;6:162-166.
- den Hoed CM, van Blankenstein M, Dees J, Kuipers EJ. The minimal incubation period from the onset of Barrett's oesophagus to symptomatic adenocarcinom. ABr J Cancer. 2011;105:200-205.
- 12. Lelbach WK. A 25-year follow-up study of heavily exposed vinyl chloride workers in Germany. *Am J Ind Med.* 1996;29:446-458.
- 13. Magnani C, Ferrante D, Barone-Adesi F, et al. Cancer risk after cessation of asbestos exposure: a cohort study of Italian asbestos cement workers. *Occup Environ Med.* 2008;65:164-170.
- 14. Harding AH, Darnton A, Wegerdt J, McElvenny D. Mortality among British asbestos workers undergoing regular medical examinations (1971-2005). *Occup Environ Med.* 2009;66:487-495.
- Barth PS, Hunt H. AWorker's compensation and work-related illnesses and diseases. Cambridge: MIT Press; 1980.
- 16. Loomis D, Browning SR, Schenck AP, Gregory E, Savitz D. ACancer mortality among electric utility workers exposed to polychlorinated biphenyls. *Occup Environ Med.* 1997;54:720-728.
- Schulte PA, Ringen K, Hemstreet GP, Ward E. Occupational cancer of the urinary tract. Occup Med. 1987;2:85-107.

- 18. Hauptmann M, Lubin JH, Stewart PA, Hayes RB, Blair . AMortality from solid cancers among workers in formaldehyde industries. *Am J Epidemiol*. 2004;159:1117-1130.
- 19. National Research Council. Health Risks from Exposure to Low Levels of Ionizing Radiation: BEIR VII Phase 2. Washington, DC: The National Academies Press; 2006.
- 20. Berrington de Gonzalez A, Apostoaei AJ, Veiga LHS, et al. RadRAT: a radiation risk assessment tool for lifetime cancer risk projection *J Radiol Prot.* 2012;32:205-222.
- 21. Hayes RB, Yin SN, Dosemeci M, et al. Benzene and the dose-related incidence of hematologic neoplasms in Chin. AChinese Academy of Preventive Medicine--National Cancer Institute Benzene Study Group. J Natl Cancer Inst. 1997;89:1065-1071.
- 22. Straube S, Westphal GA, Hallier E. Comment on: Implications of latency period between benzene exposure and development of leukemia—A synopsis of literature. *Chemico-Biological Interactions.* 2010;186:248-249.
- 23. Beane Freeman LE, Blair A, Lubin JH, et al. Mortality from lymphohematopoietic malignancies among workers in formaldehyde industries: the National Cancer Institute Cohort. J Natl Cancer Inst. 2009;101:751-761.
- 24. Richardson DB, Wing S, Schroeder J, Schmitz-Feuerhake I, Hoffmann W. Ionizing radiation and chronic lymphocytic leukemi. A*Environ Health Perspect*. 2005;113:1-5.
- 25. Bennett MH, MacLennan KA, Vaughan Hudson G, Vaughan Hudson B. Non-Hodgkin's lymphoma arising in patients treated for Hodgkin's disease in the BNLI: a 20-year experience. British National Lymphoma Investigation. *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO*. 1991;2 Suppl 2:83-92.
- 26. Tucker MA, Coleman CN, Cox RS, Varghese A, Rosenberg S. ARisk of second cancers after treatment for Hodgkin's disease. *N Engl J Med.* 1988;318:76-81.
- 27. Larson RA, LeBeau MM, Vardiman JW, Rowley JD. Myeloid leukemia after hematotoxins. *Environ Health Perspect*. 1996;104 Suppl 6:1303-1307.
- American Cancer Society. Cancer in Children. 01/18/2013. Available at: <u>http://www.cancer.org/cancer/cancerinchildren/detailedguide/cancer-in-children-types-of-childhood-cancers</u>.
- 29. National Research Council. Childhood Cancer Survivorship: Improving Care and Quality of Life. Washington, DC: The National Academies Press; 2003.

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

Mei Chen, PhD, MS, Chi-Hsuan Chang, MSc, Lin Tao, PhD, Chensheng Lu, PhD, MS

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

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

MATA 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; $I^2 = 30\%$) and childhood lymphomas (OR = 1.43; 95% CI, 1.15–1.78; $I^2 = 0\%$). A significant increase in risk of leukemia was also associated with herbicide exposure (OR = 1.26; 95% CI, 1.10–1.44; $I^2 = 0\%$). Also observed was a positive but not statistically significant association between childhood home pesticide or herbicide exposure and childhood brain tumors.

IMITATIONS: 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.



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Dr Chen participated in the study conception, design, identification of studies, data collection, study selection, data extraction, data analysis and interpretation, and drafting and revision of the article; Ms Chang participated in data collection, study selection, data analysis, and revision of the article; Dr Tao participated in data collection, study selection, and data analysis; Dr Lu participated in the study conception, design, identification of studies, data collection, study selection, data extraction, analysis, and interpretation, and critical revision of the article; and all authors approved the final manuscript as submitted.

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Downloaded from by guest on September 11, 2017 PEDIATRICS Volume 136, number 4, October 2015 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 posticides 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, adolescent, toddler, infant, neonate, prenatal or postnatal] AND [cancer, tumor, malignancy, neoplasm, neuroblastoma, lymphoma, leukemia, sarcoma, astrocytoma, glioma, craniopharyngioma, 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 metaanalysis. 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, hematopoletic 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 χ^2 test (Cochran's Q) has low power when there are few studies,23 we used the l^2 statistic to quantify the amount of variation in results across studies that is due to heterogeneity. l^2 can be interpreted as a measure of the percentage of the total variation that cannot be explained by chance.23 An /2 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 Mus-

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 metaanalysis.28-43

The characteristics of the studies used in the meta-analysis are shown in Table 1. All 16 studies are casecontrolled 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
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FIGHRE V

PRISMA 2009 Flow Diagram. (Reprinted with permission from Moher D. Liberati A. Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med. 2009;6(6):e1000097)

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% Cl, 1.26–1.72; I^2 = 30%) and childhood lymphomas (OR = 1.43; 95% Cl, 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 (/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; $l^2 \le 5\%$). 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; $l^2 = 23\%$) and this association decreased after data were combined with those for professional home treatment (OR = 1.11; 95% CI, 0.87-1.42; $l^2 = 5\%$).

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 l^2 were 0%) after extreme ORs were removed in the sensitivity analyses. When we replaced the indoor pesticide data of Ma et al37 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.

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Study	Sample Size (case/control)	Age (y)	Study Population. Location, and Period	Exposure Assessment	Cases	Controls
Davis et al (1993), USA	45/85	≤10	Patients in Missouri, diagnosed 1985–1989	Maternal phone interview	CBT	Noncancer friends or other cancer matched with age and gender
Leiss et al (1995), USA	252/222	<15	Patients in Denver, 1976-1983	Parental interview	CBT, Leu, Lym, STS	Noncancer population matched by gender, age, region
Pogoda et al (1997), USA	224/218	≤19	Patients from West Coast, 1984-1991	Maternal phone interview	CBT	Noncancer population matched by gender, age, region
Infante-Rivard et al (1999), Canada	491/491	≤9	Patients from metropolitan Montreal, diagnosed 1980–1993	Parental phone interview	ALL	Noncancer population matched by age, gender, region
Meinet et al (2000), Germany	1184,234, 940/2588	≤15	Patients from West Germany, diagnosed 1992–1994	Mail and parental phone interview	Leu, NHL	Noncancer population matched by gender, age, region
Buckley et al (2000), USA	268/268	≤20	Patients in US, 1986-1990	Maternal phone interview	NHL	Noncancer population matched by age, gender, and race
Daniel et al (2001), USA	390/296	<19	Hospital patients in US and Canada, 1992–1994	Parental phone interview	Neuroblastoma	Noncancer population matched by age, region
Ma et al (2002), USA	162/162	≤14	Hospital patients in northern California, 1995–1999	Maternal in-home personal interview	ALL, Leu	Noncancer population matched by gender, age, mother's race, region
Menegaux et al (2006), France	280/288	<15	Hospital patients in France, diagnosed 1995–1999	Maternal personal interview	AL	Hospital noncancer children matched by age, gender, hospital, race
Rudant et al (2007), France	1060/1681	<15	Patients in France, diagnosed 2003–2004	Maternal phone interview	AL, HL, NHL	Noncancer population matched by age, gender
Urayama et al (2007), USA	294/369	<15	Patients from northern and central California, diagnosed since 1995	In-home interviews with caretaker	ALL	Noncancer children matched by age. gender. Hispanic status, maternal race, region
Cooney et al (2007), USA	523/517	<16	Patients in US and Canada, 1999-2002	Maternal phone interview	Wilms tumor	Noncancer children matched by age and region
Nielsen et al (2010), USA	201/285	≤10	Patients in US west coast, 1984-1991	Maternal in-person interview	CBT	Noncancer children matched by age and gender
Bailey et al (2011), Australia	388/870	<15	Patients in Australia, 2003–2007	Parental questionnaires and phone interviews	ALL	Noncancer population matched by gender, age, region
Ding et al (2012), China	176/180	≤14	Hospital patients in Shanghais China, 2010–2011	Maternal in-person interview and children's urine collections	ALL	Noncancer hospital children matched by gender and age
Greenop et al (2013), Australia	288/917	≤14	Patients in Australia, 2005-2010	Maternal in-person interview	CBT	Noncancer population matched by gender, age, and region

ALL, acute lymphoblastic leukemia; HL, Hodgkin lymphoma; Leu, leukemia; Lym, lymphoma; NHL, non-Hodgkin lymphoma; STS, soft tissue sarcoma.

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

Subgroup	Study N	Su	Summary		Heterogeneity	
		OR	95% CI	P	12	
Indoor pesticides ^{w.h.}						
(A) AL	6	1.59	1.40-1.80	.839	0	
Add professional home treatment	7	1.55	1.38-1.75	,794	0	
Indoor insecticides	5	1,59	1.39-1.81	.725	0	
(B) Leukemia	В	1.48	1.29-1.70	267	20	
Add professional home treatment	9	1.46	1.29-1.65	.327	13	
Dose and multiple agents effects ^e	3	1.92	1.27-2.89	.959	0	
Professional treatment only	3	2.04*	1.05-3.95	.061	64	
Indoor insecticides	7	1.47	1.26-1.72	197	30	
(C) Lymphoma	4	1.43	1.15-1.78	,578	0	
Indoor insecticides	4	1.43	1.15-1.78	.578	0	
(D) Hematopoietic cancers	12	1.47	1.33-1.62	.457	0	
Add professional home treatment	13	1.46	1.32-1.60	.513	0	
Indoor insecticides	11	1.46	1.31-1.63	.388	5	
Dosc and multiple agents effect ^e	4	2.04	1.40-2.97	.894	0	
(E) CBTs ^{d,e,t}	4	1.22	0.83-1.81	.275	23	
Add professional home treatment	5	1.11	0.87-1.42	.380	5	
(F) All cancers ^{1,g}	20	1.40	1.28-1.52	.390	5	
Outdoor pesticidea.b						
(A) Leukemia	6	1.15	0.95-1.38	.190	33	
Herbicide	5	1.26	1.10-1.44	.762	0	
Yard insecticides"	3	1.11	0.60-2.05	.002	84	
(B) Lymphoma	4	0.86	0.62-1.19	.131	47	
Herbicide	3	1.52*	1.02-2.27	.090	58	
Yard insecticides ¹	2	1,12	0,78-1,59	.314	2	
(C) Hematopoietic cancers	10	1.04	0.88-1.23	.086	41	
Herbicide	8	1.33	1.16-1.52	.350	10	
Yard insecticides	5	1.09	0.75-1.58	.007	71	
(D) CBTs	3	0.95	0.47-1.89	.012	77	
Herbicide	2	1.98	0.94-4.14	.409	0	
Yard insecticides	2	1.29	0.86-1.92	548	0	
(E) All cancers ⁸	16	1.10	0.93-1.32	.001	62	
Herbicide	12	1.35	1.16-1.55	221	23	
Yard insecticides ^k	8	1.14	0.89-1.45	.028	55	

"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. Rematoporetic cancers include leukemia and lymphoma All cancers include neuroblastoma and Wilms tumor and solt tissue sercomas in outdoor pesiticides. Study results with case numbers <3 are not included in the summary.

In the study³⁰ where insectiondes against different types of nuisance were reported, data with the highest OR were used.
In the studies where results of different exposure windows in the same study were reported, the windows away from birth were used.

 \circ The data of $>\!i0$ per year were used in the study, sa and the data of $>\!5$ per year were used in the study sr

" When both cancer-free controls and cancer controls were reported, cancer-free controls were used

" The crude OR and 95% CI were calculated based on the data in the article.42

Where >1 home pesticide usage was reported, home pesticides for nuisance pests were used.

* In the study³⁰ where the results were essentially the same during pregnancy and during childhood, the data reported from pregnancy through childhood were treated as during childhood.

^b Includes studies^{35,30,41} and ORs associated with yard pesticides were replaced by yard insectloides in studies^{25,30,41} I Includes 2 data from the study⁴¹

I Includes 2 studies.^{32 an}

In addition to all yard insecticides in each subgroup, an additional study^{ab} was included and ORs associated with yard pesticides were replaced by yard insecticides.

Part of the reason could be the small number of studies included.

Combining all studies reporting childhood cancers (including neuroblastoma³¹ and Wilms tumor³⁰) 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 (l^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 $(OR = 1.26; 95\% Cl, 1.10-1.44, I^2 =$ 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 neuroblastoma³¹ and Wilms tumor,³⁰ a statistically significant association with residential herbicide exposure was observed (OR = 1.35; 95% Cl, $1.16-1.55; I^2 = 23\%$). 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 residential indoor insecticides but not outdoor insecticides during childhood was significantly associated with an

Study name	% Weight	Odds ratio [95% CI]
Childhood Brain Tumor		
Davis et al. 1993	▶ 5	3.40 [1.10 - 10.55]
Leiss et al. 1995	- 6	1.10 [0.40 - 3.01]
Pogoda et al. 1997	26	1.00 (0.63 - 1.58)
Nielson et al. 2010	- 17	1.19 [0.67 - 2.11]
Greenop et al. 2013*	46	1.03 [0.74 - 1.44]
Subtotal ($l^2 = 4.7\%_{n}$, P-value = .380)	100	1,11 [0.87 - 1,42]
Leukemia		
Leiss et al. 1995	5	0.90 [0.54 - 1.51]
Infante-Rivard et al. 1999		2.13 [1.30 - 3.48]
Meiner et al. 2000	15	1.20 [0.90 - 1.60]
Malei al. 2002	6	1.60 [0.97 - 2.63]
Menegaux et al. 2006		1.70 [1.15 - 2.51]
Rudant et al. 2007	33	1.50 [1.27 - 1.77]
Urayama et al. 2007		1.85 [1.10 - 2.47]
Baney et al. 20117	- 12	1.33 (0.97 - 1.83)
Ding et al. 2012	7	1.63 [1.04 - 2.55]
Subtotal (I ² = 12,9%, P-value = .327)	100	1.46 [1.29 - 1.65]
Lymphoma .		
Leiss et al. 1995.	14	1.60 [0.89 - 2.87]
Meinet et al. 2000	- 17	1.70 [1.00 - 2.89]
Rudant el al. 2007, HL -	24	1.10 [0.71 - 1.71]
Rudant et al. 2007, NHL -	- 45	1.56 [1.09 - 2.07]
Subtoral (1 ² = 0.0%, P-value = .578)	- 100	1.43 [1.15 - 1.78]
	1 1	
0.25 0.50 1.00	2,50 7,50	
Odds Ra	alio	

FIGURE 2

Meta-analysis of the association between childhood cancers and exposure to home pesticides during childhood. *Professional home treatments.

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 metaanalysis, 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.13,14 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 al¹⁴ but not by Turner et al,13 and both reported a high degree of heterogeneity (l^2 of 61%) and 72%, respectively). Neither our study nor the study of Turner et al13 observed any association between childhood leukemia and exposure to outdoor insecticides during childhood. Like Van Maele-Fabry et al,14 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,20 However, Vinson et al20 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

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Study name	% Weight	Odds ratio (95% CI)
Childhood Brain Tumor		
Davis et al. 1993	72	2.40 [1.01 - 5.73]
Pogoda et a), 1997		1.20 [0.30 - 4,85]
Subtotal (1 ² = 0.0%, P-value = .409)	100	1.98 [0.94 - 4.14]
Leukemia		
Ding et al. 2012		1.98 [0.63 - 6,24]
Infante-Rivard et al. 1999	- 23	1.41 (1.06 - 1.87)
Ma et al. 2002	5	1_10 [0.59 - 2.06]
Menegaux et al. 2006		1.40 [0.81 - 2.42]
Rudant et al. 2007	65	1.20 [1.01 - 1.42]
Subtotal (1 ² = 0.0%, P-value = .762)	100	1.26 [1.10 - 1.44]
Lymphoma		
Buckley et al. 2000	28	2.35 [1.37 - 4.03]
Rudant et al. 2007. HL	- 35	1.10 [0.73 - 1.66]
Rudani et al. 2007, NHL	37	1.50 [1.01 - 2.22]
Subtotal (1 ² = 58.4%, P-yalue = ,090)	> 100	1.52 [1.02 - 2.27]
j 	- <u>i</u> i	
0.25 0.50 1.00	2,50 7,50	

FIGURE 3

Meta-analysis of the association between childhood cancers and exposure to residential herbicides during childhood.

could not directly compare our results with those reported by Vinson et al.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 al¹⁴ 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,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.¹⁴

Unlike Van Maele-Fabry et al's¹⁴ report and our observation, Turner et al¹³ 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 $(l^2 \le 13\%)$ 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

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Study name	% Weight	Odds ratio (95% CI)
Childhood Brain Tumor		
Dovis et al. 1993	- 27	1.60 [0.71 - 3.63]
Loiss ol al. 1995	36	0.50 [0.31 - 0.82]
Pogoda et al. 1997	37	1,20 [0,76 - 1,90]
Subtotal (l ² = 77.6%, P-value = .012)	100	0.95 [0.47 - 1.89]
Leukomia		
Leiss et al. 1995	- 21	1.10 [0.80 - 1.51]
Infante-Rivard et al. 1999		2.27 [0.93 - 5.55]
Meinet et al, 2000	32	1.00 [0.82 - 1.22]
Ma ei al. 2002	9	1.20 [0.68 - 2.13]
Menegaux et al. 2006	13	1.70 [1.09 - 2.66]
Rudani et al. 2007	- 21	1.00 [0.73 - 1.36]
Subtotal (l ² = 32.8%, P-value = .190)	> 100	1.15 [0.95 - 1.38]
Lymphoma		
Loiss et al. 1995	26	0.60 [0.38 - 0.95]
Meinet et al. 2000		0.80 (0.52 - 1.24)
Rudant et al. 2007, HL	21	0,90 (0.52 - 1,56)
Rudant et al. 2007, NHL	26	1.30 [0.82 - 2.06]
Subtotal (I ² = 46.7%, P-value = ,131)	100	0.86 [0.62 - 1.19]
0.25 0.50 1.00	2.50 7.50	
Odo	is Ratio	

FIGURE 4

Meta-analysis of the association between childhood cancers and exposure to residential outdoor pesticides during childhood.

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 al32 and Menegaux et al³⁹ 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 al¹⁴ assessed the impact of exclusion of nonpublished data and studies in languages other than English, they found that rerunning the metaanalysis 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.^{47,48} 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.^{49,50} Every effort should be made to limit children's exposure to pesticides.

ABBREVIATIONS

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

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REFERENCES

- Adgate JL, Kukowski A, Streebel C, et al. Pesticide storage and use patterns in Minnesota households with children. J Expo Anal Environ Epidemial. 2000;10(2): 159–167
- Bass JK, Ortega L, Rosales C, Petersen NJ, Philen RM. What's being used at home: a household pesticide survey. *Rev Panam Salud Publica*, 2001;9(3):138–144
- Guha N, Ward MH, Gunier R, et al. Characterization of residential pesticide use and chemical formulations through self-report and household inventory: the Northern California Childhood Leukemia study. Environ Health Perspect. 2013; 121(2):276-282
- Kim HH, Lim YW, Yang JY, et al. Health risk assessment of exposure to chlorpyrifos and dichlorvos in children at childcare facilities, *Sci Totol Environ*. 2013;444: 441–450
- Gilden R, Friedmann E, Sattler B, Squibb K, McPhaul K. Potential health effects related to pesticide use on athletic fields. *Public Health Nurs*. 2012;29(3):198–207
- Alarcon WA, Calvert GM, Blondell JM, et al. Acute illnesses associated with pesticide exposure at schools. JAMA. 2005;294(4):455–465
- Faustman EM, Silbernagel SM, Fenske RA, Burbacher TM, Ponce RA. Mechanisms underlying children's susceptibility to environmental toxicants. *Environ Health Perspect.* 2000;108(suppl 1):13–21

- Sheets LP. A consideration of agedependent differences in susceptibility to organophosphorus and pyrethroid insecticides. *Neurotoxicology*. 2000; 21(1–2):57–63
- Landrigan PJ, Claudio L, Markowitz SB, et al. Pesticides and inner-city children exposures, risks, and prevention. *Environ Health Perspect*. 1999;107 (suppl 3): 431–437
- Spann MF, Blondell JM, Hunting KL. Acute hazards to young children from residential pesticide exposures. Am J Public Health. 2000;90(6):971–973
- Infante-Rivard C, Weichenthal S.. Pesticides and childhood cancer: an update of Zahm and Ward's 1998 review. J Toxicol Environ Health B Crit Rev. 2007; 10(1-2):81-99
- Metayer C, Buffler PA, Residential exposures to pesticides and childhood leukaemia. *Radiat Prot Dosimetry*. 2008; 132(2):212–219
- Turner MC, Wigle DT, Krewski D. Residential pesticides and childhood leukemia: a systematic review and metaanalysis. *Environ Health Perspect*. 2010; 118(1):33–41
- Van Maele-Fabry G, Lantin AC, Hoet P, Lison D, Residential exposure to pesticides and childhood leukaemia: a systematic review and meta-analysis. *Environ Int.* 2011;37(1):280–291
- Wigle DT, Turner MC, Krewski D. A systematic review and meta-analysis of

childhood leukemia and parental occupational pesticide exposure. Environ Health Perspect 2009;117(10):1505–1513

- Zahm SH, Ward MH. Pesticides and childhood cancer. Environ Health Perspect. 1998;106(suppl 3):893–908
- López-Cervantes M, Torres-Sánchez L, Tobias A, López-Carrillo L.
 Dichlorodiphenyldichloroethane burden and breast cancer risk: a meta-analysis of the epidemiologic evidence. *Environ Health Perspect*. 2004;112(2):207–214
- Merhi M, Raynal H, Cahuzac E, Vinson F, Cravedi JP, Gamet-Payrastre L. Occupational exposure to pesticides and risk of hematopoietic cancers: metaanalysis of case-control studies. *Cancer Causes Control*. 2007;18(10):1209-1226
- Van Maele-Fabry G, Duhayon S, Lison D. A systematic review of myeloid leukemias and occupational pesticide exposure. *Cancer Causes Control.* 2007;18(5): 457–478
- Vinson F, Merhi M, Baldi I, Raynal H, Gamet-Payrastre L. Exposure to pesticides and risk of childhood cancer: a meta-analysis of recent epidemiological studies. Occup Environ Med. 2011;68(9):694–702
- Meinert R, Kaatsch P, Kaletsch U, Krummenauer F, Miesner A, Michaelis J, Childhood leukaemia and exposure to pesticides: results of a case-control study in northern Germany. Eur J Cancer. 1996;32A(11):1943–1948

- Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis of Observational Studies in Epidemiology (MOOSE) group. JAMA. 2000;283(15):2008–2012
- Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327(7414): 557–560
- Egger M, Davey Smith G. Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*, 1997, 315(7109):629–634
- Metayer C, Colt JS, Buffler PA, et al. Exposure to herbicides in house dust and risk of childhood acute lymphoblastic leukemia. J Expo Sci Environ Epidemiol. 2013;23(4):363–370
- 26. Searles Nielsen S, Mueller BA, De Roos AJ, Viernes HM, Farin FM, Checkoway H, Risk of brain tumors in children and susceptibility to organophosphorus insecticides: the potential role of paraoxonase (PON1). Environ Health Perspect. 2005;113(7):909–913
- Soldin OP, Nsouli-Maktabi H, Genkinger JM, et al. Pediatric acute lymphoblastic leukemia and exposure to pesticides lpublished correction appears in Ther Drug Monit. 2009;31(5):668] Ther Drug Monit. 2009;31(4):495–501
- Bailey HD, Armstrong BK, de Klerk NH, et al; Aus-ALL Consortium. Exposure to professional pest control treatments and the risk of childhood acute lymphoblastic leukernia. Int J Cancer. 2011;129(7):1678–1688
- Buckley JD, Meadows AT, Kadin ME, Le Beau MM, Siegel S, Robison LL. Pesticide exposures in children with non-Hodgkin lymphoma. *Cancer*. 2000;89(11): 2315–2321
- Cooney MA, Daniels JL, Ross JA, Breslow NE, Pollock BH, Olshan AF. Household pesticides and the risk of Wilms tumor. *Environ Health Perspect.* 2007;115(1): 134–137

- Daniels JL, DIshan AF, Teschke K, et al. Residential pesticide exposure and neuroblastoma. *Epidemiology*. 2001; 12(1):20–27
- Davis JR, Brownson RC, Garcia R, Bentz BJ, Turner A. Family pesticide use and childhood brain cancer. Arch Environ Contam Taxicol. 1993;24(1):87–92
- Ding G, Shi R, Gao Y, et al. Pyrethroid pesticide exposure and risk of childhood acute lymphocytic leukemia in Shanghai. *Environ Sci Technol*, 2012;46(24): 13480–13487
- Greenop KR, Peters S, Bailey HD, et al. Exposure to pesticides and the risk of childhood brain tumors. *Cancer Gauses Control.* 2013;24(7):1269–1278
- Infante-Rivard C, Labuda D, Krajinovic M, Sinnett D. Risk of childhood leukemia associated with exposure to pesticides and with gene polymorphisms. *Epidemiology.* 1999;10(5):481–487
- Leiss JK, Savitz DA. Home pesticide use and childhood cancer: a case-control study. Am J Public Health. 1995;85(2): 249–252
- Ma X, Buffler PA, Gunler RB, et al. Gritical windows of exposure to household pesticides and risk of childhood leukemia. Environ Health Perspect. 2002; 110(9):955–960
- Meinert R, Schüz J, Kaletsch U, Kaatsch P, Michaelis J. Leukemia and non-Hodgkin's lymphoma in childhood and exposure to pesticides: results of a register-based case-control study in Germany. Am J Epidemiol. 2000;151(7):639–648, discussion 647–650
- Menegaux F, Baruchel A, Bertrand Y, et al. Household exposure to pesticides and risk of childhood acute leukaemia. Occup Environ Med. 2006;63(2):131–134
- Pogoda JM, Preston-Martin S. Household pesticides and risk of pediatric brain tumors. *Environ Health Perspect*. 1997; 105(11):1214–1220
- Rudant J, Menegaux F, Leverger G, et al. Household exposure to pesticides and

risk of childhood hematopoietic malignancies: The ESCALE study (SFCE). Environ Health Perspect. 2007;115(12): 1787–1793

- Searles Nielsen S, McKean-Cowdin R, Farin FM, Holly EA, Preston-Martin S, Mueller BA. Childhood brain tumors, residential insecticide exposure, and pesticide metabolism genes. Environ Health Perspect. 2010;118(1):144–149
- 43. Urayama KY, Wiencke JK, Buffler PA, Chokkalingam AP, Metayer C, Wiemels JL. MDR1 gene variants, Indoor Insecticide exposure, and the risk of childhood acute lymphoblastic leukemia. *Cancer Epidemiol Biomarkers Prev.* 2007;16(6): 1172–1177
- Eden T. Aetiology of childhood leukaemia. Cancer Treat Rev. 2010;36(4):286–297
- 45. Kim AS, Eastmond DA, Preston RJ. Childhood acute lymphocytic leukemia and perspectives on risk assessment of early-life stage exposures. *Mutat Res.* 2006;613(2–3):138–160
- Rossig C, Juergens H. Aetiology of childhood acute leukaemias: current status of knowledge. *Radiat Prot Dosimetry*. 2008;132(2):114–118
- US Environmental Protection Agency. Integrated pest management (IPM) in schools. Available at. www.epa.gov/ pesticides/Ipm/. Accessed December 16, 2014
- US Centers for Disease Control and Prevention. Integrated pest management (IPM). Available at: www.cdc.gov/nceh/ ehs/elearn/ipm.htm. Accessed March 6, 2013
- US Environmental Protection Agency. Pesticides, topical & chemical fact sheets. Read the label first. Available at: www.epa.gov/pesticides/label/. Accessed May 9, 2012
- 50. US Environmental Protection Agency. Citizen's guide to pest control and pesticide safety. Read the label first. EPA 735-K-04-002, March 2005. Available at: www.epa.gov/oppfead1/Publications/Cit_ Guide/. Accessed, March 13, 2015



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Pesticide Exposures in Children with Non-Hodgkin Lymphoma

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METHODS. The Children's Cancer Group conducted a study comparing 268 children who developed NHL or leukemia with bulk disease with a group of matched, randomly selected regional population controls. The telephone interviews of both the case and control mothers included selected questions regarding occupational and home exposures to pesticides around the time of the index pregnancy ac.d exposure of the child.

RESULTS. A significant association was found between risk of NHL and increased frequency of reported pesticide use in the home (odds ratio |OR| = 7.3 for use most days; trend P = 0.05), professional exterminations within the home (OR = 3.0; P = 0.002), and postnatal exposure (OR = 2.4; P = 0.001). Elevated risks were found for T-cell and B-cell lymphomas; for lymphoblastic, large cell, and Burkitt morphologies; and in both young (age < 6 years) and older children. There was an increased risk of NHL with occupational exposure to pesticides (OR = 1.7) that was not significant overall, but that was significant for Burkitt lymphoma (OR = 9.6; P < 0.05).

CONCLUSIONS. The results of the current study provide further evidence linking pesticide exposure to the risk of NHL, but the authors were unable to implicate any specific agent. *Cancer* 2000;89:2315–21. © 2000 American Cancer Society.

KEYWORDS: non-Hodgkin lymphoma, childhood, case-control, pesticides.

Lymphomas are the third most common tumor of childhood, with an incidence rate of 21.7 per million in children age < 15 years.¹ Approximately 60% of these cases are non-Hodgkin lymphoma

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(NHL). The incidence rate of NHL has increased over the last few decades² for reasons remain largely unknown, but some attention has been focused on increasing pesticide exposures as a contributing factor. Investigations into the association between pesticide exposures and NHL risk among adults have included both cohort⁴ and case-control studies.⁴⁻¹⁷

A central difficulty in these studies has been accurate exposure assessment. In the cohort studies, exposure may be assigned in aggregate rather than individually (e.g., agricultural workers may be assumed to have exposure to herbicides) and the nature of the exposure (the pesticides in use) may not be documented adequately. Despite such obvious and substantial exposure misclassification, cohort studies have shown a surprising degree of consistency in linking pesticide-related activities to the risk of NHL. Case-control studies have the advantage of assigning exposure to individuals, but misclassification of the specific agent(s) involved and the intensity and duration of exposure still may be substantial. Again, despite problems of exposure assessment, findings from case-control studies have lent support to the pesticide hypothesis.

Few studies to date have been conducted in pediatric populations.^{18,19} The Children's Cancer Group (CCG) recently completed a case–control study of childhood NHL (CCG-E08) to evaluate the potential etiologic role of environmental factors (primarily infectious agents) but with additional questions concerning a broad range of exposures including pesticides. The current study reports the findings of the CCG-E08 study with respect to self-reported home pesticide use and occupational exposures to pesticides.

MATERIALS AND METHODS

Children and adolescents age ≤ 20 years with NHL that was newly diagnosed between February 1986 and June 1990 were eligible for the current study. Institutional review board approval was obtained in each participating institution before any patients from that institution were entered onto the study. In December 1986, eligibility was extended to include "lymphomatous leukemia," defined as leukemia with bulk disease in the mediastinum, peripheral lymph nodes, liver, spleen, or other abdominal site and ≥ 25% lymphoblasts in the bone marrow. These children, in the absence of bone marrow involvement, would have been diagnosed as having NHL. For simplicity of presentation, we generally will refer to the patient population for this study as "NHL" patients, recognizing that a more accurate designation is "NHL plus lymphomatous leukemia."

Of the 311 patients who met the eligibility requirements, 5 (2%) were excluded because permission to contact was not given by the treating physician, 26 families (8%) declined to participate, and in 12 cases (4%) no suitable control could be identified.

Pathology slides were requested for central review. For the analysis, the review diagnosis (which was available in 81% of cases) was used to classify cases histopathologically, Similarly, tumors were classified according to cell type (predominantly B-cell or T-cell) based on immunopathology studies conducted in a CCG reference laboratory (supervised by M.E.K.) or, when fresh tumor tissue was not available for central review, on information provided by the treating institution regarding the presence of B or T specific cell surface markers. For some rumors that lacked either central or institutional data concerning cell type, a cell type was inferred based on well established correlations between histopathology and cell lineage. Thus, Burkitt lymphoma was inferred to be of B-cell origin. In the absence of any data, lymphoblastic tumors were inferred to be T-cell, and both large cell and undifferentiated tumors were considered to be of B-cell origin. Of the 137 tumors considered to be of B-cell origin, 33 were inferred with high confidence (i.e., Burkitt lymphoma) and 33 were probable B-cell tumors. Of 115 tumors classified as T-cell tumors, 47 were inferred.

Additional eligibility criteria included that the natural mother speak either English or Spanish and be available for an interview and that the household have a telephone. Children meeting the eligibility criteria were registered with the CCG. Approximately 1–2 months after diagnosis, the treating physician was contacted for permission to contact the mother for an interview. On receiving permission, the study coordinator sent a letter to the mother explaining the study and followed the letter with a telephone call to schedule a telephone interview.

Controls were ascertained by a method of random digit dialing that has been described elsewhere.20 Controls were matched individually to the cases based on date of birth (within 12 months when the case was age < 3 years and within 24 months otherwise), gender, and race (black vs. non-black). If no match was found after 150 numbers had been tried and excluded, matching criteria were relaxed. In the final dataset, 252 controls (94%) were race matched, 254 controls (95%) were matched based on gender, and 243 controls (91%) differed in age from the case by < 2 years. A reference date was established for the case as the date 1 year prior to diagnosis for children aged > 2years. 6 months prior to diagnosis for those children aged 12-24 months, and the date of diagnosis for children age < 12 months at the time of diagnosis.

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Questions concerning the child were restricted to the period between birth and the reference date. For the control, an equivalent reference date was chosen so that the control had a reference age (age at the reference date) that was as close as possible to the case's reference age. The reference age for 254 controls (95%) was within 12 months of the reference age of the case.

The interview included a broad range of questions regarding other factors of possible interest such as medications, X-rays, parental occupation, medical history of the child and family members (including a history of lymphoma or other malignancies), childhood infections, allergies, vaccinations, and immunerelated disorders as well as pesticide exposures of the parents and the child. Questions relating to pesticide use were brief and relatively nonspecific; four guestions were asked concerning household exposure in the month before the pregnancy, during the pregnancy, or while nursing (with the index child). Specifically, questions elicited information regarding frequency of use by the mother of household insect and garden sprays, whether the house had been treated by professional exterminators, and whether the index child came into frequent contact with herbicides or insecticides. In the occupational section, respondents were asked about a list of possible exposures that included "pesticides and weedkillers."

Statistical Methods

Conditional logistic regression was used to estimate relative risks of NHL for each covariate.²¹ For some analyses, when the asymptotic estimates were infinite, an exact conditional logistic approach was necessary.²² To adjust for possible residual socioeconomic confounding, regression models included covariates representing maternal educational achievement (coded as college graduate, some college, high school graduate, and less educated) and maternal race (coded as white, non-Hispanic vs. others).

An overall assessment of pesticide exposure was obtained by combining data from all five pesticiderelated questions to create an ad hoc "score." This score was obtained by adding points for each subject: one point for each of 1) either parent occupationally exposed; 2) the child reported as "frequently" exposed to herbicides/pesticides; 3) insect extermination around the home; 4) the use of garden sprays (more than once a month); and 5) the use of household insecticides at least once per week. An extra point was added for household insecticides used "most days." This scoring system was arbitrary but had the advantage of combining data from several questions in a way that tended to smooth out small sample fluctuations.

TABLE 1

Morphology and Cell Type for Cases Included in the Current Study

		Cell type	Other"
Morphology	T-cell	B-cell	
Lymphoblastic	70	12	2
Large cell	11	25	5
Burkitt	0	61	Ð
Undifferentiated	0	26	1
Lymphomatous Ignkemia	32	12	5
NEL, NOS	2	4	3
Total	113	137	16

NHL non-Hodgkin lymphoma; NOS not otherwise specified.

" "Other" category includes null cell, histiocytic, and not classifiable.

RESULTS

Of the 268 patient cases included in the final data set, 49 had lymphomatous leukemia and the remainder were diagnosed with NHL; 38% of cases with NHL were of lymphoblastic subtype, 28% were Burkitt lymphoma, 12% were undifferentiated (non-Burkitt) lymphoma, and 19% were large cell NHL. Table 1 shows the relation between histopathology and the documented (or inferred) cell type. The majority of large cell tumors with T-cell phenotype were Ki-1 positive (8 of 11 tumors). Four of the 12 B-cell lymphoblastic tumors were recorded as pre-B phenotype or prepre-B phenotype. In three instances the histologic diagnosis was uncertain; in two instances the immunopathology was not definitive, with a mixed lineage in one case and B-cell polyclonality in the other.

Control mothers were slightly, but not significantly, more educated than case mothers (Table 2), but the cases and controls were matched adequately by age and gender. There was the same proportion of white mothers in the case and control groups, but there were differences in the numbers of other racial categories. We attempted to match cases and controls with respect to black versus non-black race during control selection, but this was the criterion most often omitted when the matching rules needed to be relaxed. To control for possible residual confounding by race due to the distribution differences seen in Table 2, a race variable was included in the majority of analyses (coding separately to the two most common categories; white and Hispanic).

Comparisons of cases and controls for the four pesticide-related questions are shown in Table 3. The frequency of use by the mother of household insecticides around the time of the pregnancy was associated positively with NHL risk (odds ratio |OR| = 2.62 for use on 1–2 days per week and OR = 7.33 for use more frequently; *P* value for trend = 0.05). Professional in-

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TABLE 2

Comparison of Cases and Controls with Respect to Age at the Reference Date, Gender, and the Race and Level of Education of the Mother^a

		Cases	Controls
Age (yrs)	<1	16 (6%)	18 (7%)
10 LE	1-2	11 (月%)	9 (3%)
	3-5	64 (24%)	59 (22%)
	6-10	116 (43%).	119 (44%)
	11+	61 (23%)	63 (24%)
Gender	Male	197 (74%)	192 (72%)
	Female	71 (26%)	76 (28%)
Race (mother)b	White	231 (86%)	231 (86%)
	Bluck	10 (4%)	15 (6%)
	Hispanic	22 (8%)	16 (6%)
	Astin	2 (1%)	4 (1%)
Education (mother) ¹⁰	College degree	44 (16%)	52 (19%)
	Sume college	80 (30%)	78 (29%)
	High school graduate.	112 (42%)	107 (40%)
	Less educated	29 [11/5]	26 (10%)

" None of the case-control differences were significant

""Some columns do not add op to 268 because of missing data.

sect treatment to the home also was related significantly to NHL risk (OR = 2.98; P = 0.002). Direct (postnatal) exposure of the child to pesticides, as reported by the child's mother, was associated with NHL (OR = 2.35; P = 0.001). Occupational exposures and the use of pesticide sprays in the garden showed poslitive, but not significant, associations with NHL.

ORs were examined within immunopathologic, histologic, and age categories to determine whether the observed risks were due to associations within a subgroup (Table 4). OR estimates in Table 4 were not adjusted for maternal education and race because the small subgroup size frequently led to cell frequencies of zero, with associated infinite estimates. Significant associations were observed (for at least one exposure variable) for each subgroup of cases with the exception of the small group of undifferentiated lymphomas. The greatest ORs were observed for household insecticide use in the lymphoblastic lymphoma subgroup, for occupational exposure in the Burkitt lymphoma group, and for professional insect extermination in the large cell and Burkitt lymphoma groups. The most statistically significant associations tended to be for the child's direct exposure, which showed a P value < 0.01 in 4 of the subgroups and a P < 0.05 in 4 other subgroups.

There were several questions that had indirect relevance to the potential for pesticide exposures. These included the area of residence (OR = 0.96; 95% confidence interval [95% CI], 0.65-1.41, for rural vs. urban), dog ownership (OR = 0.97; 95% CI, 0.67-1.41),

cat ownership (OR = 0.99; 95% CI, 0.69-1.42), and frequent contact with farm animals (OR = 0.86; 95% CI, 0.56-1.31).

The results for the pesticide score are shown in Table 5. Significantly elevated risks were present for an increasing pesticide score overall (OR for 2+ point = 4.0; *P* value for trend < 0.0001); within B-cell and T-cell subgroups (OR = 4.1 and 3.8, respectively); within lymphoblastic (OR = 10.9; *P* < 0.01), large cell (OR = 6.5; *P* = 0.03), and Burkitt lymphoma (OR = 7.1; *P* = 0.01) morphologic groups; and for both the younger (age < 6 years) and older age divisions.

DISCUSSION

Zahm and Blair²⁸ compiled reports from 21 cohort studies regarding adult NHL and farming. They found 11 risk estimates of NHL greater than unity (3 of which were statistically significant), with risks ranging from 0.6–2.6. Of 19 case–control and cross-sectional studies (which might be expected to provide more specific exposure data), 12 gave risk estimates greater than unity (8 of which were statistically significant). The authors concluded that these data were equivocal, possibly due to the fact that exposure is inferred from a broad occupational category: "farming." However, in a more recent review, the same authors³⁷ reported that NHL has been linked epidemiologically with phenoxyacetic acid herbicides, organochlorine pesticides, and organophosphate pesticides.

Studies based on more specific exposure data generally have shown higher risk estimates. Hardell et al.¹⁵ reported a 5.5-fold increased risk of lymphoma for persons with exposure to phenoxyacetic acid herbicides (a class including 2,4-D and 2,4,5-T), and risk estimates of 2.4 for DDT (dichlorodiphenyltrichloroethane) and 4.8 for chlorophenol. Hoar et al.6 found a 2.2-fold risk for NHL in farmers who used phenoxy herbicides, with a > 7-fold increased risk for those individuals reporting > 20 days' use of 2,4-D per year. Risk also was increased in those individuals not reporting the use of protective equipment. In a similar study in Nebraska, the risk was 3.3 for farmers handling 2,4-D for > 20 days per year.²⁰ La Vecchia et al.²⁵ reported a significant positive trend with duration of exposure to herbicides, and Persson et al.17 reported an NHL risk of 2.3 for individuals in occupations in which they are exposed to phenoxy acids. Pearce et al.5 reported a significantly increased risk of 3.7 for orchard workers, although no association was noted with potential exposure to phenoxy herbicides or chlorophenols. Olsson and Brandt²⁶ reported a 10-fold elevated risk of cutaneous NHL with exposure to phenoxy acids, but a much smaller risk of 1.3-fold overall. Woods et al.11 did not find any association with occu-

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TABLE 3

OR for Childhood NHL Associated with Pesticide Exposures (the Person Exposed is Given in Parentheses)

Exposure	Category	Cases/controls"	OR ^b	95% CI	P value (trend)
Household insecticides (mother)	Never	185/198	1.00		
	< 1 per wk	46/51	0.98	0.60-1.58	
	1-2 per wk	17/10	2.62	0.96-7.18	
	Most days	6/1	7.33	0.84-63.85	0.05
Garden sprays (mother)	Never	237/252	1.00		
	< 1 per mo	9/6	1.82	0.61-5.45	
	≥ 1 per mo	1378	1.71	0.67-4.37	0.29
Exterminate around home (mother)	No	237/256	1.00		
	Yes	31/12	2.98	1.44-6.16	0.002
Herbicides or pesticides (child)	No	214/243	1.00		
	Yes	50/23	2.35	1.37-4.03	0.001
Occupational pesticides (parent)	No	247/255	1.00		
a come se marie à sur.	Yes	21/13	1.74	0.82-3.69	0.21

OR: odds ratio; 95% CI: 95% confidence interval.

^a Frequencies may not add up to 268 because of missing data.

^b Adjusted for maternal education and race.

TABLE 4

Adjusted Odds Ratios for Pesticide-Related Questions, within Subgroups of Cases

	No	Household	Garden	Insect	Child's	Occupational
	IND.	exposure	spruys	extermination	exposure	exposure
Lineage						
B-cell lymphoma	179	4.2"	2.0	2.7 ^{ts}	2,2 ^h	1.5
T-cell lymphoma	81	4.0 ¹⁵	1.4	3.2 ^h	2.5 ^b	1.7
Histology						
Lymphoblastic	84	12.5 ^{b.c}	1.8	3.5 ⁿ	2.9	0.9
Large cell	41	2.4	0.9	6.7 ^a	7.0 ^b	5.3
Burkitt	61	3.2	1.2	8.0 ^{a.c}	4.7ª	9.6 ^{a,c}
Undifferentiated	27	d	3.2	0.7	0.2	1.4
Lymphomatous						
ALL	49	0.4	2.5	0.8	3.9°	2.1
Age group						
< 6 yrs	91	1.1°	8.0"	1.3	11.0 ^b	1.9
≥ 6 yrs	177	2,9 ^a	1.5	4.3 ^h	1.8*	3.2ª

ALL: acute lymphoblastic leukemia.

* 0.01 < P < 0.05 (adjusted for maternal education and race).

^b P < 0.01 (adjusted for maternal education and race).

^c Exact estimation used.

d No exposed cases or controls.

For household exposure the odds ratio is given for use more than once per week (vs. less often) and for garden sprays the odds ratio is for some use (vs. none).

pational exposure to phenoxy herbicides or chlorophenols, but there were significant associations with two specific occupations: farming and forestry herbicide applicators. A Norwegian study¹⁹ of a cohort of 323,292 children showed an increased risk of NHL associated with parental occupation in agricultural activities, suggesting that whatever factor is involved may affect children in the home. To our knowledge other studies have failed to demonstrate any association between inferred pesticide exposure and NHL risk.^{4,7} Rothman et al.¹² measured serum concentrations of polychlorinated biphenyls (PCBs) and DDT in NHL patients and controls and were able to demonstrate a highly significant association with PCB but no relation between serum DDT levels and NHL risk.

