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TITLE

An evaluation of glyphosate use and the risk of non-Hodgkin lymphoma major histological sub-types in the North American Pooled Project (NAPP)

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WHAT THIS PAPER ADDS

- Exposure to glyphosate, a broad-spectrum and frequently used herbicide, may be associated with non-Hodgkin lymphoma (NHL). Little is known about how risks may differ by glyphosate exposure levels and NHL sub-types.
- To address this research gap, this analysis integrated detailed, self-reported glyphosate use information with assessments of NHL risk overall and by major histological sub-type using pooled data from 1690 NHL cases and 5131 controls from the U.S. Midwest and Canada.
- Subjects who ever used glyphosate had elevated odds ratios for NHL overall and for all subtypes except follicular lymphoma. Significant or nearly significant risks of NHL overall were observed for >2 days per year (OR=2.42, 95% CI: 1.48, 3.96) and >7 lifetime days (OR=1.55, 95% CI: 0.99, 2.44) of glyphosate use, with some differences in risk by sub-type.
- Glyphosate use may be associated with elevated NHL risk. Although the pattern of risks was not clear across exposure categories, these findings from a large dataset offer more precision than results from previous studies.

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ABSTRACT (249)

Objectives: Glyphosate is the most frequently used herbicide worldwide. Some epidemiological studies have found positive associations between glyphosate exposure and non-Hodgkin lymphoma (NHL). This study aimed to evaluate NHL risk overall and by major histological sub-type using detailed glyphosate use metrics.

Methods: The NAPP, composed of pooled case-control studies from the U.S. and Canada, includes NHL cases (N=1690) and controls (N=5131) who provided information on pesticide use. Cases (follicular lymphoma [FL], diffuse large B-cell lymphoma [DLBCL], small lymphocytic lymphoma [SLL], other) from cancer registries and hospitals were frequency-matched to population-based controls. Logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (CI) by ever/never, duration, frequency, and lifetime days of glyphosate use. Models were adjusted for age, sex, location, proxy respondent, family history of lymphohematopoietic cancer, and personal protective equipment.

Results: Cases who ever used glyphosate (N=133) had a significantly elevated risk of NHL overall (OR=1.43, 95% CI: 1.11, 1.83). Subjects who used glyphosate for >3.5 years had increased SLL risk (OR=1.98, 95% CI: 0.89, 4.39) and those who handled glyphosate for >2 days/year had significantly elevated odds of NHL overall (OR=2.42, 95% CI: 1.48, 3.96) and DLBCL (OR=2.83, 95% CI: 1.48, 5.41). There were suggestive increases (p-trend ≤0.02) in risk of NHL overall, FL, and SLL with more days/year of glyphosate use.

Conclusions: Glyphosate use may be associated with increased NHL risk. Although risk differences by histological sub-type were not consistent across glyphosate use metrics, the NAPP's large sample size yielded more precise results than possible in previous studies.

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INTRODUCTION

Glyphosate [N-(phosphonomethyl)glycine] is a broad-spectrum herbicide that is one of the most frequently applied pesticides in the world. First developed commercially for agricultural use in the early 1970s, glyphosate quickly became a popular chemical; as of 2012, it was used in more than 750 products with an annual global production volume exceeding 600,000 tonnes (1). In the U.S., the highest levels of agricultural use occur in the mid-west on crops such as corn, soybeans, and wheat (2). These crops are also examples of the many different types of plants that have been genetically engineered to be resistant to glyphosate.

Commented [AB1]: Check to make sure all these crops have genetically modified seed on the market. I do not think that is the case for wheat yet. I think rice was to be available this year.

Glyphosate has been examined as a potential risk factor for lymphatic and hematopoietic cancers including non-Hodgkin lymphoma (NHL). In Canada, NHL ranks as the fifth most incident cancer in males following neoplasms of the prostate, colorectum, lung, and bladder (3). In the American mid-west NHL accounts for an unusually large number of cancers in agricultural areas where populations tend to have lower cancer rates overall (4). The causes of NHL are largely unknown (Hartge P, Wang SS, Bracci PM, Devesa SS, Holly EA. Non-Hodgkin Lymphoma. In Cancer epidemiology and Prevention, 3rd Edition. Shottenfeld D, Fraumeni JF, Jr. (Eds.). Oxford University Press, NY, Ny, 2006), pp. 898-918.). ~~Male~~ NHL has been associated with farming (Blair et al., 1992)~~gender, advanced age, and immune suppression are the best-known risk factors. Agricultural exposures are hypothesized to be involved in the development of NHL~~ and this has prompted studies focused on pesticides.

