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Agricultural Exposures and Cancer Trends in Developed Countries

Devra Lee Davis,[1] Aaron Blair,[2] and David G. Hoel[3]

Recent increases have been reported in industrial countries for several sites of cancer. The causes of these increases remain unknown. Efforts should proceed to identify those occupational groups with increases in the same sites, as these may indicate relevant exposures. Two analyses were undertaken: trends in cancer mortality in industrial countries were reviewed to identify recently increasing sites and summaries were compiled of studies on farmers which have shown increased risks for these same sites of cancer. Using data provided by the World Health Organization, age-specific rates were developed for a number of sites of cancer from 1968 to 1986. Trends in the ratio of male to female cancer mortality were also assessed for several of these countries. Based on a literature review by the National Cancer Institute, patterns of cancer in farmers reported in 20 studies from 8 countries are summarized, weighting each study by its size to create combined relative risks. In industrial countries, rates of cancer mortality increased for a number of sites, including melanoma, prostate, non-Hodgkin's lymphoma, multiple myeloma, breast, brain, and kidney cancer. The ratio of male to female cancer mortality (for all sites of cancer excluding lung) has generally increased in several countries during this same time period. Many of the same sites that have increased in the general population have also been found to be increasing in farmers. Significant excesses occurred for Hodgkin's disease, multiple myeloma, leukemia, skin melanomas, and cancers of the lip, stomach, and prostate. Nonsignificant increases in risk were also noted for non-Hodgkin's lymphoma and cancers of connective tissue and brain in many surveys. These excesses occurred against a background of substantial deficits among farmers for total mortality, heart disease, and many other specific diseases. Epidemiologic studies of farmers, and other occupational groups with excess rates of these same sites of cancer, may help to identify specific causal exposures that partly account for the rising trend of certain cancers in developed countries. Despite a number of common causes, heart disease and some sites of cancer show opposite trends in the general population, with the former decreasing and the latter increasing. Thus, the causes of the increases in cancer are not likely to stem from those that are shared with heart disease, but to represent some as-yet-unrecognized risk factors. Among those that should be carefully reviewed are solvents, pesticides, engine exhausts, and animal viruses, materials to which both farmers and the general population are exposed in increasing amounts.

Introduction

Much of cancer is believed to be preventable because rates vary substantially between populations. Environmental factors, broadly conceived, are likely to account for much of this variation. Trends in cancer rates are, therefore, often used to provide indications of the diminution or increase in environmental factors that might be contributing to the cancer burden. A series of studies have reported increasing rates for a number of cancers in industrial countries (*1–3*). Factors contributing to the rising rates for several of these cancers have not been identified. Studies of cancer among farmers, however, may provide clues (*4*). This paper briefly reviews the pattern of increasing cancer rates in the general population, provides some speculations about the causes that might be involved, and suggests a research approach that might identify relevant environmental factors.

[1]U.S. National Research Council, 2101 Constitution Avenue NW, Washington, DC 20418.
[2]Occupational Studies Section, National Cancer Institute, Executive Plaza North, Room 418, Bethesda, MD 20892.
[3]National Institute of Environmental Health Sciences, P.O. Box 12233, Research Triangle Park, NC 27709.
Address reprint requests to D. L. Davis, U.S. National Research Council, 2101 Constitution Avenue NW, Washington, DC 20418.

Methods

Cancer rates were evaluated using data from the World Health Organization. Time trends were calculated using simple normal theory linear regression analysis applied to yearly age-specific cancer mortality rates.

For the analysis of cancer among farmers, data on cancer and other causes of death from 21 broad occupational surveys had previously been assembled from 8 industrial countries (*4*). In these surveys, the risk of cancer among farmers was usually compared with the risk in the general population. Inclusion of surveys which systematically provided cancer risks on many occupations reduced the potential for a bias toward reporting positive findings. Observed and expected numbers for various causes of death were added across the studies to create combined relative risks (CRRs) to minimize the influence of unusual chance findings from individual studies on the overall interpretation. Statistical significance for the CRRs was evaluated using 95% confidence intervals (CI) (*5*). This procedure weights the contribution of each study by its size. We also determined for each cancer the range in relative risks, the number of studies where the relative risk exceeded unity, and number of statistically significant excesses to evaluate the distribution and consistency of individual risk estimates. This approach weights individual studies equally.

