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Case–Control Studies of Cancer in Illinois Farmers Using Data From the Illinois State Cancer Registry and the U.S. Census of Agriculture

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A series of case–control studies have been carried out to compare farmers reported to the Illinois State Cancer Registry (ISCR) with other males reported to the ISCR between 1986 and 1988. Data on the number of farms in each Illinois county producing given agricultural commodities were obtained from the United States Census of Agriculture and used as surrogate exposure indicators. Employment as a farmer was found to be associated with cancer of the eye [odds ratio (OR) = 6.49, 95% confidence interval (CI) = 1.78, 23.71], lip (OR = 4.42, 95% CI = 2.46, 7.94), prostate (OR = 1.15, 95% CI = 0.99, 1.35) and leukaemia (OR = 1.51, 95% CI = 1.01, 2.25). Wheat and soybean production were found to be positively associated with leukaemia. Hay and beef production were found to be positively associated with cancer of the prostate.
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INTRODUCTION

As an occupational group with one of the highest exposures to agricultural chemicals, farmers offer a unique opportunity to examine the potential cancer risk of exposure to pesticides, fertilisers, herbicides and farm animals. Since most farmers live and work in rural areas, their rates of cancer may reflect baseline cancer rates that would occur in the absence of industrial exposures, lifestyle factors and urban pollution associated with living and working in metropolitan areas. Blair and colleagues [1] reviewed the studies of farming and cancer published from 1949 to 1985, and concluded that the cancers occurring most frequently in excess among farmers were Hodgkin's disease, leukaemia, non-Hodgkin's lymphoma, multiple myeloma and cancers of the lip, stomach, prostate, skin, brain and connective tissue.

Case–control studies using incident cases have shown numerous associations between farming and cancer.

Leukaemia

In a study of New Zealand leukaemia cases, Pearce and colleagues [2] found an elevated odds ratio for livestock farmers. Brown and colleagues [3] found a positive association between leukaemia and insecticides used in animal husbandry. In a study of multiple myeloma cases, Pearce and colleagues [4] reported elevated odds ratios for sheep farming and exposure to beef cattle, but no significant elevation for potential exposure to phenoxy herbicides, chlorophenols or other agricultural chemicals.

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Brain

Musicco and colleagues [5] found an elevated odds ratio for brain gliomas which was attributable to the farmers' reports of farm chemicals use. Reif and colleagues [6] also reported excesses of brain cancer in farmers, with the greatest risk found in livestock farmers. McDuffie and colleagues [7] found an elevated odds ratio for lung cancer and farming, although other studies have not [8, 9].

Lymphoma

Lymphoma is the cancer most extensively examined by case–control studies. In a study of Kansas cancer cases, Hoar and colleagues [10] found that non-Hodgkin's lymphoma was associated with herbicide use, but soft tissue sarcoma and Hodgkin's disease were not. Pearce and colleagues [11] reported an elevated odds ratio for farming among malignant lymphoma and multiple myeloma cases from New Zealand. In a further study, Pearce and colleagues [12] found that non-Hodgkin's lymphoma was associated with orchard farming. A cohort mortality study by Wigle and colleagues [13] found an association between non-Hodgkin's lymphoma and herbicide use.

Soft tissue sarcomas

Hardell and Sandstrom [14] reported that soft tissue sarcomas were associated with phenoxy herbicide exposure, as did Erikson and colleagues [15] and Wingren and colleagues [16]. Other studies have not supported this association [17, 18].

A series of case–control studies was carried out to compare farmers reported to the Illinois State Cancer Registry (ISCR) with other persons reported to the ISCR between 1986 and 1988. The analysis excluded cases from large urban and suburban counties in the Chicago metropolitan area. Data on the number of farms in each Illinois county that produced given agricultural commodities were obtained from the United States Census of Agriculture and used as surrogate exposure indicators.

MATERIALS AND METHODS

Study population

All cases of cancer among males reported to the ISCR diagnosed from 1986 through 1988, excluding those cases in Cook, Du Page, Grundy, Kane, Kendall, Lake, McHenry and Will counties, were included in the study. More than 98% of the farmers on the Registry were white. Thus, all farmers were compared with all other white male cases reported to the registry.

Selection of cases and controls

For each site-specific analysis, cases were all cases of the site in farmers or white males. Controls were all other sites in farmers or white males.

Data elements

ISCR includes data on race, sex, age, county and zip code of residence, history of tobacco and alcohol use, cancer site, site morphology, current occupation and industry, and longest lifetime occupation and industry. Occupations and industries are coded using the U.S. Census Occupation Classification System.

Data coding

Subjects were classified as farmers using the U.S. Census Occupation Classification System codes. A subject was classified as a farmer if any of the four employment variables specified a farming occupation (codes 473–379, 485, 488, 489) or industry (codes 010, 011, 029, 021). The remaining subjects were classified as non-farmers if at least one of the employment variables indicated employment not related to farming, or as non-codable if all four employment variables were incomplete or too non-specific to be coded.

