Cancer Mortality in Four Northern Wheat-Producing States

Dina M. Schreinemachers

National Health and Environmental Effects Research Laboratory, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina, USA

Chlorophenoxy herbicides are used both in cereal grain agriculture and in nonagricultural settings such as right-of-ways, lawns, and parks. Minnesota, North Dakota, South Dakota, and Montana grow most of the spring and durum wheat produced in the United States. More than 90% of spring and durum wheat is treated with chlorophenoxy herbicides, in contrast to treatment of approximately 30% of winter wheat. In this ecologic study I used wheat acreage as a surrogate for exposure to chlorophenoxy herbicides. I investigated the association of chlorophenoxy herbicides with cancer mortality during 1980–1989 for selected counties based on level of agriculture (≥ 20%) and rural population (≥ 50%). Age-standardized cancer mortality rates were determined for grouped counties based on tertiles of wheat acreage per county or for individual counties for frequently occurring cancers. The cancer sites that showed positive trends of increasing cancer mortality with increasing wheat acreage were esophagus, stomach, rectum, pancreas, larynx, prostate, kidney and ureter, brain, thyroid, bone, and all cancers (men) and oral cavity and tongue, esophagus, stomach, liver and gall bladder and bile ducts, pancreas, cervix, ovary, bladder, and other urinary organs, and all cancers (women). Rare cancers in men and women and cancers in boys and girls were studied by comparing counties above and below the median of wheat acreage per county. There was increased mortality for cancer of the nose and eye in both men and women, brain and leukemia in both boys and girls, and all cancers in boys. These results suggest an association between cancer mortality and wheat acreage in counties of these four states. *Key words*: adults, agriculture, cancer mortality, children, chlorophenoxy herbicides, 2,4-D, herbicides, human, MCPA, pesticides, wheat. *Environ Health Perspect* 108:873–881 (2000). [Online 1 August 2000]
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Chlorophenoxy herbicides such as 2,4-dichlorophenoxyacetic acid (2,4-D) and 4-chloro-2-methylphenoxyacetic acid (MCPA) were first produced after the Second World War. They have been one of the most widely used class of herbicides since the mid-1960s, not only in the United States but also in other parts of the world. They are used in agriculture to control growth of broadleaf weeds in cereal grains and in nonagricultural settings to control growth of unwanted brush in rangeland, forests, noncrop land, rights-of-way, and in roadside maintenance. In addition, 2,4-D is one of the most commonly used herbicides in urban areas for the maintenance of parks, golf courses, playgrounds, playing fields, and home lawns and gardens (*1–4*). Chlorophenoxy herbicides are often mixed with other herbicides and fertilizer. Dioxins are unwanted contaminants (*2,5–7*). One of the most toxic dioxins, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), a contaminant of the chlorophenoxy herbicide 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), is a potent carcinogen in animals (*6*). Most registrations for 2,4,5-T were canceled in 1979 by the U.S. Environmental Protection Agency (*2,6–8*). Contamination of 2,4-D and MCPA by TCDD is not likely (*5*). More than 60% of all agricultural herbicides used in the United States, including 2,4-D and MCPA, reportedly have the potential to disrupt the endocrine and/or reproductive system of animals (*1*).

Because chlorophenoxy herbicides are among the most common herbicides, widespread exposure to them is likely. Not only are people working in the agricultural industry exposed (e.g., farmers, farm workers, pesticide manufacturers and mixers, and crop duster pilots) but their families are also exposed because of contaminated clothing or dust tracked into the house (*9*). Lawn care workers and highway maintenance workers are also exposed. Other routes of exposure are drift from aerial pesticide application to crops, contamination of surface or groundwater, or walking in recently sprayed lawns and fields. A study of household pesticide use observed that 2,4-D is one of the most prevalent herbicides used by home owners (*1,10*). Suburban lawns and gardens probably receive the heaviest applications of pesticides of any land area in the United States (*1,11*). Home owners may be less careful than farmers in following instructions on the use of herbicides and may apply more than is needed (*3*). In contrast to most home owners, farmers are knowledgeable about the chemicals they use (*12*). Information on pesticide exposure obtained from interviews of farmers is thought to be reliable. Agricultural or seasonal workers, on the other hand, are not necessarily informed about which chemicals they are exposed to in the field.

Use of and exposure to chlorophenoxy herbicides is widespread. Therefore, it may be difficult to find a group of unexposed subjects to be used as a referent in studies investigating the effect of exposure to chlorophenoxy herbicides on human health. However, it is possible to find regions with a gradient of low and high exposures to chlorophenoxy herbicides in wheat-growing states of the United States. Most of the durum and spring wheat (spring planted) grown in the United States is produced in four states (93% in 1982): Minnesota (MN), North Dakota (ND), South Dakota (SD), and Montana (MT) (*13*). Herbicide use on durum and spring wheat is similar: > 90% of the acreage is treated with mostly chlorophenoxy herbicides (2,4-D and MCPA). In contrast, only 30% of the winter wheat acreage is usually treated (*14,15*). The 1982 percentages of combined spring and durum wheat acreage compared to all wheat acreage in MN, MT, ND, and SD were 97, 57, 98, and 65%, respectively (*13*).

In the current study I used wheat acreage per county as a surrogate for exposure to chlorophenoxy herbicides because information on crop acreage was more readily available than the amount of applied herbicides. To study the effect of herbicide using crop acreage as a surrogate, it is preferable that no other herbicides are used on the same crop and that no other crops are treated with the same herbicides. Agriculture in MN, ND, SD, and MT approaches this ideal situation because these four states grow few crops [wheat, corn, and soybeans are the main crops (Table 1)] and only have one crop season. Chlorophenoxy herbicides are used on wheat but not on soybeans, and little is used on corn (*14,15*). Barley, grown in the same regions as wheat, is also treated with chlorophenoxy herbicides. Because the wheat acreage in these four states is approximately 4–5 times larger than the barley acreage, I used wheat acreage

Address correspondence to D.M. Schreinemachers, Epidemiology and Biomarkers Branch, Human Studies Division, NHEERL, U.S. EPA, MD 58A, Research Triangle Park, NC 27711 USA. Telephone: (919) 966-5875. Fax: (919) 966-7584. E-mail: schreinemachers.dina@epa.gov

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as a measure of exposure to chlorophenoxy herbicides. Estimates of the wheat acreage by county were obtained from the 1982 Agricultural Census conducted by the U.S. Department of Agriculture (USDA) (*16*).

In a previous study Schreinemachers et al. (*17*) reported excess mortality in Northwestern Minnesota during 1980–1989 for cancer of the prostate, thyroid, and bone in men and for cancer of the eye in women. This region has a high level of agriculture: most of the available land is used to grow spring wheat. The objective of the current study was to confirm the previous results using a larger data set by including additional states and conduct more detailed analyses.

Materials and Methods

Cancer mortality. Cancer mortality data (underlying cause of death) for 1980–1989 collected by the National Center for Health Statistics (*18*) were summarized for 34 cancer groups by 5-year age intervals, sex, race, and county and state of residence based on methods used by the National Cancer Institute to summarize cancer mortality data for previous decades. (*19*). Estimates for the population at risk during 1980–1989 by 5-year age groups, sex, race, and county and state of residence for non-Census years were obtained by interpolation between the 1980 and 1990 Census population estimates (*20,21*) and by summing these estimates for 1980–1989.

