Cancer Incidence in a Cohort of Licensed Pesticide Applicators in Florida

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This study is a standardized incidence ratio (SIR) analysis of cancer incidence of licensed pesticide applicators in Florida, compared with that of Florida's general population. Through extensive data linkages, 33,658 applicators were assembled who had 1266 incident cancers and 279,397 person-years from January 1, 1975, to December 31, 1993. Disease risk from ethanol and tobacco use were significantly decreased. Among males, prostate cancer (SIR = 1.91; 95% confidence interval [CI], 1.72–2.13) and testicular cancer (SIR = 2.48; 95% CI, 1.57–3.72) were significantly elevated. No confirmed cases of soft tissue sarcoma (STS) were found, and the incidence of non-Hodgkin's lymphoma was not increased. There were few female applicators; nevertheless, cervical cancer incidence (SIR = 3.69; 95% CI, 1.84–6.61) was significantly increased, while the incidence of breast cancer was significantly decreased. Cancers that have been associated with estrogen disrupters were found in male, but not female, pesticide applicators. The lack of soft tissue sarcoma is at odds with prior literature associated with the use of phenoxy herbicides.

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Exposure to pesticides has become ubiquitous to workers and the general public because of increasing and extensive applications and environmental contamination. The acute health effects of pesticides in humans are well documented, if underreported under current surveillance systems; chronic health effects are currently being investigated.[1–9] The most obvious groups in which to study the chronic effects of pesticides in humans are those occupational groups of workers who apply pesticides in high doses as part of their daily activities. Genotoxicity studies and some recent epidemiologic studies in the occupationally exposed populations point to the real possibility of carcinogenic health effects in humans exposed to pesticides.[1–6,10–12]

Despite a variety of methodologic issues,[1,4–6,10–20] based on the weight of evidence, conclusions can be drawn from the aggregate of available chronic disease studies in pesticide-exposed worker populations. Farmers, manufacturers, and pesticide applicators, the main worker groups that have been studied, tend to be healthier, compared with the general population, especially with respect to cardiovascular disease and the diseases associated with heavy tobacco and ethanol use. They are at increased risk from accidents, some of this possibly pesticide-related (eg, aerial sprayers). Farmers are more likely to die of infectious and nonmalignant respiratory diseases; to the extent that certain pesticides have immunologic effects, pesticide exposure may contribute toward these risks, although this aspect has not been studied rigorously as yet.[1,4,20-22]

With respect to cancer, pesticide applicator groups (as opposed to farmers) have an increased risk of cancer, compared with the general population and with other worker groups in most studies. Pesticide applicators and arsenic-exposed manufacturing workers are at risk for lung cancer. Testicular cancer may also be increased among pesticide applicators. Farmers have increased risks of leukemia, multiple myeloma, and prostate cancer. Farmers and pesticide applicators can have elevated risks of stomach cancers. Increased skin cancer risk is seen in both populations but may be unrelated to pesticide exposure (ie, ultraviolet radiation exposure). Brain cancer appears to be increased, not only in these worker populations but possibly in their offspring. Finally, results from numerous studies suggest that the worker populations exposed to the phenoxy acids and other herbicides have an increased risk for soft tissue sarcoma and non-Hodgkin's lymphoma.[1,4-6,15,20,23-27]

To examine the issue of cancer incidence in farmers and pesticide applicators, a large cohort of licensed applicators in the state of Florida was assembled. This study is a standardized incidence ratio (SIR) study of cancer incidence in this cohort of licensed pesticide applicators in Florida.

Materials and Methods

As enforced under the Environmental Protection Agency since 1970, the Federal Insecticide, Fungicide, and Rodenticide Act requires that persons who buy or use the approximately 125 restricted-use pesticides currently available must be certified as competent pesticide applicators or must be directly supervised by a certified applicator. Persons who are not certified pesticide applicators may not purchase or use restricted pesticides unless directly supervised by a certified applicator (up to 15 persons per certified applicator). Certification requires training and written testing for competency in the safe and effective handling and use of these pesticides. Licenses are renewed every 4 years based on continuing education credits and/or written testing; for this study, licensure was assumed to be continuous from the date of first licensure until 4.5 years after date of last licensure. *Private applicators* are persons who use or supervise the use of restricted-use pesticides in agriculture on property owned or rented by themselves or their employer. Examples of private applicators are farmers, ranchers, floriculturists, and orchardists. Therefore, private applicators are considered to be farmers. *Commercial applicators* are persons who use restricted-use pesticides for hire on property other than their own full-time and government workers (*Public applicators*) who apply pesticides as a major component of their jobs. Therefore, members of the combined group of commercial and public applicators are considered to be pesticide applicators.

