

Cancer incidence in the Agricultural Health Study

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Objectives This large, prospective cohort study of private applicators, commercial applicators, and spouses of farmer applicators was undertaken to ascertain the etiology of cancers elevated in agriculture.

Methods The participants were matched to cancer registry files in Iowa and North Carolina. Incident cases were identified from enrollment through 31 December 2002. Standardized incidence ratios (SIR) were used to compare the cancer incidence of the participants with that of the total population in the two states.

Results The overall cancer incidence among farmers [SIR 0.88, 95% confidence interval (95% CI) 0.84–0.91] and their spouses (SIR 0.84, 95% CI 0.80–0.90) were significantly lower than expected, particularly for respiratory and urinary cancers. Commercial pesticide applicators had an overall cancer incidence comparable with the expected (SIR 1.01, 95% CI 0.84–1.20). Smoking prevalence was significantly lower than the national average. Prostate cancer was elevated among private applicators (SIR 1.24, 95% CI 1.18–1.33) and commercial applicators (SIR 1.37, 0.98–1.86). Excess ovarian cancer was observed for female applicators (SIR 2.97, 95% CI 1.28–5.85), but not for female spouses (SIR 0.55, 95% CI 0.38–0.78). Female spouses had a significant excess of melanoma (SIR 1.64, 95% CI 1.24–2.09), which was not observed among pesticide applicators.

Conclusions Low overall cancer incidence rates seem to be a result of low overall smoking prevalence and other lifestyle factors, while excess cancer of the prostate and ovaries among applicators may be occupationally related. The excess risk of melanoma observed among spouses was unexpected.

Key terms agricultural exposure; cancer etiology; commercial applicator; farmer; melanoma; ovarian cancer; prostate cancer; spouse of farmer; standard incidence ratio.

Despite low mortality and cancer incidence rates overall, farmers and other agricultural populations may experience an excess risk of several cancers (1–20). These excesses have been observed in some, but not all, retrospective epidemiologic studies of agricultural workers in several countries (21). Excess risk has been observed for cancers of the lymphatic and hematopoietic system, connective tissue, skin, brain, prostate, stomach, and lips. Several of these tumors (brain, non-Hodgkin's lymphoma, multiple myeloma, and prostate) are increasing in the general population (22, 23). This change suggests that a common set of exposures may explain the higher

rates among farmers and the rising rates in the general population (5). Farmers, their families, and other pest control workers may have contact with a variety of potentially hazardous substances including pesticides, solvents, fuels and oils, engine exhaust, dust, and zoonotic viruses and other microbes (7). All of these exposures have potential health effects that need to be assessed. The multiplicity of these occupational exposures in the agricultural environment and the lifestyle of farm families (that is distinctive from typical urban lifestyles) present both challenges and opportunities for the epidemiologic assessment of cancer risk.

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Previous epidemiologic studies of farmers, other agricultural workers, and pesticide applicators have been limited by inadequate exposure information. In some studies, exposures were imputed from characteristics of the farm, the job, or the industry of the study participant. In other studies, exposure information was collected from the study participant directly but only after the onset of the disease under investigation, possibly resulting in recall bias. The use of retrospective histories of lifetime exposures in case-control studies has been criticized because of the opportunity for exposure misclassification that could be introduced, although, in most cases, this use would result in bias towards the null. In most previous studies, regardless of the study design, the statistical power has been limited.

The Agricultural Health Study was designed to mitigate previous design limitations by collecting detailed information about occupational and environmental pesticide exposures, other occupational exposures, lifestyle characteristics, and personal and family health histories prior to the onset of cancer in a large cohort of licensed pesticide applicators and their spouses (24). The information from the cohort is updated every 5 years by means of computer-assisted telephone interviews on the entire cohort. The occupational exposure information on individual pesticides collected in the study includes duration of use (years), frequency of use (applications days/year), and intensity of use (ie, application methods, protective equipment, work practices) (25). Updating the exposure data every 5 years should improve the accuracy of the data. The questionnaire data on pesticide exposure are validated with environmental and biological measurements of pesticides and metabolites, as well as direct observation of selected cohort members. The study is conducted in two important agricultural states, which are representative of agricultural practices in a large portion of the United States (ie, mid-west and southeast). Cancer incidence is ascertained by linking the cohort to the population-based cancer registries in Iowa and North Carolina. Loss to follow-up for determining cancer incidence is minimized by the use of the National Death Index to ascertain vital status and a variety of address registries, which help identify the year a study participant moved out of the states of Iowa and North Carolina and are, therefore, no longer available for cancer incidence follow-up.

