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Occupational Exposure to Pesticides and Other Biocides and Risk of Thyroid Cancer

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Abstract

Objectives—To assess the associations between occupational exposure to biocides and pesticides and risk of thyroid cancer.

Methods—Using data from a population-based case-control study involving 462 incident thyroid cancer cases and 498 controls in Connecticut collected in 2010–2011, we examined the association with occupational exposure to biocides and pesticides through a job-exposure matrix. We used unconditional logistic regression models to estimate odds ratios (OR) and 95% confidence intervals (95% CI), adjusting for potential confounders.

Results—Individuals who were occupationally ever exposed to biocides had an increased risk of thyroid cancer (OR=1.65, 95% CI: 1.16, 2.35), and the highest risk was observed for the high cumulative probability of exposure (OR=2.18, 95%CI: 1.28–3.73). The observed associations were similar when we restricted to papillary thyroid cancer and well-differentiated thyroid cancer.

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Stronger associations were observed for thyroid microcarcinomas (tumor size ≤1cm). No significant association was observed for occupational exposure to pesticides.

Conclusions—Our study provides the first evidence linking occupational exposure to biocides and risk of thyroid cancer. The results warrant further investigation.

Keywords

thyroid cancer; occupational exposure; job-exposure matrix

BACKGROUND

Over the past decades, thyroid cancer incidence has increased considerably worldwide.[1–3] In the United States, the average annual increase in thyroid cancer incidence rate was 5% over the last 10 years.[4] It is now the fifth most commonly diagnosed cancer in women in the United States. The reasons for growing thyroid cancer incidence have been highly debated. Recent evidence suggests that "over-diagnosis" may be responsible for about half of the increase.[5,6] Nevertheless, increased thyroid cancer incidence across all tumor sizes suggests that increased diagnostic scrutiny is not the sole explanation, and other explanations, including environmental exposures, should be investigated.[3,7] According to the International Agency for Research on Cancer, carcinogenic agents for thyroid cancer with sufficient evidence in humans are radioiodine (including Iodine-131), X-radiation, and gamma-radiation.[8] However, many thyroid cancers cannot be explained by ionizing radiation exposure.[5,9]

Research on occupational risk factors for thyroid cancer has been limited for exposures other than radiation and has predominantly occurred in population-based studies (e.g., case-control studies, registry-based cohorts) to obtain sufficient thyroid cancer cases. In a recent review of these studies, suggestive, but inconsistent, associations with thyroid cancer risk were observed in studies of pesticide-exposed workers, agricultural workers, and agricultural occupations, but no consistent associations were observed for other chemical exposures.[10] Our recent study suggested an increased risk of thyroid cancer associated with working as building cleaners and pest control workers.[11] These studies have been hampered by too few exposed cases and evaluations have been based primarily on occupational group. Only one study used a job-exposure matrix (JEM) to assess exposure.[12] A JEM links information from both job titles and industry types with specific exposures, providing a mechanism to evaluate exposures that may occur in multiple occupations or industries. This can significantly increase the statistical power compared with use of job or industrial titles.[13]

While currently no chemical substance has been consistently associated with thyroid cancer in humans, accidental or occupational exposures to high levels of some chemicals may cause mild changes in the thyroid.[10,14] Thyroid gland anomalies have been associated with many chemicals and solvents found in the workplace such as organochlorine pesticides, polychlorinated biphenyls, polybrominated diphenyl ethers, hexachlorobenzene, phthalates, polyhydroxyphenols/phenol derivatives, dioxins, and anions including perchlorate and nitrate[10,14–18]. In addition, emerging evidence from animal studies has demonstrated that drinking water disinfectants (i.e., chlorine, chlorine dioxide, and monochloramine) decreases

thyroid hormone levels in pigeons and rabbits.[19,20] Experimental studies have also documented that triclosan, a chlorinated phenolic antibacterial compound agent used in a variety of personal care and industrial products, decreases thyroid hormones in various laboratory animals.[21–24]

To fill the knowledge gap between occupational risk factors for thyroid cancer, we analyzed data from a population-based case-control study in Connecticut using exposure estimates for pesticides and biocides obtained from CANJEM.[25] CANJEM is a JEM developed for North American populations (www.canjem.ca). Pesticides refer to a diverse group of chemicals used in agricultural, commercial, and home settings to control insects, fungi, and weeds,[26] which have had mixed results in previous studies of thyroid cancer risk.[27–34] Biocides are chemicals used to disinfect, deodorize, sterilize, and sanitize, and have not been previously evaluated in thyroid cancer studies. Biocides includes bactericides, algicides, fungicides, germicides, and preservatives.[25]

