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An Update of Cancer Incidence in the Agricultural Health Study

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Abstract

Objective—Our objective is to re-evaluate cancer incidence among Agricultural Health Study participants.

Methods—Standardized incidence ratios (SIR) and Relative Standardized Ratios were calculated.

Results—A significant excess of prostate cancer was seen for private and commercial applicators, SIR = 1.19 (95% Confidence Interval (CI) 1.14, 1.25) and SIR = 1.28 (95% CI 1.00, 1.61), respectively. Excesses were observed for lip cancer, SIR = 1.97 (95% CI 1.02, 3.44), and multiple myeloma, SIR = 1.42 (95% CI 1.00, 1.95) among private applicators from North Carolina and for marginal zone lymphoma among Iowa spouses, SIR = 2.34 (95% CI 1.21, 4.09).

Conclusions—While lower rates of smoking and increased physical activity probably contribute to the lower overall cancer incidence, agricultural exposures including pesticides, viruses, bacteria, sunlight, and other chemicals may increase risks for specific cancer sites.

INTRODUCTION

Agricultural populations tend to have lower overall cancer incidence and mortality rates than the general population.(1;2) A reported deficit of tobacco-related cancers such as cancer of the lung and bladder has been attributed to lower smoking prevalence in these populations. (3) The lower incidence of colorectal cancer may be influenced by the high rates of physical activity associated with farm activities.(4;5) On the other hand, lymphohematopoietic cancers, prostate cancer, melanoma, and brain tumors have been reported to be in excess among agricultural workers.(6–10) Similarly, excess mortality has been reported for these same cancer sites in agricultural populations (2) which could be linked to exposures such as pesticides, viruses, bacteria, fungi, sunlight, dusts, and other chemicals.

While occupational agricultural exposures may be associated with an increased cancer risk among applicators, there is also a potential hazard experienced by the spouses of farmer-applicators who may have similar exposures.(11) Spouses may also be directly involved in

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farming related activities including the handling and application of pesticides and tending to animals.(12) Thus, the cancer experience of this group may offer insight about direct and indirect agricultural exposures and cancer risk.

In a previous cancer incidence report from the Agricultural Health Study (AHS), a large prospective study of private and commercial licensed pesticide applicators and spouses of private applicators, we reported on the overall cancer incidence among AHS participants. In that earlier report, which included 3,831 incident cancer cases through 2002, excesses were observed for prostate and ovarian cancer among applicators.(13) A significant excess of melanoma was observed among spouses as well. In the current study, we update the standardized incidence ratios (SIR) in the AHS cohort with 2,600 additional incident cases of cancer through 2006, which represents a 68% increase in accrued cases.

METHODS

The AHS is a prospective cohort study of 52,394 licensed private pesticide applicators in Iowa (IA) and North Carolina (NC), 32,346 spouses of these private applicators, and 4,916 licensed commercial applicators from IA. A detailed description of this cohort has been described.(14) Briefly, applicators were recruited at pesticide licensing stations from December 1993 through December 1997. Private applicators are generally farmers or nursery workers, and commercial applicators are persons employed by pest control companies or businesses that use pesticide applications, such as grain elevators. At enrollment, applicators completed a self-administered questionnaire that provided detailed information on various agricultural exposures, basic demographics, and lifestyle information. Spouses provided such information through a mailed questionnaire sent home with applicators.

We calculated SIRs to compare the cancer experience of licensed private pesticide applicators and their spouses in IA and NC to the general populations in those states. Commercial applicators were only recruited from Iowa and incidence rates were compared to those for the general population of that state. Cohort members were linked to cancer registry files for case identification and to the state death registries and to the National Death Index to ascertain vital status. AHS data release P1REL0712.01 was used, which includes observed numbers of cases for each cancer site that were accrued from the time of enrollment into the AHS (1993–1997) through December 31, 2006; cancer cases identified by the cancer registries as having occurred prior to enrollment were not included. Person-year accumulation began on the date of enrollment in the study and ended on December 31 2006, the last date known alive, the date of cancer diagnosis, or the date the study participant left the state of IA or NC, whichever came first. Cohort members were matched annually to current address records of the Internal Revenue Service, motor vehicle registration offices, and pesticide license registries of state agricultural departments to identify whether the participants continued to reside in Iowa or North Carolina. Less than 1% of the cohort moved out of state (N=390). Expected numbers of cases were calculated by applying 5-year age, calendar year, race and gender-specific incidence rates from IA or NC to the person-year distribution of the cohort using SEER*Stat Version 6.6.1 (<http://seer.cancer.gov/seerstat/>). Statistical significance of the SIRs was calculated based on Poisson 95% confidence intervals (CIs) as described by Breslow and Day.(15) SIRs were reported when there were at least 5 observed cases. Stratified SIRs by smoking status (never, former, current smoker) and state/subject type (private applicators from IA, private applicators from NC, IA spouses, and NC spouses) were also evaluated. Expanded subgroups for non-Hodgkin lymphoma (NHL) were presented to account for the known etiologic heterogeneity among various subtypes.(16) These subgroups include B-cell subtypes, diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), chronic

lymphocytic leukemia/small lymphocytic lymphoma/mantle cell lymphoma (CLL/SLL/MCL), marginal zone lymphoma (MZL), and all T-cell subtypes combined.

