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The association between non-Hodgkin lymphoma and organophosphate pesticides exposure: A meta-analysis☆

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ABSTRACT

Several epidemiological studies show the association between organophosphate pesticides (OPs) and the risk of non-Hodgkin lymphoma (NHL), yet various research results remain controversial. To explore the hazard of OPs exposure to human health, three kinds of OPs (Terbufos, Malathion, and Diazinon) that are non-halogenated aliphatic compounds were included in the meta-analysis. We searched PubMed and Web of Science Databases for articles published from 1985 to February 2017. The databases were also searched for eligible studies through a manual references search. The random-effect model was utilized to compute the odds ratios (ORs) and 95% confident intervals (CIs). A total of ten observational studies (five cohort, four case-control, and one nested case-control) were included in our meta-analysis, with a pooled OR of 1.22 (95% CI 1.04 to 1.43) of Malathion, Terbufos and Diazinion. The general heterogeneity for OR was moderate ($P_h = 0.032$, $I^2 = 41.2\%$). The OR estimates in the subset analyses were utilized to compare the association between the three kinds of OPs and NHL; Terbufos (OR = 1.07, 95% CI 0.85 to 1.36) and Malathion (OR = 1.17, 95% CI 0.82 to 1.67) had a statistically non-significant relationship, whereas Diazinon (OR = 1.39, 95% CI 1.11 to 1.73) was significantly associated with an increased NHL risk. Because immune dysfunction was thought to increase NHL risk, the toxicity levels in the immune system of the three types of OPs were compared. Malathion attacked immune cells via a direct effect and Diazinon disrupted the neuro-immune system, which involves the cholinergic system of lymphocytes via indirect immune damage, whereas an immunotoxic effect involving Terbufos was not reported. Overall, the present meta-analysis indicated a statistically significant association between Diazinon exposure and NHL risk.

1. Introduction

Non-Hodgkin lymphoma (NHL), a heterogeneous group of malignancies of the lymphatic system, is the fifth most common cancer in many developed countries worldwide (Morton et al., 2014). Both infectious and environmental pathogeneses have been associated with the development of NHL. On the other hand, 15%–20% of NHL cases are caused by viral and bacterial infections, including HIV, hepatitis C virus (HCV), hepatitis B virus (HBV), Epstein–Barr virus, human herpesvirus 8, human T-lymphotropic virus type 1, and *Helicobacter pylori* (Dalia et al., 2015). Moreover, certain environmental factors are related with the onset of NHL, and farming is the main cause (Pahwa et al., 2012). Numerous studies have suggested that exposure to agricultural chemicals, including insecticides, fungicides, herbicides, and other potential carcinogens, may increase the potential risk for NHL (Alavanja et al., 2013, 2014; Burns, 2005; Clapp et al., 2008). In fact, exposure to some special pesticides was associated with NHL risk (Dreiher and Kordysh, 2006; Hohenadel et al., 2011; Luo et al., 2016). Recently, organophosphate pesticides (OPs) have been used as a substitute for the persistently problematic organochlorine pesticides (OCPs), which play a significant role in the incidence of NHL (Pahwa et al., 2012).

OPs are widely sold and used as ingredients by all American market sectors, accounting for approximately 35% of all pesticide use (Lerro et al., 2015). OPs as non-arsenical insecticides have

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similar properties, such as high lipophilicity, easy organism enrichment, low persistence in the environment, and high acute toxicity. On the contrary, some OPs, such as Malathion, Diazinon, and Terbufos, are structural analogs, with an unexpectedly different potential risk for carcinogenicity. For example, Malathion and Diazinon (Group 2A) were classified by the International Agency for Research on Cancer as a probable carcinogen to humans (Lerro et al., 2015), whereas Terbufos is classified by the United States Environmental Protection Agency (USEPA) as a Group E carcinogen (non-carcinogenic to humans) in toxicity category I (high acute toxicity) (Bonner et al., 2010). Because of their abundant use in the household and occupational environments, their special potential risk should be investigated in epidemiological studies.

To date, numerous studies have reported the association between pesticide exposure and NHL risk, including OPs, with conflicting results. Hohenadel et al. (2011) showed that exposure of different types of OPs was significantly associated with the risk of NHL in men from six Canadian provinces. Lee et al. (2004) performed a population-based case-control study in the United States and depicted that the risk of NHL that is related to exposure to multiple pesticides increased in people with a history of asthma, in which individuals with asthma had a higher odds ratio (OR) of exposure to OPs than those who are not asthmatic. Meanwhile, other studies were not able to determine the relationship between exposure to OPs and NHL risk (Bonner et al., 2010; Lerro et al., 2015; Orsi et al., 2009).