MATERIALS AND METHODS

Study Population

A population-based case–control study was conducted in Connecticut in 2010–2011.[9] Eligible patients were aged more than 20 years old at diagnosis, had no previous diagnosis of cancer, with the exception of non-melanoma skin cancer, and were alive at the time of interview. Cases were identified through the Yale Cancer Center's Rapid Case Ascertainment Shared Resource (RCA), which functions as a field arm of the Connecticut Tumor Registry. Cases were histologically confirmed, incident thyroid cancer patients from Connecticut, diagnosed in 2010 and 2011. Population-based controls with Connecticut addresses were recruited using a random digit dialing method. Controls were frequency matched to cases within 5-year age groups. All procedures were performed in accordance with a protocol approved by the Human Investigations Committee at Yale and the Connecticut Department of Public Health. After approval by the hospitals and by each participant's physician (cancer cases), or after selection through random sampling (control population), potential participants were approached by letter and then over the phone. Those who agreed were interviewed by trained study interviewers, either at their homes or at a convenient location. A total of 701 eligible thyroid cancer cases were identified during the study period, with 462 (65.9%) completing in-person interviews. A total of 498 control individuals participated in the study, with a participation rate of 61.5%. After obtaining written consent, a standardized, structured questionnaire was used to collect information on demographics, medical history, smoking and alcohol consumption, physical activity, lifetime occupational history, and diet.

Occupational Exposure Assessment

Participants were asked to report all jobs held for one year or longer during their lifetime. For each reported type of occupation, detailed information was elicited on job title, activities or duties, company name, type of industry, year began, and year ended. Occupations were coded according to the 2010 Standard Occupational Classification (SOC) Manual by incorporating the information about job title, industry type, and specific duties.[35] Exposures

to biocides or pesticides were each assessed separately by linking each 6-digit SOC code to the CANJEM. If a 6-digit SOC code could not be linked to the CANJEM, the next most detailed level (e.g., 5-digit or 3-digit) was used for exposure estimates.

CANJEM is a general population job-exposure matrix created from a database of expert assessments performed during four community-based case-control studies of cancer (lung, breast, brain, and multisite) conducted in Montreal since the 1980s.[25] CANJEM is based on information derived from expert retrospective exposure assessments conducted on over 6000 men and 2500 women, totaling more than 30000 individual jobs held between 1931 and 2005, representing approximately 50 expert-years of exposure assessment. For the purpose of this analysis, a version of CANJEM based on the SOC system was used, with exposure estimates available for 3, 5 and 6-digit SOC codes. The JEM was produced for 2 agents "pesticides" and "biocides", defined by the experts as follows. Pesticides are substances capable of killing some form of organism that is deemed to be undesirable. Pesticides include insecticides, herbicides, rodenticides, fungicides, molluscicides and nematodicides. Farming is the main occupation in which pesticides are used in large quantities, and are likely to be handled in an unsafe manner. Biocides include all products used to disinfect, deodorize, sterilize and sanitize. This implies the capability of killing micro-organisms (algae, bacteria, viruses, etc.). This group therefore includes bactericides, algicides, fungicides, germicides and preservatives.

The CANJEM exposure metrics used in this study include probability of exposure and frequency weighted intensity (FWI) of exposure. Probability of exposure represents the proportion of jobs deemed exposed within a matrix-cell (i.e., an occupational code in this case, 6, 5, or 3 digits). FWI combines measures of intensity (low, medium, high) and frequency of exposure (hours per week) in the original studies into a quantitative metric representing time weighted average exposure. For the calculations, the experts considered that low, medium, and high levels of intensity corresponded approximately to relative absolute values of 1, 5, and 25. This varied from agent to agent but these weights were thought to represent the best overall estimate of the ratios for the three intensity categories across the 258 CANJEM agents. In a previous investigation comparing different JEMs, exposure estimates derived from using alternative weighting scales, including the 1–5–25 scale and others (namely 1–2–3, 1–3–9, 1–10–100) were compared; the choice of scale within that range did not greatly influence the results.[36] Final FWI of exposure for a matrix cell was defined as the median FWI value across all exposed jobs within that matrix cell. As an illustration, a FWI value of 5 corresponds to exposure at the medium level for 40 hours per week, or at high level for 8 hours per week. A matrix cell was deemed informative if it was based on information from at least 10 jobs in the original Montreal studies.