Other pesticides have been studied less extensively, but statistically significant positive associations have been reported for atrazine, chlorophenols, and fungicides in general.

In the CCG-E08 study, the primary focus of which

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TABLE 5

Adjusted Odds Ratios (with 95% CIs) for the Pesticide Score, Based on All Pesticide-Related Questions

		Pesticide score					
	Zero	Une	(95% CI)	Two or more	(95% CI)	Trend P value	
All cases	1.00	2.5	(1.5-4.1)	4.0	(1.8-8.3)	< 0.0001	
Lineage							
B-cell lymphoma	1.00	2.6	(1.5 - 4.4)	4.1	(1.7 - 9.9)	< 0.0001	
T-cell lymphoma	1.00	2.8	(1.6-5.1)	3.8	(1.6 - 9.2)	< 0.0001	
Histology							
Lymphoblastic	1.00	3.5	(1.4-9.0)	10,9	(1, 1-103, 4)	< 0.01	
Large cell	1.00	4.4	(0.9 - 20.9)	6.5	(0.8-53,7)	0.03	
Burkitt	1.00	5.3	(1.2-22.7)	7.1	(1.2-42.4)	0.01	
Undifferentiated*	1.00	6/9		2/2		0.49	
Lymphomatous ALL	1.00	1.9	(0,6-5.8)	2.5	(0, 4-15, 1)	0.44	
Age group							
< 6 yrs ^h	1.00	20/18		10/1		0.003	
≥ 6 yrs	1.00	3.1	(1.6-5.8)	2.6	(1.1-5.7)	0.0001	

95% CI: 95% confidence interval; ALL: acute lymphoblastic leukenna.

" Case-control frequencies shown instead of odds ratios. No convergence on logistic regression

Adjusted for maternal education and race.

was the potential role of infections in NHL, questions relating to pesticide exposure were very limited. However, we found evidence of an increased risk of NHL in those households with the highest pesticide use. This association was apparent for all histologies except undifferentiated (non-Burkitt) lymphoma, for both B-cell and T-cell lymphoma (although more significantly for the former), and both in children age < 6 years and in older children. Significant associations were observed for both maternal exposures during pregnancy (i.e., in utero exposure) and direct exposures of the child, although clearly these exposures are correlated and, with our limited sample size, it was not possible to determine which period was the more crucial. Given the small number of cases in the morphologic subgroups, substantial variations in the ORs are to be expected across these groups for individual questions. For this reason, the aggregate analyses presented in Table 5 are more reliable, and the overall impression is that the increase in risk related to pesticide exposure is not limited to any one subgroup.

There are several explanations for these findings, other than a causal one, that bear consideration. It is possible that the significant associations are a "statistical artifact," due to multiple testing. However, the pesticide association was investigated specifically because of data from previous studies. In addition, chance cannot reasonably be invoked as an explanation for the more extreme *P* values of < 0.0001 in some instances. Alternatively, the association could be due to confounding, but the cases and controls were matched for age, race, and gender and the random

digit dialing procedure, which commonly draws a control from the same neighborhood as the case,²⁷ has a tendency to match with regard to other sociodemographic factors. The results of the current study did not appear to be affected by adjustment for the mother's education or race.

The influence of selection bias must be considered, particularly for control ascertainment, because random digit dialing refusals tend to bias the control group toward the upper socioeconomic classes. However, adjustment for sociodemographic characteristics was made in the analyses. Perhaps more telling is the observation that very little difference was noted in case-control responses to the many nonpesticide questions (data not shown). It is difficult to determine how selection factors would create biases targeted specifically toward this one section of the questionnaire.

The same cannot be said for recall bias, which selectively could affect questions concerning certain topics. An overall recall bias, such as a tendency for the more highly motivated parents of cases to overreport exposures, would produce systematically elevated ORs for a wide range of exposures; in fact, there was no such pattern of responses in the data from the current study. However, this does not rule out the possibility of selective recall bias; the case parents overreport pesticide exposures for NHL, presumably because they are aware of reported links between the two. This is an issue that will have to be addressed in future studies. Validation of exposure is likely to be very difficult, particularly because the exposures of

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interest happened many years ago. An alternative approach may be to attempt to determine biomarkers of exposure within these families.

The term "pesticides" refers to a group of chemicals that have little in common except their ability to kill insects, plants, mammals (particularly rodents), or fungi. There literally are thousands of pesticides in use, hundreds of which may be used around the home, that differ enormously in their structure and mode of action. It is likely that a limited number of these compounds may be capable of inducing lymphoma; thus our measurement of exposure (to "pesticides") is subject to substantial misclassification (both in terms of identifying the agent of interest and quantitation of the dose) and the true OR is higher than that reported in the current study.

The current study provided an opportunity to examine pesticide exposures in a pediatric population of NHL patients. Although the exposure assessment data were limited, the observed significant associations warrant further investigation. The CCG currently is conducting a larger case-control study of NHL that focuses on the role of pesticides in the development of this malignancy.

REFERENCES

- Parkin DM, Pisani D, Ferlay I. Estimates of worldwide incidence of eighteen major cancers in 1985. Int J Cancer 1993; 54:594–606.
- Rabkin CS, Devesa SS, Zahm SH, Gail MH. Increasing incidence of non-Hodgkin's lymphoma. *Semin Hematol* 1993; 30:286–96.
- Blair A, Zahm SH. Agricultural exposures and cancer. Environ Health Perspect 1995;103:205-8.
- Franceschi S, Serraino D, Bidoli E, Talamini R, Tirelli U, Carbone A, et al. The epidemiology of non-Hodgkin's lymphoma in the north-east of Italy: a hospital-based casecontrol study. *Leuk Res* 1989;13:465–72.
- Pearce NE, Sheppard RA, Smith AH, Teague CA. Non-Hodgkin's lymphoma and farming: an expanded case-control study. Int J Caucer 1987;39:155–61.
- Hoar SK, Blair A. Holmes FF, Boysen CD, Robel RJ. Hoover R. et al. Agricultural herbicide use and risk of lymphoma and soft-tissue sarcoma. JAMA 1986:256:1141–7.
- Brownson RC, Reif JS. A cancer registry-based study of occupational risk for lymphoma, multiple myeloma and leukemia. Int J Epidemiol 1988;17:27–32.
- Blair A, White D. Death certificate study of leukemia among farmers from Wisconsin. J Natl Cancer Inst 1981;66:1027–30.
- Blair A, Thomas TL. Leukemia among Nebraska farmers: a death certificate study. Am J Epidemiol 1979;110:264–73.
- Zahm SH, Weisenburger DD, Saal RC, Vaught JB, Babbitt PA, Blair A. The role of agricultural pesticide use in the development of non-Hodgkin's lymphoma in women. Arch Environ Health 1993;48:353-8.

- Woods JS, Polissar L, Severson RK, Heuser LS, Kulander BG. Soft tissue sarcoma and non-Hodgkin's lymphoma in relation to phenoxyherbicide and chlorinated phenol exposure in western Washington. J Natl Cancer Inst 1987;78:899–910.
- Rothman N, Cantor KP, Blair A, Bush D, Brock JW, Heleisouer K, et al. A nested case–control study of non-Hodgkin's lymphoma and serum organochlorine residues. *Lancet* 1997; 350:240–4.
- Burmeister LP, Everett GD, Van Lier SF, Isacson P. Selected cancer mortality and farm practices in Iowa. Am J Epidemiol 1983;118:72–7.
- Hardell L, Eriksson M, Lenner P, Lundgren E, Malignant lymphoma and exposure to chemicals, especially organic solvents, chlorophenols and phenoxy acids: a case-control study. Br J Cancer 1981;43:169–76.
- Hardell L, Etiksson M, Degerman A. Exposure to phenoxyacetic acids, chlorophenols, or organic solvents in relation to histopathology, stage, and anatomical localization of non-Hodgkin's lymphoma. *Cuncer Res* 1994;54:2386–9.
- Hardell L, Van Bavel B, Lindstrom G, Fredrikson M, Hagberg H, Liljegren G, et al. Higher concentrations of specific polychlorinated biphenyl congeners in adipose tissue from non-Hodgkin's lymphoma patients compared with controls without a malignant disease. Int J Oncol 1996;9:603–8.
- Persson B, Fredriksson M, Olsen K, Boeryd B, Axelson O. Some occupational exposures as risk factors for malignant lymphomas. *Cancer* 1993;72:1773–8.
- Adami J, Glimelius B, Coatfingius S, Ekbom A, Zahm SH, Linet M, et al. Maternal and perinatal factors associated with non-Hodgkin's lymphoma among children. Int J Cancer 1996;65:774–7.
- Kristensen P, Andersen A, Irgens LM, Bye AS, Sundheim L. Cancer in offspring of parents engaged in agricultural activities in Norway: incidence and risk factors in the farm environment. Int J Cancer 1996;65:39-50.
- Robison LL. Daigle A. Control selection using random digit dialing for cases of childhood cancer. Am J Epidemiol 1984; 120:164-6.
- Breslow NE, Day NE, Statistical methods in cancer research. Volume 1: the analysis of case-control studies, Lyon, France: IARC Scientific Publications, 1980.
- Hirji KF, Mehta CR, Parel NR. Computing distributions for exact logistic regression. J Am Stat Assoc 1987;82:1110–7.
- Zahm SH, Blair A. Pesticides and non-Hodgkin's lymphoma. Cancer Res 1992;52:5485s-8s.
- Zahm SH, Weisenburger DD, Babbit PA, Saal RC, Vaught JB, Cantor KP, et al. A case-control study of non-Hodgkin's lymphoma and the herbicide 2,4-dichlorophenoxyacetic acid (2,4-D) in castern Nebraska. *Epidemiology* 1990;1:344– 56.
- La Vecchia C, Negri E, D'Avenzo B, Franceschi S. Occupation and lymphoid neoplasms. Br J Cancer 1989;60:385–8.
- Olsson H, Brandt L. Non-Hodgkin's lymphoma of the skin and occupational exposure to herbicides. *Lancet* 1989;2:579.
- Sakkenin PA, Severson RK, Ross JA, Robsion LL. Random digit dialing for control selection in childhood cancer studies: the geographic proximity and demographics within matched sets. Am J Public Health 1995;85:555–7.

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

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

DBJECTIVE. 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; $l^2 = 30\%$) and childhood lymphomas (OR = 1.43; 95% CI, 1.15–1.78; $l^2 = 0\%$). A significant increase in risk of leukemia was also associated with herbicide exposure (OR = 1.26; 95% CI, 1.10–1.44; $l^2 = 0\%$). Also observed was a positive but not statistically significant association between childhood home pesticide or herbicide exposure and childhood brain tumors.

UMITATIONS: 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.



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Dr Chen participated in the study conception, design, identification of studies, data collection, study selection, data extraction, data analysis and interpretation, and drafting and revision of the article; Ms Chang participated in data collection, study selection, data analysis, and revision of the article; Dr Tao participated in data collection, study selection, data analysis, and revision of the article; Dr Tao participated in data collection, study selection, design, identification of studies, data collection, study selection, data extraction, and data analysis; Dr Lu participated in the study conception, design, identification of studies, data collection, study selection, data extraction, analysis, and interpretation, and critical revision of the article; and all authors approved the final manuscript as submitted.

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Downloaded from by guest on September 11, 2017 PEDIATRICS Volume 136, number 4, October 2015 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, adolescent, toddler, infant, neonate, prenatal or postnatal] AND [cancer, tumor, malignancy, neoplasm, neuroblastoma, lymphoma, leukemia, sarcoma, astrocytoma, glioma, craniopharyngioma, 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 metaanalysis. 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 \geq 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 Haleropeneity

Because the current review includes a limited number of studies, and the conventional statistical approach to evaluating heterogeneity using a χ^2 test (Cochran's Q) has low power when there are few studies,23 we used the l^2 statistic to quantify the amount of variation in results across studies that is due to heterogeneity. l^2 can be interpreted as a measure of the percentage of the total variation that cannot be explained by chance,23 An 12 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.

Publicution Blas

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 metaanalysis,28-43

The characteristics of the studies used in the meta-analysis are shown in Table 1. All 16 studies are casecontrolled 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



FIGURE 1

PRISMA 2009 Flow Diagram. (Reprinted with permission from Moher D. Liberati A. Tetzlaff J. Altman DG; The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med. 2009;6(6):e1000097)

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; l^2 = 30%) and childhood lymphomas (OR = 1.43; 95% CI, 1.15–1.78; l^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% Cl, 1.32–1.60; $l^2 \le 5\%$). A positive but not statistically significant association between home pesticide exposure during childhood and CBT was observed (OR = 1.22; 95% Cl, 0.83–1.81; l^2 = 23%) and this association decreased after data were combined with those for professional home treatment (OR = 1.11; 95% Cl, 0.87–1.42; l^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 l^2 were 0%) after extreme ORs were removed in the sensitivity analyses. When we replaced the indoor pesticide data of Ma et al37 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.

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TABLE 1 Overview of the Case-Controlled Studies Included in the Meta-Analysis

Study	Sample Size (case/control)	Age (y)	Study Population, Location, and Period	Exposure Assessment	Cases	Controls
Davis et al (1993), USA	45/85	≤10	Patients in Missouri, diagnosed 1985–1989	Maternal phone interview	CBT	Noncancer friends or other cancer matched with age and gender
Leiss et al (1995), USA	252/222	<15	Patients in Denver, 1976-1983	Parental interview	CBT, Leu, Lym, STS	Noncancer population matched by gender, age, region
Pogoda et al (1997), USA	224/218	≤19	Patients from West Coast, 1984–1991	Maternal phone interview	CBT	Noncancer population matched by gender, age, region
Infante-Rivard et al (1999), Canada	491/491	≤9	Patients from metropolitan Montreal, diagnosed 1980–1993	Parental phone interview	ALL	Noncancer population matched by age, gender, region
Meinet et al (2000), Germany	1184,234, 940/2588	≤15	Patients from West Germany, diagnosed 1992–1994	Mail and parental phone interview	Leu, NHL	Noncancer population matched by gender, age, region
Buckley et al (2000), USA	268/268	≤20	Patients in US, 1986-1990	Maternal phone interview	NHL	Noncancer population matched by age, gender, and race
Daniel et al (2001), USA	390/296	<19	Hospital patients in US and Canada, 1992–1994	Parental phone interview	Neuroblastoma	Noncancer population matched by age, region
Ma et al (2002), USA	162/162	≤14	Hospital patients in northern California, 1995–1999	Maternal in-home personal interview	ALL, Leu	Noncancer population matched by gender, age, mother's race, region
Menegaux et al (2006), France	280/288	<15	Hospital patients in France, diagnosed 1995–1999	Maternal personal interview	AL	Hospital noncancer children matched by age, gender, hospital, race
Rudant et al (2007), France	1060/1681	<15	Patients in France, diagnosed 2003–2004	Maternal phone interview	AL, HL, NHL	Noncancer population matched by age, gender
Urayama et al (2007), USA	294/369	<15	Patients from northern and central California, diagnosed since 1995	In-home interviews with caretaker	ALL	Noncancer children matched by age, gender, Hispanic status, maternal race, region
Cooney et al (2007), USA	523/517	<16	Patients in US and Canada, 1999-2002	Maternal phone interview	Wilms tumor	Noncancer children matched by age and region
Nielsen et al (2010), USA	201/285	≤10	Patients in US west coast, 1984–1991	Maternal in-person interview	CBT	Noncancer children matched by age and gender
Bailey et al (2011). Australia	388/870	<15	Patients in Australia, 2003-2007	Parental questionnaires and phone interviews	ALL	Noncancer population matched by gender, age, region
Ding et al (2012), China	176/180	≤14	Hospital patients in Shanghais China, 2010–2011	Maternal in-person interview and children's urine collections	ALL	Noncancer hospital children matched by gender and age
Greenop et al (2013), Australia	288/917	≤14	Patients in Australia, 2005–2010	Maternal in-person interview	CBT	Noncancer population matched by gender, age, and region

ALL, acute lymphoblastic leukemia; HL, Hodgkin lymphoma; Leu, leukemia; Lym, lymphoma; NHL, non-Hodgkin lymphoma; STS, soft tissue sarcoma.

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

Subgroup	Study N	Su	mmary	Heterog	geneity
		OR	95% CI	P	12
Indoor pesticides ^{ab}					
(A) AL	6	1.59	1.40-1.80	839	0
Add professional home treatment	7	1.55	1.38-1.75	.794	0
Indoor insecticides	5	1,59	1.39-1.81	.725	0
(B) Leukemia	8	1.48	1 29-1.70	.267	20
Add professional home treatment	9	1,46	1.29-1.65	.327	13
Dose and multiple agents effects ^c	3	1.92	1.27-2.89	.959	0
Professional treatment only	3	2.04*	1.05-3.95	.061	64
Indoor insecticides	7	1.47	1.26-1.72	197	30
(C) Lymphoma	4	1.43	1.15-1.78	578	0
Indoor insecticides	-4	1.43	1,15-1.78	578	0
(D) Hematopoietic cancers	12	1.47	1.33-1.62	,457	0
Add professional home treatment	13	1.46	1.32-1.60	,513	0
Indoor insecticides	11	1.46	1.31-1.63	.388	5
Dose and multiple agents effect ^e	4	2.04	1.40-2.97	894	0
(E) CBTs ^{d,e,1}	4	1.22	0.83-1.81	.275	23
Add professional home treatment	5	1.11	0.87-1.42	.380	5
(F) All cancers ^{LR}	20	1.40	1.28-1.52	390	5
Outdoor pesticide ^{ab}					
(A) Leukemia	6	1.15	0.95-1.38	.190	33
Herbicide	5	1.26	1.10-1.44	.762	0
Yard insecticides"	3	1.11	0.60-2.05	.002	84
(B) Lymphoma	4	0.86	0.62-1.19	131	47
Horbicide	3	1,52*	1.02-2.27	.090.	58
Yard insecticides	2	1,12	0.78-1.59	.314	2
(C) Hematopoietic cancers	10	1.04	0.88-1.23	.086	41
Herbicide	8	1.33	1.16-1.52	.350	10
Yard insecticides	5	1.09	0.75-1.58	.007	71
(D) CBTs	3	0.95	0.47-1.89	.012	77
Herbicide	2	1.98	0.94-4.14	.409	0
Yard insecticides ^L	2	1.29	0.86-1.92	.548	0
(E) All cancers [®]	16	1.10	0.93-1.32	.001	62
Herbicide	12	1.35	1.16-1.55	.221	23
Yard insecticides"	В	1.14	0.89-1.45	.028	55

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

In the study³⁵ where insecticides against different types of nuisance were reported, data with the highest DR were used.
In the studies where results of different exposure windows in the same study were reported, the windows away from birth were used.

* The data of >10 per year were used in the study.³⁴ and the data of >5 per year were used in the study.³⁷

^d When both cancer-iree controls and cancer controls were reported, cancer-iree controls were used.

" The crude OR and 95% CI were calculated based on the data in the article.42

1 Where >1 home pesticide usage was reported, home pesticides for nuisance pests were used.

In the study^{an} where the results were essentially the same during pregnancy and during childhood, the data reported from pregnancy through childhood were treated as during childhood.

Includes studies^{35,39,41} and ORs associated with yard pesticides were replaced by yard insecticides in studies^{35,39} Includes 2 data from the study⁴¹

I Includes 2 studies 32.40

^b In addition to all yard insecticities in each subgroup, an additional study³⁰ was included and ORs associated with yard pesticides were replaced by yard insecticides.

Part of the reason could be the small number of studies included.

Combining all studies reporting childhood cancers (including neuroblastoma³¹ and Wilms tumor³⁰) 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 $(OR = 1.26; 95\% Cl, 1.10-1.44, I^2 =$ 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 neuroblastoma31 and Wilms tumor,30 a statistically significant association with residential herbicide exposure was observed (OR = 1.35; 95% CI, 1.16–1.55; $l^2 = 23\%$). 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 residential indoor insecticides but not outdoor insecticides during childhood was significantly associated with an

Study name	% Weight	Odds ratio (95% CI)
Childhood Brain Tumor		
Davis et al. 1993		3.40 (1.10 - 10.55)
Leiss el al, 1995		1.10 (0.40 - 3.01)
Pogoda ol al. 1997	- 26	1,00 (0.63 - 1,58)
Nielsen et al. 2010	- 17	1.19 (0.67 - 2.11)
Greenop et al. 2013*	- 46	1,03 [0.74 = 1.44]
Subtotal (I ² = 4.7%, P-value = ,380)	100	1.17 [0.87 - 1.42]
Leukemia	8	
Leiss et al. 1995	5	0.90 (0.54 - 1.51)
Infante-Rivard et al. 1999	6	2.13 [1.30 - 3.48]
Meinet et al. 2000	15	1.20 (0.90 - 1.60]
Malet al. 2002	6	1.60 [0.97 - 2.63]
Menegaux et al. 2006 -	9	1.70 (1.15 - 2.51)
Rudant st at. 2007	33	1.50 (1.27 - 1.77)
Urayama et al. 2007	. 8	1.65 (1.10 - 2.47]
Bailey et al. 2011	12	1.33 [0.97 - 1.83]
Ding et al. 2012	- 7	1.63 [1.04 - 2,55]
Subtotal (1 ⁴ = 12,9%, P-value = ,327)	\$ 100	1.46 [1.29 - 1,65]
Lymphoma		
Leiss at al. 1995	u 14	1.60 (0.89 - 2.87)
Meinet et al. 2000	· • 17	1.70 [1.00 - 2.89]
Rudant et al. 2007, HL	24	1,10 [0,71 - 1.71]
Rudani el al. 2007, NHL	- 45	1.50 [1.09 - 2.07]
Subtotal (1 ⁴ = 0.0%, P-value = .578)	> 100	1.43 [1.15 - 1.78]
	1 1	
0.25 0.50 1.00	2,50 7.50	
Odds	Rabo	

FIGURE 2

Meta-analysis of the association between childhood cancers and exposure to home pesticides during childhood. *Professional home treatments.