In the present study, we conducted a meta-analysis of the exposure to OPs and NHL risk based on the observational studies, and three kinds of OPs, namely, Malathion, Diazinon, and Terbufos, were included in the study. These OPs contained phosphothioates (P=S), which are more lipophilic than phosphates (P=O), and were stored extensively in adipose tissues. Furthermore, the phosphothioates could be biotransformed to active phosphate (P=O) analogs through oxidative desulfuration. Therefore, after exposure to phosphothioate pesticides, the appearance of toxic symptoms may be delayed (Kwong, 2002). Consequently, long-term and low-level exposure to these three widely used OPs may cause serious harm to human health. This study aimed to evaluate the harmful effects and potential risks from exposure to these three kinds of OPs.

2. Materials and methods

2.1. Search strategy

The meta-analysis was conducted to interpret the association between exposure to OPs and NHL risk by searching articles published from 1985 to February 2017 from databases. For the exposure, the keywords used were pesticide*, insecticide*, organophosphate*, and organophosphorus. For the outcome, the keywords used were cancer risk, notably leukemia, non-Hodgkin's lymphoma, multiple myeloma, Hodgkin's disease, and lymphohematopoietic. For the object, the keywords used were farm*, agricultu*, occupation*, resident*, and household. For the study design, the keywords used were epidemiolog*, cross-sectional, case-control, and cohort. The search term in PubMed and Web of Science was selected with “All Fields” and “theme” in sequence. Our search was conducted from 11th March 2016, different topics about organophosphate exposure and related outcomes were chosen. The final theme was ascertained on organophosphate exposure and lymphohematopoietic cancer until 3rd May 2016. Eventually, search records from PubMed and Web of Science were updated two times. The two points of time were July 2016 and February 2017, respectively. Meanwhile, the databases were searched for eligible studies through a manual reference search. All included articles were published in English. The results of the meta-analysis were reported by following the PRISMA checklists and guidelines (Moher et al., 2009).

2.2. Inclusion and exclusion criteria

Studies are considered eligible for further review if they met the following criteria: (1) studies of exposure to pesticides that contained one or more of the OPs ingredients; (2) studies that included unexposed and exposed groups; (3) studies that were observational, such as cohort, case-sectional, or case-control; (4) the outcome of the studies showed the presence of NHL; (5) the association between OPs exposure and NHL risk was reported as ORs, risk ratios (RRs), rate ratios (RRs), or hazard ratios (HRs) with corresponding 95% CIs or provided some information to calculate relevant values. Studies that did not specify any kind of OPs exposure were not included. Furthermore, those that focused on child exposure to OPs and only reported the symptoms of acute organophosphate poisoning were not considered. We also excluded studies in which further analysis did not stem from original results, such as meta-analyses, reviews, meetings, abstracts, letters, and comments. In addition, studies of animal experiments or laboratory tests were not included.

2.3. Data extraction

To summarize the characteristics of the ten included studies, the following data were independently extracted by two reviewers: (1) study design (cohort and case-control study); (2) sample size; (3) study gender; (4) sources of study population; (5) sources of OPs exposure; and (6) methods of assessment of OPs exposure (see Supplementary Tables S1 and S2). We preferred to extract quantitative exposure to specific pesticides; otherwise, semi-quantitative or qualitative exposure was chosen in sequence. Thus, higher intensity-weighted lifetime exposure days to specific pesticides were first selected, and high-exposure group or ever exposure to special OPs was then considered. Meanwhile, OPs exposure should be considered as the primary factor for the risk of NHL to avoid the existence of confounding factors (immunological conditions and whether with protective equipment), and the information about pesticides exposure of farmers collected from proxy was substituted by direct respondent to decrease the information bias as much as possible; (7) covariates adjusted for ORs, RRs, or HRs; vital confounding factors, such as whether any adjustment was made for pesticides and family history of cancer were included; (8) types of exposure to OPs; and (9) ORs, RRs, or HRs and corresponding 95% CI (when different adjusted models coexisted, the relevant value with more adjusted confounding factors were chosen for further statistical analysis). All the data collected from the two reviewers were compared and any disagreements were resolved.

2.4. Quality assessment

The quality scores of the case-control and cohort studies were assessed systematically according to the Newcastle–Ottawa Scale (NOS) (Stang, 2010), which are comprehensively shown in Supplementary Tables S3 and S4. The NOS contains three dimensions with eight items. The three dimensions are selection (0–4 stars), comparability (0–2 stars), and outcome (0–3 stars) for a case-control study or exposure (0–3 stars) for a cohort study. Apart from the item of comparability, two points are assigned if satisfied, and other items will obtain a maximum of one point if the response options are met. Therefore, the range of NOS is from zero to nine points, in which the scores of 0–3, 4–6, and 7–9 were categorized as low, moderate, and high quality.