The core database for this study was the list of pesticide applicators licensed in the state of Florida by the Florida Department of Agriculture and Consumer Services since 1975. This database included each worker's name, Social Security number, and address, but date of birth was missing for approximately 50% of the cohort, predominantly those licensed prior to 1982. In order to locate additional important information (eg, date of birth, date of death, and incident cancer), linkages using a variety of algorithms were performed with other available databases, including the Florida Cancer Data System (FCDS), Florida Department of Motor Vehicles, the Florida Death Tapes (from the Division of Vital Statistics), the Florida Agency for Healthcare Administration, and the Agency for Healthcare Financing, as well as two commercial groups, Equifax and Epidemiologic Resources. The first three databases were linked with the entire pesticide applicator database, whereas the other four databases were only linked for possible lost-to-follow-up cases because of limited resources. The FCDS incident cancer registry database began in 1981; therefore, there are no incident cases of cancer prior to 1981, even though the earliest date of official exposure (ie, licensure) for the cohort was January 1, 1975. The International Classification of Disease diagnosis codes were standardized to the 8th Revision for comparison purposes.

The retrospective cohort study of cancer incidence was performed as an SIR study with the following subpopulation analyses: all applicators, compared with the general Florida population generated by the FCDS; male and female applicators separately, compared with the gender-specific Florida population; and private and public/commercial male applicators separately, compared with the Florida population. The SIRs were age-adjusted and calendar time–adjusted but not race-adjusted, because race information was only available for the deaths and incident cancer cases.

The age-adjusted SIRs were calculated according to the method of Breslow and Day.[28] The 95% confidence intervals (CIs) for the SIRs were calculated as per Rothman, assuming a constant denominator.[29-31] Person-years started upon the first calendar year and month of licensure as of 1981 (the year when the FCDS began to collect incident cases of cancer) and ended with the date of cancer diagnosis, the date of death, or December 31, 1993, the end of the study period; persons licensed prior to 1981 were included in the incidence cohort, but their person-years were not counted until 1981. Because of comparisons with other studies performed on the same cohort, the age and calendar-year groupings are presented in 5-year groups, starting with age 20. For comparisons of means, the two-sample *t* test is utilized. All statistical analyses were performed using SAS version 6.11 software (SAS Institute, Cary, NC).

The protocol for this study was approved by the University of Miami School of Medicine Human Subjects Committee and the FCDS.

Results

From the 39,090 original licenses, Social Security numbers and names were used to identify 37,072 unduplicated licenses. Licensed individuals were excluded from the final cohort (because of limited resources) for the following reasons: license had no date of birth listed (n = 2664); license was missing information (including gender [n = 386]); licensee's date of death or date of licensure occurred before he had reached 18 years of age (n = 21); and/or licensee's death occurred out of state.[51] The vast majority (>95%) of those persons with missing information had obtained their licenses prior to 1980 and had not renewed their licenses.

After the data linkages, 34,211 (92%) unique individuals had complete information. From this total cohort, there were 33,658 applicators aged 20 years and older with 1266 cases of cancer. Over half of these cancer cases (54%) had been diagnosed by 1988. Of these 1266 incident cancer cases, 518 (41%) had died by December 31, 1993, with a mean age at death of 56.85 ± 11.47 years. The total number of person-years for the entire cohort was 279,397 from January 1, 1975, to December 31, 1993.

Of the 33,658 workers aged 20 years and older, there were 3503 (10%) women and 30,155 (90%) men (Table 1). Using last-name assignment as described above, only 1362 (4%) of the cohort were Hispanic. Information on race was only available for 7417 (22%) of the cohort (predominantly the deaths and incident cancer cases); the majority of these individuals (97%) were white.

The mean age at first licensure issue (± standard deviation) was 39.26 ± 13.19 years, with a range of 18 to 89 years; the mean age at first licensure for the women was significantly younger than that for men ($P < 0.0001$) (Table 2). The mean number of years licensed was 6.93 ± 4.27, with a range of 1 month to 19.64 years; for the women, the mean number of years licensed was significantly less than that for the men ($P < 0.0001$).

TABLE 1
Gender and Licensure Distributions

Group	Female (n)	Male (n)	Total (n)
Entire cohort			
Private	2522	20505	22873
Commercial	596	6936	7591
Public	385	2714	3194
Total	3503	30155	33658
Cancer incidence cases			
Private	94	966	1060
Commercial	8	120	128
Public	5	73	78
Total	107	1159	1266
All deaths			
Private	86	1527	1613
Commercial	7	165	172
Public	5	85	90
Total	98	1777	1875

Of the different types of licensure, 22,873 (68%) were Private licenses, 7591 (23%) Commercial, and 3194 (9%) Public. As shown in Table 2, those persons having a Private license were significantly older at first licensure (41.43 ± 13.66 years) and at death (67.57 ± 12.52 years) ($P < 0.0001$); this group was licensed, on average, significantly longer (7.52 ± 4.38 years) than were the workers with Commercial and Public licenses ($P < 0.0001$).