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In the 1980s and 1990s Four~~four~~ population-based case-control studies were conducted in the U.S. mid-west and six Canadian provinces to examine putative associations between agricultural exposures and pesticides and the risk of NHL. Individual study results showed positive associations between self-reported glyphosate use and NHL risk, although there was variation in the magnitude and statistical significance of risks between studies. In an analysis of the Canadian study the odds ratio [OR] for NHL was 1.26 (95% confidence interval [CI]: 0.87, 1.80) for the use of glyphosate with adjustment for age and province (N=51 exposed cases) (5). The OR was slightly higher from~~A similar risk estimate was found in a separate analysis of men who reportedly ever handled glyphosate in Iowa and Minnesota (6) and higher odds were calculated in~~ a pooled analysis that included 36 exposed male cases from Iowa, Minnesota, Kansas, and Nebraska (logistic regression OR=2.1, 95% CI: 1.1, 4.0 adjusted for age, study site, and other pesticides) (7).

Other studies involving glyphosate exposure and NHL risk have been conducted and many were included in a systematic literature review and meta-analysis of epidemiological studies of pesticide exposure and NHL risk (8). This meta-analysis found~~demonstrated~~ that glyphosate exposure was significantly associated with ~~elevated risks of~~ NHL ~~overall~~ (meta risk ratio [mRR]=1.5, 95% CI: 1.1-2.0, 6 papers). The OR for ~~and~~ B cell lymphoma, ~~(mRR=2.0, 95% CI: 1.1-3.6, 2 papers),~~ a commonly diagnosed NHL sub-type in the regions from which included studies were drawn, was (mRR=2.0, 95% CI: 1.1-3.6, 2 papers). ~~However, meta-analyses were based on a small number of included papers and each study contained low numbers of exposed subjects. Only one included study (9) reported risks by NHL sub-type and only three (5, 9, 10) reported risks by glyphosate exposure level.~~

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A comprehensive evaluation of glyphosate carcinogenicity was recently undertaken by the International Agency for Research on Cancer (IARC) (11). This review of mechanistic, animal, and epidemiological evidence classified~~led to the evaluation of~~ glyphosate as a "probable" (group 2A) carcinogen for NHL based on limited evidence in humans and sufficient evidence in experimental animals. The assessment of limited evidence from epidemiological studies was based on case-control studies~~primarily focused on evidence from case-control studies of occupational glyphosate exposure~~ in the U.S., Canada, and Sweden that reported increased risks of NHL that persisted after adjustment for other pesticides. No association between NHL and use of glyphosate was seend in the Agricultural Health Study (AHS), a large prospective study of farmers and commercial pesticide applicators in the U.S.(11). In bioassays, g~~G~~lyphosate was was associated with renal tubule carcinoma, pancreatic islet-cell adenoma, and skin tumors (11). ~~able to cause different cancers in mice, postulated to occur through initiation and promotion~~. Mechanistic and other data supported the "probable" carcinogen conclusion by providing strong evidence for genotoxicity and oxidative stress, both of which are mechanisms of action that can take place in humans (11).

There are several research gaps that need to be addressed in order to better understand the role and impact of glyphosate exposure on the development of~~cancer risk, specifically~~ NHL. Individual studies often have limited power for glyphosate exposure, lack evaluation of NHL by sub-type, and do not adjust risk estimates for other pesticides and other exposures (8, 11). M~~Additionally, m~~ost studies do not have quantitative exposure data needed to perform more sensitive epidemiological analyses and few have addressed potential effect modifiers to identify if glyphosate exposure has a different impact on NHL risk under certain circumstances. Schinasi and Leon (8) ~~have~~ suggested pooling studies ~~as an attempt~~ to overcome some of these limitations. ~~;~~ AGRICOH, a consortium of agricultural cohorts, is a global effort of this kind (12). Other existing studies can be similarly leveraged for enhancing our knowledge and understanding about glyphosate exposure and NHL risk.

The North American Pooled Project (NAPP) is a pooled resource of population-based case-control studies previously conducted in the U.S. and Canada. The primary objective of this effort~~study~~ was to provide larger numbers for more detailed analyses of possible relationships between NHL and pesticide use. In this paper we evaluate the association between glyphosate use and the risk of NHL among men and women in the NAPP. ~~in the North American Pooled Project (NAPP), a pooled resource of population-based case-control studies previously conducted in the U.S. and Canada. NHL risk was assessed overall and by histological sub-type using detailed self-reported glyphosate use information and adjustment for other pesticides and possible risk factors. The secondary aim of this study was to examine the effects of personal protective equipment (PPE) on the association between glyphosate use and NHL risk overall.~~