Our previous analysis revealed a deficit for all cancers in AHS farmers and spouses.(13) Consequently, a test of the null hypothesis of one for a cause-specific SIR fails to account for this overall cancer deficit. Therefore, we also evaluated whether there was an excess or deficit of cancer cases for each specific cause relative to the overall deficit of cancers in AHS subjects. To do this, we calculated the ratio of the SIR for each site to the SIR for all cancer sites overall minus that site of interest [i.e., site_x vs. $\text{site}_{\text{not } x}$]. This approach is related to the comparison of SMRs for exposed and unexposed groups as described in Breslow and Day.(15) These relative standardized incidence ratio (RSIR) and 95% CIs are presented for private applicators and spouses. Interpretability of the RSIR is predicated on the assumption that those factors responsible for the observed deficit for all cancers apply across the individual cancer sites in the absence of applicator-related factors.

RESULTS

Through 2006, applicators and spouses contributed 953,557 person-years of follow-up. During this time, we observed 4,316 incident cancers among 52,394 private applicators, 219 among 4,916 commercial applicators, and 1,896 among 32,346 spouses of private applicators (Tables 1, 2). As of 2006, cohort members from IA were generally younger (46.1% of private applicators, 68.4% of commercial applicators, 47.3% of spouses <55 years) while cohort members from NC were older (19.7 % private applicators, 15.1% spouses 75+ years). AHS subjects were predominantly White (98% in IA and 89% in NC). Private and commercial applicators were mostly male (95.5% and 98.6%) while spouses were mostly female (98.6 and 99.7%). AHS participants tended to be never smokers, with commercial applicators contributing the largest percentage of current smokers (26.1%). The prevalence of current smokers in NC exceeded that for IA among private applicators (21.6% vs. 11.3%) and spouses (14.0% vs. 7.8%).

Table 2 shows that private applicators and spouses had a significantly lower incidence of cancer overall compared with the general populations in IA and NC (all site SIR = 0.85 95% CI (0.83, 0.88); SIR = 0.82 95% CI (0.79, 0.86) respectively), whereas commercial applicators had an overall cancer incidence that was not statistically different than the general population, (all site SIR = 0.93 95% CI (0.81, 1.07)). Statistically significant deficits were observed for oral, colon, lung, bladder, and kidney cancers among private applicators and spouses; significant deficits in esophageal and pancreatic cancers were observed among private applicators, whereas these deficits were observed in rectal and ovarian cancers among spouses. Private applicators had significant excesses of ovarian cancer, SIR = 2.45 (95% CI 1.12, 4.65), while both private and commercial applicators had a significant excess of prostate cancer, SIR = 1.19 (95% CI 1.14, 1.25) and SIR = 1.28 (95% CI 1.00, 1.61) respectively.

Table 3 shows the SIR for all cancers for private applicators was reduced in IA and NC, SIR = 0.80 (95% CI 0.77, 0.83) and SIR = 0.92 (95% CI 0.88, 0.96), respectively. Deficits for lung cancer were greater among applicators in IA than in NC. Significant deficits for brain, esophagus, colon, rectum, liver, pancreas, and kidney cancers were observed among applicators in IA but not in NC. The observed prostate cancer excess among private applicators was similar in IA and NC. Additional excesses for lip cancer, SIR = 1.97 (95% CI 1.02, 3.44), and multiple myeloma (MM), SIR = 1.42 (95% CI 1.00, 1.95) among private applicators from NC were also observed. Non-significant increases were evident for CLL/SLL/MCL, SIR = 1.45 (95% CI 0.92, 2.18), among private applicators in IA and for DLBCL, SIR = 1.40 (95% CI 0.98, 1.92) among private applicators in NC.

Spouses from both states had significant deficits for all cancers, IA spouse SIR = 0.80 (95% CI 0.75, 0.84) and NC spouse SIR = 0.87 (95% CI 0.81, 0.94), however, several differences were also apparent between IA and NC spouses (Table 3). Deficits for lung, bladder, kidney, and other cancers were evident among IA spouses but not among NC spouses. Although lymphohematopoietic cancers were less common among spouses than applicators, a significant excess of MZL was observed among IA spouses, SIR = 2.34 (95% CI 1.21, 4.09). Non-significant excess were also observed for melanoma and FL among IA spouses and for thyroid and stomach cancer among NC spouses.

Relative SIRs for selected cancers among private applicators and spouses are presented in Table 4. Even after taking into account the overall deficit of cancers in private applicators, significant relative deficits for oral, lung, and bladder cancer remained. In addition to the already observed excesses of prostate and ovarian cancer among private applicators, significant excess RSIRs were observed for NHL RSIR = 1.17 (95% CI 1.01, 1.35) and MM RSIR = 1.41 (95% CI 1.11, 1.78). For NHL, the DLBCL RSIR = 1.27 (95% CI 1.01, 1.60) and CLL/SLL/MCL RSIR = 1.51 (95% CI 1.08, 2.12) subtypes appear to be driving the observed excess; for leukemia the CLL and AML subtypes appear to be contributing to the observed relative excess. A significant relative excess was also observed for lip cancer among applicators, RSIR = 1.53 (95% CI 1.09, 2.15).

