From:	Kristin Foster
To:	Amy Rusko
Subject:	FW: No to Galvanizing
Date:	Tuesday, June 25, 2024 3:08:06 PM
Attachments:	ChildhoodGalv.pdf MammographGalv.pdf image001.png

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From: Kandi Gilbert <kasondragilbert@gmail.com>
Sent: Tuesday, June 25, 2024 2:43 PM
To: Shared-VM-CED <Teams-VM-CED@arlingtonwa.gov>
Subject: No to Galvanizing

This message is from an External Sender

This message came from outside the City of Arlington

Good afternoon,
I am renting a home just up the road from this, in Gleneagle. Not only am I worried for the health of my family, but everyone around the proposed plant- Including the Boys and Girls club and the Quake Ball field.
I am attaching two papers stating the health impacts of being exposed to the heavy metals and toxins in the galvanizing process.
If Arlington officials REALLY do care about the people of Arlington, not profit, they will hopefully do the right thing and vote no.
Thank you,
-Kasondra Gilbert

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Association between residential proximity to environmental pollution sources and childhood renal tumors

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ABSTRACT

Background: Few risk factors for childhood renal tumors are well established. While a small fraction of cases might be attributable to susceptibility genes and congenital anomalies, the role of environmental factors needs to be assessed.

Objectives: To explore the possible association between residential proximity to environmental pollution sources (industrial and urban areas, and agricultural crops) and childhood renal cancer, taking into account industrial groups and toxic substances released.

Methods: We conducted a population-based case-control study of childhood renal cancer in Spain, including 213 incident cases gathered from the Spanish Registry of Childhood Tumors (period 1996–2011), and 1278 controls individually matched by year of birth, sex, and region of residence. Distances were computed from the respective subject's residences to the 1271 industries, the 30 urban areas with $\geq$75,000 inhabitants, and the agricultural crops located in the study area. Using logistic regression, odds ratios (ORs) and 95% confidence intervals (95%CIs) for categories of distance to pollution sources were calculated, with adjustment for matching variables and socioeconomic confounders.

Results: Excess risk (OR; 95%CI) of childhood renal tumors was observed for children living near ($\leq$2.5 km) industrial installations as a whole (1.97; 1.13-3.42) – particularly glass and mineral fibers (2.69; 1.19-6.08), galvanization (2.66; 1.14-6.22), hazardous waste (2.59; 1.25-5.37), ceramic (2.35; 1.06–5.21), surface treatment of metals (2.25; 1.24–4.08), organic chemical industry (2.22; 1.15-4.26), food and beverage sector (2.19; 1.18-4.07), urban and waste-water treatment plants (2.14; 1.07–4.30), and production and processing of metals (1.98; 1.03–3.82) –, and in the proximity of agricultural crops (3.16; 1.54–8.89 for children with percentage of crop surface $\geq$24.35% in a 1-km buffer around their residences).

Conclusions: Our study provides some epidemiological evidence that living near certain industrial areas and agricultural crops may be a risk factor for childhood renal cancer.

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Abbreviations: PAHs, Polycyclic Aromatic Hydrocarbons; RETI-SEHOP, Spanish Registry of Childhood Tumors; IPPC, Integrated Pollution Prevention and Control; E-PRTR, European Pollutant Release and Transfer Register; ORs, Odds Ratios; 95%CIs, 95% Confidence Intervals; IARC, International Agency for Research on Cancer; PACs, Polycyclic aromatic chemicals; Non-HPCs, Non-halogenated phenolic chemicals; POPs, Persistent organic pollutants; VOCs, Volatile organic compounds

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1. Introduction

Childhood renal tumors account for approximately 6–7% of cancer cases among children less than 15 years of age, and the main histologic type is Wilms' tumor, or nephroblastoma, which comprises approximately 90–95% of all diagnosed renal cancers (Bernstein et al., 1999; Parkin et al., 1998). Incidence rates of Wilms' tumor (and other non-epithelial renal tumors) among children under the age of 15 years are higher in the more developed regions, as Canada and the US (8.0 per million), Europe (8.2 per million), and Australia and New Zealand (9.0 per million), whereas lower rates have been observed in developing regions, as East Asia (2–4 per million), Central and South America (3–8 per million), and Africa (4–8 per million) (Chu et al., 2010; Howlader et al., 2011).

Although advances in diagnosis and treatment have improved 5-year survival rates, which are now as high as 85–90% (Howlader et al., 2011; Pastore et al., 2006; Shrestha et al., 2014), children treated for Wilms' tumor are at risk of short- and long-term adverse effects of treatment, specifically, surgery-related complications (intraoperative ruptures, bowel obstruction, and extensive hemorrhage), congestive heart failure due to treatment with doxorubicin, radiation-induced pulmonary compromise, radiation pneumonitis, chemotherapy-induced nephrotoxicity, development of malignant second neoplasms, orthopedic sequelae, and gonadal failure (Dome et al., 2013; Green et al., 2001; Kaste et al., 2008). On the other hand, even though most cases of Wilms' tumor cannot be linked to a specific cause, the etiology of this tumor is under constant research (Hohenstein et al., 2015). Taking into account that roughly only 2% of Wilms' tumor cases have another relative who has had the same type of cancer, investigation has been based on the study of constitutional syndromes, e.g., aniridia, genitourinary anomalies, and Beckwith-Wiedemann syndrome, in which Wilms' tumors appear at an elevated rate (Hohenstein et al., 2015).

In contrast with these advances on genetic susceptibility, little is known about environmental agents that might play a key role either as mutagens or in the epigenetic mechanisms presumptively involved in childhood renal cancer (Hohenstein et al., 2015). The sporadic nature of occurrence in the majority of cases (98–99%) and the high incidence in the first few years of life suggest that other perinatal and early childhood factors may be etiologically important (Crump et al., 2014; Ruteshouser and Huff, 2004; Shrestha et al., 2014). However, few environmental risk factors for childhood renal tumors display great consistency. Most studies refer to Wilms' tumor, and several authors have reported increased risks of this tumor with parental exposure to pesticides (e.g., insecticides) (Chu et al., 2010; Sharpe et al., 1995), paternal occupation with exposure to inorganic compounds (Bunin et al., 1989) and known or suspected carcinogens, as hydrocarbons (e.g., polycyclic aromatic hydrocarbons (PAHs)) and metals (e.g., lead) (Chu et al., 2010; Colt and Blair, 1998; Shrestha et al., 2014), or exposures to the mother during pregnancy or birth, as use of coffee or tea, hair dye, and medications (Ross and Spector, 2006). Moreover, an American study found positive associations between Wilms' tumor in children and exposure during the third trimester of pregnancy to formaldehyde, acetaldehyde, perchloroethylene, and PAHs, all known carcinogens (Shrestha et al., 2014). On the other hand, other studies revealed inconsistent associations between paternal occupational or maternal hormonal exposures during pregnancy and risk of Wilms' tumor (Breslow et al., 1993) or do not support the hypothesis that Wilms' tumor is associated with residing near toxic waste sites (Tsai et al., 2006). However, there are no epidemiologic studies that have analyzed the risk of childhood renal cancers in the vicinity of industrial plants (by industrial group), urban areas, and agricultural crops, in the same paper. Accordingly, it would seem appropriate to ascertain whether residential proximity to these environmental pollutant sources might have an influence on the frequency of these tumors.

In this paper, we analyze the association between residential proximity to environmental pollution sources (industrial plants – including different industrial groups, and groups of carcinogenic and other toxic substances –, urban areas, and agricultural crops) and childhood renal cancer risk, in the context of an ongoing population-based case control study of incident cancer in Spain (Garcia-Perez et al., 2015; Ramis et al., 2015).

2. Materials and methods

2.1. Study area and subjects

We designed a population-based case-control study of childhood renal cancer in Spain. Cases were incident cases of childhood renal cancer (0–14 years), gathered from the Spanish Registry of Childhood Tumors (RETI-SEHOP) for those Autonomous Regions with 100% coverage (Catalonia, the Basque Country, Aragon, and Navarre, for the period 1996–2011, and Autonomous Region of Madrid, for the period 2000–2011), and corresponded to diseases coded as nephroblastoma and other non-epithelial renal tumors, renal carcinomas, and unspecified malignant renal tumors – code VI (International Classification of Diseases for Oncology, 3rd revision) (Steliarova-Foucher et al., 2005). Six controls per case were selected by simple random sampling from among all single live births registered in the Spanish National Statistics Institute between 1996 and 2011, individually matched to cases by year of birth, sex, and autonomous region of residence. The final study population comprised 213 cases and 1278 controls.

2.2. Residential locations

Each individual's last residence was geocoded using Google Map Javascript API v3 (Google Maps, 2015) and QGIS software (Open Source Geospatial Foundation, 2016), and converted into the Universal Transverse Mercator Zone 30 (ED50) coordinates, where the last digit of coordinates (X, Y) was assigned randomly in order to preserve their confidentiality.

With respect to cases, we successfully validated 98% of their addresses. The remaining 2% of cases were fairly uniformly distributed along the different regions and, therefore, we did not think that data were biased in this sense. With respect to controls, only 2% of controls did not have valid coordinates. Having had a small number of failures, we decided to select more controls to replace this 2%, and we geocoded and validated this last group to end up with 6 controls with valid coordinates for every case.

2.3. Industrial facility locations

We used the industrial database – industries governed by the Integrated Pollution Prevention and Control (IPPC) Directive and facilities pertaining to industrial activities not subject to IPPC but included in the European Pollution Release and Transfer Register (E-PRTR) – provided by the Spanish Ministry for Agriculture, Food & Environment in 2009, which includes information on the geographic location and industrial pollution emissions of all industrial plants in Spain.

Each of the installations was classified into one of the 25 categories of industrial groups listed in Supplementary Data, Table S1. These groups were formed on the basis of the similarity of their pollutant emission patterns. Additionally, Supplementary Data, Fig. S1 shows the distribution of the years of commencement of operations of the 1271 installations studied, by industrial group. The mean year of commencement of operations for industries as a

whole was 1974.

Owing to the presence of errors in the initial location of industries, the geographic coordinates of the industrial locations recorded in the IPPC+E-PRTR 2009 database were previously validated (Garcia-Perez et al., 2015). We selected the 1271 industrial facilities that reported their releases to air and water in 2009, and Supplementary Data, Table S1 shows the distribution of the number of industrial facilities by industrial group and autonomous region.

2.4. Urban locations

For the purposes of this study, we considered as urban areas those towns with more than 75,000 inhabitants (named "big cities" by the Spanish Act 57/2003) according to 2001 census, where a total of 30 towns were identified in the areas under study.

2.5. Global crop index

Because of lack of data about individual exposure to pesticides and specific pesticides that were used in the Spanish crop fields, we estimated that individual exposure by means of a variable named "Global Crop Index". To build this index, we calculated the percentage of total crop surface in a 1-km buffer around each individual's last residence, using the Corine Land Cover 2006 inventory (European Environment Agency, 2015). More detailed information on this index is provided by Gomez-Barroso et al (Gomez-Barroso et al., 2016).

2.6. Exposure coding and statistical analysis

For each subject, the following Euclidean distances were calculated: a) industrial distance: distance between the subject's residence and any of the previously mentioned 1271 industrial installations; and b) urban distance: distance between the subject's residence and the centroid of the town in which it resides (in Spain, municipal centroids are computed by taking only the inhabited area of the designated town into account, and are situated in the center of the most populous zone where the town hall or the main church tend to be located).

