ORIGINAL ARTICLE

Risk of lymphatic or haematopoietic cancer mortality with occupational exposure to animals or the public

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Background: Occupational exposure to animals or the public could result in exposure to infectious agents, which may play a role in the aetiology of lymphohaematopoietic (LH) cancers.

Aims: To conduct a population based, case-control study of death certificate data from 1984 to 1998 in 24 US states in order to evaluate the risk of mortality from LH neoplasms associated with occupational exposure to animals or the public.

Methods: Cases were selected as those with an underlying cause of death of non-Hodgkin's lymphoma (NHL, n = 72 589), Hodgkin's disease (HD, n = 5479), multiple myeloma (n = 35 857), or leukaemia (n = 68 598); 912 615 controls were randomly selected from all remaining deaths, frequency matched on age, sex, race, and geographic region.

Results: Occupational exposure to animals was associated with modest increased risks of mortality from all four LH cancers; these associations varied by region. Occupational exposure to the public was associated with only negligible increased risk with LH cancer outcomes. Occupations involving animal exposure were predominantly agricultural, and the risks associated with employment in the livestock industry exceeded the corresponding risks associated with the crop industry for all outcomes except HD.

Conclusions: Increased risks of NHL, HD, multiple myeloma, and leukaemia were associated with occupations that involved animal exposure. Regional differences in risk imply that the risks may be associated with exposure to specific livestock or farming practices. However, these associations may be confounded by other farming related exposures, such as pesticides. Because the use of death certificates to classify occupation may result in misclassification during aetiologically relevant time periods, these hypotheses should be further explored in studies with detailed information on lifetime occupation.

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Because the haematopoietic and lymphatic systems are involved in immune processes, triggers of immune response (that is, infectious agents) may influence the occurrence of lymphatic or haematopoietic malignancies, possibly by stimulating lymphocyte proliferation. Consequently, the frequency of exposure to infectious agents could have bearing on the risk of developing these diseases. A common route of exposure is occupational contact with animals or with other people

Numerous studies relate lymphohaematopoietic (LH) cancers with farming and other occupations involving contact with animals or animal products. Blair *et al* describe excess LH cancer mortality among white male farmers and excess non-Hodgkin's lymphoma (NHL) mortality among white farmers in general.[1] Other studies have also reported farmers to be at increased risk for NHL, chronic lymphoid leukaemia (CLL), Hodgkin's disease, and multiple myeloma.[2–7] Veterinarians are undoubtedly occupationally exposed to zoonotic infectious agents and several studies of cancer in veterinarians have been conducted. Figgs and colleagues[8] reported a significant increased risk of multiple myeloma and Blair *et al* found elevated proportions of LH cancer deaths among veterinarians.[9]

Lymphohaematopoietic malignancies have been associated with several occupations that entail interaction with the public. Healthcare workers have increased risks of multiple myeloma, leukaemia, and other LH cancers in some studies.[10–17] University faculty and school teachers have been overrepresented among cases of multiple myeloma,[8 18] NHL,[3 11 19–21] leukaemia,[3 18–20 22 23] and Hodgkin's disease,[19] compared to controls. Increased risks of some or all of these diseases have also been found among child care workers,[18 23] administrative occupations,[11 24 25] hairdressers and cosmetologists,[18 19 23 25 26] and food service workers.[25]

We conducted a case-control study of death certificate data from 24 US states to evaluate the risk of mortality from LH neoplasms associated with occupational exposure to animals or the public.

MATERIALS AND METHODS

The 24 states dataset is comprised of all death certificates from 24 US states (Northeast: Maine, New Hampshire, New Jersey, Rhode Island, Vermont; North Central: Indiana, Kansas, Missouri, Nebraska, Ohio, Wisconsin; South: Georgia, Kentucky, North Carolina, Oklahoma, South Carolina, Tennessee, West Virginia; West: Colorado, Idaho, Nevada, New Mexico, Utah, Washington) for the years 1984–98. This dataset is maintained by the National Cancer Institute, the National Institute for Occupational Safety and Health, and the National Center for Health Statistics.[11]

Cases were identified from data on underlying cause of death as reported on the death certificate (International Classification of Diseases, 9th revision (ICD-9) code). The four case groups were non-Hodgkin's lymphoma (NHL) (ICD-9 200.0–200.9, 202.0–202.1, 202.7–202.9; n = 72 589), Hodgkin's disease (HD) (ICD-9 201.0–201.9; n = 5479), multiple myeloma (ICD-9 203.0–203.9, excluding 203.1 and 203.8; n = 35 857), and leukaemia (ICD-9 202.4, 203.1, 204.0–208.9, excluding 207.1; n = 38 598).

