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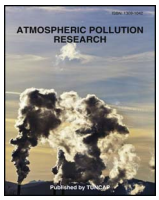

Thyroid cancer incidence in women and proximity to industrial air pollution sources: A spatial analysis in a middle size city in Colombia

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ABSTRACT

Manizales, a mid-size city in Colombia, hosts industries like metallurgy, electrical, chemical, and rubber and plastic industrial facilities that have released into atmosphere some pollutants postulated as thyroid cancer (TC) promoters, such as dioxins and furans, dichloromethane, lead and copper. In this article we aim to detect clusters of TC and analyze their spatial association with industrial pollution. TC cases (2003–2010) were obtained from Manizales' Population-based Cancer Registry (PCR-Mz). Atmospheric emissions from industries were obtained from official reports of environmental authority. Data was spatially aggregated into census tracts and analyzed with Bayesian Besag-York and Mollié (BYM) models. Three exposure approaches were used: i) presence or absence of industries into census tracts, ii) sum of air discharges, and iii) an exposure index (EI) that considered the distance and orientation of the census tract regard to industries, average wind direction and speed, and population mobility. Models were fitted by exposure definition and sex, and included traffic and socioeconomic variables for adjustment. Using the Kulldorff's spatial exploration statistic we also performed point-data analyses in order to detect and localize clusters with individual data.

Ecological regression models showed that, for women, smoothed standardized incidence ratio (sSIR) increase in 15% [95% credibility interval: 3–27%] and 63% [95%CI: 18–125%] per one standard deviation increase in EI for dichloromethane and PCDDs/Fs, respectively. Point-data analysis confirmed a cluster of female cases close to an industry emitting chlorinated solvents. These results suggest that dichloromethane and PCDDs/Fs emitted from industrial sources might be suspected as thyroid cancer risk factors.

1. Introduction

Manizales is a city localized in a high altitude valley (2150 m.a.s.l) in the Andean region of Colombia, South America, with about 400,000 mostly (93%) urban inhabitants (DANE, 2005). It has a tradition of industrial activities, spanning several decades, with main activities being metallurgy and metal processing, manufacture of electrical appliances, chemical industry, rubber and plastic, food products and other manufactures (Soto-Vallejo et al., 2009). Local researchers have warned against the risks of air pollution in Manizales due to the high presence of industrial sources besides its topography, meteorology, traffic emissions and population crowding in urban zones (Aristizábal et al., 2011). In a recent paper, we identified 36 industrial facilities in Manizales that have emitted air pollutants such as metals, polychlorinated dioxins and furans, and chlorinated solvents, which have been pointed out like potential thyroid carcinogens. Atmospheric emissions from several industries have exceeded regulatory limits, including those of potential carcinogens (Arias-Ortiz and Ruiz-Rudolph, 2017).

In this context, health surveillance became critical, and one outcome that has shown unusually high rates in Manizales is thyroid cancer, with rates much higher than other cities in Colombia and South America. Age-standardized incidence rates (ASIR) for 2003–2007 were 12.4 per 100,000 person-year for women and 3.7 for men (López-Guarnizo et al., 2012), while in other Colombian cities -Bucaramanga, Cali and Pasto-the ASIRs were 9.6, 11.3, y 8.4 for women and 2.6, 2.3 y 2.4 for men, respectively (Bravo et al., 2012; Uribe et al., 2012; Yépez et al., 2012). Worldwide, Manizales is in the top 50 of cities with population-based cancer registries (IARC et al., 2014). Incidence

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Abbreviations

ASIR	age-standardized incidence rates
m.a.s.l	meters above sea level
BYM	Besag, York and Mollié Bayesian models
sSIR	smoothed standardized incidence ratio
US-EPA	United States Environmental Protection Agency
EDC	endocrine disruptor chemical
HHT	hypothalamic-hypophysis-thyroid axis
PCB	polychlorinated byphenyls
PBDE	polybrominated byphenyls
DANE	National Department of Statistics, by its Spanish acronym
CAR	convolution auto-regressive distribution
PCR-Mz	Population-based Cancer Registry of Manizales
PP	posterior probability from BYM model
RFs	reporting facilities, or industrial facilities required to report atmospheric emissions of specific pollutants
Non-RFs	non-reporting facilities, or industrial facilities not required to report atmospheric emissions of specific pollutants but belonging to the same standard industrial classification (SIC) that RFs
PCDDs/Fs	poly-chlorinated dibenzo-dioxins and furans
LCI	living-conditions index
MPL	maximum permitted limits

estimations for 2008–2012 are even higher, with ASIR of 23.2 y 4.6 per 100.000 in women and men, respectively (Bray et al., 2017).

Despite a marked worldwide increase in thyroid cancer incidence in recent decades (Pellegriti et al., 2013), few risk factors have been demonstrated (Meinhold et al., 2010), being ionizing radiation the only one confirmed (Brown et al., 2012; Hard, 1998). Iodine intake deficiency has been only associated with follicular carcinoma (Pellegriti et al., 2013), but it is a less relevant risk factor because many countries, including Colombia, are adding iodine to salt for human consumption.

Some environmental risk factors for thyroid cancer have been proposed, including intake of nitrates in food and water (Ward et al., 2010), and occupational exposure to industrial solvents, formaldehyde and pesticides (WHO-UNEP, 2013). Pesticides have been shown to induce tumors in rodents follicular cells by non-mutagenic mechanisms (Hurley, 1998), or showed inhibitory activity on thyroid peroxidase, increased hepatic metabolism and excretion of thyroid hormones (WHO-UNEP, 2013). Several chemicals have been postulated as endocrine disruptors (EDCs) of the hypothalamic-hypophysis-thyroid (HHT) axis (WHO-UNEP, 2013). Evidences have been observed for phthalates, PCB and PBDEs both in animals and humans (Baccarelli et al., 2008; Chevrier et al., 2007; Hombach-Klonisch et al., 2013; Meeker et al., 2007; Shen et al., 2011; Zhang et al., 2009). However, evidence of these mechanism as risk factor of thyroid cancer in human populations remains unclear (Aschebrook-Kilfoy et al., 2015, 2014; WHO-UNEP, 2013).

In this context Manizales presents many opportunities to study the impacts of industrial pollution on thyroid cancer. First, industrial facilities have been present close or within urban areas for decades, with many of them releasing suspected thyroid carcinogens postulated by Leux and Guénel (2010); second, the high thyroid cancer incidence reported suggests a major risk factor affecting the city; and third, the existence of a population-based cancer registry with high quality data.

The aim of this study is to detect clusters of thyroid cancer using spatial analysis of aggregated data (smoothed standardized incidence ratio at census tracts) and point data (individual cases location), and assess whether the clusters are associated with industrial sources of specific air pollutants.