Four types of statistical analysis, including mixed multiple unconditional logistic regression models, were performed to estimate odds ratios (ORs) and 95% confidence intervals (95%CIs). All models included matching factors (year of birth, sex, and autonomous region of residence (as a random effect)), and other potential confounders provided by the 2001 census at a census tract level, such as percentage of illiteracy, percentage of unemployed, and socioeconomic status:

1) Analysis 1: in a first phase, we evaluated the possible relationship between childhood renal tumors and residential proximity to any industrial installation (taking the following industrial distances 'D' into account: 5, 4, 3, 2.5, 2, 1.5, and 1 km), urban sites – as a proxy of residential traffic exposure –, and agricultural crops – as a proxy of pesticides exposure – (7 independent models). For the *industrial and urban areas* analysis (sub-analysis 1.a), each of the subjects was classified into one of the following 4 categories of exposure variable for each model: a) residence in an *"industrial area (only) – D km"*, defined in terms of proximity to industrial facilities, on the basis of the industrial distance 'D'; b) residence in the *"urban area (only)"*, taking the areas defined by the following urban distances, according to the size of the municipality: 8 km (for towns $\geq$ 2,000,000 inhabitants), 4 km (between 1,500,000 and 1,999,999 inhabitants), 2 km (between 1,000,000 and 1,499,999 inhabitants), 1.5 km (between 500,000 and 999,999 inhabitants), 1.25 km (between 300,000 and 499,999 inhabitants), 1 km (between 200,000 and 299,999 inhabitants), 0.75 km (between 150,000 and 199,999 inhabitants), 0.5 km (between 100,000 and 149,999 inhabitants), and 0.25 km (between 75,000 and 99,999 inhabitants); c) residence in the intersection between industrial and urban areas (*"both"*); and, d) residence within the *"reference"* area, consisting of zones with children having no (IPPC+E-PRTR)-registered industry within 5 km of their residences and far from urban areas. For the *global crop index* analysis (sub-analysis 1.b), we categorized every subject into one of the following 5 categories, according to the distribution of those percentages with value > 0 among the control group: *0* (0% of crop surface, *reference* group), *Q1* (1st quartile), *Q2* (2nd quartile), *Q3* (3rd quartile), and *Q4* (4th quartile);
2) Analysis 2: we evaluated the relationship between childhood renal tumors and residential proximity to industries by different categories of industrial groups defined in Supplementary Data, Table S1, using the above-described mixed multiple unconditional logistic regression model for the industrial distance 'D' which yield stabilized ORs for the three categories of exposure in the *industrial and urban areas* analysis (industrial area (only), urban area (only), and both) (25 independent models). To this end, we created an exposure variable for each model in which the subject was classified as resident near a specific *"industrial group"*, if it resides at $\leq$'D' km from any installation belonging to the industrial group in question, and resident in the *"reference area"*, if it resides at > 5 km from any (IPPC+E-PRTR)-registered industry and far from urban areas;
3) Analysis 3: we assessed the relationship between childhood renal tumors and residential proximity to any industrial focus releasing substances classified by the International Agency for Research on Cancer (IARC) as carcinogenic (Group 1), probably carcinogenic (Group 2A) and possibly carcinogenic (Group 2B) to humans, and other toxic chemical substances (9 groups) – including metals, pesticides, polycyclic aromatic chemicals (PACs), non-halogenated phenolic chemicals (non-HPCs), plasticizers, persistent organic pollutants (POPs), volatile organic compounds (VOCs), solvents, and other. For this purpose, the industrial distance chosen in the second analysis was used to define an "exposed subject" as any child who lived close to any facility releasing the above-defined groups of carcinogenic and toxic substances (12 independent models). To this end, we created an exposure variable for each model, analogous to the second analysis; and,
4) Analysis 4: finally, we performed an additional analysis to assess the risk gradient in the vicinity of industrial installations, described in detail in Supplementary Data, Appendix A.

Regression equations of the models for the first three analyses are shown in Supplementary Data, Appendix B.

As we have considered a frequency matched study, given that matching conditions, i.e., year of birth, sex, and autonomous region of residence, are very general and controls can fit the criteria for more than one case (the corresponding pair can be interchangeable), the standard methodology is to use unconditional logistic regression including the matched characteristics in the model (Rothman et al., 2008).

3. Results

The analysis covered 213 cases and 1278 controls. Distribution by sex, year of birth, autonomous region, percentages of unemployment and illiteracy, socioeconomic status, global crop index, and histologic type of case is summarized in Table 1.

Table 1
Characteristics of cases of childhood renal tumors and controls.

Characteristic	n (%)	
	Cases (n=213)	Controls (n=1278)
Sex		
Male	101 (47.4)	606 (47.4)
Female	112 (52.6)	672 (52.6)
Year of birth, mean (SD)	2003.4 (4.0)	2003.4 (4.0)
Autonomous region		
Catalonia	95 (44.6)	570 (44.6)
Madrid	68 (31.9)	408 (31.9)
Basque country	21 (9.9)	126 (9.9)
Aragon	18 (8.4)	108 (8.4)
Navarre	11 (5.2)	66 (5.2)
Unemployment, mean (SD)	10.9 (4.0)	11.1 (3.9)
Illiteracy, mean (SD)	9.5 (6.7)	9.6 (6.3)
Socioeconomic status, mean (SD)	1.1 (0.1)	1.1 (0.1)
Global crop index		
Reference: 0%	162 (76.1)	1126 (88.1)
1st quartile (Q1): (0–1.91]	9 (4.2)	40 (3.1)
2nd quartile (Q2): (1.91–7.64]	7 (3.3)	37 (2.9)
3rd quartile (Q3): (7.64–24.35]	22 (10.3)	37 (2.9)
4th quartile (Q2): (24.35–100]	13 (6.1)	38 (2.9)
Histologic type		
Nephroblastoma	202 (94.8)	
Rhaboid renal tumor	6 (2.8)	
Kidney sarcomas	4 (1.9)	
Renal carcinomas	1 (0.5)	

Distribution by sex was slightly higher in girls (52.6%) than boys (47.4%). Moreover, Catalonia was the autonomous region with the highest proportion of cases and controls (44.6%), and histologically, nephroblastoma (94.8%) was the main type of childhood renal cancer.

In order to provide a global view of the different components of the study, Fig. 1 shows the locations of residences of cases and controls, industrial installations, and towns with more than 75,000 inhabitants.

Estimated ORs of childhood renal tumors associated with residential proximity to industrial and urban areas, and agricultural crops, using different industrial distances, are shown in Table 2. With respect to the *industrial and urban areas* analysis, a statistically significant increased risk of childhood renal tumors was observed near industrial areas (only) for all distances analyzed, from 1 km (OR=2.05; 95%CI=1.12–3.73) to 5 km (OR=1.85; 95% CI=1.07–3.18). On the other hand, children living near urban areas (only) registered an excess risk of childhood renal cancer, although non-statistically significant, for all industrial distances, from 1 km (OR=1.69; 95%CI=0.89–3.21) to 5 km (OR=1.28; 95%CI=0.35–4.75). For the intersection area between industrial and urban areas, however, there was a statistically significant risk of childhood renal tumors for all industrial distances, from 1 km (OR=3.95; 95%CI=1.36-3.21) to 5 km (OR=1.90; 95%CI=1.00–3.59), with this being higher than industrial area (only) and urban area (only) separately (synergic effect). Insofar as the *global crop index* analysis is concerned, children with percentages of total crop surface $>7.64\%$ (category Q3) and $>24.35\%$ (category Q4) in a 1-km buffer around their residences showed high excess risks of childhood renal tumors. Moreover, a statistically significant trend was detected in the four categories for the global crop index (p-value <0.001 for all industrial distances analyzed). Lastly, the industrial distance of 2.5 km was used to define industrial proximity in subsequent analyses, inasmuch as it yielded stabilized ORs for the three categories of exposure in the *industrial and urban areas* analysis, and has the advantage of being able to better discriminate the risk and furnish a series of cases and controls which would have enough statistical power in the three categories of exposure analyzed in the *industrial and urban areas* analysis (see Table 2).

Estimated ORs of childhood renal tumors, both overall and by industrial group, are shown in Table 3. An increased risk was observed for all sectors as a whole (OR=1.97). When type of industrial activity was taken into account, all industrial groups in the study area – with the exception of 'Mining industry' – showed an increased risk of childhood renal cancer in their environs (≤ 2.5 km), with this reaching statistically significance in the case of 'Pre-treatment or dyeing of textiles' (OR=4.12, although only with 4 cases) , 'Glass and mineral fibers' (OR=2.69), 'Galvanization' (OR=2.66), 'Hazardous waste' (OR=2.59), 'Ceramic' (OR=2.35), 'Surface treatment of metals and plastics' (OR=2.25), 'Organic chemical industry' (OR=2.22), 'Food and beverage sector' (OR=2.19), 'Urban and waste-water treatment plants' (OR=2.14), and 'Production and processing of metals' (OR=1.98). Detailed information on emission amounts by groups of substances, and type of specific pollutants released by the industrial groups analyzed is provided in Supplementary Data, Table S2 and Table S3, respectively.

Table 4 shows the estimated ORs of childhood renal tumors by reference to groups of carcinogens and other toxic chemical substances released by industries. The results showed high and statistically significant ORs in children living close (≤ 2.5 km) to industrial facilities releasing carcinogenic substances (ORs=2.02 for facilities releasing Group-1 carcinogens, 2.13 for Group 2A, and 2.26 for Group 2B), and all groups of toxic substances – with the exception of 'Plasticizers' –, principally near 'Pesticides' (OR=2.88), 'POPs' (OR=2.51), 'Solvents' (OR=2.37), 'non-HPCs' (OR=2.18), and 'PACs' (OR=2.16). Detailed information on emission amounts by specific pollutants released by facilities is provided in Supplementary Data, Table S4.

Finally, Supplementary Data, Table S5 shows the ORs of childhood renal tumors for ever-decreasing radiuses within a 50-kilometer area surrounding each facility, both overall and by industrial group (risk gradient analysis), and we detected statistically significant radial effects in all sectors as a whole (OR=1.16, p-trend=0.0067), especially near 'Surface treatment of metals and plastic' (OR=1.18, p-trend=0.0120), 'Urban waste-water treatment plants' (OR=1.19, p-trend=0.0338), 'Food and beverage sector' (OR=1.15, p-trend=0.0399), and 'Glass and mineral fibers' (OR=1.28, p-trend=0.0463).

4. Discussion

Childhood cancer is an important concern for public health, medical care, and society (Peris-Bonet et al., 2010), but regrettably, little is known about its etiology (including childhood renal tumors). To our knowledge, this is the first study that analyzes the effects of exposure to environmental pollution sources, as industrial plants, urban areas, and agricultural crops, on childhood renal tumors (including Wilms' tumor and other histologic types), according to different industrial groups, and groups of carcinogens and other toxic pollutants. Our findings support the hypothesis that industrial pollution and proximity to agricultural crops – which are, generally, treated with pesticides – might be a risk factor for childhood renal cancer incidence. Indeed, our analyses show an excess of risk of childhood renal tumors among children living in the proximity of industrial installations (between 1 and 5 km) and their intersections with urban nuclei ($\geq 75{,}000$ inhabitants), and agricultural crops (in a radius of 1 km), inasmuch as the statistical analysis about proximity to pollution sources detected higher risk due to these tumors for various industrial and toxic substances groups, and the risk gradient analysis detected statistically significant radial effects.