Crop acreage. The 1982 USDA Agricultural Census database (*16*) provided information on acreage of total land area, total crop land, and individual harvested crop acreage by county. Although most of the wheat grown in MN, ND, SD, and MT was spring or durum wheat, some of the acreage was winter wheat. Because this database did not distinguish between acres of winter, durum, and spring wheat by county, I used total wheat acreage as a surrogate for chlorophenoxy herbicide exposure. For a few counties with very low levels of wheat agriculture in 1982, the harvested wheat acreage was withheld to avoid disclosing data for individual farms, although the number of farms was listed. Estimates were obtained by multiplying the number of farms with the average wheat acreage per farm from the 1987 Agricultural Census (*16*).

Statistical methods. I excluded counties with < 20% crop land (i.e., total land area dedicated to crop land) or with an urban population of > 50% from the analyses. These exclusions were made to ensure that risk estimates would reflect rural populations which are more likely to be exposed to agricultural pesticides than urban populations. I divided the remaining counties (≥ 20% crop land and ≥ 50% rural population) into three groups based on tertiles of wheat acreage per county as estimated by the 1982 USDA Agricultural Census (*16*). I calculated age-standardized mortality rate ratios (SRRs) comparing the second and third tertile to the first tertile for each cancer site for men and women ≥ 15 years of age. SRRs for a cancer site were calculated only if each of the two groups being compared included at least five deaths. Only white subjects were included because data for nonwhites were too sparse to allow for reliable analysis. SRRs for rare cancers in men and women and cancers in boys and girls (< 15 years of age) were calculated by dividing counties into two groups based on the median of wheat per county, provided at least five deaths were reported for each group. The 1970 U.S. population was used for the age standardization using the direct method (*22*). Confidence intervals (95%) for the SRRs were calculated based on a Poisson model using a method described by Rothman and Greenland (*22*).

In addition to analyses for grouped counties, I also investigated the more frequently occurring cancers using individual counties as the unit of observation. Kendall's rank correlation was used as a measure of association between wheat acreage and age-standardized cancer mortality rates by county. Counties reporting less than five deaths were excluded. For selected cancer sites these significant associations were further illustrated by plotting age-adjusted cancer mortality rates versus the logarithm (base 10) of wheat acreage per county. A smooth line was fitted using a spline routine.

For those cancer sites showing a positive trend with increasing wheat acreage, a significantly increased mortality for at least one of the two higher tertiles of combined counties, or a positive correlation with wheat acreage per county, I calculated SRRs separately for age groups < 65 and ≥ 65 years of age for both sexes.

I used SAS software (*23*) for all statistical analyses.

Results

The distribution of harvested crops by state according to the 1982 Agricultural Census is presented in Table 1. Most of the available crop land in MN, MT, ND, and SD is used

Table 1. Percent harvested crop of total crop land.[a]

	Minnesota	North Dakota	South Dakota	Montana
Total crop land (acres × 10^6)	22.2	28.1	18.8	16.5
Harvested crop land (%)	88.9	72.2	76.6	56.9
Wheat	13.4	34.9	17.7	31.7
Corn	26.6	1.9	13.7	0.1
Soybeans	20.3	1.5	4.1	NA
Barley	3.7	6.4	2.8	9.8
Oats	5.8	3.4	9.6	1.0
Potatoes	0.4	0.4	NA	NA
Sugar beets	1.2	0.5	NA	0.2
Hay	11.3	9.4	20.1	13.6
Sunflower seeds	2.1	11.1	2.6	NA
Average farm size (acres)	294	1,104	1,179	2,568

Data from the 1982 Agricultural Census (*16*). NA, not available.

Table 2. Characteristics of three groups of combined counties based on wheat acreage.

	Wheat acreage per county		
Characteristics	< 23,000	23,000–110,999	≥ 111,000
Number of counties			
Minnesota	33	16	7
North Dakota	0	10	30
South Dakota	17	21	3
Montana	0	4	11
Total	50	51	51
Land			
Approximate land area, acres × 10^6 (%)	19.5 (100)	35.3 (100)	50.4 (100)
Total crop land, acres × 10^6 (%)	12.1 (62)	16.5 (47)	29.0 (58)
Harvested crop land, acres × 10^6 (%)	10.5 (100)	12.9 (100)	20.2 (100)
Wheat, acres × 10^6 (%)	0.3 (3)	3.6 (28)	10.6 (53)
Corn, acres × 10^6 (%)	4.1 (39)	2.0 (16)	0.6 (3)
Soybeans, acres × 10^6 (%)	2.4 (23)	1.5 (11)	0.4 (2)
Average size of annual population at risk			
Men	454,149	203,944	174,945
Women	459,225	205,598	172,397
Population ≥ 65 years of age (%)	14.6	17.8	17.6
Rural population (%)	72	79	84
Living on farm (%)	20	26	26
Average farm size (acres)	300	889	1,221
Average 1979 median family income	15,821	14,428	15,665

for the agriculture of wheat, corn, soybeans, and hay.

Among the 262 counties in MN, ND, SD, and MT, 110 counties (42%) were excluded from the analyses because they had < 20% crop land and/or had a rural population of < 50%. These counties were located in the Rocky Mountains of MT; rangeland regions of MT, ND, and SD; forested and wetland regions of MN; and urban regions in each of the four states. The remaining 152 counties were divided into three groups based on tertiles of wheat acreage per county (< 23,000; 23,000–110,999; and ≥ 111,000). The median, minimum, and maximum were 72,000, 135, and 453,148 acres per county, respectively. Characteristics for the three groups of counties are presented in Table 2. Several differences were observed. Counties in the lowest wheat category were located in MN and SD; counties in the highest wheat category were located mostly in ND and MT. Average county and farm size and percentages of rural and farm population increased with increasing wheat acreage per county; average population-at-risk decreased. The population in counties with < 23,000 acres of wheat was slightly younger than in the two other groups of counties.

Age-adjusted cancer mortality rates per 100,000 and rate ratios comparing counties with 23,000–110,999 and ≥ 111,000 acres of wheat to counties with < 23,000 acres of wheat are presented in Table 3 (men) and Table 4 (women) ≥ 15 years of age. In general, men showed higher cancer mortality rates than women. Increasing cancer rates for the three tertiles of counties, or a statistically significant increased rate for either the second or the third tertile of counties, were observed for the following cancer sites: salivary gland, esophagus, rectum, pancreas, larynx, prostate, kidney, thyroid, bone and jaw, Hodgkin disease, and all cancers (men); oral cavity and tongue, esophagus, stomach, rectum, liver and gall bladder and bile ducts, pancreas, cervix, bladder, and other urinary organs, secondary or unspecified sites, and all cancers (women). It is conceivable that stronger effects would have been obtained if the referent group had been composed of counties with a smaller wheat acreage, e.g., 10,000 acres per county. The use of grouped counties based on tertiles of wheat acreage per county, as presented in Tables 3 and 4, was a more conservative approach.

Table 5 presents mortality for men and women from rare cancers and cancer mortality in boys and girls. There was increased cancer mortality for nose and eye cancer in both men and women and brain cancer and leukemia in both boys and girls. Mortality from all cancers was also increased in boys. None of these increased cancer rates were statistically significant except cancer of the eye among women (borderline significant). Mortality from cancers of the eye, nose and nasal cavity, and oral cavity were increased in high wheat-producing counties. These cancer sites may represent mucosa exposed to aerially applied pesticides.

Table 6 presents correlations between age-standardized cancer mortality rates and wheat acreage per county for cancers with > 400 deaths reported for the combined 152 counties during 1980–1989. I excluded counties with less than five deaths for the cancer being analyzed. Statistically significant correlations

Table 3. Age-standardized cancer mortality rates and ratios for white men, 1980–1989.

