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Farm residence and lymphohematopoietic cancers in the Iowa Women's Health Study

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Abstract

Background—Cancer incidence in male farmers has been studied extensively; however, less is known about risk among women residing on farms or in agricultural areas, who may be exposed to pesticides by their proximity to crop fields. We extended a previous follow-up of the Iowa Women's Health Study cohort to examine farm residence and the incidence of lymphohematopoietic cancers. Further, we investigated crop acreage within 750 m of residences, which has been associated with higher herbicide levels in Iowa homes.

Methods—We analyzed data for a cohort of 37,099 Iowa women aged 55–69 years who reported their residence location (farm, rural (not a farm), town size based on population) at enrollment in 1986. We identified incident lymphohematopoietic cancers (1986–2009) by linkage with the Iowa Cancer Registry. Using a geographic information system, we geocoded addresses and calculated acreage of pasture and row crops within 750 m of homes using the 1992 National Land Cover Database. Cox regression was used to estimate hazard ratios (HR) and 95% confidence intervals (CI) in multivariate analyses of cancer risk in relation to both residence location and crop acreage.

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Results—As found in an earlier analysis of residence location, risk of acute myeloid leukemia (AML) was higher among women living on farms (HR= 2.23, 95%CI: 1.25–3.99) or rural areas (but not on a farm) (HR= 1.95, 95%CI: 0.89–4.29) compared with women living in towns of > 10,000 population. We observed no association between farm or rural residence and non-Hodgkin lymphoma (NHL; overall or for major subtypes) or multiple myeloma. In analyses of crop acreage, we observed no association between pasture or row crop acreage within 750 m of homes and risk of leukemia overall or for the AML subtype. Chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) risk was nonsignificantly elevated among women with pasture acreage within 750 m of their home (HRs for increasing tertiles= 1.8, 1.8 and 1.5) and with row crop acreage within 750 m (HRs for increasing tertiles of acreage= 1.4, 1.5 and 1.6) compared to women with no pasture or row crop acreage, respectively.

Conclusions—Iowa women living on a farm or in a rural area were at increased risk of developing AML, which was not related to crop acreage near the home. Living near pasture or row crops may confer an increased risk of CLL/SLL regardless of residence location. Further investigation of specific farm-related exposures and these cancers among women living on farms and in agricultural areas is warranted.

Keywords

Farm residence; Pesticides; Iowa Women's Health Study; GIS; Land use

1. Introduction

Cancer incidence and mortality in male farmers in the United States has been studied extensively (Blair and Freeman, 2009; Koutros et al., 2010; Blair et al., 1992; Waggoner et al., 2011 and Weichenthal et al., 2010). Compared with the general U.S. population, male farmers tend to have lower overall cancer incidence and mortality, which is likely attributed to their lower smoking prevalence and greater physical activity levels (Blair et al., 1992; Koutros et al., 2010; Waggoner et al., 2011 and Weichenthal et al., 2010). However, risk of certain cancers, including lymphohematopoietic cancers, have been reported to be elevated among farmers (Blair and Freeman, 2009 and Schenk et al., 2009).

Exposure to pesticides is one potential explanation for the excess of lymphohematopoietic cancers among farmers, although they can also be exposed to a variety of other chemical, physical, and biological hazards including chemical fertilizers, solvents, engine fuels and exhausts, mycotoxins, and zoonotic viruses (Coble et al., 2002; Blair and Freeman, 2009; Weichenthal et al., 2010). Associations between specific agricultural pesticides and lymphohematopoietic cancers have been evaluated in the Agricultural Health Study (AHS) cohort of pesticide applicators in Iowa and North Carolina (Weichenthal et al., 2010). Among pesticide applicators, significant dose–response relationships were reported between heptachlor/chlordane, diazinon, s-Ethyl dipropylthiocarbamate (EPTC), and fonofos and the incidence of leukemia (Beane Freeman et al., 2005; Purdue et al., 2007; van Bemmel et al., 2008 and Mahajan et al., 2006), between lindane and the incidence of non-Hodgkin lymphoma (NHL) (Purdue et al., 2007), and between permethrin and the incidence of multiple myeloma (Rusiecki et al., 2009). Evidence of pesticide-related lymphatic cancer risk is also supported by the European EPILYMPH study, a multicenter case-control study

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of 2348 incident lymphoma cases and 2462 controls (Cocco et al., 2012), which found a relationship between specific lymphoma subtypes and occupational exposure to organophosphate pesticides.

Substantially less information is available on lymphohematopoietic cancer risk for women who live on a farm. These women may be exposed to pesticides through their proximity to farmland (Coronado et al., 2011), participation in pesticide application (Kirrane et al., 2004), and/or take-home exposures (Curwin et al., 2005). In addition, women on farms may have other farming-related exposures, such as to animals, dust, bacteria, and endotoxin, among others previously mentioned (Omland, 2002).

In the Iowa Women's Health Study (IWHS) cohort, a large cohort of postmenopausal women in Iowa, we previously reported positive associations between farm residence and incident NHL for follow-up through 1992 (Folsom et al., 1996), and farm or rural residence and incident acute myeloid leukemia (AML) through 2002 (Sinner et al., 2005). Residential proximity to crop fields, which has been shown to increase pesticide exposures (Coronado et al., 2011) and pesticide levels in homes (Ward et al., 2006; Gunier et al., 2011), has not been previously evaluated in the IWHS. Corn and soybeans, the two major crops in Iowa, are almost universally treated with herbicides, and increasing acreage within 750 m of homes has been associated with higher herbicide concentrations in homes (Ward et al., 2006).

Here, we updated the analysis of residence location and lymphatic and hematopoietic cancer with follow-up through 31 December 2009, which allowed us to evaluate multiple myeloma and NHL subtypes for the first time. We also evaluated acreage of crops near homes as a surrogate for agricultural pesticide exposure and examined its relationship with lymphohematopoietic cancers.

