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Original Contribution

Mortality in the Agricultural Health Study, 1993–2007

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Comparing agricultural cohorts with the general population is challenging because the general healthiness of farmers may mask potential adverse health effects of farming. Using data from the Agricultural Health Study, a cohort of 89,656 pesticide applicators and their spouses ($N = 89, 656$) in North Carolina and Iowa, the authors computed standardized mortality ratios (SMRs) comparing deaths from time of the enrollment (1993–1997) through 2007 to state-specific rates. To compensate for the cohort's overall healthiness, relative SMRs were estimated by calculating the SMR for each cause relative to the SMR for all other causes. In 1,198,129 person-years of follow-up, 6,419 deaths were observed. The all-cause mortality rate was less than expected ($SMR_{applicators} = 0.54$, 95% confidence interval (CI): 0.52, 0.55; $SMR_{spouses} = 0.52$, 95% CI: 0.50, 0.55). SMRs for all cancers, heart disease, and diabetes were significantly below 1.0. In contrast, applicators experienced elevated numbers of machine-related deaths (SMR = 4.15, 95% CI: 3.18, 5.31), motor vehicle nontraffic accidents (SMR = 2.80, 95% CI: 1.81, 4.14), and collisions with objects (SMR = 2.12, 95% CI: 1.25, 3.34). In the relative SMR analysis for applicators, the relative mortality ratio was elevated for lymphohematopoietic cancers, melanoma, and digestive system, prostate, kidney, and brain cancers. Among spouses, relative SMRs exceeded 1.0 for lymphohematopoietic cancers and malignancies of the digestive system, brain, breast, and ovary. Unintentional fatal injuries remain an important risk for farmers; mortality ratios from several cancers were elevated relative to other causes.

agriculture; healthy worker effect; mortality; neoplasms; pesticides; wounds and injuries

Abbreviations: AHS, Agricultural Health Study; CI, confidence interval; SMR, standardized mortality ratio; rSMR, relative standardized mortality ratio.

Compared with the general population, farmers have lower rates of mortality from all causes combined, heart disease, all cancers combined, and lung cancer (1–6). This may be attributed to lower tobacco and alcohol use and the higher physical demands of farm work (3), but other factors may also be involved. On the other hand, farmers experience higher rates of unintentional fatal injuries (7–9). Machine-related fatality has been identified as a leading cause of death in agriculture (10). Additionally, farmers experience higher mortality rates from certain types of cancer, including lymphohematopoietic malignancies and cancers of the prostate, lip, and eye, when compared with the general population (2–5).

Although the number of farms and farmers decreased during the 20th century, nearly 3 million people in the United States were still involved in agriculture in the year 2000 (11). Farming is a complex and changing business that requires extensive use of large machinery, pesticides, and commercial fertilizers. Hazards posed by these practices warrant further study of mortality rates in agricultural populations. The Agricultural Health Study (AHS), a large prospective cohort study of pesticide applicators and their spouses in North Carolina and Iowa, was established to examine occupational and environmental factors affecting morbidity and mortality rates of farmers and pesticide applicators (12).

Although other agricultural cohorts exist, the large size of the AHS enhances the ability to examine death from less common causes. The AHS includes individuals with a wide range of pesticide-use history, from spouses with little use to farmers who use pesticides on their own farms to commercial pesticide applicators who apply pesticides for a living. A wide variety of other agricultural exposures is also captured by this cohort.

A previous mortality study in the AHS based on follow-up from enrollment (1993–1997) through December 31, 2000, found deficits when compared with the general populations of Iowa and North Carolina. Overall rates of morbidity and mortality from cardiovascular disease, diabetes, chronic obstructive pulmonary disease, all cancers, and lung, esophageal, and stomach cancer were all reduced (1). Some of these deficits were likely due to the healthy-worker effect, observed when occupational cohorts, typically in good health, are compared with the general population (13, 14), which can mask risks associated with occupational exposures. With an additional 750,976 person-years of follow-up, we enhanced our prior analysis by examining mortality rates in the cohort from additional rare causes of death. We also made a formal adjustment to account for the healthy-worker effect.

MATERIALS AND METHODS

Study population

The AHS includes 52,394 private pesticide applicators (mainly farmers) in North Carolina and Iowa, 4,916 commercial applicators in Iowa, and 32,346 spouses of farmers. Applicators enrolled in the study from 1993 to 1997 at pesticide licensing facilities by completing a self-administered questionnaire. A spouse questionnaire was sent home with the applicator for his or her spouse to complete and return by mail. Institutional review boards of the National Institutes of Health and its contractors approved the study; consent was implied by return of the questionnaire. At enrollment, the number of farmers registered represented 82% of those eligible, the number of commercial applicators enrolled represented 47% of those licensed in Iowa, and 75% of spouses of farmers enrolled. In general, commercial applicators tended to be younger than farmers and applied pesticides more days per year. Except for all-cause and all-cancer deaths, we combined farmers and commercial applicators into a single group named applicators because too few deaths occurred among commercial applicators for stand-alone analysis.

Outcome classification

Person-year accumulation extended from enrollment through the end of follow-up (December 31, 2007) or the date of death. Deaths were identified through annual linkage with death registries in North Carolina and Iowa and the National Death Index. We coded the underlying cause of death according to the edition of the *International Classification of Diseases* that was in effect at the time of death (Ninth or Tenth) (15, 16).

Statistical analysis

We calculated standardized mortality ratios (SMRs) using AHS data release AHSREL0905.00, distinguishing results by applicator status (applicator or spouse). We used the National Institute for Occupational Safety and Health Life Table Analysis System.Net version 2.0.16 (Cincinnati, Ohio) (17, 18), which groups deaths into 28 major and 119 minor categories, to calculate SMRs for any category with $\geq$5 deaths. The program groups some cancers together. For the general population comparison, state-specific rates were stratified by race, gender, and 5-year age and calendar time period. Rates for 2005 were assumed to apply through 2007. We calculated summary SMRs from the state-specific observed and expected counts and used a formula based on Byar's approximation to the exact Poisson test (19) to calculate 95% 2-sided confidence intervals.