Subjects were also classified by history of tobacco use as noted on the medical record and reported to the ISCR. If reported to be a current or past user of tobacco products, a subject was classified as having had a history of tobacco use. A subject was classified as not having a history of tobacco use only if the medical record specifically stated the subject had never used tobacco. If the wording in the record was not explicitly "never smoked", the subject was placed in the "tobacco use unknown" category.

Specific exposures were characterised by county of residence and the percentage of farms in that county that produced a given agricultural commodity in four years: 1954, 1964, 1974 and 1982 (Censuses of Agriculture compiled by the U.S. Census Bureau). The U.S. Census Bureau published these data every 5 years, but Illinois farming practices did not vary substantially between any single 5-year period. The years used for the analysis were chosen to reflect exposures between 5 and 33 years prior to the development of cancer.

To be included in this analysis, an agricultural commodity had to be produced in at least 70% of the farms of some of the Illinois counties and a potential exposure gradient throughout the state had to exist. Three agricultural commodities, poultry, sheep and dairy cows, were excluded from further analysis because the percentage of farms producing these commodities was less than 70 for some of the years studied. Corn was excluded from the analysis because it was produced in large proportions of farms in almost all Illinois counties. The remaining agricultural commodities studied were hay, wheat, soybeans, beef cattle and pigs.

Cancers selected for analysis

Logistic analyses were performed on the tumours and malignancies found to be associated with employment as a farmer by proportional analyses (Table 1) or reportedly associated with employment as a farmer. The sites studied were cancers of the lung, prostate, eye, lip, oral cavity, rectum, stomach, muscle and connective tissue and brain as well as leukaemia, melanoma, Hodgkin's disease, myeloma, non-Hodgkin's lymphoma and soft tissue sarcoma. The Appendix lists the sites studied.

Data analysis

Two types of logistic analysis were first performed: (1) proportional analysis that controlled for age and the association of the cancer site with tobacco use, by analysing sites associated with tobacco use separately from sites not associated with tobacco use; and (2) proportional analysis that controlled for age and history of tobacco use.

Associations between employment as a farmer and each cancer site were then examined using logistic regression to control for age and history of tobacco use. Sites found to be significant ($P < 0.05$) or marginally significant ($P < 0.10$) and to have sufficient subjects for further analysis were then selected for logistic modelling with more specific indicators of agricultural exposures. In addition, three of these sites, leukaemia and cancers of the eye and lip, were selected for more detailed review of histology and specific sites since several investigators have suggested that potential excesses may be confined to specific subtypes [2, 3, 19].

After the initial selections, logistic regression was used to study the association between each agricultural commodity and the cancer sites selected. The commodities were examined in two ways: (1) as dichotomous variables with exposure to a commodity considered to have occurred if a farmer lived in a county where at least 70% of the farms produced that commodity; and (2) as continuous variables. Commodities found to be associated with a given cancer site during all of the 4 years studied were selected for further modelling.

Table 1. Age-adjusted proportional analysis, farmers, all sites, controlling for history of tobacco use

Site	Observed	Expected	Ratio	*P*
Oral cavity	61	50.14	1.22	0.15
Oesophagus	16	23.05	0.69	0.16
Stomach	36	39.63	0.91	0.63
Colon	243	233.67	1.04	0.54
Rectum	98	98.94	1.01	0.97
Liver	6	7.31	0.82	0.81
Pancreas	45	38.93	1.16	0.36
Lung	290	363.28	0.80	<0.01
Bone	2	1.78	1.12	0.99
Melanoma	41	32.55	1.26	0.17
Prostate	505	448.36	1.13	<0.01
Testis	9	9.29	0.97	0.99
Bladder	128	137.34	0.93	0.43
Kidney	43	43.37	1.01	0.99
Nervous system	30	25.97	1.16	0.47
Hodgkin's disease	6	5.68	1.06	0.99
Non-Hodgkin's lymphoma	58	59.92	0.97	0.87
Myeloma	23	20.80	1.11	0.68
Leukaemia	51	39.90	1.28	0.10
All othe cancer sites	157	168.15	0.93	0.39

Source: Illinois State Cancer Registry, December 3, 1990.

When the commodities were treated as continuous variables, principal component analysis was used to develop factors that adjusted for multicollinearity among all commodities studied for each of the 4 years considered. The factors identified by principal component analysis were then considered for the final models. Selection of the summary variables used in the final models was based on statistical significance when age and tobacco use were included in the model.

