

Meta-analysis of Hodgkin's disease among farmers

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Objectives This study examined the association between Hodgkin's disease and farming.

Methods A series of meta-analyses of peer-reviewed studies was performed, using 30 studies published between 1981 and 1998. 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 1.25 [95% confidence interval (95% CI) 1.11—1.42] for all the studies, and 1.08 (95% CI 0.91—1.29) for the studies involving female farmers. Significant heterogeneity among the studies was detected, and a stratified analysis was carried out by study design, country of study, and time of publication. Significantly elevated RR values were obtained for the case-referent studies (odds ratio 1.53, 95% CI 1.18—1.98) and proportionate mortality studies (PMR) (PMR 1.18, 95% CI 1.02—1.36). A decrease in risk was eminent in the more recent studies.

Conclusions The findings suggest that male farmers have a slightly elevated risk of developing Hodgkin's disease. No specific etiologic exposure was identified, but exposures commonly experienced by farmers (infectious microorganisms, herbicides and insecticides) may contribute to the occurrence of the disease.

Key terms farmers, Hodgkin's disease, infections, meta-analyses, pesticides.

Hodgkin's disease is a malignancy of the immune system. It is believed that much of the immune dysfunction is explicable by lymphocyte hyperactivity induced by chronic antigenic stimulation (1). The nature of this antigenic stimulant is currently not well defined. Over the last decade, evidence has accumulated implicating Epstein-Barr virus (EBV) in the pathogenesis of Hodgkin's disease (2). However, EBV cannot account for the current incidence rate of Hodgkin's disease (3).

Various occupational and environmental exposures have been discussed in relation to Hodgkin's disease. Elevated risks have been reported for exposure to fabric dust (3), creosote (4), organic solvents (4, 5), chlorophenols (5), and phenoxy acids (4, 5). Elevated risks have been reported for wood-related occupations (6), fishermen (7), meat processors (8), and farmers (9—16).

A meta-analysis of epidemiologic studies of cancer in farmers, performed by Blair et al (17), reported a significant excess of Hodgkin's disease [odds ratio (OR) 1.16, 95% confidence interval (95% CI) 1.03—1.29]. Since this meta-analysis, the number of published studies on this topic has more than doubled. In an attempt to corroborate the finding of Blair et al (17) and assess the

relationship between farming and Hodgkin's disease, a series of meta-analyses was performed and evaluated in the context of what is known about the etiology of the disease.

Material and methods

The Medical Abstract and Cancer Abstracts data bases were searched for articles about farming and Hodgkin's disease. The search of MEDLINE data was from 1981 until 1 December 1998. The Cancer Abstracts data-base search included articles published from 1980 until 1 December 1998. 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 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

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design examining a greater number of subjects, and (iv) the disease studied was not specifically designated as Hodgkin's disease.

The remaining articles were then examined, and estimators of the relative risks were extracted independently by author. The estimators of the relative risks were odd ratios (OR) for case-referent studies, standardized mortality ratios (SMR) or standardized incidence ratios (SIR), or proportional mortality ratios (PMR) for cohort, 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 (18). This is a chi-square test with degrees of freedom equal to the number of studies minus one, and 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 effect model (19) was used to obtain the combined relative risk and its standard error (SE). Statistical analysis was performed using an SAS software program (20).

The first meta-analysis examined all studies that met the criteria for inclusion. A second meta-analysis was restricted to female farmers (studies reporting on farmers who were female or on female relatives of farmers who assisted in farming). Additional meta-analyses were conducted following the guidelines by Blair et al (21), to reduce the heterogeneity within the groups of studies. These meta-analyses accounted for possible sources of heterogeneity among studies, such as study design, place, and time of publication.

Potential publication bias due to study size was explored by plotting the natural logarithm of the estimator of relative risk ($\ln RR$) versus the inverse of standard error ($1/SE$). An adjusted rank correlation test (22) was used to test for potential bias due to study size. The absence of a significant correlation is reassurance that the studies have been selected in an unbiased manner.

Results

Thirty-eight studies examining the association between farming and Hodgkin's disease and published after 1980 were identified. Four studies (23—26) were excluded from the analyses because the data were included in other studies (27—30). Two studies (8, 31) were excluded because the exposure studied was not restricted to occupational exposure as a farmer. Two more studies (32, 33) were excluded because the cases studied were not exclusively Hodgkin's disease. The remaining 30 studies included in the meta-analyses are listed in table 1.

