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Pesticide exposure and incident thyroid cancer among male pesticide applicators in Agricultural Health Study

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Abstract

Background: Many pesticides are known to have thyroid-disrupting properties. However, few studies have evaluated the association between specific pesticide ingredients and risk of thyroid cancer. We investigated self-reported pesticide use and incident thyroid cancer in the Agricultural Health Study (AHS), a large cohort of occupationally-exposed male pesticide applicators.

Methods: The AHS is a prospective cohort of licensed pesticide applicators in Iowa and North Carolina. At enrollment (1993–1997) and follow-up (1999–2005), participants reported use of 50 pesticides. We characterized exposure as ever use (44 pesticides with ≥5 exposed cases) and by cumulative intensity-weighted lifetime days (22 pesticides with ≥10 exposed cases), a metric that accounts for factors that influence exposure. We estimated hazard ratios (HR) and 95% confidence intervals (CI) using Cox regression for incident thyroid (n=85 cases) cancer among male participants using follow-up through 2014/2015.

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Declaration of competing financial interests

The authors declare they have no actual or potential competing financial interests.

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Results: Use of the fungicide metalaxyl (HR=2.03, CI:1.16–3.52) and the organochlorine insecticide lindane (HR=1.74, CI:1.06–2.84) was associated with increased risk of thyroid cancer. The herbicide chlorimuron-ethyl was inversely associated with risk when we restricted to papillary thyroid cancer, the most common subtype (HR=0.52, CI:0.28–0.96). High use of the insecticide carbaryl (>median intensity-weighted days) was inversely associated with thyroid cancer (HR=0.20, CI:0.08–0.53, p_{trend}=0.001).

Conclusions: In this large cohort study, we observed increased risk of thyroid cancer associated with use of metalaxyl and lindane, and an inverse association with carbaryl. More work is needed to understand the potential role of these chemicals in thyroid carcinogenesis.

Keywords

Pesticides; thyroid cancer; agriculture; epidemiology

BACKGROUND

Over the past several decades, thyroid cancer incidence rates have increased worldwide (Engholm et al. 2010; Kilfoy et al. 2009). While improved detection of small, non-aggressive tumors may in part explain this upward trend, incidence rates for larger and advanced-stage thyroid cancers are also on the rise (Enewold et al. 2009; Lim et al. 2017). The North American Association of Central Cancer Registries estimates that thyroid cancer incidence overall among white men has been relatively stable (7.8 per 100,000 population) in recent years, with similar trends for Iowa (IA) and North Carolina (NC) (NAACCR 2018). Compared to women, men are more likely to be diagnosed with more aggressive late stage disease (Olson et al. 2019). Environmental exposures may also be contributing to rising thyroid cancer incidence. Specifically, chemicals with endocrine disrupting properties have garnered interest as potential risk factors. Certain organochlorine, organophosphate, carbamate, and pyrethroid insecticides can interfere with thyroid function (IARC 2001; Boas et al. 2009). Additionally, degradation products of the ethylenebisdithiocarbamate (EBDC) fungicides inhibit thyroid peroxidase activity and cause thyroid tumors in laboratory animals (Chhabra et al. 1992). Other thyroid disrupting mechanisms for pesticides have been posited, such as inhibiting iodine uptake, binding to thyroid hormone receptors and transport proteins, interfering with iodothyronine deiodinase and thyroid peroxidase activities, increasing clearance of thyroid hormones, interfering with cellular uptake of thyroid hormones, and modifying thyroid gene expression (Boas et al. 2006; Boas et al. 2009; Zoeller 2007).

Several epidemiologic studies have evaluated the association between pesticide use and thyroid cancer. Thyroid cancer incidence is elevated in the Agricultural Health Study (AHS) cohort compared to the general population (Lerro et al. 2019), though no excess was observed in a French agricultural cohort (Lemarchand et al. 2017). Among predominately male pesticide applicators in the AHS, atrazine, a commonly-used corn herbicide, was associated with elevated risk of thyroid cancer with 29 exposed cases (Freeman et al. 2011). In the AHS, use of malathion, an organophosphate insecticide, was associated with elevated thyroid cancer risk among women living and working on farms (Lerro et al. 2015). In population-based Norwegian studies, some serum organochlorine pesticide

metabolites have been positively (chlordane, hexachlorobenzene [HCB]) and inversely (dichlorodiphenyltrichloroethane [DDT]) associated with incident thyroid cancer (Grimalt et al. 1994; Lerro et al. 2018b). A case-control study in the US found that occupational pesticide exposure, based on a job-exposure matrix, was not associated with thyroid cancer, though the authors did observe positive associations with occupational use of biocides (e.g. disinfection products) (Zeng et al. 2017). A 2014 review of occupation and thyroid cancer found that occupation as a farmer or agricultural worker was generally not associated with elevated thyroid cancer risk (Aschebrook-Kilfoy et al. 2014). The only positive results were from a Scandinavian study that observed increased thyroid cancer incidence among female farmers (Pukkala et al. 2009). A recent US case-control study also found that occupation in the pest control industry was associated with elevated risk of papillary thyroid cancer (Ba et al. 2016). Notably, none of the studies assessing occupation as a farmer/pesticide applicator or utilizing a job-exposure matrix to estimate pesticide exposure were able to distinguish specific pesticide products or ingredients.