Table 1. Mortality rates per 100,000 from brain cancer, 1986, and percent annual change, 1969–1986.[a]

Age group	Rate (% change)					
	U.S.A.	Japan	U.K.	France	Italy	W. Germany
Males						
45–54	7 (−1.3)	1 (3.4)	9 (0.4)	6 (2.5)	7 (2.7)	7 (2.0)
55–64	13 (−0.4)	2 (4.1)	15 (1.0)	11 (2.3)	15 (3.7)	13 (2.8)
65–74	20 (1.6)	3 (5.6)	19 (2.8)	17 (3.6)	19 (5.1)	15 (4.8)
75–84	21 (4.2)	4 (5.0)	11 (4.5)	13 (4.2)	16 (4.9)	13 (4.5)
45–84[b]	13 (0.9)	2 (4.6)	14 (1.7)	11 (3.0)	14 (4.2)	11 (3.4)
Females						
45–54	4 (−1.9)	1 (3.9)	5 (0.6)	4 (1.9)	4 (2.9)	5 (1.5)
55–64	8 (−0.1)	2 (4.4)	11 (0.8)	7 (2.4)	10 (3.7)	8 (3.1)
65–74	14 (1.9)	2 (5.5)	12 (3.2)	11 (4.0)	13 (5.2)	10 (4.6)
75–84	15 (4.3)	3 (4.3)	7 (4.5)	8 (4.2)	10 (5.3)	9 (4.9)
45–84[b]	9 (1.5)	2 (4.7)	9 (2.0)	7 (3.2)	9 (4.4)	8 (3.6)

[a]Percent annual change is based on the average annual change for the period 1969–1986 expressed as a percentage of the 1986 rate.
[b]Age-adjusted rate based on 1986 U.S. population.

Table 2. Mortality rates per 100,000 from melanoma 1986, and percent annual change, 1969–1986.[a]

Age group	Rate (% change)					
	U.S.A.	Japan	U.K.	France	Italy	W. Germany
Males						
45–54	5 (0.2)	0 (0.4)	3 (3.5)	2 (5.1)	3 (3.0)	3 (0.9)
55–64	7 (1.9)	1 (0.3)	4 (3.0)	3 (4.3)	4 (5.4)	5 (1.8)
65–74	10 (2.3)	1 (2.1)	4 (3.7)	5 (3.8)	6 (4.4)	9 (2.8)
75–84	15 (3.8)	1 (4.5)	7 (2.7)	7 (3.4)	9 (4.6)	12 (2.7)
45–84[c]	8 (2.1)	1 (1.9)	3 (4.1)	4 (3.3)	4 (4.4)	6 (2.2)
Females						
45–54	3 (−0.4)	0 (−1.2)	3 (1.4)	2 (4.3)	2 (2.9)	2 (−1.0)
55–64	3 (0.1)	0 (1.6)	4 (2.2)	2 (4.0)	3 (3.7)	3 (1.8)
65–74	5 (1.1)	1 (3.8)	5 (3.3)	5 (3.4)	4 (4.4)	6 (2.5)
75–84	8 (1.4)	1 (1.7)	8 (2.9)	6 (3.5)	6 (5.2)	7 (1.9)
45–84[c]	4 (0.7)	0 (2.0)	3 (3.7)	5 (2.5)	3 (4.2)	4 (1.6)

[a]Percent annual change is based on the average annual change for the period 1969–1986 expressed as a percentage of the tabled 1986 rate.
[b]Eight years of data from 1979 to 1986.
[c]Age-adjusted rate based on 1986 U.S. population.

