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Epidemiologic Studies of Cancer in Agricultural Populations: Observations and Future Directions

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Abstract

This paper reviews epidemiologic studies of cancer among agricultural populations to identify possible associations and to provide a focus for future investigations. Meta-analyses of mortality surveys of farmers find excesses of several cancers, including connective tissue, non-Hodgkin lymphoma, Hodgkin disease, and multiple myeloma and cancers of the skin, stomach and brain and deficits for total mortality, heart disease, total cancer, and cancers of the esophagus, colon, lung and bladder. Meta-analyses of studies of individual cancers also support these findings indicating a need to identify exposures and lifestyle factors that might account for this mortality pattern. Although cancer studies of other occupations that might have pesticide exposures in common with farmers show some similarities with observations among farmers, the overall patterns are quite different. This suggests that pesticides are not likely to fully explain the cancer and other disease patterns observed among farmers. Because exposures vary by type of farm operation, exposures for individual farmers can differ considerably. Studies in the future need to focus on the full range of exposures to fully understand the cancer pattern in farmers.

Keywords

cancer; epidemiology; agriculture

Background

The meeting on Public Health and the Agricultural Rural Ecosystem held in October, 2008 in Saskatoon, Canada underscores the public and scientific interest in health issues among farm populations. This is the 5th international meeting on this topic that began with the conference in Iowa in 1991, which launched a number of activities to expand health research on agricultural populations. Concern about cancer among farmers was raised at the 1991 meeting and it remains a concern today.

Surveys around the world have provided information on the mortality experience of farmers. Meta-analyses of these studies indicate farmers have significantly lower mortality rates than the general population.[1,2] Despite this overall favorable mortality experience, farmers appear to have higher than expected rates for a few cancers. Early epidemiologic research was focused on characterizing the cancer pattern among farmers, while more recent efforts have attempted to identify factors that might account for the cancer patterns observed. In this paper, we have reviewed the literature on cancer among farmers and other relevant occupations (farm workers, golf course superintendents, gardeners, and pesticide applicators and manufacturers) to characterize the state of the field and to identify future research needs.

Methods

Because our goal was to broadly describe the state of the current knowledge on agricultural exposures and cancer, we relied heavily on previous reviews on this topic and synthesized results from studies of both cancer incidence and mortality. We realize that findings from incidence and mortality studies may sometimes differ, but in general they are quite consistent and these inconsistencies can inform areas of further research. Our broad overview, including these reviews plus a few citations of individual studies can be used to evaluate the possibility for a role of agricultural exposures in the development of cancer and to suggest needs for future research in this area.

Results

Table 1 shows results from two meta-analyses of surveys of diseases among farmers.[1,2] Both analyses show significant, though often small, excesses for leukemia and cancers of the lip and prostate. Cancers with excesses in both meta-analyses, although not necessarily statistically significant ones, include connective tissue, non-Hodgkin lymphoma, Hodgkin disease, and multiple myeloma and cancers of the skin, stomach and brain. Significant deficits occur in both meta-analyses for total mortality, total cancer, and cancers of the esophagus, colon, lung and bladder, as well as heart disease.

The recently published cancer incidence experience of the Agricultural Health Study (AHS)[3] cohort in the U.S. was not included in these meta-analyses and found significant deficits among farmers from all cancer combined (Standardized Incidence Ratio (SIR)=0.88, 95% CI=0.84−0.91), and cancers of the rectum (SIR=0.81, 95% CI=0.65−0.99), pancreas (SIR=0.73, 95% CI=0.53−0.97), lung (SIR=0.47, 95% CI=0.41−0.53), and urinary system (SIR=0.65, 95% CI=0.56−0.75). Significant excesses were observed for cancers of the prostate (SIR=1.26 95% CI=1.18−1.33) and ovary (SIR=2.97, 95% CI=1.28−5.85). Non-significant excesses occurred for thyroid and other endocrine tumors (SIR=1.29, 95% CI=0.77−1.76) and multiple myeloma (SIR=1.34, 95% CI=0.97−1.81).