Several statistical approaches for reduction of the healthy-worker effect in occupational studies have been suggested. For instance, instead of comparing the primary cohort with the general population, we could compare it with a different occupational cohort (20). A comparable occupational population in North Carolina and Iowa would be our preferred reference group; however, none are readily available. An alternative would be to compare the observed and expected counts for each specific cause of interest with an independent referent set of values consisting of the all-cause observed and expected values minus the observed and expected values from the outcome of interest. Thus, we define the relative SMR (rSMR) as the ratio of the cause-specific SMR to the SMR for all other causes, omitting the cause of interest (i.e., $rSMR_x = SMR_x/SMR_{\text{not } x}$). This approach allows us to calculate confidence limits for rSMRs using standard procedures (19).

Because SMRs represent weighted sums of stratum-specific SMRs, a comparison of 2 SMRs is informative if either of the following 2 conditions is met: 1) all stratum-specific SMRs are the same within each disease subgroup ($cause_x$ and $cause_{\text{not } x}$) (no heterogeneity across state, race, gender, age, or calendar period); or 2) within each stratum, the stratum-specific weight for $cause_x$ equals the stratum-specific weight for $cause_{\text{not } x}$ (a stratum-specific weight for a given cause is the expected number of deaths in that stratum divided by the total expected number of deaths across all strata) (19). To examine these conditions, we computed stratum-specific SMRs and weights for selected common and rare causes of death. We did not observe heterogeneity and thus have found no evidence to contradict the validity of the rSMRs.

To calculate rSMRs, we used Poisson regression in Statistical Analysis Software version 9.2 (SAS Institute, Inc., Cary, North Carolina), because for each $cause_x$, the observed deaths for $cause_x$ and $cause_{\text{not } x}$ are independent Poisson variables. This approach is related to comparing SMRs for exposed and unexposed groups as described by Breslow and Day (19). We calculated rSMRs for chronic diseases only, not for injuries, which we do not believe would be influenced by the healthy-worker effect.

RESULTS

Applicators were mainly male and spouses were mainly female in this predominantly white cohort (Table 1). Among 89,656 applicators and spouses, there were 6,419 deaths: 4,675 farmers, 205 commercial applicators, and 1,539 spouses. The mean follow-up period was 13.4 years, providing 1,198,129 person-years (farmers, 696,419; commercial applicators, 67,484; spouses, 434,227). Although most applicators were from Iowa (64%), more deaths occurred among applicators in North Carolina (57%), which is consistent with the overall older age of the North Carolina sample. Decedents were older and had more years of applying pesticides at enrollment than did the overall cohort.

Compared with the general populations of North Carolina and Iowa, applicators in the cohort were less likely to die from all causes (SMR = 0.54, 95% confidence interval (CI): 0.52, 0.55). The all-cause mortality rate for farmers (SMR = 0.54, 95% CI: 0.52, 0.55) was similar to that of commercial applicators (SMR = 0.59, 95% CI: 0.52, 0.68). Spouses also experienced lower mortality rates during the study period (all-cause SMR = 0.52, 95% CI: 0.50, 0.55).

Injury

Applicators experienced significantly higher rates of mortality from certain unintentional fatal injuries than did the general population (Table 2). Incidence of machinery-related deaths (SMR = 4.15, 95% CI: 3.18, 5.31) was most elevated, followed by motor vehicle nontraffic accidents (SMR = 2.80, 95% CI: 1.81, 4.14) and collisions with objects (SMR = 2.12, 95% CI: 1.25, 3.34). Mortality rates among applicators were lower than in the general population for motor vehicle accidents involving pedestrians, falls, accidental poisoning, and violence.

Among spouses, the rate of injury mortality was not significantly elevated compared with the general population. Transportation-related deaths were reduced, especially deaths from motor vehicle accidents in which the driver was injured (SMR = 0.56, 95% CI: 0.31, 0.92). The numbers of fatal falls and of deaths from violence were also lower than expected.

Noncancer internal causes of death

The mortality rate from nearly all noncancer internal causes of death was significantly lower among applicators than in the general population (Table 3). Death rates from heart disease were half those expected (SMR = 0.54, 95% CI: 0.51, 0.56), as were death rates from other diseases of the circulatory system (cerebrovascular and arterial diseases; SMR = 0.51, 95% CI: 0.46, 0.57). We also observed a reduced rate of mortality from diabetes. Rates of death from chronic lung and liver diseases commonly associated with tobacco and alcohol use were significantly lower (e.g., chronic obstructive pulmonary disease (SMR = 0.31, 95% CI: 0.26, 0.36) and cirrhosis (SMR = 0.24, 95% CI: 0.16, 0.34)). No SMRs for noncancer internal causes were significantly greater than 1.0.

Compared with the general population, spouses also experienced lower rates of mortality from most noncancer internal causes (Table 3). Rates of death from heart disease and other circulatory diseases were both near half the expected rates (SMR = 0.47, 95% CI: 0.42, 0.53; and SMR = 0.55, 95% CI: 0.46, 0.64, respectively). Mortality rates were also significantly reduced for diseases of the respiratory, digestive, and genitourinary systems and for diabetes. Like applicators, spouses experienced fewer tobacco- and alcohol-related deaths; for example, rates of both chronic obstructive pulmonary disease (SMR = 0.27, 95% CI: 0.20, 0.35) and cirrhosis (SMR = 0.40, 95% CI: 0.22, 0.67) showed significant deficits compared with the general population.