METHODS

Study population

The NAPP is a ~~large and newly established resource of~~ pooling of~~ed~~ data from four previously conducted case-control studies of men and women who were diagnosed with soft tissue sarcoma and lymphatic

and hematopoietic cancers, including NHL, in the U.S. and Canada. NHL cases were recruited from cancer registries and hospitals during the 1980s in four states (Iowa, Minnesota, Kansas, and Nebraska) and between 1991 and 1994 in six provinces (Quebec, Ontario, Manitoba, Saskatchewan, Alberta, and British Columbia). Cases were 19 years of age or older in all jurisdictions (I think the 19 age cut is correct, just check each study to make sure). Controls were selected from the general population in each state or province. Selection procedures varied by study but included ~~by~~ random digit dialing, voters' lists, health insurance records, Medicare listings for those older than 65 years, and from state mortality files for deceased cases. Controls were matched to NHL cases in each state/province on the basis of age (±2 or 5 years). In some states, cases and controls were matched on the additional variables of sex (Nebraska), race (Nebraska), and vital status and year of death for deceased cases (Iowa, Minnesota, Nebraska, Kansas). All states and provinces included men; women were only included in Nebraska. Deceased cases and controls were eligible for inclusion in the U.S. ~~case-control~~ studies. The Canadian study only considered alive cases and controls. The present analysis used data from both men and women and from alive and deceased NHL cases (N=1690) and controls (N=5131).

Data collection

Participants, or surrogates, provided detailed information about demographic characteristics, pesticide use, agricultural exposures, and exposure to other known or suspected NHL risk factors including lifestyle, medical and occupational history. Interviewer-administered questionnaires were conducted by telephone (Kansas and Nebraska) or in person (Iowa and Minnesota) with cases and controls or their surrogates if subjects were deceased or too ill to respond themselves. In Canada, all cases and controls were mailed a questionnaire to complete themselves (or by their surrogates). Participants who indicated that they had used pesticides were subsequently interviewed over the telephone for details about their pesticide exposure. The Canadian questionnaire was modified from the telephone interview questionnaires that were used in Kansas and Nebraska. The questionnaires from all case-control studies were very similar since they shared a common research objective, involved overlapping groups of principal investigators, and were developed during the same time period. This made the data highly amenable to pooling ~~at present~~. The complete methodologies of each case-control study have been described by Cantor et al., 1992 (Iowa and Minnesota) (6), Hoar et al., 1986 (Kansas) (13), Zahm et al., 1990 (Nebraska) (14), and McDuffie et al., 2001 (Canada) (5).

The NAPP contains extensive information about pesticide use and agricultural exposures reported by cases and controls. In general, pesticide classifications are available from~~data were collected beginning with the~~ broad~~est~~ categories (e.g. occupations with potential pesticide exposure), to ~~followed by~~ major chemical classes (e.g. herbicides), to chemical groups (e.g. phenoxy herbicides), and finally individual compounds (e.g. 2,4-D). For each individual compound reported, information was collected for dichotomous use (ever/never), duration of use (number of years), and frequency of personal handling (number of days/year). Duration data were not collected in Kansas and frequency information was not collected in Iowa, Minnesota, and Kansas~~ and Kansas~~. In Kansas participants were asked to open-endedly recall the details of their pesticide use whereas in all other jurisdictions subjects were prompted by a list of chemicals and their trade names. Participants were also asked to report if they had used any

type of PPE in general (Nebraska and Canada) and with herbicides (Iowa, Minnesota, and Kansas) and specific individual pesticides (Iowa and Minnesota).

Assessment of glyphosate use

Self-reported glyphosate use was examined using several different metrics: dichotomous, duration, frequency, and lifetime days (derived by multiplying number of years used with number of days/year handled). Ordinal categories were created for duration, frequency, and lifetime days analyses based on the median of glyphosate used/handled in controls. Since information about duration of glyphosate use was not collected in Kansas, cases and controls from Kansas were omitted from duration analyses. Similarly, cases and controls from Iowa, Minnesota, and Kansas were excluded from frequency and lifetime days analyses owing to the lack of frequency data collected in these states. Participants who had missing or unknown glyphosate use information, but who were from jurisdictions where glyphosate use information was collected, were coded as "never used" in dichotomous analyses. ; fFor duration and frequency analyses, missing values were assigned based on the median duration or frequency by state/province, age, and NHL sub-type (simple imputation, rounded to the nearest whole number). Subjects who reported that they used glyphosate were coded as "ever used" or used/handled for the number of years and days/year that they had reported. Continuous analyses were also conducted in order to determine possible trends and changes in risk for every 5 years, 5 days/year, and 10 lifetime days of glyphosate use.

NHL classification

NHL cases in these s tudies were diagnosed at different time periods during the 1980s and 1990s. NHL cases were classified in Iowa, Minnesota, and Nebraska according to the Working Formulation (15, 16); in Kansas and Quebec by the International Classification of Diseases for Oncology First Edition (ICD-O-1) (1976) (17); and in Ontario, Manitoba, Saskatchewan, Alberta, and British Columbia by ICD-O-2 (1990) (18). The original histology codes used in each study were revisited to classify NHL cases using a single or similar scheme for the NAPP. We used ICD-O-1 to code NHL overall and sub-types in the NAPP since histological sub-types were classified in all jurisdictions according to ICD-O-1. These sub-types were follicular lymphoma (FL), diffuse large B cell lymphoma (DLBCL), small lymphocytic lymphoma (SLL), and other. The "other" sub-type included all cases whose histologies were unknown or not FL, DLBCL, or SLL. Pathology reviews were conducted on 84% of Canadian cases (5), 87% of Kansas cases (13), and for all interviewed cases in Iowa and Minnesota (6) and Nebraska (14) in order to validate NHL diagnoses.