While the associations between pesticides and thyroid disease and thyroid hormone disruption have been systematically evaluated in the AHS cohort (Goldner et al. 2010; Goldner et al. 2013; Lerro et al. 2018a; Shrestha et al. 2018a; 2018b), the associations between pesticides and thyroid cancer have not. We utilized data from male pesticide applicators in the prospective AHS cohort to comprehensively evaluate the association between self-reported use of specific pesticides and incident thyroid cancer.

METHODS

Study Population

The AHS is a prospective cohort that includes 57,310 licensed private and commercial pesticide applicators enrolled during 1993–1997 in IA and NC (Alavanja et al. 1996). Applicators were recruited when they applied for or renewed their restricted use pesticide license and enrolled by completing a self-administered questionnaire. We conducted follow-up via computer-assisted telephone interview approximately five years after enrollment during 1999–2005. Questionnaires are available at https://aghealth.nih.gov/collaboration/questionnaires.html. The study protocol, including implied consent for completion of questionnaires, was approved by all relevant institutional review boards.

Case Ascertainment and Classification

We obtained incident thyroid cancer diagnoses via linkage with IA and NC state cancer registries. We analyzed first primary cancers diagnosed from enrollment through date of death, movement out of state, or last study follow-up (December 31, 2015 for IA, December 31, 2014 for NC), whichever was earliest. Thyroid cancer (C73) was classified according to the International Classification of Diseases for Oncology, third revision (ICD-O-3) (Fritz 2000). We also separately evaluated papillary thyroid cancers (ICD-O-3 morphology codes 8050, 8260, 8340–8344, 8350, 8450–8460). We evaluated tumor characteristics of incident thyroid cancer cases in the AHS including Surveillance, Epidemiology and End Results (SEER) stage (1,2,3, missing/unknown), histologic subtype (papillary, follicular, medullary,

other/NOS), tumor size (<1 cm, 1–2 cm, >2 cm), and grade (I, II, III, IV, missing/unknown) and compared them to characteristics of thyroid tumors in the general population.

Exposure Assessment

At enrollment, applicators provided information on ever use of 50 pesticides. Duration (years) and frequency (average days/year) of pesticide use in categories were assessed in the initial enrollment questionnaire for 22 pesticides. The applicators were given a questionnaire to take home and complete, which collected detailed exposure for an additional 28 pesticides (completed by n=25,391, 44%). We used category midpoints to estimate cumulative days of exposure at enrollment. In the follow-up computer-assisted telephone interview, applicators reported days/year they applied each pesticide in the last year they farmed. If the last year farmed was after study enrollment, we assumed the applicator applied the pesticide for the days/year reported at follow-up interview for each year from enrollment through the last year farmed. We used a multiple imputation procedure to estimate pesticide exposures at follow-up for individuals who did not complete the interview (n=20,968, 37%) (Heltshe et al. 2012).

We evaluated ever use of pesticides at enrollment, as well as cumulative lifetime days and intensity-weighted days of pesticide use through the follow-up interview. Intensity-weighted days is lifetime days multiplied by an intensity-weighting factor, which incorporates information on factors that influence pesticide exposure, including repair and cleaning of equipment, application method, whether the applicator mixed pesticides, and personal protective equipment use (Coble et al. 2011). Lifetime days and intensity-weighted days were categorized as above or below the median among thyroid cancer cases for pesticides with 10–19 exposed cases, and in quartiles for pesticides with 20+ exposed cases (Supplementary Table S1). We excluded applicators missing information for a pesticide of interest from that analysis.

Statistical Analysis

We excluded participants with prevalent cancer at enrollment (n=1,096), those who lived outside of IA/NC at enrollment (n=341), female pesticide applicators (n=1,531 including 5 thyroid cancer cases), and those who did not answer any pesticide questions at enrollment (n=1,246), leaving 53,096 male applicators for our analysis.

We computed hazard ratios (HR) and 95% confidence intervals (CIs) for use of each pesticide relative to never users with Cox proportional hazards regression, using age as the time scale. All models were adjusted for state (IA, NC), applicator type (private, commercial), cigarette smoking history at enrollment (never, former smoker [≥100 lifetime cigarettes], current smoker, missing), body mass index (BMI, <25 kg/m^2, 25–29.9, ≥30, missing), and correlated pesticides (Spearman ρ>0.4, Supplemental Table S1). The rationale for adjusting for state of residence and applicator type is to account for potential residual confounding that may exist after adjustment for known demographic and behavioral risk factors for thyroid cancer (Lerro et al. 2019), as well as latent differences in farming practices between states and applicator type that may influence both exposure and risk. Farmers apply multiple pesticides, and although the correlations between pesticides were

modest, we adjusted for the most highly correlated pesticide exposures to evaluate whether the observed effects for a single ingredient were influenced by other pesticides.