Cancer

Among applicators, the number of deaths from all cancers combined was significantly lower than expected (SMR = 0.61, 95% CI: 0.58, 0.64). For commercial applicators, the all-cancer SMR was significantly reduced when compared with the general population (72 deaths; SMR = 0.75, 95% CI: 0.59, 0.93). The same was true for farmers (1,372 deaths; SMR = 0.60, 95% CI: 0.57, 0.64). Mortality rates for several individual cancer sites (Table 4) were also lower than expected, including the digestive system, lung, prostate, bladder, and brain. Rates of cancers of the eye, ovary, and thyroid were not significantly elevated among applicators.

Spouses also experienced a significantly lower rate of all cancers combined compared with the general population (all-cancer SMR = 0.65, 95% CI: 0.60, 0.70). Fewer deaths than expected were observed for cancers of the digestive system and of female genital organs (Table 4). Rates of death from lung, breast, and ovarian cancer were also significantly lower than expected. Rates of leukemia and non-Hodgkin's lymphoma were elevated, but not significantly so.

rSMRs for cancer deaths

The rSMR analysis for cancer mortality identified some aspects that were potentially masked in the SMR analysis (Table 5). For applicators, the rSMR analysis showed that the rates of death from all cancers were greater than expected relative to other causes within the cohort (rSMR = 1.20, 95% CI: 1.13, 1.27). This finding was true for both commercial applicators (rSMR = 1.39, 95% CI: 1.11, 1.75) and farmers (rSMR = 1.18, 95% CI: 1.11, 1.26). Among all applicators, rSMRs were significantly elevated for prostate cancer, multiple myeloma, leukemia, non-Hodgkin's lymphoma, melanoma, brain cancer, kidney cancer, and digestive cancers (specifically cancers of the intestine and pancreas). Relative mortality ratios from cancers of the eye (rSMR = 3.69, 95% CI: 1.54, 8.87), ovary (rSMR = 3.00, 95% CI: 1.25, 7.21), and thyroid (rSMR = 2.85, 95% CI: 1.43, 5.71) were also significantly elevated, but numbers were small. Only the combination of lung, trachea, and bronchus cancers (rSMR = 0.78, 95% CI: 0.71, 0.86) and other respiratory cancers (rSMR = 0.27, 95% CI: 0.11, 0.65) had significantly reduced relative mortality.

Table 1. Characteristics (%) of the Agricultural Health Study Cohort Participants and Decedents From North Carolina and Iowa From Study Enrollment (1993–1997) Through 2007

	Applicators		Spouses	
	Cohort (n = 57,310)	Deceased (n = 4,880)	Cohort (n = 32,346)	Deceased (n = 1,539)
Age at enrollment, years				
<40	34	6	31	4
40–59	47	32	52	36
60–79	18	59	17	57
≥80	0	3	0	3
Age in 2006 or age at death, years				
<40	8	2	5	1
40–59	50	19	53	21
60–79	37	58	39	60
≥80	5	21	4	17
State				
Iowa	64	43	67	53
North Carolina	36	57	33	47
Race				
Asian/Pacific Islander	0	0	0	0
Black	2	5	1	2
Native American	0	1	0	1
White	97	94	98	97
Other	0	0	0	0
Gender				
Male	97	98	1	2
Female	3	2	99	98
Education level				
High school or less	57	73	46	62
Beyond high school	43	27	54	38

Table continues

Like with applicators, death rates among spouses from all cancers were elevated relative to other causes in the cohort (all-cancer rSMR = 1.43, 95% CI: 1.30, 1.58; Table 5). Leukemia (rSMR = 2.10, 95% CI: 1.49, 2.97) and non-Hodgkin's lymphoma (rSMR = 2.15, 95% CI: 1.58, 2.93) had the highest rSMRs. For spouses, cancers of the breast, ovary, brain, and digestive system (specifically, the intestine and pancreas) showed rSMRs that were significantly greater than 1.0. Neoplasms of benign and unspecified nature were also significantly elevated relative to all other causes of death. Only lung cancer had a significantly decreased rSMR.

Relative SMRs for noncancer internal causes of death

For noncancer internal causes of death, only 1 elevated rSMR was observed among applicators and spouses (Table 6). Among applicators, the rate of death from cardiomyopathy was elevated (rSMR = 1.29, 95% CI: 1.03, 1.62) relative to all other causes. Also relative to all other causes, findings were similar to those expected for heart disease (rSMR = 0.99, 95% CI: 0.93, 1.06) and other circulatory diseases (rSMR = 0.95, 95% CI: 0.86, 1.06). The rSMRs for cirrhosis, chronic obstructive pulmonary disease, pneumonia, diabetes, and mental and psychological disorders were significantly less than 1.0.

For spouses, the rSMR analysis showed that the rate of mortality from heart disease was lower than expected (rSMR = 0.88, 95% CI: 0.77, 1.00); specifically, the rate of ischemic heart disease remained lower than expected (rSMR = 0.84, 95% CI: 0.73, 0.97). However, rSMRs for other circulatory diseases did not differ significantly from 1.0, and neither did the rSMR for diabetes. The rSMRs for mental and psychological disorders and respiratory diseases were significantly lower than expected.