	Wheat acreage per county							
	< 23,000		23,000–110,999			≥ 111,000		
Cancer site (*ICD-9* code)	*n*	Rate	*n*	Rate	SRR (CI)	*n*	Rate	SRR (CI)
Salivary gland (142)	6	**0.13**	12	**0.53**	3.96 (1.47–10.67)	5	0.28	2.08 (0.62–6.94)
Oral cavity including tongue (141, 143–146, 148, 149)	111	3.08	60	2.90	0.94 (0.68–1.30)	55	3.34	1.08 (0.78–1.51)
Esophagus (150)	212	**5.66**	116	**5.74**	1.01 (0.80–1.28)	103	**5.87**	1.04 (0.82–1.32)
Stomach (151)	404	10.23	221	10.05	0.98 (0.83–1.16)	199	10.59	1.04 (0.87–1.23)
Large intestine (153, 159)	1,070	26.82	599	27.43	1.02 (0.92–1.13)	494	26.23	0.98 (0.88–1.09)
Rectum (154 excluding 154.3)	186	**4.75**	103	**4.94**	1.04 (0.81–1.33)	117	**6.26**	1.32 (1.04–1.67)
Liver, gallbladder including bile ducts (155, 156)	179	4.62	112	5.48	1.19 (0.93–1.51)	100	5.23	1.13 (0.88–1.45)
Pancreas (157)	453	**11.78**	266	**12.82**	1.09 (0.93–1.27)	270	**14.53**	1.23 (1.06–1.44)
Larynx (161)	67	**1.75**	39	**1.95**	1.12 (0.75–1.67)	48	**2.69**	1.54 (1.06–2.25)
Trachea, bronchus, lung (162, 163, 165)	2,499	66.69	1,355	66.24	0.99 (0.93–1.06)	1,169	66.25	0.99 (0.93–1.07)
Prostate (185)	1,368	**31.12**	836	**34.24**	1.10 (1.01–1.20)	808	**38.64**	1.24 (1.14–1.36)
Kidney, ureter (189, excluding 189.3)	272	**7.04**	147	**7.10**	1.01 (0.82–1.24)	129	**7.28**	1.03 (0.83–1.28)
Bladder, other urinary organs (188, 189.3)	306	7.19	147	6.07	0.84 (0.69–1.03)	129	6.36	0.88 (0.72–1.09)
Malignant melanoma (172)	121	3.39	50	2.67	0.79 (0.56–1.11)	41	2.68	0.79 (0.55–1.14)
Nonmelanoma skin (173, 154.3)	54	1.26	28	1.24	0.98 (0.61–1.57)	24	1.25	0.99 (0.60–1.62)
Brain, other parts of nervous system (191, 192)	264	7.48	131	6.96	0.93 (0.75–1.15)	130	8.16	1.09 (0.88–1.35)
Thyroid (193)	10	**0.27**	9	**0.39**	1.45 (0.58–3.63)	10	**0.51**	1.88 (0.76–4.62)
Thymus and other endocrine glands (194, 164.0)	11	0.32	5	0.26	0.82 (0.28–2.42)	8	0.45	1.42 (0.56–3.59)
Bone including jaw (170)	19	**0.56**	12	**0.66**	1.18 (0.56–2.47)	16	**1.08**	1.94 (0.98–3.84)
Connective and soft tissue (171, 164.1)	51	1.37	20	1.00	0.73 (0.43–1.24)	24	1.45	1.06 (0.64–1.75)
Hodgkin disease (201)	38	**1.01**	32	**1.81**	1.80 (1.11–2.92)	14	0.80	0.80 (0.43–1.49)
Lymphosarcoma, reticulum cell sarcoma including other lymphoma (159.1, 200, 202.0, 202.1, 202.8, 202.9)	418	10.83	186	8.82	0.81 (0.68–0.97)	176	9.68	0.89 (0.75–1.07)
Multiple myeloma (203, excluding 203.1)	197	4.96	108	4.95	1.00 (0.78–1.27)	75	3.89	0.79 (0.60–1.03)
Leukemia (204–208, 202.4, 203.1)	471	11.90	246	11.60	0.97 (0.83–1.14)	248	13.25	1.11 (0.95–1.30)
Secondary, site unspecified, not previously listed (152, 158, 159.2–159.9, 164.2–164.9)	579	14.67	331	15.77	1.07 (0.94–1.23)	224	11.95	0.81 (0.70–0.95)
All cancers (140–208)	9,442	**240.88**	5,205	**243.23**	1.01 (0.98–1.05)	4,639	**250.05**	1.04 (1.00–1.08)

ICD-9, *International Classification of Diseases, 9th Revision* (World Health Organization, Geneva). Comparison of grouped counties based on tertiles of wheat acreage per county. Rates per 100,000 are age-adjusted and are calculated only if at least five deaths are reported in each of the two groups being compared. The average annual population at risk for combined counties with < 23,000, 23,000–110,999, and ≥ 111,000 acres of wheat was 338,471, 155,468, and 134,419, respectively. Bold text indicates increasing cancer rates for the three tertiles of counties or a statistically significant increased rate for either the second or the third tertile of counties.

were observed for the following sites: stomach, rectum, pancreas, prostate, brain, and leukemia (men); stomach, pancreas, ovary, and secondary and unspecified cancers (women). Figure 1A–F illustrates cancer mortality rates and wheat acreage by county for some of these results: pancreas, prostate, and leukemia in men and pancreas, ovary, and secondary and unspecified sites in women.

Those cancer sites showing a trend of increasing cancer mortality with increasing wheat acreage for the three groups of counties, a statistically significant increase in either the second or third tertile of grouped counties (Tables 3 and 4), or a significant correlation between cancer mortality and wheat acreage per county (Table 6), were further analyzed by age (< 65 and ≥ 65 years of age), as presented in Tables 7 and 8 for men and women, respectively. If an effect was observed for all ages for only one of the sexes, the analyses by age group were still done for both sexes so that mortality rates for the same cancer sites could be compared between men and women. Subjects ≥ 65 years of age had higher rates than those < 65 years of age. Many of the trends showing increased cancer mortality with increasing wheat acreage [observed for all ages (Tables 3 and 4)] were also observed for one or both age groups (Tables 7 and 8): salivary gland (men ≥ 65), oral cavity including tongue (women < 65 and ≥ 65), stomach (women < 65), rectum (men ≥ 65), pancreas (men ≥ 65; women < 65 and ≥ 65), cervix uteri (women < 65), prostate (men < 65 and ≥ 65), kidney and ureter (men < 65), bladder and other urinary organs (women ≥ 65), thyroid (men, ≥ 65; women ≥ 65), bone (men < 65 and ≥ 65), and Hodgkin disease (men < 65 and ≥ 65; women ≥ 65). Trends for thyroid cancer and Hodgkin disease were observed for women ≥ 65 years of age, although no effect was seen for women of all ages (Tables 4 and 8). Although cancer mortality rates were generally higher in men for either age group, women ≥ 65 years of age had a higher rate for thyroid cancer mortality then men of the same age. For other sites showing trends of increasing mortality rates for all ages, like larynx in men and esophagus, rectum, liver, and secondary and unspecified sites in women, the trend was not observed for either age group, although increased rates were observed for either one of the two higher wheat groups, some of which were statistically significant.