Abbreviations: ALL, acute lymphoid leukaemia; AML, acute myeloid leukaemia; CLL, chronic lymphoid leukaemia; HD, Hodgkin's disease; LH, lymphohaematopoietic; NHL, non-Hodgkin's lymphoma; RUCC, rural-urban continuum code; SES, socioeconomic status

Table 1 Characteristics of LH cancer mortality cases and controls, United States 1984–98*

	Controls (n = 912615)	Non-Hodgkin's lymphoma (n = 72589)	Hodgkin's disease (n = 5479)	Multiple myeloma (n = 35857)	Leukaemia (n = 68598)
Race					
White	90.4	93.2	91.1	82.9	91.2
Black	8.8	5.8	8.6	16.3	7.9
Other	0.9	1.0	0.4	0.8	0.9
Marital status					
Single	8.4	6.8	13.1	5.3	6.2
Married	48.9	57.3	59.4	57.1	57.2
Widowed	32.6	28.9	17.8	31.2	29.6
Divorced	9.9	6.8	9.6	6.3	6.9
Unknown	0.2	0.1	0.1	0.1	0.1
Gender					
Male	52.3	50.9	58.2	50.5	54.3
Female	47.7	49.2	41.9	49.5	45.7
Age					
25–44	6.8	6.7	32.4	1.7	7.7
45–64	22.4	23.7	25.1	22.7	20.6
65+	70.8	69.6	42.6	75.6	71.8
Socioeconomic status†					
I	14.2	10.9	12.4	13.6	12.5
II	19.2	16.5	19.2	17.6	17.1
III	50.4	51.6	47.7	49.6	49.8
IV	12.8	16.0	15.4	15.1	15.6
V	3.5	5.0	5.3	4.2	5.0
Region of occurrence					
Northeast	15.2	16.2	16.4	14.4	14.4
North Central	36.6	37.1	36.6	34.8	36.9
South	35.0	33.2	34.2	38.1	35.3
West	13.3	13.4	12.9	12.8	13.4
Level of rurality					
Urban	68.6	70.3	71.5	69.4	68.4
Suburban	27.3	26.1	24.8	26.6	27.3
Rural	4.1	3.6	3.7	4.0	4.3
Occupational title available					
Yes	98.2	98.6	97.9	98.6	98.5
No	1.8	1.4	2.1	1.4	1.5

*Data expressed as percentages.
†Higher Roman numeral indicates higher socioeconomic status.

Controls were randomly selected from all deaths, excluding only deaths attributed to LH cancers, and frequency-matched by 5-year age groups, sex, race (white, black, or other), and geographic region of occurrence (Northeast, North Central, South, and West) to the aggregate of all four case groups, with 5 controls per case. The entire dataset was restricted to decedents of at least 25 years of age.

Each decedent's ''usual occupation'',[27] as reported on the death certificate, was coded by the state health departments according to the 1980 US Census Bureau three-digit classification system, which includes 231 industries and 509 occupations.[28] Occupational exposures were assigned by an industrial hygienist (MD). Examples of occupations classified as having animal exposure were biological and life scientists, veterinarians, animal caretakers, and agricultural occupations. Occupations considered as having exposure to the public included health professionals (physicians, dentists, nurses, pharmacists, dieticians, therapists, etc), teachers, clergy, performers, sales occupations, some clerical occupations (travel agents, receptionists, bank tellers, etc), law enforcement, and service occupations, such as food service or hairdressers. A numerical index for socioeconomic status (SES), derived from Green,[29] was created based on occupation as reported on the death certificate; we categorised this index into five SES levels. Occupational title was available for over 98% of subjects and missing occupation did not differ by case or control status; analyses of animal or public exposures included 896 480 controls, and 71 600 NHL, 5366 HD, 35 340 multiple myeloma, and 67 570 leukaemia cases.

A rural-urban continuum code (RUCC) was assigned to each decedent, based on county of residence. The RUCC was created by the US Department of Agriculture Economic Research Service to characterise the degree of rurality or urbanisation of each county, as well as the proximity to a metropolitan area. RUCC is a categorical variable ranging from the most urban (0) to the most rural (9).[30] To classify the level of residence rurality for this analysis, the 1993 RUCCs were grouped into three categories: urban, suburban, and rural. Urban classification (codes 0–3) was assigned to counties in metro areas, defined as central counties with one or more cities of at least 50 000 residents or with an urbanised area of 50 000+ and total area population of at least 100 000, suburban counties (codes 4–7) ranged from a total area population of 2500 to 20 000+ and were either adjacent or not adjacent to a metro area, and rural counties (codes 8–9) had an urban population of less than 2500 and were either adjacent or not adjacent to a metro area.

Data analysis

All statistical analyses were conducted using Statistical Analysis Software, version 9.0 (SAS Institute, Cary, NC). We used logistic regression modelling to generate risk estimates in the form of odds ratios (ORs) and 95% confidence intervals. ORs were adjusted for the matching factors. We also considered marital status and SES as potential confounders and, though the addition of marital status did not change our results, the addition of SES to our models changed the odds ratios associated with animal exposure by at least 20%, thus the final models were adjusted for SES. To check the consistency of our results across different demographic subgroups, analyses were also done separately for each age group (25–44, 45–64, 65+ years),

Table 2 Animal or public exposure; odds ratios (95% CIs) for association with non-Hodgkin's lymphoma, Hodgkin's disease, multiple myeloma, and leukaemia*

	Controls (n = 896480)	Non-Hodgkin's lymphoma (n = 71600)		Hodgkin's disease (n = 5366)		Multiple myeloma (n = 35340)		Leukaemia (n = 67570)	
	%	%	OR (95% CI)	%	OR (95% CI)	%	OR (95% CI)	%	OR (95% CI)
Exposure to animals	4.4	3.9	1.24 (1.18–1.30)	3.1	1.21 (1.02–1.44)	4.7	1.24 (1.17–1.32)	4.9	1.33 (1.27–1.39)
Exposure to the public	13.6	16.1	1.08 (1.06–1.11)	16.1	1.06 (0.97–1.14)	15.2	1.06 (1.03–1.10)	15.3	1.04 (1.02–1.07)