Each job held by participants in our study was linked with CANJEM and assigned values of probability of exposure and FWI of exposure. Cumulative probability of exposure to each agent was calculated as the sum of (probability of exposure × correspondent job duration) for each reported job. Cumulative intensity of exposure to biocides and pesticides was the sum of (FWI of exposure × job duration) for each reported job. Average probability of exposure was calculated as cumulative probability of exposure divided by total duration of employment. Average intensity of exposure was calculated as cumulative intensity of

exposure divided by total duration of employment. Exposures occurring within one year of diagnosis/interview were excluded since they occurred after any plausible etiologic window of time.

To derive an "ever exposure" variable from the linkage with CANJEM, we need to select a cutpoint on the probability of exposure scale above which the subject would be considered exposed and below which the subject would be considered unexposed. If we chose a cutpoint as low as 5%, it would be very sensitive and most of the subjects labelled as exposed would have had a low probability of exposure. On the other hand, if we chose a cutpoint as high as 95%, it would be very specific and a large fraction of workers truly exposed would be labelled as unexposed. In order to give greater weight to sensitivity than specificity, but not to exaggerate this choice unduly, we used ≥30% as the *a priori* threshold probability. Thus, ever exposure to a given agent was defined as having held at least one job with a probability of exposure of at least 30% and for at least one year. Subjects who had held jobs with a probability of exposure of less than 30% but greater than 0% were considered to be of possible but "uncertain" exposure status and were included as a separate category.

Statistical Analyses

Unconditional logistic regression models were used to estimate odds ratios (ORs) and 95% confidence intervals (CIs). Models were adjusted for age (continuous), gender, race, education, body mass index (BMI), family history of thyroid cancer, previous diagnosis of benign thyroid disease, smoking, alcohol consumption, and physical activity listed in Table 1. Adjustment for other variables, such as family income, diagnostic x-ray exposure, and radiation treatment did not result in material changes in the observed associations and therefore were not included in the final models. The cumulative and average exposure variables were divided into tertiles (low, medium, high) based on the distributions among controls, and were analyzed as categorical variables. Continuous variables were included in the logistic regression models for testing of linear trends among exposed participants. All tests of statistical significance were two-sided, with alpha of 0.05. Sub-analyses were performed for papillary thyroid cancer, well-differentiated thyroid cancer (including papillary and follicular thyroid cancers), and for papillary and well-differentiated thyroid cancer by tumor size (≤1cm, >1cm). Because of the small number of cases, we did not analyze the data separately for follicular, anaplastic and medullary thyroid cancers. We also conducted stratified analyses by gender (male, female), and statistically assessed potential multiplicative interaction between gender and occupational biocide and pesticide exposure. All statistical analyses were conducted using SAS version 9.4 software (SAS Institute, Inc., Cary, North Carolina).

RESULTS

Compared to controls, cases were more likely to be younger, female, and less educated (Table 1). The distributions of obesity, family history of thyroid cancer, and previous diagnosis of benign thyroid disease were higher among cases compared to controls. Cases

were also less likely to exercise and drink alcohol compared to controls. The distributions of race, family income, and smoking were similar between the cases and controls.

The 960 subjects in our study held 1,920 jobs. Out of the 1,920 jobs, 1,320 were linked to CANJEM with 6-digit codes, 291 with 5-digit codes, 274 with 3-digit codes, and 35 could not be linked to CANJEM. Jobs could not be linked were considered to have “unknown” exposure status and were treated as a separate category (not reported). Among the 318 jobs deemed exposed to biocides after linkage, the three most frequent were 1) health diagnosing and treating practitioners; 2) nursing, psychiatric, and home health aides, and 3) building cleaning workers. For the 20 jobs deemed exposed to pesticides after linkage, the three most frequent were 1) farmers, ranchers, and other agricultural managers, 2) postal service workers; and 3) first-line supervisors of landscaping, lawn service, and grounds keeping workers.

Ever being occupationally exposed to biocides was significantly associated with an increased risk of thyroid cancer (OR=1.65, 95% CI: 1.16, 2.35, Table 2). The highest risk was observed among people who had high cumulative probability of exposure (OR=2.18, 95%CI: 1.28–3.73) and medium cumulative intensity of exposure (OR=1.99, 95%CI: 1.14–2.47). Similar associations were observed for papillary thyroid cancer and well-differentiated thyroid cancers. Possible but uncertain biocide exposure status was not statistically significantly associated with thyroid cancer risk, though odds ratios were elevated compared to the reference group. No significant association was observed for ever being occupationally exposed to pesticides and risk of thyroid cancer (OR=0.95, 95%CI: 0.33–2.72). Because the number of pesticide-exposed cases was small (N=7), further detailed analyses by probability and intensity of exposure were not explored.