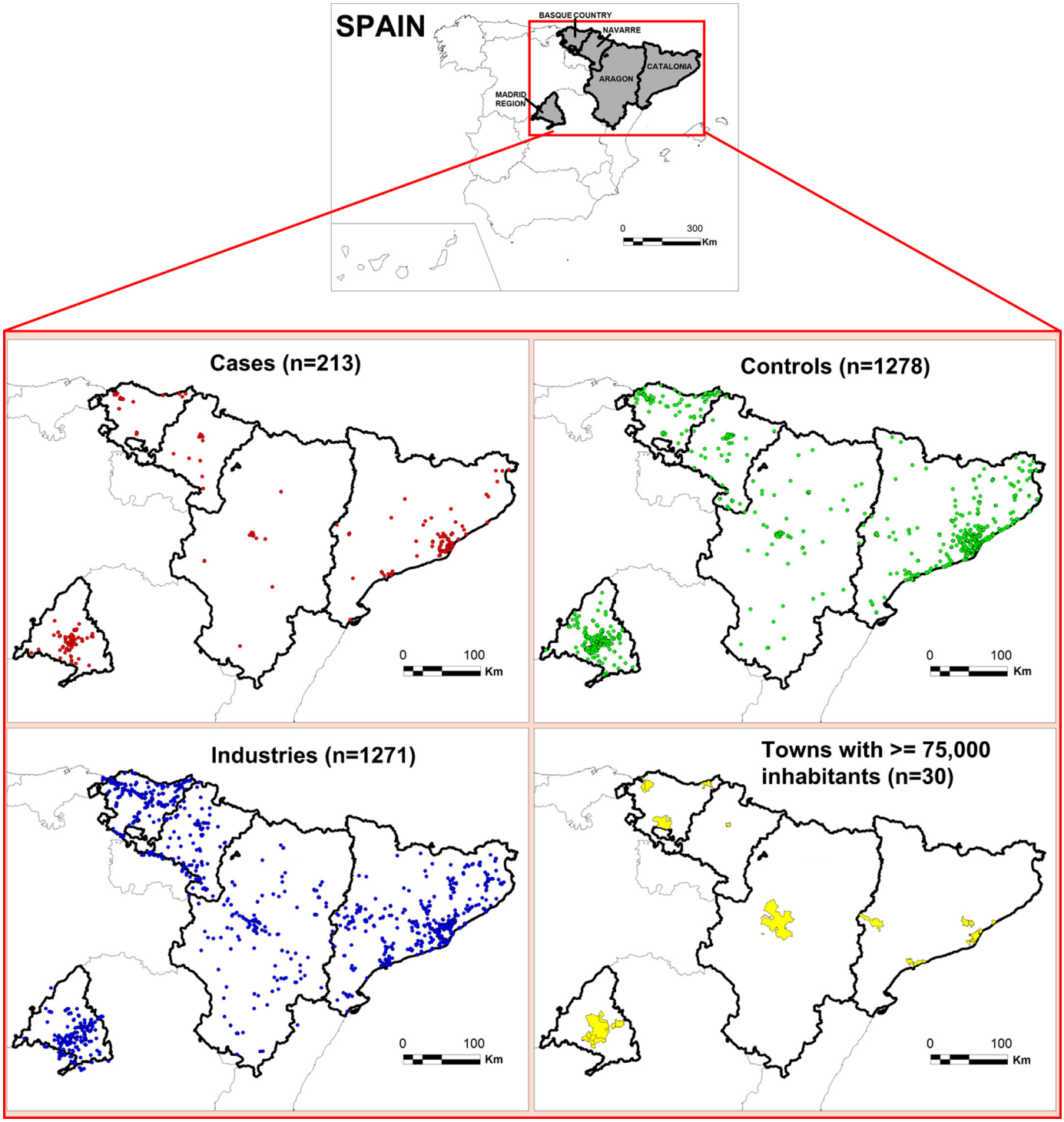

Fig. 1. Geographic distribution of cases, controls, industrial facilities, and towns with more than 75,000 inhabitants.

With respect to the results broken down by industrial group, attention should be drawn to the ORs registered in children living near plants involved in the metal sector (production and processing of metals, galvanization, and surface treatment of metals and plastics), glass and mineral fibers, ceramic, organic chemical industry, hazardous waste, urban waste-water treatment plants, pretreatment or dyeing of textiles, and food and beverage sector, and facilities releasing, principally, carcinogens, pesticides, POPs, solvents, non-HPCs, PACs, metals, and VOCs.

The study of childhood cancer in areas surrounding environmental pollution sources is beginning to assume growing importance (Boothe et al., 2014; Danysh et al., 2016; Heck et al., 2013; Weng et al., 2008), and industrial pollution emission registers, such as E-PRTR, afford a very useful tool for the surveillance and monitoring of possible effects of industrial pollution on the health of the children (Wine et al., 2014).

Insofar as environmental exposures and childhood renal tumors are concerned, the studies existing in the literature are almost exclusively focused on Wilms' tumor, and, especially, about parental exposures. Some papers have examined the relationship between risk of Wilms' tumor and maternal smoking, alcohol, coffee or tea consumption, with inconsistent results (Chu et al.,

Table 2
Odds ratios of childhood renal tumors by industrial distance and exposure category. Statistically significant results are in bold.

Industrial distance[a]	Exposure category	Controls (n)	Cases (n)	OR (95%CI)[b]	*p*-value for trend
5 km					
	Industrial and urban areas				
	Reference	147	19	–	
	Industrial area – 5 km (only)	831	149	**1.85 (1.07–3.18)**	
	Urban area (only)	28	3	1.28 (0.35–4.75)	
	Both[c]	272	42	**1.90 (1.00–3.59)**	
	Global crop index (%)				
	Reference: [0]	1126	162	–	
	Q1: (0–1.91]	40	9	1.67 (0.78–3.57)	
	Q2: (1.91–7.64]	37	7	1.40 (0.60–3.26)	
	Q3: (7.64–24.35]	37	22	**4.83 (2.69–8.68)**	
	Q4: (24.35–100]	38	13	**3.00 (1.47–6.12)**	< **0.001**
4 km					
	Industrial and urban areas				
	Reference	147	19	–	
	Industrial area – 4 km (only)	784	144	**1.91 (1.11–3.29)**	
	Urban area (only)	81	11	1.65 (0.71–3.81)	
	Both[c]	219	34	**1.92 (1.00–3.71)**	
	Global crop index (%)				
	Reference: [0]	1126	162	–	
	Q1: (0–1.91]	40	9	1.67 (0.78–3.56)	
	Q2: (1.91–7.64]	37	7	1.40 (0.60–3.27)	
	Q3: (7.64–24.35]	37	22	**4.89 (2.72–8.79)**	
	Q4: (24.35–100]	38	13	**3.03 (1.49–6.19)**	< **0.001**
3 km					
	Industrial and urban areas				
	Reference	147	19	–	
	Industrial area – 3 km (only)	722	134	**1.96 (1.13–3.39)**	
	Urban area (only)	150	14	1.12 (0.52–2.43)	
	Both[c]	150	31	**2.62 (1.34–5.12)**	
	Global crop index (%)				
	Reference: [0]	1126	162	–	
	Q1: (0–1.91]	40	9	1.66 (0.78–3.56)	
	Q2: (1.91–7.64]	37	7	1.45 (0.62–3.38)	
	Q3: (7.64–24.35]	37	22	**4.91 (2.73–8.84)**	
	Q4: (24.35–100]	38	13	**3.17 (1.55–6.49)**	< **0.001**
2.5 km					
	Industrial and urban areas				
	Reference	147	19	–	
	Industrial area – 2.5 km (only)	659	122	**1.97 (1.13–3.42)**	
	Urban area (only)	184	21	1.38 (0.67–2.81)	
	Both[c]	116	24	**2.62 (1.30–5.30)**	
	Global crop index (%)				
	Reference: [0]	1126	162	–	
	Q1: (0–1.91]	40	9	1.68 (0.79–3.60)	
	Q2: (1.91–7.64]	37	7	1.41 (0.61–3.29)	
	Q3: (7.64–24.35]	37	22	**4.94 (2.74–8.89)**	
	Q4: (24.35–100]	38	13	**3.16 (1.54–6.46)**	< **0.001**
2 km					
	Industrial and urban areas				
	Reference	147	19	–	
	Industrial area – 2 km (only)	552	106	**2.02 (1.16–3.52)**	
	Urban area (only)	219	25	1.37 (0.69–2.73)	
	Both[c]	81	20	**3.14 (1.50–6.58)**	
	Global crop index (%)				
	Reference: [0]	1126	162	–	
	Q1: (0–1.91]	40	9	1.69 (0.79–3.62)	
	Q2: (1.91–7.64]	37	7	1.43 (0.61–3.33)	
	Q3: (7.64–24.35]	37	22	**4.84 (2.69–8.70)**	
	Q4: (24.35–100]	38	13	**3.10 (1.52–6.32)**	< **0.001**
1.5 km					
	Industrial and urban areas				
	Reference	147	19	–	
	Industrial area – 1.5 km (only)	428	79	**1.92 (1.09–3.40)**	
	Urban area (only)	247	31	1.52 (0.78–2.95)	
	Both[c]	53	14	**3.35 (1.49–7.55)**	

Table 2 (*continued*)

Industrial distance[a]	Exposure category	Controls (n)	Cases (n)	OR (95%CI)[b]	*p*-value for trend
	Global crop index (%)				
	Reference: [0]	1126	162	–	
	Q1: (0–1.91]	40	9	1.70 (0.80–3.64)	
	Q2: (1.91–7.64]	37	7	1.42 (0.61–3.30)	
	Q3: (7.64–24.35]	37	22	**4.83 (2.69–8.68)**	
	Q4: (24.35–100]	38	13	**3.06 (1.50–6.23)**	< **0.001**
1 km					
	Industrial and urban areas				
	Reference	147	19	–	
	Industrial area – 1 km (only)	242	49	**2.05 (1.12–3.73)**	
	Urban area (only)	281	39	1.69 (0.89–3.21)	
	Both[c]	19	6	**3.95 (1.36–11.47)**	
	Global crop index (%)				
	Reference: [0]	1126	162	–	
	Q1: (0–1.91]	40	9	1.69 (0.79–3.61)	
	Q2: (1.91–7.64]	37	7	1.42 (0.61–3.31)	
	Q3: (7.64–24.35]	37	22	**4.80 (2.67–8.64)**	
	Q4: (24.35–100]	38	13	**3.01 (1.48–6.14)**	< **0.001**

[a] Industrial distance referred to the industrial area (only) in the exposure category.
[b] ORs were estimated from various mixed multiple logistic regression models (an independent model for each of the categories of industrial distance), that included year of birth, sex, autonomous region of residence (as a random effect), percentage of illiteracy, percentage of unemployed, and socioeconomic status.
[c] Intersection area between industrial area defined by the corresponding industrial distance and urban area (only).

Table 3
Odds ratios of childhood renal tumors by category of industrial group. Statistically significant results are in bold.

	Individuals residing at ≤2.5 km		
Industrial group (no. industries)	Controls (n)	Cases (n)	OR (95%CI)[a]
Reference	147	19	–
All sectors (1271)	659	122	**1.97 (1.13–3.42)**
Combustion installations (42)	66	9	1.37 (0.56–3.32)
Refineries and coke ovens (4)	14	2	1.73 (0.35–8.53)
Production and processing of metals (119)	160	30	**1.98 (1.03–3.82)**
Galvanization (19)	49	11	**2.66 (1.14–6.22)**
Surface treatment of metals and plastic (197)	341	66	**2.25 (1.24–4.08)**
Mining industry (39)	8	1	0.93 (0.10–8.35)
Cement and lime (33)	35	5	1.29 (0.43–3.83)
Glass and mineral fibers (20)	66	14	**2.69 (1.19–6.08)**
Ceramic (86)	57	13	**2.35 (1.06–5.21)**
Organic chemical industry (106)	151	31	**2.22 (1.15–4.26)**
Inorganic chemical industry (46)	60	10	1.75 (0.74–4.14)
Fertilizers (10)	6	2	3.33 (0.58–19.11)
Biocides (12)	25	3	1.33 (0.35–5.02)
Pharmaceutical products (41)	133	22	1.98 (0.98–4.01)
Explosives and pyrotechnics (9)	6	1	1.99 (0.22–17.97)
Hazardous waste (60)	88	20	**2.59 (1.25–5.37)**
Non-hazardous waste (86)	59	10	1.94 (0.81–4.62)
Disposal or recycling of animal waste (18)	45	7	1.87 (0.71–4.95)
Urban waste-water treatment plants (53)	112	23	**2.14 (1.07–4.30)**
Paper and wood production (63)	92	11	1.32 (0.58–3.01)
Pre-treatment or dyeing of textiles (9)	7	4	**4.12 (1.01–16.85)**
Tanning of hides and skins (2)	3	0	0 (0-INF)
Food and beverage sector (145)	188	41	**2.19 (1.18-4.07)**
Surface treatment using organic solvents (50)	83	13	1.75 (0.79–3.86)
Production of electro-graphite (2)	0	0	–

[a] ORs were estimated from various mixed multiple logistic regression models (an independent model for each of the categories of industrial groups), that included year of birth, sex, autonomous region of residence (as a random effect), percentage of illiteracy, percentage of unemployed, socioeconomic status, and global crop index.

2010; Ross and Spector, 2006), whereas other studies have found associations between Wilms' tumor and paternal occupations with exposure to toxic substances (Colt and Blair, 1998; Sharpe et al., 1995; Sharpe and Franco, 1995). However, an English study suggested that it is unlikely that paternal occupational exposure is an important etiological factor for Wilms' tumor (Fear et al., 2009).

With regard to the specific groups of industrial pollutants of our study, few papers have analyzed childhood renal cancer and residential proximity to toxic substances, excluding occupational studies: a case-control study analyzed prenatal air toxics exposure and Wilms' tumor in children < 6 years residing within a 15-mile radius of an air monitoring site and found a statistically significant increased risk in children exposed during the third trimester of pregnancy to some carcinogens, as formaldehyde, acetaldehyde, perchloroethylene, and PAHs (Shrestha et al., 2014). In our study, we have found high statistically significant excess risks in children living close to industrial installations releasing perchloroethylene and PAHs (data not shown). However, another American case-

Table 4
Odds ratios of childhood renal tumors by groups of carcinogenic and toxic substances.

