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**Key terms:** [farmer](#); [infection](#); [pesticide](#)

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## Meta-analyses of non-Hodgkin's lymphoma and farming

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**Objectives** This study examined the association between non-Hodgkin's lymphoma (NHL) and farming.

**Methods** A series of meta-analyses of peer-reviewed studies was performed using 36 studies published between 1982 and 1997. Prior to the meta-analyses, all the studies were reviewed and evaluated for heterogeneity and publication bias. Combined relative risks (RR) were calculated using the random effect model.

**Results** The combined RR was 1.10 [95% confidence interval (95% CI) 1.03–1.19] for all the studies and 0.93 (95% CI 0.82–1.06) for studies involving female farmers. Significant heterogeneity was detected for study design and country of study among the studies. Significantly elevated RR values were obtained for case-referent studies (combined RR 1.19, 95% CI 1.06–1.33) and for studies conducted on farmers residing in the United States (combined RR 1.26, 95% CI 1.15–1.37). These findings were not influenced by a publication bias.

**Conclusions** The findings suggest that male farmers residing in the United States have a slightly elevated risk of contracting NHL. Commonly experienced exposures that might contribute to the occurrence of NHL in this group include infectious microorganisms, herbicides, and insecticides.

**Key terms** farmers, infections, pesticides.

Non-Hodgkin's lymphoma (NHL) is a group of cancers that arise from the neoplastic clone of the B- and T-lymphocyte differentiation pathways (1). NHL is increasing rapidly in the United States and most industrialized countries. Between 1973 and 1991, the incidence of NHL in the United States increased at the rate of 3.3% per year, making it the third fastest-growing cancer. In recent years, AIDS (acquired immunodeficiency syndrome) patients have contributed to this trend, but a steady rise in the incidence of NHL was apparent long before the AIDS epidemic (2).

The reported increases in the incidence of NHL in industrialized countries suggest that exposures related to occupational and environmental hazards might be associated with the disease. Inconsistent results of comparisons of the incidence of the disease in urban areas to the incidence of the disease in rural areas suggest, however, that exposures found in both urban and rural environments might contribute to the increase in incidence (3). Pickle et al (4) noted that, in the United States, the rising mortality from NHL has been the most pronounced in the farming states of the country.

Farmers are a group uniquely suited for assessing the potential contribution of a given exposure to the occurrence of a disease. Since farmers use alcohol and tobacco less than the general population (5) and their work requires more physical activity than do most other occupations, excesses of a given disease in this group suggest that the relative contributions of smoking and alcohol to the occurrence of the disease are minimal. Most farmers live in nonmetropolitan areas with limited exposure to urban environmental pollution, and excesses of a disease in this group suggest that risk factors relatively specific to farming are associated with the disease.

Risk factors potentially associated with NHL include microorganisms (6, 7), antigenic stimulation (8, 9), pesticides (10–19), and solvents (19–21). Since farmers experience all of these exposures (22), assessing their contribution to the occurrence of the disease can be accomplished by examining the association between NHL and farming. To assess the potential contributions of these exposures to the occurrence of NHL, a series of meta-analyses of studies examining the association between farming and NHL was performed.

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**Materials and methods**

The Medical Abstract and Cancer Abstracts data bases were searched for articles about farming and NHL. The search of MEDLINE data was from 1981 until 30 June 1997. The Cancer Abstracts data base search included articles published from 1980 until 30 June 1997. References cited in the studies found by examining the 2 data bases were also included in the meta-analyses. Articles were excluded from the analyses for any one of the following reasons: (i) occupations other than farming were included in the definition of exposure and no data specific to farmers were published, (ii) insufficient data for determining an estimator of relative risk or a confidence interval were published, (iii) the group studied was included in another study of similar design examining a greater number of subjects, (iv) the disease studied was not specifically designated as NHL.

The remaining articles were then examined and estimators of the relative risks (RR) were extracted independently by the authors. The estimators of RR were odds

ratios (OR) for case-referent studies, standardized mortality ratios (SMR) or standardized incidence ratios (SIR) or proportional mortality ratios (PMR) for cohort and mortality and morbidity studies.

Once the studies had been selected, a series of meta-analyses was conducted, and the results were evaluated in the context of the published literature. The homogeneity of the estimators of relative risk was tested using Cochran's Q statistics. This is a chi-square test with degrees of freedom equal to the number of studies minus one; it tests the null hypothesis that the within-study estimates of relative risk are homogeneous across studies. Significant heterogeneity was detected within the groups of studies; therefore, the random effects model (23) was used to obtain the combined risk ratio and its standard error (SE).