An increased risk of thyroid cancer was associated with ever occupational exposure to biocides among both women (OR=1.48, 95%CI: 1.00–2.19) and men (OR=3.11, 95%: 1.25–7.72, Table 3). For probability of exposure to biocides, while a significantly increased risk of thyroid cancer was associated with high average and cumulative probabilities of exposure among women (OR=1.77, 95%CI: 1.02–3.09 and OR=2.13, 95%CI: 1.20–3.79 respectively), such a risk was associated with medium average probability of exposure among men (OR=5.31, 95%CI: 1.39–20.29). For intensity of exposure to biocides, medium average and high cumulative intensities of exposure were associated with an increased risk of thyroid cancer among women (OR=1.75, 95%CI: 1.05–2.90 for medium average, OR=1.95, 95%CI: 1.08–3.52 for cumulative high exposure), while medium cumulative intensity of exposure was associated with an increased risk of thyroid cancer among men (OR=6.26, 95%CI: 1.35–28.93). No significantly increased risk of thyroid cancer was associated with occupational exposure to pesticides among men or women.

After stratification by tumor size, we noted a stronger association with microcarcinomas (tumor size ≤1cm) for occupational exposure to biocides (Table 4). Statistically significant associations with microcarcinoma were mainly seen for ever occupational exposure to biocides (OR=1.89, 95%CI: 1.20–2.97 for papillary, OR=1.82, 95%CI: 1.18–2.79 for well-differentiated), and stronger associations were shown for high probability of exposure (papillary: OR=2.65, 95%CI: 1.43–4.91 for average and OR=2.88, 95%CI: 1.51–5.47 for

cumulative; well-differentiated: OR=2.40, 95%CI: 1.32–4.36 for average and OR=2.74, 95%CI: 1.48–5.04 for cumulative) and high cumulative intensity of exposure (OR=2.83, 95%CI: 1.48–5.39 for papillary, OR=2.58, 95%CI: 1.39–4.76). Significant associations with larger tumors were observed for occupational exposure to biocides at medium average probability (papillary: OR=2.09, 95%CI: 1.07–4.08; well-differentiated: OR=1.96, 95%CI: 1.01–3.78) and medium cumulative intensity (OR=2.26, 95%CI: 1.13–4.55 for papillary; OR=2.26, 95%CI: 1.15–4.44 for well-differentiated). No significant associations were observed for occupational exposure to pesticides and thyroid cancer by tumor size.

DISCUSSION

Our study found increased risk of thyroid cancer was associated with occupational exposure to biocides. Biocides are a diverse group of products used defend against harmful organisms, generally formulated using one or more active ingredients.[37] Major chemical classes used in biocides include halogenated organics, inorganics, nitrogen-based compounds, phenolics, organo-sulfur compounds, and organometallics.[37] Biocides are widely used in wood preservation, cosmetics, paints and coating, disinfectants, recreational water, papers, for hospital and medical uses, and more. In Western Europe, halogenated specialty biocides were the leading products and wood preservation was the leading end use application.[37] Because of the growing attention to health, safety, and sanitation, demand for disinfectant and antimicrobial chemicals in the US has increased significantly during the past decades with an estimated 6% annual increase to $1.6 billion in 2017.[38] The global disinfectant market is projected to cross $6 billion by 2020.[39] Given the parallel increase in thyroid cancer incidence and exposure to biocides, and potential thyroid hormone disrupting properties of certain biocides, it is necessary to explore whether exposure to biocides increases the risk of thyroid cancer.

While few studies have examined the direct association between biocides and thyroid cancer, several studies have reported a positive association with certain occupations that could involve exposure to biocides in addition to other exposures. Fincham et al.[33] reported that individuals employed in wood processing and pulp and papermaking experienced an increased risk of thyroid cancer. Lope et al.[28] found higher risk of thyroid cancer among men employed as construction carpenters/joiners, and among women in the prefabricated wooden-building industry. Carstensen et al.[32] found that workers in the canning and preserving industry were at significantly elevated risk of thyroid cancer. Several studies reported an increased risk among healthcare professionals including dentists, pharmacists, physicians, and nurses.[2840–45] In these studies, hospital workers, particularly operating room scrub technicians are exposed to significant and repetitive quantities of disinfectants. In our recent study, a significantly increased risk of thyroid cancer was found among healthcare practitioners and technical workers including health diagnosing and treating practitioners, as well as building, ground cleaning and maintenance workers, especially those working as building cleaners and pest control workers.[11] A stronger association was found among those with thyroid microcarcinomas. The two jobs most likely exposed to biocides were 1) health diagnosing and treating practitioners and 2) nursing, psychiatric, and home health aides. One might speculate that individuals who hold these jobs had easier access to medical care, thus their thyroid cancers were more likely to be diagnosed earlier or before a microcarcinoma

progresses. However, the distributions of microcarcinomas and larger size tumors were similar among individuals who had these jobs, suggesting that early screening was less likely to explain these findings.