Groups of pollutants	Individuals residing at ≤ 2.5 km		
	Controls (n)	Cases (n)	OR (95%CI)[a]
Reference	147	19	–
IARC groups[b]			
Group 1	586	110	2.02 (1.15-3.52)
Group 2A	382	74	2.13 (1.19-3.81)
Group 2B	241	48	2.26 (1.22-4.19)
Groups of toxic substances[c]			
Metals	504	93	2.05 (1.16-3.63)
Pesticides	123	31	2.88 (1.46-5.65)
PACs	214	43	2.16 (1.16-4.03)
Non-HPCs	105	22	2.18 (1.07 – 4.45)
Plasticizers	67	8	1.32 (0.53-3.29)
POPs	291	64	2.51 (1.38-4.56)
VOCs	507	91	1.90 (1.08 – 3.35)
Solvents	279	58	2.37 (1.30-4.34)
Other	530	100	2.04 (1.16-3.59)

[a] ORs were estimated from various mixed multiple logistic regression models (an independent model for each of the categories of groups of pollutants), that included year of birth, sex, autonomous region of residence (as a random effect), percentage of illiteracy, percentage of unemployed, socioeconomic status, and global crop index.

[b] IARC carcinogenic classification: Group 1: carcinogens to humans (arsenic and compounds, cadmium and compounds, chromium and compounds, nickel and compounds, lindane, dioxins + furans, polychlorinated biphenyls, trichloroethylene, vinyl chloride, benzene, ethylene oxide, polycyclic aromatic hydrocarbons, particulate matter (PM_{10}), total suspended particulate matter, and benzo(*a*)pyrene); group 2A: probably carcinogenic to humans (lead and compounds, dichloromethane, tetrachloroethylene, DDT, and hexabromobiphenyl); Group 2B: possibly carcinogenic to humans (chlordane, 1,2-dichloroethane, dichloromethane, heptachlor, hexachlorobenzene, 1,2,3,4,5,6-hexachlorocyclohexane, lindane, mirex, pentachlorophenol, tetrachloromethane, trichloromethane, ethyl benzene, naphthalene, di-(2-ethyl hexyl) phthalate, cobalt and compounds, benzo(*b*)fluoranthene, benzo(*k*)fluoranthene, and indeno(1,2,3-cd)pyrene).

[c] Metals (arsenic and compounds, cadmium and compounds, chromium and compounds, copper and compounds, mercury and compounds, nickel and compounds, lead and compounds, zinc and compounds, thallium, antimony, cobalt, manganese, and vanadium); pesticides (alachlor, aldrin, atrazine, chlordane, chlorfenvinphos, chlorpyrifos, DDT, dieldrin, diuron, endosulfan, endrin, heptachlor, lindane, mirex, pentachlorobenzene, pentachlorophenol, simazine, isoproturon, organotin compounds, tributyltin and compounds, triphenyltin and compounds, trifluralin, and isodrin); PACs: Polycyclic aromatic chemicals (anthracene, polycyclic aromatic hydrocarbons, fluoranthene, benzo(*g,h,i*)perylene, benzo(*a*)pyrene, benzo (*b*)fluoranthene, benzo(*k*)fluoranthene, and indeno(1,2,3-cd)pyrene); non-HPCs: Pon-halogenated phenolic chemicals (nonylphenol and nonylphenol ethoxylates, and octylphenols and octylphenol ethoxylates); plasticizers (di-(2-ethyl hexyl) phthalate); POPs: Persistent organic pollutants (aldrin, chlordane, DDT, dieldrin, endosulfan, endrin, heptachlor, hexachlorobenzene, 1,2,3,4,5,6-hexachlorocyclohexane, lindane, mirex, dioxins + furans, pentachlorobenzene, polychlorinated biphenyls, brominated diphenylethers, organotin compounds, polycyclic aromatic hydrocarbons, hexabromobiphenyl, benzo(*a*)pyrene, benzo(*b*) fluoranthene, and benzo(*k*)fluoranthene); VOCs: volatile organic compounds (non-methane volatile organic compounds, 1,2-dichloroethane, dichloromethane, hexachlorobutadiene, tetrachloroethylene, trichlorobenzenes, 1,1,1-trichloroethane, trichloroethylene, trichloromethane, vinyl chloride, benzene, ethyl benzene, ethylene oxide, and naphthalene); solvents (1,2-dichloroethane, dichloromethane, tetrachloroethylene, trichlorobenzenes, 1,1,1-trichloroethane, trichloroethylene, trichloromethane, benzene, ethyl benzene, toluene, and xylenes); other (tetrachloromethane, particulate matter (PM_{10}), and total suspended particulate matter).

control study examined the association between risk of Wilms' tumor and residential exposures to hazardous chemicals commonly found at toxic waste sites, located within a distance of 1 mile, and the findings did not support that hypothesis (Tsai et al., 2006). It is known that some metals and PAHs have been implicated in DNA damage in fetuses and also been associated with increased risk of kidney cancer or kidney damage in adults (IARC, 1990, 2006, 2012; Perera et al., 1999), a finding that could be related to the high excess risk found by us in the proximity of installations which release these groups of pollutants. It is possible that these substances also increase susceptibility to childhood renal tumors, especially during the early life since this developmental period is believe to be more vulnerable to DNA damage and to higher absorption of toxics than in adulthood (Shrestha et al., 2014).

Insofar as exposure to pesticides and Wilms' tumor is concerned, the studies existing in the literature focused on parental or residential exposures are inconsistent. On the one hand, a meta-analysis for the association between maternal exposure to pesticides and Wilms' tumor revealed a significantly increased risk (Chu et al., 2010), and several reviews found increased risks for exposure to pesticides for child and parental exposures (Chu et al., 2010; Infante-Rivard and Weichenthal, 2007; Sharpe and Franco, 1995). However, other studies did not find evidence of major risk of childhood renal cancer associated with parental (Nasterlack, 2007) or residential exposure to pesticides (Cooney et al., 2007). With respect to agricultural pesticides and risk of childhood renal tumors, the studies are not conclusive: in a study of Wilms' tumor in Brazil, risk increased with frequency of parental agricultural use of pesticides (Sharpe et al., 1995), whereas other studies did not confirm associations between risk of childhood renal tumors with proximity of birth residence to agricultural use land (Carozza et al., 2009) or paternal occupation in agriculture at the time of birth (Pearce and Parker, 2000). Specific pesticides, such as organochlorine insectides (e.g.: aldrin, dieldrin, chlordane, and lindane), are highly lipid soluble and are sequestered in body tissues with a high lipid content, such as kidneys. In our study, we have found high ORs in children living near industries releasing pesticides (OR = 2.88) and in the proximity of agricultural crops (OR = 3.16 for children with percentage of crop surface ≥ 24.35% in a 1-km buffer around their residences).

Insofar as exposure to other chemicals is concerned, some studies have found increased risks of Wilms' tumors with paternal exposure to hydrocarbons, metals – such as lead –, and inorganic compounds (Chu et al., 2010; Colt and Blair, 1998; Shrestha et al., 2014). This finding could be related to the excess risk observed by us in the environs of industries releasing metals, PACs, and POPs (see Table 4).

In relation to the industrial groups of our study, there are no epidemiologic studies about residential proximity to these types of installations and childhood renal cancer risk. However, occupational studies have suggested an increased risk of Wilms' tumor in children whose fathers have been employed as welder or mechanic (Clapp et al., 2005). In this sense, one of the most noteworthy results of our study is the high excess risks found in children in the proximity of the metal industry (production and processing of metals, galvanization, and surface treatment of metals and plastics), a finding that could be related with occupational exposure of fathers who live close to the factories. Emissions from metal sector installations arouse great social concern due to the health problems that may be generated among their workers and the surrounding population. According to the IARC, a number of substances released by such installations, including metals (arsenic, cadmium, and chromium), PACs (PAHs), POPs (dioxins), and solvents (benzene, tetrachloroethylene, and trichloroethylene), are recognized as known or suspected carcinogens. Moreover, it should be stressed that effluents from the metal industries are genotoxic: they induce cytogenetic damage, mutations, and DNA damage in repair process (Houk, 1992). Lastly, residential proximity to metal industries has been associated with other childhood tumors, as childhood leukemia (Garcia-Perez et al., 2015).

Another important result of our study is the increased risk of childhood renal cancer found in the environs of urban waste-water treatment plants. This industrial group was the main emitter of pesticides released to water, and the second emitter of metals

released to air and water (see Supplementary Data, Table S2). In this case, two possible routes of exposure to the pollution released by these installations are considered: direct exposure to pollutants released to air; and indirect exposure, both to pollutants and liquid effluents which are released to water and can then pass into the soil and aquifers, and pollutants which are released to air and then settle on plants. In such cases, the toxins may pass into the trophic chain, affecting the population, including children.

One aspect to consider is the problem of multiple comparisons or multiple testing (to find associations that are falsely positive by random chance). We estimated that for $\alpha = 0.05$, random chance would account for 0.6 positive associations (number of comparisons x percentage of statistically significant ORs > 1 expected under the null hypothesis, i.e., 2.5%) for the analysis by category of industrial group shown in Table 3, a figure lower than the number of associations observed. From an epidemiologic point of view, we have preferred to discuss the results in the light of a series of factors, namely, the magnitude of risk *per se*, the consistency of the associations observed, and biologic plausibility.

One of this study's limitations is the non-inclusion of possible confounding factors that might be associated with the distance, as socioeconomic variables or life-style-related factors, and other possible confounders, as high fetal growth, maternal smoking or constitutional syndromes (Crump et al., 2014; Hohenstein et al., 2015; Stjernfeldt et al., 1986), for their unavailability at an individual level. However, we included some socioeconomic variables at a census tract level – such as percentages of illiteracy and unemployed, and status socioeconomic –, so we assigned to every subject the information of the corresponding census tract, as other similar studies (Mezei et al., 2006; Shrestha et al., 2014). Moreover, this study uses distances to the pollution sources as a proxy of exposure, assuming an isotropic model, something that could introduce a problem of misclassification, since real exposure is critically dependent on prevailing winds, geographic landforms, and releases into aquifers. In our case, however, this problem would amount to a non-differential bias (it would affect children in both exposed and unexposed areas) which would limit the capacity to find positive results but in no way invalidating the associations found. Lastly, we did not have any information about parental occupational exposures at an individual level. In this sense, workers can carry hazardous substances home from work on their clothes, bodies, tools, and other items. Workers can unknowingly expose their families to these substances, causing various health effects.

It should be noted that we have the home address of the cases at the moment of diagnosis (i.e., residence at the time of incidence, because in childhood renal cancer, the time difference between disease onset and diagnosis is usually very small), and the home address of the mother at birth for the controls. This difference could introduce bias in the analysis, but according to official data in Spain, only around 1% of children change their residence to a different province (National Statistics Institute, 2016). Therefore, we considered that the home address at time of diagnosis is the same as the home address at birth for the most of the cases.

One of the main strengths of our study is the large control group (6 controls per case, which were randomly selected from birth certificates). In this sense, the control group should give a clear view of the spatial distribution of the population at risk and should have the same risk of exposure as the cases. We matched the controls by sex, year of birth, and region of residence to account for the temporal and regional variation in the child population.

Further advantages of the study are: the stratification of the risk by industrial group and groups of carcinogenic and toxic substances, which provides a description more exhaustive of childhood renal cancer risk; and inclusion of the same reference area (children having no industry within 5 km of their residences and far from urban areas) in the analyses for all industrial distances analyzed, something that allows for the establishment of a "cleaner" reference zone than other similar case-control studies (Garcia-Perez et al., 2015).

5. Conclusions

In conclusion, our study provides some epidemiological evidence that living in the proximity of industrial areas and agricultural crops may be a risk factor for childhood renal cancer. Specifically, children living near plants involved in the metal industry, glass and mineral fibers, ceramic, organic chemical industry, hazardous waste, urban waste-water treatment plants, and food and beverage sector showed an increased risk. In addition, analysis by group of substances showed a statistically significant excess risk of childhood renal tumors in the proximity of installations releasing carcinogens, pesticides, POPs, solvents, non-HPCs, PACs, metals, and VOCs.