RESULTS

Information on both employment and tobacco use was available for 9514 of the 21 186 eligible cases (44.9%). Information on tobacco use was available for 13 949 of the eligible cases (65.8%). The proportion of farmers using tobacco was less than that of the other cases [odds ratio (OR) = 0.54, 95% confidence interval (CI) 0.47, 0.62, $P < 0.01$]. The mean age of the farmers at time of diagnosis was greater than that of the other subjects (71.3 versus 65.5 years).

With respect to morphological subtypes, the distributions of leukaemia and cancer of the lip in farmers did not differ from those in all other occupations. Cancer of the conjunctiva of the eye occurred more frequently in farmers than in all other occupations (OR = 9.0, 95% CI 1.5–54.0, $P = 0.02$).

Table 2 shows results of logistic analyses of the general associations between farming and specific cancer groups or types. Significant ($P < 0.05$) associations were found between farming and cancer of the eye, cancer of the lip and leukaemia. Prostate cancer was marginally associated ($P < 0.10$) with farming. A strong negative association ($P < 0.01$) between farming and lung cancer was found. Since only 7 cases of cancer of the eye occurred in farmers, no further analysis was performed for this site.

The logistic regressions of lung cancer and agricultural commodities for each of the years studied while controlling for age and history of tobacco use consistently found significant negative associations ($P < 0.01$) for each of the variables examined. Similarly, significant positive associations ($P < 0.01$) were consistently found for lip cancer and each of the variables studied.

Logistic regression analyses of leukaemia and agricultural commodities for each of the years studied with controlling for age and history of tobacco use showed consistent positive associations for wheat, hogs and soybean production. Principal component analysis of the wheat, pigs and soybean variables yielded a factor that included only the wheat and soybean variables (Table 3).

Logistic regression analyses of prostate cancer and agricultural commodities for each of the years studied with controlling for age and history of tobacco use found consistently positive associations for hay and beef cattle production. The factor indicated by principal component analysis as statistically significant in the model included only beef production during 1964, 1974 and 1982, and hay production during 1974 and 1982 (Table 4).

Table 2. Odds ratios for farming occupation, controlling for age and history of tobacco use

Cancer site	Odds ratio	95% confidence interval	P
Leukaemia	1.51	1.01–2.25	0.04
Prostate	1.15	0.99–1.35	0.07
Lung	0.71	0.62–0.83	<0.01
Eye	6.49	1.78–23.71	<0.01
Lip	4.42	2.46–7.94	<0.01
Melanoma	1.29	0.77–2.14	0.34
Oral cavity	1.12	0.80–1.57	0.52
Hodgkin's disease	1.21	0.42–3.48	0.72
Rectum	1.01	0.77–1.33	0.94
Stomach	1.06	0.71–1.57	0.78
Myeloma	1.30	0.74–2.26	0.36
Brain	1.39	0.86–2.24	0.17
Non-Hodgkin's lymphoma	1.09	0.77–1.54	0.64
Soft tissue sarcoma	0.91	0.31–2.64	0.86
Muscle and connective tissue	1.28	0.59–2.76	0.53

Table 3. Final logistic model, leukaemia

Variable	Odds ratio	95% confidence interval	P
Age*	0.91	0.81–1.03	0.130
Smoking	0.69	0.49–0.98	0.037
Wheat and soy production †‡	1.20	1.03–1.39	0.013

*Based on an increase in age of 10 years. †The Eigen vector values for this variable were: wheat production, 1954: 0.952, wheat production, 1964: 0.928, wheat production, 1974: 0.924, wheat production, 1982: 0.857, soybean production, 1954: 0.778, soybean production, 1964: 0.729, soybean production, 1974: 0.607, soybean production, 1982: 0.639. ‡Based on an increase of 20% in each of the component variables.

DISCUSSION

The associations with specific agricultural commodities have not been previously reported. Numerous studies have linked leukaemia with farming but the specific exposures implicated have been related to livestock production rather than wheat or soybean production [2, 3, 20, 21]. Wheat and soybean production in Illinois correlated closely with beef production. The statistical association between wheat and soybean production and leukaemia may reflect an actual causal relationship between beef production and leukaemia.

Positive associations between farming and prostate cancer have also been reported [21, 22], but no precise agricultural practices have been implicated. The specific association between beef production and hay production found by this study may reflect exposures specific to hay and beef production rather than general farming exposures.

Table 4. Final logistic model, prostate cancer

Variable	Odds ratio	95% confidence interval	P
Age*	1.73	1.64–1.84	<0.001
History of tobacco use	0.38	0.34–0.43	<0.001
Beef and hay†‡	1.09	1.02–1.18	0.018

*Based on an increase in age of 10 years. †The Eigen vector values for this variable were: beef production, 1964: 0.794, beef production, 1974: 0.905, beef production, 1982: 0.975, hay production, 1974: 0.857, hay production, 1982: 0.946. ‡Based on an increase of 20% in each of the components of this factor.