Sixteen of the studies included in the analyses were restricted to white males (10, 11, 13, 15, 27, 28, 30, 34—42). Five studies reported results only for men (4, 12, 43—45). One study (46) was restricted to women, and 7 studies reported results for both genders (9, 14, 16, 16, 47—49).

Out of the 30 studies included, 5 studies (16, 34, 38, 43, 40) reported a negative association between Hodgkin's disease and farming, and 25 studies reported a positive association. The estimator of relative risk for the negative studies ranged from 0.78 to 0.99 and included 193 exposed cases. None of these negative studies was significant (confidence interval included 1). In contrast, the estimator of relative risk for the positive studies ranged from 1.01 to 4 and included 1032 exposed cases. Seven of these studies (11, 12, 14, 15, 16, 38, 42) had an estimated relative risk that was statistically 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 ($P=0.07$). The homogeneity test revealed significant heterogeneity among the studies, and further analyses were carried out to reduce the sources of heterogeneity.

The meta-analysis including all the studies (table 2) yielded a combined relative risk of 1.25 [95% confidence interval (95% CI) 1.11—1.42]. The estimator of relative risk for the case-referent studies was 1.53 (95% CI 1.18—1.98), and it was 1.18 (95% CI 1.02—1.36) for the mortality and morbidity studies. Only 1 cohort study (14) reported a significant elevation in relative risk. The combined estimate for the cohort studies was 1.08 (95% CI 0.97—1.20).

With regard to the geographic distribution, most of the studies were conducted in Europe, and they involved 895 exposed cases. The combined estimate for these studies was 1.26 (95% CI, 1.06—1.49).

The combined estimates were significantly elevated for studies published before or after 1990. However, there seemed to be a decrease in risk in more recent studies.

Table 3 presents the estimates of relative risks for female farmers. None of the studies reported a significant elevation in relative risk. The combined estimate was 1.08 (95% CI, 0.91—1.29).

Discussion

The significant association between Hodgkin's disease and farming resulting from the meta-analysis of the 30 selected studies suggests that farming may be a weak risk factor for the disease. The preponderance of studies with a positive association and the slight increase in the magnitude of the relative risk with an increasing number of

Table 1. Description of the studies included in the meta-analysis of Hodgkin's disease among farmers. (RR = relative risk, 95% CI = 95% confidence interval)

Reference	Country	Study period	Method	Exposed cases	RR	95% CI
Case-referent studies						
Persson et al, 1989 (4)	Sweden	1964—1986	Questionnaire	6	1.20	0.32—4.46
Dubrow et al, 1988 (10)	United States	1960—1979	Death certificate	3	2.70	0.87—8.37
Balarajan, 1988 (11)	England & Wales	1973—1977	Cancer register	16	3.09	1.89—5.25
Giles et al, 1984 (12)	Tasmania	1972—1980	Interview	3	3.20	1.11—11.2
La Vecchia et al, 1989 (13)	Italy	1983—1988	Questionnaire	15	2.00	1.00—3.70
Ronco et al, 1992 (16)	Italy	1981—1982	Cancer register	12	2.37	1.35—4.16
Brownson et al, 1989 (27)	United States	1984—1988	Medical record	9	1.09	0.51—2.26
Reif et al, 1989 (30)	New Zealand	1980—1984	Cancer register	24	1.19	0.76—1.87
Francheschi et al, 1993 (47)	Italy	1985—1991	Interview	16	1.60	0.90—2.80
Forastiere et al, 1993 (34)	Italy	1980—1986	Farmers' pension	5	0.84	0.18—3.95
Keller & Howe, 1994 (35)	United States	1986—1988	Medical record	6	1.06	0.48—2.36
Fincham et al, 1992 (36)	Canada	1983—1989	Questionnaire	9	1.24	0.56—2.75
Hoar et al, 1986 (37)	United States	1976—1982	Interview	71	0.80	0.50—1.20
Mortality and morbidity studies						
Eriksson et al, 1992(9)	Sweden	1979—1984	Census data	115	1.20	1.00—1.44
Saftlas et al, 1987 (15)	United States	1968—1976	Death certificate	52	1.55	1.18—2.03
Wiklund, 1983 (29)	Sweden	1961—1973	Census data	226	1.02	0.89—1.17
Burmeister et al, 1981(38)	United States	1964—1978	Death certificate	47	1.37	1.03—1.82
Une et al, 1987 (39)	United States	1983—1984	Death certificate	2	4.00	1.00—16.0
Blair et al, 1993 (43)	United States	1984—1988	Death certificate	58	0.99	0.76—1.30
Delzell & Grufferman, 1985 (40)	United States	1976—1978	Death certificate	8	0.90	0.60—1.40
Inskip et al, 1996 (48)	United Kingdom	1979—1990	Death certificate	131	1.05	0.88—1.25
Olsen & Jensen, 1987 (44)	Denmark	1970—1980	Census data	18	1.13	0.71—1.79
Cerhan et al, 1998 (42)	Denmark	1987—1993	Death certificate	38	1.62	1.04—2.54
Cohort studies						
Pukkala and Notkola, 1997(14)	Finland	1979—1993	Farm register	105	1.22	1.01—1.49
Ronco et al, 1992 (16)	Denmark	1970—1980	Cancer registry	51	0.78	0.59—1.03
Gunnarsdottir & Rafnsson, 1991 (28)	Iceland	1984—1988	Farmer pension	5	2.51	0.83—7.63
Wiklund & Dich, 1994 (46)	Sweden	1983—1989	Census	25	1.13	0.73—1.67
Kristensen et al, 1996 (49)	Norway	1964—1978	Agriculture census	37	1.29	0.93—1.79
Wiklund & Dich, 1995 (45)	Sweden	1980—1986	Census	111	1.01	0.83—1.22
Mastrangelo et al, 1996 (41)	Italy	1970—1992	Farm register	1	1.16	0.03—6.46