2. Materials and methods

2.1. Study population

Details of the IWHS cohort have been published elsewhere (Folsom et al., 1996). Briefly, in 1986, a baseline questionnaire was mailed to 98,030 women aged 55–69 years selected randomly from Iowa 1985 driver's license records. Forty-two percent (*N*= 41,836) of the women responded and were followed for mortality and cancer incidence. Compared with respondents, non-respondents were less likely to live in rural counties, were slightly younger, had an average 0.4 kg/m^2 higher body mass index (BMI), and developed more smoking-related disease (Bisgard et al., 1994).

The baseline questionnaire included information on demographics, anthropometry, reproductive history, hormone-replacement therapy, medical conditions, smoking, alcohol consumption, dietary information, physical activity, and family history of cancer. Participants were also asked their residence location and chose from the following responses: on a farm; a rural area, but not a farm; city or town under 1000 residents; city or town of 1000 to 2499 residents; city or town of 2500 to 10,000 residents; or city or town of over 10,000 residents. Of the initial 41,836 women participating, we excluded a total of 4737 women reporting a prior cancer other than non-melanoma skin cancer or previous

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cancer chemotherapy, who had missing residence location, or who were still menstruating at the time of the baseline survey (not mutually exclusive).

We did not have a residential history for IWHS participants, and duration of residence was not asked at the time of enrollment. However, 31,732 (85.5%) women participated in a 1989 follow-up and were asked to indicate the main source of drinking water at their residence (public water supply, private well, bottled water, other, or don't know) and how long they drank from this source (< 1 year, 1–5 years, 6–10 years, 11–20 years, > 20 years, or don't know). We used the duration of use of the residential water source as a surrogate for residential duration. In 1989, nearly 90% of the women reported using their drinking water source for 6 or more years, and 69% for ≥ 20 years. Fewer than 4% of women reported primarily using bottled water, other, or an unknown water source. We did not take into account changes in residence after 1989.

2.2. Cohort follow-up

Incident lymphohematopoietic cancers diagnosed between 1986 and 2009, including 39 additional leukemia cases since 2003 and 439 NHL cases since 1993, were identified by linkage with the Iowa Cancer Registry, which is part of the National Cancer Institute Surveillance, Epidemiology and End Results (SEER) program. Topography and morphology codes from the International Classification of Diseases for Oncology, Third Edition (ICD-O-3) (Fritz et al., 2000) were used to classify cancers. For this update, we included only first primary cancers. Further, we evaluated NHL overall and by major subtypes, and we included multiple myeloma. Incident lymphoid neoplasms were classified according to the International Lymphoma Epidemiology Consortium (InterLymph) guidelines (Morton et al., 2007), whereas subtypes of myeloid leukemias were grouped using the SEER site recode ICD-O-3 definition (SEER, 2003). We limited analyses to lymphohematopoietic cancers and subtypes with at least 50 cases, including all leukemias (ICD-O-3 codes: 9733, 9742, 9801, 9805, 9840, 9845-9846, 9861, 9863, 9866-9867, 9871-9874, 9875-9876, 9800, 9860, 9870, 9891, 9895-9897, 9910, 9920, 9930, 9931, and 9963-9964), AML (9840, 9861, 9866-9867, 9871-9874, 9891, 9895-9897, and 9910, 9920), multiple myeloma (9732), NHL (9670, 9678-9680, 9684, 9690-9691, 9695, 9698, 9823, 9689, 9691, 9671, 9673, 9675, 9684, 9699, 9700-9701, 9702, 9760, 9764, 9675, 9705, 9708-9709, 9714, 9716-9718, 9728, 9835-9836, 9729, 9837, 9761-9762, 9827, 9931-9934, and 9940), and NHL subtypes diffuse large B-cell lymphoma (DLBCL) (9678-9680 and 9684), follicular lymphoma (9690-9691, 9695 and 9698), and chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) (9823 and 9670).

Person-years of follow-up were calculated from the date of the baseline questionnaire until the earliest of 1) the date of incident cancer diagnosis, 2) the date of death, 3) the date of emigration from Iowa, 4) the midpoint between the date of last contact and the date the subject was located outside Iowa, 5) (for deaths outside Iowa, for whom we don't know the precise date of emigration) the midpoint between the date of last contact and the date of death, or 6) 31 December 2009.

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2.3. Residential proximity to crop acreage

In order to estimate crop acreage in proximity to the women's homes, residential addresses at enrollment and follow-up were first geocoded in a Geographic Information System (GIS). Rural route addresses were sent to a commercial firm for comparison to a U.S. postal service database of rural routes, which had been converted to street addresses for 911 emergency systems. All addresses were then geocoded via batch matching with ESRI's ArcGIS 9.3 software using TeleAtlas Matchmaker Professional© (2006). For addresses that were not geocoded by batch matching, we checked for misspellings and attempted to geocode the corrected addresses. Geocoded addresses were classified by their match status into an exact match (matched to a street address, e.g., 123 Main Street), short street segment match (matched to a street that was located within a single zip code), intersection match, nearest intersection match, and zip code centroid match. To decrease the potential for exposure misclassification, we limited the analyses of crop acreage to women whose residential address geocode was a street-level match (defined hereafter as exact match, short street segment match, intersection match, or nearest intersection match, N= 27,749).

We used the U.S. Geological Survey 1992 National Land Cover Database (NLCD) to characterize land use in our study area (Vogelmann et al., 2001, Appendix), because of its closeness in time to the residential information. An internal validation process indicated that the 1992 NLCD agreed well with a 1992 crop map by the Iowa Department of Natural Resources. Of the 17 land use types that were present in Iowa (of 21 in the NLCD), row crops, pasture/hay, and small grain crops were the land use types with substantial agricultural pesticide applications (USDA, 1993). Corn and soybeans (row crops) comprise over 90% of the crop acreage in Iowa, and historically these two crops were rotated on a regular basis (Stern et al., 2012). Hay and alfalfa (pasture crops) account for the next largest acreage; whereas oats and wheat (small grains) constitute only a small percentage of agricultural land in Iowa (USDA, 2007). In the GIS, we calculated the acreage of row crops and pasture within 250, 500, 750, and 1000 m of each geocoded address (Appendix). Residential address was reported at enrollment (1986) and updated at the time of two follow-up surveys in 1987 and 1989. We chose the earliest reported address with the most accurate geocode (i.e., best match status) to assign the land use variables to participants, because many rural route addresses were being converted to street addresses during this period.