A previous study (*17*) reported significantly increased cancer mortality in Northwestern MN for prostate, thyroid, and bone for men and eye for women. The comparison region in that study was the urban/forested region of MN. To ensure that MN was not driving the results in the current study, I calculated the SRRs for these four cancer sites separately for MN and combined ND, SD, and MT and compared counties with ≥ 72,000 acres of wheat to counties with < 72,000 acres. The SRRs for MN and combined ND, SD, and MT, respectively, for men were prostate, 1.14 (CI, 1.00–1.30) and 1.23 (CI, 1.07–1.41) and bone, 2.79 (CI, 1.09–7.15) and 1.82 (CI, 0.66–4.99). Because only two deaths were reported for cancer of the thyroid in men and eye cancer in women for the referent group of combined counties in MT, ND, and SD, I did not calculate SRRs for these two cancer sites. These numbers are probably low because these two cancers are rare and the population size of combined ND, SD, and MT is low (less than half of the MN population). The results for prostate and bone cancer mortality do not indicate that MN is driving the results.

Table 4. Age-standardized cancer mortality rates and ratios for white women, 1980–1989.

	Wheat acreage per county							
	< 23,000		23,000–110,999			≥ 111,000		
Cancer site (ICD-9 code)	*n*	Rate	*n*	Rate	SRR (CI)	*n*	Rate	SRR (CI)
Oral cavity including tongue (141, 143–146, 148, 149)	37	**0.67**	24	**0.87**	1.30 (0.73–2.29)	27	**1.32**	1.96 (1.14–3.38)
Esophagus (150)	58	**1.06**	34	**1.11**	1.05 (0.67–1.64)	27	**1.17**	1.11 (0.67–1.83)
Stomach (151)	240	**4.20**	127	**4.39**	1.05 (0.82–1.33)	125	**5.61**	1.34 (1.05–1.70)
Large intestine (153, 159)	1,070	19.87	601	21.13	1.06 (0.95–1.19)	472	19.75	0.99 (0.88–1.12)
Rectum (154 excluding 154.3)	131	**2.19**	89	**3.00**	1.37 (1.02–1.84)	61	2.46	1.12 (0.81–1.57)
Liver, gallbladder including bile ducts (155, 156)	241	**4.65**	126	**4.72**	1.01 (0.80–1.28)	127	**5.51**	1.19 (0.94–1.49)
Pancreas (157)	454	**8.54**	259	**9.61**	1.13 (0.95–1.33)	241	**10.55**	1.24 (1.04–1.46)
Trachea, bronchus, lung (162, 163, 165)	889	20.97	433	19.31	0.92 (0.81–1.04)	420	22.15	1.06 (0.93–1.19)
Breast (174, 175)	1,578	36.23	818	35.62	0.98 (0.90–1.08)	661	35.52	0.98 (0.89–1.08)
Cervix uteri (180)	82	**2.02**	40	**2.21**	1.09 (0.73–1.64)	50	**3.09**	1.53 (1.05–2.22)
Chorion, uterus (179, 181, 182)	249	4.79	123	4.81	1.00 (0.80–1.27)	95	4.37	0.91 (0.71–1.18)
Ovary, fallopian tube, broad ligament (183)	511	11.27	246	10.28	0.91 (0.78–1.07)	230	11.95	1.06 (0.90–1.25)
Kidney, ureter (189, excluding 189.3)	177	3.86	85	3.42	0.89 (0.67–1.17)	90	4.13	1.07 (0.82–1.40)
Bladder, other urinary organs (188, 189.3)	123	**1.96**	67	**2.14**	1.10 (0.79–1.51)	59	**2.21**	1.13 (0.80–1.58)
Malignant melanoma (172)	85	1.99	59	2.44	1.22 (0.85–1.76)	29	1.48	0.74 (0.47–1.16)
Nonmelanoma skin (173, 154.3)	27	0.43	9	0.36	0.85 (0.36–2.01)	13	0.54	1.27 (0.60–2.70)
Brain, other parts of nervous system (191, 192)	189	4.66	94	4.45	0.95 (0.73–1.24)	95	5.39	1.16 (0.89–1.50)
Thyroid (193)	25	0.49	12	0.38	0.78 (0.38–1.62)	13	0.45	0.93 (0.45–1.90)
Bone including jaw (170)	22	0.54	8	0.36	0.66 (0.27–1.63)	11	0.64	1.19 (0.53–2.69)
Connective and soft tissue (171, 164.1)	56	1.28	38	1.65	1.29 (0.82–2.01)	27	1.58	1.23 (0.75–2.02)
Hodgkin disease (201)	29	0.72	19	0.74	1.03 (0.55–1.94)	14	0.62	0.86 (0.43–1.69)
Lymphosarcoma, reticulum cell sarcoma including other lymphoma (159.1, 200, 202.0, 202.1, 202.8, 202.9)	389	7.71	202	7.41	0.96 (0.80–1.16)	162	7.32	0.95 (0.78–1.16)
Multiple myeloma (203, excluding 203.1)	171	3.47	91	3.46	1.00 (0.76–1.31)	77	3.35	0.97 (0.72–1.29)
Leukemia (204–208, 202.4, 203.1)	373	7.20	183	6.81	0.95 (0.78–1.15)	146	6.70	0.93 (0.76–1.15)
Secondary, site unspecified, not previously listed (152, 158, 159.2–159.9, 164.2–164.9)	555	**10.53**	350	**12.48**	1.19 (1.02–1.37)	268	11.71	1.11 (0.95–1.30)
All cancers (140–208)	7,824	**162.65**	4,161	**164.44**	1.01 (0.97–1.05)	3,574	**171.34**	1.05 (1.01–1.10)

ICD-9, *International Classification of Diseases, 9th Revision* (World Health Organization, Geneva). Comparison of grouped counties based on tertiles of wheat acreage per county. Rates per 100,000 are age-adjusted and are calculated only if at least five deaths are reported in each of the two groups being compared. The average annual population at risk for combined counties with < 23,000, 23,000–110,999, and ≥ 111,000 acres of wheat was 349,660, 160,200, and 134,105, respectively. Bold text indicates increasing cancer rates for the three tertiles of counties or a statistically significant increased rate for either the second or the third tertile of counties.

Discussion

This ecologic study investigated cancer mortality rates in counties of MN, ND, SD, and MT, where the population was mostly rural and where at least 20% of the available land was dedicated to crop land. Because of these inclusion criteria, the percentage of rural and farm population was higher in this study population of 152 counties than if all 262 counties had been included. The study population of the combined 152 counties can be categorized as follows: rural and living on farms, 23%; rural not living on farms, 54%; and nonrural, 23%. For the combined 262 counties these percentages would have been as follows: rural and living on farms, 10%; rural not living on farms, 29%; and nonrural, 61%. It is conceivable that the "rural not living on farms" population included people working on a farm. Because occupational information was not available for this mortality dataset, it was not

Table 5. Mortality rates and ratios during 1980–1989 for rare cancers in white men and women and cancers in white boys and girls.