Although the underlying mechanisms linking biocides and risk of thyroid cancer is currently unclear, several experimental studies have found that biocides could alter thyroid hormones. Triclosan is widely used in cleaning products. Triclosan and its environmentally transformed derivative, methyl-triclosan, have been detected in sewage discharged from wastewater treatment plants. Studies have shown that triclosan decreases total serum thyroxine (T4) and triiodothyronine (T3) in animal models.[21–24] Many drinking water disinfectants (i.e., chlorine, chlorine dioxide, and monochloramine) have been found to reduce T4 levels in pigeons and rabbits.[1920] Pentachlorophenol (PCP), a wood preservative, has been shown to bind transthyretin and reduce T4 levels in rats.[46–48] While several studies reported no association between thyroid hormones and thyroid cancer,[49–53] two studies reported an increased risk of thyroid cancer associated with lower thyroid hormones.[5455] Future prospective studies are warranted to investigate the association and identify potential causal agents. Additionally, biocides could alter the oral and/or gut microbiota, which has been linked to thyroid gland health.[56–58] Approximately 20% of the conversion of inactive T4 to active T3 happens in the gastrointestinal tract. Animal studies have shown that gut microbes can either directly convert T4 into T3 sulfate, which can then be recovered as active T3 by intestinal sulfatase,[59] or indirectly through metabolize bile acids to increase activity of iodothyronine deiodinase, a main enzyme of converting T4 into T3.[60] Future investigation on the role of the microbiome on thyroid cancer will provide insights into the link between biocides and risk of thyroid cancer.

Our results showed an increased risk of thyroid cancer associated with exposure to pesticides among women but not among men, though the relationship was not monotonic and the observed difference was not statistically significant. Previous studies have also reported an elevated risk of thyroid cancer associated with exposure to pesticides and related occupations among women but not among men.[2829] Goldner et al. found a positive association between self-reported pesticide use and hypothyroidism among both men and women.[6162] We noted that the sample size of men was small in our study, which hampered the ability to detect small to moderate effect of pesticides among men. It is also possible that the differences in association between men and women due to differences in the specific pesticides to which they are each exposed. The observed association with pesticides was not among the highest exposure group, rather among the low exposure group. While a chance finding or potential exposure misclassification cannot be ruled out, the specific carcinogen may be specific to jobs seen in the low exposure group.

Several potential limitations should be considered in interpreting our study results. Although the gender distribution was different in cases and controls, we avoided potential confounding by either adjusting for gender in the analyses or presenting analyses stratified by gender. Although controls were frequency-matched (±5 years) to cases, cases were significantly younger than controls. Though we adjusted for age as well as gender in all models, potential residual confounding by age may still exist, but it would probably be quite minimal in magnitude. Individuals with benign thyroid disease are more likely to have increased thyroid

surveillance and as such, may be more likely to be detected with thyroid cancer. This may contribute to the observed higher prevalence of benign thyroid diseases in the thyroid cancer cases compared to the population controls. We adjusted for history of benign thyroid disease in the final model. Regarding exposure assessment, one limitation of JEMs is that they do not capture within-job heterogeneity in exposure. Additionally, JEMs are typically best assigning exposure when people within an occupation are either all not exposed (0% probability) or when they are all exposed (100% probability). In our study, probability of exposure in the cells linked to our jobs varied from 0% to 95%, with a median of 3.56%. Therefore, misclassification was likely to have occurred to some extent although we used 30% as a cutoff to define ever exposure. Moreover, the JEM relies on linkage with self-reported occupational histories, and error associated with reported occupational histories might also introduce exposure misclassification. Biocides and pesticides represent diverse groups of chemicals with varying structures, bioavailability, and toxicity. While it would have been informative to conduct analyses for specific biocides and pesticides, this was unfortunately not possible, since CANJEM does not provide such detailed information. With regard to the validity of CANJEM estimates, while there has been no formal validation of the JEM itself, CANJEM is a summary of past assessments conducted using a well-recognized approach, the results of which have been widely cited in such authoritative reviews as the International Agency for Research on Cancer monographs. Moreover, studies evaluating the reliability and repeatability of the exposures assigned by the chemists have shown encouraging results.[63–66] Another potential limitation of the study is the relatively small number of exposed cases for certain sub-group analyses. A small sample size with low exposure prevalence reduces statistical power to detect an association, and additionally may increase the possibility of spurious associations.