2. Methods

2.1. Study design

We performed a spatial analysis combining two approaches. First, an ecological small-area incidence study, using census tracts as the unit of analysis, in order to determine tracts with unusually high incidence rates and estimate associations between industrial sources of air pollutants and thyroid cancer. Second, we performed a point-data analysis, in order to detect and locate spatial clusters of thyroid cancer cases. Both methodological approaches have been widely used and have important developments in the last two decades (Beale et al., 2008; Elliott and Wartenberg, 2004; Lawson et al., 1999; Lertxundi-Manterola, 2006; Santamaría-Ulloa, 2003). We adopt these two approaches because they are considered the first step in the exploration and verification of hypotheses in the ecological level, which serve as a justification for more complex and costly later studies.

We focused on industrial facilities that were more likely to affect thyroid cancer incidence, and thus were selected following these criteria: i) facilities located in urban Manizales, as they are more likely to produce higher exposures in the population; ii) those operating before 1994, considering likely latency periods for thyroid cancer (Hallquist et al., 1993; Ron et al., 1995); and iii) industrial facilities reporting air emissions of suspected thyroid carcinogens like polychlorinated dioxins and furans (PCDDs/DFs) (Pesatori et al., 2009), metals such as cadmium, copper, lead, mercury, nickel, or zinc (Kouniavsky and Zeiger, 2010; Leux and Guénel, 2010; Vigneri et al., 2015), and chlorinated solvents (Barragán-Martínez et al., 2012; Benvenga et al., 2015; Lope et al., 2005; Wingren et al., 1995; Wong et al., 2006).

2.2. Industrial facilities

We performed an exhaustive search of industrial facilities in the urban area of Manizales, geo-referenced them, and characterized their emissions. Industrial facilities were identified from environment official records and from enterprise census. In order to estimate the atmospheric discharges of pollutants two approaches were followed, depending on whether facilities were required to report air pollutants. In the first, industries required to state air pollution releases – reporting facilities (RFs)– were identified using official records, and data about emissions of specific pollutants were extracted; also, a per-employee emission rate was calculated for each pollutant. Detailed information about kind of contaminants, methods and years of available data in official records can be found in Supplementary Table 1. In the second approach, industrial facilities not required to state air pollution releases – non-reporting facilities (non-RFs)–, but belonging to the same Standard Industrial Classification codes than the RFs, were also identified from enterprise census. According to current legislation, these industries are exempt from reporting air emissions primarily by its size, as most of them are micro and small businesses, but including them is critical because they are companies with less infrastructure and capacity to implement clean technologies, and some of them are still using quasi-artisanal methods that might be more polluting. Emissions of specific pollutants from non-FRs were calculated based on the number of employees and the per-employee rates calculated previously (Dolinoy and Miranda, 2004). Initially, we identify 36 industrial facilities that have emitted PCDDs/DFs, lead, copper, and dichloromethane (Arias-Ortiz and Ruiz-Rudolph, 2017). After applying selection criteria described in section 2.1 (only industries located in urban zone that started operations before 1994), only 28 industries met the selection criteria. Geographical coordinates and addresses were obtained for each facility and geo-referenced using the Google© Street View tool.

2.3. Exposures to industrial emissions

Three surrogate definitions of potential exposure to pollution in each census tract were used. First, the presence of one or more sources of PCDD/DFs, lead, copper and dichloromethane within the census tract as a dichotomous variable (1 if present, 0 otherwise), following definitions used in similar studies (Fernández-Navarro et al., 2012; García-Pérez et al., 2013; López-Abente et al., 2012; Ramis et al., 2011). Second, the sum of air discharges of specific pollutants from facilities located in the census tract, normalized to a mean of 0 and a standard deviation of 1 (z-score). And third, we used an exposure index (EI) similar to one used before (Hu et al., 2001), but adapted to Manizales. The index took into account the orientation of the census tract from the industrial facility, along with prevailing winds direction and speed, and population's mobility, as shown in Eq. (1):

$$EI = (dw*t)/(d^2*ws) \quad (1)$$

where: *dw* represents proportion of the annual time downwind from the facility, *t* is the 'time spent at home', according to the classification of municipal mobility plan (areas of high, moderate and low mobility according to the number of daily trips generated) (Flórez-Valero and González-Rodríguez, 2007), d^2 is the squared distance of the census tract centroid to the source, and *ws* is the average wind speed in each direction. Wind speed and direction were extracted from the annual mean values (from 1980 to 1999) of the wind rose reported by the Institute of Hydrology, Meteorology and Environmental Studies of Colombia (IDEAM, for its acronym in Spanish) (Instituto de Hidrología Meteorología y Estudios Ambientales (Colombia), 1999). An EI was calculated for each facility and tract and weighted by the proportion of its emissions of specific air pollutants to the total amount released by all facilities. Then, for each census tract a unique EI was obtained as the sum of the EI's estimated for all facilities. The EI was also normalized to z-scores to facilitate the computational process.

2.4. Health outcome and incident rates

Thyroid cancer cases were obtained from PCR-Mz (Arias-Ortiz and López-Guarnizo, 2013) over the period 2003–2010. The PCR-Mz uses the third edition of the International Disease Classification for Oncology (CIE-O 3) according to standards defined by IARC and IACR. From PCR-Mz database we filtered cases of malignant neoplasms localized in thyroid gland (topography code 739 for CIE-O 3), including all histological subtypes. A total of 312 confirmed cases of Manizales residents were observed, with only 3.6% (n = 12) living in rural areas. The latter were excluded due to low relevance for the study (93% of the population was urban) and because cartography for rural zones was not available. Of the remaining, most cases (251, 83.7%) were women. For each case, address of residence at diagnosis was geo-referenced and assigned to a census tract. Seven cases had no address (6 women and 1 man) and were excluded. Table 1 describes the cases by age, histology, extension, health insurance and socioeconomic position.

Population broken down by sex and 17 age groups (quinquennial) for each census tract were extracted from 2005 population census database (DANE, 2007). Due that population projections are estimated by DANE only at the municipal level, the persons-year in each area were obtained by multiplying this population by the number of observation years, as proposed by Lopez-Abente et al. (2006). Sex and age-specific incidence rates for urban Manizales as a whole were used as reference. Expected cases at census tracts were calculated by the indirect method, applying reference rates by sex and age groups to census tract population groups.

2.5. Ecological analysis

Smoothed Standardized Incidence Ratios (SIRs) –denoted by θ_i – were obtained for each census tract using the Besag, York and Mollie (BYM) model (Besag et al., 1991). BYM model is based on fitting Poisson spatial models with observed cases (Y_i) as a dependent variable, expected cases (E_i) as offset, and two random effects which take into account a spatial term (v_i) and a non-spatial term (u_i) (Lopez-Abente et al., 2006). The model is described in Eq. (2) to Eq. (5):

$$Y_i \sim Poisson\ (E_i\theta_i), \quad (2)$$

$$\widehat{\theta_i} = Y_i/E_i,\ \ i = 1,\ ...,N, \quad (3)$$

$$log\theta_i = \log(E_i) + \ \alpha + (u_i + v_i), \quad (4)$$

$$\theta_i = exp^{\alpha+u_i+v_i} \quad (5)$$

where α is the intercept, u_i is the unstructured variability component that assumes a normal distribution and v_i is the random spatially structured variability component that follows a convolution autoregressive (CAR) - Normal distribution, with adjacent boundaries of the areas as the criteria of contiguity, that takes into account for autocorrelation between neighboring areas (Lopez-Abente et al., 2006).