Power and sample size

A power and sample size analysis was conducted using the U.S. National Cancer Institute's (NCI) Power Version 3.0 program (19, 20) by inputting the following parameters: number of controls = 5131; number of cases = 1690; control:case ratio = 3; type I error (two-sided) = 0.05; type II error = 0.2; probability of NHL at baseline = 0.04 (21).

Of all 5131 controls available in the NAPP, 244 (4.76%) reported that they ever used glyphosate. A 5% prevalence of pesticide exposure in controls corresponds to aperfect power of {1.00} to detect ORs of

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2.00 or higher and a~~, but lower~~ power of~~(~~0.4~~6~~) to detect an OR of 1.25. Given that approximately 5% of controls reported ever being exposed to glyphosate, at a power level of 0.80, a total of 1103 NHL cases would be required to detect an OR of 1.50 (Appendix 1). The numbers of NHL cases and controls in the NAPP appear to be suitable to~~for~~ detecti~~ng~~ low to moderate relative risks associated with glyphosate exposure in this population.

Statistical analyses

Descriptive statistics were used to characterize the study population and identify potentially confounding variables. Based on previously published literature, a priori possible confounders included age, sex, state/province, use of a proxy respondent (5, 6, 22), lymphatic or hematopoietic cancer in a first-degree relative (23), and diagnosis with select medical conditions related to immune suppression (any allergies, food allergies, drug allergies, asthma, hay fever, mononucleosis, arthritis, or tuberculosis; ever received chemotherapy or radiation) (24-26). History of living or working on a farm or ranch was also evaluated as a potential confounder.

It was possible that the use of other pesticides in the NAPP may confound the relationship between glyphosate use and NHL risk. A two-pronged approach was used to identify potentially confounding by other pesticides. First, a correlation matrix of pooled data was produced to determine the presence and extent of correlation between glyphosate and each individual herbicide, insecticide, and fungicide reportedly used by NAPP subjects. Second, previously published articles based on the individual case-control studies comprising the NAPP were searched to identify any positive or significant relationships between individual pesticides and NHL risk, as would be required for confounding to occur. Pesticides that were most strongly correlated with glyphosate (defined in this study as Spearman coefficients ≥0.35 and Cohen's Kappa value ≥0.30) and that were significantly or strongly associated with NHL in previous studies were evaluated as confounders. These were the herbicides 2,4-D (2,4-dichlorophenoxyacetic acid) (5, 6) and dicamba (5, 7), as well as the insecticide malathion (5, 7).

The use of PPE with glyphosate could theoretically modify NHL risk by reducing subjects' exposure to glyphosate. Although such information was sought in some studies, data were on a sizable~~There was a large~~ proportion of the study subjects~~missing data for the more specific variables of PPE used for herbicides and glyphosate~~ and~~. Therefore,~~ effect modification analyses could only be conducted using involving any lifetime PPE use were conducted using data reported by~~ cases and controls from~~in~~ Nebraska and Canada. Any lifetime PPE usage was also included as a confounding variable in models where it was not evaluated as a possible effect modifier.

Unconditional multiple logistic regression was performed using the LOGISTIC procedure of~~on~~ the SAS 9.2 statistical software package (SAS Institute, Cary, North Carolina) to calculate pooled ORs and 95% CIs for associations between glyphosate exposure (dichotomous, duration, frequency, lifetime days, and as a continuous variable) and the risk of NHL overall and by histological sub-type (FL, DLBCL, SLL, and other). Primary logistic regression models (OR[a]) contained the following variables as confounders: age, sex, state/province, lymphatic or hematopoietic cancer in a first-degree relative, use of a proxy respondent, and use of any PPE. Secondary logistic regression models (OR[b]) contained the covariates in the primary

model plus reported use of the pesticides 2,4-D, dicamba, and malathion. Medical conditions and history of living or working on a farm or ranch were found not to~~did not appear to play a role in~~ confound~~ing~~ the relationship between glyphosate use and NHL risk and were not included in the models. Use-response trends for duration, frequency, and lifetime days analyses were deemed to be statistically significant if the two-sided p-value for the ordinal glyphosate use category was ≤0.05. The reference group for all analyses was subjects who never used glyphosate. There was a small proportion of subjects (N=175, 2.57% of all participants) with missing age values; these were imputed based on state/province- and case/control-specific means rounded to the nearest whole number.

Sensitivity tests were conducted by excluding proxy respondents from the main analyses. Proxy respondents were excluded from the analyses of PPE as a potential effect modifier in order to minimize the possibility of bias. For the effect modification analyses, glyphosate use was classified dichotomously and by duration, frequency, and lifetime days and overall NHL risks were calculated using logistic regression models adjusted for age, sex, state/province, lymphatic or hematopoietic cancer in a first-degree relative, and use of 2,4-D, dicamba, and malathion.

