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Pesticide exposure and end-stage renal disease risk among wives of pesticide applicators in the Agricultural Health Study☆

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ABSTRACT

Background: Pesticide exposure has been found to cause renal damage and dysfunction in experimental studies, but epidemiological research on the renal effects of chronic low-level pesticide exposure is limited. We investigated the relationships between end-stage renal disease (ESRD) among wives of licensed pesticide applicators (N=31,142) in the Agricultural Health Study (AHS) and (1) personal pesticide use, (2) exposure to the husband's pesticide use, and (3) other pesticide-associated farming and household activities.

Methods: AHS participants reported pesticide exposure via self-administered questionnaires at enrollment (1993–1997). ESRD cases were identified via linkage to the United States Renal Data System. Associations between ESRD and pesticide exposures were estimated with Cox proportional hazard regression models controlling for age at enrollment. Models of associations with farming and household factors were additionally adjusted for personal use of pesticides.

Results: We identified 98 ESRD cases diagnosed between enrollment and 31 December 2011. Although women who ever applied pesticides (56% of cohort) were less likely than those who did not apply to develop ESRD (Hazard Ratio (HR): 0.42; 95% CI: 0.28, 0.64), among women who did apply pesticides, the rate of ESRD was significantly elevated among those who reported the highest (vs. lowest) cumulative general pesticide use (HR: 4.22; 95% CI: 1.26, 14.20). Among wives who never applied pesticides, ESRD was associated with husbands' ever use of paraquat (HR=1.99; 95% CI: 1.14, 3.47) and butylate (HR=1.71; 95% CI: 1.00, 2.95), with a positive exposure–response pattern for husband's cumulative use of these pesticides.

Conclusions: ESRD may be associated with direct and/or indirect exposure to pesticides among farm women. Future studies should evaluate indirect exposure risk among other rural populations.

1. Introduction

Experimental animal studies and case studies of human poisonings suggest that pesticide exposure may cause permanent kidney damage (Chargui et al., 2012; Choudhary et al., 2003; Kackar et al., 1999; Kaur et al., 2012; Shah and Iqbal, 2010; Uyanikgil et al., 2009; Van Vleet and Schnellmann, 2003), but epidemiological research on the effects of prolonged low-level exposure is limited. In animal studies, renal damage and dysfunction have been observed with exposure to a range of pesticides, including organophosphate (Poovala et al., 1999; Shah and Iqbal, 2010), organochlorine (Choudhary et al., 2003; Sobel et al., 2005), carbamate (Kaur et al., 2012), and pyrethroid (Chargui et al., 2012) insecticides and triazine (Santa Maria et al., 1986) and chlorophenoxy (Uyanikgil et al., 2009) herbicides. We previously

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reported that long-term use of several specific pesticides was associated with end-stage renal disease (ESRD) among a large cohort of male pesticide applicators (Lebov et al., 2015). The wives of pesticide applicators are likely to have patterns of pesticide exposure that differ from those of their husbands, including less frequent use of pesticides and use of less toxic pesticides (Kirrane et al., 2004), and they may experience indirect exposures by virtue of living close to where pesticides are applied. Wives of pesticide applicators may also be exposed through take-home exposures, i.e. pesticide residues carried home on their husband's boots, clothing, and skin (Fenske et al., 2013) or by washing pesticide-contaminated clothing. Women who live on farms where pesticides are applied may experience exposure through spray drift and water contamination; proximity of household to pesticide application areas has been positively correlated with levels of pesticides found in household dust (Lu et al., 2000; Simcox et al., 1995), and several large drinking water surveys have found widespread contamination of community water systems and domestic wells by pesticides (Cohen et al., 1995; Fenske et al., 2002; U.S. Environmental Protection Agency, 1990; Wiles and Cook, 1994).

The Agricultural Health Study (AHS) provides a unique opportunity to study a variety of exposure pathways among a large population of wives of private pesticide applicators (i.e. farmers). Using AHS data, we examined rates of ESRD among wives in relation to their personal use of specific pesticides and pesticide use by their applicator husbands. We also evaluated the association between other non-application pesticide exposure opportunities and ESRD.