Table 1
Characterization of thyroid cancer cases in urban Manizales, 2003–2010.
Source: proper elaboration based on data from PCR-Manizales

	Women (n = 245)		Men (n = 48)	
Age at diagnosis (years), mean (sd)	**48.5**	**(15.6)**	**56**	**(18.1)**
Morphology[a], n (%)				
Papillary carcinoma	211	(86.1)	36	(75.0)
Follicular carcinoma	29	(11.8)	8	(16.7)
Anaplastic carcinoma	**0**	**(0.0)**	**3**	**(6.3)**
Medullary carcinoma	2	(0.8)	0	(0.0)
Unknown	3	(1.2)	1	(2.1)
Differentiation, n (%)				
Well diferentiated	**196**	**(80.0)**	**29**	**(60.4)**
Moderately diferentiated	27	(11.0)	10	(20.8)
Poorly diferentiated	16	(6.5)	4	(8.3)
Undifferentiated	2	(0.8)	3	(6.3)
Unknown	3	(1.2)	2	(4.2)
Missing	1	(0.4)	1	(2.1)
Dissemination, n (%)				
Localized	137	(55.9)	22	(45.8)
Regional	43	(17.6)	8	(16.7)
Metastatic	59	(24.1)	14	(29.2)
Unknown	4	(1.6)	2	(4.2)
Missing	2	(0.8)	1	(2.1)
Health insurance regime[b], n (%)				
Contributory/Special	181	(73.9)	38	(79.2)
Subsidized	55	(22.4)	6	(12.5)
No Insurance	7	(2.9)	2	(4.2)
Unknown	2	(0.8)	2	(4.2)
LCI[c], mean (sd)	77.3	(4.6)	77.7	(4.5)
Incidence rate, by age groups[d]				
25–29	17.3			
30–34	15.5			
35–39	17.2			
40–44	20.1			
45–49	32.0			
50–54	45.1		11.6	
55–59	37.5		14.7	
60–64	28.7		7.5	
65–69	25.3		6.3	
70–74	37.5		32.5	
75–79	23.0		16.9	
80+	29.0		18.8	

Variables in bold mean that there were statistical differences between sex (at 95% confidence level; p-values < 0.05 from two sample test of means or proportions).

[a] Morphology was coded according to CIE-O 3rd edition rules.

[b] Contributory is the most generous health insurance. Subsidized is a public health social security affiliation.

[c] LCI: living-condition index between 0 and 100, where the highest value, the better socioeconomic position; this index includes variables of education, ownership of durable goods, material housing conditions, and demographic composition of households.

[d] These incidence rates for urban Manizales as a whole were used to calculate expected cases at census tracts; age groups with incidence < 5 cases per 100.000 are not shown.

Models were fitted using Bayesian Markov Chain Monte Carlo simulations in WinBUGS© 1.4.3 (1996–2007, Imperial College and Medical Research Council, UK), with non-informative priors proposed by Bilancia & Fedespina (Bilancia and Fedespina, 2009) for the precision of σ_u^2 and σ_v^2 as follows:

$\alpha \sim flat()$

$\beta_1 \sim Normal(0,\ 0.00005)$

$\beta_2 \sim Normal(0,\ 0.00005)$

$\beta_3 \sim Normal(0,\ 0.00005)$

$u_i \sim Normal(0,\ \sigma_u^2)$

$v_i \sim CAR.\ normal(\sigma_v^2)$

$\sigma_u^2 \sim Gamma(0.01,\ 0.01)$

$\sigma_v^2 \sim Gamma(0.5,\ 0.005)$

A 'burn-in' period of 50,000 iterations was performed to ensure convergence, and the posterior distributions were extracted from 150,000 subsequent iterations saving 1 of 50 iterations from two independent chains (6000 samples). Models convergence was checked by graphical methods and by Gelman-Rubin statistics. Models were fitted for each sex separately.

SIRs were treated as the relative risk (RR) in each census tract in comparison with the incidence in urban Manizales as a whole. The estimations of RR (SIRs) were assessed through the mean of the posterior distribution and its 95% Credibility Interval (95%CI). Mean estimates of thyroid cancer risk (estimates for θ_i or SIRs) –for each census tract were mapped. To identify tracts with elevated incidence, we used the posterior probability (PP) that SIRs > 1.0 considering cutoff values of around 0.7–0.8 as proposed by Richardson (Richardson et al., 2004). Maps were plotted using ArcMap 10.2™ (ESRI, Redlands, CA, USA).

The associations between pollution exposures and thyroid cancer incidence were estimated from further BYM models (one for each exposure definition and by sex), specified in Eq. (6):

$$\log(\theta_i) = \alpha + \beta_1 Dioxins_m + \beta_2 PbCu_m + \beta_3 Dclmet_m + \beta_4 LCI_m + \beta_5 Traffic_m + (v_i + u_i) \quad (6)$$

where α is the intercept; $Dioxins_m$ is the exposure to industries releasing PCDDs/Fs into air in each census tract ($m = 93\ tracts$); $PbCu_m$ is the exposure to industries releasing lead and copper; and $Dclmet_m$ is the exposure to industries emitting dichloromethane into air; LCI_m is a term for socioeconomic condition fix effect (Living Conditions Index, LCI) and $Traffic_m$ is a higher vehicles traffic area indicator. The LCI was obtained from a survey conducted by local researchers in 2009 following the standards of DANE (DANE, 2008), which includes variables of education, ownership of durable goods, material housing conditions, and demographic composition of households. Higher socioeconomic status adopts higher LCI values. Traffic indicator takes the value of 1 if the census tract is located in downtown Manizales or shares any of its limits with the main roads of the city, and 0 otherwise.

Three modeling approaches were used according to the three exposure definitions. In the first (model 1: dichotomous indicator), exposures to industrial sources emitting pollutants were modeled as binary as the presence or absence of the industry inside the census tract. In the second (model 2: sum of discharges), the exposure was modeled as the sum of air pollutants emitted from industries located into each census tract. Last, in the third (model 3: exposure index), the exposure was modeled using the unique EI obtained as the sum of the EI's estimated for all facilities. In model 1, coefficients were interpreted as RRs in tracts with facilities vs tracts without. In models 2 and 3, coefficients were interpreted as change in RR per one standard deviation in the sum of emission discharges or change in exposure index, respectively.

Table 2
Characteristics of cases and *pseudo*-controls for point-data analyses.