The SIR results for cancer incidence for the male, female, and license subcategories, compared with the Florida population, are presented in Tables 3 and 6. Of note, there was only one case of soft tissue cancer (International Classification of Disease code 171.9), but review of the morphology revealed that it was not a sarcoma; therefore, there were no cases of soft tissue sarcoma death in this cohort, although 2.71 cases were expected.

Male Applicators

There were 30,155 male subjects in the cohort 20 years of age or older with 1159 incident cancers. The total number of person-years for males was 252,486. The mean age at first licensure was 55.91 ± 10.81 years, the mean age at death was 57.96 ± 10.41 years, and the mean number of years licensed was 9.12 ± 3.94 for the male incident cases of cancer; these were all significantly greater than the overall means for the rest of the cohort. The SIR results for cancer incidence for all male applicators, compared with the Florida population, are presented in Table 3.

The SIR for all malignancies was significantly decreased, compared with the general Florida population (SIR = 0.71; 95% CI, 0.67–0.76). In general, most site-specific cancer incidence rates were lower for the male pesticide applicators, compared with the rates for the Florida population. The incidence of cancers associated with tobacco exposure was significantly decreased, such as that for respiratory tract (SIR = 0.77; 95% CI, 0.67–0.88) and lung (SIR = 0.80; 95% CI, 0.70–0.92) cancers. The exceptions to this were increased cancer incidences for testicular (SIR = 2.48; 95% CI, 1.57–3.72), prostate (SIR = 1.91; 95% CI, 1.72–2.13), eye (SIR = 1.79; 95% CI, 0.53–4.18), and bone (SIR = 1.56; 95% CI, 0.50–3.64) cancers; prostate and testicular cancer incidences were significantly elevated, while there were only five cases each of eye and bone cancers.

Female Applicators

There were 3503 female subjects in the cohort with 107 female incident cancers. The total number of person-years for females was 26,911. The female applicators with cancer diagnosis were significantly younger (with a mean age at first licensure 49.58 ± 12.71), were significantly younger at cancer death (mean age

TABLE 2
Mean (± Standard Deviation) Age at Licensure, Length of Time Licensed, and Age at Death by Gender, and License Type

Group	Female	Male	Total	*t* Test *P* Value
Cohort				
Mean age at first licensure	37.68 ± 12.32	39.45 ± 13.27	39.26 ± 13.19	0.0001
Mean number of years licensed	5.47 ± 3.04	7.09 ± 4.36	6.93 ± 4.27	0.0001
Mean age at death	62.43 ± 15.45	66.12 ± 13.52	65.92 ± 13.65	0.02
Cancer incidence cases				
Mean age at first licensure	49.58 ± 12.71	55.91 ± 10.81	54.87 ± 11.41	0.0001
Mean number of years licensed	7.25 ± 3.11	8.94 ± 3.68	8.80 ± 3.67	0.0001
Mean age at death	54.47 ± 9.34	57.96 ± 10.41	56.85 ± 11.47	0.05
All deaths				
Mean age at first licensure	53.37 ± 13.26	56.55 ± 12.35	56.38 ± 12.42	0.02
Mean number of years licensed	7.27 ± 2.73	8.23 ± 2.99	8.18 ± 2.98	0.001
Mean age at death	62.43 ± 15.45	66.12 ± 13.52	65.92 ± 13.65	0.02
	Private	**Commercial/ Public**	**Total**	***t* Test *P* Value**
Cohort				
Mean age at first licensure	41.42 ± 13.65	35.91 ± 10.59	39.26 ± 13.19	0.0001
Mean number of years licensed	7.52 ± 4.38	5.68 ± 3.74	6.93 ± 4.27	0.0001
Mean age at death	67.55 ± 12.52	55.31 ± 12.59	65.92 ± 13.65	0.0001

54.47 ± 9.34), and had significantly less exposure (mean number of years licensed 7.38 ± 3.31) than their male colleagues with cancer. The SIR results for cancer incidence for all female applicators compared to the Florida population are presented in Table 3.

The SIR for all malignancies was significantly decreased for female applicators (SIR = 0.72; 95% CI, 0.59–0.87). In general, most site-specific cancer incidence rates were decreased for the female pesticide applicators, compared with the rates for the Florida population. There were no cases of cancer of the esophagus, stomach, liver, larynx, bone, skin, or eye, nor were there any cases of Hodgkin's lymphoma. The incidence of cancers associated with tobacco exposure was decreased, such as that for respiratory tract (SIR = 0.56; 95% CI, 0.31–0.92) and lung (SIR = 0.62; 95% CI, 0.35–1.02) cancers. The incidence of female genital cancers was significantly increased, including that for all genital (SIR = 2.07; 95% CI, 1.31–3.10) and cervical (SIR = 3.69; 95% CI, 1.84–6.61) cancers; breast cancer incidence was significantly decreased (SIR = 0.61; 95% CI, 0.40–0.90). The thyroid cancer incidence was slightly elevated (SIR = 1.32; 95% CI, 0.15–4.77), but this was statistically insignificant and based on very low numbers.

