Annals of Epidemiology 25 (2015) 803–810

Contents lists available at ScienceDirect

Annals of Epidemiology

journal homepage: www.annalsofepidemiology.org

Original article

Insecticide exposure and farm history in relation to risk of lymphomas and leukemias in the Women's Health Initiative observational study cohort

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ARTICLE INFO

Article history:
Received 17 February 2015
Accepted 3 August 2015
Available online 19 August 2015

Keywords:
Pesticides
Insecticides
Women
Lymphoma
Leukemia

ABSTRACT

Purpose: Relationships of farm history and insecticide exposure at home or work with lymphohematopoietic (LH) neoplasm risk were investigated in a large prospective cohort of US women.
Methods: In questionnaires, women self-reported history living or working on a farm, personally mixing or applying insecticides, insecticide application in the home or workplace by a commercial service, and treating pets with insecticides. Relationships with non-Hodgkin lymphoma (NHL), chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), diffuse large B-cell lymphoma (DLBCL), follicular lymphoma, plasma cell neoplasms, and myeloid leukemia were investigated using Cox proportional hazard models. Age and farming history were explored as effect modifiers.
Results: The analysis included 76,493 women and 822 NHL cases. Women who ever lived or worked on a farm had 1.12 times the risk of NHL (95% confidence interval [CI] = 0.95–1.32) compared to those who did not. Women who reported that a commercial service ever applied insecticides in their immediate surroundings had 65% higher risk of CLL/SLL (95% CI = 1.15–2.38). Women aged less than 65 years who ever applied insecticides had 87% higher risk of DLBCL (95% CI = 1.13–3.09).
Conclusions: Insecticide exposures may contribute to risk of CLL/SLL and DLBCL. Future studies should examine relationships of LH subtypes with specific types of household insecticides.

Introduction

Elevated rates of non-Hodgkin lymphoma (NHL) have been observed among farmers [1–4]. Other lymphohematopoietic (LH) neoplasms, including multiple myeloma, Hodgkin lymphoma, and some myeloid leukemias, have been associated with farming occupation [5–7]. Various exposures are hypothesized to contribute to these excess risks. Of these, pesticides have received considerable attention.

Indeed, NHL has been associated with organochlorine, organophosphate, and carbamate insecticide exposure [8–11]. Pesticides may contribute to NHL risk through a variety of mechanisms, including genotoxicity, immunotoxicity [12,13], increased cell proliferation [13], and chromosomal aberrations [14]. Nevertheless, associations with insecticides have been inconsistent and could be confounded by other exposures, including dusts, sunlight, or infectious agents [2].

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http://dx.doi.org/10.1016/j.annepidem.2015.08.002
1047-2797/

Insecticide use in the general population is common. In data from the National Health and Nutrition Examination Survey from 2011 to 2012, approximately 10% of respondents with complete data reported using insecticides in the past 7 days [15]. In Minnesota (1997), approximately 98% of a representative sample of households with children ages 3 to 13 years was storing pesticide products, and 88.4% reported using pesticides in the previous year [16]. In California (2001–2006), 95% of 259 households surveyed had at least one stored pesticide product; insecticides were found in 46% of the households with any pesticides [17].

Despite widespread use, there is limited research on the relationship of LH cancer risks with pesticide use in the general population. In a population-based case-control study conducted at four US Surveillance, Epidemiology, and End-Results sites (1057 cases), termite insecticides, but not other insecticide treatments, were associated with a small increased risk of NHL [18,19]. In that same study, measured levels of dichlorodiphenyldichloroethylene (DDE), a metabolite of the insecticide dichlorodiphenyltrichloroethane (DDT), and chlordane in carpet dust from participants' homes were associated with increased risk of NHL [19]. In a case-control study of women in upstate New York (376 cases), residential and occupational insecticide exposures were associated with increased risk of NHL [20]. Because these two studies were retrospective, the questionnaire responses could have been subject to recall bias. Furthermore, there has been virtually no research on associations of residential insecticide exposures with other LH neoplasms, such as plasma cell neoplasms or myeloid leukemia.

The objective of these analyses was to investigate associations of LH cancer risk with farming history and insecticide use at home and/or work using data from the Women's Health Initiative Observational Study (WHI OS), a large, prospective cohort study of women from 40 US sites.