2.4. Data analysis

We conducted two primary risk analyses for incident lymphohematopoietic cancers diagnosed between 1986 and 2009, one of residence location and one of residential proximity to crop acreage (based on address in 1986based on address in 1987, or 1989, depending on which was the most accurate geocode). We compared risk factor and demographic characteristics, geocoding match status, and crop acreage across residence locations. Potential covariates for multivariate models were selected based on identified risk factors from the literature and from bivariate analyses, and included sociodemographic and lifestyle characteristics (e.g., smoking, alcohol intake, physical activity), and family history of cancer. Covariates were selected for inclusion in final models in a stepwise fashion based on a change in parameter estimates by ≥ 10% for one or more cancer type and included age

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at baseline, pack years of smoking (0, ≤1 to 19, 20 to 39, ≥ 40), marital status (married, other), blood transfusion history (yes/no), and alcohol consumption (none, < 4 g/day, ≥ 4 g/day). Though physical activity level was included in prior evaluations of AML and lymphoma in this cohort (Sinner et al., 2005 and Cerhan et al., 2002), models were unchanged following its adjustment.

After the baseline exclusions, there were 37,099 women who had information about residence location from the 1986 survey. Of these, 36,306 had complete information for covariate adjustment in multivariate analysis of residence location. Multivariate-adjusted hazard ratios (HR) and 95% confidence intervals (95% CI) were calculated using Cox proportional hazards regression. We estimated relative risks for lymphohematopoietic cancers by residence location, comparing each residence location to a referent group of women living in cities of over 10,000 residents.

A total of 27,749 women from the residence analysis with a street-level address match for their residence were eligible for the crop acreage analysis, and 27,184 of these had complete covariate information for inclusion in multivariate models. We categorized acreage of pasture and row crops into tertiles and estimated the HRs and 95% CIs for lymphohematopoietic cancers in relation to women with no acreage of pasture or row crops, respectively, within 250, 500, 750 and 1000 m of the residence. For tests of linear trend with increasing acreage of pasture or row crops, we assigned the median of the acreage within tertile categories and treated it as a continuous variable. We also modeled continuous acreage for both row and pasture crops and calculated the HRs per 10 acres. The 750 m buffer size was selected as the primary metric for analysis on the basis of another Iowa study (Ward et al., 2006), which found a stronger association between corn and soybean acreage and herbicide levels in Iowa homes for the 750 m buffer compared to smaller distances. We also calculated the proportion of land area within the 750 m buffer that was comprised of pasture and row crop acreage. We evaluated the other buffer sizes for comparison, based on previous studies that identified these as a range of distances for drift from pesticide applications (AgDRIFT Task Force, 1997; Woods et al., 2001).

We conducted additional analyses in order to minimize or examine the impact of potential biases. We compared the residence location analyses for the entire cohort to results for the street-level geocode subset. To evaluate risk among more residentially stable women, we repeated both residence location and crop acreage analyses after restricting to the subset of women reporting ≥ 6 years at their drinking water source (i.e., longer duration at residence) in 1989. To examine the likelihood that occupational exposures may have confounded observed associations, models excluding women reporting their usual occupation as farmers were compared to those including the full cohort. We further adjusted models of crop acreage for residence location to examine the influence of this variable on the results. Because we did not know specifically which pesticides were applied to each crop type, and because many women had both row and pasture crops within 750 m of their home, we also examined lymphohematopoietic cancer risk in relation to a combined acreage variable (i.e., total of row and pasture crop acreages) comparing to women with no pasture or row crop acreage within 750 m.

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All analyses were conducted using SAS (version 9.3, SAS Institute, Cary, NC), and $p \leq 0.05$ served as the criterion for significance tests.

3. Results

3.1. Residence location

The 37,099 women included in our analysis of residence location contributed a total of 636,633 person-years. A total of 7262 women (20%) lived on a farm and 2744 (7%) lived in a rural area (not on a farm). Compared with women living in other locations, farm residents were more likely to be homemakers or farmers, non-smokers, non-drinkers, and married (Table 1). Women living in cities/towns of over 10,000 residents had more years of education and were more likely to be past or current smokers and to have a lower BMI than women living in other residence locations.

The multivariate-adjusted associations of lymphohematopoietic cancers and residence location are presented in Table 2. Women who lived on a farm were 1.5 times (95% CI: 0.96–2.34) more likely to develop leukemia compared with women living in a city of over 10,000 residents. Risk of AML was significantly increased among farm residents (HR= 2.23, 95% CI: 1.25–3.99) and was also higher among women living in rural areas, but not on a farm (HR= 1.95, 95% CI: 0.89–4.29). There was no apparent association between residence location and NHL, nor were there significant associations with NHL subtypes. In sensitivity analyses, excluding farmers or restricting to the subgroup of women reporting ≥ 6 year duration at their residence (*N*= 20,881) did not appreciably change risk estimates, and the 95% CIs overlapped with those from models using the full cohort.

3.2. Geocoding quality

The quality of geocoding matches varied by residence location (Table 3). The percentage of women in cities over 10,000 residents with a street-level match status was greater than 97%. In contrast, about half of addresses on farms, in rural areas, or in cities/towns under 1000 residents were matched to zip code centroids (58.7%, 50.5, and 53.5%, respectively). Fewer than 2% of addresses were matched to a short street segment, intersection, or nearest intersection each, regardless of residence location, and only 378 (1.3%) addresses could not be geocoded. Our findings for farm residence and risk of AML held when we restricted our analysis to the subgroup of women with a street-level geocoded address, indicating that this subgroup had risks by residence location that were similar to the cohort overall.