Table 3. Mortality rates per 100,000 from multiple myeloma, 1986, and percent annual change, 1969–1986.[a]

Age group	Rate (% change)					
	U.S.A.	Japan	U.K.	France	Italy[b]	W. Germany[b]
Males						
45–54	2 (0.1)	1 (2.1)	2 (0.4)	1 (0.5)	1	1
55–64	7 (0.7)	3 (1.3)	7 (1.2)	4 (0.0)	4	4
65–74	19 (1.1)	9 (3.6)	19 (1.8)	14 (2.5)	10	7
75–84	34 (2.2)	13 (5.7)	32 (3.7)	30 (4.3)	18	11
45–84[c]	11 (1.3)	5 (3.6)	11 (2.5)	8 (2.6)	6	4
Females						
45–54	2 (0.7)	1 (0.9)	1 (0.5)	1 (−0.2)	1	0
55–64	5 (0.7)	3 (1.9)	5 (0.8)	4 (0.0)	3	2
65–74	13 (1.1)	6 (3.7)	12 (1.7)	10 (2.5)	8	5
75–84	23 (2.5)	10 (5.7)	20 (3.0)	21 (3.8)	12	10
45–84[c]	9 (1.6)	4 (3.9)	8 (2.0)	7 (2.5)	5	4

[a]Percent annual change is based on the average annual change for the period 1969–1986 expressed as a percentage of the 1986 rate.
[b]Coding change occurred in 1979 for Italy and W. Germany, and therefore the regressions for the percent change were not done.
[c]Age-adjusted rate based on 1986 U.S. population.

Results

Multiple myeloma (International Classification of Diseases [ICD] code 203), non-Hodgkin's lymphoma, melanoma of the skin (ICD 172), and cancers of the brain (ICD 191-192) and prostate (ICD 185) increased significantly in six industrial countries among persons ages 64 to 84 from 1969 to 1986 (*1,3*). Tables 1–5 show the annual percentage change for these sites for specific 10-year age groups and the age-adjusted rate for those ages 45–84, adjusted to the population distribution in the United States. Data for non-Hodgkin's lymphoma were analyzed only for U.S. incidence and U.K. mortality.

Table 4. Mortality rates per 100,000 from prostate cancer 1986, and percent annual change, 1969–1986.[a]

Age group	Rate (% change)					
	U.S.A.	Japan	U.K.	France	Italy	W. Germany
45–54	3 (0.4)	1 (1.1)	3 (−1.0)	2 (1.4)	2 (−1.1)	2 (1.2)
55–64	25 (0.4)	3 (−0.1)	22 (−1.5)	21 (0.0)	16 (−0.7)	18 (−0.6)
65–74	111 (0.3)	23 (1.8)	111 (1.7)	116 (0.9)	84 (0.2)	115 (0.9)
75–84	322 (0.6)	79 (3.1)	328 (0.7)	398 (0.7)	266(0.8)	372 (0.9)
45–84[b]	68 (0.5)	15 (2.4)	68 (1.2)	76 (0.7)	53 (0.4)	72 (0.8)

[a]Percent annual change is based on the average annual change for the period 1969–1986 expressed as a percentage of the tabled 1986 rate.
[b]Age-adjusted rate based on 1986 U.S. population.

Table 5. Non-Hodgkin's lymphoma 1986 rates and percent annual change.[a]

Age group	U.S. incidence		England mortality	
	Male	Female	Male	Female
45–54	21 (2.8)	12 (1.0)	6 (5.5)	3 (5.7)
55–64	33 (2.5)	25 (2.7)	11 (6.0)	7 (5.9)
65–74	61 (2.3)	48 (2.1)	24 (5.6)	16 (5.8)
75–84	85 (3.3)	69 (3.4)	35 (5.4)	24 (5.6)
45–84[b]	41 (2.7)	33 (2.5)	15 (5.6)	10 (5.7)

[a]Percent annual change is based on the average annual change for the period 1969–1986 expressed as a percentage of the 1986 rate.
[b]Age adjusted rate based on 1986 U.S. population.
[c]Eight years of data from 1979 to 1986.