*Odds ratios adjusted for age, sex, race, geographic region of occurrence, and socioeconomic status.

gender, year-of-death subgroup (three-year categories), region of occurrence (Northeast, North Central, South, West), and level of residence rurality. Because the aetiology of leukaemia and NHL may vary by subtype, we also examined the risks separately for acute lymphoid leukaemia (ALL, ICD-9 204.0), chronic lymphoid leukaemia (CLL, ICD-9 204.1), acute myeloid leukaemia (AML, ICD-9 205.0), chronic myeloid leukaemia (CML, ICD-9 205.1), other leukaemia (ICD-9 202.4, 203.1, 204.2, 204.8, 204.9, 205.2, 205.3, 205.8–206.2, 206.8–207.0, 207.2, 207.8), leukaemia of unknown or unspecified cell type (ICD-9 208.0–208.2, 208.8, 208.9), diffuse NHL (ICD-9 200.0), and follicular NHL (ICD-9 202.0, 202.1).

Other occupational exposures were considered as potential confounders. Pesticides, solvents, dusts, and radiation are among a few exposures that have been previously associated with some or all of our diseases of interest;[31–34] exposure to these agents may also differ between occupations with greater and less exposure to animals or the public. Occupational exposures considered as potential confounders were asbestos, benzene, formaldehyde, solvents, radiation, inorganic dust, pesticides (including insecticides, herbicides, and fungicides), metal dust, lead dust and fumes, wood dust, polycyclic aromatic hydrocarbons (PAHs), fertilisers, nitrogen oxides, and nitrosamines. We determined a priori to adjust for any of these exposures that changed the OR of any of the main associations of interest between LH cancers and animal or public exposures by 20% or greater, either when any individual factor was added to the model, or when combinations of factors were added.

Because the occupations entailing exposures to the public were so varied, we categorised them into health care, teaching, social service workers (social workers, religious), sales, law enforcement/corrections, food service, hairdressers/barbers, and other (for example, service occupations, clerks, librarians) and estimated relative risks for each of these subgroups, to assess whether any association was observed for a specific subgroup. Animal exposed occupations were divided into farming and non-farming occupations and risks for these subgroups were calculated. Non-farming occupations with animal exposure were veterinarians, biological and life scientists, animal caretakers (except farm), and supervisors (related agricultural occupations); the risks for each of these four occupational subgroups were estimated in addition to the risk for non-farming occupations as a whole. Previous research has suggested an association between handling of meat products and LH cancer,[35–37] and exposures in these occupations may be similar to those encountered in animal exposed occupations; therefore, risks for butchers and meat cutters, which were not coded as having animal exposure, were also calculated.

To assess whether any risk associated with animal exposure was due to other exposures common to farming (for example, pesticides), we computed relative risks associated with the livestock and crop agricultural industries, as well as specific farming occupations within those industries. Although farming occupations in both industries were considered to have animal exposure, we assumed that subjects in livestock industry would have greater animal exposure than the crop industry. The occupational subgroups within both industries were defined as follows: farmers, farm managers or supervisors of farm workers combined, farm workers, and all other occupations in the industry combined.

The exclusion of deaths from other malignancies, infectious diseases, or both from the control group had no substantial effect on the risk estimates.

RESULTS

Age, gender, and racial distributions for both NHL and leukaemia cases were similar to those of controls (table 1).

Table 3 Animal or public exposure by region of occurrence; odds ratios (95% CIs) for association with non-Hodgkin's lymphoma, Hodgkin's disease, multiple myeloma, and leukaemia*

	Controls (n = 896480)	Non-Hodgkin's lymphoma (n = 71600)		Hodgkin's disease (n = 5366)		Multiple myeloma (n = 35340)		Leukaemia (n = 67570)	
	%	%	OR (95% CI)	%	OR (95% CI)	%	OR (95% CI)	%	OR (95% CI)
Exposure to animals									
Northeast	1.2	1.1	1.25 (1.03–1.51)	0.8	1.05 (0.49–2.27)	1.6	1.56 (1.22–1.99)	1.3	1.30 (1.07–1.58)
North Central	4.6	4.7	1.41 (1.31–1.52)	3.9	1.35 (1.04–1.75)	5.1	1.44 (1.31–1.60)	6.0	1.60 (1.49–1.71)
South	5.7	4.5	1.10 (1.02–1.19)	3.1	0.98 (0.73–1.32)	5.4	1.05 (0.96–1.15)	5.5	1.11 (1.03–1.19)
West	4.4	3.8	1.23 (1.07–1.40)	4.0	1.78 (1.12–2.83)	5.0	1.52 (1.27–1.82)	4.5	1.40 (1.23–1.60)
Exposure to the public									
Northeast	14.3	16.0	1.02 (0.97–1.08)	16.5	1.00 (0.83–1.21)	16.2	1.04 (0.96–1.13)	15.5	1.02 (0.96–1.08)
North Central	13.2	15.7	1.10 (1.06–1.15)	15.7	1.09 (0.95–1.24)	14.1	1.03 (0.97–1.09)	14.7	1.05 (1.00–1.09)
South	12.8	15.6	1.11 (1.07–1.16)	15.4	1.03 (0.90–1.19)	15.1	1.10 (1.05–1.17)	14.8	1.07 (1.03–1.11)
West	16.2	18.4	1.05 (0.99–1.11)	18.7	1.10 (0.90–1.35)	17.6	1.04 (0.96–1.13)	17.6	1.01 (0.95–1.08)

*Odds ratios adjusted for age, sex, race, geographic region of occurrence, and socioeconomic status.