DISCUSSION

Consistent with previous mortality findings from this cohort (1), we observed lower overall mortality rates in participants in the AHS than in the general populations of North Carolina and Iowa. The AHS is larger than most agricultural cohorts, and this analysis not only provides new information

Table 1. Continued

	Applicators		Spouses	
	Cohort (n = 57,310)	Deceased (n = 4,880)	Cohort (n = 32,346)	Deceased (n = 1,539)
Smoking history				
Never	53	36	72	64
Past	30	42	17	21
Current	17	22	10	15
Alcohol consumption, drinks/month				
0	33	53	46	67
<1	13	11	25	16
1–5	14	10	15	8
6–10	11	6	7	4
>10	29	19	8	7
Body mass index[a], kg/m^2				
<25	26	29	49	44
25–30	51	48	32	34
>30	23	23	19	23
Years spent applying pesticides				
Never	2	1	51	61
≤1	3	2	5	4
2–5	13	9	13	7
6–10	16	13	9	6
11–20	32	23	11	9
21–30	23	25	6	5
>30	12	26	4	9

[a] Defined as weight in kg divided by height in meters squared.

on rare causes of death but is also more recent than most of the previously published studies. Similar to what was seen in other studies (2, 4, 5, 21), applicators and spouses in our study showed a mortality experience reflective of a healthy lifestyle. Despite this, applicators had increased rates of death due to unintentional fatal injuries compared with the general population. Additionally, after adjusting for the lower overall mortality rate of the cohort, applicators experienced higher rates of mortality from lymphohematopoietic cancers, melanoma, and malignancies of the digestive system, prostate, kidney, brain, thyroid, eye, and ovary, as well as from cardiomyopathy. Spouses experienced higher rates of death from lymphohematopoietic cancers and malignancies of the digestive system, breast, ovary, and brain after adjustment for the lower overall mortality rate.

The increased risk of unintentional fatal injuries among applicators is consistent with what has been seen in other studies (7–9) but was not observed previously in this cohort (1), possibly because there were fewer deaths. Farmers face significant occupational hazards from machines, as highlighted by the observed SMRs, which exceeded 2 for machine injury, motor vehicle nontraffic accidents, and collisions with objects. Deaths from machine accidents and motor vehicle nontraffic accidents may be related, as tractor deaths can be classified as either, depending on whether they occur on or off the roadway (15, 16). Combining deaths from these 2 categories, we observed an annual rate of 6.9 machine-related deaths per 100,000 person-years (which includes deaths from tractor rollovers), which is approximately 25% higher than the 2007 US annual average of 5.5 tractor-overturn deaths per 100,000 person-years in the agricultural population, as calculated from a report by the National Institute for Occupational Safety and Health (22). Animals are a known risk factor for fatal and nonfatal farm injury (23, 24); however, we did not see an increased rate of animal-related fatalities. Although Iowa is ranked seventh in the United States for cattle and calf production, poultry and hogs are the most common livestock raised in Iowa and North Carolina (25). Therefore, our failure to observe an elevated animal-related fatality rate may be due to a lower level of large animal production than in other agricultural regions.

Consistent with our previous mortality analysis (1), we continued to observe lower rates for several major causes of death, including cardiovascular disease, all cancers, lung cancer, and diabetes. The all-cause mortality rate was approximately half that expected, similar to the previous mortality study and other studies of farmers (1–5). The higher physical activity level inherent to farming likely plays a significant protective role in these deficits. The deficit in smoking-related deaths (e.g., chronic obstructive pulmonary disease and lung cancer) is reflective of a higher prevalence of never smokers (53% of applicators and 72% of spouses,

Table 2. Standardized Mortality Ratios for Deaths From Injuries in the Agricultural Health Study Cohort, North Carolina and Iowa, 1993–2007[a]

Cause of Death	Applicators ($n = 496$)				Spouses ($n = 66$)			
	Observed	Expected	SMR[b]	95% CI[c]	Observed	Expected	SMR[b]	95% CI[c]
Transportation injuries	167	196	0.85*	0.73, 0.99	29	50	0.58*	0.39, 0.83
Railway, water, and air transportation	8	12	0.67	0.29, 1.32	0			
Motor vehicle—driver	99	117	0.85	0.69, 1.03	15	27	0.56*	0.31, 0.92
Motor vehicle—passenger	9	15	0.59	0.27, 1.12	10	12	0.81	0.39, 1.49
Motor vehicle—pedestrian	5	14	0.36*	0.12, 0.85	1			
Motor vehicle—other and unspecified	18	23	0.78	0.46, 1.24	2			
Motor vehicle—nontraffic	25	9	2.80*	1.81, 4.14	0			
Other transportation injuries	3	6			1			
Falls	43	68	0.63*	0.46, 0.85	6	18	0.34*	0.12, 0.73
Falls into holes	12	15	0.78	0.40, 1.37	3			
Falls from buildings or structures	7	4	1.76	0.65, 3.84	0			
Other falls	24	49	0.49*	0.32, 0.73	3			
Other injury (major)	164	169	0.97	0.83, 1.13	17	41	0.42*	0.24, 0.67
Collision with objects	18	9	2.12*	1.25, 3.34	1			
Machine	62	15	4.15*	3.18, 5.31	3			
Suffocation	15	22	0.69	0.39, 1.14	3			
Fire	8	15	0.53	0.23, 1.04	0			
Accidental poisoning	15	39	0.39*	0.22, 0.64	4			
Medical complications	7	10	0.67	0.27, 1.38	3			
Forces of nature	5	6	0.83	0.34, 2.41	0			
Other injuries	34	53	0.64*	0.44, 0.90	3			
Violence	122	219	0.56*	0.46, 0.67	14	36	0.39*	0.21, 0.65
Intentional self-harm	106	187	0.57*	0.46, 0.69	9	28	0.32*	0.15, 0.61
Assault and homicide	16	32	0.50*	0.28, 0.81	5	8	0.61	0.20, 1.43

Abbreviations: CI, confidence interval; SMR, standardized mortality ratio.
* Significant at $P = 0.05$ based on confidence interval excluding 1.0.
[a] All estimates were adjusted for age, calendar year, gender, race, and state.
[b] SMRs were not estimated for <5 observed deaths.
[c] Calculated using Byar's approximation to the Poisson exact test.

versus 46% of US adults ≥45 years of age in 1995 (26)). Although these deficits may reflect a healthy lifestyle, they are also consistent with the healthy-worker effect that is typically observed in working populations.