Methods

Study population

From October 1, 1993 through December 31, 1998, 93,676 postmenopausal women enrolled in the WHI OS. Participants were followed through March 2005 and subsequently invited to enroll for continued follow-up in WHI extension studies [21,22]. Women were eligible for the current analysis if they responded to a 1-year follow-up questionnaire, which included questions on insecticide use. The follow-up questionnaire was mailed to participants 2 months before the 1-year anniversary of their enrollment in the observational study.

Exclusions

In addition to being excluded if they did not participate in the 1-year follow-up questionnaire ($n = 4278$), women were excluded if they had incident tumors but no histologic information ($n = 2$), reported history of cancer diagnosis at baseline ($n = 11{,}725$), lacked cancer follow-up information ($n = 428$) and/or were diagnosed with a cancer before the 1-year follow-up questionnaire ($n = 750$).

Cancer

Medical history was updated annually by mailed questionnaire. Reports of incident cancers were confirmed by centrally trained cancer adjudicators based on review of medical records and pathology reports. Trained coders from the surveillance, epidemiology, and end-results program classified the case morphology using ICD-O-3 coding [23]. LH neoplasms were categorized into World Health Organisation subtypes [24] according to InterLymph Consortium recommendations [25]. Here, results for subtypes with 100 or more cases (exposed and nonexposed) are reported—specifically, NHL overall ($n = 822$), diffuse large B-cell lymphoma (DLBCL, $n = 172$), follicular lymphoma ($n = 127$), chronic lymphocytic leukemia and/or small lymphocytic lymphoma (CLL/SLL, $n = 171$), plasma cell neoplasms ($n = 156$), and myeloid leukemia (acute myeloid leukemia and chronic myeloid leukemia combined, $n = 110$).

Exposure

Relationships with the following exposures were investigated: history of living or working on a farm, personally mixing or applying insecticides, having insecticides applied at home or work by someone else, and insecticide pet treatment.

History of living or working on a farm (ever and/or never and duration, less than 5 years, 5–9 years, 10–14 years, 15–19 years, and 20 years or more) was reported in the WHI OS baseline questionnaire. Information on insecticide use and pet treatment was self-reported in the 1-year follow-up questionnaire. Specifically, women reported if, since age 21 years, they or someone else had poured, mixed, sprayed, or applied insecticides in their immediate surroundings at home or work. If yes, then women reported if they mixed or sprayed insecticides themselves and/or if a commercial service applied them. They reported total years (duration) and average number of times per year (frequency) that they personally mixed and/or applied insecticides, and/or that someone else applied insecticides. They reported duration and frequency using the following categories, respectively: never or less than 1 year, 1–4, 5–9, 10–14, 15–19, or 20 years or more duration; and never or less than 1, 1–5, 6–12, 13–24, or 25 times/year or more frequency. "I don't know" responses to the question about insecticide exposure were coded as missing and excluded from the main analyses.

Women also reported if they ever lived with a pet in their home, and if so, if they used insecticides to treat their pet(s) for fleas, mites, or ticks. If yes, they reported the method (none, flea/tick collars, powder or spray, dips, and other).

Intensity measures of personal or commercial insecticide use were calculated by first assigning the midpoint value or a value equal to 50% more than the highest category (e.g., 30 years was assigned to the 20 years or more category) to the duration and frequency variables and then multiplying the two numbers. To calculate intensity measures for women missing either duration or frequency (but not both), the missing value was assigned the value most commonly reported by noncases in the same duration or frequency category that was nonmissing.

Farm history, personal mixing of insecticides, personal application of insecticides, commercial service application of insecticides in the home, and lawn service application of insecticides were investigated using ever or never dichotomous coding; women without the exposure comprised the referent.

Additionally, dose-response relationships with duration of farm history and with duration, frequency, and intensity of personal or commercial insecticide use were investigated. Trend tests were performed by entering the categorical scored variables into models as continuous variables. Wald tests were performed, and two-sided P was calculated.

Duration and frequency categories were based on those listed in the questionnaire and collapsed because of small cell sizes. Intensity measure categories were never or low (0–2, referent), low-moderate (3–100), and high/very high (more than 100). In analyses of duration or frequency, referent categories contained women who neither personally applied or mixed insecticides nor had a lawn or commercial service apply insecticides. In most analyses of pet insecticides, the referent contained women who had a pet but did not