Multiple myeloma cases were also similar to controls with regard to gender; however, they were more likely than controls to be older and black. There was a higher proportion of younger cases and a higher proportion of males in the HD group, although their racial distribution was similar to controls. All of the case groups had higher socioeconomic status than the control group but cases and controls were similar with regard to level of rurality. The proportion of deaths occurring in each geographical region was similar among all groups.

Occupational exposure to the public occurred more frequently in cases than controls (table 2). Occupational exposure to animals was more common among multiple myeloma and leukaemia cases than controls, but was lower than controls for NHL and HD cases. In adjusted models, however, those who were occupationally exposed to animals had modest increased risks of mortality from all four cancers (21–33%). In contrast, there were only negligible associations between LH cancer risk and exposure to the public. All models were adjusted for the matching factors and SES; none of the other factors we considered confounded the associations, including marital status or the additional occupational exposures mentioned previously. Animal exposure was associated with increased mortality for all six leukaemia histological subtypes (OR [95% CI]: ALL = 1.54 [1.26 to 1.89]; CLL = 1.24 [1.14 to 1.36]; AML = 1.43 [1.31 to 1.56]; CML = 1.33 [1.17 to 1.51]; other = 1.34 [1.15 to 1.57]; unknown = 1.22 [1.12 to 1.33]) and both NHL subtypes; however the risk was slightly greater for diffuse NHL than follicular (OR [95% CI]: diffuse NHL = 1.46 [1.27 to 1.69]; follicular NHL = 1.12 [0.79 to 1.59]).

The risks associated with animal exposure were consistent across age, gender, and year of death subgroups of each case type, although patterns of risk varied among regions (table 3). While the risk associated with animal exposure was elevated in the North Central and West regions for all four outcomes, the association diminished when restricted to the South. Those in the Northeast exposed to animals experienced an increased risk of NHL, multiple myeloma, and leukaemia, but not HD. There remained little association between public exposure and the mortality outcomes across regions or other demographic subgroups. Risks did not vary by level of residence rurality (table 4) except that decedents residing in rural counties had a modest significant increase in NHL risk associated with exposure to the public. The risks for HD were less precise after stratifying our results by regional, rural, and occupational subgroups due to the small number of cases; however, there was a modest increased risk associated with exposure to the public among rural residents.

Analysis of occupational subgroups within those considered to have exposure to the public revealed some associations that were not apparent in analysis of the overall exposure variable (table 5). Teaching occupations were associated with all four outcomes, with increases of 11–47%. We also observed increases of 15–26% for hairdresser/barber occupations for all four LH cancers. Risks of all four LH cancer types were significantly decreased in association with food service occupations.

Non-farming occupation with exposure to animals (veterinarians, biological and life scientists, animal caretakers [except farm], and supervisors [related agricultural occupations]) showed some increased risks of mortality with LH cancers (table 6). Veterinarian occupation was associated with a significantly increased risk of multiple myeloma, and non-significantly elevated ORs were also observed for leukaemia and HD. Other non-farming occupations with imprecise increased risks were biological and life scientists with multiple myeloma, animal caretakers with NHL, HD, and leukaemia, and supervisors (related agricultural occupations)

Table 4 Animal or public exposure by rurality of residence; odds ratios (95% CIs) for association with non-Hodgkin's lymphoma, Hodgkin's disease, multiple myeloma, and leukaemia*

	Controls (n = 896480)	Non-Hodgkin's lymphoma (n = 71600)		Hodgkin's disease (n = 5366)		Multiple myeloma (n = 35340)		Leukaemia (n = 67570)	
	%	%	OR (95% CI)	%	OR (95% CI)	%	OR (95% CI)	%	OR (95% CI)
Exposure to animals									
Urban	2.1	1.8	1.21 (1.12–1.31)	1.5	1.23 (0.93–1.64)	2.2	1.25 (1.14–1.38)	2.3	1.29 (1.20–1.38)
Suburban	8.5	8.0	1.28 (1.19–1.38)	7.3	1.30 (1.00–1.68)	9.2	1.22 (1.11–1.35)	9.6	1.29 (1.20–1.38)
Rural	15.0	13.7	1.30 (1.09–1.57)	7.8	0.78 (0.40–1.52)	16.6	1.18 (0.95–1.47)	16.0	1.31 (1.11–1.54)
Exposure to the public									
Urban	14.4	16.7	1.07 (1.04–1.10)	16.7	1.02 (0.93–1.12)	16.1	1.05 (1.01–1.09)	16.1	1.04 (1.01–1.07)
Suburban	12.1	14.6	1.09 (1.04–1.15)	14.7	1.17 (0.99–1.38)	13.5	1.08 (1.01–1.16)	13.7	1.07 (1.02–1.12)
Rural	10.2	13.5	1.29 (1.13–1.49)	14.5	1.26 (0.79–1.98)	10.9	1.01 (0.82–1.23)	11.0	0.97 (0.84–1.11)

*Odds ratios adjusted for age, sex, race, geographic region of occurrence, and socioeconomic status.