To account for the lower overall mortality rate in the cohort, we used an rSMR analysis that compared the SMR for each cause with the SMRs for all other causes. These rSMRs were meant to be exploratory and to be interpreted in relation to the mortality rates from all other causes of death in the cohort. In doing so, we identified an unusually high relative mortality rate from lymphohematopoietic cancers, digestive cancers, and cancers of the prostate, breast, brain, and ovary that were not apparent in the SMR analysis. We did not observe any increased rSMRs for noncancer internal causes, with the exception of cardiomyopathy among applicators.

We observed increased rSMRs for lymphohematopoietic cancers for applicators and spouses, consistent with meta-analyses among farmers (27–29). Svec et al. (30) noted that an increased risk of lymphohematopoietic cancers was associated with occupational exposure to animals, which occurred primarily in agricultural settings, though this effect could have been confounded by pesticides. Previous findings from the AHS have implicated several individual pesticides as being associated with these cancers (31).

Farmers are at a higher risk of prostate cancer (32), which is possibly associated with specific pesticides (33, 34). Chlorinated pesticides and methyl bromide were significantly associated with increased risk among applicators >50 years of age (35). Increased prostate cancer mortality rates have been seen in some (5, 36) but not all (7, 21) other farming populations. We observed an elevated mortality ratio for prostate cancer only in the rSMR analysis.

An analysis of cancer incidence in the AHS through 2002 identified an increased incidence of ovarian cancer among the 1,563 female applicators but not among the 32,127 female spouses (37). We observed increased rates of ovarian cancer death among applicators and spouses relative to all

Table 3. Standardized Mortality Ratios for Noncancer Internal Causes of Death in the Agricultural Health Study Cohort, North Carolina and Iowa, 1993–2007[a]

Cause of Death	Applicators (n = 2,743)				Spouses (n = 797)			
	Observed	Expected	SMR[b]	95% CI[c]	Observed	Expected	SMR[b]	95% CI[c]
Blood and blood-forming organs' diseases	27	40	0.68*	0.45, 0.98	12	13	0.89	0.46, 1.56
Coagulation and hemorrhagic conditions	7	9	0.76	0.31, 1.57	4			
Other diseases of blood-forming organs	20	31	0.65	0.40, 1.00	8	10	0.82	0.35, 1.62
Diabetes mellitus	98	242	0.48*	0.33, 0.49	42	95	0.44*	0.32, 0.60
Mental and psychological disorders	33	139	0.24*	0.16, 0.33	9	45	0.20*	0.09, 0.38
Alcoholism	10	46	0.22*	0.10, 0.40	0			
Other mental disorders	23	93	0.25*	0.16, 0.37	9	40	0.23*	0.10, 0.43
Nervous system disorders	126	272	0.46*	0.39, 0.55	64	114	0.56*	0.43, 0.72
Multiple sclerosis	0				3			
Other nervous system diseases	126	260	0.48*	0.40, 0.58	61	104	0.59*	0.45, 0.76
Heart diseases	1,376	2,569	0.54*	0.51, 0.56	292	620	0.47*	0.42, 0.53
Rheumatic heart disease	8	12	0.69	0.30, 1.36	7	10	0.72	0.29, 1.49
Hypertension with heart disease	40	78	0.52*	0.37, 0.70	7	24	0.29*	0.12, 0.59
Ischemic heart disease	1,099	2,105	0.52*	0.49, 0.55	211	467	0.45*	0.39, 0.52
Chronic diseases of the endocardium	32	50	0.64*	0.44, 0.90	14	20	0.70	0.38, 1.17
Cardiomyopathy	75	109	0.69*	0.54, 0.87	13	27	0.48*	0.26, 0.83
Conductive disorder	61	104	0.59*	0.45, 0.75	22	34	0.64*	0.40, 0.97
Other heart diseases	61	112	0.54*	0.42, 0.70	18	38	0.47*	0.28, 0.75
Other circulatory system diseases	376	731	0.51*	0.46, 0.57	147	270	0.55*	0.46, 0.64
Cerebrovascular disease	236	457	0.52*	0.45, 0.59	105	176	0.60*	0.49, 0.72
Hypertension without heart disease	15	42	0.35*	0.20, 0.58	6	18	0.34*	0.13, 0.74
Diseases of arteries/veins/lymphatic vessels	125	231	0.54*	0.45, 0.64	36	76	0.47*	0.33, 0.65
Respiratory system diseases	346	903	0.38*	0.34, 0.43	92	303	0.30*	0.24, 0.37
Pneumonia	76	192	0.40*	0.31, 0.50	17	58	0.29*	0.17, 0.47
Chronic obstructive pulmonary disease	165	539	0.31*	0.26, 0.36	50	187	0.27*	0.20, 0.35
Asthma	8	10	0.79	0.34, 1.56	4			
Other respiratory diseases	97	162	0.60*	0.49, 0.73	21	50	0.42*	0.26, 0.64
Digestive system diseases	125	324	0.39*	0.32, 0.46	50	109	0.46*	0.34, 0.61
Stomach and duodenum diseases	12	21	0.58	0.30, 1.02	5	7	0.72	0.23, 1.68
Hernia and intestinal obstruction	11	19	0.58	0.29, 1.04	2			
Cirrhosis and other liver diseases	33	138	0.24*	0.16, 0.34	14	35	0.40*	0.22, 0.67
Other digestive system diseases	69	146	0.47*	0.37, 0.60	29	58	0.50*	0.33, 0.72
Skin and subcutaneous tissue diseases	5	9	0.53	0.17, 1.23	1			
Musculoskeletal and connective system diseases	15	30	0.50*	0.28, 0.83	14	24	0.58*	0.32, 0.97
Arthritis and spondylitis	6	12	0.50	0.18, 1.08	6	8	0.73	0.27, 1.59
Other musculoskeletal system diseases	9	18	0.51*	0.23, 0.96	8	16	0.50*	0.21, 0.98
Genitourinary system diseases	69	141	0.49*	0.38, 0.62	28	52	0.53*	0.35, 0.77
Acute glomerulonephritis, renal failure	7	17	0.42*	0.17, 0.86	2			
Chronic and unspecified nephritis, renal failure	43	79	0.54*	0.39, 0.73	15	26	0.58*	0.32, 0.96
Other genitourinary diseases	19	46	0.42*	0.25, 0.65	11	21	0.52*	0.26, 0.94
Tuberculosis and human immunodeficiency virus	3				0			
Symptomatic and ill-defined conditions	15	40	0.37*	0.21, 0.62	1			
Other and unspecified causes	129	252	0.51*	0.43, 0.61	45	98	0.46*	0.33, 0.61