	Wheat acreage/county				
	< 72,000		≥ 72,000		
Cancer site (ICD-9 code)	*n*	Rate	*n*	Rate	SRR (CI)
Men					
Nose, nasal cavities, middle ear, accessory sinuses (160)	16	0.29	11	0.44	1.49 (0.67–3.31)
Breast (174, 175)	16	0.29	7	0.26	0.89 (0.36–2.19)
Eye (190)	8	0.15	7	0.30	1.95 (0.69–5.47)
Women					
Salivary gland (142)	17	0.28	6	0.16	0.58 (0.20–1.62)
Nose, nasal cavities, middle ear, accessory sinuses (160)	15	0.20	8	0.37	1.81 (0.72–4.55)
Eye (190)	9	0.13	9	0.36	2.77 (1.00–7.63)
Thymus and other endocrine glands (194, 164.0)	16	0.31	9	0.33	1.07 (0.45–2.56)
Boys					
Brain, other parts of nervous system (191, 192)	13	0.87	9	1.58	1.82 (0.78–4.26)
Leukemia (204–208, 202.4, 203.1)	29	1.92	15	2.69	1.40 (0.75–2.62)
All cancers (140–208)	67	4.46	34	6.14	1.38 (0.91–2.08)
Girls					
Brain, other parts of nervous system (191, 192)	8	0.59	5	0.96	1.63 (0.53–4.99)
Leukemia (204–208, 202.4, 203.1)	10	0.69	5	0.98	1.43 (0.49–4.18)
All cancers (140–208)	38	2.68	14	2.73	1.02 (0.55–1.88)

ICD-9, *International Classification of Diseases, 9th Revision* (World Health Organization, Geneva). Comparison of grouped counties based on the median of wheat acreage per county. Rates per 100,000 are age-adjusted, and are calculated only if at least five deaths are reported in each of the two groups being compared. The average annual population-at-risk for combined counties with < 72,000 and ≥ 72,000 acres of wheat were 447,300 and 181,058, respectively (men); 462,676 and 181,289, respectively (women); 149,973 and 54,707, respectively (boys); and 141,707 and 51,548, respectively (girls).

Table 6. Mortality for frequent cancers during 1980–1989.

Cancer site (ICD-9 code)	Counties (*n*)	Cancer deaths(*n*)	Kendall's tau-b coefficient	*p*-Value
Men				
Esophagus (150)	32	257	0.10	0.43
Stomach (151)	68	656	0.28	0.0008
Large intestine (153, 159)	125	2,093	0.01	0.90
Rectum (154 excluding 154.3)	29	223	0.32	0.016
Pancreas (157)	81	829	0.32	0.0001
Trachea, bronchus, lung (162, 163, 165)	146	5,004	–0.07	0.21
Prostate (185)	131	2,959	0.22	0.0002
Kidney, ureter (189, excluding 189.3)	43	358	0.09	0.40
Bladder, other urinary organs (188, 189.3)	44	373	0.04	0.69
Brain, other parts of nervous system (191, 192)	48	379	0.21	0.03
Lymphosarcoma, reticulum cell sarcoma including other lymphoma (159.1, 200, 202.0, 202.1, 202.8, 202.9)	61	623	0.07	0.40
Leukemia (204–208, 202.4, 203.1)	82	861	0.27	0.0003
Secondary, site unspecified, not previously listed (152, 158, 159.2–159.9, 164.2–164.9)	88	1,023	0.02	0.82
All cancers (140–208)	152	19,387	0.05	0.39
Women				
Stomach (151)	40	314	0.26	0.02
Large intestine (153, 159)	117	2,062	0.02	0.76
Liver, gallbladder including bile ducts (155, 156)	38	314	0.19	0.08
Pancreas (157)	76	794	0.26	0.001
Trachea, bronchus, lung (162, 163, 165)	109	1,634	0.10	0.14
Breast (174, 175)	132	3,007	0.00	0.96
Ovary, fallopian tube, broad ligament (183)	70	811	0.18	0.03
Lymphosarcoma, reticulum cell sarcoma including other lymphoma (159.1, 200, 202.0, 202.1, 202.8, 202.9)	63	589	0.13	0.12
Leukemia (204–208, 202.4, 203.1)	63	566	0.16	0.07
Secondary, site unspecified, not previously listed (152, 158, 159.2–159.9, 164.2–164.9)	92	1,051	0.19	0.006
All cancers (140–208)	150	15,606	0.08	0.14

ICD-9, *International Classification of Diseases, 9th Revision* (World Health Organization, Geneva). Correlations between age-standardized cancer rates and wheat acreage by county.

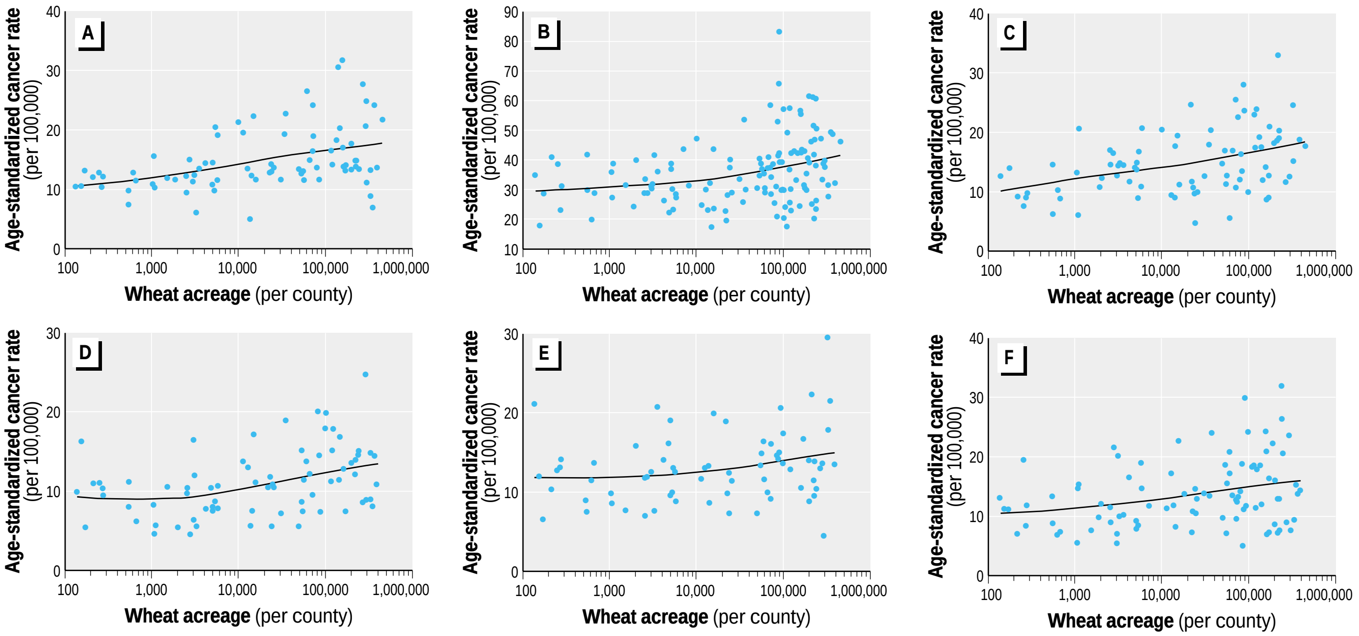

Figure 1. Age-standardized mortality rates per 100,000 during 1980–1989, for counties of MN, MT, ND, and SD, excluding counties reporting less than five deaths for the cancer site. Rates for adults 15–85+ years of age. (*A*) Cancer of the pancreas (men). (*B*) Cancer of the prostate (men). (*C*) Leukemia (men). (*D*) Cancer of the pancreas (women). (*E*) Cancer of the ovary (women). (*F*) Cancer of secondary or unspecified sites (women).

possible to check how many of the cancer deaths could be attributed to farmers and other agricultural workers. Although people living or working on a farm most likely have the highest exposures to pesticides, rural people not living or working on a farm may be exposed to drift of aerially applied pesticides or through their well water.