In conclusion, this is the first study to apply a JEM to evaluate the association between occupational exposure to biocides and pesticides and the risk of thyroid cancer. We found an increased risk of thyroid cancer with occupational exposure to biocides, and no evidence of an association for occupationally pesticide use and thyroid cancer among women. Future evaluation of this relationship is warranted, with attention paid to examination of specific chemicals.

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What this paper adds?

- Limited studies have investigated occupational exposure to pesticides in relation to thyroid cancer and have reached inconsistent results.
- No study has investigated exposure to biocides in relation to thyroid cancer.
- We investigated the associations between occupational exposure to pesticides and biocides using a job exposure matrix and risk of thyroid cancer in a population-based case-control study in Connecticut.
- Our study provides the first evidence linking occupational exposure to biocides and risk of thyroid cancer.
- Future evaluation of this relationship is warranted, with attention paid to examination of specific chemicals.

Table 1

Distribution of selected characteristics among thyroid cancer cases and controls.

Characteristics	Cases (n=462)		Controls (n=498)		P
	Number	%	Number	%	
Age (years)					
Mean (SD)	51.2 (12.3)		54.1 (13.1)		0.0004
Gender					<0.0001
Male	87	18.8	154	30.9	
Female	375	81.2	344	69.1	
Race					0.78
White	415	89.8	450	90.4	
Other	47	10.2	48	9.6	
Education					0.0021
High school or less	129	27.9	88	17.7	
College or Technical school	216	46.8	261	52.4	
Graduate school	100	21.7	130	26.1	
Other	17	3.7	19	3.8	
Family income per capita					0.9
Low	128	27.7	133	26.7	
Medium	113	24.5	131	26.3	
High	74	16.0	82	16.5	
Confidential or unknown	147	31.8	152	30.5	
Body mass index (kg/m^2)					0.0003
<25	145	31.4	203	40.8	
25–29.9	146	31.6	168	33.7	
≥30	166	35.9	118	23.7	
Missing	5	1.1	9	1.8	
First-degree relatives with thyroid cancer					0.025
Yes	55	11.9	38	7.6	
No	407	88.1	460	92.4	
Previous diagnosis of benign thyroid diseases					<0.0001

Characteristics	Cases (n=462)		Controls (n=498)		P
	Number	%	Number	%	
Yes	62	13.4	14	2.8	
No	400	86.6	484	97.2	
Smoking *					0.18
Yes	141	30.5	172	34.5	
No	321	69.5	326	65.5	
Alcohol consumption **					<0.0001
Yes	188	40.7	267	53.6	
No	274	59.3	231	46.4	
Exercise and sports activities (hours/week)					0.0094
0	156	33.8	135	27.1	
1–5	168	36.4	170	34.1	
>5	138	29.9	193	38.8	

* Ever smoking was defined as ever smoked a total of 100 cigarettes or more during the lifetime.

** Ever alcohol consumption was defined as ever had more than 12 drinks of alcoholic beverages during the lifetime, such as beer, wine, or liquor. 1 drink beer=1 can or bottle; 1 drink wine =14 oz glass; 1 drink liquor=1 shot.

Table 2

Occupational exposure to biocides and pesticides and risk of thyroid cancer.