exposed cases also support an association between Hodgkin's disease 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 our meta-analyses are consistent with the findings of Blair et al (17), who reported a significant association between Hodgkin's disease and farming.

Significant heterogeneity was detected between the studies included in these meta-analyses. We investigated the sources of heterogeneity and identified study design, place of study, time of study inception, and time of publication as possible sources of heterogeneity between the studies. We followed the recommendation of Blair et al (21) to stratify the studies by the source of heterogeneity and conduct separate meta-analyses on the different subgroups. Accordingly, we conducted additional meta-analyses by the possible sources of heterogeneity. The first analysis was for the design of studies, and the combined relative risk was significantly elevated for the case-referent studies and mortality studies. It is interesting to note that the 13 case-referent studies involved the least number of exposed cases. Only 2 of these studies

showed a significant elevation of Hodgkin's disease among farmers. The largest case-referent study (37) reported a lower risk for Hodgkin's disease among farmers. The limitations of mortality studies are well known. The quality of death certificate data for occupation is questionable (50). The inaccuracy of occupational information on death certificates could diminish risk estimates and dilute the exposure-response effect.

A second meta-analysis was conducted for place, and the combined relative risk was significantly elevated in Europe. However, table 2 indicates that there does not seem to be any great heterogeneity in risk between regions, at least between the United States and Europe, where most studies have been conducted.

The lack of association between the exposure and the disease when the meta-analysis was limited to female farmers is difficult to explain and suggests that exposures other than employment as a farmer may be associated with the disease. Although this meta-analysis does not support an association between female farmers and Hodgkin's disease, the statistically significant positive association of the meta-analysis limited to male farmers suggests that an association between Hodgkin's disease and exposures selectively experienced by subgroups of farmers may exist. Besides farming, farmers (and

specifically male farmers) often serve in the role of mechanic, carpenter, welder, pesticide applicator, and veterinarian (51). Therefore, it is possible that the level of exposure to other risk factors may be different for male farmers.

The etiology of Hodgkin's disease is not well understood, but several factors have been implicated in many studies. EBV has been implicated as a major etiologic factor for Hodgkin's disease (2). There have been several case reports of Hodgkin's disease development in close association with serologically documented EBV primary infection (52). An elevated risk of Hodgkin's disease has been seen in meat works employees (3) and veterinarians. Kristensen et al (53) reported a significant association between chicken farming and Hodgkin's disease in later childhood. Chickens have been suspected of inducing malignancies in farming through poultry viruses or chronic antigenic stimulation (17). Kristensen et al (49) noted that exposure to organic dust containing microorganisms is very high in hen houses, and it may be associated with the increased risk of Hodgkin's disease among farmers who raise chickens.

Agricultural chemicals have been implicated in the etiology of Hodgkin's disease. Hardel et al (5) reported an association between exposure to phenoxy acid herbicide and a subsequent increased risk of Hodgkin's disease. However, Hoar et al (37) did not show any increased risk of Hodgkin's disease in relation to herbicide exposure. Wiklund & Dich (46) found that Hodgkin's disease was highest in the oldest birth cohort and in regions where the use of pesticides was assumed to be lowest and animal exposures was highest. They noted that a plausible explanation for the elevated Hodgkin's disease could be exposure to animals. The implication of agricultural chemicals is biologically plausible because many of these chemicals are known or suspected human carcinogens (54).