These findings support the need for more detailed exposure assessment and health risk analysis of certain toxic substances by these types of industries. It would be of great interest to assess the possibility of using better exposure markers, such as biomarkers, for studying what is happening in the environs of each specific installation.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.envres.2016.02.036.

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Short Communication

Mammographic density in the environs of multiple industrial sources

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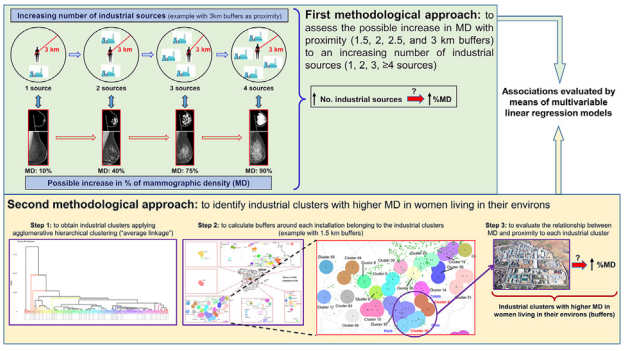
HIGHLIGHTS

- First assessment on mammographic density (MD) and multiple industrial sources
- Two approaches used to identify industrial clusters associated to a higher MD
- Increased MD with the proximity to an increasing number of industrial sources
- 6 industrial clusters with a higher MD in their environs were identified in Madrid.

GRAPHICAL ABSTRACT



Abbreviations: MD, mammographic density; BMI, body mass index; EDCs, endocrine disrupting chemicals; IPPC, Integrated Pollution Prevention and Control; *E*-PRTR, European Pollutant Release and Transfer Register; 95%CI, 95 % confidence interval; SD, standard deviation; PAHs, polycyclic aromatic hydrocarbons; TSP, total suspended particulate matter; POPs, persistent organic pollutants; PM_{10}, particulate matter with a diameter between 2.5 and 10 μm; $PM_{2.5}$, particulate matter <2.5 μm..

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ABSTRACT

Background: Mammographic density (MD), defined as the percentage of dense fibroglandular tissue in the breast, is a modifiable marker of the risk of developing breast cancer. Our objective was to evaluate the effect of residential proximity to an increasing number of industrial sources in MD.

Methods: A cross-sectional study was conducted on 1225 premenopausal women participating in the DDM-Madrid study. We calculated distances between women's houses and industries. The association between MD and proximity to an increasing number of industrial facilities and industrial clusters was explored using multiple linear regression models.

Results: We found a positive linear trend between MD and proximity to an increasing number of industrial sources for all industries, at distances of 1.5 km (p-trend = 0.055) and 2 km (p-trend = 0.083). Moreover, 62 specific industrial clusters were analyzed, highlighting the significant associations found between MD and proximity to the following 6 industrial clusters: cluster 10 and women living at ≤1.5 km (β = 10.78, 95 % confidence interval (95%CI) = 1.59; 19.97) and at ≤2 km (β = 7.96, 95%CI = 0.21; 15.70); cluster 18 and women residing at ≤3 km (β = 8.48, 95% CI = 0.01; 16.96); cluster 19 and women living at ≤3 km (β = 15.72, 95%CI = 1.96; 29.49); cluster 20 and women living at ≤3 km (β = 16.95, 95%CI = 2.90; 31.00); cluster 48 and women residing at ≤3 km (β = 15.86, 95%CI = 3.95; 27.77); and cluster 52 and women living at ≤2.5 km (β = 11.09, 95%CI = 0.12; 22.05). These clusters include the following industrial activities: surface treatment of metals/plastic, surface treatment using organic solvents, production/processing of metals, recycling of animal waste, hazardous waste, urban waste-water treatment plants, inorganic chemical industry, cement and lime, galvanization, and food/beverage sector.

Conclusions: Our results suggest that women living in the proximity to an increasing number of industrial sources and those near certain types of industrial clusters have higher MD.

1. Introduction

In 2020, breast cancer was the most diagnosed cancer worldwide (Sung et al., 2021). In Spain, 34,088 new cases were estimated, representing 31 % of all cancer cases in women (European Commission, 2022). Mammographic density (MD), defined as the amount of dense fibroglandular tissue (composed of epithelial and stromal elements) compared with the amount of fatty tissue (Lester et al., 2022), is the main phenotype marker for breast cancer risk. It has been described that women with a MD >75 % have almost 4 times more risk of developing breast cancer (Bond-Smith and Stone, 2019) and it is also the factor with the highest attributable fraction (Assi et al., 2012). The risk attributable to high MD appears to be greater in premenopausal women (accounting for approximately one-third of breast tumors in white, Hispanic, and Asian women) than in postmenopausal women (with risks between 13 and 14 %) (Bissell et al., 2020).

Like some other modifiable risk factors for breast cancer, MD has the potential to change throughout women's life (Lester et al., 2022). There is evidence that MD decreases progressively with age, with the transition to menopause, with the number of children and with the body mass index (BMI). In contrast, the use of hormone replacement therapy, particularly treatments that combine estrogen and progesterone, appears to increase it (Assi et al., 2012; Huo et al., 2014).

Some environmental exposures, such as exposure to traffic or to specific pollutants (pesticides, dioxins, polycyclic aromatic hydrocarbons (PAHs), and polychlorinated biphenyls), have been associated with breast cancer risk (Gray et al., 2017; Hiatt and Brody, 2018; Rodgers et al., 2018), but fewer studies have analyzed their association with MD (Eslami et al., 2022). Outdoor air pollution (a complex mixture of pollutants originating from natural and anthropogenic sources) was classified as carcinogenic to humans by the International Agency for Research on Cancer (International Agency for Research on Cancer, 2016), and industrial facilities are responsible for the release of many of these known and suspected human carcinogens (Fernández-Navarro et al., 2017). Previous studies have shown that women living in urban areas, with high levels of air pollution, have higher breast density (Emaus et al., 2014; Perry et al., 2008). Moreover, industries release endocrine disrupting chemicals (EDCs), which can alter the development of the mammary gland (Fenton, 2006; Mandrup et al., 2015). In this sense, higher MD has been observed in women exposed to cobalt and lead (White et al., 2019), in girls and adolescents with high levels of phthalates in urine (Binder et al., 2018) or in women with high levels of urinary magnesium (Mora-Pinzon et al., 2018).

In relation to exposure to industrial pollution sources, the epidemiological studies involving individual data often use the distance from the participant's residence to the industrial facility as a proxy of exposure (García-Pérez et al., 2019; Hii et al., 2022; Pan et al., 2011). However, industries are usually grouped into industrial clusters, so independent analyses of each single industrial source may not give a realistic picture of the exposure. In this sense, some authors consider that most pollutants are highly correlated to each other, so that an additive or synergic effect cannot be excluded and, consequently, single pollutant models may be difficult to interpret (Billionnet et al., 2012). On the other hand, in relation to cumulative and multiple exposures, some authors have assessed the impact of multipollutant air exposures and breast cancer risk, suggesting that multipollutant approaches are more precise than single pollutant models (Amadou et al., 2020). Moreover, in a recent study that assessed the relationship between breast cancer and exposure to several mixtures of metals, the authors found that the concentrations of these mixtures were different in women with breast cancer and those without cancer, which could be due to synergistic or antagonistic effects between metals (Mérida-Ortega et al., 2022). Accordingly, it would be interesting to assess the increased risk of chronic diseases near industrial areas with multiple pollutant sources, where the population is exposed to different sources and complex mixtures of toxic substances released into the environment (Cocozza et al., 2021; García-Pérez et al., 2012; Ramis et al., 2011).

In a previous study of our group, we detected potential associations between higher MD and residential proximity to certain industrial sectors and plants releasing specific pollutants, in a sample of Spanish premenopausal women (Jiménez et al., 2022). Now, in the present paper, we have deepened in the study of MD and its relationship with industrial pollution, using methodological approaches whose application in this field is novel, with the purpose of: 1) assessing the possible increase in MD with the proximity to an increasing number of industrial sources (for all industries jointly and according to industrial sectors), and 2) identifying industrial clusters with higher MD in women living in their environs.

2. Materials and methods

2.1. Study population

DDM-Madrid is a cross-sectional study that recruited 1466 Spanish premenopausal women (39–50 years) at the Medical Diagnostic Centre of Madrid City Council (*Madrid Salud*), between June 2013 and May 2015, where they attended for their routine gynecological examination

(Jiménez et al., 2021; Lope et al., 2020). Women were invited to participate in the study by phone, and 88 % agreed to collaborate. The DDM-Madrid study was conducted in accordance with the Declaration of Helsinki guidelines, was formally approved by the Ethics and Animal Welfare Committee of the Carlos III Institute of Health, and all participants signed an informed consent.

2.2. Data collection

Trained interviewers administered a face-to-face epidemiological questionnaire, which included sociodemographic information, personal and family medical background, gynecological, obstetric and occupational history, physical activity, tobacco smoking and alcohol consumption. Dietary information was collected through a validated self-fulfilled semiquantitative food frequency questionnaire (Vioque et al., 2013).

Percent MD was measured from the digital cranio-caudal mammographic images of the left breast using DM-Scan, a free semi-automated computer tool to measure MD that has shown high validity and reproducibility (Llobet et al., 2014).

Data about industrial pollution sources located in the study area were provided by the Spanish Ministry for the Ecological Transition and the Demographic Challenge. These industrial sources include facilities governed by the Integrated Pollution Prevention and Control (IPPC) Directive and installations pertaining to industrial activities not subject to IPPC but included in the European Pollutant Release and Transfer Register (European Environment Agency, 2022). In our analyses, we included all industries releasing pollutants (to air and water) with emission amounts >0 kg/year (i.e., all industries, not only those exceeding a certain established threshold for some pollutant). The locations of each industry and women's postal addresses were geocoded and validated, prior to performing the analyses, into Universal Transverse Mercator ED50 zone 30 N coordinates, using a previously published methodology (García-Pérez et al., 2019).

2.3. Statistical analyses

After excluding 24 women with analogical images, 17 participants whose MD could not be measured, 24 without available address, and 176 women with missing data in the covariates used in the analyses, the final sample size was based on 1225 participants.

The main characteristics of the women were summarized with absolute values and percentages. MD, in relation to these characteristics, was described using arithmetic means, their 95 % confidence intervals (95% CIs), and standard deviations (SDs). Moreover, two-sided Chi-square test was used to compare descriptive characteristics between women residing at ≤3 km from any industrial source and women residing at >3 km.

We calculated Euclidean distances between industries and women's residences. We considered as proximity ("exposure") to industrial sources those zones with women living at ≤'D' km from any industrial source, taking into account several distances 'D' (1.5, 2, 2.5, and 3 km) to calculate buffers around each installation. The reference zone was consisted of areas with women residing at >3 km from any industrial source.

Two methodological approaches were used to evaluate this association, using multivariable linear regression models to estimate β coefficients and their 95%CIs. All analyses were adjusted for potential confounders associated with MD (Huo et al., 2014) and proximity to industrial sources (García-Pérez et al., 2018). These variables were: age (continuous), previous breast biopsies (yes/no), family history of breast cancer (none, second degree, first degree), BMI (continuous), oral contraceptives use (never, past use, current use), smoking (never, former smoker, current smoker), alcohol consumption (0, <10 g/d, ≥10 g/d), number of children (0,1,2,>2), education (primary school or less, secondary school, university graduate) and energy intake (continuous). To carry out the analyses, we used:

1) First methodological approach (to assess the possible increase in MD with the proximity to an increasing number of industrial sources): for each distance "D', we categorized the proximity variable as follows: "1 source", if the woman resided at ≤'D' km from 1 industrial facility; "2 sources", if the woman resided at ≤'D' km from 2 industrial facilities; "3 sources", if the woman resided at ≤"D' km from 3 industrial facilities; "≥4 sources", if the woman lived at ≤'D' km from 4 or more industrial facilities; and "0 sources" (reference), if the woman resided at >3 km from any industrial source. This approach was applied to all industries jointly (an independent model for each distance), and according to industrial sectors (an independent model for each distance and industrial sector). *P*-value for linear trend (*p*-trend) was calculated including the proximity variable as continuous.