The spouses of farmer applicators generally live near the fields where pesticide applications occur and are, therefore, exposed to relatively high environmental (ie, "bystander") exposures (26). Including spouses in the cohort makes it possible for the researchers to assess the potential hazards associated with nonoccupational agricultural exposures, which is a concern to a broad cross-section of the general population. Since many spouses also engage in some farming activities,

including pesticide mixing and application, spouses can also provide information about occupational exposures.

This is the first report on the overall cancer incidence among the study cohort. Etiologic investigations that focus on the exposure-response patterns of individual pesticides and cancer outcomes and investigations that focus on individual cancers and occupational exposures are the subject of separate reports.

Study population and methods

The Agricultural Health Study is a large prospective, cohort study of 89 658 people including 52 395 private applicators licensed to apply restricted use pesticides, 4916 commercial applicators, and the 32 347 spouses of farmer applicators from Iowa and North Carolina. Private applicators are farmers or nursery workers, and "commercial" applicators are persons employed by pest control companies or businesses that use pesticide applications (eg, warehouse operators, grain mills). To enroll, each pesticide applicator completed a 21-page, enrollment questionnaire. Spouses enrolled by completing a questionnaire sent home with the applicator after enrollment. A small percentage of the spouses completed this questionnaire by phone. In Iowa, both commercial and farmer applicators attended the same pesticide certification testing sessions, and both were invited to participate in the study. In North Carolina, because private and commercial applicators attend separate training, only private applicators were enrolled. Private applicators and commercial applicators were also asked to complete a second questionnaire at home. Women in the study (spouses or female applicators) completed an additional questionnaire about their reproductive histories and children. The recruitment of applicators extended over a period of approximately 4 years, from 13 December 1993 through 31 December 1997.

Cohort members were matched to cancer registry files in Iowa and North Carolina for case identification and to the state death registries and to the National Death Index to ascertain vital status. Matching was based on social security number, last name, first name, date of birth, and gender. Incident cases were identified from enrollment through 31 December 2002. The study participants who were alive but no longer residing in Iowa or North Carolina were identified through the Federal Internal Revenue Service address file, motor vehicle registration records, and the restricted-use pesticide license and certification records of the departments of agriculture in Iowa and North Carolina. Less than 1% of the cohort was lost to mortality or cancer incidence follow-up (N=319). The cancer cases identified by the

cancer registries as having occurred prior to enrollment were not included in the analyses.

Standardized incidence ratios (SIR) were used to compare the cancer incidence experience of licensed private pesticide applicators and their spouses in Iowa and North Carolina to the total population of Iowa and North Carolina, respectively. The cancer incidence experience of licensed commercial applicators was compared with that of the total population of Iowa (since Iowa was the source of all commercial applicators in the study). Person-year accumulation began in the cohort on the date of enrollment in the study and ended for this analysis on 31 December 2002, the last date known alive, the date of cancer diagnosis, or the date the study participant left the state of Iowa or North Carolina (whichever was appropriate). Expected numbers were calculated for the SIR values by applying 5-year age and calendar incidence rates (ie, 1994–1998) from the appropriate race–gender group of the population of Iowa or North Carolina to the person-year distribution of the cohort. Ninety-five percent confidence intervals (95% CI) were calculated using standard methods (27, 28). A chi-square test was used to evaluate the statistical significance of the SIR values (27, 28).