3.3. Crop acreage analyses

Row crop acreage within 750 m of the homes was substantially greater than pasture acreage for each residence location (Table 4). As expected, women living in cities/towns of over 10,000 residents had the lowest acreage near their homes (pasture acreage median= 0.2, interquartile range [IQR]= 0–14.7; row crop median= 2.5; IQR= 0–62.1). Women living in towns of fewer than 1000 residents had the highest acreage of pasture and row crops (median [IQR] 25.1[6.2–58.1] and 127.7 [33.4–236.9], respectively), followed by women living on farms and towns of 1000 to 2499 residents. In contrast, women living in rural areas, but not on farms, had median acreage of both pasture and row crops that were about

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30–40% less than farm and small town residents. Median pasture crop acreage comprised only a small percentage of the total area within the 750 m buffer (from < 1% to 5.7%), whereas the row crop acreage made up a larger proportion (up to 29.2%) (Table 4). These results indicate that residence location was not strongly correlated with acreage near the home.

Multivariate-adjusted models of most lymphohematopoietic cancers and tertiles of pasture crop acreage within 750 m of the home yielded non-significant HRs or non-monotonic risk patterns (Table 5). There was a significant inverse trend for risk of leukemia with increasing pasture crop acreage. However, compared to women with no pasture acreage within 750 m of their residences, there was no association with AML across tertiles of pasture acreage. There was a significantly greater NHL risk for women with > 0 to ≤9.1 acres of pasture (HR= 1.34, 95% CI: 1.03–1.75), but not in the second (9.2–37.1 acres) or third (≥ 37.2 acres) tertiles of acreage. These results were driven primarily by the DLBCL subtype; a 67% greater risk of developing DLBCL (95%CI: 1.04–2.64) was identified in the lowest tertile of pasture crop acreage, but risk was not increased in the higher tertiles. For CLL/ SLL, risk was significantly increased in the first and second tertile (HRs= 1.81, 95%CI: 1.08–3.05 and HR= 1.80, 95%CI: 1.08–3.02).

Row crop acreage within 750 m of the home was not associated with risk of AML. There was a borderline increased risk of multiple myeloma for women with > 0 to 31.6 acres of row crops (HR= 1.74, 95%CI:0.97–3.14), but risk estimates in the second and third tertiles of acreage (HR= 1.54, 95%CI:0.85–2.80 and HR= 1.21, 95%CI:0.65–2.27, respectively) did not reach statistical significance, and there was no trend apparent with increasing acreage. Row crop acreage was associated with elevated but non-significant risks of CLL/SLL that increased monotonically with tertiles (HRs 1.35, 1.46, and 1.57), although the positive trend was not significant. Adjustment for residence location did not change these results.

There was no elevated risk evident per 10-acre increase in either crop type (Table 5). Similar to results for row crops, a tertile analysis of the total crop acreage (row crops and pasture combined) within 750 m of the home compared to those with no crop acreage showed elevated but non-significant risks for CLL/SLL (data not shown). As with analyses of residence location, restriction to women who reported longer duration at the home or to non-farmers had minimal impact on risk estimates. Analyses of crop acreage within 500 m and 1000 m of homes showed similar associations as those based on 750 m for CLL/SLL. Specifically, risk of CLL/SLL was elevated in association with both crop types (and point estimates were higher for the 1000 m buffers). However, associations for crop acreage and multiple myeloma and DLBCL were weaker at these distances (data not shown).

4. Discussion

Consistent with an earlier report (Sinner et al., 2005), we found that IWHS participants who lived on a farm or in a rural area at enrollment continued to have an increased risk of AML compared with women living in a city of over 10,000 residents. In contrast, a previous finding of a positive association between farm residence and NHL risk (Folsom et al., 1996) did not persist in this extended follow-up. Acreage of pasture and row crops within 750 m of

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residences, which was highest for farms but comparable for some non-farm residence locations, was not associated with AML risk. Analyses of crop acreage were most suggestive of an increased risk of the NHL subtype CLL/SLL in relation to pasture and row crop acreage near the home. Weaker associations were observed for other subtypes.

We observed a greater than two-fold risk of AML among women living on a farm compared to those living in cities of more than 10,000 residents. A recent analysis of cancer in the AHS cohort did not find greater AML risk among farmers' spouses compared with the general population (standardized incidence ratio [SIR]= 0.98; 95% CI: 0.56–1.59) (Koutros et al., 2010), although an analysis of mortality in the same group found elevated total leukemia mortality (relative standardized mortality ratio [rSMR]= 2.10; 95% CI: 1.49–2.97) relative to the lower overall mortality rate in the cohort (Waggonner et al., 2011). The fact that we observed a positive association with AML incidence among farm residents, which remained even after restriction to women who did not consider their occupation to be farmers, suggests that occupational farming exposures may not explain the increased risk we observed. However, the number of women reporting their usual occupation as farmers was small (*N*= 1333), and it is possible that women residing on farms are involved in farming-related activities that increase their exposure to pesticides (Kirrane et al., 2004), animals, and to other farming exposures, or that they have indirect 'take-home' exposures from an occupationally-exposed family member (Gladen et al., 1998). Increases in AML risk have been previously reported among those occupationally exposed to pesticides. A meta-analysis of 17 cohort studies and 16 case-control studies examining myeloid leukemias reported a marginally significant increased risk of AML among pesticide applicators (meta-RR= 1.07; 95% CI: 0.98–1.07) (Van Maele-Fabry et al., 2007). The increased risk of AML was stronger when restricted to cohort studies (meta-RR= 1.55; 95% CI: 1.02–2.34), and there were non-significant increased risks for both men and women (meta-RR= 1.10, 95% CI: 0.98–1.25, meta-RR= 1.29; 95% CI: 0.63–2.64, respectively).