Among spouses, significant relative deficits for lung cancer only remained (Table 4). Significant relative excess of melanoma RSIR = 1.64 (95% CI 1.33, 2.02), female breast cancer RSIR = 1.66 (95% CI 1.51, 1.82), and uterine cancer RSIR = 1.32 (95% CI 1.11, 1.56) were observed. Similar to applicators, significant relative excesses were also observed for NHL overall RSIR = 1.38 (95% CI 1.11, 1.72) and DLBCL RSIR = 1.48 (95% CI 1.05, 2.10) but not for CLL/SLL/MCL. Marginal zone lymphoma was significantly increased among spouses, RSIR = 2.45 (95% CI 1.42, 4.23). Nonsignificant relative excesses were also observed for CLL (leukemia), AML, and MM.

DISCUSSION

Private pesticide applicators and their spouses experience a significant deficit for cancer overall compared with the general population, while the cancer experience of commercial applicators appears to be more similar to the general population. This is consistent with previous observations among farmers tending to have lower overall cancer incidence and mortality rates than the general population. Nonetheless, significant excesses for some cancers are evident including several new excess risks in this update of cancer incidence in the AHS.

Although the numbers are small, a newly identified significant excess of lip cancer is observed among NC applicators. Several studies have identified significant excess risks of lip cancer among farmers.(2;17;18) Ultraviolet light is a well-accepted cause of lip cancer and suggests that increased sun exposure from farming may account for the observed excess. However, since melanoma, a cancer known to be related to ultraviolet radiation was not elevated among applicators in NC, other factors may also contribute to the lip cancer excess. For example, smoking is an important risk factor for lip cancer.(19) Survey data show that rates of smoking in NC are observed to be higher than in IA(20) and this pattern is consistent among AHS participants with higher rates of smoking in NC. Given that smoking rates in the AHS are generally lower than the general population, smoking may only explain part of the excess of lip cancer. However, the use of other tobacco products may also be important for the development of lip cancer.(21) AHS applicators from NC also report a higher prevalence of other tobacco products compared to their counterparts in IA, including: chewing tobacco (19.7% in NC vs. 11.7% in IA), cigars (9.7% in NC vs 6.5% in IA), and

cigarillos (7.8% in NC vs. 5.4% in IA). Pesticides, viral infection, and immune suppression have all been hypothesized to additionally influence lip cancer risk. (18) All of these exposures may vary according to the different agricultural settings in each state though all are relevant risk factors that need to be explored in these populations.

An additional new finding that was not evident in the previous follow-up is the significant excess of MM among private applicators from NC. Meta-analyses of several cohort and case-control studies have suggested a significant association between MM and farming. (2;22;23) Furthermore, several studies have directly implicated pesticides for this excess, including the AHS.(24–26) We also recently reported the prevalence of the MM precursor entity, monoclonal gammopathy of undetermined significance, among pesticide applicators in the AHS was twice that of a population-based sample (27) suggesting a role for farming in the etiology of MM in the AHS. The MM difference by state could be chance, or due to the different exposures, including crop/pesticide profiles and requires further examination.

With the additional follow-up time and more accrued cases, we were able to evaluate risk of NHL overall and by NHL subtype to investigate possible etiologic heterogeneity among the various subtypes. We observed no significant excesses for NHL overall. Although the numbers are small, a significant excess of MZL among spouses in IA is apparent. Evidence suggests that MZL is associated with chronic antigen-driven immune stimulation by autoantigens and/or microbial pathogens. For example, three autoimmune conditions (i.e., lupus, Sjogren syndrome, hemolytic anemia) have been associated with MZL.(28;29) We had information on these conditions for 10 of the 12 IA spouses diagnosed with MZL; none reported a history of these autoimmune conditions suggesting that other factors may be etiologically relevant in this population. No data were available for hemolytic anemia. Five distinct microbial pathogens have been identified to be related to MZL; *Helicobacter pylori* (30), *Borrelia burgdorferi* (31), *Campylobacter jejuni* (32), *Chlamydia psittaci* (33), and hepatitis C virus.(34;35) *Campylobacter jejuni* and *Chlamydia psittaci* are bacteria commonly found in birds and animals including cattle (*Campylobacter jejuni*) and poultry (*Campylobacter jejuni* and *Chlamydia psittaci*). Evidence suggests that occupational exposure to animals increases the risk of developing NHL.(36;37) We have previously reported that Iowa farmers raise more livestock compared with NC farmers.(38) While no specific infections were ascertained in the AHS, these and other infections associated with exposure to animals on the farm may contribute to MZL among IA spouses. Pesticide exposure has been linked to NHL in many studies (39;40) and specifically to MZL in one study (41); thus an exploration of several farm-related exposures among spouses is needed to elucidate the observed MZL excess.