Meta-analyses have also been performed using studies of individual cancers among farmers (Table 2). These find significant excesses for Hodgkin disease,[4] non-Hodgkin lymphoma,[5] multiple myeloma,[6] leukemia,[7] and cancers of the brain[8] and prostate.[9] A meta-analysis of studies of myeloid leukemias among workers with exposure to pesticides found a meta-RR of 1.38 (95% CI=0.99−1.48).[7] The meta-RR for manufacturing workers was 6.32 (95% CI=1.90−21.01) and 2.14 (95% CI=1.39−3.31) for applicators.

Studies of other occupations that may have some exposures, especially pesticides, in common with farmers can also provide useful information to assess carcinogenic potential of agricultural exposures. Migrant and seasonal farm workers represent a group with significant overlap of exposures. Findings from proportionate mortality (PMR)[10] and incident (PIR)[11] cancer studies available on this occupational group are shown in Table 3. Excess mortality occurred for cancers of the esophagus, stomach, larynx, and cervix, while deficits occurred for non-Hodgkin lymphoma and cancers of the colon, breast and kidney.[10] In an incidence study,[11] Mills and Kwong found significant excesses for leukemia and cancers of the stomach and cervix among migrant or seasonal workers belonging to the United Farmworkers of America. Although not shown in Table 3, the mortality study[10] also found excesses for tuberculosis (PMR=165, 95% CI=125−214), pneumonia (PMR=116, 95% CI=109−123), cerebrovascular disease (PMR=114, 95% CI=109−119), and gastric and duodenal ulcer (PMR=128, 95% CI 102−159) and deficits for diabetes (PMR=88, 95% CI=81−96) and all cancers combined (PMR=81, 95% CI=79−84).

Golf course superintendents may also have many exposures in common with farmers. Kross et al.[12] evaluated the mortality experience of members of the Golf Course Superintendents Association of America and found excesses for all cancer combined (PMR=136, 95% CI=121−152), diseases of the nervous system (PMR=202, 95% CI=123−333), arteriosclerotic heart disease (PMR=236, 95% CI=127−155), emphysema (PMR=186, 95% CI=101−342), non-Hodgkin lymphoma (PMR=237, 95% CI=137−410), colon (PMR=175, 95% CI=125−245), and prostate cancer (PMR=293, 95% CI=187−460).

Market gardeners and orchardists are another agricultural group who may share exposures with farmers. A mortality study of these occupations in Sweden[13] found significantly reduced mortality from all causes (SMR=0.8, 95% CI=0.7−0.9) and cardiovascular diseases (SMR=0.8, 95% CI=0.7=0.9), reduced morbidity from cancers of the respiratory tract (SMR=0.6, 95% CI=0.4−0.9), and a significant excess for melanoma of the skin (SMR=2.1, 95% CI=1.2−3.5). Non-significant excesses occurred for cancers of the female genital organs (SMR=2.3, 95% CI=0.7−5.3) and brain cancer (SMR=1.5, 95% CI=0.8−2.7)[13].

Burns reviewed the literature on cancer among pesticide manufacturers and applicators.[14] Detail analyses were provided for all cancer combined, non-Hodgkin lymphoma and lung cancer, but no meta-analyses were performed. No significant excesses or deficits for these cancers occurred in any of the studies reviewed. Among the 21 studies reviewed, two had non-significant excesses for all cancer combined and three had deficits. For lung cancer, six had non-significant excesses and three had deficits. For non-Hodgkin lymphoma, four had non-significant excesses and one had a deficit.