Results

The characteristics of the study cohort are summarized in table 1, while table 2 summarizes the length of follow-up for each component of the cohort. Most of the private applicators, the largest fraction of the cohort (N=52 395, 59% of the cohort), were male (97.4%) and white (94.6%). Similarly, the commercial applicators (N=4916) were male (95.9%) and white (98.7%). The commercial applicators had somewhat more years of formal education than the private applicators in the cohort. Only 3% of the commercial applicators had not graduated from high school and almost 20% had graduated from college with a bachelor's degree, whereas nearly 10% of the private applicators had not completed high school and 13.5% had graduated from college with a bachelor's degree. Only 15% of the private applicators were current smokers (ie, approximately 10% in Iowa and 18% in North Carolina). Alcohol was never used by 32.1% of the private applicators, and only 20% drank alcoholic beverages more than once a week. The commercial applicators smoked more cigarettes and drank more alcohol than the private applicators. Twenty-five percent of the commercial applicators were current smokers, and 38% drank alcoholic beverages more than once a week. Thirty-two percent of the private applicators never drank alcohol, while only 12.5% of the commercial pesticide applicators never drank alcoholic beverages.

Table 1. Characteristics of the participants in the Agricultural Health Study.^a

Characteristic	Private applicators (N=52 395)		Commercial applicators (N=4 916)		Spouses of private applicators (N=32 347)	
	N	%	N	%	N	%
Education (highest level)						
Less than high school	5 225	10.0	148	3.0	1 582	4.9
High school graduate	24 065	45.9	2049	41.7	11 336	35.0
Some college or post-high school training	12 120	23.1	1413	28.7	8 502	26.3
Bachelor's degree	7 095	13.5	980	19.9	4 941	15.3
Some graduate school	1 610	3.1	177	3.6	1 788	5.5
Missing	2 280	4.4	149	3.0	4 198	13.0
Smoking						
Never smoker	26 938	51.4	2 312	47.0	21 999	68.0
Current smoker	8 051	15.4	1 245	25.3	3 179	9.8
Former Smoker	15 510	29.6	1 282	26.1	5 324	16.5
Missing	1 896	3.6	77	1.6	1 845	5.7
Alcohol						
Never	16 840	32.2	631	12.8	14 074	43.5
≤ 1 time per month	7 508	14.3	642	13.1	8 316	25.7
1–3 times per month	8 137	15.5	944	19.1	4 873	15.1
1 time per week	6 079	11.6	767	15.6	1 945	6.0
2–4 times per week	7 304	13.9	1 281	26.1	1 361	4.2
Almost every day or every day	2 944	5.6	558	11.4	433	1.3
Missing	3 583	6.8	93	1.9	1 345	4.2
State of residence						
Iowa	31 877	60.8	4916	100.0	21 771	67.3
North Carolina	20 518	39.2	0		10 576	32.7
Race						
White	49 546	94.6	4848	98.6	30 787	95.2
African American	1 172	2.2	6	0.1	357	1.1
American Indian or Alaskan native	236	0.5	6	0.1	124	0.4
Asian or Pacific Islander	11	0.02	6	0.1	24	0.1
Other	73	0.1	8	0.2	38	0.1
Missing	1 357	2.6	42	0.9	1 017	3.2
Gender						
Male	51 036	97.4	4712	95.9	219	0.7
Female	1 359	2.6	204	4.1	32 128	99.3
Years personally applied pesticides						
Unexposed	602	1.2	447	9.1	13 760	42.5
≤ 1 year	1 115	2.1	438	8.9	1 259	3.9
2–5 years	5 571	10.6	1 235	25.1	3 548	11.0
6–10 years	7 469	14.3	912	18.6	2 548	7.9
11–20 years	15 988	30.5	1 071	21.8	3 079	9.5
21–30 years	11 673	22.2	410	8.3	1 619	5.0
>30 years	6 497	12.4	124	2.5	1 168	3.6
Missing	3 480	6.6	279	5.7	5 366	16.6
Days per year personally applied						
Unexposed	602	1.2	447	9.1	13 760	42.5
<5 days	8 691	16.6	490	10.0	6 525	20.2
5–9 days	11 331	21.6	447	9.1	3 020	9.3
10–19 days	14 350	27.3	684	13.9	2 294	7.1
20–39 days	9 240	17.6	895	18.2	959	3.0
40–59 days	2 410	4.6	593	12.1	196	0.6
60–150 days	1 572	3.0	816	16.6	173	0.5
>150 days	349	0.7	241	4.8	55	0.2
Missing	3 850	7.4	303	6.2	5 365	16.6

^a The demographic characteristics describe the cohort at the time of enrollment.

Table 2. Cohort follow-up.