Occupational exposure	Controls	Overall		Papillary		Well-differentiated	
		Cases	OR* (95% CI)	Cases	OR* (95% CI)	Cases	OR* (95% CI)
Biocides							
Never	262	201	1.00	169	1.00	198	1.00
Uncertain	146	137	1.30 (0.94–1.78)	116	1.34 (0.96–1.87)	130	1.26 (0.91–1.73)
Ever	88	121	1.65 (1.16–2.35)	104	1.67 (1.15–2.43)	117	1.61 (1.13–2.30)
Probability							
Average							
Low	30	32	1.21 (0.69–2.14)	44	1.15 (0.63–2.09)	52	1.17 (0.66–2.07)
Medium	28	45	2.03 (1.19–3.47)	72	2.03 (1.16–3.55)	84	1.95 (1.13–3.35)
High	30	44	1.76 (1.03–3.00)	93	1.90 (1.10–3.31)	101	1.76 (1.03–3.02)
$P_{for\ trend}$**			*0.16*		*0.082*		*0.11*
Cumulative							
Low	29	34	1.38 (0.78–2.42)	28	1.30 (0.72–2.35)	33	1.32 (0.75–2.32)
Medium	30	41	1.46 (0.85–2.50)	37	1.54 (0.88–2.69)	40	1.43 (0.83–2.46)
High	29	46	2.18 (1.28–3.73)	39	2.27 (1.30–3.97)	44	2.15 (1.25–3.70)
$P_{for\ trend}$**			*0.081*		*0.048*		*0.041*
Intensity							
Average							
Low	30	38	1.44 (0.83–2.49)	30	1.27 (0.71–2.28)	36	1.34 (0.77–2.34)
Medium	39	60	1.87 (1.17–2.99)	54	2.06 (1.27–3.34)	59	1.86 (1.16–2.99)
High	19	23	1.54 (0.78–3.04)	20	1.55 (0.76–3.15)	22	1.52 (0.77–3.03)
$P_{for\ trend}$**			*0.91*		*0.73*		*0.82*
Cumulative							
Low	32	36	1.15 (0.67–1.99)	31	1.12 (0.63–1.99)	35	1.11 (0.64–1.92)
Medium	27	40	1.99 (1.14–3.47)	35	2.02 (1.13–3.60)	39	1.96 (1.12–3.42)
High	29	45	1.95 (1.14–3.34)	38	2.06 (1.17–3.60)	43	1.92 (1.12–3.31)
$P_{for\ trend}$**			*0.41*		*0.25*		*0.28*

Occupational exposure	Controls	Overall		Papillary		Well-differentiated	
		Cases	OR* (95% CI)	Cases	OR* (95% CI)	Cases	OR* (95% CI)
Pesticides							
Never	385	347	1.00	301	1.00	339	1.00
Uncertain	100	125	1.19 (0.85–1.66)	84	1.09 (0.76–1.56)	100	1.16 (0.83–1.64)
Ever	11	7	0.95 (0.33–2.72)	4	0.52 (0.14–1.88)	6	0.84 (0.28–2.56)

*Adjusted for age (continuous), gender, race, education, BMI, family history of thyroid cancer, history of benign thyroid disease, smoking status, alcohol consumption, and physical activity.

**Calculated by continuous variables among exposed participants.

Table 3

Occupational exposure to biocides and pesticides and risk of thyroid cancer by gender.

Occupational exposure	Female			Male			*P for interaction*
	Cases	**Controls**	**OR* (95% CI)**	**Cases**	**Controls**	**OR* (95% CI)**	
Biocides							
Never	157	170	1.00	44	92	1.00	
Uncertain	112	95	1.44 (0.99–2.11)	25	51	1.10 (0.57–2.09)	
Ever	103	77	1.48 (1.00–2.19)	18	11	3.11 (1.25–7.72)	*0.18*
Probability							
Average							
Low	24	24	1.02 (0.53–1.95)	8	6	2.19 (0.65–7.43)	
Medium	36	24	1.61 (0.89–2.94)	9	4	5.31 (1.39–20.29)	
High	43	29	1.77 (1.02–3.09)	1	1	1.46 (0.07–28.82)	
$P_{for\ trend}$**			*0.16*			*0.45*	*0.22*
Cumulative							
Low	25	22	1.13 (0.58–2.17)	9	7	2.16 (0.68–6.84)	
Medium	35	29	1.22 (0.68–2.18)	6	1	9.82 (0.99–97.51)	
High	43	26	2.13 (1.20–3.79)	3	3	3.33 (0.59–18.82)	
$P_{for\ trend}$**			*0.092*			*0.70*	*0.23*
Intensity							
Average							
Low	31	26	1.17 (0.63–2.15)	7	4	3.63 (0.92–14.32)	
Medium	54	36	1.75 (1.05–2.90)	6	3	3.37 (0.72–15.76)	
High	18	15	1.40 (0.64–3.06)	5	4	2.37 (0.53–10.61)	
$P_{for\ trend}$**			*0.59*			*0.39*	*0.23*
Cumulative							
Low	31	28	1.07 (0.59–1.94)	5	4	1.76 (0.41–7.60)	
Medium	32	24	1.53 (0.83–2.82)	8	3	6.26 (1.35–28.93)	
High	40	25	1.95 (1.08–3.52)	5	4	2.61 (0.58–11.71)	
$P_{for\ trend}$**			*0.27*			*0.69*	*0.25*

Occupational exposure	Female			Male			*P for interaction*
	Cases	Controls	OR* (95% CI)	Cases	Controls	OR* (95% CI)	
Pesticides							
Never	284	272	1.00	63	113	1.00	
Uncertain	86	64	1.25 (0.84–1.86)	19	36	1.14 (0.57–2.32)	
Ever	2	6	0.26 (0.04–1.61)	5	5	3.33 (0.80–13.85)	*0.48*

*Adjusted for age (continuous), gender, race, education, BMI, family history of thyroid cancer, history of benign thyroid disease, smoking status, alcohol consumption, and physical activity.