Variable	Women			Men		
	Cases	*Pseudo*-controls	p- value[a]	Cases	*Pseudo*-controls	p- value[a]
Count	245	490		48	96	
Age, mean (sd)	48.5 (15.6)	50.5 (15.9)	0.06	56.0 (18.1)	59.7 (15.9)	0.21
LCI, mean (sd)	77.3 (4.6)	76.5 (4.3)	0.07	77.7 (4.5)	78.0 (4.1)	0.58
Health Insurance Regime (%)						
Contributory/ Special	73.9	74.1	0.95	79.2	77.0	0.77
Subsidized	22.4	22.2	0.95	12.5	21.9	0.18
No Insurance	2.9	3.9	0.48	4.2	1.0	0.22

LCI: living-condition index between 0 and 100, where the highest value, the better socioeconomic position; this index includes variables of education, ownership of durable goods, material housing conditions, and demographic composition of households.

[a] From two sample test of means or proportions.

2.6. Point-data analysis

Point-data analysis tries to identify and locate potential clusters of cases in the study area. Analysis were made using the Kulldorff's spatial exploration statistic, following the Bernoulli model for case-control data type (Kulldorff, 1997). Spatial pattern of cases were contrasted against randomly selected *pseudo*-controls obtained from the PCR-Mz for other causes, considering 2 controls per case matched by sex and age (± 5 years). Cervix-uteri, stomach and skin cancer cases were selected as *pseudo*-control for women, while skin cancer cases for men. Residence at diagnosis was georeferenced for both cases and *pseudo*-controls. Table 2 compares cases and *pseudo*-controls by age, health insurance and socioeconomic conditions. We explored global (through all the study area) and focused clusters (around industries). According to Kulldorff (1997), the global detection test is able to detect the location of clusters and evaluate their statistical significance without problems with multiple testing. Focused cluster test allows evaluating whether there is a disease cluster around one or more pre-determined foci like industries or toxic waste sites. For each possible cluster, we report its approximate geographical position, radius and RR compared with the area outside the cluster as reference. Statistical significance of RRs were estimated from log-likelihood ratio test adjusted for multiple clusters (Zhang et al., 2010). Models were implemented using the software SaTScan™ version 9.0. This is a free program that analyzes spatial, temporal and space-time data using the spatial, temporal, or space-time scan statistics. It was designed, among other purposes, to perform geographical surveillance of disease, to detect spatial or space-time disease clusters, and to see if they are statistically significant; to test whether a disease is randomly distributed over space, over time or over space and time; and to evaluate the statistical significance of disease cluster alarms (Kulldorff, 2010a, 2010b).

3. Results

3.1. Industrial sources of pollution

Fig. 1 shows the spatial pattern of industrial facilities that met the selection criteria, by size and class (RFs or non-RFs). We included eight RFs and twenty non-RFs that met the selection criteria. More usual industrial activities were metal works (manufacture of metal products, smelters), rubber and plastic manufactures, electric and electronic devices manufacture, and manufacture of auto parts. Industries were mainly clustered at the southeast with some others located downtown along the main road running east-west. Table 3 summarizes the emission of specific pollutants from RF and non-RFs that exceeds maximum

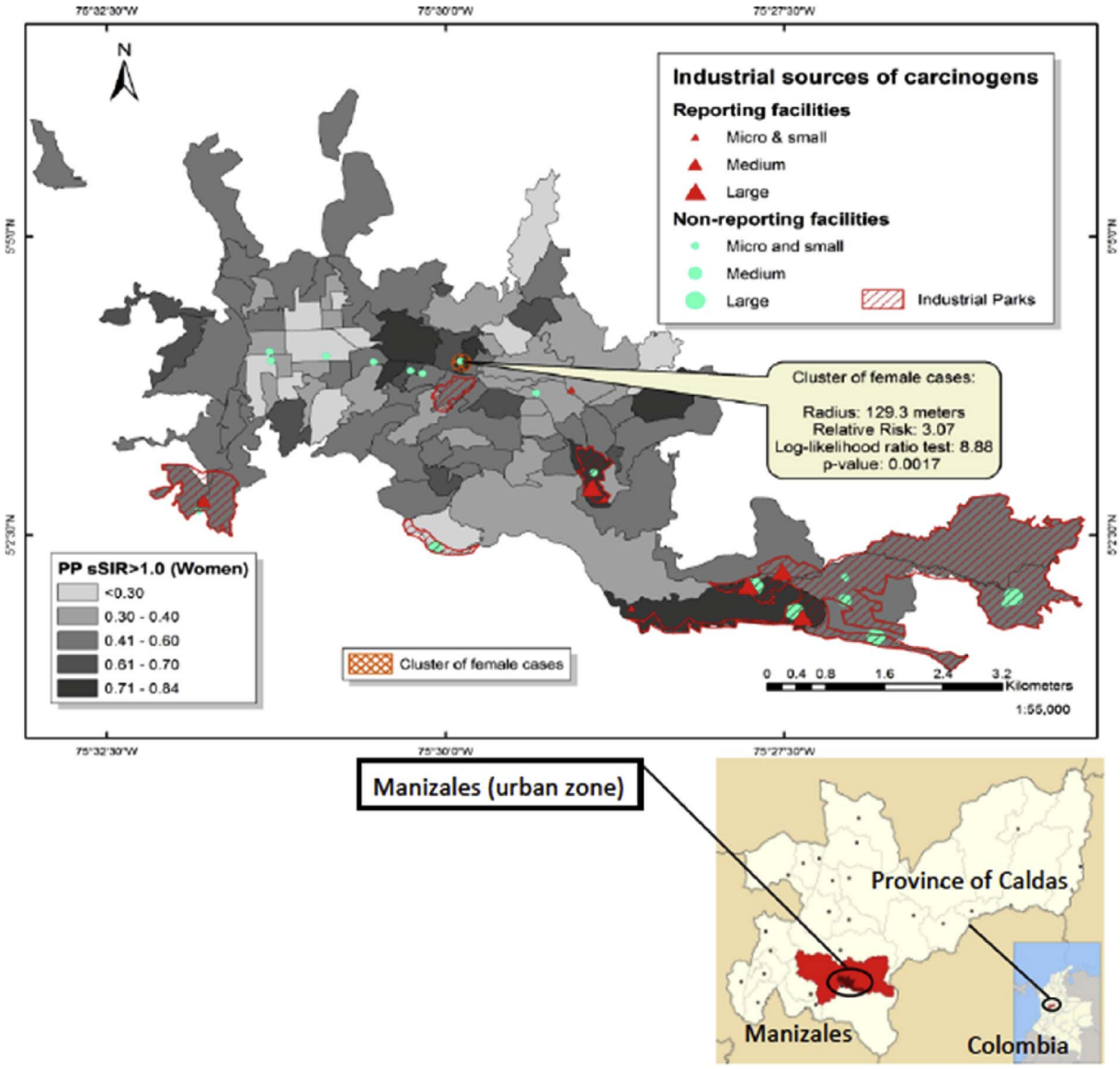

Fig. 1. Spatial pattern of industries releasing potential thyroid carcinogens, by size, and location of cluster of female cases.

permitted limits set in Colombian law. Several of these pollutants have been classified by IARC as carcinogens (group 1, 2A, and 2B) for other cancer sites.