Cohort group	Survival (years)	Persons ^a (N)	Average sur- vival (years)	Average age at entry (years)	Average age at end of follow- up (years)
Private applicators	378 709.8	51 211	7.4	47.3	54.7
Commercial applicators	36 684.8	4 725	7.8	38.5	46.3
Spouses	211 386.4	31 350	6.7	47.2	53.9
Total	626 781.0	87 286	7.2	46.8	54.0

^a At the end of the follow-up, 31 December 2002.

The median period of pesticide application was 16 years for the private applicators and 7.3 years for the commercial applicators. Approximately 1% of the private applicators never personally mixed or applied pesticides, while approximately 9% of the commercial applicators never personally mixed or applied pesticides. While 37% of the private applicators personally applied pesticides for >20 years, only 11% of the commercial applicators applied pesticides that long. However, the median frequency of pesticide applications was 13 days/

year for the private applicators and almost 29 days/year for the commercial applicators. While approximately 28% of the private applicators used pesticides >20 days/year, more than 50% of commercial applicators used pesticides more than 20 days/year.

The spouses of private applicators (N=32 347) smoked less than farmers (9.8% current smokers) and drank less alcohol (only about 5% drank more than one alcoholic beverage a week). Approximately 95% of the spouses graduated from high school, 26.3% had some college, <15.3% graduated from college, and approximately 5% had some graduate education. While 41% of the spouses reported personal use of pesticides on the farm, only 9% used pesticides >10 days/year, making their use far less than that of the private or commercial applicators. The spouses that applied pesticides did not hold pesticide application licenses.

The SIR values are summarized for cancers among the private applicators in table 3, for commercial applicators in table 4, and for spouses of private applicators in table 5. After 5.3 years of follow-up the overall cancer incidence of the farmers (SIR 0.88, 95% 0.84–0.91) and the spouses of farmers (SIR 0.84, 95% CI 0.80–0.90) were

Table 3. Observed and expected cancer incidence cases among the private pesticide applicators in the Agricultural Health Study. (95% CI = 95% confidence interval)

Cancer site	Observed ^a (N)	Expected ^a (N)	Observed / expected	95% CI
All Sites combined	2587	2966.6	0.88	0.84–0.91
Buccal cavity	66	100.6	0.66	0.51–0.83
Lip	25	17.5	1.43	0.93–2.11
Digestive system	462	553	0.83	0.76–0.91
Colon	208	236.3	0.88	0.76–1.01
Rectum	94	116.5	0.81	0.65–0.99
Liver	35	35.7	0.98	0.68–1.37
Gallbladder	8	3.5	2.26	0.97–4.45
Pancreas	46	63.0	0.73	0.53–0.97
Respiratory system	294	630.5	0.47	0.41–0.52
Lung	266	569.9	0.47	0.41–0.53
Soft tissue	10	15.3	0.65	0.31–1.20
Melanomas	100	104.9	0.95	0.78–1.16
Female breast	27	24.7	1.09	0.72–1.59
Female genital system	11	8.7	1.26	0.63–2.26
Ovary	8	2.7	2.97	1.28–5.85
Male genital system	1071	861.4	1.24	1.17–1.32
Prostate	1046	833.2	1.26	1.18–1.33
Testis	23	21.9	1.05	0.67–1.58
Urinary system	184	282.2	0.65	0.56–0.75
Brain and central nervous system	33	41.4	0.80	0.55–1.12
Thyroid and other endocrine	29	22.4	1.29	0.77–1.76
Hodgkin's disease	11	12.5	0.88	0.44–1.57
Non-Hodgkin's lymphoma	114	112.0	1.02	0.84–1.22
Multiple myeloma	43	32.0	1.34	0.97–1.81
Leukemia	70	77.2	0.91	0.71–1.15
Mesothelioma	7	7.1	0.98	0.39–2.02
Others	55	80.7	0.68	0.49–0.84

^a Excludes nonmelanoma skin cancer.**Table 4.** Observed and expected cancer incidence cases among the commercial pesticide applicators in the Agricultural Health Study. (95% CI = 95% confidence interval)