Exposure

The majority of the cohort (54%) had obtained their pesticide licenses by 1984, with 39 ± 13.19 years as the mean age of first licensure; the mean number of years of licensure for the entire cohort was 6.93 ± 4.27 years, ranging from 1 month to 19.64 years, with a total number of person-years for the cohort of 320,250 from January 1, 1975, to December 31, 1993.

The SIRs for overall cancer incidence were consistently and significantly less than that of the Florida population (Table 4). However, a trend of decreasing cancer incidence from the earliest years of licensure (1975–1979: SIR = 0.76; 95% CI, 0.71–0.82) to the most recent (1990–1994: SIR = 0.34; 95% CI, 0.20–0.54) was observed, despite age adjustment. Similar results and trends were seen by gender subgroup and for testicular and prostate cancer, but not for cervical cancer.

However, for the overall cancer incidence by numbers of years licensed, in 4-year groupings (Table 5), there was an inverse dose-response relationship in which the trend is one of decreasing risk with increasing years of licensure, from the fewest years of licensure (0–4 years: SIR = 0.84; 95% CI, 0.65–1.06) to the greatest number (16–20 years: SIR = 0.42; 95% CI, 0.33–0.53). Similar results were seen for cervical cancer (not shown). Testicular cancer incidence showed a suggestion of a trend of increasing risk with increasing number of years exposed, especially in the calendar year subpopulations; prostate cancer had an uniformly elevated risk despite increasing years of exposure, although, again for the earliest 1975–1979 subcohort, there is a suggestion of a positive dose-response (latter not shown).

Private (Farmers) Male Applicators

Only male applicators were included in these subpopulation analyses because of the relatively small numbers of female applicators in each licensure subpopulation. There were 20,505 Private (Farmer) male applicators with 966 (76%) of the entire cohort incident cancers. The SIR results for causes of cancer in-

TABLE 3
Male and Female Applicators: Cancer Incidence Standardized Incidence Ratios (SIRs) and 95% Confidence Intervals (95% CIs)†

Cancer Cause	Males		Females	
	Observed Number	Florida SIR (95% CI)	Observed Number	Florida SIR (95% CI)
All sites	1159	0.71 (0.67–0.76)*	107	0.72 (0.59–0.87)*
Buccal/pharynx	35	0.66 (0.46–0.92)*	5	1.03 (0.33–2.40)
Digestive	227	0.76 (0.66–0.87)*	15	0.55 (0.31–0.91)*
Esophagus	14	0.84 (0.46–1.41)	0	0.33 (0.00–3.11)
Stomach	15	0.53 (0.30–0.88)*	0	0.19 (0.00–1.80)
Large intestine	98	0.70 (0.57–0.85)*	10	0.78 (0.37–1.44)
Rectum	52	0.88 (0.66–1.15)	3	0.56 (0.11–1.63)
Liver	18	1.13 (0.67–1.78)	0	0.34 (0.00–3.14)
Pancreas	26	0.85 (0.56–1.25)	1	0.36 (0.01–2.00)
Respiratory	230	0.77 (0.67–0.88)*	15	0.56 (0.31–0.92)*
Larynx	12	0.47 (0.24–0.83)*	0	0.22 (0.00–2.06)
Lung	216	0.80 (0.70–0.92)*	15	0.62 (0.35–1.02)
Bone	5	1.56 (0.50–3.64)	0	1.53 (0.00–14.23)
Skin	48	0.93 (0.69–1.24)	5	0.93 (0.30–2.17)
Bladder	59	0.96 (0.73–1.24)	3	0.54 (0.11–1.58)
Kidney	26	0.74 (0.48–1.08)	1	0.31 (0.01–1.71)
Eye	5	1.79 (0.58–4.18)	0	1.88 (0.01–17.56)
Brain/central nervous system	24	1.09 (0.70–1.62)	2	0.92 (0.10–3.31)
Thyroid	6	0.42 (0.15–0.92)*	2	1.32 (0.15–4.77)
All lymphopoietic	76	0.90 (0.71–1.13)	6	0.74 (0.27–1.60)
Lymphosarcoma	32	0.90 (0.62–1.27)	2	0.58 (0.07–2.11)
Hodgkin's	8	1.06 (0.46–2.10)	0	0.59 (0.00–5.47)
Leukemia	25	0.93 (0.60–1.37)	3	1.17 (0.24–3.42)
Other lymphatic	11	0.78 (0.39–1.39)	1	0.77 (0.01–4.30)
Soft tissue sarcoma	0	0.41 (0.01–2.26)	0	2.06 (0.01–19.19)
Male and female cancers				
Prostate	353	1.91 (1.72–2.13)*	0	
Testis	23	2.48 (1.57–3.72)*	0	
Breast	2	0.52 (0.06–1.87)	26	0.61 (0.40–0.90)*
All genital	0		23	2.07 (1.31–3.10)*
Cervix	0		11	3.69 (1.84–6.61)*
Uterus	0		11	1.44 (0.72–2.58)
Other genital	0		3	0.90 (0.18–2.62)