3.2. Thyroid cancer incidence and ecological models

As shown in Table 1, thyroid cancer was five times more frequent in women than in men (female/male ratio 5:1). Most of the cases were well-differentiated tumors, mainly papillary carcinomas, both in women and men. Age-adjusted incidence rate in urban Manizales as a whole for 2003–2010 were 15,2 per 100.000 in women and 3,7 per 100.000 men. In women, age-specific rates showed a peak on the 50–54 years old group, while in men the higher incidence was observed for the 70–74 years old group. More than 70% of cases were covered by health insurance, meaning that they likely had good access to health care, which may explain early diagnosis or even incidental diagnosis of tumors. However, 42% and 46% of the cases presented regional spread or metastases at diagnosis in women and men, respectively.

Estimates of SIR for thyroid cancer in urban Manizales are shown in Figs. 2 and 3, for women and men, respectively. It can be noted that smoothing reduced dispersion and stabilized SIR (smoothed SIRs were between 0.80 and 1.10 in most census tracts). Areas with high incidence estimations (SIR > 1.25) were reduced after smoothing, especially in women, leaving them mostly near downtown and at the southeast section. When considering posterior probabilities (PP SIR > 1.0), 6 census tracts show PPs above 0.7, for women, while only 3 were observed for men.

Table 4 shows the model estimations for the effect of exposure to industries releasing PCDDs/Fs, lead and copper, and dichloromethane into air on the SIR of thyroid cancer incidence at census tracts. No significant associations were found for men, except in model 1 for sources emitting dichloromethane, which was also showed large credibility intervals. Thyroid cancer incidence in women was significantly associated with proximity to industrial facilities releasing dichloromethane. This association was consistent between the three modeling approaches, and showed impacts ranging from increases of 97% in SIR for the presence of facilities in the census tract (model 1) to increases in 15% per each standard deviation in exposure score (model 3). We also found a statistically significant association between proximity to sources emitting PCDDs/Fs and SIR in women (model 3), with average increase of 63% per one standard deviation increase in the exposure index.

Table 3
Industrial facilities with emissions of specific pollutants above maximum permitted limits (MPL).
Source: prepared by the authors based on data from CORPOCALDAS

	SIC code	Industrial sector	MPL (mg/m^3)	Highest emission reported (mg/m^3)	Excess ratio[b]	*Comuna*
Reporting facilities						
Lead[a]	D2893	Metal works	1	24.00	24.0	*Cerro de Oro*
PCDDs/Fs[a]	D2731	Metal works	0.1[c]	0.14[c]	1.4	*Tesorito*
Copper	D2893	Metal works	8.0	15.0	1.9	*Cerro de Oro*
Non-reporting facilities				**Estimated emissions (mg/m^3)[d]**		
Lead	D2893	Metal works	1	348.5	348.5	*Tesorito*
				200.6	200.6	*Tesorito*
				184.9	184.9	*Tesorito*
				62.9	62.9	*Tesorito*
				34.2	34.2	*Tesorito*
				22.2	22.2	*Tesorito*
				20.3	20.3	*Tesorito*
				9.2	9.2	*Tesorito*
Copper	D2893	Metal works	8.0	209.9	26.2	*Tesorito*
				120.8	15.1	*Tesorito*
				111.3	13.9	*Tesorito*
				37.8	4.7	*Tesorito*
				20.6	2.6	*Tesorito*
				13.4	1.7	*Tesorito*
				12.2	1.5	*Tesorito*
PCDDs/Fs[a]	D2731	Metal works	0.1[c]	0.103[c]	1.03	*Tesorito*

MPL = maximum permit limits of emission for each pollutant and each industry or process - Resolution 909/2008 Environmental Ministry of Colombia.
[a] Agents classified in groups 1, 2A or 2B of IARC.
[b] Excess ratio = maximum emission/MPL.
[c] PCDDs/Fs were measured and reported in ng-TEQ/R-m3.
[d] Emissions from non-RFs were estimated using the per-employee algorithm described in section 2.5.

Socioeconomic conditions at census tract level was positively associated with cancer incidence (higher SES, higher rate), but it did not reach statistical significance. The inclusion of LCI and high-traffic indicator as adjustment variables did not modify estimations and the direction and significance of the association were retained.

3.3. Point-data analysis

In both global and focused analyses, we found only one statistically significant cluster in women. This cluster includes 8 observed cases and 2.67 expected cases into a radius of 129.3 m (RR = 3.07; log-likelihood ratio test = 8.88, p-value = 0.0017). It was located close to an industrial facility that, according to environmental authority reports, has released dichloromethane and tetrachloroethylene (see Fig. 1). Contrary to ecological analyses, no significant clusters were detected in men.

4. Discussion

This study analyzed the relation between proximity to industries releasing air pollutants suspected to promote thyroid carcinogenesis, and the incidence of thyroid cancer at the census tract level using data from a population-based cancer registry and a spatial approach with analysis of data aggregated into small-areas and analysis of point-data. Most of thyroid cancer cases included in this study were well differentiated tumors, mainly papillary carcinomas, which is in agreement with literature (Malandrino et al., 2013; Pellegriti et al., 2009).

Epidemiological studies of impacts of industrial activities on thyroid cancer are scarce. In the early 80's, Gaitán (Gaitan, 1983) found presence of various contaminants (phthalates, resorcinol, organic compounds) in the drinking water in southwestern Colombia geographic areas with high prevalence of goiter in children. Recently, Ruiz-Rudolph et al. (2016) reported impacts of large industrial emission sources on cancer mortality in Chile, especially for oil- and coal-fired power plants and copper smelters. Although the studies present the case that industrial emission might produce cancer, none of these have examined their impact on thyroid cancer.

Occupational studies in Sweden showed increased risk of thyroid cancer in female workers exposed to solvents in the shoe and leather industry (Lope et al., 2009) and in women working in manufacture of prefabricated wooden buildings, electric installations and wholesale of agricultural products, as well as in men working in manufacture of agricultural machinery, manufacture of computing/accessories and public administrators (Lope et al., 2005). In China, Wong et al. found similar results in women exposed to benzene and formaldehyde in the textile industry in China (Wong et al., 2006). In a review article, Aschebrook-Kilfoy et al. reported suggestive but inconsistent associations for agricultural works (pesticides), and warns about the potential impacts of metals (cadmium, copper, nickel, zinc) and solvents, because of their capacity to disrupt thyroid homeostasis (Aschebrook-Kilfoy et al., 2014).