Residents of counties where the main crop was spring or durum wheat were at an increased mortality risk for several types of cancer. This gave rise to the question of whether other factors associated with wheat could have played a role. Percent rural and farm population and average farm size were associated with wheat acreage (Table 2). The correlation coefficients for wheat acreage per county with percent rural and farm population were 0.23 (p = 0.0001) and 0.13 (p = 0.02), respectively. Average farm size per county was correlated with wheat acreage (correlation coefficient = 0.47, p = 0.0001). We would expect farms to be large when large plots of land are available for wheat agriculture in these regions. In other words, farm size may be a consequence of land available for wheat agriculture. Farmers are generally exposed to a variety of hazardous substances such as pesticides, fuels, oils, engine exhausts, and organic solvents (*12*). Farm families living on large farms have potentially higher exposures to these compounds than families living on small farms. Methods of pesticide application may also be different on large farms. Age is a risk factor for cancer mortality. People living in counties with > 23,000 acres of wheat were slightly older than subjects living in counties with less wheat (Table 2). I used age standardization in the analyses to adjust for these differences. Another factor to be considered is delayed diagnosis, which may occur among the rural population because of long distances from medical facilities. In that case, we would expect increased mortality for all cancer sites. This was not observed in the current study.

This study had other limitations. The use of wheat acreage as a surrogate measure of exposure to chlorophenoxy herbicides was a major disadvantage because it provided no information on when and how often exposures occurred. Migration into or out of counties was unknown, although residential stability in farming communities tends to be higher than in urban communities (*12*). Individual information on smoking, alcohol use, and ethnic background was not available.

Smoking-related cancers (lung, larynx, oral cavity, esophagus, and bladder) are increased in urban populations and decreased in farmers (*9,12,24,25*). Mortality rates for these cancer sites for the 60 counties that were excluded from the analyses because of their mostly urban population confirmed this finding. Using the same referent group of rural counties as in Tables 3 and 4 (< 23,000 acres of wheat per county), age-standardized rates per 100,000 and SRR (CI) were obtained for the combined 60 urban counties as follows:

- Trachea and bronchus and lung—men: rate = 84.13, SRR = 1.26 (CI, 1.21–1.32); women: rate = 31.52, SRR = 1.50 (CI, 1.39–1.62)
- Larynx—men: rate = 3.02, SRR = 1.73 (CI, 1.33–2.25); women: rate = 0.49, SRR = 1.52 (CI, 0.83–2.78)
- Oral cavity—men: rate = 4.80, SRR = 1.56 (CI, 1.27–1.92); women: rate = 1.72, SRR = 2.55 (CI, 1.75–3.71)
- Esophagus—men: rate = 7.04, SRR = 1.24 (CI, 1.07–1.45); women: rate = 1.65, SRR = 1.55 (CI, 1.15–2.11)
- Bladder—men: rate = 8.19, SRR = 1.14 (CI, 1.00–1.30); women: rate = 2.31, SRR = 1.18 (CI, 0.95–1.46).

In the current study with a mostly rural population, there was increased mortality for some of these same cancer sites in counties with higher wheat acreage: oral cavity (women) and larynx (men) were significantly increased; there were nonsignificant increases for esophagus and bladder (Tables 3 and 4). Because there was no effect for lung cancer and because there is no reason to suspect that smoking would be related to acres of wheat grown, the increases observed for these cancer sites might be related to herbicide exposure. However, increased lung cancer mortality in association with pesticide exposure cannot be ruled out. An increase of lung cancer mortality was observed for Florida pest control workers with increasing duration of licensure after adjusting for smoking (*26*). These subjects were exposed to several pesticides, including phenoxyacetic acids. This Florida study (*26*) illustrates the need to adjust for smoking when lung cancer in farmers, which may be associated with pesticide exposure, is compared to lung cancer in an urban population, which is mostly smoking related (*27*). In the

Table 7. Age-standardized cancer mortality rates and ratios for selected cancer sites for white men < 65 and ≥ 65 years of age, 1980–1989.

		Wheat acreage/county							
		< 23,000		23,000–110,999			≥ 111,000		
Cancer site (*ICD-9* code)	Age (years)	*n*	Rate	*n*	Rate	SRR (CI)	*n*	Rate	SRR (CI)
Salivary gland (142)	≥ 65	6	0.97	11	3.36	3.46 (1.27–9.44)	ND	–	–
Oral cavity including tongue	< 65	50	1.90	20	1.42	0.75 (0.44–1.26)	24	2.07	1.09 (0.67–1.79)
(141,143–146, 148, 149)	≥ 65	61	10.43	40	12.13	1.16 (0.78–1.74)	31	11.21	1.07 (0.70–1.66)
Esophagus (150)	< 65	65	2.50	36	2.73	1.09 (0.73–1.65)	29	2.52	1.01 (0.65–1.57)
	≥ 65	147	25.41	80	24.51	0.96 (0.73–1.27)	74	26.81	1.05 (0.80–1.40)
Stomach (151)	< 65	98	3.65	41	3.15	0.86 (0.60–1.25)	45	3.85	1.05 (0.74–1.51)
	≥ 65	306	51.26	180	53.13	1.04 (0.86–1.25)	154	52.68	1.03 (0.85–1.25)
Rectum (154 excluding 154.3)	< 65	50	1.91	27	2.12	1.11 (0.69–1.78)	24	2.07	1.08 (0.66–1.77)
	≥ 65	136	22.52	76	22.54	1.00 (0.75–1.33)	93	32.41	1.44 (1.10–1.88)
Liver, gallbladder including	< 65	46	1.78	37	2.80	1.57 (1.01–2.42)	18	1.47	0.82 (0.48–1.43)
bile ducts (155, 156)	≥ 65	133	22.31	75	22.20	1.00 (0.75–1.32)	82	28.66	1.28 (0.97–1.69)
Pancreas (157)	< 65	127	4.86	75	5.64	1.16 (0.87–1.55)	60	5.11	1.05 (0.77–1.43)
	≥ 65	326	54.98	191	57.64	1.05 (0.88–1.25)	210	73.33	1.33 (1.12–1.59)
Larynx (161)	< 65	15	0.59	15	1.07	1.80 (0.87–3.70)	10	0.86	1.44 (0.64–3.23)
	≥ 65	52	8.93	24	7.44	0.83 (0.51–1.35)	38	14.16	1.58 (1.04–2.41)
Prostate (185)	< 65	82	3.02	55	3.78	1.25 (0.89–1.76)	54	4.30	1.42 (1.01–2.01)
	≥ 65	1,286	206.47	781	224.38	1.09 (0.99–1.19)	754	253.04	1.23 (1.12–1.34)
Kidney, ureter (189,	< 65	70	2.71	45	3.32	1.23 (0.84–1.79)	43	3.61	1.33 (0.91–1.95)
excluding 189.3)	≥ 65	202	34.08	102	30.70	0.90 (0.71–1.14)	86	30.16	0.88 (0.69–1.14)
Bladder, other urinary organs	< 65	32	1.24	10	0.72	0.58 (0.29–1.20)	13	1.02	0.83 (0.43–1.58)
(188, 189.3)	≥ 65	274	44.36	137	39.46	0.89 (0.72–1.09)	116	39.68	0.89 (0.72–1.11)
Brain, other parts of nervous	< 65	140	5.17	56	4.29	0.83 (0.61–1.13)	65	5.66	1.10 (0.81–1.47)
system (191, 192)	≥ 65	124	21.90	75	23.63	1.08 (0.81–1.44)	65	23.75	1.08 (0.80–1.47)
Thyroid (193)	≥ 65	6	1.02	7	2.02	1.99 (0.66–5.95)	8	2.58	2.54 (0.88–7.35)
Bone including jaw (170)	< 65	12	0.46	7	0.53	1.16 (0.45–2.96)	10	0.92	2.00 (0.86–4.65)
	≥ 65	7	1.17	5	1.43	1.22 (0.39–3.86)	6	2.11	1.80 (0.60–5.39)
Hodgkin disease (201)	< 65	20	0.68	19	1.46	2.15 (1.14–4.07)	ND	–	–
	≥ 65	18	3.04	13	4.01	1.32 (0.64–2.70)	11	4.10	1.35 (0.63–2.86)
Leukemia (204–208,	< 65	126	4.70	56	4.53	0.96 (0.70–1.32)	56	4.77	1.01 (0.74–1.39)
202.4, 203.1)	≥ 65	345	56.81	190	55.71	0.98 (0.82–1.17)	192	66.19	1.16 (0.98–1.39)
Secondary, site unspecified,	< 65	146	5.54	81	6.16	1.11 (0.85–1.46)	48	4.00	0.72 (0.52–1.00)
not previously listed (152, 158, 159.2–159.9, 164.2–164.9)	≥65	433	71.67	250	75.72	1.06 (0.90–1.24)	176	61.58	0.86 (0.72–1.02)
All cancers (140–208)	< 65	2,369	89.78	1,218	91.60	1.02 (0.95–1.09)	1,065	90.84	1.01 (0.94–1.09)
	≥ 65	7,073	1184.10	3,987	1189.70	1.00 (0.97–1.04)	3,574	1243.80	1.05 (1.01–1.09)