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 metaanalysis, 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.13,14 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 al¹⁴ but not by Turner et al,13 and both reported a high degree of heterogeneity (12 of 61%) and 72%, respectively). Neither our study nor the study of Turner et al13 observed any association between childhood leukemia and exposure to outdoor insecticides during childhood. Like Van Maele-Fabry et al,14 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.20 However, Vinson et al20 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

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Study name	% Weight	Odds ratio [95% CI]
Childhood Brain Tumor	ł	
Davis et al. 1993		2.40 [1.01 - 5.73]
Pogoda et al. 1997	28	1.20 [0.30 - 4.85]
Subtotal (1 ² = 0.0%, P-value = ,409)	100	1,98 [0,94 - 4,14]
Leukomia		
Ding et al. 2012	1	1.98 [0.63 - 6.24]
Infante-Rivard et al. 1999	- 23	1.41 [1.06 - 1.87]
Malet al. 2002		1,10 [0.59 - 2.06]
Menegaux et al. 2006	6	1.40 [0.81 - 2,42]
Rudant et al. 2007	65	1 20 [1,01 - 1 42]
Subto(al (l ² = 0.0%, P-value = .762)	100	1.26 [1.10 - 1.44]
Lymphoma		
Buckley et al. 2000 -	28	2.35 [1.37 - 4.03]
Rudant et al. 2007, HL.	35	1.10 [0.73 - 1.66]
Rudant et al. 2007, NHL	37	1.50 [1.01 - 2.22]
Subtotal (1 ² = 58,4%, P-value = .090)	5 100	1.52 [1.02 - 2.27]
	1 1	
0.25 0.50 1.00	2.50 7.50	

FIGURE 3

Meta-analysis of the association between childhood cancers and exposure to residential herbicides during childhood.

could not directly compare our results with those reported by Vinson et al.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 al¹⁴ 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,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.¹⁴

Unlike Van Maele-Fabry et al's¹⁴ report and our observation, Turner et al¹³ 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 $(l^2 \leq 13\%)$ 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

Study name	% Weight	Odds ratio [95% CI]
Childhood Brain Tumor		
Davis et al. 1993	27	1.60 [0.71 - 3.63]
Leiss et al. 1995	36	0.50 [0.31 - 0.82]
Pogoda et al. 1997	37	1,20 [0,76 - 1,90]
Subtotal (1 ² = 77.6%, P-value = .012)	100	0.95 [0.47 - 1.89]
Leukemia		
Leiss et al. 1995 -	- 21	1 10 [0.80 - 1.51]
Infante-Rivard et al. 1999	4	2.27 (0.93 - 5.55]
Meinel et al. 2000 -	32	1.00 (0.82 - 1.22)
Malet al. 2002		1.20 [0.68 - 2.13]
Menegaux et al. 2006	13	1.70 [1.09 - 2.66]
Rudant et al. 2007	- 21	1.00 [0.73 - 1.36]
Subtotal (I ² = 32.8%, P-value = .190)	> 100	1.15 [0.95 - 1.38]
Lymphoma		
Leiss et al. 1995	26	0.60 (0.38 - 0.95)
Meinet et al. 2000	- 27	0.80 (0.52 - 1.24)
Rudant et al. 2007, HL	21	0.90 (0.52 - 1.56)
Rudant et al. 2007, NHL	26	1.30 [0.82 - 2.06]
Subtotal (l ² = 46.7%, P-value = .131)	100	0,86 [0,62 - 1,19]
i		
0,25 0,50 1,00	2.50 7.50	
Orte	s Balio	

FIGURE 4

Meta-analysis of the association between childhood cancers and exposure to residential outdoor pesticides during childhood.

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 al32 and Menegaux et al³⁹ 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 al¹⁴ assessed the impact of exclusion of nonpublished data and studies in languages other than English, they found that rerunning the metaanalysis 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.^{47,48} 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.^{49,50} Every effort should be made to limit children's exposure to pesticides.

ABBREVIATIONS

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

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REFERENCES

- Adgate JL, Kukowski A, Stroebel C, et al. Pesticide storage and use patterns in Minnesota households with children. J Expo Anal Environ Epidemiol. 2000;10(2): 159–187
- 2 Bass JK, Ortega L, Rosales C, Petersen NJ, Philen RM, What's being used at home: a household pesticide survey. *Rev Panam Salud Publica*. 2001;9(3):138–144
- Guha N, Ward MH, Gunier R, et al. Characterization of residential pesticide use and chemical formulations through self-report and household inventory: the Northern California Childhood Leukemia study. Environ Health Perspect. 2013; 121(2):276–282
- Kim HH, Lim YW, Yang JY, et al. Health risk assessment of exposure to chlorpyrifos and dichlorvos in children at childcare facilities. Sci Total Environ 2013;444 441–450
- Gilden R, Friedmann E, Sattler B, Squibb K, McPhaul K. Potential health effects related to pesticide use on athletic fields *Public Health Nurs*. 2012;29(3):198–207
- Alarcon WA, Calvert GM, Biondell JM, et al. Acute illnesses associated with pesticide exposure at schools. JAMA. 2005;294(4):455–465
- 7 Faustman EM, Silbernagel SM, Fenske RA, Burbacher TM, Ponce RA. Mechanisms underlying children's susceptibility to environmental toxicants. *Environ Health Perspect*. 2000;108(suppl 1):13-21

- Sheets LP. A consideration of agedependent differences in susceptibility to organophosphorus and pyrethroid insecticides. *Neurotoxicology*, 2000; 21(1–2):57–63
- Landrigan PJ, Claudio L, Markowitz SB, et al. Pesticides and inner-city children: exposures, risks, and prevention. *Environ Health Perspect.* 1999;107 (suppl 3): 431–437
- Spann MF, Blondell JM, Hunting KL, Acute hazards to young children from residential pesticide exposures. Am J Public Health, 2000;90(6):971–973
- Infante-Rivard C, Weichenthal S, Pesticides and childhood cancer: an update of Zahm and Ward's 1998 review. J Toxicol Environ Health B Crit Rev. 2007; 10(1-2):81-99
- Metayer C, Buffler PA. Residential exposures to pesticides and childhood leukaemia. *Radiat Prot Dosimetry*. 2008; 132(2):212–219
- Turner MC, Wigle DT, Krewski D. Residential pesticides and childhood leukemia: a systematic review and metaanalysis. *Environ Health Perspect*. 2010; 118(1):33–41
- Van Maele-Fabry G, Lantin AC, Hoet P, Lison D, Residential exposure to pesticides and childhood leukaemia: a systematic review and meta-analysis. *Environ Int.* 2011;37(1):280–291
- Wigle DT, Turner MC, Krewski D. A systematic review and meta-analysis of

childhood leukemia and parental occupational pesticide exposure, Environ. Health Perspect, 2009;117(10):1505-1513.

- Zahm SH, Ward MH. Pesticides and childhood cancer. Environ Health Perspect. 1998;106(suppl 3):893–908
- López-Cervantes M, Torres-Sánchez L, Tobias A, López-Cerrillo L.
 Dichlorodiphenyldichloroethane burden and breast cancer risk: a meta-analysis of the epidemiologic evidence. Environ Health Perspect. 2004;112(2):207–214
- Merhi M, Raynal H, Cahuzac E, Vinson F, Gravedi JP, Gamet-Payrastre L. Occupational exposure to pesticides and risk of hematopoietic cancers. metaanalysis of case-control studies. *Cancer Causes Control.* 2007;18(10):1209-1226
- Van Maele-Fabry G, Duhayon S, Lison D, A systematic review of myeloid leukemias and occupational pesticide exposure. *Cancer Causes Control.* 2007;18(5): 457–478
- Vinson F, Merhi M, Baldi I, Raynal H, Gamet-Payrastre L. Exposure to pesticides and risk of childhood cancer: a meta-analysis of recent epidemiological studies. *Occup Environ Med.* 2011;68(9):694–702
- Meinert R, Kaatsch P, Kaletsch U, Krummenauer F, Miesner A, Michaelis J, Childhood leukaemia and exposure to pesticides: results of a case-control study in northern Germany. Eur J Cancer, 1996;32A(11):1943–1948

- Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis of Observational Studies in Epidemiology (MOOSE) group. JAMA. 2000;283(15):2008–2012
- Higgins JP, Thompson SG, Deeks JJ, Altman DG, Measuring inconsistency in meta-analyses. *BMJ*. 2003;327(7414): 557–560
- Egger M. Davey Smith G. Schneider M. Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*, 1997; 315(7109):629-634
- Metayer C, Colt JS, Buffler PA, et al. Exposure to herbicides in house dust and risk of childhood acute: lymphoblastic leukemia. J Expo Sci Environ Epidemiol. 2013;23(4):363–370
- Searles Nielsen S, Mueller BA, De Roos Ad, Viernes HM, Farin FM, Checkoway H Risk of brain tumors in children and susceptibility to organophosphorus insecticides, the potential role of paraoxonase (PON1). Environ Health Perspect, 2005;113(7):909–913
- Soldin OP, Nsouli-Maktabi H, Genkinger JM, et al. Pediatric acute lymphoblastic leukemia and exposure to pesticidos [published correction appears in Ther Drug Monit. 2009;31(5):668] Ther Drug Monit. 2009;31(4):495–501
- Bailey HD, Armstrong BK, de Klerk NH, et al; Aus-ALL Consortium. Exposure to professional pest control treatments and the risk of childhood acute lymphoblastic leukemia. *Int J Cancer.* 2011;129(7):1678–1688
- Buckley JD, Meadows AT, Kadin ME, Le Beau MM, Siegel S, Robison LL Pesticide exposures in children with non-Hodgkin lymphoma. *Cancer*. 2000;89(11): 2315–2321
- Cooney MA, Daniels JL, Ross JA, Breslow NE, Pollock BH, Olshan AF. Household pesticides and the risk of Wilms tumon *Environ Health Perspect*. 2007;115(1): 134–137

- Daniels JL, Olshan AF, Teschke K, et al. Residential pesticide exposure and neuroblastoma. *Epidemiology*, 2001; 12(1):20–27
- Davis JR, Brownson RC, Garcia R, Bentz BJ, Turner A, Family pesticide use and childhood brain cancer. Arch Environ Contom Toxicol. 1993;24(1):87–92
- 33 Ding G, Shi R, Gao Y, et al. Pyrethroid pesticide exposure and risk of childhood acute lymphocytic (eukemia in Shanghai. *Environ Sci Technol.* 2012;46(24): 13480–13487
- 34. Greenop KR, Peters S, Bailey HD, et al. Exposure to pesticides and the risk of childhood brain tumors. *Cancer Causes Control*, 2013;24(7):1269–1278
- Infante-Rivard C, Labuda D, Krajinovic M, Sinnett D. Risk of childhood leukemia associated with exposure to pesticides and with gene polymorphisms. *Epidemiology*, 1999;10(5):481–487
- Leiss JK, Savitz DA. Home pesticide use and childhood cancer: a case-control study. Am J Public Health. 1995;85(2): 249–252
- Ma X, Buffler PA, Gunier RB, et al. Critical windows of exposure to household pesticides and risk of childhood leukemia. *Environ Health Perspect*. 2002; 110(9):955–960
- Meinert R, Schüz J, Kaletsch U, Kaatsch P, Michaelis J. Leukemla and non-Hodgkin's lymphoma in childhood and exposure to pesticides: results of a register-based case-control study in Germany. Am J Epidemiol. 2000;151(7):639–646, discussion 647–650
- Menegaux F, Baruchel A, Bertrand Y, et al. Household exposure to pesticides and risk of childhood acute leukaemia. Occup Environ Med. 2006;63(2):131–134
- Pogoda JM, Preston-Martin S, Household pesticides and risk of pediatric brain tumors. *Environ Health Perspect*, 1997; 105(11):1214–1220
- Rudant J, Menegaux F, Leverger G, et al. Household exposure to pesticides and

risk of childhood hematopoietic malignancies: The ESCALE study (SFCE). Environ Health Perspect. 2007;115(12): 1787–1793

- 42. Searles Nielsen S, McKean-Cowdin R, Farin FM, Holly EA, Preston-Martin S, Mueller BA. Childhood brain tumors, residential insecticide exposure, and pesticide metabolism genes. *Environ Health Perspect.* 2010;118(1):144–149
- 43. Urayama KY, Wiencke JK, Buffler PA, Chokkalingam AP, Metayer C, Wiemels JL. MDR1 gene variants, indoor insecticide exposure, and the risk of childhood acute lymphoblastic leukemia. Cancer Epidemial Biomarkers Prev. 2007;16(6): 1172–1177
- Eden T. Aetiology of childhood leukaemia. Cancer Treat Rev. 2010;36(4):286–297
- Kim AS, Eastmond DA, Preston RJ. Childhood acute lymphocytic leukemia and perspectives on risk assessment of early-life stage exposures. *Mutat Res.* 2006;613(2–3):138–160
- Rossig C, Juergens H. Aetiology of childhood acute leukaemias: current status of knowledge. *Radiat Prot Dosimetry*. 2008;132(2):114–118
- US Environmental Protection Agency. Integrated pest management (IPM) in schools. Available at: www.epa.gov/ pesticides/ipm/. Accessed December 16, 2014
- US Centers for Disease Control and Prevention. Integrated pest management (IPM). Available at: www.cdc.gov/nceh/ ehs/elearn/ipm.htm. Accessed March 6, 2013
- US Environmental Protection Agency. Pesticides: topical & chemical fact sheets. Read the label first. Available at: www.epa.gov/pesticides/label/. Accessed May 9, 2012
- US Environmental Protection Agency. Citizen's guide to pest control and pesticide safety. Read the label first. EPA 735-K-04-002, March 2005. Available at: www.epa.gov/oppfead1/Publications/Cit_ Guide/. Accessed, March 13, 2015

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

Mei Chen, Chi-Hsuan Chang, Lin Tao and Chensheng Lu Pediatrics; originally published online September 14, 2015; DOI: 10.1542/peds.2015-0006

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

Mei Chen, Chi-Hsuan Chang, Lin Tao and Chensheng Lu Pediatrics; originally published online September 14, 2015; DOI: 10.1542/peds.2015-0006

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analysis (3), the interpretation of the authors and editorialists is perplexing. The warning issued last year by the American Statistical Association (ASA) (4) about this type of misinterpretation of data should be embraced by researchers and journal editors. In particular, the ASA stated: "Scientific conclusions ...should not be based only on whether a p-value passes a specific threshold." Editors in particular ought to guide their readership and the public at large to avoid such mistakes and foster more responsible interpretation of medical research.

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References

Journal of the American Medical Association

Inappropriate Reliance on P-values in Medical Research

To the editor:

Lappe et al. (1) reported that women receiving vitamin D and calcium supplementation had 30% lower cancer risk than women receiving placebo after four years (hazard ratio (HR)=0.70, 95% confidence interval (CI): 0.47 to 1.02). Remarkably, they interpreted this result as indicating no effect. So did the authors of the accompanying editorial (2), who described the 30% lower risk for cancer as "the absence of a clear benefit," because the P-value was 0.06. Given the expected bias toward a null result in a trial that comes from non-adherence coupled with an intent-to-treat analysis (3), the interpretation of the authors and editorialists is perplexing. The warning issued last year by the American Statistical Association (ASA) (4) about this type of misinterpretation of data should be embraced by researchers and journal editors. In particular, the ASA stated: "Scientific conclusions ...should not be based only on whether a p-value passes a specific threshold." Editors in particular ought to guide their readership and the public at large to avoid such mistakes and foster more responsible interpretation of medical research.

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References

- Lappe J, Watson P, Travers-Gustafson D, et al. Effect of vitamin D and calcium supplementation on cancer incidence in older women. JAMA. 2017; 317:1234-1243. doi:10.1001/jama.2017.2115
- Manson JE, Bassuk SS, Buring JE. Vitamin D, Calcium, and Cancer. Approaching Daylight? JAMA 2017; 317:1217-1218.
- Rothman KJ. Six persistent research misconceptions. J Gen Intern Med 2014; 29:1060-1064. doi: 10.1007/s11606-013-2755-z
- ASA statement on statistical significance and P-values. <u>Am Stat. 2016. doi:10.1080/</u> 00031305.2016.1154108.

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ORIGINAL REPORT



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Both M.M.S. and K.M.W. contributed equally to this work. Both E.L.G. and L.A.M. share service authorship.

Authors' disclosures of potential conlicts of interest and author contributions are found at this and of this article.

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Vasectomy and Risk of Aggressive Prostate Cancer: A 24-Year Follow-Up Study

Mohummad Minhaj Siddiqui, Kathryn M. Wilson, Maru M. Epstein, Jennifer R. Rider, Neil E. Martin, Meir J. Stampfer, Edward L. Giovannucci, and Lorelei A. Mucci

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Purpose

Conflicting reports remain regarding the association between vasectomy, a common form of male contraception in the United States, and prostate cancer risk. We examined prospectively this association with extended follow-up and an emphasis on advanced and lethal disease.

Patients and Methods

Among 49.405 US men in the Health Professionals Follow-Up Study, age 40 to 75 years at baseline in 1986, 6,023 patients with prostate cancer were diagnosed during the follow-up to 2010, including 811 lethal cases. In total, 12,321 men (25%) had vasectomies. We used Cox proportional hazards models to estimate the relative risk (RR) and 95% CIs of total, advanced, high-grade, and lethal disease, with adjustment for a variety of possible confounders.

Results

Vasectomy was associated with a small increased risk of prostate cancer overall (RR, 1.10; 95% Cl, 1.04 to 1.17). Risk was elevated for high-grade (Gleason score 8 to 10; RR, 1.22; 95% Cl, 1.03 to 1.45) and lethal disease (death or distant metastasis; RR, 1.19; 95% Cl, 1.00 to 1.43). Among a subcohort of men receiving regular prostate-specific antigen screening, the association with lethal cancer was stronger (RR, 1.56; 95% Cl, 1.03 to 2.36). Vasectomy was not associated with the risk of low-grade or localized disease. Additional analyses suggested that the associations were not driven by differences in sex hormone levels, sexually transmitted infections, or cancer treatment.

Conclusion

Our data support the hypothesis that vasectomy is associated with a modest increased incidence of lethal prostate cancer. The results do not appear to be due to detection bias, and confounding by infections or cancer treatment is unlikely.

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INTRODUCTION

Vasectomy is a common form of contraception in the United States with a prevalence of 15%.1.2 Two large cohort studies published in 1993, including the Health Professionals Follow-Up Study (HPFS), found an increased risk of prostate cancer among men with vasectomy3,4; other studies have not found an association.5,6 A meta-analysis of 22 studies estimated a pooled relative risk (RR) for total prostate cancer of 1.37 (95% CI, 1.15 to 1.62) comparing men with and without vasectomy, although there was significant heterogeneity between studies. Among the five cohort studies included, the RR was 1.22 (95% CI, 0.90 to 1.64).7 Since then, additional studies have been published. One prospective cohort of Maryland men reported an RR of 2.03 (95% CI, 1.24 to 3.32) for the association between vasectomy and incident prostate cancer.8 However, two

population-based case-control studies in Washington state⁹ and New Zealand¹⁰ and a hospital-based case-control study in China, Nepal, and the Republíc of Korea¹¹ found no association.

Criticisms of the studies reporting positive associations of vasectomy with prostate cancer risk focus on bias and confounding. Detection bias may explain the positive results because men who opt for vasectomy may choose more medical care in general and see a unologist at an earlier age than do men who do not choose vasectomy.¹⁰ This might lead to increased screening and increased diagnosis of early stage and low-grade prostate cancers. Publication bias has also been proposed given the small effect size noted in most studies.¹² Possible confounding by sexually transmitted infections (STIs)⁷ has also been discussed.

In this study, we extend follow-up from the prospective HPFS cohort by two decades with more

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than 6,000 patients with prostate cancer to investigate more comprehensively the association between vasectomy and prostate cancer risk,³ including the risk of advanced, high-grade, and lethal cancers. To address previous criticiams, we controlled for intensity of prostatespecific antigen (PSA) screening and other possible confounders. To further reduce the potential for bias due to screening and to increased clinical relevance, we focus on the incidence of advanced and lethal prostate cancer, as well as the incidence of prostate cancer in a highly screened subgroup.

PATIENTS AND METHODS

The HPPS is a prospective cohort study of 51,529 male health professionals in the United States age 40 to 75 years at baseline in 1986. The men are sent biennial questionnaires collecting information on lifestyle and health outcomes. Men who reported a cancer diagnosis (except nonmelanoma skin cancer) before baseline were excluded, leaving 49,405 men who were observed prospectively until 2010. The HPPS is approved by the Human Subjects Committee at the Harvard School of Public Health.

Assessment of Vasectomy History

Men were asked on the 1986 questionnaire whether they had had a vasectomy and, if so, to identify the period: 1955 to 1964, 1965 to 1974, 1975 to 1979, or 1980 to 1986. Men were asked on each biennial questionnaire through 2000 if they had had a vasectomy since the previous questionnaire and, if so, in which year. By 2000, only 58 men (0.1%) reported a new vasectomy in the previous 2 years (the youngest age in the cohort in 2000 was 54 years), and the question was not asked in subsequent years.

In 1992, men were asked at what age they had had a vasectomy if it was before 1986. This more precise timing information was used to assign the date and age at vasectomy for 70% of the 11,113 men who had reported a vasectomy before 1986. Date and age at vasectomy for the remaining men were assigned by using the midpoint of the 10-year period categories from the 1986 questionnaire.

Ascertainment of Prostate Cancer Cases

Prostate cancer diagnoses were initially identified by self-reports from the participants or their next of kin and confirmed by review of medical records and pathology reports. Deaths were ascertained through reports from family unembers and searches of the National Death Index. An end points committee, which used all available data, assigned cause of death. Medical records confirmed approximately 90% of prostate cancer cases, and the remaining 10% were based on self-reports or death certificates. We observed men with prostate cancer by sending additional questionnaires every 2 years and collecting medical records to ascertain treatment, disease progression, and diagnosis of metastases.

We excluded men with stage T1s cancers. We defined advanced stage prostate cancer as stage T3b, T4, N1, or M1 at diagnosisi development of lymph node or distant metastasis; or death as a result of prostate cancer before the end of follow-up. Lethal cancers, a subset of advanced cancers, were those that caused death or metastasis to bone or other organs before the end of follow-up. Localized cancers were stage T1 or T2 and N0, M0 at diagnosis and did not progress to any metastasis or death during the follow-up period. Cancers were also categorized as high grade (Gleason score 8 to 10), Gleason grade 7, or low grade (Gleason score 2 to 6) at diagnosis based on prostatectomy or biopsy pathology reports; Gleason grade was not available for all men.

Statistical Analysis

Each participant contributed person-time from the date that he returned the basell ne questionnaire in 1986 until prostate cancer diagnosis, death, or the end of follow-up, January 31, 2010. We used Cox proportional bazards regression to calculate age-adjusted and multivariable-adjusted hazard ratios (HRs) and 95% CIs of total prostate cancer and lethal, advanced, localized, highgrade, G Jeason grade 7, and low-grade prostate cancers. All models were stratified by age and calendar time. Participants were classified according to vasectomy status in each period, comparing risk among men with and without vasectomy. In addition, we divided men with vasectomy into exposure groups based on median timesince vasectomy (< 23, \geq 23 years) and median uge at vasectomy (< 38, \geq 38 years).

Multivariable models were adjusted for race, height (quartiles), body mass index (six categories or missing), vigorous physical activity (quintiles), smoking (never, former smoker who quit \geq 10 years ago, former smoker who quit < 10 years ago, current, or missing), type 2 diabetes mellitus (yes or no), family history of prostate cancer, history of PSA testing, multivitamin use (yes or no), and intakes of supplemental vitamin E and alcohol (quintiles) calculated from food frequency questionnaires. To account for diagnostic bias, we adjusted for PSA testing in the previous period (yes or no) and for higher intensity of past testing (yes for men reporting PSA tests in half or more of all questionnaires since 1994). All covariates except race and height were updated in each questionnaire cycle. Geographical region, religion, self-reported history of gonorrhea and syphilis, frequency of cjaculation, intakes of tomato sauce and α -intolenic acid, and body mass index at age 2) years were not included in the final models because they were not associated with vasectomy and had little effect on the RR estimates.

To investigate the effects of PSA testing on the results, we did additional unalyses within a highly screened subcohort of men who reported having PSA tests in 1994 (the first year PSA testing was asked) and 1996, with follow-up from 1996 through 2010. These results were also adjusted for intensity of PSA testing during follow-up.