For those sites on which data were compared in all six countries, brain cancer mortality showed the greatest rate of increase in every country in all age groups, excepting those under age 65 in the United States. For this same time period, brain cancer mortality increased at least 50% for persons over age 64 in all countries, except those under age 75 in the United States. Mortality from non-Hodgkin's lymphoma increased at an even greater rate in the U.K. at all age groups. U.S. incidence for this site increased at all age groups at slightly lower rates than those of the U.K., with the greatest increases occurring in the oldest age groups.

Increases in mortality from multiple myeloma, melanoma of the skin, and prostate cancer increased significantly in most age groups throughout this same time period. While the rate of increase was great for melanoma and multiple myeloma, these diseases remain relatively rare in all countries. In contrast, prostate cancer is a common, but increasing, cause of deaths in all countries, especially in older men. Rates in France for men ages 65–84 are about 40% higher than those in the U.K. and five times those in Japan.

Figure 1 shows that in the United States, Japan, England, France, Italy, and West Germany the ratio of the age-adjusted rate of male to female cancer mortality (for all causes excluding lung) increased significantly from 1969 to 1986. This increase was not seen with lung cancer due primarily to increasing rates of smoking and subsequent lung cancer among women in several countries (Fig. 2).

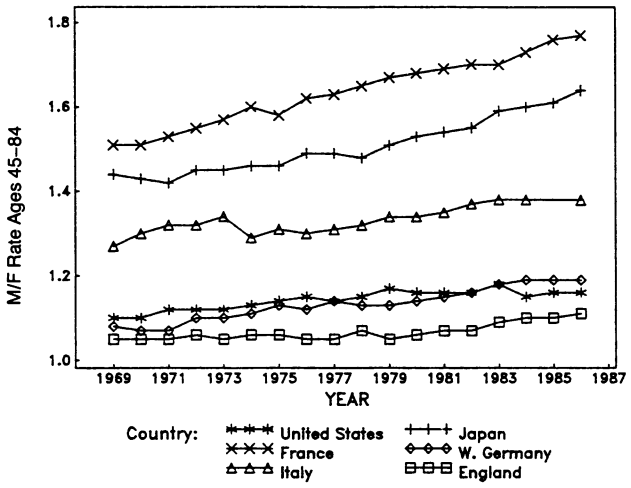

FIGURE 1. Ratio of male to female cancer mortality rates (ALL cancers except lung, 1969–1986).

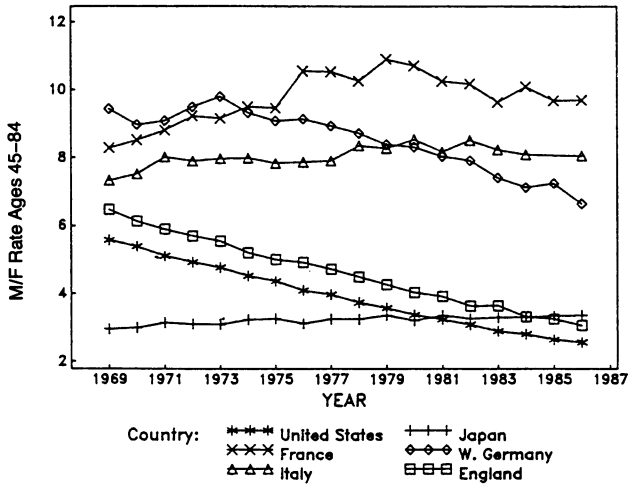

FIGURE 2. Ratio of male to female lung cancer mortality rates (1969–1986).

Table 6. Summary of risks for cancer and other causes of death among farmers (*14,37,47–64*).