Though farm residence was associated with AML risk, acreage of row and pasture crops near the home was not. The increased AML risk observed among women on farms, the 2-fold elevated risk among women in rural residences that were not farms, and the lack of association with crop acreage suggest that farm exposures other than crop pesticides may be important AML risk factors. For example, links between animal husbandry and increased leukemia risk have been reported in the AHS (Beane Freeman et al., 2012) and by others (Svec et al., 2005), though AML was not specifically examined. The etiologic pathway for animal exposures in the development of these cancers has not been clearly elucidated, but is hypothesized to involve infectious agents (Svec et al., 2005). Our finding of no association between farm residence and NHL or specific NHL subtypes is consistent with findings within the AHS, in which farmers' spouses had a similar risk of NHL, DLBCL, CLL and multiple myeloma compared to the general population, though there were fewer cases in this comparatively younger cohort (Koutros et al., 2010). In contrast, one study of men found a positive association between farm residence and NHL risk after adjusting for occupational pesticide exposure (McDuffie et al., 2002). Farm occupation has been associated with increased NHL risk in men and women in past studies. Two older reviews of this topic reported some elevated but non-significant associations between farming and NHL risk;

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both found substantial heterogeneity in risks by study design and size (Blair et al., 1992 and Khuder et al., 1998). A more recent meta-analysis supports an excess of NHL risk among farmers, including both men and women (Boffetta and de Vocht, 2007). However, these studies may not be generalizable to women living rather than working on farms.

Analyses of acreage of pasture and row crops near homes yielded suggestive positive associations with the incidence of CLL/SLL, and a monotonic trend in relation to row crops, the most prevalent land use. Associations were present between row crops and risk of multiple myeloma and between pasture crops and DLBCL, but risks did not increase with added acreage. A few other studies have used crop acreage as a surrogate for indirect agricultural pesticide exposure to evaluate childhood cancers (Carozza et al., 2008; Reynolds et al., 2005). The results of these studies were equivocal; there were null results for childhood lymphohematopoietic malignancies in Calfornia (Reynolds et al., 2005) and elevated risks for both childhood NHL and childhood leukemias across the U.S., including AML (Carozza et al., 2008). To the best of our knowledge, no studies have evaluated adult lymphohematopoietic cancers using these methods.

There is evidence that occupational exposure to agricultural pesticides increases lymphoma risk. Associations between occupational pesticide exposures, particularly organophosphates, and CLL were identified in a European case-control study, but sex-specific analyses were not conducted (Cocco et al., 2012). The Pesticide Users Health Study, a cohort of nearly 66,000 commercial pesticide applicators in England, found that incidence of multiple myeloma among licensed applicators was higher than expected for men (SIR: 1.49 95% CI: 1.05–2.13), and for women based on 4 cases (SIR:10.9, 95%CI: 4.10–29.1) (Frost et al., 2011). They did not examine the CLL or DLBCL subtypes of NHL specifically, but report no elevation in NHL risk overall among men (there was only 1 reported case among women). In the AHS, occupational exposure to atrazine was weakly associated with leukemia overall and with the CLL/SLL/MCL subtype (Beane Freeman et al., 2011), and glyphosate was linked to multiple myeloma risk (De Roos et al., 2005).

Shifts in herbicide use over time and their varying environmental persistence highlight the challenge in using acreage as a surrogate for specific agrochemical exposures. Iowa leads the U.S. in corn crop acreage and is the second-largest producer of soybean crops (USDOC, 1994; USDA, 2013a); 97% of this acreage is treated with herbicides (USDA, 2007). Iowa pesticide use data for 1990–2006 indicates widespread use of atrazine on corn, as well as high use of dicamba, acetochlor, and metolachlor, though the use of each has changed over time. Up to half of Iowa's soybean crops were treated with trifluralin in the early 1990s, but this herbicide was gradually replaced with glyphosate, which is also used on corn (NASS, 2013). A study by Ward et al. (2006) found detections of metolachlor (21.4%) and trifluralin (15.2%) in house dust sampled from Iowa homes in 1998–2000, though several high-use herbicides (e.g., atrazine and acetochlor) were detected less frequently and glyphosate was not measured. This same study found that the percentage of homes with herbicide detections increased monotonically with increasing crop acreage within 750 m of the home, even after adjusting for an agricultural worker in the home. The distribution of concentrations in homes with >200 acres within 750 m overlapped with that of homes with an agricultural worker. In our study, only ~1% of pasture acreage and 19% of row crop acreage within 750 m of our

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study homes exceeded 200 acres, therefore only some individuals in the top tertile of crop exposures met this threshold in our analyses. If crop acreage is a valid surrogate for pesticide exposures, this may in part explain the weak associations we observed, and particularly our lack of association with crop acreage as a continuous variable.

Our study had several limitations. IWHS was not designed to assess farm-related exposures; therefore, we did not have detailed information on exposures such as pesticide applications by the women or other farming activities. However, analyses of residence location excluding women who reported farming as their occupation did not change our results. Geocoding error was a potential source of exposure misclassification, but we limited analyses of crop acreage to street-level geocodes. This resulted in the exclusion of nearly 60% of women residing on farms from the crop analyses; but demographic and lifestyle characteristics of the excluded women residing on farms did not differ from those retained for analysis. Further, the elevation in AML risk among women on farms remained when we restricted to the subset of women with street-level geocodes. Most poor quality geocodes in our analyses were for rural route addresses, which subsequently have been converted to street addresses to improve 911 emergency response, reducing this concern for future studies.