Table 5 Public exposed occupations; frequencies and odds ratios (95% CIs) for association with non-Hodgkin's lymphoma, Hodgkin's disease, multiple myeloma, and leukaemia*

	Controls (n = 896480)	Non-Hodgkin's lymphoma (n = 71600)		Hodgkin's disease (n = 5366)		Multiple myeloma (n = 35340)		Leukaemia (n = 67570)	
	%	%	OR (95% CI)	%	OR (95% CI)	%	OR (95% CI)	%	OR (95% CI)
All occupations without public exposure	86.2	83.8	1.0 (ref.)	83.8	1.0 (ref.)	84.7	1.0 (ref.)	84.6	1.0 (ref.)
Health	2.90	3.36	1.02 (0.97–1.07)	3.07	0.94 (0.79–1.11)	3.21	0.96 (0.90–1.03)	3.15	0.99 (0.95–1.04)
Teachers	2.65	3.67	1.15 (1.10–1.20)	3.69	1.41 (1.20–1.66)	3.82	1.21 (1.13–1.29)	3.52	1.11 (1.06–1.16)
Social, recreation, and religious workers	0.87	1.20	1.29 (1.20–1.38)	1.12	1.14 (0.88–1.48)	1.18	1.27 (1.14–1.40)	1.21	1.24 (1.15–1.34)
Sales	4.20	4.64	1.03 (0.99–1.07)	4.51	0.98 (0.86–1.12)	4.15	1.01 (0.96–1.07)	4.52	1.01 (0.88–1.12)
Law enforcement/corrections	0.44	0.50	1.15 (1.05–1.27)	0.61	1.15 (0.82–1.63)	0.44	1.10 (0.94–1.30)	0.44	0.99 (0.88–1.12)
Food service	0.74	0.58	0.87 (0.79–0.96)	0.61	0.59 (0.42–0.84)	0.45	0.75 (0.64–0.88)	0.52	0.81 (0.73–0.91)
Hairdressers/barbers	0.60	0.67	1.16 (1.05–1.27)	0.82	1.26 (0.93–1.70)	0.73	1.24 (1.09–1.41)	0.67	1.17 (1.07–1.29)
Other	1.32	1.57	1.18 (1.11–1.27)	1.81	1.11 (0.91–1.36)	1.31	1.03 (0.93–1.13)	1.36	1.05 (0.98–1.12)

*Odds ratios adjusted for age, sex, race, geographic region of occurrence, and socioeconomic status.
†Occupations with exposure to the public were modelled together to calculate ORs, using all occupations without public exposure as the referent.

Table 6 Animal exposed occupations; frequencies and odds ratios (95% CIs) for association with non-Hodgkin's lymphoma, Hodgkin's disease, multiple myeloma, and leukaemia*

	Controls (n = 896480)	Non-Hodgkin's lymphoma (n = 71600)		Hodgkin's disease (n = 5366)		Multiple myeloma (n = 35340)		Leukaemia (n = 67570)	
	%	%	OR (95% CI)	%	OR (95% CI)	%	OR (95% CI)	%	OR (95% CI)
All occupations without animal exposure	95.57	96.08	1.0 (ref.)	96.87	1.0 (ref.)	95.29	1.0 (ref.)	95.06	1.0 (ref.)
Non-farming occupations with animal exposure†‡	0.10	0.11	1.11 (0.89–1.40)	0.15	0.99 (0.49–1.99)	0.12	1.33 (0.98–1.81)	0.13	1.22 (0.98–1.52)
Veterinarians§	0.02	0.02	0.80 (0.47–1.36)	0.06	1.99 (0.63–6.35)	0.04	1.96 (1.15–3.34)	0.04	1.34 (0.88–2.07)
Biological and life scientists§	0.02	0.03	1.01 (0.63–1.63)	0.02	0.47 (0.07–3.42)	0.03	1.35 (0.71–2.58)	0.03	1.14 (0.72–1.82)
Animal caretakers, except farm§	0.02	0.02	1.27 (0.71–2.29)	0.04	1.65 (0.40–6.74)	0.01	1.05 (0.43–2.58)	0.02	1.62 (0.95–2.75)
Supervisors, related agricultural occupations§	0.04	0.05	1.34 (0.95–1.90)	0.04	0.61 (0.15–2.45)	0.04	1.04 (0.60–1.81)	0.04	1.05 (0.71–1.54)
Farming occupations with animal exposure‡	4.33	3.81	1.25 (1.19–1.31)	2.98	1.22 (1.03–1.47)	4.58	1.24 (1.17–1.32)	4.81	1.34 (1.28–1.40)

*Odds ratios adjusted for age, sex, race, geographic region of occurrence, and socioeconomic status.
†Non-farming occupations with exposure to animals consist of veterinarians, biological and life scientists, and animal caretakers, except farm.
‡Non-farming animal exposed and farming animal exposed occupations were modelled together to calculate overall ORs, using all other occupations as the referent.
§Specific non-farming animal-exposed occupations were modelled together with farming animal exposed occupations to calculate ORs for each occupation, using all other occupations as the referent.

with NHL. Butchers and meat cutters were not found to be at increased risk for any of the four outcomes of interest (results not shown in tables; OR [95% CI]: NHL = 0.83 [0.69 to 0.99]; HD = 0.81 [0.43 to 1.51]; multiple myeloma = 0.91 [0.72 to 1.15]; leukaemia = 1.01 [0.86 to 1.19]).