We evaluated Schoenfeld residuals to check the proportional hazard assumption. To address issues related to latency, we lagged intensity-weighted days of pesticide use in five year increments up to 30 years; we present 15-year exposure lags as the number of exposed cases becomes very small with longer lags. We conducted sensitivity analyses restricting models to papillary thyroid cancer, the most common histologic subtype (77.7%). We also conducted sensitivity analyses (for ever/never pesticide exposures) restricted to applicators who never reported diagnosis of non-malignant thyroid disease (including hyperthyroidism, hypothyroidism, goiter, and other thyroid conditions) at either enrollment (1993–97), first follow-up (1999–2005), or second follow-up (2005–2010). Missing thyroid disease status was imputed five times; additional detail for these methods is provided in the supplemental material. Analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC). All statistical tests were two-sided with α=0.05.

RESULTS

There was a median of 12.5 and 19.8 years of follow-up among 85 thyroid cancer cases and 53,011 non-cases, respectively. Sociodemographic and farm characteristics for cases and non-cases are displayed in Table 1. The distributions of age, state of residence, applicator type, body mass index, and major farm crops and animals grown and raised did not significantly differ for thyroid cancer cases and non-cases. Thyroid cancer cases were significantly less likely to be current smokers at enrollment compared to non-cases (5.9% versus 16.9%, respectively). Thyroid cancer cases were also more likely to self-report a diagnosis of non-malignant thyroid disease at enrollment or during study follow-up (17.4% versus 6.0%, respectively). Thyroid tumors in the AHS were comparable to thyroid tumors diagnosed 1994–2015 among white men in SEER (NCI 2018) with respect to stage at diagnosis, histologic subtype, size, and grade (Supplemental Table S2).

We evaluated ever use at study enrollment of 44 pesticide ingredients with at least five exposed thyroid cancer cases (Table 2). For thyroid cancer overall, the fungicide metalaxyl was associated with increased thyroid cancer risk (HR=2.03, CI:1.16–3.52). The organochlorine insecticide lindane was associated with increased risk of thyroid cancer (HR=1.74, CI:1.06–2.84. No other pesticides were statistically significantly associated with thyroid cancer risk, although the suggestive inverse association with chlorimuron ethyl became statistically significant when cases were restricted to papillary tumors (HR=0.52, CI:0.28–0.95). Other associations were generally similar in magnitude and direction when considering only papillary tumors (Table 2) and restricting to applicators without a history of thyroid disease (Supplementary Table S3).

We evaluated the association between intensity-weighted days of pesticide use and risk of thyroid cancer for sites with at least 10 exposed cases (Table 3). Certain pesticides for which detailed exposure (e.g. total days of use) was assessed on the enrollment take-home questionnaire could not be evaluated here due to small numbers of exposed cases (see Methods for questionnaire participation rates and Supplementary Table S1 for information

on the questionnaire at which each pesticide was comprehensively assessed). We observed elevated risk of thyroid cancer among those with ≤median intensity-weighted days of captan use (HR_{low}=2.19, CI:0.94–5.13, p_{trend}=0.89) and no association with high use. We had insufficient exposed cases to evaluate the association with a 15-year exposure lag. High carbaryl use was inversely associated with thyroid cancer risk (HR=0.20, CI:0.08–0.53, p_{trend}=0.001); the lagged results were consistent with unlagged findings. The results for cumulative lifetime days were generally similar in magnitude and direction to the results for intensity-weighted days (Supplementary Table S4).

DISCUSSION

Pesticides have long been suspected to have thyroid-disrupting properties, but few studies have evaluated the relationship between occupational pesticide use and thyroid cancer. In the first comprehensive analysis of thyroid cancer in the AHS cohort, we observed positive associations with metalaxyl and lindane, and inverse associations with carbaryl and chlorimuron ethyl (for papillary cancers only). These associations appear to be independent of thyroid disease diagnosis (Shrestha et al. 2018b).

Fungicides have been linked to both thyroid cancer and thyroid hormone dysfunction. A study in Minnesota found elevated thyroid cancer mortality in the agricultural region of the state with the highest reported use of fungicides (Schreinemachers et al. 1999). Fungicide exposure has been associated with increased serum thyroid-stimulating hormone (TSH) in Minnesota pesticide applicators (Garry 2005; Garry et al. 2003). Specific pesticides were not evaluated in these studies; however, based on the major crops grown authors hypothesized that the thyroid-disrupting effects were due to the fungicides maneb, mancozeb, and triphenyltin. Though we did not have enough exposed cases to evaluate these fungicides in our analysis, we observed elevated risk of thyroid cancer among applicators reporting ever use of metalaxyl. According to the EPA, metalaxyl does not show evidence of carcinogenicity for humans based on laboratory studies using mice and rats (US EPA 1994), and epidemiologic studies have not previously evaluated the association with cancer or thyroid cancer specifically. An analysis in the AHS found that metalaxyl was associated with increased risk of hypothyroidism in female spouses of pesticide applicators (Shrestha et al. 2018a); this finding was not observed among male applicators (Shrestha et al. 2018b).