Fleming et al. published an interesting study that included both private and commercial licensed pesticide applicators in Florida.[15] Private applicators were largely farmers, ranchers and horticulturists. Mortality among private and commercial applicators was depressed for all cancers combined (SMR=0.77, 95% CI=0.70−0.85 and SMR=0.83, 95% CI=0.66−1.03, respectively), as it was for cancers of the mouth and pharynx (SMR=0.41, 95% CI=0.13−0.95 and SMR=0.78, 95% CI=0.09−2.83), large intestine (SMR=0.81, 95% CI=0.57−1.12 and SMR=0.84, 95% CI=0.31−1.82), rectum (SMR=0.78, 95% CI=0.29−1.71 and SMR=0.74, 0.01−4.11), pancreas (SMR=0.85, 95% CI=0.53−1.30 and SMR=0.72, 95% CI=0.15−2.11). Bladder cancer mortality was reduced in private applicators (SMR=0.74, 95% CI=0.30−1.52), with no deaths occurring in the commercial applicators. Leukemia (SMR=1.31, 95% CI=0.75−2.12 and SMR=1.23, 95% CI=0.25−3.61, for private and commercial applicators, respectively) and cancers of the liver (SMR=1.18, 95% CI=0.63−2.02 and SMR=1.52, 95% CI=0.31−4.43), bone (SMR=2.29, 95% CI=0.26−8.27 and SMR=4.38, 95% CI=0.06−24.35), skin (SMR=1.17, 95% CI=0.61−2.05 and SMR=1.19, 95% CI=0.24−3.49), and brain and central nervous system (SMR=1.28, 95% CI=0.74−2.04 and SMR=1.62, 95% CI=0.52−3.79) were slightly elevated, although most were not statistically significant. Cancer of the eye was significantly elevated among private applicators (SMR=5.52, 95% CI=1.11−16.12), but no deaths occurred among commercial applicators. Cancers of the esophagus, stomach and kidney were slightly elevated among commercial applicators, but had small deficits among private applicators.

Cancer risks among farmers reporting use of specific pesticides have been reported in several papers from the Agricultural Health Study cohort (See the AHS website (http://aghealth.nci.nih.gov/) for citations of these papers and abstracts of results). Associations with pesticides have been evaluated for cancers of the prostate, lung, breast and colon/rectum. Leads from these papers that deserve future evaluation include associations between two herbicides (metolachlor and pendimethalin) and two insecticides (chlorpyrifos and diazinon) and lung cancer; between butylate, chlorpyrifos, coumaphos, fonofos, phorate, terbufos, and permethrin and prostate cancer (but only among individuals with a first degree relative with this tumor); between the herbicide 2,4,5-TP, insecticide dieldrin, and fungicide captan and breast cancer among farmer's wives; between chlorpyrifos and rectal cancer; and between aldicarb and colon cancer. Seventeen AHS papers on specific pesticides (7 herbicides, 9 insecticides, and 1 fungicide) have been published that evaluate cancer risks from these chemicals. Possible associations with herbicides that deserve future attention were reported for leukemia and multiple myeloma and alachlor, for non-Hodgkin's lymphoma, multiple myeloma and cancers of the lung and bladder and atrazine; for multiple myeloma and glyphosate; for rectal cancer and pendimethalin; for lung and colon cancer and dicamba; and for prostate and lung cancer for metolachlor. No suggestion of any cancer associations occurred with cyanazine. Findings of possible associations with insecticides include lung cancer with chlorpyrifos and carbofuran ; leukemia and lung cancer with diazinon; prostate cancer and phorate (but only among individuals with first degree relatives who have had prostate cancer); leukemia and prostate cancer (among those with first degree relatives with prostate cancer) and fonofos; melanoma and malathion; melanoma and NHL and a lower risk for prostate cancer with carbaryl; lung cancer with dieldrin; non-Hodgkin lymphoma with lindane; melanoma wotj toxaphene; leukemia with chlordane/heptachlor; colon cancer with aldrin; and no cancer was associated with captan use.