Elevated SIRs were also apparent for some other NHL subtypes. CLL/SLL/MCL was elevated in private applicators from IA, while DLBCL was elevated in private applicators from NC, although these elevations were not statistically significant. This may be a chance occurrence or this difference by NHL subtype may reflect actual differences in farm or other occupational exposures in IA and NC. In our analysis, the RSIRs suggest that the risk is limited to B-cell lymphomas, which were elevated among both private applicators and spouses. Studies have generally, but not uniformly, reported positive associations between NHL and phenoxyacetic acid herbicides. (42;43) Associations with other pesticide classes have been studied less, but positive associations have also been observed for carbamate, organochlorine, and organophosphate insecticides. (44;45) Few studies of pesticides have been able to evaluate NHL risk by subtype. While spouses may also be exposed to pesticides and other agricultural exposures, on average spousal exposure is less than among applicators. The timing of spousal exposure may also differ from that of applicators. Adequate immune stimulation early in life has been hypothesized to protect from allergy and illness later in life.(46–48) Thus, the risk of NHL among spouses who often marry into farm

life at a later age may be greater due to a less robust immune response to various agricultural inflammatory triggers compared with applicators that are more likely to have grown up on farms and been exposed at a young age.(49)

Aside from these new observations, several previously reported associations were updated. The previously reported excess of prostate cancer among private and commercial applicators (13) persisted in this extended follow up. This excess is also observed in both states. Excesses in prostate cancer linked to pesticide use among other agricultural populations have been previously reported.(2;10;50–52) The role of specific chemicals has not been established, although other studies have implicated associations with organochlorine (53;54) or organophosphate (51) insecticides. Increasing evidence from the AHS has also linked these pesticides with prostate cancer. (55–59) We also previously reported an excess of ovarian cancer among female applicators.(13) While this excess persisted, no additional ovarian cancers were accrued since the previous analysis. Exposure to triazine herbicides has been linked to ovarian cancer although not in all studies.(60;61) Because some pesticides have been shown to have estrogenic and antiestrogenic properties, increased attention has been paid to the role of endocrine disrupting chemicals in the etiology of both prostate and ovarian cancers.(62;63) The suggested relative excess for two other hormonal cancers, breast and uterine cancer among spouses, could also be due to hormonal properties of some pesticides. Aside from pesticides, other agricultural exposures may also contribute to the observed excesses.

The previously reported significant excess of melanoma among AHS spouses did not clearly persist. An elevated SIR among IA and NC spouses was observed but was not statistically significant. A significant relative excess of melanoma (RSIR) among spouses suggests, however, that farm-related activities may contribute to melanoma incidence. In a case-control analysis of cutaneous melanoma in the AHS, Dennis et al. found significant associations between several pesticides and melanoma risk.(64) Another hypothesized explanation for the observed relative excess is increased exposure to sunlight among spouses who engage in active farm work. Ultraviolet light exposure is the key established environmental risk factor for melanoma (65). No excess risks, however, were observed among applicators that, presumably, have the highest exposure to sunlight. Thus, it is unclear what other agricultural exposures may be responsible for the elevated melanoma risk among spouses.

Overall, AHS subjects are at a lower risk of cancer than the general population with several cancer sites showing significant deficits. This provides evidence that the farm lifestyle reduced the risk of many cancers. In particular, there is a consistent deficit among smoking-related cancers including, oral, esophageal, pancreatic, lung, and bladder cancer. Except for commercial applicators, the rates of smoking among AHS participants appear to be much lower than rates in comparable gender/state groups as reported by the Behavioral Risk Factor Surveillance System.(20) The relative deficit of lung cancer could also be due to other factors associated with participation in the AHS, such as high levels of occupational physical activity on the farm, which has been associated with decreased lung cancer risk in several studies.(66–69) Farmers are also potentially exposed to endotoxin from animals, grains, and dusts from hay and straw. (70) Endotoxin exposure has been associated with decreased lung cancer risk.(71) Thus, the lung cancer deficit observed among farmers compared to the general population, may be also be due in part, to endotoxin exposure.

In summary, cancer incidence overall in the AHS continues to be lower than expected compared to the general populations of IA and NC, although excesses for some cancers are apparent. These patterns are likely influenced by lifestyle and occupational factors. Occupational agricultural exposures are varied and can influence cancer risk in different

ways. We have hypothesized several explanations for the observed trends. More detailed exploration of the causes of cancers that show both deficits and excesses are important in furthering our understanding of the contribution of agricultural exposures to these cancer risks.