Ethics approval

Approval to conduct this analysis was obtained from the University of Toronto Health Sciences Research Ethics Board (#25166) and an ethics exemption was obtained from the U.S. NCI Office of Human Subjects Research (#11351). Individual studies had obtained human subjects approval prior to collection of the data and a~~A~~ll participants provided informed consent before taking part in the studies included in the NAPP analyses.

RESULTS

Characteristics of NHL cases and controls

A total of 1690 NHL cases and 5131 controls were available in the NAPP for analysis. All participants were included in analyses that encompassed proxy respondents. For assessments involving the duration of glyphosate use, 1520 cases and 4183 controls were available; in frequency and lifetime days analyses, 898 cases and 2938 controls were included. The numbers of cases and controls available for the sensitivity analyses excluding proxy respondents were smaller~~lower~~ (Figure 1).

The most frequently diagnosed histological sub-type was DLBCL (38.28%), followed by FL (27.69%), other (23.91%), and SLL (10.12%) (Table 1). Nebraska yielded the highest proportion of cases (22.78%) and controls (27.91%) compared to other states and provinces. The average ages of cases and controls were 62.72 and 61.66 years, respectively. The majority of subjects were male. A similar proportion of proxy respondents were used by cases and controls. Cases were more than twice as likely to report that a first-degree relative was diagnosed with lymphatic or hematopoietic cancer compared to controls (OR=2.13, 95% CI: 1.69, 2.67). Medical history variables were evaluated as potential confounders but they did not have an appreciable impact on adjusted ORs in the main analyses (OR^a and OR^b) and were thus excluded from logistic regression models.

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Missing glyphosate use data

There were 7 cases with missing values for the number of years of glyphosate used and 13 cases with missing values for the number of days/year of glyphosate handled in the jurisdictions where duration and frequency of glyphosate use data were collected. The median values for the number of years of glyphosate use in cases all subjects with missing values ranged from 0-2 based on jurisdiction, NHL sub-type, and age. The median value for days/year for subjects with missing information was 0 (zero).

Glyphosate use and NHL risks overall and by major histological sub-type

Overall, 113/1690 cases (6.69%) and 244/5131 (4.76%) controls reported that they had used glyphosate at any point in their lifetime. There was a significant association between glyphosate use and the risk of NHL overall (OR^a=1.43, 95% CI: 1.11, 1.83) (Table 2). Risks were elevated for most NHL sub-types but the magnitude of risk differed by sub-type. The greatest risk was observed in SLL cases (OR^a=1.77, 95% CI: 0.98, 3.22) and the lowest risk was found for FL (OR^a=1.00, 95% CI: 0.65, 1.54). Similar and significant excesses were observed for DLBCL (OR^a=1.60, 95% CI: 1.12, 2.29) and other (OR^a=1.66, 95% CI: 1.04, 2.63) sub-types. Associations were attenuated and no longer statistically significant when the model represented by OR^a was further adjusted for ever use of 2,4-D, dicamba, and malathion (OR^b). The odds of SLL did not change even after adjusting risk estimates for these three pesticides.

When glyphosate use was examined by duration (Table 2), there was a general inverse trend in risks except for cases of SLL, where the odds increased with longer duration of glyphosate use (OR^a=1.98, 95% CI: 0.89, 4.39 for >3.5 years versus OR^a=1.49, 95% CI: 0.63, 3.58 for >0 and ≤3.5 years) and this trend was of borderline statistical significance (p-trend for OR^a=0.08). Additional adjustment for the chemicals 2,4-D, dicamba, and malathion generally resulted in attenuated risk estimates (OR^b) compared to models unadjusted for these pesticides (OR^a) except for SLL, for which the addition of these agents in logistic regression models had no substantial effect on risk (e.g. for >3.5 years of glyphosate use, OR^b=1.94, 95% CI: 0.79, 4.80).

In contrast to duration of glyphosate use, a more consistent pattern of NHL risk emerged in association with frequency of glyphosate personally handled (Table 2). Subjects who handled glyphosate for >2 days/year had NHL risks that were approximately two times the odds observed in participants who handled glyphosate for >0 and ≤2 days/year. This finding was consistent for NHL overall and all sub-types. Elevated risks in the highest category (>2 days/year) were significant for NHL overall (OR^a=2.42, 95% CI: 1.48, 3.96) and DLBCL (OR^a=2.83, 95% CI: 1.48, 5.41) compared to subjects who did not handle glyphosate at all. Significant trends in risk were also found for NHL overall (p-trend for OR^a=0.02) and DLBCL (p-trend for OR^a=0.04). For NHL overall and DLBCL, ORs associated with handling glyphosate for >2 days/year were attenuated but remained statistically significant even after adjusting for the use of 2,4-D, dicamba, and malathion. The pattern of increased risks with more frequent glyphosate handling was still apparent for NHL overall and all sub-types although trends were no longer statistically significant upon adjusting for these three pesticides.