Discussion

If cancer excesses occur among agricultural populations, understanding the magnitude and causes of these excesses is important to initiate cancer preventive actions in these populations. Such an understanding would also provide useful information about cancer etiology in general because many exposures experienced by farmers also occur in other occupations and in the general population. As with many occupations, farmers may come into contact with many potentially hazardous chemicals during the performance of their duties. Exposures on the farm, however, differ from those in other occupations in a number of ways. First, the range of types of exposures in agriculture is quite broad.[16] Although workers in most occupations may be exposed to a number of substances at the workplace, in agriculture these exposures cover many different exposure categories. For example, petrochemical workers may have exposure to many different chemicals, but farmers can be exposed to pesticides, chemical fertilizers, solvents and other chemicals, engine fuels and exhausts, organic and inorganic dusts, welding fumes, mycotoxins and zoonotic viruses, heat, noise, and vibration. Providing an adequate characterization of so many exposures for an epidemiologic study is challenging. Second, the specific constellation of exposures experienced by an individual farmer varies by the type of farm operation. Thus, exposures among individual farmers can differ considerably and different grouping of farmers in the various studies, although valuable at some level, would likely result in a very heterogeneous mixture of exposure situations. This heterogeneity of exposure could account for some of the inconsistencies observed. For example, a striking example of the effect of differences in exposures is evident for lung cancer where most studies of farmers show a striking deficit, but sugar cane farmers and sugar mill workers show an excess. The excess among sugar cane workers is thought to be due to the high concentration of silica in sugarcane stems.[17] Third, although exposures can be quite intense during the actual performance of some specific farm tasks, many tasks are performed only a few days each year and the cumulative exposure may not be great. For example, exposure to pre-emergent pesticides used on corn would typically occur during only a few weeks out of the year because of the narrow time window for planting. On the other hand, pesticide exposure among orchardists may be considerably more frequent and span a longer time period each year. Disease risks from the same pesticide exposure could be quite different in these two situations. Fourth, farmers and other family members may have additional exposure from inadvertent in-season and out of season contact with some substances because of close proximity to areas with chemicals are stored, handled, or used. Curwin[18] found that urinary levels for the metabolite of atrazine were higher in fathers, mothers and children in farm households and those from

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nonfarm households. These results indicate that family members, as well as the farmer, may experience indirect exposures. In another study, Bakke [19] found that farmers had higher urinary levels for 2,4-D during the winter than nonfarmers indicating that exposure was occurring at times other than during handling, mixing, or application. This pattern that did not occur for atrazine, which suggests this out of season effect is chemical specific. Evidence for the occurrence of indirect exposure means that a full and accurate characterization of exposure would need to take into account such bystander and off-season exposures.

Meta-analyses of mortality, or cancer incidence, from surveys among farmers find reasonably consistent excesses for cancers of the lip, stomach, skin, brain, prostate, connective tissue and lymphatic and hematopoietic system. Consistent deficits occur for cancers of the colon, lung, and bladder. These findings are reinforced by studies of individual cancers. Meta-analyses of studies of specific cancers find excesses for non-Hodgkin lymphoma,[5] Hodgkin disease,[4] leukemia,[7] multiple myeloma,[6] and cancer of the brain[8] and prostate.[9] Some of these associations, however, are quite small. This could reflect that weak carcinogenic impact of agricultural exposures, but it could also reflect exposure misclassification that likely occurs from the complexity of exposures in agriculture and the lack of specific exposure classification in most studies of farmers.

Low smoking rates undoubtedly contribute to the observed deficits for lung and bladder cancer.[1] Endotoxin exposures may also influence lung cancer rates and endotoxins can be found in many farm situations.[20] The impact of some factors other than smoking is indicated by the finding from the Agricultural Health Study in the U.S. that smoking farmers have a lower risk of lung cancer than the general population, in which over half would have smoked at some time.[21] Physical inactivity may have an impact. It is a recognized risk factor for colon cancer and a suspected risk factor for lung cancer.[22] Farming requires considerable physical activity, which may contribute to lower rates for some cancer and other diseases. This might change in the future because the level of physical activity required in farming is likely to diminish as agriculture continues to become more mechanized.

Studies season and migrant farmworkers, golf course superintendents, gardeners, and pesticide applicators and manufacturers also provide information to interpret the cancer experience observed among farmers. None of these groups display the exact pattern seen among farmers. Migrant and seasonal farmworkers, two occupational groups that might have very similar exposures to those experienced by farmers, show some of the cancer excesses observed in farmers (, i.e., stomach and possibly lip and leukemia), but not others.[10,11] They appear to have excesses of cancer of the esophagus and larynx, which are not observed among farmers. Golf course superintendents,[12] gardeners and horticulturalists,[13] and pesticide applicators and manufacturers[14] have excesses for some cancers elevated among farmers, but the overall pattern is somewhat different. If pesticides were the sole explanation for the mortality pattern among farmers, we might expect mortality patterns of other pesticide-exposed occupations to be quite similar to that among farmers, but this does not appear to be the case. The inconsistencies point to the need for careful evaluation of specific agricultural exposures and lifestyle factors in future studies to more clearly characterize the cancer excesses and deficits observed among farmers.