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Table 1

Characteristics of participants in the Agricultural Health Study through 2006

Characteristic	Private Applicators		Commercial Applicators		Spouses	
	IA N=31,876	NC N=20,518	IA N=4,916	NC N=10,575	IA N=21,771	NC N=10,575
Person-years of follow-up	344,131.10	220,868.84	54,108.93	110,378.06	224,070.09	110,378.06
Mean length of follow-up (sd)	10.8 (2.4)	10.8 (2.8)	11.0 (3.1)	10.4 (2.3)	10.3 (2.2)	10.4 (2.3)
Age* n (%)						
<55	14,687 (46.1)	7,303 (35.6)	3,362 (68.4)	3,826 (36.2)	10,288 (47.3)	3,826 (36.2)
55–64	7,806 (24.5)	4,895 (23.9)	950 (19.3)	2,760 (26.1)	5,591 (25.7)	2,760 (26.1)
65–74	6,055 (19.0)	4,288 (20.9)	449 (9.1)	2,393 (22.6)	4,239 (19.5)	2,393 (22.6)
75+	3,328 (10.4)	4,032 (19.7)	155 (3.2)	1,596 (15.1)	1,653 (7.6)	1,596 (15.1)
Race/Ethnicity n (%)						
White	31,478 (98.8)	18,253 (89.0)	4,855 (98.8)	9,549 (90.3)	21,349 (98.1)	9,549 (90.3)
Black	15 (0.1)	1,176 (5.7)	6 (0.1)	363 (3.4)	<0.01	363 (3.4)
American Indian/Alaskan Native	10 (0.03)	229 (1.1)	6 (0.1)	113 (1.1)	12 (0.1)	113 (1.1)
Asian/Pacific Islander	<0.01	9 (0.04)	6 (0.1)	9 (0.1)	15 (0.1)	9 (0.1)
Other	24 (0.1)	49 (0.2)	8 (0.2)	14 (0.1)	24 (0.1)	14 (0.1)
Missing	347 (1.1)	802 (3.9)	35 (0.7)	527 (5.0)	370 (1.7)	527 (5.0)
Gender n (%)						
Male	31,433 (98.6)	19,602 (95.5)	4,712 (95.8)	150 (1.4)	69 (0.3)	150 (1.4)
Female	443 (1.4)	916 (4.5)	204 (4.2)	10,425 (98.6)	21,702 (99.7)	10,425 (98.6)
Education n (%)						
<12 years	1,716 (5.4)	3,508 (17.1)	148 (3.0)	1,022 (9.7)	559 (2.6)	1,022 (9.7)
High school graduate/GED	15,729 (49.3)	8,332 (40.6)	2,049 (41.7)	3,764 (35.6)	7,572 (34.8)	3,764 (35.6)
Vocational/Some college	8,368 (26.3)	3,751 (18.3)	1,413 (28.7)	2,348 (22.2)	6,154 (28.3)	2,348 (22.2)
College degree	4,530 (14.2)	2,566 (12.5)	980 (19.9)	1,449 (13.7)	3,492 (16.0)	1,449 (13.7)
Graduate or Professional School	717 (2.3)	776 (3.4)	164 (3.3)	586 (5.5)	1,149 (5.3)	586 (5.5)
Something else	57 (0.2)	60 (0.3)	13 (0.3)	640 (6.1)	2,255 (10.4)	640 (6.1)
Missing	759 (2.4)	1,525 (7.4)	149 (3.0)	766 (7.2)	590 (2.7)	766 (7.2)

Characteristic	Private Applicators		Commercial Applicators	Spouses	
	IA N=31,876	NC N=20,518	IA N=4,916	IA N=21,771	NC N=10,575
Smoking status at enrollment n (%)					
Missing	483 (1.52)	1,417 (6.9)	77 (1.6)	858 (3.9)	987 (9.3)
Never smoker	19,067 (59.8)	7,870 (38.4)	2,312 (47.0)	15,750 (72.3)	6,248 (59.1)
Former smoker	8,715 (27.3)	6,795 (33.1)	1,245 (25.3)	3,469 (15.9)	1,855 (17.5)
Current smoker	3,611 (11.3)	4,436 (21.6)	1,282 (26.1)	1,694 (7.8)	1,485 (14.0)
Prevalence of current smoking adults in 1995 [†] (± SD)	24.8 (± 2.4)	30.2 (± 2.8)	24.8 (± 2.4)	21.7 (± 1.9)	21.8 (± 2.1)

* Age on 12/31/2006

[†] Behavioral Risk Factor Surveillance System. Rates are reported by state and gender.

Abbreviations: Iowa (IA); North Carolina (NC). Standard Deviation (SD).

Table 2
Observed incident cases through 2006 and Standardized Incidence Ratios (SIRs) for participants in the AHS