Cancer site	Observed ^a (N)	Expected ^a (N)	Observed / expected	95% CI
All sites combined	132	130.2	1.01	0.85–1.20
Buccal cavity	5	5.3	0.94	0.30–2.18
Lip	3	1.1	2.74	0.55–8.00
Digestive system	24	24.7	0.97	0.62–1.44
Colon	12	10.0	1.20	0.62–2.10
Rectum	7	5.6	1.25	0.50–2.58
Liver	–	0.9	0	0–4.20
Gallbladder	–	0.1	0	0–35.8
Pancreas	3	2.7	1.10	0.22–3.20
Respiratory system	14	23.0	0.61	0.33–1.02
Lung	12	20.4	0.59	0.30–1.03
Soft tissue	–	1.0	0	0–3.82
Melanomas	7	6.7	1.05	0.42–2.17
Female breast	1	1.6	0.63	0.1–3.52
Female genital system	–	0.7	0	0–4.92
Ovary	–	0.2	0	0–16.0
Male genital system	46	33.5	1.37	1.00–1.83
Prostate	41	30.0	1.37	0.98–1.86
Testis	4	3.2	1.24	0.33–3.17
Urinary system	13	12.1	1.08	0.57–1.84
Brain and central nervous system	5	2.7	1.85	0.59–4.31
Thyroid and other endocrine	3	1.9	1.58	0.34–4.99
Hodgkin's disease	1	1.3	0.76	0.1–4.21
Non-Hodgkin's lymphoma	6	6.2	0.96	0.35–2.10
Multiple myeloma	–	1.4	0	0–2.71
Leukemia	4	4.3	0.92	0.25–2.36
Mesothelioma	–	0.3	0	0–13.45
Others	3	4.1	0.73	0.27–4.17

^a Excludes nonmelanoma skin cancer.

significantly lower than that expected, whereas the overall cancer incidence of the commercial pesticide applicators from Iowa was comparable to that of the population of Iowa (SIR 1.01, 95% CI 0.85–1.20). The cancer incidence of the respiratory system was significantly lower than expected among both the private applicators (SIR 0.47, 95% CI 0.41–0.52) and spouses (SIR 0.41, 95% CI 0.32–0.51), while the respiratory cancer incidence was low, but not significantly lower than that expected, among the commercial pesticide applicators (SIR 0.61, 95% CI 0.33–1.02).

Cancer incidence of the buccal cavity was also significantly lower than expected among the private applicators (SIR 0.66, 95% CI 0.51–0.83), with the exception of lip cancer, for which there was a small nonsignificant excess (SIR 1.43, 95% CI 0.93–2.11). Cancer of the buccal cavity was close to the expected value for the spouses of the private applicators (SIR 0.73, 95% CI 0.40–1.22) and the commercial applicators (SIR 0.94, 95% CI 0.30–2.18). Both the spouses of the private applicators (SIR 1.40, 95% CI 0.16–5.05) and the commercial applicators (SIR 2.74, 95% CI 0.55–8.00) were observed to have a nonsignificant excess risk of lip cancer.

The cancer incidence of the urinary system was lower than expected for the private applicators (SIR 0.65, 95% CI 0.56–0.75) and the spouses of the private applicators (SIR 0.69, CI 0.40–1.11) and close to expected for the commercial applicators (SIR 1.08, CI 0.57–1.84). Similarly, the cancer incidence of the digestive system was significantly lower than expected for both the private applicators (SIR 0.83, 95% CI 0.76–0.91) and the spouses of the private pesticide applicators (SIR 0.85, 95% CI 0.72–0.99), while the digestive cancer incidence was approximately that expected for the commercial pesticide applicators (SIR 0.97, 95% CI 0.62–1.44). For the private pesticide applicators, a significantly lower cancer incidence was observed for colon cancer, rectal cancer, and pancreatic cancer, while a nonsignificant excess was observed for gall-bladder cancer among the private applicators (ie, 8 cases of gallbladder cancer were observed among the private applicators, whereas 3.5 were expected). Somewhat similar, though nonsignificant, deficits were observed for the spouses of the private pesticide applicators with respect to colon and pancreatic cancer, and a significant deficit was observed for rectum cancer. Nonsignificant elevations in cancer risk were observed among the commercial applicators for colon cancer and rectum cancer.