*, Statistically significant 95% CI.
† All ratios are age- and calendar year-adjusted; where no cases exist, SIRs and CIs were calculated assuming $n = 0.5$.

cidence for all Private (Farmer) male applicators, compared with the entire Florida population, are listed in Table 6.

Cancer incidence for the Private male applicators was significantly decreased, compared with the Florida population (SIR = 0.72; 95% CI, 0.67–0.77). The majority of site-specific cancer incidences were decreased, compared with the Florida population, including tobacco-related respiratory tract (SIR = 0.75; 95% CI, 0.65–0.87) and lung (SIR = 0.78; 95% CI, 0.67–0.90) cancers. Testicular (SIR = 2.37; 95% CI, 1.33–3.91) and prostate cancer (SIR = 1.97; 95% CI, 1.76–2.20) incidences were significantly elevated. Hodgkin's lymphoma (SIR = 1.50; 95% CI, 0.65–2.96) and eye (SIR = 1.33; 95% CI, 0.27–3.89) cancer incidences were somewhat elevated but not significantly.

Commercial and Public Male Applicators

There were 9650 Commercial and Public male applicators with 193 (15%) of the cohort incident cancers. Of these combined male applicators, 6963 were Commercial applicators (72%) and 2714 were Public (28%). The SIR results for cancer incidence for all Commercial and Public male applicators, compared with the entire Florida population, are listed in Table 6.

Cancer incidence for the Public and Commercial male applicators was significantly decreased, compared with the Florida population (SIR = 0.69; 95% CI, 0.59–0.79). The majority of site-specific cancer incidences were decreased, compared with the Florida population, including tobacco-related respiratory tract (SIR = 0.86; 95% CI, 0.62–1.15) and lung (SIR = 0.91; 95% CI, 0.65–1.24) cancers. Testicular

TABLE 4
All, Male, and Female Applicators: Cancer Incidence SIRs and 95% CIs, by Calendar Year of First Licensure†

Licensure Year	Observed Number	Florida SIR (95% CI)
Overall cancer incidence		
All applicators		
1975–1979	865	0.76 (0.71–0.82)*
1980–1984	259	0.68 (0.60–0.77)*
1985–1989	124	0.61 (0.50–0.72)*
1990–1994	18	0.34 (0.20–0.54)*
All males		
1975–1979	807	0.77 (0.71–0.82)*
1980–1984	232	0.68 (0.59–0.77)*
1985–1989	104	0.58 (0.47–0.70)*
1990–1994	16	0.33 (0.19–0.54)*
All females		
1975–1979	58	0.73 (0.56–0.95)*
1980–1984	27	0.69 (0.45–1.00)
1985–1989	20	0.78 (0.48–1.21)
1990–1994	2	0.46 (0.05–1.66)
Testicular cancer incidence		
All males		
1975–1979	11	3.18 (1.58–5.69)*
1980–1984	8	2.90 (1.25–5.72)*
1985–1989	4	1.73 (0.47–4.44)
1990–1994	0	
Prostate cancer incidence		
All males		
1975–1979	256	1.98 (1.75–2.24)*
1980–1984	65	1.86 (1.44–2.38)*
1985–1989	29	1.79 (1.20–2.57)*
1990–1994	3	0.71 (0.14–2.07)
Cervical cancer		
All females		
1975–1979	2	2.19 (0.25–7.91)
1980–1984	1	1.06 (0.01–5.88)
1985–1989	8	8.54 (3.68–16.82)*
1990–1994	0	

* Statistically significant 95% CI.
† All ratios are age-adjusted.

(SIR = 2.72; 95% CI, 1.17–5.36) and prostate cancer (SIR = 1.54; 95% CI, 1.09–2.13) incidences were significantly elevated. Eye (SIR = 3.74; 95% CI, 0.42–13.51), bone (SIR = 2.67; 95% CI, 0.30–9.63), stomach (SIR = 1.33; 95% CI, 0.48–2.89), and large intestine (SIR = 1.28; 95% CI, 0.84–1.88) cancer incidence rates were elevated but not significantly; there were only two cases each for eye and bone cancers.