Cancer site	Private Applicators		Commercial Applicators		Spouses	
	Obs (N)	SIR (95% CI)	Obs (N)	SIR (95% CI)	Obs (N)	SIR (95% CI)
All Sites	4,316	0.85 (0.83, 0.88)	219	0.93 (0.81, 1.07)	1,896	0.82 (0.79, 0.86)
Oral Cavity and Pharynx	93	0.56 (0.45, 0.69)	5	0.54 (0.18, 1.27)	22	0.64 (0.40, 0.97)
Lip	33	1.30 (0.90, 1.83)	3	--	2	--
Brain	51	0.78 (0.58, 1.03)	5	1.19 (0.39, 2.78)	26	0.94 (0.61, 1.37)
Thyroid	39	0.98 (0.69, 1.33)	5	1.40 (0.45, 3.26)	49	0.90 (0.67, 1.19)
Esophagus	52	0.64 (0.48, 0.85)	2	--	2	--
Stomach	61	0.86 (0.66, 1.10)	2	--	15	0.91 (0.51, 1.50)
Colon	339	0.87 (0.78, 0.97)	17	0.98 (0.57, 1.57)	144	0.83 (0.70, 0.98)
Rectum	117	0.90 (0.74, 1.08)	8	1.17 (0.50, 2.30)	30	0.69 (0.47, 0.99)
Liver	32	0.73 (0.50, 1.03)	1	--	6	0.76 (0.28, 1.66)
Gallbladder	8	1.33 (0.57, 2.61)	0	--	7	1.09 (0.44, 2.25)
Pancreas	80	0.72 (0.57, 0.89)	5	0.99 (0.32, 2.31)	32	0.72 (0.49, 1.01)
Lung and Bronchus	436	0.48 (0.43, 0.53)	26	0.75 (0.49, 1.09)	133	0.42 (0.35, 0.50)
Mesothelioma	14	1.12 (0.61, 1.89)	0	--	3	--
Urinary Bladder	191	0.59 (0.51, 0.68)	16	1.18 (0.68, 1.92)	29	0.60 (0.40, 0.86)
Kidney and Renal Pelvis	148	0.82 (0.69, 0.96)	2	--	39	0.71 (0.50, 0.97)
Melanoma of the Skin	173	0.89 (0.76, 1.03)	13	1.09 (0.58, 1.86)	92	1.17 (0.94, 1.43)
Female Breast	33	0.95 (0.65, 1.33)	0	--	770	1.00 (0.93, 1.08)
Uterus	4	--	1	--	148	0.94 (0.79, 1.10)
Ovary	9	2.45 (1.12, 4.65)	0	--	58	0.72 (0.55, 0.93)
Prostate	1,719	1.19 (1.14, 1.25)	73	1.28 (1.00, 1.61)	7	1.05 (0.42, 2.15)
Testis	32	0.97 (0.67, 1.37)	6	1.21 (0.45, 2.64)	0	--
Hodgkin Lymphoma	18	0.96 (0.57, 1.52)	1	--	7	0.85 (0.34, 1.74)
Non-Hodgkin Lymphoma	195	0.99 (0.86, 1.14)	9	0.82 (0.38, 1.56)	86	0.99 (0.79, 1.22)
B-cell	167	1.03 (0.88, 1.20)	8	0.86 (0.37, 1.69)	78	1.06 (0.83, 1.32)
DLBCL	74	1.08 (0.85, 1.36)	3	--	32	1.07 (0.73, 1.51)

Cancer site	Private Applicators		Commercial Applicators		Spouses	
	Obs (N)	SIR (95% CI)	Obs (N)	SIR (95% CI)	Obs (N)	SIR (95% CI)
FL	42	1.02 (0.73, 1.38)	3	--	23	0.99 (0.62, 1.48)
CLL/SLL/MCL	34	1.28 (0.89, 1.79)	1	--	4	--
MZL	10	0.84 (0.40, 1.54)	1	--	13	1.77 (0.94, 3.03)
T-cell	12	0.83 (0.43, 1.45)	0	--	4	--
NHL, NOS	15	0.79 (0.44, 1.30)	1	--	4	--
Leukemia	133	0.96 (0.81, 1.14)	7	0.93 (0.37, 1.92)	37	0.83 (0.58, 1.14)
Lymphatic	70	0.97 (0.75, 1.22)	5	1.24 (0.40, 2.88)	17	0.85 (0.49, 1.36)
ALL	3	--	2	--	1	--
CLL	61	1.01 (0.78, 1.30)	3	--	16	0.95 (0.55, 1.55)
Myeloid	58	0.97 (0.74, 1.25)	2	--	18	0.80 (0.47, 1.26)
AML	42	1.04 (0.75, 1.41)	1	--	16	0.98 (0.56, 1.59)
CML	14	0.81 (0.44, 1.35)	1	--	2	--
Multiple Myeloma	71	1.20 (0.93, 1.51)	1	--	21	0.94 (0.58, 1.44)
Other Cancers	54	0.53 (0.40, 0.69)	3	--	28	0.67 (0.44, 0.97)

Abbreviations: Diffuse large B-cell lymphoma (DLBCL); Follicular lymphoma (FL); Chronic lymphocytic leukemia/Small lymphocytic lymphoma/Mantle cell lymphoma (CLL/SLL/MCL); Marginal zone lymphoma (MZL); Not otherwise specified (NOS); Acute lymphoblastic leukemia (ALL); Acute myeloid leukemia (AML); Chronic myeloid leukemia (CML).

Table 3

Observed incident cases through 2006 and Standardized Incidence Ratios (SIRs) by state and subject type