Lindane, an organochlorine insecticide, was positively associated with thyroid cancer in our analysis. We also noted an elevated papillary thyroid cancer, though it did not reach statistical significance likely due to the smaller number of exposed cases (n=17). Lindane is designated as carcinogenic to humans (Group 1) by the International Agency for Research on Cancer, based on epidemiologic studies demonstrating associations with non-Hodgkin lymphoma (IARC 2018). A single study observed excess thyroid C-cell adenoma among lindane-exposed female rats (NCI 1977). Due to limited information regarding intensity and duration of lindane use (assessed on the enrollment take-home questionnaire), we were not able to evaluate the exposure-response relationship with thyroid cancer. Future work should evaluate the association between lindane and thyroid cancer, particularly among women based on reported associations in the animal literature.

In this first epidemiologic study of carbaryl and thyroid cancer, we observed decreased risk of thyroid cancer among high carbaryl users, with significant exposure-response trend that persisted even after lagging exposure 15 years. Carbaryl is a non-persistent carbamate insecticide that is used both agriculturally and residentially in the US. Carbaryl has been shown to act as a thyroid antagonist *in vitro*, disrupting the thyroid hormone receptor-signaling pathway (Sun et al. 2008). A cross-sectional study of US men found suggestive evidence that carbaryl exposure (measured via urinary metabolite) was associated with elevated thyroid-stimulating hormone (TSH), though no associations were observed for total triiodothyronine (T3) or free thyroxine (T4) (Meeker et al. 2006). In a subset of AHS applicators, those with the highest lifetime carbaryl use (>2315 intensity-weighted days) had lower total triiodothyronine, though there was limited evidence of a linear trend (p_{trend}=0.08) and no association with TSH or total T4 (Lerro et al. 2018a). Epidemiologic studies have generally observed that higher pre-diagnostic TSH levels are associated with lower risk of thyroid cancer (Hrafnkelsson et al. 2000; Huang et al. 2017; Rinaldi et al. 2014; Thoresen et al. 1988), though one study found that higher TSH combined with a history of thyroid nodules was associated with elevated risk of thyroid cancer (Fiore and Vitti 2012). Carbaryl may potentially be influencing thyroid cancer risk via subtle alterations in thyroid hormone function.

We observed an inverse association between use of the herbicide chlorimuron ethyl and thyroid cancer in our analysis, though the finding was only significant for the papillary subtype. There is limited evidence regarding the carcinogenicity of chlorimuron ethyl. The US EPA classifies this herbicide as not likely to be carcinogenic to humans, based on a lack of treatment-related tumors in laboratory animals and absence of evidence for mutagenicity and teratogenicity (US EPA 2009). Chlorimuron ethyl has been associated with elevated risk of lung cancer in the AHS (Bonner et al. 2017). The inverse association we observe has not been corroborated in the epidemiologic or animal literature and could be due to chance.

Previous analyses in the AHS observed elevated thyroid cancer risk associated with atrazine (triazine herbicide) among pesticide applicators (Freeman et al. 2011), and malathion (organophosphate insecticide) among female spouses of pesticide applicators (Lerro et al. 2015). We did not observe an association with atrazine exposure, with an additional eight years of follow-up and an additional 27 atrazine-exposed cases. This earlier excess may be due to chance and the small number of exposed cases. The lack of an observed association between malathion and thyroid cancer in our study, compared to the earlier analysis in AHS spouses, could be due to differing exposure patterns between spouses and applicators or sex differences in the effect of pesticides on thyroid homeostasis. Though these sex differences have not been evaluated for malathion specifically, persistent organochlorine compounds and certain metals demonstrate different effects on thyroid function for men and women (Abdelouahab et al. 2008).

We noted in our descriptive analyses that thyroid tumors in AHS applicators were similar to those diagnosed in a representative sample of white men in the US based on histologic type, state, grade, and tumor size. In line with prior work, we observed that current tobacco users at study baseline were less likely to have thyroid cancer (Kitahara et al. 2012). Though BMI has been associated with elevated risk of thyroid cancer, particularly in men (Kitahara et al.

2016), we did not note any difference in BMI distribution at baseline between participants who developed thyroid cancer and those who did not develop thyroid cancer. This may be due, in part, to the large number of study participants with missing BMI (>25%), or due to the self-reported nature of this variable at a single point in time, and thus the potential for exposure misclassification.

To our knowledge, this is the first prospective study to comprehensively evaluate occupational pesticide use and thyroid cancer risk. An extensive literature exists demonstrating the effects of pesticides on thyroid function (Brucker-Davis 1998; Zoeller 2007). Though risk of thyroid cancer has been evaluated for some pesticides with long serum half-lives (Lerro et al. 2018b), the effect of long-term exposure to non-persistent pesticides is more difficult to evaluate. Our study utilizes self-reported pesticide exposure information that has been shown to be highly reliable for occupational users (Blair et al. 2002), making the AHS a unique population in which to evaluate associations with pesticides and thyroid cancer. However, we had relatively few incident thyroid cancer cases in our study making it difficult to evaluate rarer pesticide exposures. More than 30% of US thyroid cancers are diagnosed before the age of 40 (Lim et al. 2017). Our analysis in the AHS would have missed some younger thyroid cancer cases, as the median age of cohort enrollment in 1993–97 was 45. Although thyroid cancer is more common in women than men, we restricted our analysis to men because of the demographics of the AHS applicators (97% male). We performed analyses excluding participants with thyroid disease diagnosis to evaluate whether associations might potentially be mediated through thyroid disease. However, and important limitation of this analysis is that we were not able to differentiate between hyperthyroid and hypothyroid disease. Hypothyroidism is the most common type of thyroid disease (Taylor et al. 2018). Due to the small number of cases we were only able to evaluate the most common histologic subtype of papillary thyroid cancer (78% of cases). If the other subtypes have distinct etiologies, combining them may mask potential associations. It is possible that based on the large number of hypotheses tested we might observe some spurious findings as we did not account for multiple testing. We evaluated the strength of each finding in the context of the existing epidemiologic, molecular, and toxicologic literature, summarizing the totality of the evidence in order to inform our discussion of our findings. Similarly, we noted where previously-observed associations in the cohort (i.e., atrazine) were no longer present with extended follow-up and additional cancer cases.