Discussion

These licensed Florida pesticide applicators have significantly decreased incidences of cancer, compared with the general Florida population, even in the subpopulations analyzed by gender and license type. Furthermore, as seen in many other studies of agricultural and pesticide-exposed workers, this cohort has a decreased risk of cancer from etiologies associated with the use of tobacco products and ethanol.[1,4–6,15,20,23–27]

Data Limitations

This study is one of the few studies of cancer incidence, as opposed to mortality, in farmers and pesticide applicators. Nevertheless, these analyses suffer from many of the data limitations seen in previous epidemiologic studies of pesticide-exposed workers.[1,4–6,10–20] Individual and cohort-specific confounding factors (such as smoking) and detailed pesticide-exposure information were not obtained for this cohort. Additional limitations include issues of the healthy worker effect, exposure measures, and loss to follow-up.

The use of the Florida population as the major comparison population is appropriate for geographic and logistic considerations. However, in occupational studies, the use of a general population as a comparison population must inherently raise the issue of the previously discussed healthy worker effect, even for chronic diseases such as cancer; it is preferable to perform internal analyses (as done in comparing the Private to the other licensure groups) or use an external occupational cohort group.[28,30–33] Of note, additional analyses (not presented) were performed by the investigators comparing the mortality experience of this cohort to the mortality experience of the National Cancer Institute's pooled occupational data set known as CORPS (Computerized Occupational Referent Population System), excluding any cohorts with known pesticide exposure. In standardized mortality ratio analyses, this National Cancer Institute's worker data set was very similar in its mortality experience to the general Florida population, in part because of the fact that the CORPS subjects were all involved in cohort studies of workers exposed to possible carcinogens. Thus these additional analyses did not solve the bias of the healthy worker effect for this cohort.

The exposure measures are relatively crude and nonspecific, based on the licensure calendar year and years of exposure, as well as the licensure subgroup and certification subcategory. Therefore, licensure serves as a surrogate measure for exposure; this assumes that the ap-

TABLE 5
All, Male, and Female Applicators: Cancer Incidence SIRs and 95% CIs by Years of Licensure†

Years of Licensure	Observed Number	Florida SIR (95% CI)
Overall cancer incidence		
All applicators		
0 ≤ 4	69	0.84 (0.65–1.06)
4 ≤ 8	431	0.71 (0.65–0.78)*
8 ≤ 12	552	0.77 (0.71–0.84)*
12 ≤ 16	136	0.72 (0.60–0.85)*
16 ≤ 20	69	0.42 (0.33–0.53)*
All males		
0 ≤ 4	60	0.83 (0.63–1.07)
4 ≤ 8	373	0.70 (0.63–0.77)*
8 ≤ 12	520	0.79 (0.72–0.86)*
12 ≤ 16	131	0.73 (0.61–0.86)*
16 ≤ 20	66	0.41 (0.32–0.52)*
All females		
0 ≤ 4	9	0.91 (0.41–1.72)
4 ≤ 8	58	0.85 (0.65–1.10)
8 ≤ 12	32	0.58 (0.39–0.82)*
12 ≤ 16	5	0.51 (0.16–1.19)
16 ≤ 20	3	0.71 (0.14–2.08)
Testicular cancer incidence		
All males		
0 ≤ 4	0	
4 ≤ 8	12	3.06 (1.12–6.66)*
8 ≤ 12	16	6.22 (2.68–12.26)*
12 ≤ 16	8	10.13 (2.73–25.94)*
16 ≤ 20	6	7.16 (1.44–20.92)*

*, Statistically significant 95% CI.
† All ratios are age- and calendar year-adjusted.

plicator uses the restricted chemicals throughout the 4-year licensure period; that in the case of older persons, the applicator did not apply prior to the beginning of the licensure program (ie, prior to the beginning of the cohort); and that the applicator is actually applying the restricted-use pesticides rather than acting in a purely supervisory role, since each licensed applicator may oversee up to 15 other individuals. Furthermore, licensure allows the acquisition and use of over 125 different restricted-use pesticides; no individual pesticide-exposure data, beyond certain certification categories, were available. Another limitation is the lack of individual or even group measures of important confounding exposure variables, such as tobacco use or even nonoccupational pesticide exposure. The lack of these data is an important limitation on the conclusions that can be drawn from these analyses.