We lacked a complete residence history and precise information on the length of time that women lived at their enrollment residence, which was used to classify residence location. However, most women reported >20 years at their water source in 1989 and few moved between baseline and early follow-up surveys, suggesting the population was residentially stable. Further, we found similar results when we restricted analyses to women reporting longer residential duration, indicating that residential mobility is not likely to be a major source of bias in our analyses. Similarly, we assumed that the assignment of crops based on 1992 land cover data was relevant for the etiologic time period of interest (i.e., years prior to 1986). While historical land use data was not available for this analysis, corn and soybeans have dominated crop acreage in Iowa, and their production has increased over time (USDA, 2013b; Iowa State University, 2002). Further, although the type of pesticides used on corn and soybeans differs, historically these crops have been regularly rotated (Stern, 2012). For both of these reasons, we expect that exposures based on the 1992 NLCD are representative of earlier time periods. Crop acreage within a circular buffer around homes is a somewhat crude proxy for indirect agricultural pesticide exposure. Information such as crop-specific pesticide use, wind direction, and occupational pesticide exposures would likely reduce exposure misclassification in our analysis. In addition, exposure validation studies to evaluate the relationship between crop acreage and pesticides in carpet dust or biological samples would further improve our understanding of the spatial distribution of pesticides from agricultural sources.

Strengths of this study are the large sample size, its focus on older women, and the long follow-up period (mean=17.2 years), yielding a relatively large number of lymphohematopoietic cancer cases that allowed us to perform analyses by major subtypes. As an update to prior IWHS analyses, we improved the specificity of case ascertainment by applying the updated lymphoma classification criteria, incorporated a measure of residential duration, and considered potential confounding by farming occupation. Although not a direct measure of agricultural pesticide exposure, crop acreage near residences provided a

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more specific measure of residential exposure to agricultural pesticides than residence location alone. Because over 90% of Iowa's land use is agricultural (USDA, 2007), the majority of Iowa's residents, including those living in more populated cities/towns, have opportunities for indirect exposures to agricultural pesticides. This substantial agricultural land use explains why residence location categories were not highly correlated with crop acreage at any of the distances evaluated, and indicates that farm residence alone may not be a good surrogate for agricultural pesticide exposures in Iowa.

5. Conclusions

In summary, this updated analysis supports the previously observed increased risk of AML associated with farm and rural residence in this cohort. This positive association warrants further investigation of the potential etiologic role of specific farming exposures in regard to AML; our analyses of crop acreage did not suggest that indirect exposure to crop pesticides is an important AML risk factor. Our findings also suggest that density of row and pasture crop acreage near the home may be related to risk of CLL/ SLL; however, the validity of using crop acreage as a surrogate for agricultural pesticide exposures warrants further investigation. Future studies are needed to examine whether residential exposure to specific pesticides, especially at lower exposure levels, is linked to these cancers. Our results suggest that other exposures related to farm and rural living may be risk factors for AML. As most studies of farming exposures and cancer risk have been conducted in occupational settings and predominantly among men, this study contributes important clues for future research about these relationships in older women.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.envres.2014.05.028.

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Table 1

Selected characteristics by residence location, Iowa Women's Health Study (*N*= 37,099).

Characteristic	Residence location					
	Farm	**Rural area, not on a farm**	**City/town under 1000 residents**	**City/town of 1000 to 2499 residents**	**City/town of 2500 to 10,000 residents**	**City/town of over 10,000 residents**
N (%)	7262 (20)	2744 (7)	4110 (11)	4002 (11)	6426 (17)	12,555 (34)
Person-years of follow-up	132,382	46,405	71,035	68,277	109,758	208,776
Mean length of follow-up, *y* (SD)	18.2 (6.5)	16.9 (7.1)	17.3 (6.9)	17.1 (6.9)	17.1 (7.0)	16.6 (7.2)
Mean age at baseline, *y* (SD)	61.3 (4.1)	61.3 (4.2)	62.2 (4.2)	62.3 (4.3)	61.9 (4.3)	61.6 (4.2)
Occupation, *N* (%)						
Homemaker	4141 (57)	981 (36)	1552 (38)	1404 (35)	2005 (31)	3903 (31)
Professional	753 (10)	395 (14)	535 (13)	577 (14)	973 (15)	2116 (17)
Clerical	835 (12)	701 (26)	940 (23)	1060 (26)	2052 (32)	4533(36)
Crafts	659 (9)	564 (21)	917 (22)	815 (20)	1225 (19)	1895 (15)
Farmer	843 (12)	85 (3)	139 (3)	123 (3)	134 (2)	55 (0)
Other	31 (0)	18 (1)	27 (1)	23 (1)	37 (1)	53 (0)
Race, *N* (%)						
White	7153 (100)	2679 (99)	4007 (100)	3918 (100)	6288 (99)	12,285 (99)
Other	23 (0)	26 (1)	20 (0)	16 (0)	43 (1)	180 (1)
Education, *N* (%)						
Less than high school	853 (12)	297 (11)	523 (13)	487 (12)	593 (9)	568 (5)
High school	3791 (52)	1456 (53)	2266 (55)	2111 (53)	3364 (52)	6336 (51)
More than high school	2605 (36)	983 (36)	1312 (32)	1396(35)	2460 (38)	5634 (45)
Smoking status, *N* (%)						
Never	5882 (82)	1752 (65)	2812 (70)	2654 (68)	4021 (64)	6920 (56)
Current	542 (8)	418 (15)	572 (14)	577 (15)	1033 (16)	2308 (19)
Former	709 (10)	533 (20)	656 (16)	701 (18)	1276 (20)	3155 (25)
Pack-years of smoking, *N* (%)						
Never smoked	5882 (82)	1752 (65)	2812 (70)	2654 (68)	4021 (64)	6920 (56)
1–19	613 (9)	343 (13)	478 (12)	504 (13)	873 (14)	2093 (17)
20–39	364 (5)	321 (12)	437 (11)	429 (11)	791 (13)	1748 (14)
≥ 40	233 (3)	256 (10)	283 (7)	310 (8)	577 (9)	1513 (12)