Most of the early studies of cancer among farmers relied upon the occupational designation, i.e., farmer, as the sole exposure determinant. Some recent studies have focused on type of farm commodity produced, or specific exposures. Efforts to improve exposure characterization are clearly needed. Papers on exposure to specific pesticides from the AHS have suggested links between specific pesticides and some cancers, including leukemia, non-Hodgkin lymphoma, multiple myeloma, melanoma and cancers of the lung, bladder, rectum, colon, and prostate. Although these findings are far from conclusive, they do provide some important insights. They suggest that pesticides might be associated with some cancers, that no pesticide has so far been linked to vary many cancers, and that suggested cancer – pesticide links do not group by class or type of pesticide. Mechanistic studies also indicate that some agricultural factors may pose a cancer hazard. Engine exhausts, fuels and solvents, welding fumes and some pesticides have genotoxic and/or immunotoxic properties that could be involved in cancer etiology.[16]

In summary, meta-analyses of mortality surveys of farmers and reviews of specific cancers point to excesses for certain cancers among farmers. There are a wide range of exposures possible in agriculture and they can vary considerably from farm to farm depending upon the type of farm operation. Future studies must focus on specific exposures to identify and clarify exposures that might contribute to the cancer excesses observed.

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Table 1

Results from meta-analyses of cancer mortality and incidence surveys of farmers (From: Blair, 1992[1]; Acquavella, 1998[2])

	From: Blair et al., 1992		From: Acquavella et al., 1998	
Cause	**# of Studies**	**Relative Risk**	**# of Studies**	**Relative Risk**
All causes	10	0.86*	7	0.76*
Ischemic heart disease	12	0.89*	14	0.86*
All cancer	20	0.89*	22	0.84*
Lip	8	2.08*	14	1.95*
Esophagus	18	0.74	25	0.77*
Lung	24	0.66*	29	0.66*
Bladder	21	0.85*	29	0.79*
Skin	8	1.04	19	1.15*
Stomach	24	1.12*	29	1.05
Colon	15	0.87*	29	0.84*
Pancreas	20	0.98	28	0.94
Prostate	22	1.08*	30	1.07*
Testis	10	0.88	14	0.97
Brain	18	1.05	28	1.06*
Non Hodgkin lymphoma	14	1.05	23	1.03
Hodgkin disease	12	1.16*	26	1.09
Myeloma	12	1.12*	22	1.09
Leukemia	23	1.07*	27	1.10*
Connective tissue	7	1.06	6	1.06

*Statistically significant, $p<0.05$

Table 2

Results from meta-analysis of specific cancers among farmers

Cancer	# Studies	Meta-Relative Risk	Author
Brain	33	1.30*	Khuder & Matgi[6]
Prostate	22	1.13*	Maele-Fabry & Willems[9]
Hodgkin disease	30	1.25*	Khuder et al.[4]
NHL	36	1.10*	Khuder et al.[5]
Myeloma	32	1.23*	Khuder et al.[6]
Leukemia	31	1.21 1.38* for myeloid	Maele-Fabry et al.[7]

*Statistically significant

Table 3

Relative risk for cancer mortality and incidence among migrant and seasonal farm workers (From: Colt et al.[10] and Mills & Kwong)[11]

Cancer	Proportionate Mortality Ratio	Proportionate Incidence Ratio
Esophagus	1.18*	Not provided
Stomach	1.22*	1.69*
Colon	0.83*	0.75
Pancreas	0.97	1.15
Larynx	1.37*	1.00
Lung	1.02	0.95
Lip	3.23	Not provided
Melanoma	0.85	1.39
Breast	0.82*	0.77
Cervix	1.93*	1.63*
Brain	0.83	1.57
Bladder	1.05	0.67
Kidney	0.70*	1.04
Prostate	0.98	0.93
Hodgkin disease	0.58	0.84
NHL	0.80*	1.02
Multiple myeloma	0.91	0.71
Leukemia	0.96	1.59*

*Statistically significant, $p<0.05$