Prostate cancer was significantly elevated for the private applicators (SIR 1.26, 95% CI 1.18–1.33) and nonsignificantly elevated for the commercial applicators (SIR 1.37, 95% CI 0.98–1.86). Among the male spouses of the female private applicators four prostate cancers were observed and three were expected. The excess

Table 5. Observed and expected cancer incidence cases among the spouses of private pesticide applicators in the Agricultural Health Study. (95% CI = 95% confidence interval)

Cancer site	Observed ^a (N)	Expected ^a (N)	Observed / expected	95% CI
All sites combined	1112	1316.6	0.84	0.80–0.90
Buccal cavity	14	19.2	0.73	0.40–1.22
Lip	2	1.4	1.40	0.16–5.05
Digestive system	161	189.9	0.85	0.72–0.99
Colon	87	95.8	0.91	0.73–1.12
Rectum	23	38.8	0.59	0.38–0.89
Liver	3	3.5	0.86	0.17–2.51
Gallbladder	3	3.5	0.85	0.17–2.48
Pancreas	20	21.8	0.92	0.56–1.42
Respiratory system	71	175.2	0.41	0.32–0.51
Lung	68	166.4	0.41	0.32–0.52
Soft tissue	3	6.2	0.48	0.10–1.41
Melanomas	67	40.8	1.64	1.27–2.09
Female breast	474	479.0	0.99	0.90–1.08
Female genital system	132	189.3	0.70	0.58–0.83
Ovary	32	57.7	0.55	0.38–0.78
Male genital system	5	4.3	1.17	0.38–2.74
Prostate	5	4.2	1.20	0.39–2.81
Testis	–	0.1	0	0–50.2
Urinary system	17	24.5	0.69	0.40–1.11
Brain and central nervous system	15	16.6	0.90	0.51–1.49
Thyroid and other endocrine	24	28.5	0.91	0.54–1.44
Hodgkin's disease	4	5.4	0.74	0.20–1.91
Non-Hodgkin's lymphoma	42	47.5	0.88	0.64–1.19
Multiple myeloma	13	11.5	1.13	0.60–1.93
Leukemia	17	22.9	0.74	0.43–1.19
Mesothelioma	1	0.9	1.06	0.1–5.9
Others	52	54.9	0.95	0.67–1.50

^a Excludes nonmelanoma skin cancer.

risk of prostate cancer was observed among the applicators in both Iowa (SIR 1.27, 95% CI 1.17–1.38) and North Carolina (SIR 1.24, 95% CI 1.14–1.36) (data not shown). The spouses of the private applicators had a significantly lower than expected frequency of ovarian cancer (SIR 0.55, 95% CI 0.38–0.78), but the female private applicators had a significant excess risk (SIR 2.97, 95% CI 1.28–5.85). The excess risk of ovarian cancer was observed among the female applicators in Iowa (SIR 3.00, 95% CI 0.88–6.50) and North Carolina (SIR 2.87, 95% CI 0.95–6.4).

The spouses of the private applicators also had a significant excess of melanoma (SIR 1.64, 95% CI 1.27–2.09) that was not observed among either the private (SIR 0.95, 95% CI 0.78–1.16) or commercial (SIR 1.05, 95% CI 0.42–2.17) applicators.

A small nonsignificant excess risk of multiple myeloma was observed among the private applicators (SIR 1.34, 95% CI 0.97–1.81) that was not observed among the spouses of the private applicators (SIR 1.13, 95% CI 0.60–1.93). No cases of multiple myeloma had occurred among the commercial applicators, while one was expected.

Other cancers, such as brain and central nervous system cancers, thyroid cancer, Hodgkin's disease, non-Hodgkin's lymphoma, leukemia, mesothelioma, and other cancers, occurred at frequencies expected based on the cancer risk of the populations in both Iowa and North Carolina. Nonmelanoma skin cancer is not routinely reported to state cancer registries and was not, therefore, discussed in this report.

Discussion

After only 7.2 years of follow-up, the private pesticide applicators in the Agricultural Health Study and their spouses experienced significantly less cancer risk than expected according to the age-, gender-, and race-specific cancer incidence rates of Iowa and North Carolina. In part, this finding may be explained by the significantly lower prevalence of cigarette smoking among private applicators and their spouses; this low rate resulted in significantly fewer respiratory, buccal cavity, and urinary system cancers than expected. A significantly lower risk of digestive system cancers was also found among the private pesticide applicators. In part, lower smoking rates would explain some of this deficit as well. Other reasons for these digestive system cancer deficits are not clear from the available data, but they may result from the significantly greater occupational physical activity of farming when compared with that of most of the other occupations in Iowa and North Carolina.