Cancer site	Iowa Private Applicators		North Carolina Private Applicators		Iowa Spouses		North Carolina Spouses	
	Obs	SIR (95% CI)	Obs	SIR (95% CI)	Obs	SIR (95% CI)	Obs	SIR (95% CI)
All Sites	2,258	0.80 (0.77, 0.83)	2,058	0.92 (0.88, 0.96)	1,183	0.80 (0.75, 0.84)	713	0.87 (0.81, 0.94)
Oral Cavity/Pharynx	55	0.57 (0.43, 0.74)	38	0.55 (0.39, 0.76)	13	0.60 (0.32, 1.03)	9	0.70 (0.32, 1.32)
Lip	21	1.09 (0.67, 1.66)	12	1.97 (1.02, 3.44)	2	--	0	--
Brain	25	0.66 (0.42, 0.97)	26	0.96 (0.63, 1.41)	19	1.06 (0.64, 1.65)	7	0.72 (0.29, 1.48)
Thyroid	26	0.97 (0.63, 1.42)	13	0.99 (0.53, 1.69)	31	0.77 (0.52, 1.09)	18	1.28 (0.76, 2.02)
Esophagus	30	0.62 (0.42, 0.88)	22	0.68 (0.43, 1.04)	2	--	0	--
Stomach	34	0.84 (0.58, 1.17)	27	0.88 (0.58, 1.29)	5	0.52 (0.17, 1.21)	10	1.46 (0.70, 2.69)
Colon	177	0.78 (0.67, 0.91)	162	0.99 (0.84, 1.15)	92	0.81 (0.66, 1.00)	52	0.86 (0.64, 1.12)
Rectum	63	0.78 (0.60, 0.99)	54	1.10 (0.82, 1.43)	22	0.77 (0.49, 1.17)	8	0.54 (0.23, 1.05)
Liver	10	0.44 (0.21, 0.82)	22	1.04 (0.65, 1.57)	2	--	4	--
Gallbladder	5	1.40 (0.46, 3.27)	3	--	5	1.10 (0.36, 2.56)	2	--
Pancreas	38	0.60 (0.43, 0.83)	42	0.86 (0.62, 1.16)	20	0.73 (0.44, 1.12)	12	0.70 (0.36, 1.22)
Lung and Bronchus	134	0.29 (0.24, 0.34)	302	0.68 (0.61, 0.77)	65	0.35 (0.27, 0.44)	68	0.54 (0.42, 0.68)
Mesothelioma	7	1.11 (0.44, 2.28)	7	1.14 (0.46, 2.35)	2	--	1	--
Urinary Bladder	102	0.56 (0.45, 0.68)	89	0.63 (0.50, 0.77)	13	0.44 (0.24, 0.76)	16	0.85 (0.48, 1.37)
Kidney/Renal Pelvis	77	0.75 (0.59, 0.93)	71	0.92 (0.72, 1.15)	22	0.61 (0.38, 0.92)	17	0.89 (0.52, 1.43)
Melanoma of the Skin	90	0.84 (0.67, 1.03)	83	0.96 (0.77, 1.19)	63	1.20 (0.92, 1.54)	29	1.09 (0.73, 1.57)
Female Breast	10	0.94 (0.45, 1.73)	23	0.95 (0.60, 1.43)	484	0.97 (0.89, 1.06)	286	1.06 (0.94, 1.19)
Uterus	2	--	2	--	96	0.86 (0.70, 1.05)	52	1.13 (0.84, 1.48)
Ovary	3	--	6	2.36 (0.86, 5.13)	35	0.67 (0.46, 0.93)	23	0.82 (0.52, 1.23)
Prostate	979	1.22 (1.15, 1.30)	740	1.16 (1.08, 1.24)	4	--	3	--
Testis	21	0.92 (0.57, 1.40)	11	1.10 (0.55, 1.98)	0	--	0	--
Hodgkin Lymphoma	15	1.27 (0.71, 2.09)	3	--	6	1.02 (0.37, 2.21)	1	--
NHL	110	0.95 (0.78, 1.14)	85	1.06 (0.85, 1.31)	62	1.11 (0.85, 1.42)	24	0.78 (0.50, 1.16)
B-cell	94	0.95 (0.77, 1.16)	73	1.16 (0.91, 1.45)	57	1.16 (0.88, 1.50)	21	0.85 (0.53, 1.30)
DLBCL	37	0.88 (0.62, 1.21)	37	1.40 (0.98, 1.92)	21	1.06 (0.65, 1.62)	11	1.10 (0.55, 1.97)

Cancer site	Iowa Private Applicators		North Carolina Private Applicators		Iowa Spouses		North Carolina Spouses	
	Obs	SIR (95% CI)	Obs	SIR (95% CI)	Obs	SIR (95% CI)	Obs	SIR (95% CI)
FL	23	0.89 (0.56, 1.33)	19	1.24 (0.75, 1.94)	20	1.26 (0.77, 1.94)	3	--
CLL/SLL/MCL	23	1.45 (0.92, 2.18)	11	1.03 (0.52, 1.85)	0	--	4	--
MZL	7	0.89 (0.36, 1.83)	3	--	12	2.34 (1.21, 4.09)	1	--
T-cell	8	0.96 (0.42, 1.90)	4	--	2	--	2	--
NHL, NOS	7	0.82 (0.33, 1.68)	8	0.76 (0.33, 1.51)	3	--	1	--
Leukemia	83	0.94 (0.74, 1.16)	50	1.01 (0.75, 1.34)	27	0.89 (0.59, 1.30)	10	0.70 (0.34, 1.29)
Lymphatic	48	0.98 (0.72, 1.29)	22	0.95 (0.59, 1.43)	13	0.93 (0.50, 1.59)	4	
ALL	2	--	1	--	1	--	0	--
CLL	42	1.02 (0.74, 1.38)	19	1.00 (0.60, 1.56)	12	1.02 (0.52, 1.77)	4	
Myeloid	34	0.93 (0.64, 1.30)	24	1.03 (0.66, 1.53)	13	0.86 (0.46, 1.47)	5	0.68 (0.22, 1.58)
AML	24	0.99 (0.64, 1.48)	18	1.12 (0.66, 1.76)	11	1.00 (0.50, 1.79)	5	0.93 (0.30, 2.17)
CML	9	0.81 (0.37, 1.53)	5	0.80 (0.26, 1.87)	2	--	0	--
Multiple Myeloma	34	1.02 (0.71, 1.43)	37	1.42 (1.00, 1.95)	15	1.10 (0.61, 1.81)	6	0.70 (0.26, 1.52)
Other Cancers	21	0.43 (0.27, 0.65)	33	0.63 (0.43, 0.88)	11	0.46 (0.23, 0.83)	17	0.93 (0.54, 1.49)