Disease and references	Total diseased	Combined relative risk (95% confidence interval)	Range of relative risks	Number of studies	Number of RR < 1.0/number of RR significant < 1.0	Number of RR < 1.0/ Number of RR significant < 1.0	χ^2 from sign test
Ischemic heart disease (*14,37,51,52,54,55,57,58,60,63,64*)	65,898	0.89 (0.88–0.90)	0.6–1.1	12	8/6	2/0	3.00*
All cancer (*13,14,37,48,50–55,57–61,63,64*)	47,593	0.89 (0.88–0.90)	0.6–1.0	20	18/13	0/0	15.3†
Lung (*14,37,47–64*)	8,018	0.66 (0.64–0.67)	0.4–1.3	24	23/19	1/0	20.2†
Esophagus (*14,37,47–51,53,54,56–58,60–64*)	777	0.74 (0.69–0.80)	0.5–1.7	18	12/7	5/0	2.72
Bladder (*14,47–52,54–64*)	1,948	0.85 (0.81–0.89)	0.5–1.1	21	19/5	2/0	13.8†
Colon (*14,47,51,53–61,62,63*)	2,952	0.87 (0.84–0.90)	0.3–1.1	15	13/6	2/0	8.07†
Liver (*14,47,48,54,56–58,60,61,63,64*)	510	0.89 (0.81–0.97)	0.5–2.0	13	7/1	6/0	0.08
Kidney (*14,47–49,52,55,57,58,60–64*)	965	0.92 (0.86–0.98)	0.6–1.5	15	9/3	6/0	0.60
Testis (*47–49,54,56–58,60,62–64*)	161	0.88 (0.79–1.03)	0.6–1.4	10	5/1	5/0	0.03
Nose (*47,49,54,60,61,63,64*)	53	0.94 (0.70–1.23)	0.6–2.4	8	4/0	4/0	0.03
Pancreas (*14,37,47–51,53–58,60–64*)	2,415	0.98 (0.94–1.02)	0.5–1.6	20	11/2	9/0	0.20
Rectum (*14,47,53–58,60–64*)	1,512	1.00 (0.95–1.05)	0.8–1.7	13	6/1	7/1	0.08
Breast (female) (*63,64*)	163	1.02 (0.87–1.18)	1.0–1.2	2	0/0	2/0	1.13
Skin other than melanoma (*49,50,54,60,61,63,64*)	348	1.04 (0.93–1.16)	0.7–1.7	8	4/0	4/3	0.03
Female genital organs (*63,64*)	160	1.05 (0.89–1.22)	0.9–1.1	2	1/0	1/0	0.13
Non-Hodgkin's lymphoma (*37,47,48,50,51,54,56,59,60,63,64*)	911	1.05 (0.98–1.12)	0.6–1.4	14	5/0	8/1	0.64
Brain (*14,37,47–50,52,53,54–60,63*)	979	1.05 (0.99–1.12)	0.7–6.5	18	5/0	13/2	3.56*
Connective tissue (*37,47,48,54,56,60,63*)	159	1.06 (0.91–1.24)	0.9–1.5	7	2/0	5/0	1.29
Leukemia (*14,37,47–60*)	2,625	1.07 (1.03–1.11)	0.3–2.4	23	9/0	14/6	1.09
Prostate (*14,37,47–64*)	7,753	1.08 (1.06–1.11)	0.9–2.7	22	6/1	15/6	3.68*
Stomach (*14,37,47–64*)	7,182	1.12 (1.09–1.14)	0.6–2.0	24	9/2	14/8	1.04
Multiple myeloma (*37,47–51,54,56,60,62–64*)	694	1.12 (1.04–1.21)	0.4–2.5	12	2/0	9/1	4.08‡
Melanoma (*47,49,50,54,56,59,60,63,64*)	374	1.15 (1.04–1.28)	0.5–6.3	11	2/0	9/3	4.45‡
Hodgkin's disease (*47,48,50,54–58,60,63,64*)	325	1.16 (1.03–1.29)	0.9–4.1	12	2/0	10/2	5.53‡
Lip (*47,48,51,54,56,60,61,63*)	188	2.08 (1.80–2.40)	1.3–3.1	8	0/0	8/4	7.03†
Total mortality (*13,14,37,52,55,59,60,64*)	106,051	0.86 (0.86–0.87)	0.6–1.9	10	9/9	1/1	6.40†

RR, relative risk.
*$p<0.010$.
†$p<0.01$.
‡$p<0.05$.