The first meta-analysis examined all the studies that met the criteria for inclusion. A 2nd meta-analysis was restricted to female farmers (studies reporting on farmers who were female or were female relatives of farmers who assisted in farming). Additional meta-analyses were

**Table 1.** Description of the studies included in the meta-analysis of non-Hodgkin's lymphoma among farmers.

Reference	Country	Study period	Method	Exposed cases	Relative risk	95% CI
<b>Case-referent studies</b>						
Francheschi et al, 1993 (6)	Italy	1985—1991	Interview	46	0.80	0.60—1.10
Brownson et al, 1989(8)	United States	1984—1988	Medical record	63	1.40	1.04—1.85
Burmeister et al, 1983(10)	United States	1964—1978	Death certificate	1101	1.26	1.19—1.34
Cantor, 1982 (11)	United States	1968—1976	Death certificate	175	1.22	0.98—1.51
Cantor et al, 1992 (12)	United States	1980—1983	Interview	356	1.20	1.00—1.50
Hoar et al, 1986 (13)	United States	1976—1982	Interview	133	1.40	0.90—2.10
Wood et al, 1987 (14)	United States	1981—1984	Interview	173	1.33	1.03—1.70
Persson et al, 1989 (20)	Sweden	1964—1986	Questionnaire	7	0.60	0.29—1.26
Forastiere et al, 1993 (43)	Italy	1980—1986	Farmers' pension	11	0.59	0.23—1.50
Keller & Howe, 1994 (44)	United States	1986—1988	Medical record	58	1.09	0.77—1.54
Pearce et al, 1987 (45)	New Zealand	1977—1981	Cancer register	81	1.00	0.77—1.31
Fincham et al, 1992 (46)	Canada	1983—1989	Questionnaire	53	0.98	0.71—1.33
Reif et al, 1989 (47)	New Zealand	1980—1984	Cancer register	92	1.24	0.99—1.56
Schumacher, 1985 (48)	United States	1967—1982	Death certificate	24	1.30	0.84—2.02
Zahm et al, 1993 (56)	United States	1983—1986	Interview	119	1.00	0.70—1.40
Amadori et al, 1995( 65)	Italy	1987—1990	Interview	51	1.68	1.13—2.51
La Vecchia et al, 1989 (66)	Italy	1983—1988	Questionnaire	38	2.10	1.33—3.40
Dubrow et al, 1988 (41)	United States	1960—1979	Death certificate	15	1.60	0.80—3.40
<b>Mortality and morbidity studies</b>						
Blair et al, 1993 (39)	United States	1984—1988	Death certificate	891	1.19	1.11—1.27
Eriksson et al, 1992 (40)	Sweden	1979—1984	Census data	428	1.00	0.89—1.08
Delzell & Grufferman, 1985 (49)	United States	1976—1978	Death certificate	47	1.03	0.65—1.64
Gallagher et al, 1984 (50)	Canada	1950—1978	Death certificate	102	0.99	0.81—1.20
Mallin et al, 1989 (51)	United States	1979—1984	Death certificate	91	1.80	1.47—2.21
Linnet et al, 1994 (58)	Sweden	1961—1979	Census data	55	0.90	0.69—1.17
Veil & Richardson, 1993 (52)	France	1984—1986	Death certificate	184	1.09	0.94—1.26
Wiklund, 1983 (53)	Sweden	1961—1973	Census data	476	1.05	0.96—1.15
Inskip et al, 1996 (61)	United Kingdom	1979—1990	Death certificate	773	1.14	1.06—1.22
Skov & Lyngge, 1991 (62)	Denmark	1970—1980	Census data	187	1.00	0.86—1.16
<b>Cohort studies</b>						
Wigle et al, 1990 (15)	Canada	1960—1979	Agriculture census	103	0.92	0.75—1.11
Gunnarsdottir & Rafnsson, 1991 (54)	Iceland	1984—1988	Farmer pension	10	1.42	0.77—2.64
Stark et al, 1990 (55)	United States	1980—1983	Farm bureau	22	0.79	0.52—1.21
Folsom et al, 1996 (59)	United States	1986—1992	Questionnaire	28	1.38	0.90—2.12
Wiklund & Dich, 1994 (60)	Sweden	1983—1989	Census	94	0.78	0.63—0.96
Kristensen et al, 1996 (63)	Norway	1964—1978	Agriculture census	89	0.86	0.69—1.07
Ronoco et al, 1992 (64)	Denmark & Italy	1968—1976	Cancer register	190	1.03	0.89—1.20
Wiklund & Dich, 1995 (42)	Sweden	1980—1986	Census	508	0.99	0.91—1.08

conducted following the guidelines of Blair et al (24), to reduce the heterogeneity within the groups of studies. These meta-analyses accounted for possible sources of heterogeneity among studies, such as study design and place and time of publication.