We leveraged existing plasma biomarker data on a subset of men within the cohort. To further investigate possible confounding by STIs, we calculated the age-adjusted prevalence of seropositivity for *Chlamydia trachomatis*, *Trichomonas vaginalis*, human papillomavirus (HPV), and human herpesvirus type 8 (HHV-8) according to vasectomy status in a subset of 693 controls from a nested case-control study of prostate cancer. To explore possible mechanisms underlying associations with vasectomy, we compared age-adjusted plasma concentrations of sex hormones (testosterone, free (estosterone, estradiol, and sex hormone-biuding globulin) among 663 controls arcording to vasectomy status at the time of blood sample. Detailed methods describing the assays and analyses can be found in previous publications^{13,14} and in the Appendix.

RESULTS

The cohort consisted of 49,405 men at baseline in 1986, at which time 22% reported having had a vasectomy. Vasectomy status was updated every 2 years until 2000. By 2000, 12,321 of the men (25%) in the entire cohort reported having had a vasectomy. Gharacteristics of the study population at baseline among men with and without a vasectomy by 2000 are shown in Table 1. Compared with those without a vasectomy, men reporting a vasectomy were more likely to be white, to consume alcohol, and to take multivitamins. Men with vasectomy reported more PSA testing than those without vasectomy. Among men with prostate cancer, those with vasectomy had lower PSA levels at diagnosis.

During 24 years of follow-up, 6,023 cases of prostate cancer were diagnosed, including 732 high-grade and 811 lethal cases. The multivariable-adjusted relative risk of total prostate cancer in men who had a vasectomy compared with those who did not was 1.10 (95% CI, 1.04 to 1.17; Table 2). Vasectomy was not significantly associated with the risk of low-grade cancer. However, men who had a vasectomy had an increased risk of both lethal (RR, 1.19; 95% CI, 1.00 to 1.43) and advanced stage disease (RR, 1.20; 95% CI, 1.03 to 1.40). The RR of developing high-grade cancer was also increased (RR, 1.22; 95% CI, 1.03 to 1.45) for men with a vasectomy. When we examined cases of prostate cancer diagnosed since our initial report in 1990,³ findings were qualitatively similar.

Vasectomy and Risk of Aggressive Prostate Cancer

	Total (1986, Va Sta	Cohort, sectomγ tus	Highly S Subcoho Vasector	creened rt. 1996, ry Status
	No	Yes	No	Yes
N	37,084	12,321	10,161	3,740
Age, years	55.5	51.8	66.8	63.1
Time since vasectomy, years	-	15.8	-	25.5
Age at vasectomy, years	- <u>-</u>	38.6	-	39.4
Body mass index, kg/m ²	25,5	25.4	25.8	25.7
Height, inches	70	70	70	70
Race/ethnicity, %				
White	95	.97	96	98
African American	1	<1	1 -	< 1-
Asian	2	1	1	<1
Current smokers, %	10	10	4	5
Vigorous activity, % upper				
quintile	15	17	18	19
Diabetes, %	3	3	6	5
Family history of prostate	1.57			105
cancer,%	12	12	15	16
Multivitamin use, %	41	43	51	51
Alcohol intake, g/day	10.8	12,9	10.4	12.5
Supplemental vitamin E, mg/day PSA testing history, 2008	37.6	39,8	55.5	55.5
PSA test from 2006-2008 (%)	59	67	74	80
No. of blennial questionnaires with PSA test, 1994-2008	4.0	5.2	7.0	
PCA test on at loost helf of all	1410	5.2	1.0	
questionnaires, 1994-2008. %	69	75	97	97
Lase characteristics	4.400		1.000	
No. of prostate cancer cases	4,499	1,524	1,191	4/4
Age at diagnosis, years	70.7	68.1	73.0	70.2
Lethal cases, %1	15	12	8	9
Advanced cases, %1	20	16	11	12
Localized cases, %1	73	76	84	83
Gleason grade, %	2.6	1.02	1.2	
8-10	14	15	12	13
7	35	38	36	-43
2-6	50	47	53	45
Median PSA at diagnosis, ng/mL‡	7.0	6.5	6,6	6.1
Mean PSA at diagnosis, ng/mL	18.5	11.1	11.7	9.3
Primary treatment, %				
Ractical prostatectomy	45	47	37	40
Radiation	36	36	44	42
Hormonal therapy	8	7	8	8
Active surveillance	9	8	10	9
Other	2	2	2	2

Table 1. Age-Standardized Baseline Characteristics of the Study Population and

Abbreviation: PSA, prostate-specific antigen.

"Incident cases, standardized to age distribution of cases overall and within the highly screened subcohort, respectively.

TLethal prostate cancer: prostate cancer death or distant metastasis. Advanced: lethal or stage T3b or T4 or N1 or M1, or spread to lymph nodes or other metastases during follow-up. Localized: T1 or T2 and N0/M0 at diagnosis with no spread to lymph nodes or other metastases or death during follow-up. 1Median PSA was not standardized to age at diagnosis.

Presstate-specific antigen testing is one of the strongest predictors of prostate cancer diagnosis and thus may act as an important confounder of the vasectomy association. To address this concern, we examined a subcohort of 13,901 highly screened men, of whom

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27% reported a vasectomy by 2000. There were 1,665 incident cases of prostate cancer in this subcohort between 1996 and 2010, including 179 high-grade and 127 lethal cases. Characteristics of the highly screened subcohort at baseline by vasectomy status are shown in Table 1.

Vasectomy was not associated with total prostate cancer incidence or with risk of low-grade or localized prostate cancer in the highly screened subcohort (Table 2). However, vasectomy was associated with an increased risk of high-grade (RR, 1.28; 95% CI, 0.91 to 1.81) and grade 7 cancers (RR, 1.22; 95% CI, 1.02 to 1.47), although the association with high-grade cancers did not achieve statistical significance in this smaller cohort. Notably, men who had undergone vasectomy had a statistically significant 56% increased risk of lethal prostate cancer (RR, 1.56; 95% CI, 1.03 to 2.36) in the highly screened cohort.

The association between vasectomy and prostate cancer did not differ by time elapsed since vasectomy or by age at vasectomy (Table 3). The associations with lethal and advanced disease were similar by time elapsed since vasectomy, which was also true when we further divided time since vasectomy into 10-year categories (data not shown). There was a suggestion that the increased risk was more pronounced among men who were younger at the time of vasectomy (*P*value for difference = .08 for lethal, .09 for advanced); however, this pattern was not apparent when we examined age at vasectomy in quartiles (data not shown).

To examine the possibility of confounding by STIs, we compared the prevalence by vasectomy status of several pathogens measured serologically among 693 men without prostate cancer, of whom 185 (27%) had a vasectomy. Men who had undergone vasectomy had a significantly higher age-adjusted prevalence of HPV (22.2% v 14.3%, P = .01). However, there was no significant difference in age-adjusted prevalence of *Chlamydia* (4.7% v 2.7%, P = .10), *T vaginalis* (9.9% v 8.5%, P = .28), or HHV-8 infection (16.5% v 18.3%, P = .56) between men with and without vasectomy. Only *T vaginalis* and HHV-8 have been associated with prostate cancer risk in this cohort.¹³⁻¹⁵

We assessed whether treatment varied by vasectomy status. Ageand grade-adjusted distribution of active surveillance, radical prostatectomy, radiation, or hormonal treatment was similar between groups (Table 1).

To investigate the possible role of sex hormones as mediators of the association between vasectomy and prostate cancer, we analyzed levels of total testosterone, free testosterone, sex hormone-binding globulin, and estradiol among 663 men without prostate cancer at the time of blood draw. There were no significant differences in levels of any measured hormone between men with and without a vasectomy (data not shown).

DISCUSSION

With 24 years of follow-up and more than 6,000 cases of prostate cancer, our updated analysis in the HPFS supports a positive association between vasectomy and the risk of advanced or lethal prostate cancer. After accounting for differences in PSA screening, vasectomy was not associated with the risk of low-grade or localized disease.

There have been mixed findings from other cohort and casecontrol studies.^{3,5,8,16} Our analysis represents the largest cohort study with the longest follow-up to date to examine the relationship of

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		Total Coho	п, 1986-2010		Hig	hly Screened Su	bcohort, 1996-2010	
		Vasectomy Sta	itus			105		
			Yes				Yes	
	Na	BR	95% Cl	Р	No	RR	95% CI	Р
Total prostate cancer			10		1.1		. · ·	1.1.1
No. of patients	4,499	1,524		1 10	1.191	474		1.0
Age-adjusted RA*	1.00	1.14	1.08 to 1.21	< 001	1.00	1.05	0.94 to 1.18	.37
* Fully adjusted RR*	1.00	1.10	1.04 to 1.17	.001	1.00	1.05	0.94 to 1.17	1 .41
Grade 8-10 prostate cancer								
No. of patients	544	188			126	53		
Age-adjusted RR*	1.00	1.24	1.04 to 1.46	.02	1.00	1.23	0.88 to 1.72	.23
Fully adjusted RR*	1.00	1.22	1.03 to 1.45	.02	1.00	1.28	0.91 to 1.81	.15
Grade 7 prostate cancer						1	and the second	
No. of patients	1,303	524	1		374	187		1.00
Age-adjusted RR*	1.00	1.23	1.11 to 1.37	< 001	1.00	1.22	1.02 to 1.47	.03
Fully adjusted RR*	1.00	1.18	1.06 to 1,31	.002	1.00	1.22	1.02 to 1.47	.03
Grade 2-6 prostate cancer								
No. of patients	1,870	656			545	201		
Age-adjusted RR*	1.00	1.14	1.04 to 1.25	.004	1.00	0.96	0.81 to 1.13	.62
Fully adjusted RR*	1.00	1.08	0.99 to 1.19	.09	1.00	0.95	0.80 to 1.12	,52
Lethal prostate cancert								
No. of patients	644	167	1 C.		90	37		
Age-adjusted RR*	1.00	1.20	7.00 to 1.43	.05	1.00	1.48	0.99 to 2.22	06
Fully adjusted RR*	1.00	1.19	1.00 to 1.43	.05	1.00	1.56	1.03 to 2.36	.04
Advanced prostate cancert								
No. of patients	821	231			119	49		
Age-adjusted RR*	1.00	1,21	1.04 to 1.41	.01	1.00	1.32	0.93 to 1.87	12
Fully adjusted RR*	1.00	1.20	1.03 to 1.40	.02	1.00	1.35	0.95 to 1.93	10
Localized prostate cancert		1		11 1			10 C	
No. of patients	2,996	1,082			905	368		
Age-adjusted RR*	1.00	1.14	1.06 to 1.23	<.001	1.00	1.05	0.92 to 1.19	46
Fully adjusted RR*	1.00	1.09	1.02 to 1.17	.02	1.00	1.04	0.92 to 1.18	.55

Abbreviation: RR, relative risk.

*Age-adjusted model adjusted for age in months and calendar time. Multiveriable model also adjusted for race, height (quartiles), current body mass index (six categories), vigorous physical activity (quintiles), smoking (never, former smoker who quit \geq 10 years ago, former smoker who quit < 10 years ago, or current), diabetes, family history of prostate cancer, multivitamin use (yes or no), intake of supplemental vitamin E and alcohol (both quintiles), and history of prostate-specific antigen testing.

1Lethal prostate cancer: prostate cancer death or distant metastasis. Advanced: lethal or stage T3b or T4 or N1 or M1, or spread to lymph nodes or other metastases during follow-up. Localized: T1 or T2 and N0/M0 at diagnosis with no spread to lymph nodes or other metastases or death during follow-up.

vasectomy to total and lethal prostate cancer.^{7,9,10} Three previous cohort studies have examined the association of vasectomy with advanced stage disease, with all finding increased but not statistically significant RRs ranging from 1.4 to 2.1.^{3,4,8} In contrast, the six case-control studies that have examined the association of vasectomy with advanced stage disease found no statistically significant associations (RR range, 0.73 to 1.1).^{10,16-20} Only one cohort study has investigated the risk of high-grade prostate cancer with vasectomy and did not find an association.⁸ However, a retrospective review of 522 consecutive patients who underwent prostate biopsy found a statistically significant higher mean Gleason score in patients with a history of vasectomy.²¹

A criticism of previous studies is that individuals who elect vasectomy have closer medical follow-up, resulting in increased screening for and detection of prostate cancer. Indeed, in the total cohort, we noticed a trend toward more intensive screening among men with a history of vasectorny, and PSA at diagnosis was higher in men without vasectomy, suggesting that they were potentially diagnosed with more advanced disease. Thus, although detection bias might explain an increased risk of screen-detected localized cancer among men with vasectomy, it cannot explain our findings of the higher risk of lethal or advanced disease among this group. In addition, in our subcohort of highly screened men reporting early adoption of PSA screening, and with adjustment for ongoing PSA testing, we still noted increased risks of high-grade and lethal prostate cancer, further suggesting that detection bias does not explain the observed associations.

We explored relationships between vasectomy and serologic evidence of STIs, because some STIs may be associated with both vasectomy and prostate cancer risk. In this cohort, however, vasectomy was associated only with HPV, whereas prostate cancer risk was positively associated only with *T vaginalis* and HHV-8 infections.^{13,22} Thus, confounding by STIs does not seem to explain our findings, although we cannot rule out differences in an unidentified, unmeasured STI. In addition, treatment choices do not explain the association as the groups elected similar treatments when age and grade at diagnosis were controlled.

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	-	Time Since Vasectomy							Age at Vasectomy					
		1	< 23 years			≥ 23 years				< 38 years			≥ 38 years	
	None	RR	95% CI	P	RA	95% Cl	P	None	RR	95% CI	P	RR	95% CI	P
Total prostate cancer	1		1000							-			1.0	
No. of cases	4,499	378	A		1,118			4,499	615			881		
Age-adjusted RR*	1.00	1.15	1.03 to 1.29	.01	1.14	1.06 10 1.22	<.001	1.00	1.19	1.09 to 1.29	< 001	1.12	1:04 to 1.20	.004
Fully adjusted RR*	1.00	1.12	1.01 10 1.25	.04	1.10	1.02 to 1.17	.008	1.00	1.14	1.04 10 1.24	.003	1.08	1.00 10 1.16	,05
Grade 8-10 prostate cancer														
No. of cases	544	41			144			544	72			113		
Age-adjusted RR*	1.00	1.24	0.89 to 1.72	21	1.24	1.03 10 1.50	.03	1.00	1.27	0.99 to 1.64	.06	1.22	0.99 to 1.50	.06
Fully adjusted RR*	1.00	1.22	0.88 to 1.71	.23	1.22	1.01 10 1.48	.04	1.00	1,27	0.98 to 1.64	.07	1.20	0.97 to 1.48	.09
Grade 7 prostate cancer			10.0			100	20							1
No. of cases	1,303	123			387			1,303	220			290		
Age-adjusted RR*	1.00	1.18	0.97 to 1.43	.10	1.24	1.10 to 1.39	<.001	1.00	1.27	1.10 to 1.48	.001	1.19	1.04 to 1.35	.01
Fully adjusted RR*	. T. OO	1.14	0.94 to 1.38	19	1.18	1.05 to 1.32	10.	1.00	1.21	1.04 10 1.40	.D1	1.14	1.00 to 1.30	.05
Grade 2-6 prostate cancer														
No. of cases	1,870	176			472			1,870	269			379		
Age-adjusted RR*	1.00	1.24	1.06 to 1.46	.01	1.12	1.01 to 1.24	.03	1,00	1,18	1.04 to 1.35	.01	1.13	1.01 to 1.26	,03
Fully adjusted RR*	1.00	1.18	1.00 to 1.39	.05	1.06	0.95 10 1.17	30	1.00	1.11	0.97 to 1.27	0.1	1.07	0.96 to 1.20	.23
Lethal prostate cancert					1.00									-
No. of cases	GAN	.50			114			844	55			109		
Age-adjusted RR*	1.00	1.18	0.88 to 1.60	.27	1.20	0.98 to 1.48	.08	1.00	1,29	0.97 to 1.71	.08	1.16	0.94 to 1.43	.16
Fully adjusted RR*	1.00	1.18	0.87 to 1.60	.28	1.20	0.98 to 1.48	.08	1.00	1.29	0.97 to 1.72	.08	1.16	0.94 to 1.42	.17
Advanced prostate cancer t				10										
No. of cases	821	65			161			821	89			137		
Age-adjusted RR*	1.00	1.12	0.86 to 1.46	.40	1.25	1.05 to 1.48	.01	1.00	1.42	1.13 to 1.78	.003	1.11	0.92 to 1.33	.28
Fully adjusted RR*	1.00	1.11	0.85 10 1.44	44	1.23	1.04 to 1.47	.02	1.00	1.40	1.11 to 1.76	.004	1.10	0.91 to 1.32	.32
Localized prostate cancert														
No. of cases	2,996	268	2.3		796			2,996	436	0.0		628	1.1	0.00
Age-adjusted RR*	1.00	1.23	1.08 to 1.40	.002	1.12	1.04 to 1.22	.005	1.00	1,15	1.04 to 1.28	.01	1.14	1.05 to 1.25	.003
Fully adjusted RR*	1.00	1.18	1.04 to 1.35	.01	1.07	0.98 to 1.16	12	1.00	1.09	0.99 to 1.71	09	1.09	1.00 to 1.19	.05

NOTE. Totals by time since vasectomy and age at vasectomy do not sum to total number of men with vasectomy because of missing data on year of vasectomy. Abbreviation: RR, relative risk.

*Age-adjusted model adjusted for age in months and calendar time. Multivariable model also adjusted for race, height (quartiles), current body mass index (six categories), vigorous physical activity (quintiles), smoking (never, former smoker who quit > 10 years ago, former smoker quit who < 10 years ago, or current), diabetes, family history of prostate cancer, multivitamin use (yes or no), intake of supplemental vitamin E and alcohol (both quintiles), and history of prostate-specific antigen testing. fLethal prostate cancer: prostate cancer death or distant metastasis. Advanced: lethal or stage T3b or T4 or N1 or M1, or spread to lymph nodes or other

TLethal prostate cancer: prostate cancer death or distant metastasis. Advanced: lethal or stage T3b or T4 or N1 or M1, or spread to lymph nodes or other metastases during follow-up, Localized: T1 or T2 and N0/M0 at diagnosis with no spread to lymph nodes or other metastases or death during follow-up.

The biologic mechanisms behind the association between vasectomy and lethal prostate cancer are not clear. Physiologic changes in men after vasectomy are well known and range from local effects on the testis to effects that have potential systemic implications.²³ Studies to understand a potential causative association of vasectomy with prostate cancer incidence have focused on bridging these observed physiologic changes with mechanisms that may ultimately lead to the development of prostate cancer.24 The challenge lies in the fact that there is usually a 20- to 30-year interval between vasectomy and detection of prostate cancer. Previous theories as to the mechanism of increased prostate cancer incidence have included immunologic effects,25 cellular proliferative changes,26 and hormonal imbalances27 secondary to vasectomy. We observed no significant differences in circulating levels of sex hormones by vasectomy status in this cohort. However, we have only a single blood measurement and cannot assess levels over time or changes after vasectomy.

Some semen proteins are upregulated, whereas others are lost after vasectomy,²⁸ which may affect prostate carcinogenesis. For example, decreased expression of TGFBI and TGFBIII proteins in the semen of men after vasectomy versus controls has been observed.²⁸ Transforming growth factor- β signaling has been implicated in an inhibitory role in prostate tumorigenesis.²⁹ Last, infertile men have been reported to have a 2.6-fold higher risk of high-grade prostate cancer.³⁰ It is feasible that an overlapping mechanism leads to high-grade prostate cancer in men after vasectomy and men who are otherwise infertile.

Because this was an observational study, one limitation was that the decision to undergo vasectomy was a matter of preference, introducing the possibility of confounding. However, the cohort is rich in covariate data, and we have adjusted for and considered a broad range of risk factors, minimizing the chance for residual confounding. In addition, most men had a vasectomy before baseline was reported, so there may be some inaccuracies in reporting the timing of vasectomy, which could affect the associations for time since vasectomy and age at vasectomy. Information on grade of prostate cancer was abstracted from the original medical records, and there have been shifts in Gleason grading over time. Thus, there may be some misclassification of Gleason grading in the cohort.

Our study found that men with a history of vasectomy had a 10% increased risk of prostate cancer, with a 19% higher risk of lethal

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disease. Among highly screened men, the risk of lethal disease was 56% higher for those with vasectomy. The cumulative incidence of lethal prostate cancer during a 24-year follow-up was 1.6%; thus, these relative risks translate to small increases in absolute risk. The decision to opt for a vasectomy remains a highly personal one in which the potential risks and benefits must be considered. The findings of this study warrant continued epidemiologic and experimental research into clarifying the association of vasectomy with prostate cancer.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

REFERENCES

 Eisenberg ML, Henderson JT, Amory JK, et al. Baclal differences in vasectomy utilization in the United States: Data from the national survey of family growth. Urology 74:1020-1024, 2009

 Schwingl PJ, Guess HA: Safety and effectiveness of vasectomy. Fertil Steril 73:923-936, 2000

 Giovennucci E, Ascherio A, Rimm EB, et al: A prospective cohort study of vasectomy and prostate cancer in US men. JAMA 269:873-877, 1993

 Giovannucci E, Tosteson TD, Speizer FE, et al: A retrospective cohort study of vasectomy and prostate cancer in US men. JAMA 269:878-882, 1993

 Sidney S, Ouesenberry CP Jr, Sadiar MC, et al. Vasectomy and the risk of prostate cancer in a cohort of multiphasic health-checkup examinees: Second report. Cancer Causes Control 2:113-116, 1991

 Lynge E: Prostate cancer is not increased in men with vasectomy in Denmark. J Urol 168:488-490, 2002

 Dennis LK, Dawson DV, Resnick MI: Vasectomy and the risk of prostate cancer: A metaanalysis examining vasectomy status, age at vasectomy, and time since vasectomy. Prostate Cancer Prostatic Dis 5:193-203, 2002

 Rohrmann S, Paltoo DN, Platz EA, et al: Association of vasectomy and prostate cancer among men in a Maryland cohort. Cancer Causes Control 16:1189-1194, 2005

 Holt SK, Salinas CA, Stanford JL. Vasectomy and the risk of prostate cancer. J Urol 180:2565-2567; discussion 2567-2568, 2008.

 Cox B, Sneyd MJ, Paul C, et al. Vasectomy and risk of prostate cancer. JAMA 287:3110-3115, 2002 Schwingl PJ, Meirik O, Kapp N, et al: Prostate cancer and vasectomy: A hospital-based casecontrol study in China, Nepal and the Republic of Korea, Contraception 79:363-368, 2009

 Bernal-Delgado E. Latour-Perez J. Pradas-Arnal F., et al: The association between vasectomy and prostate cancer: A systematic review of the literature. Fertil Steril 70:191-200, 1998.

 Sutcliffe S, Giovannucci E, Gaydos CA, et al: Plasma antibodies against *Chlamydia trachomatis*, human papillomavirus, and human herpesvirus type.
 B in relation to prostate cancer: A prospective study.
 Cancer Epidemiol Biomarkers Prev 16:1573-1580, 2007

 Sutcliffe S, Giovannucci E, Alderete JF, et al. Plasma antibodies against *Trichomonas vaginalis* and subsequent risk of prostate cancer. Cancer Epidemiol Blomarkers Prev 15:939-945, 2006.