Impacts of environmental exposures in general population residing near industries have also been studied. After the Seveso disaster in Italy (1976), studies reported associations between dioxin exposures and thyroid cancer, but were not statistically significant (Pesatori et al., 2009, 2003). A study in Spain (Grimalt et al., 1994) found higher rates in men living in an area contaminated with hexachlorobenzene from an industrial source, although its results could not rule out occupational exposure. Proximity to mining facilities have also been associated with mortality due to thyroid cancer (Fernández-Navarro et al., 2012). As a summary, a set of suspected thyroid carcinogens, released or used in various industrial processes, has been proposed by Leux & Guénel (Leux and Guénel, 2010), which includes dioxins and furans, chlorinated solvents, and some heavy metals such as cadmium, lead and mercury.

In ecological models, we found several census tracts with incidence higher than the overall rate of Manizales, especially in women, while regression models showed impacts of exposure to dichloromethane and PCDDs/Fs on thyroid cancer in women, mainly. Then, point-data analyses allowed us to confirm the presence of one cluster of female cases located close to an industry that has released dichloromethane and tetrachloroethylene for decades.

Occupational studies (Lope et al., 2009, 2005; Wong et al., 2006) have reported associations between exposures to pollutants and risk of developing thyroid cancer in work settings, but few studies have studied thyroid cancer in relation with exposures to pollution from industrial sources in general population. Lope et al. (2006) published a descriptive study of mortality due to thyroid cancer in the municipalities of Spain, highlighting the presence of some high-risk areas, particularly in zones with a history of endemic goiter. Proximity to underground coal mining facilities were associated with higher thyroid cancer mortality in Spain municipalities (Fernández-Navarro et al., 2012). The last two studies fail to adequately describe the behavior of thyroid cancer because it has high survival rates, especially for well differentiated subtypes that represents more than 80% of malignant tumors of thyroid gland.

In our study, more consistent impacts were observed for dichloromethane exposure, both in the ecological analyses and the point-source model. These findings are consistent with those reported by Lope et al. (2009) in individuals occupationally exposed to solvents. Additionally, an association was also observed for exposures to PCDDs/Fs, which is consistent with studies of Pesatori et al. (Pesatori et al., 2009, 2003).

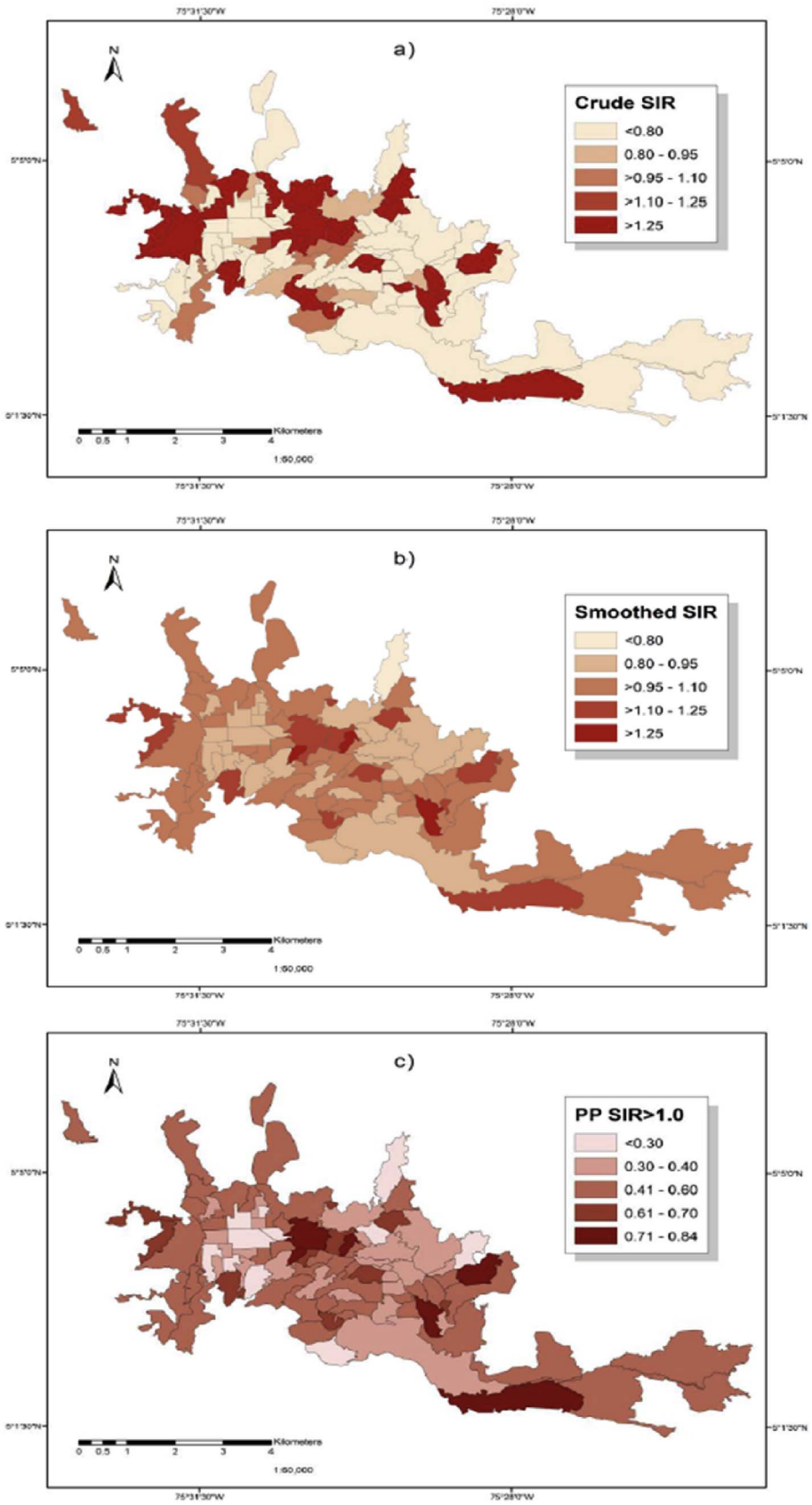

Fig. 2. Thyroid cancer crude (a) and smoothed (b) SIR and posterior probability (PP) that sSIR > 1.0 (c). Women. Manizales, 2003–2010.