Most decedents (97.8%) coded as having exposure to animals had farming occupations and, therefore, further analyses regarding specific farming industries and occupations were conducted (table 7). Employment in the livestock industry was associated with increased risks for all LH cancer outcomes except HD; these relative risks significantly exceeded the corresponding increases observed for the crop industry in that the confidence intervals associated with each outcome did not overlap between the two industries. When we analysed the risk associated with specific occupational subgroups, we observed significantly increased risks for farmer occupation within each industry; however, the risks among livestock farmers significantly exceeded the risk among crop farmers for NHL, multiple myeloma, and leukaemia. Other animal exposed occupations in the livestock and crop industry had elevated ORs for one or more LH cancers; however, these estimates were imprecise due to small numbers.

DISCUSSION

Occupations involving exposure to animals, particularly farming related occupations, were associated with increased risk of mortality from LH cancers, specifically NHL, HD, multiple myeloma, and leukaemia. Occupational exposure to the public was only negligibly associated with these outcomes. The consistency of these results across age, gender, and year-of-death subgroups strengthens our findings.

Though the broad group of occupations with exposure to the public did not experience an increased risk of LH cancer mortality, some increases were apparent for specific occupational subgroups considered to have exposure to the public. Teaching occupation was shown to have increased risk, as were childcare workers. This is consistent with previous findings suggesting elevated risks for leukaemia,[3 14 18 20 35] multiple myeloma,[8 18] and NHL in US school teachers.[3 11 20] Similarity, Linet *et al* detected a significantly higher than expected incidence of NHL among Swedish male teachers,[21] and Mele *et al* identified an elevated risk of leukaemia among Italian female teachers.[23] Exposure to childhood infections or ''carriers'' has also been suggested as a risk factor for LH cancers which adds support to biological agent hypotheses.[38] Possible aetiological agents hypothesised as responsible for increased LH cancer mortality observed for hairdressers/barbers are infectious agents or hair dyes.[39 40] Decreased mortality risk for lymphohaematopoietic cancers among food service workers has not been previously reported.

Most infectious agents that have been associated with LH cancers are viruses. Causal associations between Epstein-Barr virus (EBV) or mononucleosis and several LH cancers are well established.[31 41–44] Adult T cell leukaemia (ATL) has been associated with human T cell lymphotrophic virus type 1 (HTLV-1),[34] and several studies have detected an increased prevalence of hepatitis C virus (HCV) infection in patients with NHL[45–50] and multiple myeloma.[51] Moreover, an increased risk of NHL among people with AIDS[52–54] has been observed, especially among AIDS patients with prolonged immunodeficiency and B cell stimulation.[55] However, it should be noted that HIV is not likely a direct part of the oncogenic process and probably facilitates the expression of opportunistic oncogenic viruses, such as EBV, through immunosuppression.[52 56]

Although these viruses are commonly transmitted through human contact, the potential for animal transmitted viruses has also been investigated. Bovine leukaemia virus is related

Table 7 Farming occupations by livestock and crop industries; odds ratios (95% CIs) for association with non-Hodgkin's lymphoma, Hodgkin's disease, multiple myeloma, and leukaemia*

	Controls (n = 885779)	Non-Hodgkin's lymphoma (n = 70881)		Hodgkin's disease (n = 5301)		Multiple myeloma (n = 34963)		Leukaemia (n = 66831)	
	%	%	OR (95% CI)	%	OR (95% CI)	%	OR (95% CI)	%	OR (95% CI)
All other industries	95.54	96.06	1.0 (ref.)	96.93	1.0 (ref.)	95.30	1.0 (ref.)	95.05	1.0 (ref.)
Livestock industry†	0.93	1.00	1.45 (1.34–1.58)	0.64	1.16 (0.82–1.64)	1.03	1.45 (1.29–1.62)	1.17	1.52 (1.40–1.64)
Farmers‡	0.80	0.89	1.51 (1.39–1.65)	0.58	1.32 (0.92–1.91)	0.92	1.52 (1.35–1.71)	1.06	1.60 (1.47–1.74)
Managers or supervisors‡	0.03	0.02	0.90 (0.54–1.52)	0.04	1.69 (0.42–6.88)	0.03	1.20 (0.64–2.27)	0.02	0.88 (0.52–1.49)
Farm workers‡	0.07	0.06	1.27 (0.94–1.71)	0	–	0.06	1.18 (0.77–1.81)	0.07	1.20 (0.89–1.63)
Other occupations‡	0.03	0.03	1.07 (0.67–1.71)	0.02	0.77 (0.11–5.50)	0.02	0.68 (0.30–1.54)	0.03	1.06 (0.66–1.71)
Crop industry†	3.54	2.94	1.17 (1.11–1.23)	2.43	1.21 (1.00–1.47)	3.67	1.17 (1.09–1.25)	3.78	1.27 (1.21–1.33)
Farmers‡	3.11	2.66	1.22 (1.15–1.29)	2.13	1.29 (1.05–1.59)	3.28	1.23 (1.14–1.31)	3.44	1.32 (1.26–1.39)
Managers or supervisors‡	0.03	0.03	1.20 (0.79–1.81)	0.02	0.79 (0.11–5.69)	0.03	0.98 (0.54–1.79)	0.04	1.37 (0.93–2.00)
Farm workers‡	0.28	0.12	0.65 (0.53–0.81)	0.11	0.46 (0.21–1.04)	0.25	0.81 (0.65–1.00)	0.20	0.89 (0.75–1.06)
Other occupations‡	0.11	0.12	1.19 (0.95–1.49)	0.17	1.76 (0.91–3.41)	0.10	0.97 (0.69–1.36)	0.10	0.94 (0.73–1.21)