Potential publication bias due to study size was explored by plotting the natural logarithm of the estimator of the relative risk (ln RR) versus the inverse of the standard error (1/SE). An adjusted rank correlation test (25) was used to test for potential bias due to study size. The absence of significant correlation is reassuring that the studies have been selected in an unbiased manner.

## Results

Fifty studies examining the association between farming and NHL and published after 1980 were identified. Seven of these studies (7, 26—31) were excluded from the meta-analyses because the exposure studied was not restricted to occupational exposure as a farmer. Three studies (32—34) were excluded because the cases studied were not exclusively NHL. Four more studies (35—38) were excluded because the cases examined were included in other studies of similar design (8, 10, 39, 40) that examined greater numbers of cases. The remaining 36 studies included in the meta-analyses are listed in table 1.

Twenty-one of the studies included in the meta-analyses were restricted to white males (8, 10—15, 43—56). Four studies were restricted to female farmers (57—60), and 7 studies reported results for both male and female farmers (6, 39, 40, 61—64). Four studies (20, 53, 65, 66) lacked information about gender.

Out of the 36 studies included, 4 studies reported no association between NHL and farming, and 11 studies reported a negative association. The estimator of relative risk for the negative studies ranged from 0.59 to 0.99 and included from 7 to 508 exposed cases. Only 1 of these studies was significant (confidence interval not including 1).

Twenty-one studies reported a positive association between NHL and farming and included from 10 to 1101 exposed cases. The estimator of relative risk ranged from 1.03 to 2.10, and 8 of these estimators were significant.

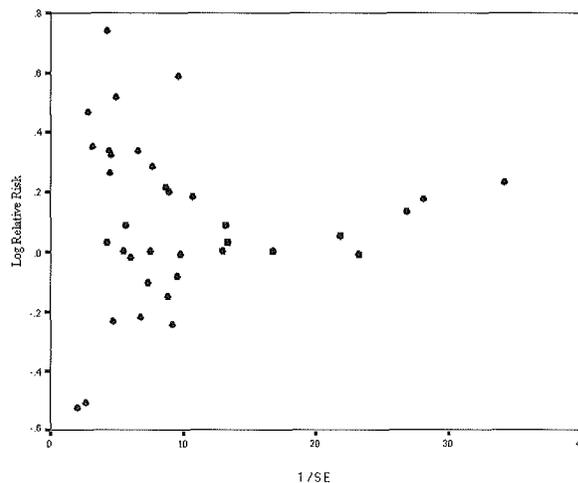
A plot of ln RR versus 1/SE showed no relation between relative risk and study size (figure 1). The test for publication bias indicated no evidence of bias due to study size ( $P=0.78$ ). The homogeneity test revealed significant heterogeneity among the studies, and additional analyses were done to reduce the sources of heterogeneity.

The meta-analysis including all the studies (table 2) yielded a combined RR of 1.10 [95% confidence interval (95% CI) 1.03—1.19]. Identical estimates were

obtained for studies published before or after 1984. The estimator of relative risk for the case-referent studies was 1.19 (95% CI 1.06—1.33), and it was 1.10 (95% CI 0.99—1.24) for the mortality and morbidity studies. None of the cohort studies reported a significant elevation in relative risk, and the combined estimate was 0.95 (95% CI 0.85—1.07). With regard to place, the highest combined estimate was 1.26 (95% CI 1.15—1.37) for studies conducted in the United States.

Table 3 presents estimates of relative risks for the female farmers. None of the studies reported a significant elevation in relative risk. Inskip et al (61) reported borderline significance (RR 1.43, 95% CI 0.96—2.04). The combined estimate was 0.93 (95% CI 0.82—1.06).

Table 4 describes the risk factors for NHL. Agricultural chemicals, especially herbicides and insecticides, along with animal sources, were the major risk factors associated with NHL among farmers. The highest risk was reported for phenoxyacetic acid herbicides. The combined estimate was 1.41 (95% CI 1.09—1.81).



**Figure 1.** Relation between the estimator of relative risk and the standard error in meta-analyses of farming and non-Hodgkin's lymphoma.