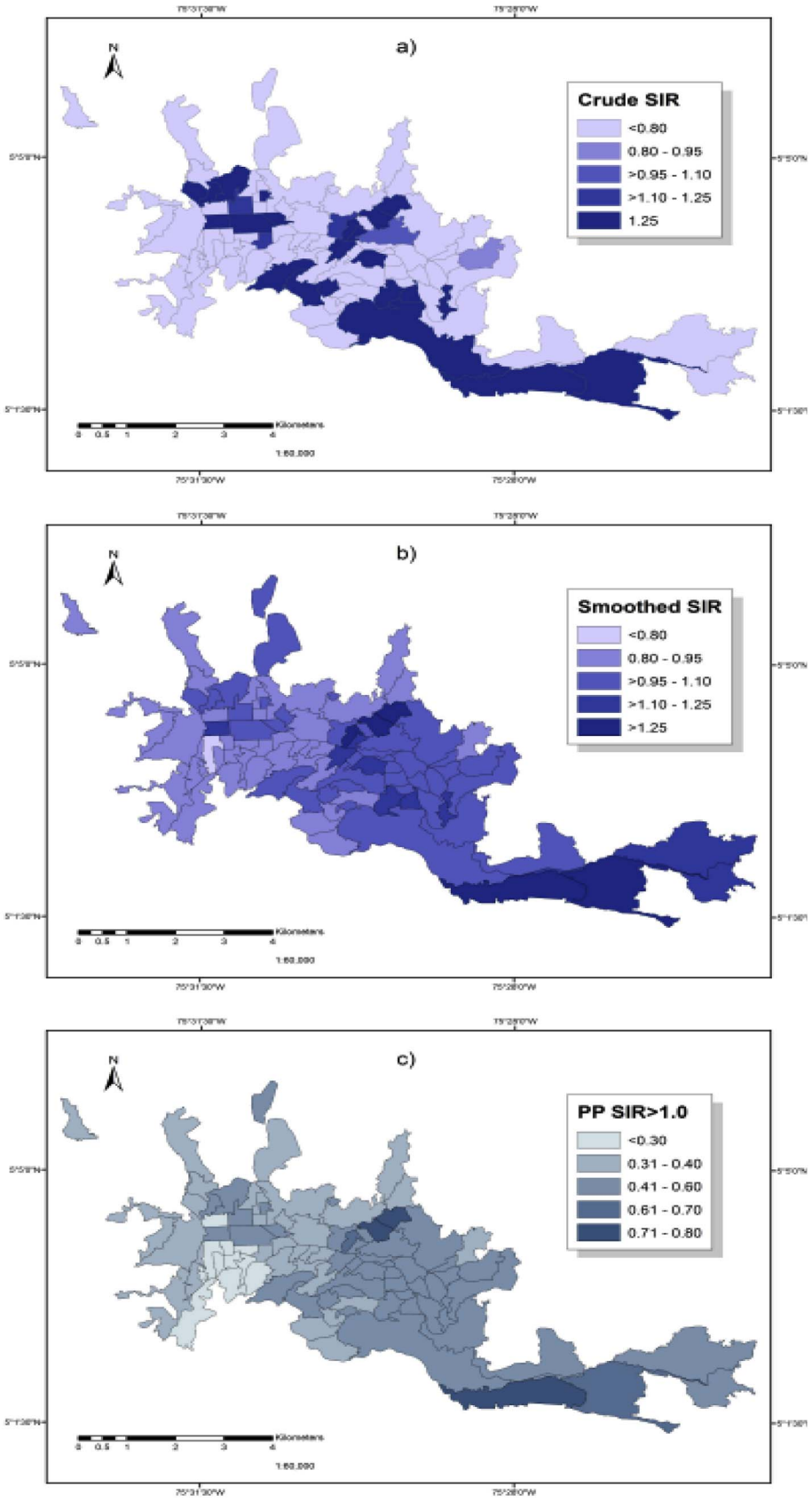

Fig. 3. Thyroid cancer crude (a) and smoothed (b) SIR and posterior probability that sSIR > 1.0 (c). Men. Manizales, 2003–2010.

Table 4
Effect of exposure to industrial sources of pollution on thyroid cancer incidence.

PCDDs/DFs	Lead	Dichloromethane	LCI	Traffic	DIC
Coefficients [95%CI] for exposure and covariates					
Women (total n = 245)					
Model 1: Dichotomous					
0.95 [0.58; 1.55]	0.88 [0.46; 1.63]	**1.97 [1.09; 3.54]**	1.02 [0.98; 1.05]	0.99 [0.73; 1.36]	329.4
Model 2: Sum of emissions					
1.06 [0.90; 1.23]	0.76 [0.57; 1.03]	**1.32 [1.01;1.72]**	1.01 [0.98; 1.05]	1.03 [0.74; 1.41]	326.2
Model 3: Exposure index					
1.63 [1.18;2.25]	0.001 [0.00002; 1.17]	**1.15 [1.03; 1.27]**	1.01 [0.98; 1.05]	0.97 [0.71; 1.31]	322.1
Men (total n = 48)					
Model 1: Dichotomous					
1.05 [0.34; 2.88]	0.32 [0.06; 1.34]	**6.22 [2.13; 19.63]**	1.04 [0.97; 1.12]	0.92 [0.46; 1.81]	154.3
Model 2: Sum of emissions					
0.81 [0.33; 1.35]	1.60 [0.71; 3.77]	0.77 [0.35; 1.53]	1.04 [0.97; 1.12]	1.29 [0.64; 2.61]	162.7
Model 3: Exposure index					
1.31 [0.97; 2.16]	0.05 [0.00004; 1.35]	1.08 [0.92; 1.26]	1.04 [0.97; 1.11]	1.18 [0.58; 2.34]	163.0

The effect of exposure is based on value (and 95%CI) of β coefficient for each pollutant. This value should be interpreted as percentage change in sSIR for exposed areas (exposure 1). For exposure 2 and 3, the exposure indexes were normalized (z_score with mean 0 and standard deviation 1) for improving computational process. Census tracts mean (standard deviation) discharges in Kg/year were 0.12 (0.65) for PCDDs/Fs, 22.77 (140.88) for Pb, and 20.5 (137.57) for dichloromethane. Mean (sd) exposure index for PCDDs/Fs = 243.87 (1468.07), for Pb = 1368.25 (11888.35), for Dichloromethane = 1468.72 (8941.25). The coefficients for exposures 2 and 3 should be interpreted as percentage change in sSIR for one-standard deviation increase.
Bold are statistically significant, i.e, credibility intervals from BYM models do not include one.

It is noteworthy that the associations were present in women but not in men. The lack of associations in men may be due to the lower frequency of thyroid cancer in men, which determines a smaller number of observed and expected cases in each area, leading models to failure to detect significant associations. In the local context, many women are housewives and, therefore, stay longer time than men at their homes, near the pollutant emission sources. On the other hand, it is plausible to assume that women were less likely to be exposed than men to these contaminants in the occupational environment, because their participation in jobs in industrial sectors that have released these pollutants in Manizales has historically been low. Then, if women are less exposed in the workplace than men, it is logical to think that their exposure would be happening in the home or in their surroundings, that is, in women the exposure misclassification may be less than in men. Therefore, if they are not exposed in work and exposure occurs mainly in the home, and women stay longer in their homes than men, this supports our hypothesis that living near industries that emit chlorinated solvents and dioxins and furans into air is associated with increased risk of thyroid cancer.