Date of birth information was not available for 2664 individuals in the cohort; this information was not collected by the state nor was it found through the multiple data linkages performed. The majority of these individuals (>95%) were licensed prior to 1980, without subsequent license renewal; had minimal exposure, since they did not renewal their licenses; and are assumed to be alive, since they were not located by multiple data linkages. Nevertheless, these persons were ultimately excluded from the master database cohort because date of birth information is essential for the statistical analyses performed. If the majority of these persons are alive, this would decrease the paradoxical dose-response effects seen in the SIR when the number of years licensed and the age at first licensure are evaluated; if of the majority these persons are dead, then the paradoxical effects would be even greater. Regardless, the loss of these persons from the cohort is an important limitation to these analyses and conclusions.

Overall, this cohort is relatively young, with relatively little post-licensure exposure (6.93 ± 4.27 mean years of exposure); therefore, much of the cancer experience of this cohort will occur in the future. Furthermore, although the licensure system started arbitrarily in 1975, substantial numbers of people in the cohort could have been exposed to pesticides prior to this licensure. In addition, the lack of cancer incidence data prior to 1980 may have lead to an underestimate of cancer incidence for this cohort (although it also effectively introduces a 5-year latency period). Therefore, given the imprecise exposure measure, the loss of subjects from the early years of the cohort, the healthy worker effect (including the selection of healthier workers' overtime), and the possibility of pesticide exposure prior to the beginning of the cohort study, the inconsistencies noted in the evaluation of dose response—especially for duration of exposure—can be understood. Of interest, subcohort analysis for 1975 to 1980 did show trends of increasing risk with increasing number of years' exposure for prostate and testicular cancer incidences.

Males

With regards to cancer among male applicators, the most consistently elevated cancer incidence rates were those for testicular and prostate cancers. However, in contrast to the literature, the incidence rates of these cancers were elevated in both licensure-type subcohorts (Private vs Commercial and Public). This suggests the possibility that previous mortality studies of pesticide-exposed workers may have underestimated the risks of these cancers since

TABLE 6
Male Private (Farmer) Versus Commercial and Public Applicators: Cancer Incidence SIRs and 95% CIs

Cancer Cause	Private		Commercial and Public (Combined)	
	Observed Number	Florida SIR (95% CI)	Observed Number	Florida SIR (95% CI)
All sites	966	0.72 (0.67–0.77)*	193	0.69 (0.59–0.79)*
Buccal/pharynx	26	0.61 (0.40–0.90)*	9	0.88 (0.40–1.68)
Digestive	181	0.72 (0.62–0.83)*	46	1.00 (0.73–1.33)
Esophagus	11	0.80 (0.40–1.43)	3	1.04 (0.21–3.05)
Stomach	9	0.38 (0.17–0.73)*	6	1.33 (0.48–2.89)
Large intestine	72	0.60 (0.47–0.76)*	26	1.28 (0.84–1.88)
Rectum	48	0.97 (0.72–1.29)	4	0.41 (0.11–1.06)
Liver	16	1.20 (0.69–1.95)	2	0.75 (0.08–2.72)
Pancreas	22	0.85 (0.53–1.29)	4	0.86 (0.23–2.21)
Respiratory	187	0.75 (0.65–0.87)*	43	0.86 (0.62–1.15)
Larynx	10	0.48 (0.23–0.89)*	2	0.44 (0.05–1.57)
Lung	175	0.78 (0.67–0.90)*	41	0.91 (0.65–1.24)
Bone	3	1.22 (0.25–3.57)	2	2.67 (0.30–9.63)
Skin	37	0.95 (0.67–1.31)	11	0.87 (0.43–1.56)
Bladder	53	1.01 (0.75–1.32)	6	0.69 (0.25–1.50)
Kidney	22	0.76 (0.47–1.15)	4	0.64 (0.17–1.64)
Eye	3	1.33 (0.27–3.89)	2	3.74 (0.42–13.51)
Brain/central nervous system	20	1.17 (0.71–1.80)	4	0.82 (0.22–2.09)
Thyroid	4	0.39 (0.10–0.99)*	2	0.53 (0.06–1.90)
All lymphopoietic	65	0.95 (0.74–1.22)	11	0.68 (0.34–1.22)
Lymphosarcoma	26	0.91 (0.59–1.33)	6	0.88 (0.32–1.91)
Hodgkin's	8	1.50 (0.65–2.96)	0	0.50 (0.00–2.35)
Leukemia	22	1.00 (0.62–1.51)	3	0.63 (0.13–1.83)
Other lymphatic	9	0.75 (0.34–1.43)	2	0.89 (0.10–3.22)
Soft tissue sarcoma	0	0.50 (0.02–7.50)	0	1.87 (0.02–10.39)
Male cancers only				
Prostate	316	1.97 (1.76–2.20)*	37	1.54 (1.09–2.13)*
Testis	15	2.37 (1.33–3.91)*	8	2.72 (1.17–5.36)*
Breast	2	0.70 (0.00–2.15)		