Conclusions

There has been speculation as to whether environmental exposures, such as pesticides, may be contributing to the rising thyroid cancer incidence rates in the US (Lim et al. 2017), especially considering the prevalence of pesticide exposures (some studies estimate >90%) in the general population. In this prospective study of thyroid cancer in male pesticide applicators, we observed positive associations for metalaxyl and lindane, and inverse associations for carbaryl and chlorimuron ethyl (for the papillary subtype). Our study is the first to evaluate the effect of long-term use of specific non-persistent pesticide active ingredients on thyroid cancer risk. Replication of these results in independent populations is important. In addition, consortial efforts may provide an opportunity to extend these findings with a larger number of thyroid cancer cases (Leon et al. 2011);

Additionally, future studies should evaluate the impact of pesticide exposures specifically on thyroid cancer risk in women, as they are at already at higher risk compared to men. Future studies might also evaluate the association between pesticides and risk of thyroid nodules, which is an established risk factor for papillary thyroid cancer (Cooper et al. 2006). Biomarker studies among pesticide applicators investigating potential effects related endocrine function, hormones, inflammatory markers, and oxidative stress may be useful to assess the biologic plausibility of the observed associations and elucidate mechanisms of carcinogenesis relevant to thyroid cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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HIGHLIGHTS

- Many pesticides are known to have thyroid-disrupting properties.
- We used data from a large, prospective study of farmers to evaluate the relationship between use of 44 pesticide ingredients and incident thyroid cancer.
- Among 85 incident thyroid cancer cases, we observed increased risk of thyroid cancer associated with use of metalaxyl (fungicide) and lindane (organochlorine insecticide), and an inverse association with carbaryl (carbamate insecticide).
- Our study is the first to comprehensively evaluate the association between pesticide use and thyroid cancer risk in a highly exposed population of farmers, with cancer incidence collected prospectively over 20+ years of follow-up.

TABLE 1.

Sociodemographic, behavioral, and farm characteristics of Agricultural Health Study applicators (N=53,096) stratified by incident thyroid cancer

	Incident Thyroid Cancer		
	No N=53,011 N (%[1])	Yes N=85 N (%)	p-value[2]
Age at enrollment			
≤30	6,191 (11.7)	12 (14.1)	0.91
31–40	13,832 (26.1)	22 (25.9)	
41–50	13,888 (26.2)	23 (27.1)	
51–60	10,591 (20.0)	14 (16.5)	
>60	8,509 (16.1)	14 (16.5)	
State			
Iowa	34,724 (65.5)	61 (71.8)	0.22
North Carolina	18,287 (34.5)	24 (28.2)	
Applicator type			
Private	48,543 (91.6)	75 (88.2)	0.27
Commercial	4,468 (8.4)	10 (11.8)	
Smoking Status			
Never	27,299 (51.5)	47 (55.3)	0.03
Former	16,237 (30.6)	33 (38.8)	
Current	8,977 (16.9)	5 (5.9)	
Missing	498 (0.9)	0 (0)	
Body Mass Index (kg/m^2)			
<25	9,898 (18.7)	16 (18.8)	0.67
25–29.9	19,569 (36.9)	36 (42.4)	
≥30	8,999 (17.0)	11 (12.9)	
Missing	14,545 (27.4)	22 (25.9)	
Thyroid Disease[3]			
No	49842 (94.0)	70 (82.4)	<0.001
Yes	3169 (6.0)	15 (17.4)	
Major Farm Crops/Animals			
Cattle	20,972 (39.6)	29 (34.1)	0.31
Hogs	16,470 (31.1)	25 (29.4)	0.74
Alfalfa	10,743 (20.3)	17 (20.0)	0.95
Field Corn	36,731 (69.3)	58 (68.2)	0.83
Hay	15,825 (29.9)	24 (28.2)	0.74
Soybeans	34,617 (65.3)	51 (60.0)	0.30
Tobacco	7,721 (14.6)	11 (12.9)	0.67
Histologic subtype[4]			

	Incident Thyroid Cancer		
	No N=53,011 N (%[1])	Yes N=85 N (%)	p-value[2]
Papillary		66 (77.7)	
Follicular		11 (12.9)	
Medullary		5 (5.9)	
Other/NOS		(3.5)	

[1] Percentages may not sum to 100 due to rounding

[2] Chi-square test for homogeneity

[3] Ns based on a single imputation

[4] ICD-O-3 morphology codes: Papillary (8050, 8260, 8340–8344, 8350, 8450), Follicular (8330–8332, 8335, 8290), Medullary (8510, 8345)

TABLE 2.