**Table 2.** Results of the meta-analysis of non-Hodgkin's lymphoma among farmers.

Stratification	Number of studies	Exposed cases	Relative risk	95% CI
Study design				
Case-referent studies	18	2596	1.19	1.06—1.33
Mortality and morbidity studies	10	3234	1.10	0.99—1.24
Cohort studies	8	1044	0.95	0.85—1.07
Place				
United states	15	3296	1.26	1.15—1.37
Europe	16	3147	1.02	0.90—1.16
Other	5	431	1.02	0.92—1.13
Time				
1982—1984	4	1854	1.14	1.01—1.27
After 1984	32	5020	1.10	1.01—1.19
All studies	36	6878	1.10	1.03—1.19

**Table 3.** Relative risks and 95% confidence intervals from studies of non-Hodgkin's lymphoma among female farmers.

Reference	Exposed cases	Relative risk	95% CI
Francheschi et al, 1993 (6)	33	0.70	0.50—1.20
Blair et al, 1993 (39)	24	1.07	0.67—1.69
Eriksson et al, 1992 (40)	62	0.90	0.70—1.15
Zahm et al, 1993 (57)	119	1.00	0.70—1.40
Linet et al, 1994 (58)	55	0.90	0.69—1.17
Folsom et al, 1996 (59)	28	1.38	0.90—2.12
Wiklund & Dich, 1994 (60)	94	.78	0.63—0.96
Inskip et al, 1996 (61)	30	1.43	0.96—2.04
Skov & Lynge, 1991 (62)	28	0.80	0.53—1.16
Kristensen et al, 1996 (63)	20	.04	0.64—1.56
Ronoco et al, 1992 (64)	29	0.90	0.62—1.29
Combined	522	0.93	0.82—1.06

**Table 4.** Description of risk factors for non-Hodgkin's lymphoma from studies included in the meta-analysis.

Type of exposure	Relative risks	95% CI
<b>Herbicides</b>		
Phenoxyacetic acids		
Cantor et al, 1992 (12)	1.20	0.90—1.60
Hoar et al, 1986 (13)	2.20	1.20—4.10
Persson et al, 1989 (20)	4.90	1.30—18.0
Triazines		
Cantor et al, 1992 (12)	1.10	0.80—1.60
Hoar et al, 1986 (13)	2.20	0.40—9.10
Zahm et al, 1993 (57)	2.20	0.10—31.5
Unspecified		
Cantor, 1982 (11)	.69	1.15—2.47
Wigle et al, 1990 (15)	1.34	0.74—2.38
La Vecchia et al, 1989 (66)	5.20	-
<b>Insecticides</b>		
Organophosphates		
Cantor et al, 1992 (12)	1.30	0.90—1.90
Zahm et al, 1993 (57)	4.50	1.10—17.9
Organochlorine		
Cantor et al, 1992 (12)	1.40	1.00—1.90
Wood et al, 1987 (14)	1.75	1.10—2.79
Zahm et al, 1993 (57)	1.70	0.50—5.80
Unspecified		
Cantor, 1982 (11)	1.67	1.15—2.45
Veil & Richardson, 1993 (52)	1.15	0.93—1.43
<b>Fertilizers</b>		
Cantor, 1982 (11)	1.67	1.15—2.44
<b>Any chemical</b>		
Delzell & Grufferman, 1985 (49)	2.20	1.10—4.40
<b>Animal source</b>		
Chicken inventory		
Cantor, 1982 (11)	1.67	1.16—2.44
Cattle inventory		
Cantor, 1982 (11)	1.67	1.14—2.43
Skov & Lynge, 1991 (62)	3.02	1.11—6.56
Sheep farm		
Pearce et al, 1987 (45)	1.10	0.70—1.60
Cowman		
Ronoco et al, 1992 (64)	3.02	1.36—6.72

## Discussion

The significant association between NHL and farming resulting from the meta-analysis of the 36 selected studies suggests that farming might be a weak risk factor for the disease. The preponderance of positive associations and relatively high estimators of relative risk found by the studies examining the greatest numbers of exposed cases also support an association between NHL and farming. Since both the rank test and figure 1 revealed no relation between the estimator of relative risk and study size (inverted funnel-shape), we feel that publication bias due to the preferential publication of large studies with positive findings does not appear to have occurred.

The results of these meta-analyses are inconsistent with the findings of Blair et al (67), whose meta-analysis of farming and NHL did not produce an association between farming and the disease. This difference in results might be due to our inclusion of studies published after Blair et al (67) performed their meta-analysis and our use of several other studies not used by Blair et al (67). We included 15 studies published after 1991, and 8 of them reported positive associations between NHL and farming.