Abbreviations: CI, confidence interval; SMR, standardized mortality ratio.

* Significant at $P = 0.05$ based on confidence interval excluding 1.0.

[a] All estimates were adjusted for age, calendar year, gender, race, and state.

[b] SMRs were not estimated for <5 observed deaths.

[c] Calculated using Byar's approximation to the Poisson exact test.

Table 4. Standardized Mortality Ratios for Deaths From Cancers and Benign-Nature Neoplasms in the Agricultural Health Study Cohort, North Carolina and Iowa, 1993–2007[a]

Cause of Death	Applicators (n = 1,641)				Spouses (n = 676)			
	Observed	Expected	SMR[b]	95% CI[c]	Observed	Expected	SMR[b]	95% CI[c]
All cancers	1,624	2,662	0.61*	0.58, 0.64	665	1,022	0.65*	0.60, 0.70
Buccal and pharynx	16	47	0.34*	0.19, 0.55	3			
Digestive and peritoneum	422	619	0.68*	0.62, 0.75	141	197	0.72*	0.60, 0.84
Esophagus	48	94	0.51*	0.38, 0.68	3			
Stomach	26	50	0.52*	0.34, 0.76	5	12	0.42*	0.14, 0.99
Intestine	158	211	0.75*	0.64, 0.88	68	80	0.85	0.66, 1.07
Rectum	32	46	0.69*	0.47, 0.97	4			
Biliary (liver and gallbladder)	50	71	0.70*	0.52, 0.93	18	22	0.81	0.48, 1.28
Pancreas	103	138	0.75*	0.61, 0.91	38	52	0.72*	0.51, 0.99
Peritoneum, other, and unspecified site	5	8	0.63	0.21, 1.48	5	6	0.91	0.29, 2.12
Respiratory	422	1,005	0.42*	0.38, 0.46	110	293	0.38*	0.31, 0.45
Trachea, bronchus, and lung	417	971	0.43*	0.39, 0.47	108	287	0.38*	0.31, 0.45
Other respiratory system	5	34	0.15*	0.05, 0.34	2			
Breast	11	12	0.94	0.47, 1.69	136	170	0.80*	0.67, 0.94
Female genital organs	8	5	1.46	0.63, 2.88	71	114	0.62*	0.49, 0.79
Cervix	1				4			
Uterus, other, and unspecified site	1				19	27	0.70	0.42, 1.09
Ovary	5	3	1.61	0.52, 3.76	45	64	0.70*	0.51, 0.94
Other female genital organs	1				3			
Prostate	171	210	0.81*	0.70, 0.95	1			
Urinary	106	146	0.73*	0.60, 0.88	21	30	0.69	0.43, 1.06
Kidney	71	82	0.87	0.68, 1.09	12	20	0.61	0.32, 1.07
Bladder and other urinary site	35	64	0.55*	0.38, 0.76	9	11	0.83	0.38, 1.58
Other and unspecified site	230	345	0.67*	0.58, 0.76	96	118	0.81*	0.66, 0.99
Bone	3				2			
Melanoma	38	50	0.76	0.54, 1.05	10	13	0.75	0.36, 1.38
Other skin	4				1			
Mesothelioma	8	11	0.71	0.29, 1.46	2			
Connective tissue	9	14	0.65	0.30, 1.46	6	6	1.00	0.37, 2.18
Brain and other nervous system	59	78	0.76*	0.58, 0.98	25	30	0.83	0.54, 1.23
Eye	5	3	1.98	0.64, 4.62	3			
Thyroid	8	5	1.53	0.66, 3.02	1			
Other and unspecified site	96	163	0.59*	0.48, 0.72	46	61	0.76	0.56, 1.01
Lymphatic and hematopoietic	238	271	0.88*	0.77, 1.00	86	88	0.97	0.78, 1.20
Hodgkin's disease	5	5	1.03	0.34, 2.41	1			
Non-Hodgkin's lymphoma	90	108	0.84	0.67, 1.03	42	38	1.11	0.80, 1.50
Multiple myeloma	52	51	1.01	0.76, 1.33	10	18	0.56	0.27, 1.04
Leukemia	91	107	0.85	0.68, 1.04	33	30	1.09	0.75, 1.53
Benign and unspecified nature neoplasms	17	26	0.66	0.38, 1.06	11	11	1.05	0.52, 1.87

Abbreviations: CI, confidence interval; SMR, standardized mortality ratio.

* Significant at $P = 0.05$ based on confidence interval excluding 1.0.

[a] All estimates were adjusted for age, calendar year, gender, race, and state.

[b] SMRs were not estimated for <5 observed deaths.

[c] Calculated using Byar's approximation to the Poisson exact test.