 Sutcliffe S, Giovannucci E, De Marzo AM, et al: Gonorrhea, syphilis, clinical prostatitis, and the nsk of prostate cancer. Cancer Epidemiol Biomarkers Prev 15:2160-2168, 2006

 Lesko SM, Louik C, Vezina R, et al. Vasectomy and prostate cancer. J Urol 161:1848-1852; discussion 1852-1853; 1999

 John EM, Whittemore AS, Wu AH, et al: Vasectomy and prostate cancer. Results from a multiethnic case-control study. J Natl Cancer Inst 87:662-669, 1995

 Zhu K, Stanford JL, Daling JR, et al: Vasectomy and prostate cancer: A case-control study in a health maintenance organization. Am J Epidemiol 144:717-722, 1996

 Stanford JL, Wicklund KG, McKnight B, et al. Vasectomy and risk of prostate cancer. Cancer Epidemiol Biomarkers Prev 8;881-886, 1999

20. Rosenberg L, Palmer JR, Zauber AG, et al: The relation of vasectomy to the risk of cancer. Am J Epidemiol 140:431-438, 1994

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 Chacko JA, Zafar MB, McCallum SW, et al: Vasectomy and prostate cancer characteristics of patients referred for prostate biopsy. J Urol 168: 1408-1411, 2002

 Stark JR, Judson G, Alderete JF, et al: Prospective study of *Trichomonas vaginalis* infection and prostate cancer incidence and mortality: Physicians' Health Study, J Natl Cancer Inst 101:1406-1411, 2009

23. Flickinger CJ: The effects of vasectomy on the testis. N Engl J Med 313:1283-1285, 1985

24. Howards SS: Possible biological mechanisms for a relationship between vasectomy and prost tic cancer. Eur J Cancer 29A:1060-1062, 1993

 Flickinger CJ, Bush LA, Williams MV, et al. Post-obstruction rat sperm autoantigens identified by two-dimensional gel electrophoresis and western blotting. J Reprod Immunol 43:35-53, 1999

26. Pereira S, Martinez M, Martinez FE, et al. Repercussions of castration and vasectomy on the ductal system of the rat ventral prostate. Cell Biol Int 30:169-174, 2006

 Mo ZN, Huang X, Zhang SC, et al: Early and late long-term effects of vasectomy on serum testosterone, dihydrotestosterone, luteinizing hormone and follicle-stimulating hormone levels. J Urol 154: 2065-2069, 1995.

28. Batruch I, Lecker I, Kagedan D, et al: Proteomic analysis of seminal plasma from normal volunteers and post-vasectomy patients identifies over 2000 proteins and candidate biomarkers of the urogenital system. J Proteome Res 10:941-953, 2011

29. Sharifi N, Hurt Em, Kawasaki BT, et al: TGFBR3 loss and consequences in prostate cancer. Prostate 67:301-311, 2007

30. Walk TJ, Schembri M, Turek PJ, et al. Increased risk of high-grade prostate cancer among infertile men. Cancer 118:2140-2147, 2010
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Appendix

We examined associations between vasectomy status and several plasma biomarkers among men without cancer to explore whether these were potential confounders or mediators of the association. Between 1993 and 1995, participants in the cohort were asked to provide a blood sample for research purposes. Chilled, EDTA-preserved blood specimens were returned to the Harvard School of Public Health via overnight courier by 18,225 participants. Among 2,077 men without a diagnosis of prostate cancer at the time of blood collection, plasma concentrations of sex steroid hormones and sex hormone–binding globulin (SHBG) were measured in the laboratory of Nader Rifai, PhD, at the Children's Hospital, Boston, MA, by using the following methods: total testosterone, a chemiluminescent immunoassay²⁶ (Elecsys autoanalyzer; Roche Diagnostics, Indianapolis, IN); free testosterone, an enzyme immunoassay²⁷ (Diagnostic Systems Laboratory); and SHBG, a coated tube noncompetitive immunoradiometric assay (Diagnostic Systems Laboratory).

Mean circulating sex hormone levels were compared between men with and without a vasectomy at the time of blood draw by one-way analysis of variance adjusted for age at diagnosis, smoking, body mass index, fasting status at blood draw, time of day at blood draw, and laboratory batch. Testosterone, free testosterone, and estradiol were log-transformed to improve normality, and levels of SHBG were normalized through the calculation of a batch-specific z score because of between-batch variation.

Plasma antibodies to the sexually transmitted infections *Chlamydia trachomatis*, *Trichomonas vaginalis*, human papillomavirus (HPV), and human herpesvirus type 8 (HHV-8) were measured in a nested case-control study of prostate cancer, including 632 controls, as described elsewhere.^{12,13} Antibody serostatus for *C trachomatis* was assessed with the *C trachomatis* IgG enzyme immunoassay (Ani Labsystems, Helsinki, Finland). Antibody serostatus for *T vaginalis* was assessed by enzyme-linked immunosorbent assay in the laboratory of John Alderete, MD. HPV-16, HPV-18, and HPV-33 IgG antibody serostatus for HHV-8 was assessed by three in-house enzyme-linked immunosorbent assays in the laboratory of Raphael Viscidi, MD. Antibody serostatus for HHV-8 was assessed by an in-house monoclonal antibody–enhanced immunofluorescent assay against multiple lytic HHV-8 antigens in the laboratory of Frank Jenkins.

To investigate potential confounding by sexually transmitted infections, the age-adjusted prevalence of seropositivity for several sexually transmitted infections was compared between men with and without vasectomy at blood draw among men without prostate cancer. Logistic regression was used to calculate age-adjusted *P* values for differences in the prevalence of the infections.



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Sleep Disruption Among Older Men and Risk of Prostate Cancer

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Abstract

Background—While positive associations have consistently been reported between sleep disruption and breast cancer, less is known about its potential role in prostate cancer.

Methods—Within the prospective AGES-Reykjavik cohort study, we followed 2,102 men recruited in 2002–2006 until the end of 2009. Participants answered questions on sleep disruption. Information on the occurrence of prostate cancer was obtained through record-linkages across the Icelandic Cancer Registry. We used Cox regression models with 95% confidence intervals [CIs] to estimate hazard ratios [HR] of prostate cancer by symptoms of sleep disruption.

Results—During follow-up, 135 men (6.4%) were diagnosed with prostate cancer. Compared to men without sleep disruption, those with problems falling and staying asleep were at significantly increased risk of prostate cancer [HR, 1.7 (95% CI, 1.0–2.9) and 2.1 (95% CI, 1.2–3.7)], respectively, with increasing sleep disruption severity. When restricted to advanced prostate cancer (\geq stage T3 or lethal disease), these associations became even stronger [HRs 2.1 (95% CI, 0.7–6.2) and 3.2 (95% CI, 1.1–9.7)]. The results did not change after excluding from the analyses men who woke up during the night, indicative of nocturia, suggesting limited risk of reverse association.

Conclusions—Our data suggest that certain aspects of sleep disruption may confer an increased risk of prostate cancer and call for additional, larger studies with longer follow-up times.

Impact—Prostate cancer is one of the leading public health concerns in men; if confirmed in future studies the association between sleep disruption and prostate cancer risk may open new avenues for prevention.

Disclosure of Potential Conflicts of Interest No potential conflicts of interest were disclosed.



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Keywords

prostate cancer; circadian disruption; sleep disruption; cohort study; melatonin; light at night

Introduction

In 2007 the International Agency for Research on Cancer (IARC) designated shift work involving circadian disruption as a probable carcinogen in humans (Group 2A) (1). In addition to extensive animal and *in vitro* studies (2), the ruling was based primarily on data showing that breast cancer risk among women working night shifts was ~50% higher as compared to those who had not worked night shifts (3). While data examining this hypothesis for prostate cancer risk among men are more sparse (4), two Japanese cohort studies and two Canadian case-control studies have suggested an association between shift work and prostate cancer risk (5–8), although a Swedish cohort study reported no association (9).

One of the major behavioral consequences of night shift work is displacement of the sleepwake cycle, which results in shift workers having difficulty falling asleep and staying asleep when they attempt to sleep during the day (10). Short night-time sleep has been shown to be associated with an increased risk of prostate cancer in non-shift working men (11), suggesting that sleep *per se* may be an important contributing risk factor. Further, current sleep problems seem to be indicative of persistent sleep disruption over time(12). We therefore examined the association between sleep disruption and prostate cancer risk in the population-based AGES-Reykjavik cohort. We hypothesized that men with disruption of sleep would have an increased risk of prostate cancer as compared to men without sleep disruption.

Materials and Methods

Study population and material

The AGES-Reykjavik study included 2,425 men aged 67 to 96 years who were randomly drawn from an established population-based cohort, the Reykjavik study, and recruited in 2002-2006. The AGES-Reykjavik study has been described in detail by Harris et al. (13). At study entry all men completed a detailed questionnaire, including the five following questions on sleep: (1) "How often do you take medicines to help you sleep?": (2) "How often do you experience not getting to sleep within 30 minutes?"; (3) "How often do you wake up during the night having difficulty getting back to sleep?"; (4) How often do you wake up early in the morning having difficulty getting back to sleep?", and; (5) "How often are you feeling unrested during the day no matter how many hours of sleep you had?". We excluded Question #5 in our analysis as it did not address sleep behaviour specifically. There were 5 answer categories: "Never or almost never", "Less than once a week", "1-2 times per week", "3-5 times per week", or "6-7 times per week". We combined the four sleep questions in various ways to group symptoms consistent with problems falling asleep, problems staying asleep, or both, and the severity of each (Figure 1). Our rationale for the combination of the sleep questions was based on the symptomology of different types of sleep problems. For example, Questions 1 and 2 are indicative of difficulty falling asleep, which might occur in sleep-onset insomnia, whereas Questions 3 and 4 denote problems staying asleep, a common compliant in sleep-maintenance insomnia. The combinations of three of more complaints was an attempt to assess severity of sleep complaints. While it is not possible to confirm a clinical sleep disorder in the current dataset, the combinations are based on logic consistent with known sleep disorders. Those with sleep problems of any

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type were classified as having any answer other than "Never or almost never", which was used for comparison.

Of the 2,425 men in the cohort we excluded 104 men who did not answer the questions on sleep and 215 men who had been diagnosed with prostate cancer before study entry. Thus, none of the participants had been diagnosed with prostate cancer at study entry. Further, 4 men who were censored at diagnosis of other cancer, leaving 2,102 men to form our base population.

Covariates

We collected information on several factors that could potentially confound the association between sleep disruption and prostate cancer. From the questionnaire at study enrollment we obtained information on age at study entry; family history of prostate cancer (father/brother/ son); visit to doctor during previous 12 months for any type of illness, injury or health check-up; level of education (elementary school/secondary school/college/university); smoking status (never smoked/ past smoker of at least 100 cigarettes or 20 cigars in lifetime/ current smoker); alcohol use (g/week); and diagnosis of benign prostate disease (yes/no). We obtained information on body mass index (BMI, m/kg²) from the clinical examination records and presence of diabetes mellitus was based on self-report, a fasting blood glucose of ≥ 126 mg/d, or medication use.

Follow-up and ascertainment of outcome

The men were followed through December 31, 2009 for the occurrence of prostate cancer and all-cause mortality. Using unique identification numbers assigned to all Icelandic citizens, we performed record linkages across: the nationwide Icelandic Cancer Registry (14–16) to obtain information on prostate cancer diagnoses (over 95% are histologically verified) (17), and; the Statistics Iceland for Causes of Death Register (18) to obtain information on prostate cancer-specific death and all-cause mortality. The cancer registry receives infomation on TNM stage of prostate cancer from medical records; the TNM stage was available for only 68% of the cases. We did not have information on Gleason grade. Advanced prostate cancer was defined as anatomic stage T3 or T4 or N1/M1 at diagnosis according to the TNM staging system, i.e. when the cancer has spread through the prostatic capsule, invaded nearby structures, or has spread to lymph nodes or other organs. To obtain a more complete picture of advanced disease, men who died from prostate cancer were also classified as having advanced disease, regardless of the stage at diagnosis; all of the deathspecific diagnoses had previously been retreived from the cancer registry (Figure 2).

Statistics

We present the distribution of potential covariates according to categories of sleep disruption. We used Cox regression models to estimate age-adjusted hazard ratios [HRs] with 95% confidence intervals [CIs] for total and advanced incident prostate cancer, as well as added potential covariates in two additional multivariable models. The covariates selected were based on potential confounding effects or factors other than circadian disruption that may be related to sleep and prostate cancer. The second model was further adjusted for family history of prostate cancer, education, visit to a doctor in previous 12 months, diagnosis of benign prostate disease, BMI and diabetes mellitus; the third model additionally controlled for smoking and alcohol consumption. As age- and multivariate-adjusted results were similar and power was limited in the analyses, we present age-adjusted HRs as our main results. We imputed missing values of BMI and alcohol use using the mean. For ordinal variables, we used the missing indicator method for handling missing data by creating a separate category for missing data and a new indicator variable to designate missingness. The category with the most missing data was education with 55 missing values

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(2.6% of all men). We used SPSS Software version 19.0 (SPSS Inc., 2010, IBM Chicago, IL, www.spss.com) for all statistical analysis.

To assess potential reverse association bias, whereby undiagnosed prostate cancer might cause sleep disturbance, we performed several sensitivity analyses. First, we repeated our analyses after excluding cases diagnosed within two years after study entry. Second, we excluded men who reported waking up during the night (Question #3) since men with nocturia related to undiagnosed prostate cancer may be more likely to wake up during the night, and hence report sleep disruption. Men reporting taking medication for sleep (Question #1) were also excluded in this sensitivity analysis. Therefore, in this secondary analysis, we limited sleep disruption to difficulties falling asleep (Question #2) and early morning awakening (Question #4).

Ethical approval

The study protocol was approved by the Icelandic Ethical Review Board and the Icelandic Data Protection Authority.

Results

Baseline characteristics

During the mean 5.0 years of follow-up, 135 of 2,102 eligible men (6.4%) were diagnosed with prostate cancer. Information on disease staging was available for 92 men (68%) of whom 16 (17%) had advanced TNM stage. In addition to the 16 men with advanced disease, 10 men who died from prostate cancer but had localized disease or unknown stage at diagnosis were classified as having advanced disease: leaving us with 26 men (19%) with advanced prostate cancer.

The characteristics of the participants are presented in Table 1, according to presence or absence of sleep disruption. Between 5.7 and 20.5 percent of the men were classified with sleep disruption, depending on the type of sleep problem. The comparison group consisted of 755 men (36% of total) who did not report any sleep disturbances for any of the four questions. The mean age of participants at baseline was 76.4 years and mean BMI 26.9 m/ kg². Men with and without sleep problems were similar with respect to age, education, family history of prostate cancer, smoking status, and BMI but those with sleep disruption were more likely to have visited a doctor in the previous 12 months and to have been diagnosed with diabetes mellitus. The men with problems getting to sleep and staying asleep (see Figure 1 for definitions) were more likely to have being prostatic disease. Only the men with very severe sleep problems were more likely to consume more alcohol.

Sleep disruption and risk of prostate cancer

Compared to men who did not report any sleep problems, in age-adjusted analyses, those who reported problems falling and staying asleep (Figure 1) were significantly at increased risk of prostate cancer with a hazard ratio of 1.6 (95% CI, 1.0–2.5), 1.7 (95% CI, 1.0–2.9), and 2.1 (95% CI, 1.2–3.7), respectively for increase in severity of problems falling or staying asleep (Table 2). The association did not change materially after adjustment for potential confounding factors. The association was stronger for advanced prostate cancer than for overall prostate cancer for all types of sleep problems, especially for very severe sleep problems (HR, 3.2; 95% CI, 1.1–9.7), when compared to men without sleep problems.

Sensitivity analyses

After excluding men who were diagnosed with prostate cancer within two years from study entry, too few advanced cases remained to conduct the 2-years lagged analyses. However,

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the association between sleep disruption and prostate cancer remained after excluding men with potential symptoms of nocturia (men who reported waking up during the night), with an age-adjusted HR of 2.2 (95% CI, 1.3–3.7) for overall prostate cancer (68 cases) and and 3.3 (95% CI, 1.2–9.3) for advanced disease (15 cases).

Discussion

In this prospective cohort study we found that men with sleep disruption were at increased risk of prostate cancer, particularly advanced prostate cancer, when compared to men who did not report any sleep problems.

The association between sleep disruption and prostate cancer was stronger for advanced disease than for overall prostate cancer. This may be a chance finding due to limited number of cases in the analyses for advanced cases. It is also possible that underlying mechanisms of sleep disturbance, such as circadian disruption and reduced melatonin levels, affect prostate cancer progression to a greater extent than prostate cancer initiation (19). Nonetheless, our data support the hypothesis that some aspect related to sleep disruption may confer an increased risk of prostate cancer.

Most epidemiological studies to date on the effect of sleep or circadian rhythm disruption have focused on the impact of shift work on cancer risk. Consistent with the hypotheses for sleep disruption, four studies found an increased risk of prostate cancer among night shift workers (5–8), although one did not (9).

To our knowledge the role of sleep disruption per se, separate from the impact of shift work, has only been assessed in one study on prostate cancer risk. Kakizaki et al. reported that men who slept for 6 hours or less were at non-significant increased risk of prostate cancer (HR, 1.34; 95% CI, 0.83-2.17) and those who slept for 9 hours or more at lower risk (HR, 0.48; 95% CI, 0.29-0.79) when compared to men who slept for 7-8 hours (11). Our data are consistent with this finding and suggest that impairment of sleep, either through reduced sleep duration or greater sleep disruption, increases the risk of prostate cancer. Limited data are indeed available on the direct role of melatonin on prostate cancer risk. Shorter sleep duration and greater sleep disruption may be viewed as a proxy for increased melatonin suppression, given that individuals are likely to be exposed to light when not asleep at night. Bartsch et al. have reported that men with prostate cancer have lower melatonin levels when compared to men with benign prostate hyperplasia (BPH) and young men (20, 21). Interestingly blind men, who may also have reduced exposure to light, have lower prostate cancer incidence when compared to the general population (22, 23), similar to lower breast cancer risk in blind compared to sighted women (24). Further work to establish causality is required, however.

Sleep disruption induced by shift work induces a number of physiological changes that have been proposed as possible mechanisms underlying the observed increase in cancer risk. The endogenous circadian pacemaker, located in the suprachiasmatic nuclei (SCN) of the hypothalamus, is a major determinant of the timing, duration and structure of sleep (25) such that sleep propensity and consolidation are maximized when sleep occurs during the night. Further, disruption of the molecular components of circadian clocks, particularly expression of the *Period2* gene (*Per2*) is thought to have tumor-suppressive properties (26, 27). Notably, expression levels of *Per2* were significantly lower in all proliferative prostate diseases compared with normal prostate tissue (28). Also, a major consequence of shift work is light-induced inhibition of pineal melatonin secretion, which is acutely suppressed by the electric light required to enable night-shift work. Melatonin is produced only during the biological night and is the biochemical correlate of darkness; light exposure during the night

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inhibits melatonin production (29). The presence of melatonin has been shown to inhibit or slow down tumor growth both *in vitro* and *in vivo*, including prostate cancer (30–35), whereas suppression of melatonin via constant light exposure or pinealectomy increases tumor growth in a dose-dependent manner in experimental models (36). Melatonin is also a potent free radical scavenger (37) and may facilitate reduction of oxidative stress implicated in prostate cancer progression (19).

The prospective design, complete follow-up and detailed information on a variety of potential confounders, constitute important strengths of our study. Nevertheless, several potential limitations should be considered. First, our definition of sleep disruption rests on the four questions included in the AGES entry questionnaire on problem falling asleep, staying asleep, early morning awakening (with difficulty falling back asleep) and use of sleep medication. These questions have not been validated against objective measures of sleep disruption. Morover, we have no information on the timing or duration of sleep, which can be important additional factors when assessing sleep disruption. Second, we had limited clinical information at diagnosis, with stage information for only two-thirds of the cases. Our analyses showed that the association was particularly strong for advanced disease, but the small number of cases with advanced disease limited our statistical power and yielded wide confidence intervals. Third, despite inclusion of a wide variety of potential confounding factors in our models, we cannot exclude the possiblity that residual confounding unknown to us may account for these associations. Lastly, and importantly, observation time in our study was short (5 years) and the men only provided information on sleep problems during the prior few months, whereas the time from prostate cancer onset to clinical detection has been estimated to be a decade or more (38, 39). If the carcinogenic effect of sleep disruption on tumour progression was mediated through melatonin suppression, laboratory studies suggest that the impact of reduced melatonin could be quite rapid (36), although there is no parallel clinical evidence in humans. It is also plausible that reports about current sleep problems are indicative of persistent sleep disruption over time (12) that may underlie a longer-term disease process. Nevertheless, the short observation time in our study may raise concerns of reverse association bias; for example, that men with undiagnosed prostate cancer may have symptoms such as nocturia before diagnosis that consequently lead to sleep disturbances. Men with urinary symptoms (hence sleep disruption) related to prostate cancer, especially advanced cancer, often suffer from nocturia (waking up during the night). To address this concern, we conducted sensitivity analyses in which we exluded men with symptoms of sleep disturbance that might be indicative of nocturia. Notably, the point estimates remained essentially unchanged, to some extent alleviating these concerns, although the number of cases were few.

These data lend support to the hypothesis that sleep disruption may affect prostate carcinogenesis. Sleep disruption and light-induced melatonin suppression represent plausible biological explanations underlying cancer risk, although prospective studies are needed to substantiate their respective roles. Large cohort studies entailing longer observation times, allowing for closer investigatons of the temporality of the association between sleep disruption and prostate cancer, will be needed to address this hypothesis further.