2) Second methodological approach (to identify industrial clusters with higher MD in women living in their environs): in the first step, with the purpose of selecting areas of proximity to multiple industrial sources, we applied the multivariate technique of cluster analysis to the industrial installations using the "agglomerative hierarchical clustering" method and the Euclidean distance (in meters) between the industries as the metric (Hair et al., 2019). The following linkage criteria were proposed: complete, average, single, Ward, median, centroid, and McQuitty/WPGMA linkage clustering. For the linkage method with the highest correlation between the industrial locations (in our case, it corresponded to the "average linkage clustering", with a Pearson's $r = 0.967$), we obtained the industrial clusters cutting the dendrogram into several groups of industries by specifying a cut height of 3000. In the second step, for each of the obtained industrial clusters, we calculated buffers (considering the previously established distances 'D' between 1.5 and 3 km) around each installation belonging to the industrial cluster under study. Finally, in the third step, we evaluated the relationship between MD and proximity (for all distances 'D') to each industrial cluster by means of multivariable linear regression models, where the proximity variable for each woman was categorized as: a) "near" the industrial cluster, if the woman lived at ≤'D' km from the industrial cluster under study; b) "intermediate area", if the woman resided at ≤3 km from any industrial cluster other than the analyzed cluster; and c) "far" from the industrial cluster (reference area), if the woman resided at >3 km from any industrial installation.

Lastly, with the purpose of introducing robustness in our analysis, a sensitivity analysis including only women living in their current domicile for ≥2 and ≥ 10 years was performed.

All analyses were performed using R 4.0.2 software.

3. Results

A total of 1225 premenopausal women were included in the analyses. The main characteristics are shown in Table 1. Mean age of participants was 44 ± 2.8 years old, and most of them had no previous breast biopsies (89.2 %), had no family history of breast cancer (77.2 %), had a normal BMI (67.0 %), used oral contraceptives in the past (58.3 %), were ex-smokers or never smokers (74.4 %), consumed ≤10 g per day of alcohol (85.7 %), had two children or more (52.1 %), and had completed a university degree (61.4 %). Lastly, regarding the time that the participants had been living at their current domicile, our study population proved to be enough stable, with 95.1 % of participants living in their current residence for ≥2 years, and 62.9 % for ≥10 years.

Participants had a mean MD of 34.82 % (SD = 17.28), being higher in younger women, in women with previous breast biopsies, in those who never used oral contraceptives, in participants with lower BMI, in those with university graduate, and in nulliparous. On the other hand, in relation to the proximity (≤3 km vs. >3 km) to industrial sources, the number of women with overweight or obesity (BMI ≥ 25) was significantly higher in those living at ≤3 km from any industrial source (*p*-value = 0.001); on the contrary, the number of women with high alcohol consumption (≥10 g/day) and with university studies was higher in those living at >3 km from any industry (*p*-values = 0.009 and < 0.001, respectively).

In relation to the association between MD and number of industrial sources in the proximity of the residence (first methodological approach), for all industries jointly (Fig. 1), the results showed a growing and positive trend, for distances of 1.5 ($\beta_{1\ source} = 1.09$, $\beta_{2\ sources} =$

Table 1
Descriptive characteristics of the study population.

Characteristic	All women			Women residing at ≤ 3 km from any industrial source			Women residing at > 3 km from any industrial source			*p*-value[b]
	n (%)	Mammographic density (%)		n (%)	Mammographic density (%)		n (%)	Mammographic density (%)		
		Mean (95%CI)	SD[a]		Mean (95%CI)	SD[a]		Mean (95%CI)	SD[a]	
Total	1225 (100.0)	34.82 (33.85; 35.79)	17.28	726 (100.0)	34.36 (33.10; 35.62)	17.27	499 (100.0)	35.49 (33.97; 37.01)	17.30	
Age (years)										0.299
< 45	654 (53.4)	36.14 (34.82; 37.46)	17.22	397 (54.7)	35.72 (34.06; 37.37)	16.79	257 (51.5)	36.81 (34.62; 38.99)	17.88	
≥ 45	571 (46.6)	33.30 (31.89; 34.72)	17.24	329 (45.3)	32.72 (30.81; 34.64)	17.71	242 (48.5)	34.09 (32.00; 36.18)	16.59	
Previous breast biopsies										0.891
No	1093 (89.2)	33.94 (32.93; 34.95)	17.07	649 (89.4)	33.50 (32.21; 34.80)	16.87	444 (89.0)	34.57 (32.96; 36.18)	17.35	
Yes	132 (10.8)	42.14 (39.17; 45.10)	17.41	77 (10.6)	41.57 (37.34; 45.80)	18.94	55 (11.0)	42.92 (38.92; 46.92)	15.14	
Family history of breast cancer										0.423
None	946 (77.2)	35.00 (33.91; 36.08)	17.07	563 (77.5)	34.97 (33.55; 36.39)	17.18	383 (76.8)	35.03 (33.34; 36.73)	16.92	
Second degree only	192 (15.7)	34.73 (32.15; 37.31)	18.27	117 (16.1)	32.97 (29.78; 36.16)	17.60	75 (15.0)	37.48 (33.16; 41.79)	19.06	
First degree	87 (7.1)	33.11 (29.43; 36.78)	17.48	46 (6.3)	30.40 (25.47; 35.32)	17.04	41 (8.2)	36.15 (30.74; 41.55)	17.67	
Body mass index (kg/m^2)										0.001
< 18.5	20 (1.6)	41.74 (33.84; 49.64)	18.03	6 (0.8)	37.98 (27.13; 48.83)	13.56	14 (2.8)	43.35 (32.94; 53.76)	19.87	
18.5–24.9	821 (67.0)	39.12 (37.98; 40.26)	16.64	468 (64.5)	39.35 (37.83; 40.87)	16.74	353 (70.8)	38.81 (37.08; 40.53)	16.52	
25–29.9	278 (22.7)	27.53 (25.84; 29.23)	14.41	178 (24.5)	27.51 (25.48; 29.54)	13.81	100 (20.0)	27.57 (24.54; 30.61)	15.48	
≥ 30	106 (8.7)	19.35 (16.80; 21.89)	13.37	74 (10.2)	18.98 (15.93; 22.02)	13.36	32 (6.4)	20.21 (15.52; 24.91)	13.55	
Use of oral contraceptives										0.314
Never	473 (38.6)	36.70 (35.08; 38.31)	17.92	268 (36.9)	35.73 (33.64; 37.81)	17.40	205 (41.1)	37.97 (35.43; 40.51)	18.55	
Past use	714 (58.3)	33.79 (32.55; 35.02)	16.82	436 (60.1)	33.70 (32.07; 35.32)	17.29	278 (55.7)	33.92 (32.03; 35.81)	16.08	
Current use	38 (3.1)	30.89 (25.82; 35.96)	15.94	22 (33.0)	30.83 (24.81; 36.84)	14.39	16 (3.2)	30.97 (21.99; 39.96)	18.35	
Tobacco consumption										0.687
Never	483 (39.4)	35.54 (33.96; 37.13)	17.74	284 (39.1)	34.76 (32.72; 36.79)	17.49	199 (39.8)	36.66 (34.15; 39.18)	18.08	
Former smoker	429 (35.0)	34.57 (32.99; 36.16)	16.74	261 (36.0)	34.80 (32.69; 36.92)	17.43	168 (33.7)	34.21 (31.85; 36.58)	15.65	
Current smoker	313 (25.6)	34.04 (32.13; 35.96)	17.31	181 (24.9)	33.09 (30.66; 35.53)	16.71	132 (26.5)	35.35 (32.26; 38.43)	18.10	
Alcohol consumption (g/day)										0.009
0	248 (20.2)	34.07 (31.89; 36.26)	17.56	157 (21.6)	32.89 (30.27; 35.50)	16.72	91 (18.3)	36.12 (32.25; 39.99)	18.84	
< 10	802 (65.5)	34.98 (33.79; 36.18)	17.30	483 (66.5)	34.79 (33.22; 36.34)	17.50	319 (63.9)	35.29 (33.42; 37.15)	17.03	
≥ 10	175 (14.3)	35.14 (32.64; 37.63)	16.87	86 (11.9)	34.68 (31.08; 38.27)	16.99	89 (17.8)	35.58 (32.08; 39.08)	16.84	
Number of children										0.141
0	306 (25.0)	37.86 (35.82; 39.90)	18.20	166 (22.9)	37.88 (35.31; 40.46)	16.94	140 (28.1)	37.83 (34.57: 41.08)	19.65	
1	280 (22.9)	35.81 (33.68; 37.95)	18.23	176 (24.2)	36.60 (33.83; 39.37)	18.77	104 (20.8)	34.48 (31.16; 37.80)	17.28	
2	576 (47.0)	33.00 (31.67; 34.33)	16.26	349 (48.1)	31.88 (30.15; 33.61)	16.48	227 (45.5)	34.71 (32.66; 36.77)	15.80	
> 2	63 (5.1)	32.32 (28.55; 36.10)	15.29	35 (4.8)	31.10 (26.29; 35.92)	14.55	28 (5.6)	33.85 (27.81; 39.89)	16.30	
Education										<0.001
Primary school or less	52 (4.2)	31.33 (26.42; 36.24)	18.05	43 (5.9)	30.34 (24.79; 35.88)	18.55	9 (1.8)	36.06 (25.93; 46.20)	15.51	
Secondary school	421 (34.4)	33.40 (31.82; 34.99)	16.61	286 (39.4)	33.86 (31.89; 35.84)	17.06	135 (27.1)	32.43 (29.79; 35.06)	15.62	
University graduate	752 (61.4)	35.85 (34.60; 37.11)	17.54	397 (54.7)	35.15 (33.46; 36.85)	17.24	355 (71.1)	36.64 (34.78; 38.50)	17.85	
Energy intake (Kcal/day)[c]										0.115
< 1674.8	408 (33.3)	33.68 (31.98; 35.37)	17.47	225 (31.0)	33.26 (30.94; 35.58)	17.76	183 (36.7)	34.19 (31.70; 36.67)	17.13	
1674.8–2151.1	409 (33.4)	35.74 (34.07; 37.40)	17.18	252 (34.7)	34.88 (32.78; 36.99)	17.01	157 (31.4)	37.11 (34.39; 39.83)	17.41	
> 2151.1	408 (33.3)	35.04 (33.38; 36.71)	17.18	249 (34.3)	34.82 (32.70; 36.94)	17.09	159 (31.9)	35.39 (32.69; 38.09)	17.37	
Women living in their current residence for ≥2 years	1165 (95.1)	34.82 (33.83; 35.82)	17.31	689 (94.9)	34.31 (33.01; 35.60)	17.31	476 (95.4)	35.57 (34.02; 37.13)	17.29	0.800
Women living in their current residence for ≥10 years	771 (62.9)	34.95 (33.71; 36.18)	17.52	466 (64.2)	34.60 (33.00; 36.21)	17.64	305 (61.1)	35.47 (33.53; 37.42)	17.33	0.302

[a] Standard deviation.
[b] Two-sided Chi-square test was used to compare descriptive characteristics between women residing at ≤3 km from any industrial source and women residing at >3 km.
[c] Variable in tertiles.

2.59, $\beta_{3\ sources}$ = 2.86, $\beta_{\geq 4\ sources}$ = 8.37, *p*-trend = 0.055) and 2 km ($\beta_{1\ source}$ = 1.03, $\beta_{2\ sources}$ = 0.06, $\beta_{3\ sources}$ = 2.28, $\beta_{\geq 4\ sources}$ = 5.56, *p*-trend = 0.083). The remaining distances studied (2.5 and 3 km) showed smaller effects and a less clear trend (*p*-trends = 0.114 and 0.132, respectively). Similar results were obtained in the sensitivity analyses considering only women living in their current domicile for ≥2 years (see Supplementary Data, Fig. S1) and ≥ 10 years (see Supplementary Data, Fig. S2), highlighting the positive trends observed for a distance of 1.5 km (*p*-trends = 0.060 (Supplementary Data, Fig. S1), and 0.040 (Supplementary Data, Fig. S2)). With respect to the analysis according to industrial sectors (data not shown), the only result of interest corresponded to "urban waste-water treatment plants", where women (*n* = 37) who resided near (≤3 km) 1 single source belonging to this industrial sector showed a higher MD (β = 2.21; 95%CI: (−3.07; 7.48), and women (*n* = 5) living near 2 sources showed a β = 8.00 (95%CI: (−5.99; 22.00)), *p*-trend = 0.192.