The analysis of lifetime days, derived from the product of number of years used and days/year handled, generally showed risk increases for NHL overall and most sub-types (except “other”) in association with

a greater number of lifetime days of glyphosate use (Table 2). These trends were significant for NHL overall (p-trend for OR[a]=0.02), FL (p-trend for OR[a]=0.02), and SLL (p-trend for OR[a]=0.01). There were elevated risks of NHL among participants who had used glyphosate for >7 lifetime days; this was most pronounced for SLL (OR[a]=2.13, 95% CI: 0.76, 5.96). Adjusting for 2,4-D, dicamba, and malathion attenuated risks compared to odds that were unadjusted for these chemicals; however, the general pattern of increased risks remained intact and in some cases (i.e. SLL), was still statistically significant (p-trend for OR[b]=0.03).

Sensitivity analysis

Proxy respondents were used for deceased cases and controls and for alive cases who were too ill to respond to the case-control study questionnaires themselves. The use of proxy respondents might have introduced misclassification of glyphosate use. To account for this possibility, glyphosate use data provided by proxy respondents were excluded from the main analysis presented in Table 2. This generally resulted in reduced ORs compared to risks that included data provided by both self- and proxy respondents, with little effect on the width of confidence intervals and the same general patterns of risks for dichotomous, duration, frequency, and lifetime days analyses (Table 3). For instance, there were significant trends for lifetime days of glyphosate use and the risks of NHL overall (p-trend for OR[a]=0.04), FL (p-trend for OR[a]=0.03), and SLL (p-trend for OR[a]=0.01) (Table 3) that paralleled the trends found in the analysis of data provided by both self- and proxy respondents (Table 2).

However, there were some exceptions to this overall observation. Odds ratios for SLL mostly strengthened with the exclusion of proxy respondents in models both unadjusted for 2,4-D, dicamba, and malathion and models adjusted for these chemicals. For instance, among subjects who ever used glyphosate the risk of SLL excluding data from proxy respondents was 1.89 (OR[a], 95% CI: 1.03, 3.49) which was slightly greater than the risk of SLL based on data provided by self- and proxy respondents (OR[a]=1.77, 95% CI: 0.98, 3.22). Trends of increasing risk of SLL in association with longer duration, greater frequency and lifetime days of glyphosate use were also marginally stronger when data from proxy respondents were excluded.

Effect of PPE

Potential effect modification by PPE usage was evaluated based on data pooled from Canadian and Nebraskan participants. The association between ever glyphosate use and NHL risk overall was generally higher among subjects who reportedly used any type of PPE in their lifetime (OR=0.83, 95% CI: 0.40, 1.73) compared to subjects who never used any type of PPE (OR=0.65, 95% CI: 0.31, 1.35) (Table 4). This pattern of elevated NHL risks in subjects who ever used PPE compared to subjects who never used PPE persisted when glyphosate use was also evaluated by duration, frequency, and lifetime days. Similar to the results in Tables 2 and 3, there were inverse associations between the duration of glyphosate use and NHL risk and positive (increasing) associations between frequency and lifetime days of glyphosate use and NHL risk, regardless of PPE use status. There were many subjects with unknown or missing PPE use information and they were separately modeled in order to reduce the possibility of analyzing

misclassified PPE use data. Risks were high and unstable in this latter group due to the small number of subjects in each glyphosate usage category.

DISCUSSION

The objective of this study was to evaluate potential associations between glyphosate use and NHL risk in the NAPP, a large pooled dataset with detailed information about glyphosate use reported by 1690 NHL cases and 5131 controls. Glyphosate use was associated with elevated NHL risk, a finding that was consistent with previous analyses. Odds somewhat differed by histological sub-type, although there wasn't a consistent pattern across glyphosate use metrics. The novelty of this analysis and increased precision of risk estimates compared to smaller individual studies were major strengths. Yet, the limitations of this study illustrate the need for more research that can better characterize the relationship between glyphosate exposure and the development of NHL.

This report confirms previous analyses indicating increased risks of NHL in association with glyphosate exposure. The odds of NHL for glyphosate use was 1.43 (OR^a, 95% CI: 1.11, 1.83), a value that was situated approximately in between the risks observed in earlier analyses of the Canadian study (OR=1.26, 95% CI: 0.87, 1.80, adjusted for age and province, N=51 exposed cases) (5) and the three pooled U.S. studies (logistic regression OR=2.1, 95% CI: 1.1, 4.0, adjusted for age, study site, and other pesticides, N=36 exposed cases) (7). Further adjusting OR^a for the pesticides 2,4-D, dicamba, and malathion resulted in an attenuated risk of NHL overall in the NAPP (OR^b=1.13, 95% CI: 0.84, 1.51). De Roos et al. (2003) (7) used a more conservative approach, a hierarchical regression model, for assessing NHL risk in the three U.S. pooled case-control studies and found that this reduced the odds of NHL overall (OR=1.6, 95% CI: 0.9, 2.8, adjusted for age, study site, and other pesticides). A statistically significant excess of NHL was found in association with more than 2 days per year of use (OR=2.12, 95% CI: 1.20, 3.73) (5) in the Canadian study, a finding that was in agreement with our analogous pooled risk estimate for NHL (OR^a=2.42, 95% CI: 1.48, 3.96).