Multivariable Cox proportional hazard regression models estimating adjusted[1] hazard ratios (HR) and 95% confidence intervals (CI) for ever pesticide use at study enrollment compared to no use

	All Thyroid Cancer		Papillary Thyroid Cancer	
	N	**HR (95% CI)**	**N**	**HR (95% CI)**
Fumigants				
Methyl Bromide	12	0.84 (0.39–1.82)	8	0.61 (0.25–1.51)
Aluminum Phosphide	5	0.98 (0.39–2.46)	2	--
Fungicides				
Metalaxyl	25	**2.03 (1.16–3.52)**	20	**2.07 (1.12–3.84)**
Captan	10	1.36 (0.70–2.65)	6	0.99 (0.43–2.32)
Benomyl	9	1.54 (0.62–3.78)	5	0.87 (0.27–2.77)
Chlorothalonil	8	1.36 (0.57–3.25)	6	1.48 (0.55–4.00)
Maneb/Mancozeb	5	0.51 (0.17–1.47)	4	--
Herbicides				
Chloroacetanilide				
Alachlor	44	1.05 (0.67–1.64)	33	1.01 (0.60–1.68)
Metolachlor	34	0.79 (0.50–1.25)	28	0.86 (0.52–1.44)
Dinitroaniline				
Trifluralin	38	0.88 (0.51–1.51)	30	0.91 (0.50–1.68)
Pendimethalin	28	0.65 (0.40–1.04)	23	0.69 (0.41–1.18)
Phenoxy				
2 4-D	64	0.87 (0.52–1.44)	46	0.66 (0.38–1.14)
2,4,5 T	17	0.83 (0.42–1.61)	12	0.80 (0.36–1.75)
2,4,5-TP	8	1.14 (0.47–2.72)	6	1.14 (0.42–3.11)
Thiocarbamate				
Butylate	26	0.98 (0.58–1.65)	19	0.84 (0.46–1.53)
EPTC	17	0.94 (0.54–1.64)	13	0.93 (0.50–1.76)
Triazine				
Atrazine	60	1.00 (0.59–1.69)	47	1.05 (0.58–1.90)
Cyanazine	34	0.92 (0.55–1.53)	26	0.90 (0.50–1.60)
Other Herbicide				
Glyphosate	58	0.70 (0.44–1.12)	44	0.62 (0.37–1.04)
Dicamba	39	0.85 (0.51–1.42)	32	0.96 (0.54–1.69)
Metribuzin	36	1.16 (0.65–2.07)	28	1.30 (0.68–2.47)
Imazethapyr	30	0.71 (0.41–1.22)	23	0.65 (0.35–1.21)
Petroleum Oil	29	0.69 (0.43–1.11)	23	0.67 (0.40–1.15)
Chlorimuron Ethyl	23	0.61 (0.36–1.04)	17	**0.52 (0.28–0.95)**
Paraquat	17	0.78 (0.44–1.39)	14	0.83 (0.44–1.56)
Insecticides				
Carbamate				

	All Thyroid Cancer		Papillary Thyroid Cancer	
	N	**HR (95% CI)**	**N**	**HR (95% CI)**
Carbaryl	41	0.73 (0.44–1.21)	30	0.60 (0.34–1.07)
Carbofuran	23	1.13 (0.69–1.84)	16	0.97 (0.54–1.72)
Aldicarb	7	0.75 (0.31–1.81)	6	0.84 (0.32–2.20)
Organochlorine				
Lindane	23	**1.74 (1.06–2.84)**	17	1.64 (0.93–2.88)
DDT	18	1.21 (0.63–2.34)	11	0.97 (0.43–2.16)
Chlordane	14	0.59 (0.31–1.11)	11	0.70 (0.34–1.44)
Heptachlor	11	1.08 (0.50–2.31)	7	1.01 (0.40–2.53)
Aldrin	10	0.55 (0.24–1.22)	6	0.49 (0.18–1.32)
Toxaphene	8	0.67 (0.32–1.42)	6	0.69 (0.29–1.64)
Organophosphate				
Malathion	59	1.07 (0.66–1.74)	46	1.09 (0.63–1.90)
Chlorpyrifos	30	0.76 (0.48–1.19)	24	0.78 (0.47–1.30)
Diazinon	26	1.25 (0.73–2.12)	21	1.42 (0.78–2.59)
Phorate	26	0.95 (0.58–1.54)	19	0.90 (0.52–1.58)
Terbufos	24	0.70 (0.43–1.15)	18	0.65 (0.37–1.14)
Fonofos	17	1.01 (0.58–1.77)	12	0.89 (0.46–1.71)
Parathion	11	0.94 (0.48–1.81)	7	0.75 (0.33–1.68)
Dichlorvos	9	1.13 (0.56–2.30)	7	1.14 (0.51–2.53)
Coumaphos	5	0.79 (0.32–1.96)	4	--
Pyrethroid				
Permethrin	17	0.80 (0.47–1.38)	14	0.83 (0.45–1.51)

Bold indicates $p<0.05$

[1] Adjusted for age, state, applicator type, smoking status, body mass index, correlated pesticides

TABLE 3.