Regarding the results for industrial clusters (second methodological approach), the cluster analysis using the "average linkage clustering" criterion revealed 62 industrial clusters, and the corresponding dendrogram is shown in Fig. 2. On the other hand, Fig. 3 shows the geographical distribution of women's residences, as well as the 154 individual industries grouped by the 62 industrial clusters (along with an example of proximity areas for a distance of 1.5 km). The association between MD and residential proximity to industrial clusters with statistically significant results and a number of participants ≥5 is shown in Table 2. Significant associations were observed between:

a) cluster 10 (industries 1996 (Production and processing of metals), 1568 and 6563 (Surface treatment of metals and plastic), and 3380 and 6557 (Surface treatment using organic solvents)) and women living at ≤1.5 km (β = 10.78; 95%CI = 1.59; 19.97) and at ≤2 km (β = 7.96; 95%CI = 0.21; 15.70);
b) cluster 18 (industries 3337, 3389, and 4195 (Surface treatment of metals and plastic), 1678 and 2032 (Hazardous waste), 1978 (Disposal or recycling of animal waste), and 6717 (Urban waste-water treatment plants)) and women residing at ≤3 km (β = 8.48; 95%CI = 0.01; 16.96);

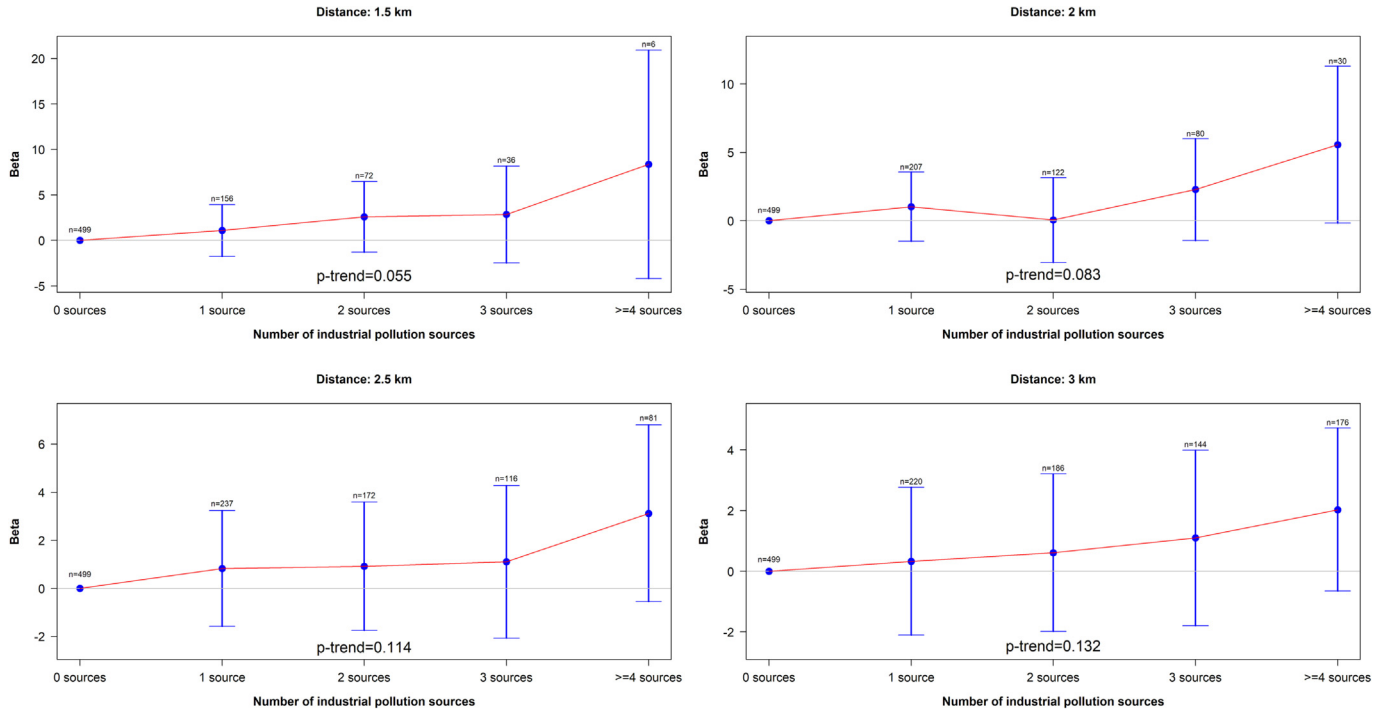

Fig. 1. Association between MD and residential proximity to an increasing number of industrial sources, for all industries jointly. Note that vertical axes are not in the same scale in the four graphics.

c) cluster 19 (industries 3507 and 5967 (Surface treatment of metals and plastic), and 1651 (Inorganic chemical industry)) and women living at ≤2.5 km, that were the same as those living at ≤3 km (β = 15.72; 95%CI = 1.96; 29.49);
d) cluster 20 (industry 1662 (Cement and lime)) and women living at ≤3 km (β = 16.95; 95%CI = 2.90; 31.00);
e) cluster 48 (industries 7736 (Galvanization), and 5437 (Surface treatment of metals and plastic)) and women residing at ≤3 km (β = 15.86; 95% CI = 3.95; 27.77); and.
f) cluster 52 (industries 6558 (Production and processing of metals), 6729 (Urban waste-water treatment plants), and 6553 (Food and beverage sector)) and women living at ≤2.5 km (β = 11.09; 95%CI = 0.12; 22.05).

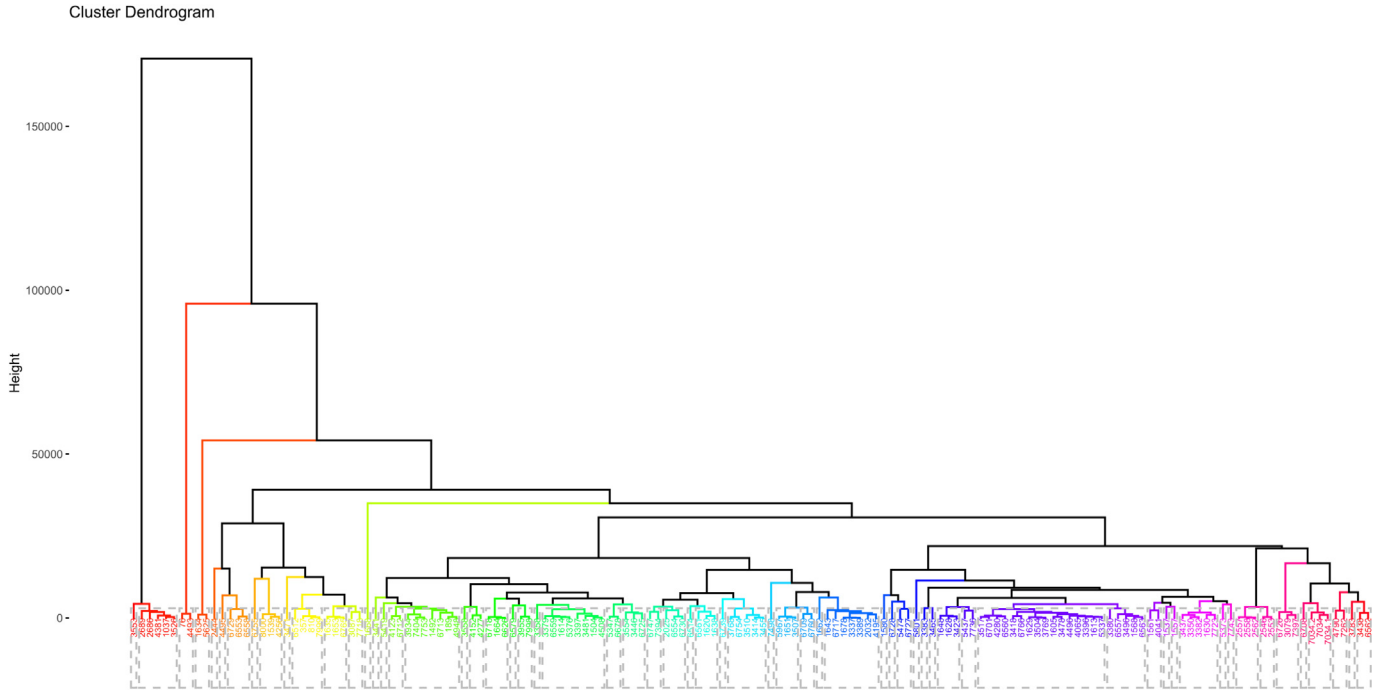

Fig. 2. Cluster dendrogram showing the industrial clusters obtained using the "average linkage clustering" method.

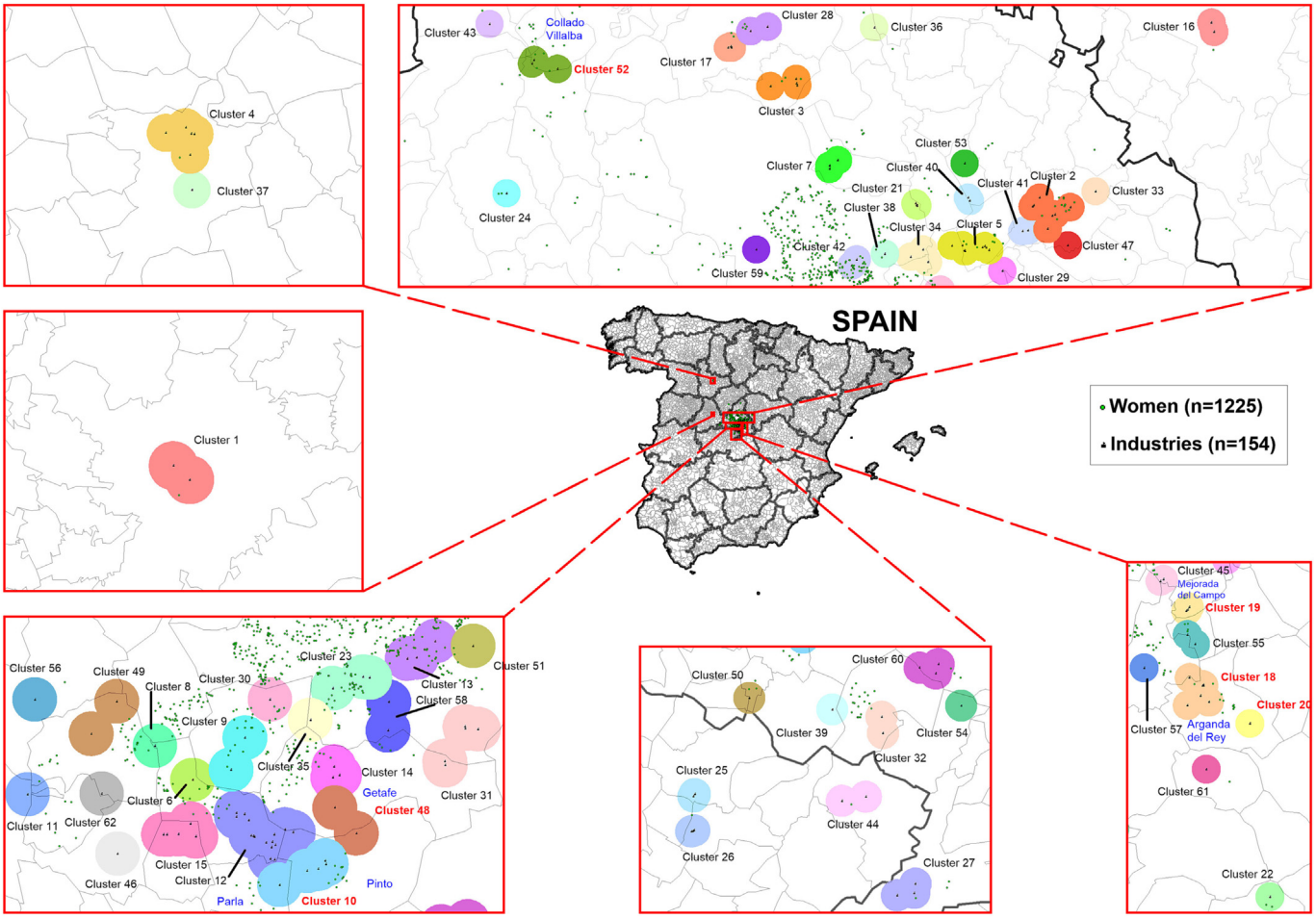

Fig. 3. Geographical distribution of women's residences (green points), as well as industries (black symbols) grouped by the 62 industrial clusters and their proximity areas for 1.5 km buffers around each industry. Note that the proximity areas for each industrial cluster are in different colors and, for those clusters with statistically significant results showed in Table 2, their names are in red color and the names of the municipalities are in blue color.