Our results are also aligned with findings from epidemiological studies of other populations that found an elevated risk of NHL for glyphosate exposure and with a greater number of days/year of glyphosate use (9), as well as a meta-analysis of glyphosate use and NHL risk (8). From an epidemiological perspective, our results were supportive of the IARC evaluation of glyphosate as a probable (group 2A) carcinogen for NHL (11).

The large sample size of the NAPP was conducive to analyzing NHL risks with different metrics of glyphosate use. Evaluations of dichotomous glyphosate use showed nearly universal increases in risks of NHL overall and by sub-type, but results were more varied upon further examination by duration, frequency, and lifetime days. The odds of NHL, overall and by sub-type, were higher among subjects who reportedly used glyphosate more often in a year or who had greater cumulative use in their lifetime compared to unexposed subjects. Subjects who used glyphosate reported mostly initiating its use in the year 1980. Glyphosate was used by cases and controls for an average of 5 years and handled for an average of 5 days/year. The short duration of use made it challenging to calculate risks associated with longer-term usage, although the mean frequency of handling was typical of how often farmers

reportedly apply glyphosate to agricultural crops (27). For the days/year and lifetime days analyses some trends and risks were statistically significant while others were not, likely due to the lack of sufficient numbers of exposed cases for some sub-types.

There were some differences in risks by sub-type but these were not consistent between the different glyphosate use metrics and were unlikely to be statistically significant. For example, the significant trends observed for lifetime days of glyphosate use and the risks of NHL overall, FL, and SLL were not present for the frequency analysis, where significant trends were only found for NHL overall and DLBCL. In the duration analysis an upward trend was observed for SLL but not for any of the other sub-types or for NHL overall. Despite these uneven results the risks of FL were consistently lower than other sub-types in association with any of the glyphosate use metrics. There was a relatively large number of FL cases in this analysis compared to the numbers available for other sub-types, lessening the likelihood that findings for FL were primarily due to chance. FL is a type of B-cell lymphoma that is the second most common type of NHL, accounting for 22% of all NHLs (28). The observation of lowered FL risks for glyphosate use in this study was a lead for further evaluation. Additionally, the classification of NHL has changed since the case-control studies in the NAPP were conducted. Multiple myeloma is now considered a sub-type of NHL but was not evaluated in this analysis.

A fairly consistent decrease in NHL risk was found when ORs were further adjusted for the pesticides 2,4-D, dicamba, and malathion. This observation suggested that elevated risks of NHL may be attributed, in part, to pesticides other than glyphosate. Formulations of glyphosate reported by NAPP subjects may have contained other active ingredients. In addition or alternatively, glyphosate may have been used in combination with other pesticide active ingredients at the time of application or in the same growing season or year. It is relatively unknown how combinations of pesticides might interact, and we were not able to evaluate this in our analysis. There is a need to further investigate other individual compounds with respect to NHL risk, such as the herbicide 2,4-D, which IARC recently assessed as possibly carcinogenic to humans based on inadequate evidence in humans and limited evidence in animals for NHL (29).

Glyphosate and covariate data provided by self-respondents generally resulted in attenuated risks compared to odds derived from information provided by both self- and proxy respondents. The proportion of proxy respondents used for cases and controls was similar (about one third). Excluding proxies appreciably reduced the numbers of subjects in the sensitivity analysis which might have partly explained differences in risks. There was also the possibility of exposure misclassification by proxy respondents due to inaccurate recall of glyphosate use, which was likely non-differential (27, 30). Non-differential pesticide exposure misclassification was also an issue amongst self-respondents (31). There was less agreement between self-respondents and surrogates for detailed glyphosate use metrics (years and days/year) compared to the dichotomous variable (32). Nevertheless, significant trends of increasing risks in association with greater lifetime days of glyphosate use persisted for NHL overall, FL, and SLL, even when the analysis was limited to self-respondents.

The evaluation of PPE as an effect modifier of the relationship between glyphosate use and overall NHL risk raised some interesting observations. We expected that the use of any PPE such as masks, gloves,

clothing and/or other equipment may confer a protective effect on the development of NHL from glyphosate use by reducing the probability and degree of dermal, respiratory, and oral contact with glyphosate. However, in this study PPE was found to have no effect on the association between glyphosate use and NHL risk overall. This analysis was limited because PPE usage was not specific to glyphosate use or the type or timing of PPE worn. It was also based on pooled data from Canada and Nebraska only and there was a large proportion of missing data. This hypothesis warrants further investigation in larger studies with more information about PPE used with glyphosate in particular.