Multivariable Cox proportional hazard regression models estimating adjusted[1] hazard ratios (HR) and 95% confidence intervals (CI) for cumulative pesticide intensity-weighted days of use[2] compared to no use

		Unlagged			15-year exposure lag		
		N	**HR (95% CI)**	**p_{trend}**	**N**	**HR (95% CI)**	**p_{trend}**
Fumigants							
Methyl Bromide	No use	72	1.00 (ref)	0.98	72	1.00 (ref)	0.61
	M1	6	0.80 (0.31–2.05)		6	1.01 (0.39–2.60)	
	M2	6	0.99 (0.37–2.64)		6	1.29 (0.48–3.44)	
Fungicides							
Captan	No use	63	1.00 (ref)	0.89	67	1.00 (ref)	
	M1	6	2.19 (0.94–5.13)		4	--	
	M2	5	1.11 (0.45–2.78)		3	--	
Herbicides							
Chloroacetanilide							
Alachlor	No use	35	1.00 (ref)	0.61	42	1.00 (ref)	0.52
	Q1	11	1.40 (0.71–2.79)		10	1.17 (0.58–2.37)	
	Q2	11	1.36 (0.68–2.70)		9	0.98 (0.47–2.04)	
	Q3	11	0.82 (0.41–1.62)		9	1.26 (0.61–2.62)	
	Q4	11	0.94 (0.47–1.86)		9	0.77 (0.37–1.60)	
Metolachlor							
	No use	44	1.00 (ref)	**0.05**	50	1.00 (ref)	0.64
	Q1	10	1.23 (0.61–2.47)		8	1.05 (0.49–2.23)	
	Q2	8	1.03 (0.48–2.21)		7	1.62 (0.73–3.61)	
	Q3	9	**0.47 (0.23–0.97)**		7	0.77 (0.35–1.71)	
	Q4	8	0.64 (0.30–1.38)		7	0.93 (0.42–2.08)	
Dinitroanaline							
Trifluralin	No use	35	1.00 (ref)	0.80	37	1.00 (ref)	0.94
	Q1	10	1.14 (0.54–2.38)		10	1.17 (0.56–2.46)	
	Q2	10	0.78 (0.36–1.66)		9	1.58 (0.72–3.46)	
	Q3	10	0.93 (0.43–2.03)		10	1.42 (0.66–3.07)	
	Q4	10	1.12 (0.51–2.46)		9	1.09 (0.49–2.45)	
Pendimethalin							
	No use	30	1.00 (ref)	0.27	35	1.00 (ref)	0.25
	Q1/M1	6	0.56 (0.23–1.37)		6	1.04 (0.43–2.52)	
	Q2/M2	5	1.22 (0.46–3.25)		4	0.52 (0.18–1.50)	
	Q3	5	0.80 (0.30–2.10)				
	Q4	5	0.52 (0.20–1.40)				
Phenoxy							
2,4-D	No use	16	1.00 (ref)	0.20	23	1.00 (ref)	0.43
	Q1	17	1.07 (0.53–2.14)		16	1.25 (0.65–2.42)	