Table 5. Relative Standardized Mortality Ratios for Deaths From Cancers and Benign-Nature Neoplasms in the Agricultural Health Study Cohort, North Carolina and Iowa, 1993–2007[a]

Cause of Death	Applicators (n = 1,641)		Spouses (n = 676)	
	rSMR[b]	95% CI[c]	rSMR[b]	95% CI[c]
All cancers	1.20*	1.13, 1.27	1.43*	1.30, 1.58
Buccal and pharynx	0.63	0.38, 1.03		
Digestive and peritoneum	1.29*	1.17, 1.43	1.41*	1.18, 1.67
Esophagus	0.95	0.71, 1.26		
Stomach	0.96	0.66, 1.42	0.81	0.34, 1.95
Intestine	1.41*	1.20, 1.65	1.65*	1.29, 2.10
Rectum	1.28	0.91, 1.82		
Biliary (liver and gallbladder)	1.31	0.99, 1.73	1.56	0.98, 2.48
Pancreas	1.40*	1.15, 1.70	1.40*	1.01, 1.93
Peritoneum, other, and unspecified site	1.18	0.49, 2.83	1.74	0.72, 4.18
Respiratory	0.76*	0.69, 0.84	0.70*	0.57, 0.85
Trachea, bronchus, and lung	0.78*	0.71, 0.86	0.70*	0.57, 0.85
Other respiratory system	0.27*	0.11, 0.65		
Breast	1.76	0.97, 3.17	1.58*	1.32, 1.88
Female genital organs	2.72*	1.36, 5.45	1.20	0.95, 1.53
Cervix				
Uterus, other, and unspecified site			1.34	0.85, 2.11
Ovary	3.00*	1.25, 7.21	1.35*	1.00, 1.82
Other female genital organs				
Prostate	1.53*	1.31, 1.78		
Urinary	1.36*	1.12, 1.65	1.33	0.86, 2.04
Kidney	1.62*	1.28, 2.05	1.18	0.67, 2.07
Bladder and other urinary site	1.02	0.73, 1.42	1.59	0.83, 3.06
Other and unspecified site	1.25*	1.10, 1.43	1.59*	1.29, 1.95
Bone				
Melanoma	1.42*	1.03, 1.96	1.44	0.77, 2.69
Other skin				
Mesothelioma	1.32	0.66, 2.64		
Connective tissue	1.21	0.63, 2.32	1.92	0.86, 4.28
Brain and other nervous system	1.42*	1.10, 1.83	1.60*	1.08, 2.37
Eye	3.69*	1.54, 8.87		
Thyroid	2.85*	1.43, 5.71		
Other and unspecified site	1.10	0.90, 1.34	1.47*	1.09, 1.97
Lymphatic and hematopoietic	1.67*	1.46, 1.90	1.92*	1.54, 2.38
Hodgkin's disease	1.93	0.80, 4.63		
Non-Hodgkin's lymphoma	1.57*	1.27, 1.93	2.15*	1.58, 2.93
Multiple myeloma	1.89**	1.44, 2.48	1.08	0.58, 2.01
Leukemia	1.59*	1.29, 1.96	2.10*	1.49, 2.97
Benign and unspecified nature neoplasms	1.23	0.76, 1.98	2.01*	1.11, 3.63

Abbreviations: CI, confidence interval; rSMR, relative standardized mortality ratio.
* Significant at $P = 0.05$ based on confidence interval excluding 1.0.
[a] All estimates were adjusted for age, calendar year, gender, race, and state.
[b] SMRs were not estimated for <5 observed deaths.
[c] Calculated using Byar's approximation to the Poisson exact test.

Table 6. Relative Standardized Mortality Ratios for Noncancer Internal Causes of Death in the Agricultural Health Study Cohort, North Carolina and Iowa, 1993–2007[a]

Cause of Death	Applicators (n = 2,743)		Spouses (n = 797)	
	rSMR[b]	95% CI[c]	rSMR[b]	95% CI[c]
Blood and blood-forming organs' diseases	1.26	0.86, 1.84	1.72	0.97, 3.03
Coagulation and hemorrhagic conditions	1.42	0.67, 2.97		
Other diseases of blood-forming organs	1.58	0.99, 2.50	1.57	0.78, 3.15
Diabetes mellitus	0.75*	0.61, 0.91	0.84	0.62, 1.14
Mental and psychological disorders	0.44*	0.31, 0.62	0.38*	0.20, 0.72
Alcoholism	0.40*	0.21, 0.74		
Other mental disorders	0.46*	0.30, 0.69	0.43*	0.22, 0.83
Nervous system disorders	0.86	0.72, 1.03	1.08	0.84, 1.38
Multiple sclerosis				
Other nervous system diseases	0.90	0.75, 1.07	1.13	0.88, 1.46
Heart diseases	0.99	0.93, 1.06	0.88	0.77, 1.00
Rheumatic heart disease	1.28	0.64, 2.57	1.39	0.66, 2.91
Hypertension with heart disease	0.96	0.70, 1.31	0.55	0.26, 1.15
Ischemic heart disease	0.96	0.90, 1.03	0.84*	0.73, 0.97
Chronic diseases of the endocardium	1.18	0.84, 1.68	1.33	0.79, 2.26
Cardiomyopathy	1.29*	1.03, 1.62	0.92	0.54, 1.60
Conductive disorder	1.09	0.85, 1.40	1.24	0.81, 1.88
Other heart diseases	1.01	0.79, 1.30	0.91	0.57, 1.44
Other circulatory system diseases	0.95	0.86, 1.06	1.05	0.88, 1.24
Cerebrovascular disease	0.96	0.84, 1.09	1.15	0.95, 1.41
Hypertension without heart disease	0.66	0.40, 1.09	0.65	0.29, 1.45
Diseases of arteries/veins/lymphatic vessels	1.00	0.84, 1.20	0.90	0.65, 1.25
Respiratory system diseases	0.69*	0.62, 0.77	0.55*	0.45, 0.68
Pneumonia	0.73*	0.58, 0.92	0.56*	0.34, 0.90
Chronic obstructive pulmonary disease	0.55*	0.47, 0.65	0.49*	0.37, 0.66
Asthma	1.47	0.74, 2.95		
Other respiratory diseases	1.11	0.91, 1.36	0.80	0.52, 1.24