The exact causes of lymphatic and hematopoietic cancers are not yet known. A suppressed immune system is the most well established risk factor for NHL. It has been hypothesized that pesticides may play a role in modifying immune function (24-26), but there is little evidence to support this hypothesis for glyphosate specifically (11, 25). An alternative or additional explanation is that pesticides may influence the risk of lymphatic and hematopoietic cancers through pathways involving oxidative stress and receptor-mediated mechanisms. The pathway that glyphosate affects in plants is not present in mammals, but there is strong evidence from mechanistic studies that glyphosate causes genotoxicity and the production of reactive oxygen species (11).

The limitations of this study were primarily related to statistical power for some analyses and the possibility of biases and unmeasured confounding. We endeavoured to use data from all subjects for this analysis as reflected by the inclusion of both men and women and alive and deceased subjects. In Canada alone, 50 NHL cases and 133 controls reported ever using glyphosate; pooling resulted in an additional 63 NHL cases and 111 controls who ever used glyphosate in Iowa, Minnesota, Kansas, and Nebraska. Nevertheless, there were small numbers for some categories of duration, frequency, and lifetime days by NHL sub-type due to the absence of duration data collected in Kansas and frequency and lifetime days information from Iowa, Minnesota, and Kansas. Risk estimates based on small numbers may be unstable and could represent chance findings.

To evaluate possible recall bias of self-reported pesticide use, in the study in Kansas, pesticide suppliers were asked to provide information on crops and pesticide purchases for a sample of 130 subjects with farming experience (13, 27). In the Iowa and Nebraska studies, case recall bias was assessed by comparing information on pesticides used that was volunteered versus information that required probing by the interviewer (14, 27, 33). In the Iowa and Minnesota study, interviews were conducted with both farmers and their wives for a sample of subjects (32). There was a moderate level of correspondence between pesticide use information reported by farmers and their pesticide suppliers in Kansas (13, 27). In Iowa and Nebraska, the number of insecticides and herbicides voluntarily identified was similar and suggested the absence of case-response bias, but probing increased the number of positive responses for individual agents (14, 27, 33). In Iowa and Minnesota, surrogate responders were generally a poorer source of information compared to farmers as they had reported a smaller number of pesticides ever used and a greater proportion of “I don’t know” answers (32). No similar analysis of recall bias has been conducted in the Canadian case-control study, but the similarity of study designs between the U.S. and Canada make it likely that recall bias is not a major concern in the Canadian study and NAPP as a whole.

Adjusting for several pesticides (2,4-D, dicamba, and malathion) was a useful way to attempt to disentangle the effect of glyphosate from other pesticides on NHL risk. These agents have been shown to be independently associated with NHL in individual case-control studies (5-7). However, they are somewhat correlated with glyphosate exposure in the NAPP and thus their inclusion as confounders may have introduced some degree of collinearity. Unmeasured confounding by other pesticides, agricultural exposures, or unknown factors cannot be ruled out.

While these results are not independent from previous studies, the evaluations by histological sub-type and for detailed glyphosate use metrics are a new and important contribution to the epidemiological literature. NHL is a constellation of heterogeneous cancers that each has its own causes, risk factors, and etiologies. Pesticides, including individual agents such as glyphosate, may exert different effects on these sub-types, and the large size of the NAPP made it possible to parse this out.

The large sample size also resulted in more precise results than possible in previous smaller studies that only had sufficient power to assess risks for dichotomous glyphosate exposure. We were able to model different glyphosate use categories and identify potential trends in NHL risk by sub-type with increasing duration, frequency, and lifetime days of glyphosate use. This made it possible to characterize possible dose-response relationships between glyphosate exposure and lymphoma risk. The effect modification analysis by PPE further allowed an examination of factors that might modify glyphosate exposure (and risk). Both agricultural and non-agricultural uses of glyphosate were reported by cases and controls in this population-based, pooled case-control study, making this evaluation externally valid.

The results of this analysis may be considered in future scientific and regulatory reviews of glyphosate in North America and globally. Stakeholders may also use these results as part of future approaches that communicate the health risks of pesticides using information directly ascertained from the North American population. This will help to inform efforts aimed at mitigating occupational and environmental exposure to pesticides. It will also provide high-quality risk estimates that can be used in future estimations of the burden of cancer from pesticide exposure.

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COMPETING INTERESTS

The authors declare no competing interests.

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AUTHORS' CONTRIBUTION

MP designed and conducted this analysis and wrote this manuscript. SAH, JJS, and LBF collectively form the NAPP Executive Committee and approved the proposal for this analysis and provided scientific input during the analytic and manuscript preparation phases. AB, SHZ, DDW, and KPC led the original case-control studies in the U.S. JJS, JAM, and JAD were among the principal investigators of the CCSPH in Canada. All co-authors reviewed and approved this manuscript for submission.

DATA SHARING

Unpublished NAPP data is available upon formal request to the NAPP Executive Committee (SAH, JJS, LBF).

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