A major limitation of the studies included in this meta-analysis is the lack of details regarding exposure. In most studies, no specific exposure assessment was undertaken, and analyses were based on the job title as farmers. Another limitation is that 9 studies (4, 10, 12, 28, 34–36, 39–41) have been based on a small number of cases. This lack of cases limits the statistical ability to adjust for age and other potential confounding factors. Proper evaluation of the dose-response relationship with regard to duration of farming was limited by the small number of cases. Our study results are also limited by the changing and subjective nature of diagnoses of Hodgkin's disease in most of the studies included in our meta-analysis. It is difficult to rule out the possibility of misclassification bias in some studies. It is possible that some of the cases of non-Hodgkin's lymphoma were inaccurately classified as Hodgkin's disease. Recently there has been a decrease in the number of reported cases of

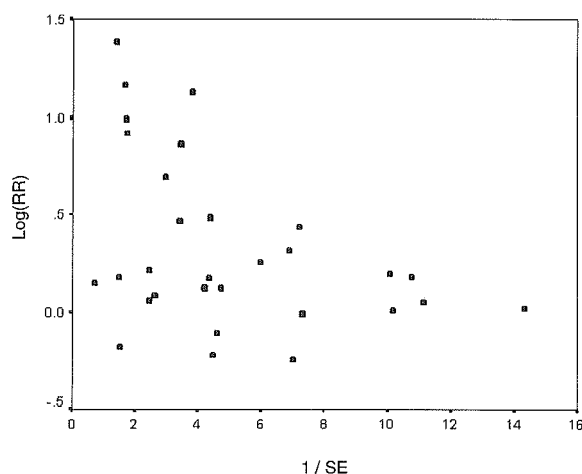


Figure 1. Relationship between the estimator of relative risk and study size in the meta-analysis of Hodgkin's and farming.

Table 2. Results of the meta-analysis of Hodgkin's disease among farmers. (N = number of studies, RR = relative risk, 95%CI = 95% confidence interval)

Stratification	N	Exposed cases	Homo-geneity		RR	95% CI
			χ^2	P-value		
All studies	30	1225	63.1	0.001	1.25	1.11–1.42
Study design						
Case-referent	13	195	25.2	0.014	1.53	1.18–1.98
Mortality and morbidity	10	695	18.0	0.036	1.18	1.02–1.36
Cohort studies	7	335	10.6	0.101	1.08	0.97–1.20
Place						
United States	10	294	18.0	0.036	1.23	0.99–1.53
Europe	17	895	40.7	0.001	1.26	1.06–1.49
Other	3	36	2.5	0.289	1.33	0.92–1.93
Time of publication						
1981–1989	14	500	38.0	0.001	1.38	1.09–1.75
After 1989	16	725	24.2	0.062	1.12	1.04–1.21

Table 3. Relative risk (RR) and 95% confidence interval (95% CI) for the studies of Hodgkin's disease among female farmers.

Reference	Exposed cases	RR	95% CI
Eriksson et al, 1992 (9)	18	1.20	0.76–1.90
Pukkala & Notkola 1997 (14)	20	0.79	0.48–1.21
Ronoco et al, 1992 (16)	1	1.87	0.26–13.28
Ronoco et al, 1992 (16)	11	0.96	0.53–1.73
Francheschi et al, 1993 (47)	8	1.50	0.60–3.40
Inskip et al, 1996 (43)	45	1.09	0.81–1.47
Wiklund & Dich, 1994 (46)	25	1.13	0.73–1.67
Kristensen et al, 1996 (49)	4	1.77	0.48–4.10
Combined	132	1.08	0.91–1.29

Hodgkin's disease. The reported decrease in the incidence of Hodgkin's disease in industrialized countries may be due to a reclassification of Hodgkin's disease as non-Hodgkin's lymphoma. Wiklund & Dich (45) noted that a histopathological re-examination of Hodgkin's disease has recently been performed in Sweden, and some diagnoses were changed to non-Hodgkin's lymphoma.

In summary, we found a small but statistically significant elevation in the risk of Hodgkin's disease among male farmers. Existing data support an association between farming and Hodgkin's disease, but they do not provide clear-cut evidence as to whether chemical or biological agents or both are involved. Further studies simultaneously examining pesticides and infectious microorganisms as risk factors for Hodgkin's disease are indicated.

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