Abbreviations: Non-Hodgkin Lymphoma (NHL); Diffuse large B-cell lymphoma (DLBCL); Follicular lymphoma (FL); Chronic lymphocytic leukemia/Small lymphocytic lymphoma/Mantle cell lymphoma (CLL/SLL/MCL); Marginal zone lymphoma (MZL); Not otherwise specified (NOS); Acute lymphoblastic leukemia (ALL); Acute myeloid leukemia (AML); Chronic myeloid leukemia (CML).

Table 4

Relative Standardized Incidence Ratios (RSIRs) for selected cancers among private applicators and spouses

Cancer site	Private Applicators		Spouses	
	Obs (N)	RSIR (95% CI)	Obs (N)	RSIR (95% CI)
Oral Cavity and Pharynx	93	0.65 (0.53, 0.80)	22	0.88 (0.58, 1.34)
Lip	33	1.53 (1.09, 2.15)	2	--
Brain	51	0.92 (0.70, 1.21)	26	1.29 (0.88, 1.90)
Thyroid	39	1.15 (0.84, 1.57)	49	1.25 (0.94, 1.66)
Colon	339	1.02 (0.91, 1.14)	144	1.15 (0.97, 1.37)
Rectum	117	1.05 (0.88, 1.27)	30	0.95 (0.66, 1.37)
Lung and Bronchus	436	0.51 (0.46, 0.57)	133	0.55 (0.46, 0.66)
Urinary Bladder	191	0.68 (0.58, 0.78)	29	0.82 (0.57, 1.19)
Melanoma of the Skin	173	1.05 (0.90, 1.22)	92	1.64 (1.33, 2.02)
Female Breast	33	1.11 (0.79, 1.56)	770	1.66 (1.51, 1.82)
Uterus	4	--	148	1.32 (1.11, 1.56)
Ovary	9	2.88 (1.50, 5.54)	58	0.99 (0.76, 1.28)
Prostate	1,719	1.66 (1.57, 1.77)	7	1.44 (0.69, 3.02)
Hodgkin Lymphoma	18	1.13 (0.71, 1.79)	7	1.16 (0.55, 2.45)
Non-Hodgkin Lymphoma	195	1.17 (1.01, 1.35)	86	1.38 (1.11, 1.72)
B-cell	167	1.22 (1.04, 1.42)	78	1.47 (1.17, 1.85)
DLBCL	74	1.27 (1.01, 1.60)	32	1.48 (1.05, 2.10)
FL	42	1.20 (0.88, 1.62)	23	1.36 (0.90, 2.05)
CLL/SLL/MCL	34	1.51 (1.08, 2.12)	4	--
MZL	10	0.99 (0.53, 1.83)	13	2.45 (1.42, 4.23)
T-cell	12	0.97 (0.55, 1.71)	4	--
NHL, NOS	15	0.92 (0.56, 1.53)	4	--
Leukemia	133	1.13 (0.95, 1.35)	37	1.15 (0.83, 1.59)
Lymphatic	70	1.14 (0.90, 1.44)	17	1.17 (0.73, 1.89)
ALL	3	--	1	--
CLL	61	1.19 (0.93, 1.54)	16	1.32 (0.80, 2.15)

Cancer site	Private Applicators		Spouses	
	Obs (N)	RSIR (95% CI)	Obs (N)	RSIR (95% CI)
Myeloid	58	1.14 (0.88, 1.47)	18	1.10 (0.69, 1.75)
AML	42	1.23 (0.90, 1.66)	16	1.35 (0.82, 2.21)
CML	14	0.95 (0.56, 1.60)	2	--
Multiple Myeloma	71	1.41 (1.11, 1.78)	21	1.30 (0.84, 2.00)

Abbreviations: Diffuse large B-cell lymphoma (DLBCL); Follicular lymphoma (FL); Chronic lymphocytic leukemia/Small lymphocytic lymphoma/Mantle cell lymphoma (CLL/SLL/MCL); Marginal zone lymphoma (MZL); Not otherwise specified (NOS); Acute lymphoblastic leukemia (ALL); Acute myeloid leukemia (AML); Chronic myeloid leukemia (CML).