		Unlagged			15-year exposure lag		
		N	HR (95% CI)	p_{trend}	N	HR (95% CI)	p_{trend}
	Q2	17	1.45 (0.72–2.93)		15	1.64 (0.83–3.23)	
	Q3	17	0.96 (0.47–1.94)		15	1.01 (0.51–2.00)	
	Q4	17	0.77 (0.38–1.56)		15	0.93 (0.47–1.83)	
Thiocarbamate							
EPTC	No use	60	1.00 (ref)	0.47	63	1.00 (ref)	0.71
	M1	9	1.24 (0.61–2.53)		7	1.54 (0.70–3.41)	
	M2	8	0.77 (0.36–1.63)		7	0.84 (0.38–1.87)	
Triazine							
Atrazine	No use	24	1.00 (ref)	0.72	29	1.00 (ref)	0.90
	Q1	15	0.68 (0.34–1.33)		13	1.05 (0.53–2.09)	
	Q2	14	1.09 (0.54–2.22)		13	1.20 (0.60–2.41)	
	Q3	14	0.79 (0.39–1.62)		13	1.06 (0.52–2.14)	
	Q4	14	0.80 (0.39–1.64)		13	1.00 (0.49–2.03)	
Cyanazine							
	No use	46	1.00 (ref)	0.15	51	1.00 (ref)	0.18
	Q1	9	0.88 (0.41–1.87)		8	1.09 (0.5–2.38)	
	Q2	8	1.84 (0.83–4.06)		7	1.48 (0.65–3.39)	
	Q3	9	1.17 (0.55–2.51)		7	1.57 (0.69–3.59)	
	Q4	8	0.55 (0.24–1.22)		7	0.55 (0.24–1.28)	
Other Herbicide							
Glyphosate	No use	19	1.00 (ref)	0.14	34	1.00 (ref)	0.70
	Q1	17	1.01 (0.53–1.95)		13	1.34 (0.7–2.57)	
	Q2	16	0.72 (0.37–1.40)		12	1.15 (0.59–2.24)	
	Q3	16	**0.48 (0.25–0.95)**		12	1.28 (0.65–2.49)	
	Q4	16	0.63 (0.32–1.25)		12	1.18 (0.6–2.31)	
Dicamba	No use	37	1.00 (ref)	0.81	44	1.00 (ref)	0.28
	Q1	11	0.81 (0.40–1.65)		9	1.03 (0.49–2.18)	
	Q2	10	0.96 (0.46–2.03)		8	1.24 (0.56–2.72)	
	Q3	10	0.60 (0.28–1.28)		8	0.64 (0.29–1.41)	
	Q4	10	1.01 (0.47–2.16)		8	1.67 (0.75–3.71)	
Metribuzin	No use	29	1.00 (ref)	0.72	31	1.00 (ref)	0.51
	M1	6	0.66 (0.25–1.75)		5	0.61 (0.22–1.69)	
	M2	6	0.76 (0.28–2.11)		5	1.32 (0.45–3.85)	
Imazethapyr	No use	46	1.00 (ref)	0.91	59	1.00 (ref)	0.82
	Q1/M1	8	0.52 (0.23–1.18)		9	1.11 (0.53–2.31)	
	Q2/M2	8	1.13 (0.50–2.57)		9	1.10 (0.53–2.31)	
	Q3	8	0.64 (0.28–1.46)				
	Q4	7	0.94 (0.39–2.27)				
Insecticides							
Carbamate							

		Unlagged			15-year exposure lag		
		N	HR (95% CI)	p_{trend}	N	HR (95% CI)	p_{trend}
Carbaryl	No use	30	1.00 (ref)	**0.001**	31	1.00 (ref)	**0.02**
	M1	7	0.78 (0.34–1.81)		6	1.14 (0.47–2.78)	
	M2	6	**0.20 (0.08–0.53)**		6	**0.33 (0.13–0.88)**	
Carbofuran	No use	55	1.00 (ref)	0.45	60	1.00 (ref)	0.61
	Q1/M1	6	1.19 (0.51–2.77)		9	1.30 (0.64–2.63)	
	Q2/M2	5	0.66 (0.27–1.67)		8	0.82 (0.39–1.73)	
	Q3	6	1.47 (0.63–3.41)				
	Q4	5	1.28 (0.51–3.24)				
Organophosphate							
Malathion	No use	18	1.00 (ref)	0.12	24	1.00 (ref)	0.13
	Q1	8	0.66 (0.28–1.58)		6	0.87 (0.35–2.19)	
	Q2	8	1.28 (0.54–3.01)		5	0.85 (0.32–2.26)	
	Q3	8	1.15 (0.50–2.67)		6	1.85 (0.75–4.57)	
	Q4	7	0.43 (0.18–1.04)		5	0.39 (0.15–1.03)	
Chlorpyrifos	No use	54	1.00 (ref)	0.59	61	1.00 (ref)	0.95
	Q1	8	0.94 (0.44–1.98)		6	0.96 (0.41–2.24)	
	Q2	7	**0.44 (0.2–0.96)**		5	0.55 (0.22–1.39)	
	Q3	7	1.24 (0.56–2.74)		6	1.69 (0.73–3.93)	
	Q4	7	0.74 (0.34–1.64)		5	0.94 (0.38–2.36)	
Phorate	No use	31	1.00 (ref)	0.94	32	100 (ref)	0.77
	M1	6	0.85 (0.34–2.13)		5	1.18 (0.44–3.17)	
	M2	5	1.02 (0.39–2.67)		5	0.88 (0.34–2.32)	
Terbufos	No use	53	1.00 (ref)	0.91	59	1.00 (ref)	0.82
	Q1/M1	6	0.45 (0.19–1.07)		9	0.53 (0.26–1.09)	
	Q2/M2	6	0.60 (0.26–1.42)		9	1.10 (0.54–2.24)	
	Q3	6	1.64 (0.70–3.84)				
	Q4	6	0.78 (0.33–1.81)				
Fonofos	No use	59	1.00 (ref)	0.57	61	1.00 (ref)	0.36
	M1	9	0.86 (0.42–1.77)		8	1.06 (0.50–2.26)	
	M2	8	1.33 (0.63–2.81)		7	1.45 (0.65–3.22)	
Pyrethroid							
Permethrin	No use	60	1.00 (ref)	0.27	62	1.00 (ref)	0.57
	M1	9	1.00 (0.49–2.03)		8	1.38 (0.65–2.90)	
	M2	9	0.67 (0.33–1.36)		8	1.22 (0.58–2.56)	

Bold indicates p<0.05

[1]Adjusted for age, state, applicator type, smoking status, body mass index, correlated pesticides

[2]Categorized as ≤median or >median for 10–19 exposed cases and quartiles for ≥20 exposed cases