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Characteristic	Residence location					
	Farm	Rural area, not on a farm	City/town under 1000 residents	City/town of 1000 to 2499 residents	City/town of 2500 to 10,000 residents	City/town of over 10,000 residents
Marital status, *N* (%)						
Married	6415 (89)	2259 (83)	3020 (74)	2913 (73)	4549 (71)	9140 (73)
Other	804 (11)	468 (17)	1052 (26)	1056 (27)	1831 (29)	3364 (27)
Body mass index (kg/m^2), *N* (%)						
< 25	2535 (35)	1023 (37)	1461 (36)	1536 (38)	2633 (41)	5515 (44)
25–29.9	2822 (39)	1010 (37)	1526 (37)	1462 (37)	2356 (37)	4512 (36)
≥ 30	1905 (26)	711 (26)	1123 (27)	1004 (25)	1437 (22)	2528 (20)
Blood transfusion, *N* (%)						
No	5346 (74)	1920 (70)	2941 (72)	2830 (71)	4581 (71)	8642 (69)
Yes	1658 (23)	738 (27)	1011 (25)	1032 (26)	1599 (25)	3391 (27)
Don’t know	258 (4)	86 (3)	158 (4)	140 (4)	246 (4)	522 (4)
Alcohol consumption (g/day), *N* (%)						
0	4773 (66)	1612 (59)	2557 (62)	2322 (58)	3599 (56)	6074 (48)
0.01–4	1699 (23)	610 (22)	913 (22)	973 (24)	1457 (23)	3176 (25)
≥ 4	790 (11)	522 (19)	640 (16)	707 (18)	1370 (21)	3305 (26)
Physical activity level, *N* (%)						
Low	3328 (47)	1258 (47)	2034 (51)	1855 (48)	3004 (48)	5753 (47)
Medium	2052 (29)	734 (27)	1069 (27)	1131 (29)	1718 (27)	3326 (27)
High	1684 (24)	704 (26)	923 (23)	917 (24)	1592 (25)	3295 (27)

Proportions within categories may sum to > 100% due to rounding.

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Table 2

Association between residence location and lymphohematopoietic cancers in the Iowa Women's Health Study, 1986–2009 (*N* = 36,306).

Cancer site	Residence location					
	Farm	**Rural area, not on farm**	**City/town under 1000 residents**	**City/town of 1000 to 2499 residents**	**City/town of 2500 to 10,000 residents**	**City/town of over 10,000 residents**
Leukemia						
Cases	40	11	15	16	12	44
Adjusted HR	1.50 (0.96–2.34)	1.16 (0.60–2.25)	1.00 (0.55–1.80)	1.11 (0.62–1.97)	0.51 (0.27–0.98)	1.0 (Ref)
Acute myeloid leukemia						
Cases	30	9	9	10	8	21
Adjusted HR	2.23 (1.25–3.99)	1.95 (0.89–4.29)	1.23 (0.56–2.69)	1.42 (0.67–3.03)	0.71 (0.31–1.60)	1.0 (Ref)
Multiple myeloma						
Cases	28	6	21	6	26	43
Adjusted HR	1.04 (0.64–1.71)	0.64 (0.27–1.52)	1.39 (0.82–2.36)	0.41 (0.18–0.97)	1.14 (0.70–1.86)	1.0 (Ref)
Non-Hodgkin lymphoma						
Cases	122	38	53	59	102	181
Adjusted HR	1.09 (0.86–1.39)	0.97 (0.68–1.38)	0.85 (0.63–1.16)	0.98 (0.73–1.32)	1.07 (0.84–1.37)	1.0 (Ref)
DLBCL						
Cases	34	14	22	13	32	51
Adjusted HR	1.03 (0.67–1.61)	1.25 (0.69–2.27)	1.22 (0.74–2.02)	0.75 (0.41–1.39)	1.17 (0.75–1.82)	1.0 (Ref)
Follicular lymphoma						
Cases	21	3	7	10	22	29
Adjusted HR	1.28 (0.72–2.31)	0.48 (0.15–1.59)	0.76 (0.33–1.75)	1.12 (0.55–2.31)	1.51 (0.87–2.63)	1.0 (Ref)
CLL/SLL						
Cases	40	5	11	22	27	57
Adjusted HR	1.11 (0.73–1.69)	0.40 (0.16–1.00)	0.55 (0.29–1.04)	1.13 (0.69–1.86)	0.90 (0.57–1.42)	1.0 (Ref)

Abbreviations: hazard ratio (HR); acute myeloid leukemia (AML); multiple myeloma (MM); diffuse large B-cell lymphoma (DLBCL); chronic lymphocytic lymphoma (CLL); small lymphocytic lymphoma (SLL).

Adjusted for baseline age, smoking, marital status, history of blood transfusion, and alcohol consumption.

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Table 3

Geocoding match status by residence location in the Iowa Women's Health Study (*N* = 37, 099).

Match status	Residence						Total
	Farm ***N* (%)**	**Rural area, not on farm** ***N* (%)**	**City/town under 1000 residents** ***N* (%)**	**City/town of 1000 to 2499 residents** ***N* (%)**	**City/town of 2500 to 10,000 residents** ***N* (%)**	**City/town of over 10,000 residents** ***N* (%)**	
[a] Street-level match	2946 (40.6)	1338 (48.8)	1869 (45.5)	3268 (81.7)	6095 (94.8)	12233 (97.4)	27,749 (74.8)
Zip code centroid	4265 (58.7)	1385 (50.5)	2200 (53.5)	703 (17.6)	239 (3.7)	69 (0.6)	8861 (23.9)
Non-geocodable	51 (0.7)	21(0.8)	41 (1.0)	31 (0.8)	92 (1.4)	142 (2.0)	378 (1.3)
Total	7262	2744	4110	4002	6426	12,555	37,099

[a] Exact, short street segment, intersection, or nearest intersection match.

Proportions within categories may sum to >100% due to rounding.

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Table 4

Acreage of pasture and row crops within 750 m of residences, by residence location[a] (*N* = 27,749).