Other investigators have reported non-specific associations found between farming and lip cancer and cancer of the eye. Gallagher and colleagues [23] reported an excess of cancer of the lip in farmers. Since this excess was associated with all the specific exposure indicators studied, it may reflect exposures common to all Illinois farmers rather than specific agricultural practices. The proportions of histological types of lip cancer in farmers did not differ from those in the other residents, which suggests that the excess cannot be attributed to excessive sunlight exposures.

Saftlas [24] also reported excesses of eye cancer in farmers. Doll [19] has remarked on reported excesses of eye cancer in rural residents. These excesses may reflect elevated rates specific to farmers or increased risks from other rural exposures. Most of the excess of eye cancer in Illinois farmers is due to an excess of cancer of the conjunctiva, which suggests a relatively specific relationship between farming and eye cancer. Further studies of the occurrence of eye cancer in Illinois residents could be illuminating.

Negative associations between lung cancer and farming have also been reported [8, 9]. These associations reflect, in part, a decreased prevalence of tobacco use in farmers. Since the negative association with lung cancer in Illinois farmers remained after controlling for tobacco use, other factors may also contribute to the low rate of lung cancer in farmers. The decreased proportion of lung cancer in farmers may reflect differences in dietary habits [25, 26], differences in exposure to passive smoke [27–29] or radon [30]. No data were available in this study to assess these exposures.

It might be asserted that the negative association between farming and lung cancer does not reflect a decreased number of lung cancer cases in farmers so much as an increased number of other cancers. The proportional analysis does not support this conclusion. When cancer sites not known to be associated with tobacco use were studied separately from cancer sites known to be associated with tobacco use, no sites were found to be elevated. If specific sites besides cancer of the prostate had been elevated, these elevations would have been apparent in the analyses that excluded lung cancer and other sites associated with tobacco use.

The decreased proportion of lung cancer cases and the decreased prevalence of tobacco use in farmers also suggests that case–control studies of farming and cancer that use other cancer cases as controls must adjust for differences in tobacco use. Without this adjustment, the decreased incidence of lung cancer in farmers may cause the rates of other cancers to appear elevated.

The use of other cancer cases as controls can also lead to biased results because other cancer cases may not reflect representative exposures. It has been suggested that all diseases known to be associated with an exposure under study should be excluded from case–control studies [31, 32]. In contrast, Pearce and Checkoway [33, 34] have suggested that when an exposure such as farming has been found to be associated with numerous cancers, excluding certain types is not feasible. This study used all other cancer cases as the controls for each case–control analysis. By excluding residents of the metropolitan Chicago area, cases more similar to farmers with respect to non-metropolitan residence were included, eliminating other potential urban biases.

This study suggests that farmers are at increased risk of leukaemia, and cancers of the lip, prostate and eye. The association between cancer of the eye and farming should be evaluated in more detail in further studies. Studies utilising precise exposure data from individual farmers will be necessary to identify the exact exposures contributing to excess cancers in this group.

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APPENDIX

Cancers studied
Oral cavity
Oesophagus
Stomach
Colon
Rectum
Liver
Pancreas
Lung
Bone
Melanoma
Prostate
Testis
Bladder
Kidney
Nervous system
Hodgkin's disease
Non-Hodgkin's lymphoma
Myeloma
Leukaemia
Miscellaneous cancers

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Death of a Husband or Marital Divorce Related to Risk of Breast Cancer in Middle-aged Women. A Nested Case–Control Study Among Norwegian Women Born 1935–1954

A. Kvikstad, L.J. Vatten, S. Tretli and S. Kvinnsland

A topic of general interest is whether important life changes may play a role in the onset of cancer. The hypothesis of this study was that death of a husband or marital divorce, is associated with an increased risk of breast cancer. The study included 4491 incident breast cancer cases and 44 910 controls, matched on age, in a population-based nested case–control study, among Norwegian women born between 1935 and 1954. The risk of breast cancer among widowed compared to married women showed an odds ratio (OR) of 1.13 [95% confidence interval (CI) 0.94–1.36], after adjusting for age at first birth and parity. For divorced women the analogous OR was 0.83 (95% CI 0.75–0.92), after adjusting for age at first birth, parity and place of residence. Thus, the results did not show any clear evidence that death of a husband or marital divorce was associated with an increased risk of breast cancer.

Key words: breast cancer, life change events, widowhood, divorce, epidemiology
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INTRODUCTION

WHETHER EMOTIONAL stress affects the risk of developing cancer is a question of general interest. Throughout history scientists have studied this topic, ranging back to Galen in the second century [1, 2]. Observations and personal impressions of numerous 18th and 19th century clinicians were given a firmer basis by the first statistical study carried out by Herbert Snow at the London Cancer Hospital, reported in 1893. Of 250 cancer patients studied, 156 had experienced "immediately antecedent trouble, often in very poignant form, as the loss of a near relative" [1].