This study has several strengths. First, the use of census tracts instead of larger units of analysis. According to Elliott and Wartenberg (2004) and Richardson et al. (2004), small-areas studies are less susceptible to ecological bias given by within-area variability, making it possible to find more homogeneity with regard to some exposures and confounding variables at the population level; small-areas study make results more easily interpreted, and are better able to detect highly localized effects, such as those related to industrial pollution. The arbitrary definition of political-administrative small areas (Wakefield, 2008) was overcame in this study by using an exposure index that take into account pollutants dispersion in the atmosphere beyond the census tract limits, and by performing point-data analyses, which are not affected by arbitrary limits. The latter analysis was able to confirm one cluster in women associated with a dichloromethane source.

Second strength is the use of different exposure definitions, as this approach can reduce misclassification error. This is a very relevant issue for studies using surrogate variables of exposure, either individually or ecologically. Regarding this, Buzzelli and Jerrett (2003) assert that measures of environmental exposures based on distance to the source are reliable and less expensive surrogates for direct pollution measurements, and they can be used flexibly to detect areas where is necessary to conduct studies with direct measurements of exposure. We move from a simple exposure definition to a more elaborate one. The definition of exposure 1 (presence/absence of industries) is, perhaps, very naive considering that atmospheric pollutants do not remain contained within census tracts; however, the atmosphere in Manizales is considered stable and the dispersion of pollutants is slow (Cortés et al., 2014), so it makes sense to assume that pollutants emitted by a source remain nearby. Exposure 2 advances by considering the amounts of pollutants emitted by the sources within the same census tract, but preserving the same limitation in relation to the dispersion of pollutants beyond the census tract polygon. Exposure 3 is more complete because it incorporates additional variables such as the predominant wind speed and direction, the mobility of the population, and the distance from each census tract to the sources. With the exception of distance, all the variables of the exposure index were obtained from secondary sources, so we have no control over the accuracy of such measurements.

Third strength is the compliance with the criterion of temporality in the association between proximity to industrial sources of pollution and the thyroid cancer risk. Industrial facilities included in the analysis have been operating for at least 10 years before 2003, assuming this period as a possible latency factor between potential environmental exposure and the occurrence of the event. This aspect is of great importance in cancer incidence studies, since it is known that the induction period of some cancers may be years or even decades.

Our study has several limitations. First, aggregated-data analysis involve ecological bias (Rothman et al., 2008); individuals can be exposed to pollutants through water or food, and in their work environments, which would be confusion factors that were not properly controlled at ecological level; moreover, information bias may be present due to differential diagnosis as thyroid cancer might be underdiagnosed in low SES areas. Second, it was not possible to adjust for the only known risk factor for thyroid cancer (i.e. ionizing radiation), either occupationally or in the general environment due to lack of data. There are no nuclear power plants in Manizales, so the most likely exposure to ionizing radiation comes from medical diagnostic tests; however, we consider that exposure to ionizing radiation in medical procedures should not act as a major risk factor in Manizales' general population because, globally, the annual average per-capita exposure to radiation in medical procedures has been estimated around 0.4 mSv, below the exposure limit set at 1.0 mSv by the International Commission on Radiological Protection (Arias, 2006). Third, it was not possible to geo-reference all incident cases (missing about 2.4% in females and 2.0% in males), issue that can be significant due the small population size; in addition, geo-referencing was carried out based on the address of residence at diagnosis, and neither residence history nor migrations were considered. Fourth, thyroid cancer is a low frequency health outcome, leading to small-areas with no observed cases, especially in men, which leads to the over-dispersion could affect models fit. Fifth, despite adjusting for socioeconomic conditions at census tracts.

In addition, cases and pseudo-controls might share exposures to industrial pollutants; therefore, it is possible that there is a bias in the selection of pseudo-controls, given that, in general, there is great uncertainty regarding the etiological agents of cancer (Boffetta et al.,

2009; Boyle and Levin, 2008). However, in the case of cervical cancer, it is known to be a cancer of mainly infectious etiology (IARC, 2016), where possibly exposures to environmental contaminants have little or no influence (Boffetta et al., 2007; Boffetta and Nyberg, 2003). Similarly, skin cancer is caused mostly by exposure to solar radiation, arsenic in water and other chemicals (IARC, 2016). For gastric cancer, etiological factors such as H. Pyllori infection, alcohol consumption, and diet habits are recognized, but it is also related to occupational exposure in rubber industry (IARC, 2016).

Recent publications (Franceschi and Vaccarella, 2015; Vaccarella et al., 2016) point out the impact of overdiagnosis on the increase in thyroid cancer incidence in high income countries, due to better access to health care or because some countries (i.e, South Korea) have implemented opportunistic screening of thyroid tumors in response to exceptional exposure to radiation after Fukushima accident in 2011. In our study most (> 70%) of the patients were covered by health insurance, and most (> 80%) of tumors were well-differentiated carcinomas. Additionally, female age-specific incidence rates showed a slight peak around 50–54 years while in men the age-specific incidence peak was in 70–74 year, which might be explained by more frequent usage of health services among women in comparison with men. These findings led us to consider that in Manizales might be also affected by over-diagnosis epidemic, particularly in women. However, we found that around half of the cases analyzed in this study had regional dissemination or metastases at diagnosis, which allows us to consider that, even if there were over-diagnosis, its magnitude would not be as high as that reported in developed countries. Regarding bias due to under-diagnosis in poorest populations, we found no differences in socioeconomic conditions between cases and pseudo-controls used in point-data analyses, and no significant association with socioeconomic conditions was observed in ecological models. Nevertheless, under-diagnosis might be a bias for men, due to the lower frequency of health care usage.

Our study suggests that industrial emissions could be involved as risk factors for thyroid cancer, particularly emissions of chlorinated solvents and dioxins and furans. But, this work is exploratory in nature, so the results should be interpreted considering their limitations, mainly the ecological bias and lack of direct measurements of exposure. It would be advisable to confirm these results with other studies at the individual level, such as a case-control study, which should consider more precise exposure measurements. Nevertheless, environmental authorities must step up actions to reduce emissions of toxic agents from industrial sources, which, independent of the result of this study, are in many cases above Colombian law and international guidelines. It must be noted that the study also included many small facilities that are not forced to declaring their emissions, and should be target of regulations also. Health authorities should continue to monitor the incidence of thyroid cancer and carry out epidemiological analyzes to clarify the role of environmental pollutants on thyroid cancer cases.

5. Conclusions

This study shows a consistent positive association between proximity to industrial facilities that releases chlorinated solvents and PCDDs/Fs into air and the incidence of thyroid cancer in census tracts of Manizales, particularly in women. Point-data analysis confirmed a cluster of women cases surrounding a facility emitting dichloromethane and tetrachloroethylene. Although the results of this study are not sufficient to establish causality, they do suggest that dichloromethane and dioxins/furans emitted from industrial sources might be suspected as thyroid cancer risk factors. These results should be interpreted with caution regarding the impact of specific agents on thyroid cancer. However, in the context of known environmental pollution in Manizales actions should be taken by environmental authorities to reduce emissions.

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Declaration of interest

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.apr.2017.11.003.

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