	Residence location					
	Farm	**Rural area, not on farm**	**City/town under 1000 residents**	**City/town of 1000 to 2499 residents**	**City/town of 2500 to 10,000 residents**	**City/town of over 10,000 residents**
N	2946	1338	1869	3268	6095	12,233
Pasture						
Median – acres	20.0	12.0	25.1	21.8	11.3	0.22
Median – % of 750 m buffer	4.6	2.7	5.7	5.0	2.6	0.05
IQR – acres	3.4, 51.6	0.22, 42.7	6.2, 58.1	4.9, 48.5	0.89, 37.1	0, 12.2
IQR – % of 750 m buffer	0.77, 11.8	0.05, 9.8	1.4, 13.3	1.1, 11.1	0.20, 8.5	0, 2.8
Row crop						
Median – acres	110.6	77.8	127.7	95.6	50.7	2.5
Median – % of 750 m buffer	25.3	17.8	29.2	21.9	11.6	56.1
IQR – acres	23.1, 230.0	4.2, 196.3	33.4, 236.9	27.1, 182.8	6.5, 144.1	0, 62.1
IQR – % of 750 m buffer	5.3, 52.6	0.97, 44.9	7.6, 54.2	6.2, 41.8	1.5, 33.0	0, 14.2

Abbreviations: IQR, Interquartile range.

[a] Analyses were restricted to addresses geocoded with an exact, short street segment, intersection, or nearest intersection match. Addresses matched to a zip code centroid were excluded.

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Table 5

Association between acreage of pasture and row crops within 750 m of the residence and lymphohematopoietic cancers in the Iowa Women's Health Study, 1986–2009 (*N* = 27,184).

Cancer	Pasture					Row crop				
	Acres within 750 m	Cases	HR	95% CI	P_{trend}	Acres within 750 m	Cases	HR	95% CI	P_{trend}
Leukemia										
	0	36	1.00	Ref	0.05	0	27	1.00	Ref	0.15
	≤9.1	24	0.91	0.54–1.53		≤31.6	26	0.89	0.52–1.53	
	9.2–37.1	18	0.65	0.37–1.14		31.7–141.7	21	0.69	0.39–1.23	
	37.2+	15	0.56	0.30–1.02		141.8+	19	0.64	0.36–1.16	
	HR/10 acres		0.93	0.87–1.00		HR/10 acres		0.99	0.97–1.01	
Acute myeloid leukemia										
	0	19	1.00	Ref	0.33	0	14	1.00	Ref	0.40
	≤9.1	16	1.14	0.58–2.21		≤31.6	16	1.05	0.51–2.16	
	9.2–37.1	8	0.53	0.23–1.22		31.7–141.7	10	0.75	0.35–1.63	
	37.2+	11	0.76	0.36–1.59		141.8+	12	0.77	0.35–1.66	
	HR/10 acres		0.96	0.89–1.04		HR/10 acres		0.99	0.97–1.02	
Multiple myeloma										
	0	32	1.00	Ref	0.90	0	17	1.00	Ref	0.61
	≤9.1	21	0.88	0.51–1.53		≤31.6	31	1.74	0.97–3.14	
	9.2–37.1	26	1.03	0.61–1.72		31.7–141.7	30	1.54	0.85–2.80	
	37.2+	23	0.93	0.54–1.58		141.8+	23	1.21	0.65–2.27	
	HR/10 acres		1.00	0.95–1.05		HR/10 acres		1.00	0.98–1.02	
NHL										
	0	110	1.00	Ref	0.19	0	87	1.00	Ref	0.75
	≤9.1	109	1.34	1.03–1.75		≤31.6	104	1.11	0.84–1.48	
	9.2–37.1	103	1.20	0.92–1.57		31.7–141.7	105	1.07	0.81–1.43	
	37.2+	80	0.96	0.72–1.28		141.8+	106	1.10	0.83–1.46	
	HR/10 acres		0.99	0.97–1.02		HR/10 acres		1.00	0.99–1.01	
DLBCL										
	0	32	1.00	Ref	0.08	0	30	1.00	Ref	0.94

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Cancer	Pasture					Row crop				
	Acres within 750 m	Cases	HR	95% CI	P_{trend}	Acres within 750 m	Cases	HR	95% CI	P_{trend}
	≤9.1	40	1.67	1.04–2.64		≤31.6	33	1.02	0.62–1.67	
	9.2–37.1	29	1.15	0.69–1.89		31.7–141.7	24	0.70	0.41–1.20	
	37.2+	20	0.80	0.46–1.41		141.8+	34	1.01	0.61–1.65	
	HR/10 acres		0.97	0.93–1.02		HR/10 acres		1.00	0.99–1.02	
Follicular lymphoma										
	0	26	1.00	Ref	0.11	0	17	1.00	Ref	0.12
	≤9.1	17	0.91	0.50–1.69		≤ 31.6	19	1.04	0.54–2.00	
	9.2–37.1	13	0.65	0.33–1.26		31.7–141.7	20	1.05	0.55–2.02	
	37.2+	11	0.57	0.28–1.15		141.8+	11	0.59	0.28–1.27	
	HR/10 acres		0.96	0.90–1.03		HR/10 acres		0.98	0.96–1.01	
CLL/SLL										
	0	25	1.00	Ref	0.62	0	21	1.00	Ref	0.21
	≤9.1	33	1.81	1.08–3.05		≤ 31.6	30	1.35	0.77–2.36	
	9.2–37.1	35	1.80	1.08–3.02		31.7–141.7	34	1.46	0.85–2.52	
	37.2+	28	1.49	0.87–2.57		141.8+	36	1.57	0.91–2.68	
	HR/10 acres		1.02	0.98–1.06		HR/10 acres		1.01	0.99–1.02	

Abbreviations: hazard ratio (HR); acute myeloid leukemia (AML); multiple myeloma (MM); non-Hodgkin lymphoma (NHL); diffuse large B-cell lymphoma (DLBCL); chronic lymphocytic lymphoma (CLL); small lymphocytic lymphoma (SLL).

Analyses were restricted to addresses geocoded with an exact, short street segment, intersection, or nearest intersection match. Addresses matched to a zip code centroid were excluded.

Fully-adjusted models adjusted for baseline age, smoking, marital status, history of blood transfusion, and alcohol consumption.