*Odds ratios adjusted for age, sex, race, geographic region of occurrence, and socioeconomic status.
†The two industries were modelled together to calculate overall ORs for each industry, using all other industries as the referent.
‡All occupations in the livestock and crop industries were modelled together to calculate ORs for each occupation, using all other industries as the referent.

to HTLV-1 and therefore speculation exists about an association between exposure to cattle, particularly those with bovine lymphosarcoma, and human leukaemia incidence.[34] However, two case-control studies[57 58] negate any association. McDuffie *et al* actually found a reduction in risk of NHL among Canadian male farmers who raised cattle, although farmers who had a large (13+ head) swine inventory or raised bison, elk, or ostriches had increased NHL risk.[59] This same population showed no association between exposure to farm animals and HD or multiple myeloma.[60] Similarly, although avian leukosis and sarcoma viruses are natural causes of tumours in poultry, most serologic studies have shown a lack of association between human malignancies and these viruses.[36 61]

Despite null or negative results from past studies and the lack of an identified oncogenic agent, results from several epidemiological studies, in addition to the current study, support animal contact as a contributing factor to LH malignancy. Multiple myeloma and leukaemia rates have been positively associated with high poultry inventory at the county level.[62 63] Amadori *et al* found the excess risk of NHL and CLL among farm workers to be restricted to those who worked with farming-animal breeding, as opposed to farmers only,[64] which suggests an increased risk among those in the occupation with greater animal exposure. In addition, a French multicentre case-control study reported increased odds of hairy cell leukaemia with agricultural employment and self-reported exposure to bovine cattle breeding.[65] Other investigators have described an increase in the risk of multiple myeloma with reported exposure to sheep[66] and cattle;[67 68] Erikkson *et al* also suggests an increased risk with exposure to horses and goats.[68] Moreover, acute lymphoid leukaemia (ALL) in Iowa males was positively correlated with cattle density by county and with the number of dairy cattle with bovine lymphosarcoma.[69]

We observed regional differences in the ORs for animal exposure with the greatest positive associations in the North Central and West regions and a diminished effect when restricted to the South. Since most occupations with animal exposure were agricultural, we investigated regional differences in agricultural characteristics, particularly in the livestock inventory, using rankings from the 1997 USDA Census of Agriculture as an indicator.[70] Relative to other states in the US, states in the South region had higher inventory of most poultry types (ducks, geese, pullets [hens], and turkeys), suggesting that the increased risk of LH malignancy associated with animal exposure may be limited to exposure to livestock types that are more prevalent in other regions. For instance, the North Central region had the highest risks associated with animal exposure; these states rank highest in cattle inventory and are among the top ranking states for inventory of hogs and pigs. This fact agrees with the findings of Fritschi *et al* and Becker *et al* who report a significantly elevated risk of LH cancers among persons exposed to cattle, and no risk increase associated with exposure to other animals.[71 72]

Other agricultural exposures, such as pesticides or herbicides, may have influenced the increased risks reported. Although our risk estimates did not change after adjustment for pesticides, we also compared the risks between crop and livestock industry. The risks for NHL, multiple myeloma, and leukaemia were significantly higher for workers in the livestock industry compared with the crop industry. A similar analysis using proportionate mortality ratios was conducted by Lee *et al*, who used US death certificate data to compare mortality patterns between livestock and crop farmers for the years 1984–93.[73] This previous study found increased mortality risks for chronic lymphoid leukaemia and multiple myeloma among both farmer types, and an increased risk of

NHL and acute leukaemia that was restricted to livestock farmers. These differences in risk between animal exposed and unexposed farming industries may be in fact due to the presence of animal exposure. However, the types of pesticides used and the methods of application differ between crop and livestock farming and pesticides or other factors may still play a role in the observed effects. Livestock farmers use mainly insecticides, whereas herbicides are used more often than insecticides on crops.[74] Moreover, although associations have been found between many types of pesticide exposures and LH cancers,[65 68 73 75–78] Brown *et al* found elevated risks of leukaemia associated with exposure to animal insecticides such as crotoxyphos, dichlorvos, and famphur, but no association with fungicides, herbicides, or crop insecticides.[79] A related study investigating NHL reported elevated risks for NHL among a greater number of chemical classes of insecticides used on livestock than insecticide families used on crops.[75]

The current study found an increased risk of mortality from LH cancers associated with non-farming animal exposed occupations, which included veterinarians. This is in agreement with previous research that has revealed an excess of LH malignancies among veterinarians.[8 9 68] Conversely, a cohort study of 3440 British veterinary surgeons showed no increase in deaths from leukaemia,[80] although the number of cases ($n = 4$) was small.