2. Methods

2.1. Study population and case definition

The AHS is a large, prospective study of Iowa and North Carolina pesticide applicators and their spouses (Alavanja et al., 1996). Approximately 84% (N=52,394) of licensed private applicators in Iowa and North Carolina enrolled in the AHS between December 1993 and December 1997 by completing a questionnaire when they received or renewed their pesticide training certification. A total of 32,346 spouses of these applicators (75% of those eligible) enrolled in the study by completing a self-administered questionnaire (81%) or a telephone interview (19%). Enrollment questionnaires collected information on demographics, medical conditions, medication use, lifestyle factors, and pesticide use. Of the enrolled applicators, 44% also completed a take-home questionnaire, which collected additional information on specific pesticide use and pesticide application practices. Because the distribution of ESRD risk factors, including hypertension and diabetes, differ by gender (Arnetz et al., 2014; Zimmerman and Sullivan, 2013), and because $<1\%$ of all spouses were male, the current analysis includes only female spouses of pesticide applicators. We also excluded spouses under age 18 (N=4), those who were diagnosed with end-stage renal disease prior to enrollment (N=25; 20% of female spouses with diagnosed ESRD), and those who did not provide data on ever use of any pesticide (N=957), leaving 31,142 wives for analysis (Fig. 1). Through a linkage with the United States Renal Data System (USRDS), we ascertained the first renal replacement therapy (i.e. dialysis initiation or renal transplantation) date for ESRD cases occurring between study enrollment and end of follow-up (December 31, 2011). Date of death from any cause was obtained by linking the cohort to state mortality files and the National Death Index. These mortality registry data were used to identify death dates for all participants; however, the USRDS also captures data on those who die of renal failure when a renal provider submits a required ESRD Death Notification (CMS-2746) form (U.S. Renal Data System, 2015). Therefore, we believe that few, if any, ESRD cases are missing from this analysis.

2.2. Exposure assessment

Pesticide exposure information from the spouse enrollment questionnaire included: (1) ever/never use of 50 specific pesticides; (2) number of years (duration) and days per year (frequency) personally mixed or applied pesticides in general; (3) number of years lived or worked on a farm; (4) specific farm tasks performed; (5) performance of household tasks involving possible pesticide exposure; (6) distance from the participant's house to fields where pesticides were applied; (7) household practices that could increase pesticide exposure (e.g. storage of pesticides in the home); and (8) treatment of the home or lawn for

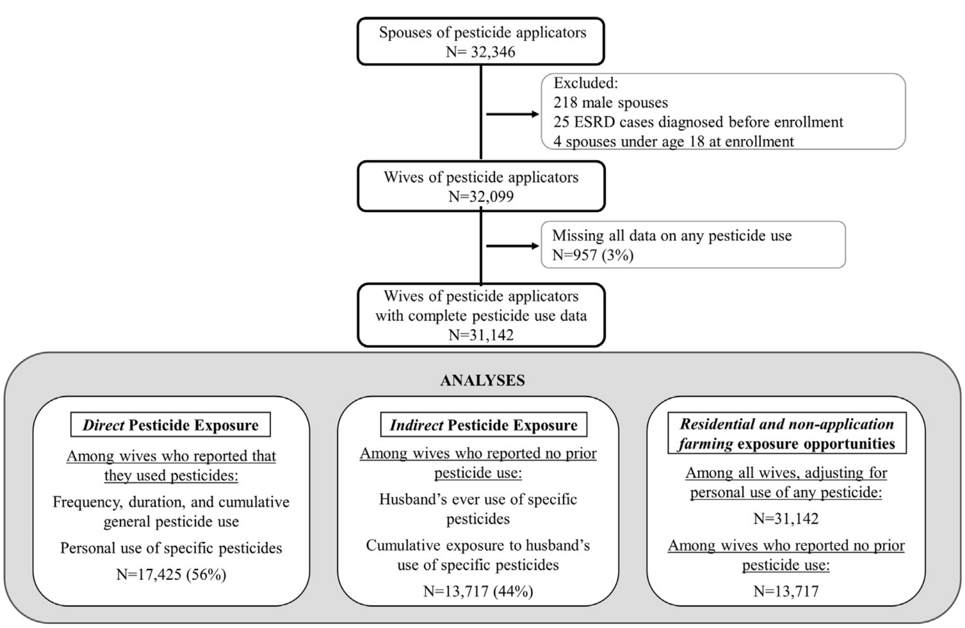

Fig. 1. Study population and numbers used for sub-analyses.