Table 6 displays summary data from 20 different occupational surveys that included farmers. Most studies surveyed only white men, but a few also included women and/or minorities. Statistically significant deficits in the CRRs occurred for all causes combined, ischemic heart disease, all cancer combined, as well as for cancers of the lung, esophagus, bladder, colon, liver, and kidney. In contrast, significantly increased CRRs occurred for Hodgkin's disease, multiple myeloma, leukemia, melanoma of the skin and cancers of the lip, stomach, and prostate. These excesses were small and some individual studies showed deficits. Although the CRRs for non-Hodgkin's lymphoma and cancers of the connective tissue and brain were not significantly elevated, they tended to be increased in most studies.

Discussion

Multiple myeloma, non-Hodgkin's lymphoma, melanoma of the skin, and cancers of the lung, prostate, bladder, brain, and breast are increasing in the general population of several industrial countries. The rates of increase are remarkably similar between countries and occur in both sexes. Mortality increases are greatest in those over age 74, but are also evident in those over age 54. For all of these sites except breast, men have higher mortality than women. In general, the male rates are increasing faster than those among women. In the U.S. SEER system, incidence is also increasing for a number of these same sites (*2,6*). Some researchers have suggested that most of these increases may be artificial resulting from improvements in health care and diagnosis (*7*), but others have concluded that these factors are unlikely to explain all of the increase (*1*).

There are few clues as to what environmental factors may contribute to the rising rates, although any of the established risk factors are potential candidates. Heart disease shares a number of etiologic factors with cancer, including cigarette smoking, heavy alcohol use, and diets high in fat and low in fiber and antioxidants. Rates for heart disease in several developed countries, however, are declining (*8*). In the United States rates have declined almost 40% since the peak in the late 1960s. It therefore seems unlikely that the causes of the recent increases in some sites of cancer would be due to those etiologic factors shared with heart disease. If environmental factors are involved, other explanations are needed. The focus should be on factors that have been increasing among the general population in prevalence and/or exposure level. HIV is now contributing significantly to increases in non-Hodgkin's lymphoma (*9*), but it cannot provide the entire explanation because the rising trend started before the AIDS epidemic. One clue for factors that might contribute to the rising rates comes from studies of farmers.

Several of the tumors that are increasing in developed countries have been found to be elevated among farmers (*10–12*). The excesses for specific cancers among farmers occur against a background of low overall risks for total mortality, heart disease, and several cancers including lung, esophagus, colon, and bladder. These relatively reduced rates may be due to the low prevalence of smoking observed globally among farmers (*13–18*), their greater levels of physical activity (*19–23*), and perhaps diets that are higher in fiber and lower in refined products.

The cancer excesses among farmers may have broad public health implications, since several appear to be increasing in the general population of many developed countries (*1,3*), including multiple myeloma, non-Hodgkin's lymphoma, melanoma of the skin, and cancers of the prostate and brain. Factors responsible for the high rates among farmers may also be contributing to rising rates in the general population. A number of etiologic clues to farming-related cancer already exist (*11*). Because of the outdoor nature of their work, farmers have considerable exposure to ultraviolet light, the major risk factor for melanoma (*24*). Exposure to pesticides, particularly phenoxyacetic acid herbicides, has been linked to increased risks for non-Hodgkin's lymphoma (*25–28*), although excesses have not been observed in some studies (*29*). Farmers who work with some insecticides have been found to have elevated rates of leukemia (*30,31*), multiple myeloma (*32,33*), and brain cancer (*34*). Although use of fertilizers has not been evaluated in relation to cancer among farmers, environmental exposures to nitrates have been associated with stomach cancer in epidemiologic and experimental investigations (*35*). The increasing contamination of drinking water sources with nitrates in many rural areas makes this an issue of special concern (*36*). A study of Canadian farmers detected an association between non-Hodgkin's lymphoma and expenditures on fuels (*37*), suggesting that exposures to fuels or engine exhausts may play an etiologic role. Other agricultural exposures including animal viruses, mycotoxins, dusts, and solvents have yet to be carefully evaluated. Many agricultural exposures have become more common among the general population in recent years. For example, pollution from engine exhausts has increased, and pesticides and fertilizers are now widely used in urban areas.