Commercial applicators were a smaller part of the entire cohort, and they were a younger group than the private applicators (ie, 38.5 years for the commercial applicators versus 47.3 years for the private applicators at enrollment). Among the commercial applicators the overall cancer incidence rate did not significantly differ from that of the Iowa and North Carolina populations with comparable rates of cancers of the buccal cavity, urinary system, and digestive system. This finding may be explained by a smoking and alcohol use pattern that was similar to that of the general populations of the two states.

Although the total number of female applicators was relatively small in this cohort (ie, 1329 private applicators and 204 commercial applicators), we have already identified a significant excess frequency of ovarian cancer that was not observed among the spouses of farmer applicators. While the small number of cases limits our ability to evaluate etiologic agents that may be responsible for this excess, triazine herbicides were associated with ovarian cancer in an earlier study (29, 30). A separate analytical investigation is planned for ovarian cancer in this cohort. It will consider occupational and nonoccupational factors.

Prostate cancer was elevated among both the private and commercial applicators. Among the private applicators this excess was statistically significant. Some occupational risk factors for prostate cancer have been identified in an earlier paper from the Agricultural Health Study (1). Methyl bromide, a widely used fumigant, was consistently associated with prostate cancer risk at higher levels of exposure. Several other pesticides were risk factors for prostate cancer among those with a family history of prostate cancer. Nested case-control studies are planned that will evaluate suggested occupational exposures and genetic susceptibility (31–33). Dietary factors and cooking practices may also play a role in the excess risk of prostate cancer observed in this cohort, and it will be the focus of additional analyses reported separately.

A nonsignificant elevation of lip cancer was observed among the private applicators, the spouses of private applicators, and the commercial applicators. Lip cancer is widely recognized as a hazard among farmers (5–7). It appears from our data that it is a hazard shared by farmer's spouses and commercial applicators as well. The efficacy of preventive measures already being employed by this population will be assessed in the future.

Melanoma, the most serious form of skin cancer, was significantly elevated among the spouses of the private applicators but not among the private or commercial applicators. The excess among the spouses was an unexpected finding, but previous reports from the Agricultural Health Study suggest that a high percentage of spouses actively engage in farm work, which will increase their exposure to sunlight. As the number of melanoma cases increases, it will be interesting to compare the melanoma risk of female applicators and the female spouses of private applicators. Hodgkin's disease and non-Hodgkin's lymphoma, multiple myeloma, leukemia, and brain cancer were not significantly elevated in this cohort overall. The wealth of the literature relating pesticide exposure to these cancers necessitates more-detailed examinations of these issues in future analyses of the Agricultural Health Study, when the numbers of cohort members with these cancers will be higher. Given the short follow-up, it may be too soon to see such a risk. While standardized incidence analyses are useful to describe cancer patterns and identify hypotheses for exploration, they are inherently limited as a tool with which to investigate cancer etiology because of the absence of relevant data on important exposures and confounders in the population at large. Future studies that compare applicators who did and did not develop specific cancers will have the ability to explore these observations more fully.

Since the patterns of pesticide exposures and lifestyle characteristics were not uniform in this cohort, caution must be exercised when both the cancer excesses

and the cancer deficits are interpreted. Deviations from expected cancer frequencies in the overall cohort as measured by standardized incidence ratios may mask larger elevations or deficits in cancer risk among those using specific pesticides or enjoying a particularly healthy lifestyle. The analyses presented here only deal with exposure information at the ecological level and are, therefore, most useful in generating hypotheses about cancer risk in association with the lifestyle characteristics and occupational exposures frequently occurring in this cohort. The cancer risks associated with particular occupational exposures or lifestyle characteristics are being evaluated in cohort analyses in which members of the cohort with low or no exposure serve as an internal comparison group, and exposure-response is being evaluated. These analytical studies are more fully utilizing the comprehensive exposure information collected in the Agricultural Health Study.

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