Abbreviations: ICD-9, *International Classification of Diseases, 9th Revision* (World Health Organization, Geneva); ND, not done (< 5 deaths reported per group). Comparison of grouped counties based on tertiles of wheat acreage per county. Rates per 100,000 are age-adjusted and are calculated only if at least five deaths are reported in each of the two groups being compared. The annual population-at-risk for combined counties with < 23,000, 23,000–110,999, and ≥ 111,000 acres of wheat for those < 65 years of age: 281,187, 123,286, and 106,711, respectively; for those ≥ 65 years of age: 57,284, 32,182, and 27,708, respectively.

current study the percent rural population for the referent group (72%) was lower than for the two other groups of counties (23,000–110,999 and ≥ 111,000 acres of wheat; 79 and 84%, respectively). It is conceivable that lung cancer mortality in the referent group is associated with smoking because of its larger percentage of nonrural population (38%), whereas lung cancer mortality in the two more rural groups of counties may be associated with higher herbicide exposure. If this were the case, the potential effect from herbicide exposure on lung cancer mortality could only be studied in these data if smoking information were available.

Because this is an ecologic study, there is the possibility of an ecologic fallacy, which occurs when the association observed for counties or groups of counties does not hold for individuals (*8,11,28,29*). However, ecologic studies do have some advantages. The current study was based on existing databases and included a large number of observations. Therefore, besides being relatively inexpensive, this study allowed investigation of rare cancers and analyses for trends. Results from this study will generate hypotheses for more resource-intensive and definitive cohort and case–control studies where exposure information can be determined for individual subjects, thereby avoiding ecologic fallacies.

Although some of the results in the current study were undoubtedly due to chance, the fact that trends of increased mortality rates were observed with increasing wheat acreage for several cancer sites strengthens the likelihood of an association. In addition, these results should be considered in conjunction with other studies. Many of the same cancer sites increased in the current study have been reported as being increased both in farmers in general and in production workers occupationally exposed to chlorophenoxy herbicides and their contaminants (*6,9,12,24,30–35*). In a review of cancer etiology in farmers, Blair et al. (*30*) noted that several cancers with excessive rates among farmers have also been on the rise in the general population. Therefore, studies of farmers, who have generally better defined and higher exposures to farm chemicals than the general population, might contribute to an explanation for these increases. Excess mortality from several cancers was observed for farmers—Hodgkin disease; non-Hodgkin lymphoma; multiple myeloma; leukemia; melanoma; other skin cancer; and cancers of the lip, eye, stomach, rectum, brain, connective and soft tissue, pancreas, kidney, bone, thyroid, prostate, and testis (*9,12,24,30–33*). In a cancer incidence study of Florida pesticide applicators, statistically significant increases were observed for cancer of the prostate, testis, and cervix (*34*). In a cancer mortality study of Florida pesticide applicators by the same authors, statistically significant increases were observed for prostate cancer only (*35*). Among children, leukemia and brain tumors are common malignancies that have been associated with pesticide exposure of the parents or the children themselves (*9,11,36,37*). Some of the increases may be explained by factors other than farm chemicals. For example, farmers

Table 8. Age-standardized cancer mortality rates and ratios for selected cancer sites for white women < 65 and ≥ 65 years of age, 1980–1989.

		Wheat acreage/county							
		< 23,000		23,000–110,999			≥ 111,000		
Cancer site (*ICD-9*)	Age (years)	*n*	Rate	*n*	Rate	SRR (CI)	*n*	Rate	SRR (CI)
Oral cavity including tongue (141,143–146, 148, 149)	< 65	7	0.26	6	0.43	1.65 (0.55–4.98)	9	0.78	2.97 (1.10–8.06)
	≥ 65	30	3.25	18	3.64	1.12 (0.60–2.07)	18	4.73	1.45 (0.79–2.69)
Esophagus (150)	< 65	8	0.31	ND	–	–	6	0.53	1.69 (0.58–4.89)
	≥ 65	50	5.71	32	7.26	1.27 (0.80–2.02)	21	5.20	0.91 (0.54–1.55)
Stomach (151)	< 65	33	1.26	24	1.85	1.47 (0.86–2.50)	34	3.01	2.39 (1.48–3.88)
	≥ 65	207	22.53	103	20.23	0.90 (0.70–1.15)	91	21.80	0.97 (0.75–1.25)
Rectum (154 excluding 154.3)	< 65	17	0.61	13	0.96	1.57 (0.76–3.26)	9	0.77	1.27 (0.56–2.86)
	≥ 65	114	12.05	76	15.76	1.31 (0.96–1.78)	52	13.01	1.08 (0.77–1.52)
Liver, gallbladder including bile ducts (155, 156)	< 65	37	1.40	29	2.08	1.49 (0.91–2.43)	19	1.65	1.18 (0.68–2.07)
	≥ 65	204	24.96	97	21.18	0.85 (0.66–1.09)	108	29.61	1.19 (0.93–1.51)
Pancreas (157)	< 65	77	2.90	49	3.71	1.28 (0.89–1.84)	50	4.13	1.42 (0.99–2.04)
	≥ 65	377	43.72	210	46.42	1.06 (0.89–1.27)	191	50.62	1.16 (0.97–1.39)
Cervix uteri (180)	< 65	42	1.58	25	2.05	1.30 (0.79–2.14)	26	2.40	1.52 (0.93–2.49)
	≥ 65	40	4.80	15	3.22	0.67 (0.36–1.26)	24	7.41	1.54 (0.92–2.60)
Ovary, fallopian tube, broad ligament (183)	< 65	149	5.61	64	4.79	0.85 (0.63–1.15)	73	6.40	1.14 (0.86–1.51)
	≥ 65	362	46.56	182	44.54	0.96 (0.80–1.15)	157	46.55	1.00 (0.82–1.21)
Kidney, ureter (189, excluding 189.3)	< 65	50	1.85	20	1.55	0.84 (0.49–1.41)	22	1.81	0.98 (0.59–1.63)
	≥ 65	127	16.41	65	15.09	0.92 (0.68–1.25)	68	18.59	1.13 (0.83–1.54)
Bladder, other urinary organs (188, 189.3)	< 65	11	0.39	8	0.54	1.37 (0.55–3.45)	6	0.52	1.33 (0.49–3.61)
	≥ 65	112	11.72	59	12.15	1.04 (0.75–1.44)	53	12.71	1.08 (0.77–1.53)
Brain, other parts of nervous system (191, 192)	< 65	90	3.28	41	3.01	0.92 (0.63–1.33)	42	3.79	1.16 (0.80–1.67)
	≥ 65	99	13.31	53	13.43	1.01 (0.72–1.42)	53	15.37	1.15 (0.82–1.63)
Thyroid (193)	≥ 65	19	2.12	11	2.39	1.13 (0.52–2.44)	13	3.29	1.55 (0.74–3.26)
Bone including jaw (170)	≥ 65	12	1.52	5	1.01	0.67 (0.23–1.94)	7	1.72	1.14 (0.42–3.04)
Hodgkin disease (201)	< 65	14	0.52	5	0.38	0.74 (0.26–2.09)	ND	–	–
	≥ 65	15	1.99	14	3.00	1.51 (0.71–3.21)	12	3.30	1.66 (0.76–3.61)
Leukemia (204–208, 202.4, 203.1)	< 65	89	3.33	38	2.95	0.89 (0.60–1.30)	38	3.27	0.98 (0.67–1.44)
	≥ 65	284	31.30	145	30.90	0.99 (0.80–1.22)	108	28.07	0.90 (0.71–1.13)
Secondary, site unspecified, not previously listed (152, 158, 159.2–159.9, 164.2–164.9)	< 65	115	4.35	63	4.87	1.12 (0.82–1.53)	51	4.30	0.99 (0.71–1.38)
	≥ 65	440	49.09	287	59.97	1.22 (1.04–1.43)	217	57.98	1.18 (1.00–1.40)
All cancers (140–208)	< 65	2,103	79.23	1,080	81.59	1.03 (0.96–1.11)	973	85.16	1.07 (1.00–1.16)
	≥ 65	5,721	683.33	3,081	681.58	1.00 (0.95–1.04)	2,601	709.28	1.04 (0.99–1.09)