The tumors with rising rates in the general population and excessive among farmers display no obvious commonality. They are blood tumors and solid cancers from the reproductive, nervous, and digestive systems. They include common (prostate) and less common tumors (multiple myeloma). Studies of immunodeficiencies may provide a mechanistic link. Patients with naturally occurring or medically induced immunodeficiencies experience striking excesses of non-Hodgkin's lymphoma (*38–43*). In addition, leukemia and stomach cancer appear among persons with primary immunodeficiency syndromes, melanoma and lip cancer among renal transplant recipients (*41,42*), and brain cancer among bone marrow recipients (*43*). This similarity between cancers associated with immunosuppression and cancers displaying rising rates and high rates among farmers suggests that environmental factors may be involved that operate through immunologic perturbations that remain to be identified (4).

Pesticides, which may contribute to cancer excesses among farmers, may operate through genetic and epigenitic mechanisms. The mechanisms of action, however, are obscure. Some pesticides appear to be genotoxic. Garrett et al. (*44*) evaluated of genetic damage from 65 pesticides in 14 *in vivo* and *in vitro* tests: 9 were active in most tests, 26 were active in several tests, and 30 were inactive in all tests. Pesticides may operate through epigenetic pathways, including the immune system. In experimental studies, pesticides have been linked to a variety of immune defects including decreased host resistance to infection, thymus atrophy, reduced delayed-type hypersensitivity response,

suppressed T-cell activity, enhanced B- and T-cell immune response, and contact hypersensitivity (*45*). Pesticides could affect a variety of cancers through an immunologic mechanism. Laboratory and epidemiologic investigations to evaluate such a link could help clarify the high rates among farmers and rising rates among the general public.

The best evidence to date regarding carcinogenic exposures among farmers derives chiefly from case–control interview studies. The retrospective nature of exposure assessment in these investigations, however, undoubtedly results in exposure misclassification (*23*). Such misclassification is likely to be nondirectional and would tend to diminish risk estimates and dilute exposure-response gradients (*46*). Because farmers are independent operators who directly order, pay for, and apply the material with which they work, they can often provide considerably more detail about their work practices and chemical exposures than workers in other industries. Still, the opportunity for recall because of the passage of time, infrequent use, or changing patterns of use of agricultural chemicals suggests that exposure assessment based entirely on recall would suffer, and true associations could be missed. Studies with improved exposure assessment approaches are needed. Prospective studies of farmers that incorporate environmental and biologic measures of exposure with data from interviews could improve the precision of exposure assessment. Inclusion of spouses and dependents in such studies would provide information on cancer risk from indirect exposure to various agricultural chemicals and thus provide an indication of whether these exposures could contribute to the rising rates for certain cancers in the general population.

In summary, several tumors including multiple myeloma, non-Hodgkin's lymphoma, melanoma of the skin, and cancers of the brain, prostate, lung, and breast appear to be increasing in many developed countries. Explanations for most of these are not available. Studies of farmers may provide a clue. Despite low risks for most major causes of death, farmers tend to be at higher risk than the general population for a number of types of cancer including multiple myeloma, non-Hodgkin's lymphoma, leukemia, melanoma of the skin, and cancers of the lip, brain, prostate, and stomach. These tumors among farmers show considerable overlap with those displaying rising rates in the general population. The occurrence of several of these cancers among patients with naturally occurring and medically induced immunosuppression suggests that the rising rates among the general public and high rates among farmers may be due to factors that affect the immune system. Studies to evaluate the influence of agricultural chemicals on the immune system are needed to follow-up this lead.

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