**Calculated by continuous variables among exposed participants.

Table 4

Associations between biocides and pesticides and risk of thyroid cancer by tumor size.

Occuational exposure	Controls	Papillary				Well-differentiated			
		≤ 1 cm		>1 cm		≤ 1 cm		>1 cm	
		Cases	OR* (95% CI)	Cases	OR* (95% CI)	Cases	OR* (95% CI)	Cases	OR* (95% CI)
Biocides									
Never	262	76	1.00	91	1.00	91	1.00	104	1.00
Uncertain	146	54	1.40 (0.90–2.16)	62	1.35 (0.89–2.05)	55	1.18 (0.77–1.79)	75	1.42 (0.96–2.11)
Ever	88	59	1.89 (1.20–2.97)	44	1.45 (0.90–2.33)	67	1.82 (1.18–2.79)	48	1.40 (0.88–2.21)
Probability									
Average									
Low	30	12	1.01 (0.46–2.21)	14	1.21 (0.58–2.53)	14	1.04 (0.50–2.15)	17	1.31 (0.66–2.62)
Medium	28	18	2.06 (1.03–4.13)	21	2.09 (1.07–4.08)	21	2.07 (1.07–4.00)	22	1.96 (1.01–3.78)
High	30	29	2.65 (1.43–4.91)	9	1.06 (0.46–2.41)	32	2.40 (1.32–4.36)	9	0.92 (0.41–2.09)
$P_{for\ trend}$**			*0.0093*		*0.79*		*0.013*		*0.51*
Cumulative									
Low	29	15	1.44 (0.70–3.00)	13	1.14 (0.54–2.41)	18	1.54 (0.78–3.04)	15	1.16 (0.57–2.37)
Medium	30	18	2.47 (0.73–2.94)	19	1.65 (0.84–3.25)	19	1.29 (0.66–2.53)	21	1.66 (0.86–3.20)
High	29	26	2.88 (1.51–5.47)	12	1.59 (0.74–3.44)	30	2.74 (1.48–5.04)	12	1.37 (0.63–2.94)
$P_{for\ trend}$**			*0.014*		*0.81*		*0.010*		*0.95*
Intensity									
Average									
Low	30	13	1.05 (0.49–2.25)	17	1.47 (0.73–2.95)	16	1.18 (0.58–2.37)	20	1.55 (0.80–3.01)
Medium	39	34	2.53 (1.43–4.47)	19	1.47 (0.77–2.81)	38	2.32 (1.34–4.01)	20	1.36 (0.72–2.55)
High	19	12	2.01 (0.87–4.64)	8	1.35 (0.54–3.42)	13	1.84 (0.82–4.12)	8	1.21 (0.48–3.05)
$P_{for\ trend}$**			*0.25*		*0.56*		*0.33*		*0.41*
Cumulative									
Low	32	17	1.32 (0.66–2.64)	14	0.98 (0.48–2.02)	19	1.30 (0.67–2.52)	16	0.99 (0.49–1.98)
Medium	27	17	1.69 (0.82–3.48)	18	2.26 (1.13–4.55)	19	1.68 (0.84–3.35)	20	2.26 (1.15–4.44)
High	29	25	2.83 (1.48–5.39)	12	1.37 (0.63–2.96)	29	2.58 (1.39–4.76)	12	1.19 (0.55–2.56)

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Occuational exposure	Controls	Papillary				Well-differentiated			
		≤ 1 cm		>1 cm		≤ 1 cm		>1 cm	
		Cases	OR* (95% CI)	Cases	OR* (95% CI)	Cases	OR* (95% CI)	Cases	OR* (95% CI)
$P_{for\ trend}$**			*0.072*		*0.97*		*0.091*		*0.76*
Pesticides									
Never	385	141	1.00	157	1.00	158	1.00	177	1.00
Uncertain	100	46	1.30 (0.84–2.02)	38	0.95 (0.60–1.50)	51	1.29 (0.85–1.96)	48	1.06 (0.69–1.63)
Ever	11	2	0.54 (0.09–3.13)	2	0.42 (0.07–2.32)	4	1.29 (0.35–4.79)	2	0.39 (0.07–2.17)

*Adjusted for age (continuous), gender, race, education, BMI, family history of thyroid cancer, history of benign thyroid disease, smoking status, alcohol consumption, and physical activity.

**Calculated by continuous variables among exposed participants.