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References

- Straif K, Baan R, Grosse Y, Secretan B, El Ghissassi F, Bouvard V, et al. Carcinogenicity of shiftwork, painting, and fire-fighting. Lancet Oncol. 2007 Dec; 8(12):1065–6. [PubMed: 19271347]
- Blask DE, Dauchy RT, Sauer LA. Putting cancer to sleep at night: the neuroendocrine/circadian melatonin signal. Endocrine. 2005 Jul; 27(2):179–88. [PubMed: 16217131]
- IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Lyon, France: World Health Organization, International Agency for Research on Cancer; 2010.
- Sigurdardottir LG, Valdimarsdottir UA, Fall K, Rider JR, Lockley SW, Schernhammer E, et al. Circadian Disruption, Sleep Loss, and Prostate Cancer Risk: A Systematic Review of Epidemiologic Studies. Cancer Epidemiol Biomarkers Prev. 2012 May 31.
- Kubo T, Oyama I, Nakamura T, Kunimoto M, Kadowaki K, Otomo H, et al. Industry-based retrospective cohort study of the risk of prostate cancer among rotating-shift workers. Int J Urol. 2011 Mar; 18(3):206–11. [PubMed: 21332815]
- Conlon M, Lightfoot N, Kreiger N. Rotating shift work and risk of prostate cancer. Epidemiology. 2007 Jan; 18(1):182–3. [PubMed: 17179764]
- Kubo T, Ozasa K, Mikami K, Wakai K, Fujino Y, Watanabe Y, et al. Prospective cohort study of the risk of prostate cancer among rotating-shift workers: findings from the Japan collaborative cohort study. Am J Epidemiol. 2006 Sep 15; 164(6):549–55. [PubMed: 16829554]
- Parent ME, El-Zein M, Rousseau MC, Pintos J, Siemiatycki J. Night work and the risk of cancer among men. Am J Epidemiol. 2012 Nov 1; 176(9):751–9. [PubMed: 23035019]
- Schwartzbaum J, Ahlbom A, Feychting M. Cohort study of cancer risk among male and female shift workers. Scand J Work Environ Health. 2007 Oct; 33(5):336–43. [PubMed: 17973059]
- Akerstedt T. Shift work and disturbed sleep/wakefulness. Occup Med (Lond). 2003 Mar; 53(2):89– 94. [PubMed: 12637592]
- Kakizaki M, Inoue K, Kuriyama S, Sone T, Matsuda-Ohmori K, Nakaya N, et al. Sleep duration and the risk of prostate cancer: the Ohsaki Cohort Study. Br J Cancer. 2008 Jul 8; 99(1):176–8. [PubMed: 18542076]
- Morphy H, Dunn KM, Lewis M, Boardman HF, Croft PR. Epidemiology of insomnia: a longitudinal study in a UK population. Sleep. 2007 Mar; 30(3):274–80. [PubMed: 17425223]
- Harris TB, Launer LJ, Eiriksdottir G, Kjartansson O, Jonsson PV, Sigurdsson G, et al. Age, Gene/ Environment Susceptibility-Reykjavik Study: multidisciplinary applied phenomics. Am J Epidemiol. 2007 May 1; 165(9):1076–87. [PubMed: 17351290]
- Icelandic Cancer Registry. ICR: Reykjavik. Available from: www.cancerregistry.is [cited 2012April 23]
- 15. Jonasson, JG.; Tryggvadottir, L., editors. Cancer incidence in five continents. Iceland: 2007.
- Moller B, Fekjaer H, Hakulinen T, Tryggvadottir L, Storm HH, Talback M, et al. Prediction of cancer incidence in the Nordic countries up to the year 2020. Eur J Cancer Prev. 2002 Jun; 11(Suppl 1):S1–96. [PubMed: 12442806]
- Sigurdardottir LG, Jonasson JG, Stefansdottir S, Jonsdottir A, Olafsdottir GH, Olafsdottir EJ, et al. Data quality at the Icelandic Cancer Registry: Comparability, validity, timeliness and completeness. Acta Oncol. 2012 Sep; 51(7):880–9. [PubMed: 22974093]
- 18. Statistics Iceland. SI: Reykjavik. Available from:www.statice.is [cited 2012 April 23]
- Nguyen HL, Zucker S, Zarrabi K, Kadam P, Schmidt C, Cao J. Oxidative stress and prostate cancer progression are elicited by membrane-type 1 matrix metalloproteinase. Mol Cancer Res. 2011 Oct; 9(10):1305–18. [PubMed: 21849471]
- Bartsch C, Bartsch H. Melatonin in cancer patients and in tumor-bearing animals. Adv Exp Med Biol. 1999; 467:247–64. [PubMed: 10721063]
- Bartsch C, Bartsch H, Schmidt A, Ilg S, Bichler KH, Fluchter SH. Melatonin and 6sulfatoxymelatonin circadian rhythms in serum and urine of primary prostate cancer patients:

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evidence for reduced pineal activity and relevance of urinary determinations. Clin Chim Acta. 1992 Aug 31; 209(3):153-67. [PubMed: 1395046]

- Pukkala E, Ojamo M, Rudanko SL, Stevens RG, Verkasalo PK. Does incidence of breast cancer and prostate cancer decrease with increasing degree of visual impairment. Cancer Causes Control. 2006 May; 17(4):573–6. [PubMed: 16596312]
- Feychting M, Osterlund B, Ahlbom A. Reduced cancer incidence among the blind. Epidemiology. 1998 Sep; 9(5):490–4. [PubMed: 9730026]
- Flynn-Evans EE, Stevens RG, Tabandeh H, Schernhammer ES, Lockley SW. Total visual blindness is protective against breast cancer. Cancer Causes Control. 2009 Nov; 20(9):1753–6. [PubMed: 19649715]
- Czeisler CA, Weitzman E, Moore-Ede MC, Zimmerman JC, Knauer RS. Human sleep: its duration and organization depend on its circadian phase. Science. 1980 Dec 12; 210(4475):1264–7. [PubMed: 7434029]
- Hua H, Wang Y, Wan C, Liu Y, Zhu B, Yang C, et al. Circadian gene mPer2 overexpression induces cancer cell apoptosis. Cancer Sci. 2006 Jul; 97(7):589–96. [PubMed: 16827798]
- Chen-Goodspeed M, Lee CC. Tumor suppression and circadian function. J Biol Rhythms. 2007 Aug; 22(4):291–8. [PubMed: 17660446]
- Jung-Hynes B, Huang W, Reiter RJ, Ahmad N. Melatonin resynchronizes dysregulated circadian rhythm circuitry in human prostate cancer cells. J Pineal Res. 2010 Aug; 49(1):60–8. [PubMed: 20524973]
- Arendt J. Melatonin and the pineal gland: influence on mammalian seasonal and circadian physiology. Rev Reprod. 1998 Jan; 3(1):13–22. [PubMed: 9509985]
- Anisimov VN, Baturin DA, Popovich IG, Zabezhinski MA, Manton KG, Semenchenko AV, et al. Effect of exposure to light-at-night on life span and spontaneous carcinogenesis in female CBA mice. Int J Cancer. 2004 Sep 10; 111(4):475–9. [PubMed: 15239122]
- Shiu SY, Law IC, Lau KW, Tam PC, Yip AW, Ng WT. Melatonin slowed the early biochemical progression of hormone-refractory prostate cancer in a patient whose prostate tumor tissue expressed MT1 receptor subtype. J Pineal Res. 2003 Oct; 35(3):177–82. [PubMed: 12932201]
- 32. Xi SC, Siu SW, Fong SW, Shiu SY. Inhibition of androgen-sensitive LNCaP prostate cancer growth in vivo by melatonin: association of antiproliferative action of the pineal hormone with mt1 receptor protein expression. Prostate. 2001 Jan 1; 46(1):52–61. [PubMed: 11170132]
- Shiu SY, Xi SC, Xu JN, Mei L, Pang SF, Yao KM, et al. Inhibition ofinalignant trophoblastic cell proliferation in vitro and in vivo by melatonin. Life Sci. 2000 Sep 15; 67(17):2059–74. [PubMed: 11057756]
- Moretti RM, Marelli MM, Maggi R, Dondi D, Motta M, Limonta P. Antiproliferative action of melatonin on human prostate cancer LNCaP cells. Oncol Rep. 2000 Mar-Apr;7(2):347–51. [PubMed: 10671684]
- Marelli MM, Limonta P, Maggi R, Motta M, Moretti RM. Growth-inhibitory activity of melatonin on human androgen-independent DU 145 prostate cancer cells. Prostate. 2000 Nov 1; 45(3):238– 44. [PubMed: 11074526]
- Blask DE. Melatonin, sleep disturbance and cancer risk. Sleep Med Rev. 2009 Aug; 13(4):257–64. [PubMed: 19095474]
- Galano A, Tan DX, Reiter RJ. Melatonin as a natural ally against oxidative stress: a physicochemical examination. J Pineal Res. 2011 Aug; 51(1):1–16. [PubMed: 21752095]
- Savage CJ, Lilja H, Cronin AM, Ulmert D, Vickers AJ. Empirical estimates of the lead time distribution for prostate cancer based on two independent representative cohorts of men not subject to prostate-specific antigen screening. Cancer Epidemiol Biomarkers Prev. 2010 May; 19(5):1201–7, [PubMed: 20406957]
- Finne P, Fallah M, Hakama M, Ciatto S, Hugosson J, de Koning H, et al. Lead-time in the European Randomised Study of Screening for Prostate Cancer. Eur J Cancer. 2010 Nov; 46(17): 3102–8. [PubMed: 21047593]

Cancer Epidemiol Biomarkers Prev. Author manuscript; available in PMC 2014 May 01.

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Figure 1.

Categorization of sleep disruption according to combination of four questions (Q) on sleep from the AGES-Reykjavik Cohort.

n=number of participants who have specified sleep problem (any other answer than "never or almost never")

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Figure 2.

Information on TNM staging and causes of death due to prostate cancer.

*All of the incident cases were identified through record linkage with the Icelandic Cancer Registry.

**Information on cause-specific death was obtained through record linkage with the Statistics Iceland.

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Characteristics of the Male Participants in the AGES-Reykjavik Cohort by Sleep Disruption (four sleep questions), Iceland, 2002-2009.

Category	Characteristic	Total (N= 2,102) No. (%) or Mean (SD)	Problem Falling Asleep ^a No. (%) or Mean (SD)	Problem Staying Asleep ^a No. (%) or Mean (SD)	Problem Falling and Staying Asleep ^a No. (%) or Mean (SD)	Severe Sleep Problem ^a No. (%) or Mean (SD)	Very Severe Sleep Problem ^a No. (%) or Mean (SD)	No Sleep Problem ^b (n=755) No. (%) or Mean (SD)
Prevalence of sleep problem		662 (31.5)	273 (13.0)	430 (20.5)	352 (16.7)	183 (8.7)	120 (5.7)	0
Number of cases		135	27	34	29	21	16	49
Age ^c , years		76.4 (5.3)	77.3 (5.1)	76.8 (5.3)	76.9 (5.4)	77.0 (5.0)	77.2 (5.1)	76.0 (5.2)
Education	Elementary	339 (16.5)	44 (16.6)	70 (16.9)	60 (17.4)	29 (16.3)	18 (15.7)	125 (16.9)
	Secondary	1091 (53.2)	146 (55.1)	218 (52.5)	191 (55.4)	97 (54.5)	59 (51.3)	391 (52.8)
	College	255 (12.4)	33 (12.5)	47 (11.3)	36 (10.4)	21 (11.8)	15 (13.0)	101 (13.6)
	University	367 (17.9)	42 (15.8)	80 (19.3)	58 (16.8)	31 (17.4)	23 (20.0)	123 (16.6)
Family history of prostate cancer		194 (9.2)	25 (9.2)	33 (7.7)	33 (9.4)	16 (8.7)	6 (5.0)	70 (9.3)
Visit to doctor in previous 12 months		1714 (81.7)	237 (86.8)	375 (87.2)	302 (85.8)	159 (86.9)	105 (87.5)	569 (75.4)
Diagnosed as diabetic		365 (15.7)	57 (20.9)	76 (17.7)	68 (19.3)	39 (21.3)	21 (17.5)	115 (15.2)
Smoking status	Never	581 (28.2)	61 (23.0)	108 (26.0)	84 (24.3)	40 (22.5)	33 (28.7)	239 (32.3)
	Previously	1234 (60.0)	177 (66.8)	268 (64.4)	218 (63.2)	121 (68.0)	75 (65.2)	428 (57.8)
	Current	242 (11.8)	27 (10.2)	40 (9.6)	43 (12.5)	17 (9.6)	7 (6.1)	74 (10.0)
Benign prostate disease		723 (34.4)	116 (42,5)	157 (36.5)	133 (37.8)	77 (42.1)	47 (39.2)	231 (30.6)
Alcohol ^C , g/week		22.4 (42.7)	24.2 (45.8)	24.3 (44.7)	24.7 (48.6)	26.5 (51.3)	29.4 (56.6)	20.8 (42.6)
Body mass index ^c , m/kg ²		26.9 (3.8)	27.0 (3.8)	26.8 (3.8)	27.0 (3.8)	27.0 (3.6)	26.8 (3.6)	27.0 (3.9)

^aLess than once per week up to 6 times per week;

b Never or almost never;

^cMean (Standard deviation)

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Table 2

Estimated Risk of Prostate Cancer by Sleep Disruption^a among Males in the AGES-Reykjavik Cohort.

Category	Characteristic	No. of Cases	Person years	Hazard Ratio ^b (95% CI)	Hazard Ratio ^c (95% CI)	Hazard Ratio ^d (95% CI)
Problem falling asleep	Total prostate cancer					
0#110#2	No sleep disruption	49	3809	Ref	Ref	Ref
QH1 + QH2	Sleep disruption	27	1385	1.6 (1.0-2.5)	1.6 (1.0-2.6)	1.6 (1.0-2.6)
	Advanced disease					
	No sleep disruption	9	3809	Ref	Ref	Ref
	Sleep disruption	6	1385	1.7 (0.6-4.8)	1.9 (0.7-5.4)	1.8 (0.6-5.3)
Problem staying asleep	Total prostate cancer					
042 1 044	No sleep disruption	49	3809	Ref	Ref	Ref
Q#5 + Q#4	Sleep disruption	34	2211	1.2 (0.8-1.9)	1.2 (0.8-1.9)	1.2 (0.8-1.9)
	Advanced disease					
	No sleep disruption	9	3809	Ref	Ref	Ref
	Sleep disruption	9	2211	1.6 (0.6-4.1)	1.7 (0.7-4.4)	1.7 (0.7-4.3)
Problem falling and staying asleep	Total prostate cancer					
042 - 042	No sleep disruption	49	3809	Ref	Ref	Ref
Q#2 + Q#3	Sleep disruption	29	1807	1.3 (0.8-2.0)	1.3 (0.8-2.0)	1.3 (0.8-2.0)
	Advanced disease					
	No sleep disruption	9	3809	Ref	Ref	Ref
	Sleep disruption	8	1807	1.7 (0.6-4.4)	1.8 (0.7-4.8)	1.7 (0.7-4.6)
Severe sleep problem	Total prostate cancer					
Q#1 + Q#2 + Q#3	No sleep disruption	49	3809	Ref	Ref	Ref
	Sleep disruption	21	952	1.7 (1.0-2.9)	1.7 (1.0-2.9)	1.7 (1.0-2.9)
	Advanced disease					
	No sleep disruption	9	3809	Ref	Ref	Ref
	Sleep disruption	5	952	2.1 (0.7-6.2)	2.2 (0.7-6.8)	2.2 (0.7-6.9)
Very severe sleep problem	Total prostate cancer					
041 + 042 + 042 + 044	No sleep disruption	49	3809	Ref	Ref	Ref
Q#1 + Q#2 + Q#3 + Q#4	Sleep disruption	16	606	2.1 (1.2-3.7)	2.1 (1.2-3.8)	2.2 (1.2-3.9)
	Advanced disease					

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Category	Characteristic	No. of Cases	Person years	Hazard Ratio ^b (95% CI)	Hazard Ratio ^C (95% CI)	Hazard Ratio ^d (95% CI)
	No sleep disruption	9	3809	Ref	Ref	Ref
	Sleep disruption	5	606	3.2 (1.1-9.7)	3.5 (1.1-10.7)	3.8 (1.2-11.7)

^aFour questions on sleep (Q#1, Q#2, Q#3, and Q#4) combined in different categories. See figure 1 for the definitions.

^bAge-adjusted HR

^CAdditional adjustment for family history of prostate cancer, benign prostate disease, education, visit to a doctor in previous 12 months, BMI, and diabetes mellitus

^dAdditional adjustment for smoking and alcohol

2



 $\mu_{1} = 0$

Exhibit B

Materials Considered List

- Acquavella, J. et al., Exposure Misclassification in Studies of Agricultural Pesticides, 17 Epidemiology 69 (2006).
- 2. Acquavella, J. et al., *Glyphosate Biomonitoring for Farmers and Their Families: Results from the Farm Family Exposure Study*, 112 Envtl. Health Persp. 321 (2004).
- 3. Agu, V. et al., Geographic Patterns of Multiple Myeloma: Racial and Industrial Correlates, State of Texas, 1969-71, 65 J. Nat'l Cancer Inst. 735 (1980).
- 4. Ahn, R. et al., Financial ties of principal investigators and randomized controlled trial outcomes: cross sectional study, 356 BMJ (2017).
- 5. Alavanja, M. et al., Non-Hodgkin Lymphoma Risk and Insecticide, Fungicide and Fumigant Use in the Agricultural Health Study, 9 PLoS One e109332 (2014).
- 6. Alavanja, M. et al., The Agricultural Health Study, 104 Envtl. Health Persp. 362 (1996).
- Alavanja, M. et al., Cancer Incidence in the Agricultural Health Study, 31 suppl 1 Scandinavian J. Work Env't & Health 39 (2005).
- 8. Alavanja, M. et al., *DRAFT-Lymphoma risk and pesticide use in the Agricultural Health Study* (Mar. 15, 2013) (unpublished study) (on file with Authors).
- 9. Alavanja, M. et al. Lymphoma risk and pesticide use in the Agricultural Health Study, Unpublished manuscript (2013).
- American Cancer Society, Types of Non-Hodgkin Lymphoma, <u>https://www.cancer.org/cancer/non-hodgkin-lymphoma/about/types-of-non-hodgkin-lymphoma.html</u> (accessed May 24, 2017).
- Anscombe, F., *The Summarizing of Clinical Experiments by Significance Levels*, 9 Statistics in Medicine 703 (1990).
- 12. Arbuckle, T. et al., *Predictors of Herbicide Exposure in Farm Applicators*, 75 Int'l Archives Occupational Envtl. Health 406 (2002).
- Aspelin, A. & A. Grube, *Pesticides Industry Sales and Usage 1996 and 1997 Market Estimates*, U.S. Environmental Protection Agency, Office of Prevention, Pesticides, and Toxic Substances (1999).
- 14. Aspelin, A., *Pesticides Industry Sales and Usage 1994 and 1995 Market Estimates*, Office of Prevention, Pesticides and Toxic Substances (1997).

- Battaglin, W. et al., Glyphosate and Its Degradation Product AMPA Occur Frequently and Widely in U.S. Soils, Surface Water, Groundwater, and Precipitation, 50 J American Water Resources Ass'n 275 (2014).
- Bekelman, J. et al., Scope and Impact of Financial Conflicts of Interest in Biomedical Research, 289 JAMA 454 (2003).
- Berkson, J., Tests of significance considered as evidence, 32 Int'l. J. Epidemiology 687 (2003).
- BfR, Assessment of IARC Monographies Volume 112 (2015); Glyphosate, Renewal Assessment Report: Glyphosate Addendum I to RAR (2015).
- 19. Blair, A. & D. White, Death Certificate Study of Leukemia Among Farmers From Wisconsin, 66 J. Nat'l Cancer Inst. 1027 (1981).
- Blair, A. & D. White, Leukemia Cell Types and Agricultural Practices in Nebraska, 10 Archives Envtl. Health 211 (1985).
- Blair, A. & L. Freeman, Ph.D., Epidemiologic Studies of Cancer in Agricultural Populations: Observations and Future Directions, 14 J. Agromedicine 125 (2009).
- Blair, A. & S. Zahm, Patterns of Pesticide Use among Farmers: Implications for Epidemiologic Research, 4 Epidemiology 55 (1993).
- 23. Blair, A. et al., *Guidelines for Application of Meta-analysis in Environmental Epidemiology*, 22 Regulatory Toxicology and Pharmacology 189 (1995).
- Blair, A. et al., Reliability of Reporting on Life-Style and Agricultural Factors by a Sample of Participants in the Agricultural Health Study from Iowa, 13 Epidemiology 94 (2002).
- 25. Blettner, M. et al., *Traditional reviews, meta-analyses and pooled analyses in epidemiology*, 28 Int'l. J. Epidemiology 1 (1999).
- Bonner, M. et al., Occupational Exposure to Pesticides and the Incidence of Lung Cancer in the Agricultural Health Study, 125 Envtl. Health Persp. 544 (2017).
- Bosch, F. & S. de Sanjosé, Chapter 1: Human papillomavirus and cervical cancer burden and assessment of causality, 31 J. Nat'l. Cancer Inst. Monographs 3 (2003).
- Bradford Hill, A., *The Environment and Disease: Association or Causation?*, 58 Proc R Soc Med 295 (1965).

- 29. Bravata, D. & I. Olkin, *Simple Pooling Versus Combining in Meta-Analysis*, 24 Evaluation & The Health Professionals 218 (2001).
- Bridger, R. & P. Sparto, Spade design, lumbar motions, risk of low-back injury and digging posture, 1 Occupational Ergonomics 157 (1998).
- 31. Brown, L. et al., Pesticide Exposures and Other Agricultural Risk Factors for Leukemia among Men in Iowa and Minnesota, 50 Cancer Res 6585 (1990).
- Brown, L. et al., Pesticide exposures and multiple myeloma in Iowa men, 4 Cancer Causes & Control 153 (1993).
- Brusick, D. et al., Genotoxicity Expert Panel Review: Weight of Evidence Evaluation of the Genotoxicity of Glyphosate, Glyphosate-Based Formulations, and Aminomethy/phosphonic Acid, 46 Critical Rev Toxicology 56 (2016).
- Buesching, D. & L. Wollstadt, Letters to the Editor Cancer Mortality Among Farmers, 72 J. Nat'l Cancer Inst. 503 (1984).
- 35. Burmeister, L. et al., *Leukemia and Farm Practices in Iowa*, 115 Am. J. Epidemiology 720 (1982).
- Burmeister, L. et al., Selected Cancer Mortality and Farm Practices in Iowa, 118 Am. J. Epidemiology 72 (1983).
- Burmeister, L., Cancer Mortality in Iowa Farmers, 1971-78, 66 J. Nat'l Cancer Inst. 461 (1981).
- Cancer Research UK (2016) Cancer incidence by age. <u>https://www.cancerresearchuk.org/health-professional/cancerstatistics/incidence/age#heading-zero</u>
- Cantor, K. & A. Blair, Farming and Mortality From Multiple Myeloma: A Case-Control Study with the Use of Death Certificates, 72 J. Nat'l Cancer Inst. 251 (1984).
- 40. Cantor, K. et al., Pesticides and Other Agricultural Risk Factors for Non-Hodgkin's Lymphoma among Men in Iowa and Minnesota, 52 Cancer Res. 2447 (1992).
- 41. Cantor, K., Farming and Mortality from Non-Hodgkin's Lymphoma: A Case-Control Study, 29 Int'l J. Cancer 239 (1982).
- 42. Chang, E. & E. Delzell, Meta-Analysis of Glyphosate Use and Risk of Non-Hodgkin Lymphoma, Exponent (2017).

- 43. Chang, E. & E. Delzell, Systematic review and meta-analysis of glyphosate exposure and risk of lymphohematopoietic cancers, 0 J. Envtl. Sci. & Health 1 (2016).
- 44. Coble, J. et al., Prevalence of exposure to solvents, metals, grain dust, and other hazards among farmers in the Agricultural Health Study, 12 J. Exposure Analysis & Envtl. Epidemiology 418 (2002).
- 45. Cocco, P. et al., Lymphoma risk and occupational exposure to pesticides: results of the Epilymph study, 70 Occupational & Envtl. Med. 91 (2013).
- 46. Coupe, R. & P. Capel, Trends in pesticide use on soybean, corn and cotton since the introduction of major genetically modified crops in the United States, 72 Pest Management Science 1013 (2016).
- 47. Cox, C., *Glyphosate Fact Sheets: Part 1, Toxicology; Part 2, Human Exposure and Ecological Effects.* 15(3 and 4) J. Pesticide Reform 1 (1995).
- Curwin, B. et al., Urinary Pesticide Concentrations Among Children, Mothers and Fathers Living in Farm and Non-Farm Households in Iowa, 51 Annals Occupational Hygiene 53 (2007).
- 49. Dancik, B., Importance of Peer Review, The Serials Librarian (1991).
- De Roos, A. et al., An Application of Hierarchical Regression in the Investigation of Multiple Paternal Occupational Exposures and Neuroblastoma in Offspring, 39 Am. J. of Indus. Med. 477 (2001).
- 51. De Roos, A. et al., Cancer Incidence among Glyphosate-Exposed Pesticide Applicators in the Agricultural Health Study, 113 Envtl. Health Persp. 49 (2005).
- 52. De Roos, A. et al., Integrative assessment of multiple pesticides as risk factors for non-Hodgkin's lymphoma among men, 60 Occupational & Envtl. Med. 1 (2003)
- Delzell, E. & S. Grufferman, Mortality Among White and Nonwhite Farmers in North Carolina, 1976-1978, 121 Am. J. Epidemiology 391 (1985).
- 54. Dong, J., Simpson's Paradox, Encyclopedia of Biostatistics 4108 (1998).
- Dreiher, J. & E. Kordysh, Non-Hodgkin Lymphoma and Pesticide Exposure: 25 Years of Research, 116 Acta Haematologica 153 (2006).
- 56. Dubrow, R. et al., Farming and malignant lymphoma in Hancock County, Ohio, 45 British J. Indus. Med. 25 (1988).