There have been a number of investigations into the cancer risks associated with the handling and processing of animal products. A case-control study conducted by Bethwaite and colleagues[35] revealed an excess risk of adult onset acute leukaemia among butchers and slaughterhouse workers; this risk was confined to butchers who worked in a slaughterhouse or on a farm and slaughterhouse workers who had direct contact with animals or animal products. Metayer and colleagues[37] found excess risks of LH tumours, especially lymphomas, throughout the meat working industry, with the exception of meatpacking plants. Occupations included in this industry include killing animals, working in chicken slaughtering plants and slaughterhouses, wrapping meat, and meat cutting. Additional case-control studies in both the USA and New Zealand identified an increased risk of NHL among meat works employment.[81–83] Johnson *et al* observed a relative risk of 2.9 ($p < 0.05$) for LH cancer mortality among white workers in poultry processing plants and slaughterhouses,[36] but a small number of cases precluded them from detecting any corresponding risk in non-white workers.[84] After examining the risk among butchers and meat cutters in our dataset, we found no association with any of the LH cancers studied; however these previous studies probably had a more accurate method of exposure assessment through job classification within the industry than the current study, which relied on occupation as reported on the death certificate.

The risk of NHL associated with public exposure was greatest among residents of rural counties. One hypothesis for such an effect is that individuals in rural areas have lower immunity to infections due to less human contact relative to urban areas,[85] given the characteristics of low population density and distance of rural areas from population centres. When considering exposures to infectious agents from public, however, one must consider that the aetiologically relevant period for these cancers may precede the time during which the decedent held the reported occupation, and would therefore not be captured by our exposure classification. There are existing hypotheses regarding childhood social contact through sibship, birth order, and residence rurality as affecting adult LH cancer, particularly HD, incidence. The concept that exposure to infectious agents at a young age through regular social contact may increase immunity to potentially oncogenic infections later in life has been addressed in several studies. Gutensohn *et al* have found the risk of HD in young adults to be inversely related to sibship size and birth order.[86 87] Vianna and Polan reported similar results for both young adult (18–44 years) and older adult (45–74 years) HD cases.[88] A study of risk characteristics from college entrance health data on male HD fatalities and controls saw no effect of sibship size but did find a history of contagious diseases during pre-college years to be inversely associated with HD mortality.[89] The unique, bimodal age-incidence curve of HD[86] has made this disease a primary target for investigating social and familial factors; however the effect of these characteristics on other LH cancers should not be dismissed. Donham *et al* report that the excess acute lymphoid leukaemia (ALL) cases observed in Iowa between 1969 and 1975 are among males living in rural counties; also shown was a clear discrepancy in the prevalence of ALL and CLL between urban and rural counties, with higher prevalence in rural counties.[69] It should be noted, however, that a decedent's level of rurality at the time of death may not be indicative of their rurality during childhood, and there are other exposures associated with rurality, such as SES, that may contribute to the discrepancy in risks.

The use of death certificate data has inherent limitations. Some residual confounding is undoubtedly present, due to the inability to account for potentially important factors such as smoking status and family history of cancer. Misclassification of the cause of death or the decedent's occupation has likely introduced bias into our risk estimates, particularly given the difficulties in classifying LH malignancies. Because the occupation recorded on the death certificate is frequently the most common occupation held or the last job before death, it may not reflect the occupation held by the decedent during an aetiologically relevant period of time, nor does it allow one to assess the duration of employment. Therefore, an occupational mortality study using death certificates will assign to some individuals occupations that have no bearing on the causation of our outcome of interest, if for no other reason than because the individual undertook that occupation after the disease process had begun. Even if this were not the case, the amount of animal or public exposure experienced by individuals with the same occupational title may vary greatly. However, if the degree of misclassification does not differ between the cases and controls, the bias will likely be towards the null.

Because the cases and controls are determined by the underlying cause of death, the sensitivity for detecting cases is compromised. For example, if an individual with multiple myeloma—diagnosed or occult—dies from injuries because of an automobile accident, this individual would not be recognised as a case and would thereby be eligible to be included in the control group.

Along the same lines, the differential survival of our outcomes may affect the implications of our findings, since our data precluded us from measuring any LH cancer outcome other than death. The five-year relative survival rates between 1995 and 2000 ranged from 32.1% for multiple myeloma to 85.2% for HD;[90] therefore, there are likely individuals in the control group who were incident cases of LH cancer but who survived the disease and died from another cause. If our findings using mortality rates are an artefact of a true association between LH cancer *incidence* and animal exposure, our results would be biased towards the null and this bias would be greatest for the disease with the highest survival rate, in this case, HD. Furthermore, because we had no measure of the stage or duration of disease, the implications of our findings are limited to the LH cancers that were severe enough to be the underlying cause of death for the individual. Nevertheless, any bias due to incident cases in the control group is unlikely to be large because of the overall low incidence rates for LH cancers.

This study contributes to the evidence for occupational causes of LH malignancies. Higher risks of NHL, HD, multiple myeloma, and leukaemia were associated with occupations that involved animal exposure. Though most public exposed occupations were not at risk, this may be due to the greater difficulties in discerning exposure to the public from death certificate occupational data. Regional differences in risk imply that the risks may be associated with exposure to specific livestock or farming practices. Therefore, further research is warranted to study the risks associated with the range of occupations involving specific types of animals and other exposures related to animal farming, such as insecticides.

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