Table continues

other causes. The larger rSMR for applicators compared with spouses is likely a chance occurrence, reflecting the small number of female applicators in the cohort. We also observed increased breast cancer relative mortality among spouses in the cohort. Although risk was not significantly increased among applicators, rSMRs were similar (spouses, 1.58; applicators, 1.76) and few applicators were female.

We conducted our analyses separately for applicators and spouses, as applicators are expected to have greater occupational exposures to pesticides and other farm risk factors than their spouses. Applicators are licensed to apply restricted-use pesticides; however, 58% of spouses in Iowa and 45% in North Carolina reported having applied at least 1 pesticide at enrollment (38). Both men and women were represented among the applicators, with 1,563 female applicators contributing 20,886 person-years to the analysis, and thus providing a unique occupationally exposed group in which we could examine female-related cancers.

The cohort includes both private and commercial pesticide applicators; private applicators (mainly farmers) dominate the cohort, but both groups use similar pesticides. Commercial applicators accounted for only 205 of the 4,880 deaths observed for applicators; thus, their inclusion in the study population had little influence on the overall findings. Additionally, when analyzed separately, the mortality rates for both groups were similar: We observed that both farmers and commercial applicators experienced significantly fewer deaths than expected overall and had elevated cancer risk in the rSMR analyses. Although an Australian study (39) focusing on cancer mortality and

Table 6. Continued

Cause of Death	Applicators (n = 2,743)		Spouses (n = 797)	
	rSMR[b]	95% CI[c]	rSMR[b]	95% CI[c]
Digestive system diseases	0.71*	0.59, 0.85	0.87	0.66, 1.16
Stomach and duodenum diseases	1.08	0.61, 1.91	1.38	0.57, 3.31
Hernia and intestinal obstruction	1.08	0.60, 1.95		
Cirrhosis and other liver diseases	0.44*	0.31, 0.62	0.76	0.45, 1.29
Other digestive system diseases	0.87	0.69, 1.11	0.96	0.66, 1.38
Skin and subcutaneous tissue diseases	0.98	0.41, 2.36		
Musculoskeletal and connective system diseases	0.93	0.56, 1.55	1.11	0.65, 1.87
Arthritis and spondylitis	0.92	0.41, 2.05	1.40	0.63, 3.13
Other musculoskeletal system diseases	0.94	0.49, 1.81	0.95	0.48, 1.91
Genitourinary system diseases	0.91	0.71, 1.15	1.02	0.70, 1.49
Acute glomerulonephritis, renal failure	0.78	0.37, 1.63		
Chronic and unspecified nephritis, renal failure	1.01	0.75, 1.37	1.11	0.67, 1.85
Other genitourinary diseases	0.77	0.49, 1.21	1.00	0.55, 1.81
Tuberculosis and human immunodeficiency virus				
Symptomatic and ill-defined conditions	0.69	0.42, 1.15		
Other and unspecified causes	0.95	0.80, 1.13	0.87	0.65, 1.18

Abbreviations: CI, confidence interval; rSMR, relative standardized mortality ratio.

* Significant at $P = 0.05$.

[a] All estimates were adjusted for age, calendar year, gender, race, and state.

[b] SMRs were estimated for <5 observed deaths.

[c] Calculated using Byar's approximation to the Poisson exact test.

incidence rates among pest-control operators found rates similar to those in the general population, Fleming et al. (5) noted SMRs <1.0 for most causes of death among commercial applicators in Florida.

SMR analyses are useful to assess the disease experience of a population relative to a general population; however, this strategy has some inherent limitations. Although we gain statistical stability by comparing data from our cohort with state and national rates, the ability to control for confounding is limited to factors reported on the death certificates. Those factors do not address the healthy-worker effect. We used the rSMR analysis, which allowed us to adjust for the overall disease experience in our study population. Both the SMR and rSMR analyses have limited ability to evaluate exposures that may contribute to elevated or lowered mortality rates. We relied on death certificates for our outcome measure. The overall validity of death certificates tends to be fairly high and is expected to be comparable across underlying causes of deaths occurring within a state (40, 41). By comparing the rates within states, we have comparable reporting for the cohort and population rates. We used the Life Table Analysis System.net program to calculate SMRs; this program groups deaths to reflect occupational hazards, as illustrated by the fine strata for falls and the peculiar combinations of cancers (e.g., colon and small intestine grouped as ''intestine''). All SMR analyses face limitations with regard to rare diseases. Our study benefited from its large sample size and high number of person-years of follow-up, which have more than doubled since the previous analysis (1).

In summary, our analysis of 6,419 deaths occurring from 1993 to 2007 among 89,656 pesticide applicators and spouses showed that applicators were at an elevated risk of death from machine injury. The cohort experienced a lower mortality rate overall when compared with the general population. After adjusting for the lower mortality of the cohort, we observed relatively higher rates of death among applicators from lymphohematopoietic cancers, melanoma, and malignancies of the digestive system, prostate, kidney, brain, thyroid, eye, and ovary. Among spouses, we observed higher adjusted mortality rates for lymphohematopoietic cancers and malignancies of the digestive system, breast, ovary, and brain. Extended follow-up of this cohort will provide valuable information through the accumulation of deaths from rare diseases as the cohort ages.

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