- 57. Engel, L. et al., Validity Study of Self-Reported Pesticide Exposure Among Orchardists, 11(5) J Exposure Analysis Envtl. Epidemiology 359 (2001).
- EPA, Cancer Assessment Review Committee, Health Effects Division, Office of Pesticide Programs, U.S. Environmental Protection Agency, *Cancer Assessment Document – Evaluation of the Carcinogenic Potential of Glyphosate* (Final Report October 1, 2015).
- 59. EPA, Glyphosate: Reregistration Eligibility Decision (RED) Facts, (Sept. 1993).
- EPA, Letter from Robert J. Taylor, Product Manager, Fungicide-Herbicide Branch, Registration Division on Roundup: EPA Reg. No. 524-308 to Mr. Hannah, Monsanto Co. (Dec. 22, 1975).
- 61. EPA, Office of Pesticide Programs, *Glyphosate Issue Paper: Evaluation of Carcinogenic Potential*, Regulations.gov (September 12, 2016).
- 62. Eriksson, M. et al., Pesticide exposure as risk factor for non-Hodgkin lymphoma including histopathological subgroup analysis, 123 Int'l J. of Cancer 1657 (2008).
- 63. European Food Safety Authority, Conclusion on the peer review of the pesticide risk assessment of the active substance glyphosate, 13 EFSA J. 4302 (2015).
- 64. Evans, S. et al., The end of the p value? 60 British Heart J. 177 (1988).
- Expert Report of Alfred I. Neugut, MD, PHD In Support of General Causation on Behalf of Plaintiffs, In Re: Roundup Products Liability Litigation, No. 16-md-02741-VC (N.D. Cal. May 1, 2017).
- Expert Report of Dr. Beate Ritz, M.D., Ph.D. In Support of General Causation on Behalf of Plaintiffs, In Re: Roundup Products Liability Litigation, No. 16-md-02741-VC (N.D. Cal. May 1, 2017).
- Expert Report of Dr. Christopher J. Portier In Support of General Causation on Behalf of Plaintiffs, In Re: Roundup Products Liability Litigation, No. 16-md-02741-VC (N.D. Cal. May 1, 2017).
- Expert Report of Dr. Dennis Weisenburger, M.D. In Support of General Causation on Behalf of Plaintiffs, In Re: Roundup Products Liability Litigation, No. 16-md-02741-VC (N.D. Cal. May 1, 2017).
- Expert Report of Dr. Chadi Nabhan In Support of General Causation on Behalf of Plaintiffs, In Re: Roundup Products Liability Litigation, No. 16-md-02741-VC (N.D. Cal. May 1, 2017).

- 70. Fasal, E. et al., *Leukemia and Lymphoma Mortality and Farm Residence*, 87 Am. J. Epidemiology 267 (1968).
- Feng, J. & D. Thompson, Fate of Glyphosate in a Canadian Forest Watershed. 2. Persistence in Foliage and Soils, 38 J. Agricultural Food Chemistry 1118 (1990).
- 72. Flower, K. et al., Cancer Risk and Parental Pesticide Application in Children of Agricultural Health Study Participants, 112 Envtl. Health Persp. 631 (2004).
- 73. Freeman, L. et al., *Poultry and Livestock Exposure and Cancer Risk among Farmers in the Agricultural Health Study*, 23 Cancer Causes Control 663 (2012).
- 74. Fritschi, L. et al., Occupational Exposure to Pesticides and Risk of Non-Hodgkin's Lymphoma, 162 Am. J. Epidemiology 849 (2005).
- 75. Gallagher, R. et al., *Cancer and Aplastic Anemia in British Columbia Farmers*, 72 J. Nat'l Cancer Inst. 1311 (1984).
- Gelman, A. & E. Loken, *The Statistical Crisis in Science*, 102 American Scientist 460 (2014).
- 77. Gelman, A. & H. Stern, *The Difference Between "Significant" and "Not Significant" is not Itself Statistically Significant*, 60 The American Statistician 328 (2006).
- 78. Geng, Z., Collapsibility of Relative Risk in Contingency Tables with a Response Variable, 54 J. Royal Statistical Society. Series B (Methodological) 585 (1992).
- 79. Gigerenzer, G., Mindless Statistics, 33 J. Socio-Economics 587 (2004).
- Glass, G., Primary, Secondary, and Meta-Analysis of Research 1, 5 Educational Researcher 3 (1976).
- Goldsmith, J. & T. Guidotti, Environmental Factors in the Epidemiology of Lymphosarcoma, 12 Pathology Ann. 411 (1977).
- Good, I. & Y. Mittal, *The Amalgamation and Geometry of Two-By-Two Contingency Tables*, 15 The Annals of Statistics 694 (1987).
- Goodman, S., Toward Evidence-Based Medical Statistics. 1: The P Value Fallacy, 130 Annals of Internal Medicine 995 (1999).

- 84. Green, M. et al., Reference Guide on Epidemiology In: Reference Manual on Scientific Evidence: Third Edition, The National Academies Press 597 (2011).
- 85. Greenland, S., Nonsignificance Plus High Power Does Not Imply Support for the Null Over the Alternative, 22 Annals of Epidemiology 364 (2012).
- 86. Grieve, A., How to test hypotheses if you must, 14 Pharmaceutical Statistics 139 (2015).
- Grube, A. et al., *Pesticides Industry Sales and Usage 2006 and 2007 Market Estimates*, U.S. Environmental Protection Agency, Office of Pesticide Programs (2011).
- Guyton, K. et al., Carcinogenicity of Tetrachlorvinphos, Parathion, Malathion, Diazinon, and Glyphosate, 16 Lancet Oncology 490 (2015).
- Hardell, L. & M. Eriksson, A Case-Control Study of Non-Hodgkin Lymphoma and Exposure to Pesticides, 85 Cancer 1353 (1999).
- Hardell, L. et al., Exposure to Pesticides as Risk Factor for Non-Hodgkin's Lymphoma and Hairy Cell Leukemia: Pooled Analysis of Two Swedish Case-control Studies, 43 Leukemia and Lymphoma 1043 (2002).
- Hardell, L. et al., Malignant Lymphoma and Exposure to Chemicals, Especially Organic Solvents, Chlorophenols and Phenoxy Acids: A Case-Control Study, 43 Br. J. Cancer 169 (1981).
- 92. Hardell, L., Relation of soft-tissue sarcoma, malignant lymphoma and colon cancer to phenoxy acids, chlorophenols and other agents, 7 Scandinavian Journal of Work, Env't & Health 119 (1981).
- 93. Hernán, M. et al., A structural approach to selection bias, 15 Epidemiology 615 (2004).
- Hoar, S. et al., Agricultural Herbicide Use and Risk of Lymphoma and Soft-Tissue Sarcoma, 256 JAMA 1141 (1986).
- 95. Hoekstra, R. et al., *Probability as certainty: Dichotomous thinking and the misuse of p values*, 13 Psychonomic Bulletin & Review 1033 (2006).
- 96. Hofmann, J. et al., Farm Characteristics, Allergy Symptoms, and Risk of Non-Hodgkin Lymphoid Neoplasms in the Agricultural Health Study, 24 Cancer Epidemiology Biomarkers & Prevention 587 (2015).
- Hohenadel, K. et al., Exposure to Multiple Pesticides and Risk of Non-Hodgkin Lymphoma in Men from Six Canadian Provinces, 8 Int'l J. Envtl. Res. & Public Health 2320 (2011).

- Hoppin, J. et al., Accuracy of self-reported pesticide use duration information from licensed pesticide applicators in the Agricultural Health Study, 12 J. Exposure Analysis & Envtl. Epidemiology 313 (2002).
- 99. Howe, G. & J. Lindsay, A Follow-up Study of a Ten-Percent Sample of the Canadian Labor Force. I. Cancer Mortality in Males, 1965-73, 70 J. Nat'l Cancer Inst. 37 (1983).
- 100. International Agency for Research on Cancer (IARC), Monograph Vol. 112 on the Evaluation of Carcinogenic Risks to Humans, Some Organophosphate Insecticides and Herbicides: Diazinon, Glyphosate, Malathion, Parathion, and Tetrachlorvinphos (2015).
- 101. Jauhiainen, A. et al., Occupational Exposure of Forest Workers to Glyphosate During Brush Saw Spraying Work, 52 American Industrial Hygiene Ass'n J 61 (1991).
- 102. JMPR, Pesticide residues in food 2004: Toxicological evaluations Toxicological Monographs and Monograph Addenda, Joint FAO/WHO Meeting on Pesticide Residues (2006).
- 103. Kachuri, L. et al., Multiple pesticide exposures and the risk of multiple myeloma in Canadian men, 133 Int'l J. Cancer 1846 (2013).
- Kaye, D., Is Proof of Statistical Significance Relevant? 61 Washington Law Review 1333 (1986).
- 105. Koutros, S. et al., An Update of Cancer Incidence in the Agricultural Health Study, 52 J. Occupational & Envtl. Med. 1098 (2010).
- 106. Landgren, O. et al., Pesticide exposure and risk of monoclonal gammopathy of undetermined significance in the Agricultural Health Study, 113 Blood 6386 (2009).
- 107. Lash, T., Bias analysis applied to Agricultural Health Study publications to estimate non-random sources of uncertainty, 2 J. Occupational Med. Toxicology 1 (2007).
- 108. Lecoutre, M. et al., Even statisticians are not immune to misinterpretations of Null Hypothesis Significance Tests, 38 Intl J. Psychology (2003).
- 109. Lee, W. et al., Non-Hodgkin's Lymphoma Among Asthmatics Exposed to Pesticides, 111 Intl. J. Cancer 298 (2004).
- 110. Lew, M., Bad statistical practice in pharmacology (and other basic biomedical disciplines): you probably don't know P, 166 British J. Pharmacology 1559 (2012).

- 111. Lukaszewicz-Hussain, A., Role of Oxidative Stress in Organophosphate Insecticide Toxicity-Short Review, 98 Pesticide Biochemistry and Physiology 145 (2010).
- Maeda, K. et al., Low Back Pain Related to Bowing Posture of Greenhouse Farmers, 9 J. Human Ergology 117 (1980).
- 113. Matthews, J. & D. Altman, Statistics Notes- Interaction 2: compare effect sizes not P values, 313 British J. Pharmacology 808 (1996).
- 114. McDuffie, H. et al., Non-Hodgkin's Lymphoma and Specific Pesticide Exposures in Men: Cross-Canada Study of Pesticides and Health, 10 Cancer Epidemiology, Biomarkers & Prevention 1155 (2001).
- 115. Melbye, M. et al., Testbook of Cancer Epidemiology 669-693 (H.O. Adami et al. eds., 2nd ed. 2008).
- Milham, S., Leukemia and Multiple Myeloma in Farmers, 94 Am. J. Epidemiology 307 (1971).
- 117. Mink, P. et al., *Epidemiologic studies of glyphosate and cancer: A review*, 63 Reg. Toxicology and Pharmacology 440 (2012).
- 118. Mink, P. et al., *Epidemiologic Studies of Glyphosate and Non-Cancer Health Outcomes: A Review*, 61 Regulatory Toxicology Pharmacology 172 (2011).
- 119. Mittal, Y., *Homogeneity of Subpopulations and Simpson's Paradox*, 86 J. American Statistical Association 167 (1991).
- 120. Montgomery, M. et al., *Characteristics of non-participation and potential for selection bias in a prospective cohort study*, 53 Am. J. Indus. Med. 486 (2010).
- 121. Morabia, A. et al., Smoking Prevalence in Neighborhood and Hospital Controls: Implications for Hospital-Based Case-Control Studies, 49 J. Clinical Epidemiology 885 (1996).
- 122. Morton, L. et al., Etiologic heterogeneity among non-Hodgkin lymphoma subtypes: the InterLymph non-Hodgkin lymphoma subtypes project, 48 J. National Cancer Institute Monographs 130 (2014).
- 123. Myers, J. et al., Concerns over Use of Glyphosate-Based Herbicides and Risks Associated with Exposures: A Consensus Statement, 15 Envtl. Health 19 (2016).

- 124. National Cancer Institute, Cancer Stat Facts: Non-Hodgkin Lymphoma https://seer.cancer.gov/statfacts/html/nhl.html (accessed May 24, 2017).
- 125. Neupane, B. et al., Community controls were preferred to hospital controls in a casecontrol study where the cases are derived from the hospital, 63 J. Clinical Epidemiology 926 (2010).
- 126. Newton, M. et al., Fate of Glyphosate in an Oregon Forest Ecosystem, 32 J. Agricultural Food Chemistry 1144 (1984).
- 127. Niemann, L. et al., A Critical Review of Glyphosate Findings in Human Urine Samples and Comparison with the Exposure of Operators and Consumers, 10 J. Fur Verbraucherschutz and Lebensmittelsicherheit 3 (2015).
- 128. Nordstrom, M. et al., Occupational exposures, animal exposure and smoking as risk factors for hairy cell leukemia evaluated in a case-control study, 77 Brit. J. of Cancer 2048 (1998).
- 129. Occupational Cancer Research Centre, An Detailed Evaluation of Glyphosate Use and the Risk of Non-Hodgkin Lymphoma in the North American Pooled Project (NAPP), (June 3, 2015).
- Orsi, L. et al., Occupational exposure to pesticides and lymphoid neoplasms among men: results of a French case-control study, 66 Occupational and Envtl. Med. 291 (2009).
- 131. Pahwa, M. et al., A detailed assessment of glyphosate use and the risks of non-Hodgkin lymphoma overall and by major histological sub-types: findings from the North American Pooled Project, Occupational Cancer Research Centre (June 10, 2016).
- 132. Pahwa, M. et al., An Evaluation of Glyphosate Use and the Risk of Non-Hodgkin Lymphoma Major Histological Sub-Types in the North American Pooled Project, Occupational Cancer Research Centre (August 31, 2015).
- 133. Pahwa, M. et al., An evaluation of glyphosate use and the risk of non-Hodgkin lymphoma major histological sub-types in the North American Pooled Project (NAPP) (Sept. 21, 2015) (unpublished article).
- 134. Pahwa, M. et al., An Evaluation of Glyphosate Use and the Risks of Non-Hodgkin Lymphoma Major Histological Sub-Types in the North American Pooled Project (NAPP), Envtl. Health Persp. (2015).
- 135. Pahwa, M., The North American Pooled Project (NAPP): Pooled Analyses of Case-Control Studies of Pesticides and Agricultural Exposures, Lymphohematopoietic Cancers and Sarcoma, BMJ (2014).

- 136. Pearce, N. et al., IARC Monographs: 40 Years of Evaluating Carcinogenic Hazards to Humans. 123 Envtl. Health Persp. 507 (2015).
- 137. Pearce N. et al, Malignant Lymphoma and Multiple Myeloma Linked with Agricultural Occupations in a New Zealand Cancer Registry-Based Study, 121 Am. J. Epidemiology 225 (1985).
- 138. Perry, A. et al., Non-Hodgkin lymphoma in the developing world: review of 4539 cases from the International Non-Hodgkin Lymphoma Classification Project, 101 Haematologica 1244 (2016).
- 139. Poole, C., Beyond the Confidence Interval, 77 American J. Public Health 195 (1987).
- 140. Portier, C. et al., *Differences in the carcinogenic evaluation of glyphosate between the International Agency for Research on Cancer (IARC) and the European Food Safety Authority (EFSA)*, 70 J Epidemiology Community Health 741 (2016).
- 141. Presutti, R. et al., Pesticide exposures and the risk of multiple myeloma in men: An analysis of the North American Pooled Project, Int'l J. Cancer (2016).
- 142. Riihimaki, H., Low-back pain, its origin and risk indicators, 17 Scandinavian J. Work Env't. Health 81 (1991).
- 143. Rinsky, J. et al., Assessing the Potential for Bias From Nonresponse to a Study Followup Interview: An Example From the Agricultural Health Study, American Journal of Epidemiology (2017).
- 144. Rose, G., Sick Individuals and Sick Populations, 14 Intl. J. Epidemiology 32 (1985).
- Rozeboom, W., The Fallacy of the Null-Hypothesis Significance Test, 57 Psychological Bulletin 416 (1960).
- 146. Ruano-Ravina, A. et al., Population-based versus hospital-based controls: are they comparable?, 22 Gaceta Sanitaria 609 (2008).
- 147. Sadetzki, S. et al., The limitations of using hospital controls in cancer etiology one more example for Berkson's bias, 18 European J. Epidemiology 1127 (2003).
- 148. Salsburg, D., *The Religion of Statistics as Practiced in Medical Journals*, 39 The American Statistician 220 (1985).

- 149. Samuels, M., Simpson's Paradox and Related Phenomena, 88 J. American Statistical Association 81 (1993).
- 150. Schinasi, L. & M. Leon, Non-Hodgkin Lymphoma and Occupational Exposure to Agricultural Pesticide Chemical Groups and Active Ingredients: A Systematic Review and Meta-Analysis, 11 Int'l J. Envtl. Res. & Public Health 4449 (2014).
- Schumacher, M., Farming Occupations and Mortality from Non-Hodgkin's Lymphoma in Utah, 27 J. Occupational Med. 580 (1985).
- 152. SEER Cancer Statistics Review, 1975-2013. Table 19.7: Non-Hodgkin Lymphoma, Incidence and mortality rates by age. 2016; https://seer.cancer.gov/archive/csr/1975_2013/results_merged/sect_19_nhl.pdf
- 153. Shamseer, L. et al., Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation, 349 BMJ (2015).
- 154. Simpson, E., *The Interpretation of Interaction in Contingency Tables*, 13 J. Royal Statistical Society. Series B (Methodoligical) 238 (1951).
- 155. Solomon, K. et al., Human Health and Environmental Risks from the Use of Glyphosate Formulations to Control the Production of Coca in Colombia: Overview and Conclusions, 72(15-16) J. Toxicology Envtl. Health A 914 (2009).
- 156. Solomon, K., Glyphosate in the General Population and in Applicators: A Critical Review of Studies on Exposures, 46 Critical Rev Toxicology 21 (2016).
- 157. Sorahan, T., Multiple Myeloma and Glyphosate Use: A Re-Analysis of US Agricultural Health Study (AHS) Data, 12 Int'l J. Envtl. Res. & Public Health 1548 (2015).
- Stark, J. et al, Toll-like Receptor Signaling Pathway Variants and Prostate Cancer Mortality, 18 Cancer Epidemiology Biomarkers Prevention 1859 (2009).
- 159. Sterne, J., *Sifting the evidence-what's wrong with significance tests?*, 322 British Medical J. 226 (2001).
- Stroup, D. et al., Meta-analysis of Observational Studies in Epidemiology, 283 JAMA 2008 (2000).
- 161. Szklo, M. & J. Nieto, Epidemiology: Beyond the Basics 165-167 (3d ed. 2014).
- 162. Tarone, R., On the International Agency for Research on Cancer Classification of Glyphosate as a Probable Human Carcinogen, 0 European J. Cancer Prevention 1 (2016).

- 163. The International Agency for Research on Cancer [IARC], *List of Participants*, Vol. 112 (Mar. 3-10, 2015).
- 164. Thompson, B., *The "significance" crisis in psychology and education*, 33 J. Socio-Economics 607 (2004).
- Trafimow, D. & M. Marks, *Editorial*, 37 Basic and Applied Social Psychology 1 (2015).
- 166. Van Tulder, M. et al., Updated method guidelines for systematic reviews in the Cochrane Collaboration Back Review Group, 28 Spine 1290 (2003).
- 167. Varona, M. et al., Effects of Aerial Applications of the Herbicide Glyphosate and Insecticides on Human Health, 29 Biomedica 456 (2009).
- Videotaped Deposition of Aaron Earl Blair, Ph.D., In Re: Roundup Products Liability Litigation, No. 16-md-02741-VC (N.D. Cal. Mar. 20, 2017).
- 169. Waddell, B. et al., Agricultural use of organophosphate pesticides ad the risk of non-Hodgkin's lymphoma among male farmers (United States), 12 Cancer Causes and Control 509 (2001).
- Walker, A., Reporting the Results of Epidemiologic Studies, 76 American J. Public Health 556 (1986).
- 171. Walker, E. et al., *Meta-analysis: Its strength and limitations*. 75 Cleveland Clinic Journal of Medicine 53 (2008).
- 172. Weber, J. et al., Étude de l'exposition professionnelle des travailleurs forestiers exposés au glyphosate, Centre de Toxicologie du Québec (1988).
- 173. Weichenthal, S. et al., A Review of Pesticide Exposure and Cancer Incidence in the Agricultural Health Study Cohort, 118 Envtl. Health Persp. 1117 (2010).
- 174. Weisenburger, D., Environmental Epidemiology of Non-Hodgkin's Lymphoma in Eastern Nebraska. 18 Am J. Indus. Med 303 (1990).
- Weisenburger, D., Lymphoid Malignancies in Nebraska: A Hypothesis, 70 Neb. Med. J. 300 (1985).
- 176. Weisenburger, D., Pathological Classification of Non-Hodgkin's Lymphoma for Epidemiological Studies, 52 Cancer Res 5456s (1992).

- 177. Wigle, D. et al., Mortality Study of Canadian Male Farm Operators: Non-Hodgkin's Lymphoma Mortality and Agricultural Practices in Saskatchewan, 82 J. Nat'l Cancer Institute 575 (1990).
- 178. Wiklund, K. et al., *A Swedish cancer-environment register available for research*, 7 Scandinavian J. Work Env't & Health 64 (1981).
- 179. Williams, G. et al., *Glyphosate Rodent Carcinogenicity Bioassay Expert Panel Review*, 46 Crit Rev Toxicology 44 (2016).
- 180. Williams, R. et al., Associations of Cancer Site and Type With Occupation and Industry From the Third National Cancer Survey Interview, 59 J. Nat'l Cancer Inst. 1147 (1977).
- 181. Woodburn, A., *Glyphosate: production, pricing and use worldwide*, 56 Pest Management Science 309 (2000).
- 182. World Health Organization, *Epidemiology*, <u>http://www.who.int/topics/epidemiology/en/</u> (accessed May 22, 2017).
- 183. Yates, W. et al., *Drift of Glyphosate Sprays Applied with Aerial and Ground Equipment*, 26 Weed Science 597 (1978).
- 184. Zahm, S. et al., A Case-Control Study of Non-Hodgkin's Lymphoma and the Herbicide 2,4-Dichlorophenozyacetic Acid (2,4-D) in Eastern Nebraska, 1 Epidemiology 349 (1990).
- 185. Zhang, C. et al., *Health effect of agricultural pesticide use in China: implications for the development of GM crops*, Scientific Reports (2016).