

EDITORIAL

Glyphosate Use and Cancer Incidence in the Agricultural Health Study: An Epidemiologic Perspective

Elizabeth M. Ward

Affiliations of author: United States Public Health Service (retired), Asheville, NC.
Former affiliation: Intramural Research, American Cancer Society, Atlanta, GA.

Correspondence to: Elizabeth M. Ward, PhD, 10 Sunset Terrace, Asheville, NC 28801 (e-mail: eward04@gmail.com).

In this issue of the Journal, Gabriela Adreioti and colleagues report the results of an updated analysis of glyphosate exposure and cancer risk in the Agricultural Health Study (AHS) (1). The AHS, a prospective cohort study of 57 310 licensed pesticide applicators and 32 347 spouses in Iowa and North Carolina, was initiated in the early 1990s, in large part to address possible causes for the higher incidence of lymphohematopoietic and certain other cancers in farmers compared with the general population (2). From an epidemiologic perspective, designing a study to investigate cancer risk factors associated with farming is challenging because of the difficulty in establishing and recruiting a well-defined population, the large number of farming-related exposures that may be associated with cancer, and the need to create and validate quantitative exposure metrics. The AHS study met these challenges by defining and recruiting the study population from applicants for a restricted-use pesticide license in two states, collecting detailed information on the frequency and duration of use of 50 common pesticides, as well as other farming-related and general population exposures, and estimating lifetime days and intensity-weighted lifetime days of exposure for specific pesticides (2). Intensity of exposure was estimated using an algorithm that accounted for reported use of personal protective equipment, method of application, and whether the applicator personally mixed the pesticides (3). Additional studies were done to validate and refine the pesticide exposure intensity metrics, and exposure information was updated in 1999–2005 by computer-aided telephone interviewing (3,4). A method for multiple imputation was developed to assign pesticide use for nonresponders to the follow-up questionnaire (5).

Associations between glyphosate use and non-Hodgkin lymphoma (NHL) were of a priori interest in the AHS study based on

positive findings from case-control studies. The first AHS analysis, published in 2005, did not find evidence for an association between glyphosate exposure and NHL or any cancer site examined; however, a statistically nonsignificantly increased risk was observed for malignant myeloma in the highest exposure category. Conclusions were limited by the relative small number of incident cases and short duration of cancer incidence follow-up. The new AHS analysis extends cancer incidence follow-up from 2001 in the previous study through 2012 (North Carolina)/2013(Iowa), which increases from 2088 to 7290 the number of incident cancer cases available for analysis; it finds little or no evidence for positive exposure response trends or elevated risk ratios (RRs) in the highest intensity-weighted lifetime days of exposure quartiles for NHL and most leukemia and lymphoma subtypes examined (1). The notable exception is a statistically nonsignificantly increased risk for acute myelogenous leukemia in the highest exposure quartile (RR = 2.44, 95% confidence interval = 0.94 to 6.32, $P_{\text{trend}} = .11$). The results did not substantially change with adjustment for potential confounders, use of lifetime days as an alternative exposure metric, applying five- and 20-year exposure lags, or restricting analysis to the 34 698 individuals who completed both the initial and follow-up surveys.

Although the Andreotti et al. study (1) adds substantially to the body of epidemiologic evidence regarding the potential association between glyphosate exposure and cancer in humans, interpreting the new findings in the context of previous studies may be difficult. Some may conclude that the null results for NHL in the AHS should carry greater weight than the results of positive case-control studies because of the strength of the study and the consistent lack of evidence for increasing risk for NHL and major subtypes with increasing glyphosate exposure,

while others may be reluctant to draw firm conclusions based on the additional evidence. Such reluctance may be based in part on historical observations where what appeared to be conflicting results among studies for positive associations with different leukemia/lymphoma subtypes were later recognized to reflect positive associations with several leukemia/lymphoma subtypes. Early studies of occupational exposure to benzene, for example, generally found positive associations primarily for leukemia (6,7), although some studies in occupational groups with lower levels of benzene exposure did not find this association. A review of epidemiologic evidence, published in 1997, found substantial support for association of benzene exposure with both acute myelogenous leukemia and total leukemias and concluded that “sporadic reports have linked benzene to non-Hodgkin lymphoma and multiple myeloma, but most studies do not report a positive association” (8). A decade later, a systematic review based on 43 case-control studies of occupational exposures related to NHL and 26 studies of petroleum refinery workers found that the majority reported some elevation of NHL risk associated with benzene exposure (9). An International Agency for Research on Cancer Monograph review of benzene (10), published in 2012, concluded that benzene “causes acute myeloid leukaemia/acute non-lymphocytic leukaemia” and that “a positive association has been observed between exposure to benzene and acute lymphocytic leukaemia, chronic lymphocytic leukaemia, multiple myeloma, and non-Hodgkin lymphoma.” Although the history of benzene suggests caution in negative interpretation of inconsistencies in subtypes for potential lymphatic/hematopoietic carcinogens, it is important to acknowledge that additional evidence from studies of glyphosate may in fact provide increasing evidence for lack of an association. It should also be recognized that given the nature of pesticide use in agriculture, applicators may only be exposed to specific pesticides for short periods of time each year. In the AHS study, median lifetime days of glyphosate among individuals with cancer was 38.75, and the median lifetime years of use was 8.0. Thus, although pesticide applicators likely provide the best opportunity for investigating the risk associated with glyphosate exposure, the intermittent nature and range of exposure may limit the ability of the studies in these populations to detect cancer hazards.

Evaluating the potential for glyphosate exposure to increase cancer risks in humans is important due to its widespread and

increasing use in the United States and globally and indications of potential carcinogenicity from toxicologic and epidemiologic studies (11,12). Epidemiologic studies have inherent limitations with respect to cancer prevention as they generally detect elevated cancer incidence and mortality cancer hazard decades after carcinogen exposure begins. The timeline for identifying cancer hazards in prospective cohort studies may be accelerated by incorporating biomarkers that may reflect carcinogenic hazards earlier than cancer incidence or mortality outcomes. Expansion of current efforts to collect biological samples from AHS participants would increase the potential to provide timely evidence to evaluate the potential for glyphosate and other pesticides to cause cancer in humans.

Note

The author has no conflicts of interest to disclose.

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