Abbreviations: ICD-9, *International Classification of Diseases, 9th Revision* (World Health Organization, Geneva); ND, not done (< 5 deaths reported per group). Comparison of grouped counties based on tertiles of wheat acreage per county. Rates per 100,000 are age-adjusted and are calculated only if at least five deaths are reported in each of the two groups being compared. The average annual population-at-risk for combined counties with < 23,000, 23,000–110,999, and ≥ 111,000 acres of wheat: < 65 years of age: 273,995, 119,295, and 100,567,; respectively; ≥ 65 years of age: 75,665, 40,905, and 33,538, respectively.

are occupationally exposed to sunlight, which is a known risk factor for melanoma and eye cancer (*25,30*).

A review of several case–control and cohort studies investigating the effect of herbicides (mostly phenoxy herbicides) on cancer observed that herbicide exposure was associated with increased risks for non-Hodgkin lymphoma; soft-tissue sarcoma; cancer of the colon, nose, prostate, and ovary; leukemia; and multiple myeloma (*27*).

A follow-up study based on a multicenter registry of chlorophenoxy herbicide production workers and sprayers created by the International Agency for Research on Cancer (IARC) was conducted; the study included nearly 22,000 subjects with an average follow-up of 22 years (*6*). Nearly 14,000 subjects had been involved in the production of 2,4,5-T and were therefore probably exposed to its contaminant TCDD. Increased mortality (not statistically significant unless otherwise noted) was observed for the following sites: all cancers (statistically significant), oral cavity and pharynx, esophagus, rectum, peritoneum and unspecific digestive organs, larynx, lung, other respiratory organs (statistically significant), connective and soft tissue, non-melanoma skin, female breast, male breast, endometrium and uterus, prostate, testis, other male genital organs, bladder, kidney (statistically significant), thyroid, other endocrine organs, ill-defined and unspecified neoplasms, non-Hodgkin lymphoma, Hodgkin lymphoma, and multiple myeloma. More than 7,500 workers had been involved in the production of chlorophenoxy herbicides excluding 2,4,5-T, and thus were not likely to have been exposed to TCDD. Increased mortality in this group was observed for the following sites: colon, peritoneum and unspecified digestive organs, nose and nasal sinuses, larynx, respiratory organs excluding lung, bone, connective and soft tissue, cervix uteri, endometrium and uterus, prostate, testis, other male genital organs, thyroid, other endocrine organs (statistically significant), multiple myeloma, and leukemia. Although exposures in the IARC study (*6*) were better defined, the current ecologic study with > 50 times more subjects resulted in a higher number of statistically significant associations.

Because of its high occurrence, prostate cancer mortality in the current study is further discussed in relation to other studies. Farming has been associated with an increased risk of this cancer (*12,24,30,31,33,38–42*). Parker et al. (*40*) found a positive trend for risk of prostate cancer with years of farming in an Iowa farming cohort study. Other epidemiologic studies have provided evidence that prostate cancer may be associated with race, lifestyle, environmental factors, high animal fat intake, and may be hormonal in origin (*38,43,44*). In a study of prostate cancer mortality in Canadian farmers from Manitoba, Saskatchewan, and Alberta, Morrison et al. (*41*) observed a dose–response effect for risk of prostate cancer mortality during 1971–1987 with the number of acres sprayed with herbicides (mostly chlorophenoxy herbicides) in 1970. In a meta-analysis of studies on prostate cancer and farming, Keller-Byrne et al. (*42*) concluded that hormonally active agricultural chemicals are most likely responsible for the association between prostate cancer and farming. Both 2,4-D and MCPA, the exposure of interest in the current study, and the potential contaminant, dioxins, are endocrine disruptors (*1,42*). In addition, adjuvants used in the application of 2,4-D to spring wheat also have endocrine-disrupting characteristics (*45*). In the IARC occupational cohort, there was a slight, non-statistically significant increase in prostate cancer mortality (*6*). The combined results from these previous investigations, in addition to those in the current ecologic study, suggest a link between prostate cancer and exposure to chlorophenoxy herbicides or their contaminants.

Both non-Hodgkin lymphoma and soft-tissue sarcoma have been associated with exposure to chlorophenoxy herbicides (*2,5,9,46–49*). The use of 2,4-D for lawn care has been associated with malignant lymphoma in pet dogs, which is the equivalent of canine non-Hodgkin lymphoma (*50*). No increase in mortality from non-Hodgkin lymphoma was observed in the current study. Connective and soft-tissue sarcoma in the current study was nonsignificantly increased in women in counties with ≥ 23,000 acres of wheat (Table 4).

Several cancers, especially prostate cancer, have been on the rise for several decades in the general population, mostly in the United States and Western Europe (*43,44,51,52*). The herbicides 2,4-D and MCPA, used since the Second World War, are widely applied for domestic use in many countries. Application rates of herbicides for domestic use are often higher than those for agricultural use (*1*). Results from the current and other published studies raise the question of whether chlorophenoxy herbicides or their contaminants are involved in the increase of prostate and other cancers in the general population.

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