The meta-analysis method has been criticized because it derives a common estimator of relative risk from studies with disparate designs and study populations and is often performed without critical review of the studies used (68). Blair et al (24) recommends stratifying the studies by the source of heterogeneity and conducting separate meta-analyses on the different subgroups. We identified three sources of heterogeneity: design and place and time of publication. The first analysis was for the design of the studies, and the combined relative risk was significantly elevated for case-referent studies only. It is interesting to note that most case-referent studies were conducted in the United States or were restricted to male farmers. The second analysis was for place, and the combined relative risk was significantly elevated for studies conducted in the United States. This result might have been due to differences between the study populations with respect to the proportional distribution of exposures that contribute to NHL.

The insignificant association between the exposure and the disease produced by the meta-analysis limited to female farmers does not support an association between farming and NHL and suggests that exposures other than employment as a farmer are associated with the disease. Although this meta-analysis did not support an association between farming and NHL, the significantly positive association of the meta-analysis limited to male farmers suggests that an association between NHL and exposures selectively experienced by subgroups of farmers might exist. Beside farming, farmers (and specifically male farmers) often serve in the role of mechanic,

carpenter, welder, pesticide applicator, and veterinarian (69). Therefore, it is possible that the level of exposure to the risk factors is high among male farmers.

The significant association between farming and NHL produced by the meta-analysis of studies on farmers residing in the United States (US) is consistent with our previous finding for farmers in the central region of the United States (70). The insignificant association between exposure and the disease produced by the meta-analyses of studies on non-US farmers suggests that specific exposures associated with NHL were experienced by US farmers only.

Since a diagnosis of NHL is frequently associated with a diagnosis of AIDS (71), impairment of the immune system probably contributes to the development of NHL. Most of the cases of NHL examined by the studies included in the meta-analyses were diagnosed before 1985, and it is unlikely that the exposure contributing to an excess of the disease among farmers is HIV (human immunodeficiency virus) infection. Exposures that result in decreased immunocompetence and predispose people to NHL include prior infectious diseases such as scarlet fever, herpes simplex, herpes zoster (7), tuberculosis, pyelonephritis, chronic bronchitis, and malaria (72). Exposure to solvents (19–21) and pesticides (10–19) has also been found to decrease immunity and predispose people to NHL.

The etiology of NHL is not well understood, but several factors have been implicated in many studies. The Epstein Barr virus (EBV) was implicated in many cases of NHL among people with compromised immunity (73). Elevated risks of NHL have been found for meat works employees (74) and veterinarians (75). Three studies (11, 62, 64) reported a significant association between NHL and animal exposure. Agricultural chemicals have been implicated in the etiology of NHL. Several studies reported that the likelihood of NHL is increased by exposure to herbicides, insecticides, fertilizer, and other agricultural chemicals (11, 13, 14, 20, 49, 57). The implication of agricultural chemicals is biologically plausible because many of these chemicals are known or suspected human carcinogens (76).

Three agricultural commodities that can serve as surrogate indicators of exposures experienced by farmers residing in the United States and potentially associated with NHL are cattle, corn, and soybeans (77). Since exposure to cattle is associated with numerous infectious diseases (78), farmers who produce beef or milk are at risk for infectious diseases, which might have contributed to an excess of NHL. The estimated proportions of farmers in the United States using pesticides to produce corn and soybeans are 86% and 93%, respectively (79). A pesticide used extensively in the production of corn and soybeans is 2,4-dichlorophenoxyacetic acid (2,4-D), which has been found to be associated with NHL (16,

17). A frequent contaminant of 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) and, less frequently, of 2,4-D, is 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) (80). Exposure to TCDD has been found to be associated with decreased cell-mediated immunity (81) and a slight increase in mortality from NHL (56). This finding suggests that exposure to 2,4-D might have resulted in decreased immunocompetence and therefore increased the occurrence of NHL in farmers residing in the United States.

The lack of a single agricultural commodity consistently produced on a majority of farms in the United States precludes inference of a specific risk factor for NHL. The high proportions of farms producing corn, soybeans, or cattle and calves in some states, however, suggest that both pesticides and infectious microorganisms might be risk factors for the disease.

### Concluding remarks

In conclusion, we found a small but significant elevation in the risk of NHL for male farmers and, specifically, for farmers residing in the United States. Exposures which are commonly experienced by this group of farmers and which might contribute to the occurrence of NHL include infectious microorganisms, herbicides, and insecticides.

Further studies simultaneously examining pesticides and infectious microorganisms as risk factors for NHL are indicated. Also indicated are studies of the association of NHL with other occupational exposures experienced by farmers. More studies are needed to explore the gender differences in the relative risk of NHL in farmers.

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