*, Statistically significant 95% CI.
† All ratios are age- and calendar year-adjusted; where no cases exist, SIRs and CIs were calculated assuming $n = 0.5$.

testicular and prostate cancers have much higher incidence rates than mortality rates, because of excellent treatment available for the former and the general indolence of the latter.[6,11,10,34-36]

As mentioned earlier, an elevated prostate cancer risk is a consistent finding in most previous studies of farmers. Given farmers' high occupational ultraviolet radiation exposure, this finding is at odds with current theories concerning the possible protective effects of vitamin D exposure.[37] One possible explanation is that these relatively healthy working populations are more likely to get prostate cancer simply because they do not die of other competing causes of mortality so common in the general population, given the extremely high prevalence of prostate cancer in elderly men. Organochlorine pesticides as possible estrogen analogs and their possible relation to worldwide increases in testicular cancer and prostate cancer are also of interest. Male alligators in Florida with heavy organochlorine exposure were found to be reproductively incompetent, while recent reports have raised the question of an overall worldwide significant decrease in human sperm counts and increases in cryptorchidism, which are possibly related to pesticide use.[38-40] More recently, some of the organochlorines have been shown in animal models to be anti-androgens.[40]

Eye and bone cancers were also elevated among the male applicators; the small number of cases makes definitive interpretation difficult, although similar elevations have been seen in other studies. Compared with other studies, the risks of leukemia and brain cancer were not elevated in this incidence study.[6,11,34,41-44]

There were no confirmed cases of soft tissue sarcoma in this cohort of pesticide applicators, although over two cases were expected, and the incidence of non-Hodgkin's lymphoma was not increased in any of the subpopulations examined. These findings are at odds with previously published literature associating the use of the phenoxy herbicides among farmers and pesticide applicators with an increased risk of non-Hodgkin's lymphoma and soft tissue sarcoma.[45-48]

Females

The number of female applicators was relatively small, as were the numbers of incident cases of cancer in this subpopulation. They were also significantly younger and had significantly decreased exposure times, compared with their male counterparts. The female applicators are definitely healthier than the comparison Florida population. Nevertheless, although comparisons cannot be made across SIRs, as described above, the female applicators, on the whole, appear to be healthier than the male applicators; this may be due to their decreased exposure time, as well as the unstable risk measurements that occurred because of the small number of female applicators. Breast cancer incidence was not elevated in any of the subpopulations, despite the presence of multiple organochlorine pesticides on the Restricted Pesticide List. Only a few studies of occupational exposure to organochlorines in women exist with which current hypotheses concerning the possible etiologic relationship between exposure to organochlorines (as estrogen analogs) and the increased risk of breast cancer can be tested. Furthermore, all studies to date have been in nonoccupational groups.[49,50]

Cervical cancer incidence was significantly increased in all women and in both subpopulations. The fact that cervical cancer was increased in the cancer incidence but not in prior mortality studies is consistent with the availability of excellent screening and treatment techniques that now exist. A significantly increased risk of cervical cancer with increased number of years of exposure was seen. Very little has been published on female pesticide applicators in general; therefore, although this study involved a small subpopulation, these findings are of interest and deserve to be studied further.[1,23–25]

Private (Farmers) Versus Commercial and Public Applicators

With regards to the comparison of licensure category, both licensure subcategories have a significantly elevated risk for prostate and testicular cancer incidence in this study but not in prior mortality studies. Prostate cancer has been found to be elevated in farmers in multiple studies, while Wiklund et al reported the elevation for incident testicular cancer in Swedish pesticide applicators and other groups reported limited elevated mortality among various worker groups.[21,35,51–56] Many of the pesticide applicator studies have been cancer mortality studies, rather than cancer incidence studies. This is important since testicular and prostate cancers have much higher incidence rates than mortality rates. This does not explain why the subpopulations would have different mortality rates but similar incidence rates, unless (1) the cancers are more aggressive in the licensure subcategories, (2) there are access-to-care issues, (3) there is a possible diagnostic bias, or (4) there is a relative lack of competing causes of death, by licensure subcategories.

Finally, as opposed to the increased risk for lung cancer seen among several cohorts of pesticide applicators (including a separate cohort of structural fumigators and household pesticide applicators in Florida), lung cancer incidence was nonsignificantly decreased among the Commercial and Public pesticide applicators.[52,57–59]

As with many of the existing studies on occupational pesticide exposure, this cohort of Florida pesticide applicators deserves further research. Completing the follow-up process for the 8% of the cohort that is currently lost to follow-up would be worthwhile, as would extending the number of years of follow-up for the entire cohort in the future. In particular, detailed individual exposure information for pesticides and confounders should be sought. Additional studies of the 15 or fewer workers supervised by an individual licensed pesticide applicator are also recommended since these individuals may be even more highly exposed than the licensed supervisor.

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