Table 2
Association between mammographic density and residential proximity to industrial clusters with statistically significant results and a number of participants ≥5. Statistically significant results are highlighted in bold.

Clusters - PRTR codes and industrial sectors	Women residing at ≤1.5 km			Women residing at ≤2 km			Women residing at ≤2.5 km			Women residing at ≤3 km		
	n	β[a]	95%CI	n	β[a]	95%CI	n	β[a]	95%CI	n	β[a]	95%CI
Cluster 10: 1996 (Production and processing of metals), 1568 and 6563 (Surface treatment of metals and plastic), and 3380 and 6557 (Surface treatment using organic solvents)	12	**10.78**	**(1.59; 19.97)**	17	**7.96**	**(0.21; 15.70)**	22	6.67	(−0.22; 13.56)	23	5.99	(−0.75; 12.72)
Cluster 18: 3337, 3389, and 4195 (Surface treatment of metals and plastic), 1678 and 2032 (Hazardous waste), 1978 (Disposal or recycling of animal waste), and 6717 (Urban waste-water treatment plants)	<5			6	0.21	(−12.51; 12.92)	8	6.44	(−4.68; 17.56)	14	**8.48**	**(0.01; 16.96)**
Cluster 19: 3507 and 5967 (Surface treatment of metals and plastic), and 1651 (Inorganic chemical industry)	<5			<5			5	**15.72**	**(1.96; 29.49)**	5	**15.72**	**(1.96; 29.49)**
Cluster 20: 1662 (Cement and lime)	<5			<5			<5			5	**16.95**	**(2.90; 31.00)**
Cluster 48: 7736 (Galvanization), and 5437 (Surface treatment of metals and plastic)	<5			<5			<5			7	**15.86**	**(3.95; 27.77)**
Cluster 52: 6558 (Production and processing of metals), 6729 (Urban waste-water treatment plants), and 6553 (Food and beverage sector)	<5			6	10.39	(−2.28; 23.05)	8	**11.09**	**(0.12; 22.05)**	9	7.9	(−2.44; 18.23)

[a] Adjusted for age, previous breast biopsies, family history of breast cancer, body mass index, oral contraceptives use, smoking, alcohol consumption, parity, education and energy intake.

Note that all the abovementioned results correspond to increases in percentages of MD above 5 %, which we considered as relevant from an epidemiologic standpoint. However, due to the small sample size of women residing in areas close to the industrial clusters, we must be cautious with the conclusions obtained from these results.

All these industrial clusters are located in the province of Madrid. Supplementary Data, Table S1 shows detailed information of the industries constituting the industrial clusters with significant results, including year of commencement of operations, industrial sector, municipality, and pollutants released to air and water.

4. Discussion

This study analyses the relationship between MD, a main biomarker of breast cancer risk, and residential proximity to multiple industrial sources. We have applied two methodological approaches to deepen in the study of MD and its relationship with industrial pollution, refining the exposure assessment with respect to multiple industrial installations. In summary, our results point towards an increase in MD with the proximity to an increasing number of industrial sources (jointly), particularly for distances of 1.5 and 2 km. Furthermore, we have detected a non-statistically significant increase in MD in women living at ≤3 km to 2 urban waste-water treatment plants, and among women living in the environs of six industrial clusters located in the province of Madrid.

In a previous study (Jiménez et al., 2022), we analyzed this association taking into account the distance between the woman's residence and the industrial facility as a single pollutant source, focusing the attention on "individual" sources. Now, in the present paper, we have applied alternative approaches focusing the attention on exposure to multiple industrial sources, giving a more realistic view of the possible relationship between MD and industrial exposures.

It is important to emphasize the importance and insights gained from using the cluster analysis in the second methodological approach applied in our study. This analytical technique has allowed us to identify clusters formed by industrial facilities located very close spatially in our study area. This is very useful when there are a large number of industries in a specific area and these industries need to be classified into a small number of mutually exclusive groups based on the similarities (distances) among the installations with the purpose of carrying out more specific studies in their environs. Using this technique, we have detected six potential industrial clusters of interest, in relation to a higher MD in women residing in their environs. This scientific base can help environmental and health authorities to carry out more specific studies in the vicinity of these industrial clusters.

In relation to the study of multiple ambient exposures, some papers have focused the attention on the characterization and identification of multiple pollution sources (Amiri et al., 2019; Cocozza et al., 2021; Coker et al., 2016; Han et al., 2020; Riccardi et al., 2008). On the other hand, some authors have proposed new approaches to the study of multipollutant exposure profiles associated with health effects (Huang et al., 2018; Oakes et al., 2014; Taylor et al., 2016; Zanobetti et al., 2014; Zhu et al., 2019). Regarding cancer, some authors have found increased risks of cancer mortality in populations close to multiple industrial sources (Ancona et al., 2015; Bauleo et al., 2019; García-Pérez et al., 2012; Ramis et al., 2011). In the specific case of breast cancer, a population-based case-control study conducted in New York (US) considered the impact on the incidence of this tumor from multiple sources of PAHs, showing associations with exposure to indoor sources, not with outdoor air pollution (White et al., 2016).

To the best of our knowledge, this is the first attempt to study the relationship between proximity to multiple industrial sources and MD. On the one hand, our results showed an increase in MD associated with residential proximity to a growing number of industrial sources, with an almost significant trend at distances less than or equal to 1.5 and 2 km. This approach could be interpreted as a proxy or surrogate of a "dose-response" analysis.

By industrial sectors, this association was stronger for the "urban waste-water treatment plants". In our previous study (Jiménez et al., 2022), a higher MD with residential proximity (≤3 km) to installations belonging to this sector was also detected ($\beta = 3.19$). Now, in the present paper, our results showed an increase in MD from $\beta = 2.21$ (in women residing at ≤3 km of one waste-water treatment plant) to $\beta = 8.00$ (in women residing at ≤3 km of two waste-water treatment plants), suggesting cumulative effects in the environmental exposure that could explain this trend observed in our results. Although there are no epidemiological studies assessing MD or breast cancer risk in women living in the environs of these installations, it is known that urban waste-water and sewage treatment plants release some carcinogens to air (e.g., total suspended particulate matter (TSP) (see Supplementary Data, Table S1)), and pollutants that have been related to higher MD (nitrogen dioxide (Eslami et al., 2022)) or breast cancer risk (nitrogen dioxide and carbon monoxide) (Batyrova et al., 2021; Cheng et al., 2022; Wei et al., 2021). Moreover, the effluents of these plants contain EDCs that can alter the development of the mammary gland (Fenton, 2006; Mandrup et al., 2015). Therefore, a more detailed exposure assessment of specific pollutants released by this type of installations is necessary to confirm our findings.

In relation to the analysis of specific industrial clusters, we have detected some industrial zones with higher MD in women who live in their environs. These clusters are grouped by industries belonging to different industrial sectors: metal industry (production and processing of metals, galvanization, surface treatment of metals and plastic), cement, inorganic chemical industry, waste management (hazardous waste, disposal or recycling of animal waste, and waste-water treatment plants), food/beverage sector, and surface treatment using organic solvents (see Supplementary Data, Table S1). Clusters of several industries located in large industrial areas could entail high concentrations of individual pollutants and complex mixtures of substances released to air, water, and soil (Satpathy et al., 2020; Yadav et al., 2022; Zhu et al., 2022). In this sense, several authors have assessed carcinogenic health risks associated with exposure to toxic substances in residents close to industrial clusters, with mixed results showing both moderate and high cancer risks (Ahamad et al., 2020, 2021; Chabukdhara and Nema, 2013; Vega et al., 2021).

Pollutants released to air and water by the installations constituting the industrial clusters of our study (Supplementary Data, Table S1) include EDCs, and other known and suspected carcinogens, such as persistent organic pollutants (POPs), PAHs, particulate matter or metals. With regard to certain POPs, a cross-sectional study found a positive association between levels of serum bisphenol A and MD in postmenopausal women (Sprague et al., 2013). Another cross-sectional study found higher MD in young women with high serum PCB levels (Rusiecki et al., 2020). However, Diorio et al. found no association with plasma levels of this contaminant in postmenopausal women (Diorio et al., 2013). With respect to PAHs, a prospective cohort study of mother-daughter pairs conducted in New York City (US) found limited evidence of an overall association between exposure to certain ambient PAHs during pregnancy and breast tissue composition in adolescent daughters and their mothers (Kehm et al., 2022). However, when the authors stratified by household smoke during pregnancy, they found that PAHs exposure was associated with higher MD. White et al. also found higher odds of dense breasts in women living in areas with higher PAH exposure. However, this association appeared to be driven by confounding with other air toxics (White et al., 2019). In relation to particulate matter, the installations of our study released particulate matter with a diameter between 2.5 and 10 μm (PM_{10}) and TSP. The studies existing in the literature about MD and exposure to particulate matter have focused, mainly, on particulate matter with a diameter < 2.5 μm ($PM_{2.5}$), showing inconsistent results: in a large population-based screening registry, the researchers found a positive association between MD and $PM_{2.5}$ (Yaghjyan et al., 2017), whereas in the Nurse's Health Study cohorts conducted in the US, the authors did not find associations between $PM_{2.5}$ and PM_{10} exposures and MD (DuPre et al., 2017). Finally, regarding metals exposure, a cross-sectional study published in 2019 showed that women living near

to high concentrations of lead and cobalt had higher MD, being this result stronger in premenopausal women (White et al., 2019).

With respect to the limitations of our study, due to its cross-sectional nature, we cannot investigate possible changes in MD across time. On the other hand, a critical aspect is the small number of women living near the industrial clusters with statistically significant results in our study (Table 2), so we must be cautious with the interpretation of these results. However, the findings in relation to the high MD found in women close to some clusters (with increases in percentages of MD >15 %) support the need for further epidemiological research on these industries. Another aspect to consider is that all women were recruited from a single center in Madrid City, limiting the generalizability of findings and causing a possible selection bias (for instance, excluding women who had a private insurance and did not attend to the gynecological examination offered by the public health service). Moreover, some covariates were self-reported and thus might have been subject to recall bias. Despite adjusting for a wide variety of potential confounders, residual confounding cannot be completely excluded. Finally, we used Euclidean distances between industrial sources and women's residences as a surrogate of the "real" exposure to the industrial pollution, assuming an isotropic model, something that could lead to a potential problem of misclassification.

On the other hand, among the main strengths of this study are the high participation rate and its novelty. This is the first attempt to analyze the possible association between MD and proximity to multiple industrial sources, applying different methodological approaches to refine the exposure assessment to industrial pollution. Another important strength is that we analyzed the Spanish facilities included in the (IPPC + *E*-PRTR) register, a public and exhaustive inventory of industrial installations releasing toxic pollutants in the EU. With respect to outcome measurement, mammograms were obtained in a single center, with the same equipment and in the context of routine clinical practice, and MD was quantified on a continuous scale, using a validated computer-assisted method (Llobet et al., 2014), and by a single reader with high internal consistency. Finally, the inclusion of a sensitivity analysis considering participants residing in their current residence for ≥ 2 and ≥ 10 years has provided a more comprehensive description of the possible association between MD and proximity to multiple industrial sources.

5. Conclusion

Since MD is considered as an intermediate phenotype for breast cancer that can be modified by environmental factors, more epidemiological studies are needed to furnish in-depth knowledge of potential risk factors related to a higher MD. In this study, we have used methodological approaches whose application in this field (MD and its relationship with industrial pollution) is novel, refining the exposure assessment with respect to multiple industrial sources. The associations found between increased MD (main phenotype risk marker of breast cancer) and residential proximity to an increasing number of industrial installations and specific industrial clusters suggest a contribution of these pollutant sources in the genesis of breast cancer, highlighting the need to design specific regulations to reduce the impact of their activity in the population's health. These findings support the need for further research on identification and control of pollutant sources related to MD.

CRediT authorship contribution statement

Tamara Jiménez: Validation, Formal analysis, Data curation, Writing – original draft, Visualization, Writing – review & editing. **Marina Pollán:** Funding acquisition, Investigation, Writing – review & editing. **Alejandro Domínguez-Castillo:** Writing – review & editing. **Pilar Lucas:** Writing – review & editing. **María Ángeles Sierra:** Writing – review & editing. **Adela Castelló:** Writing – review & editing. **Nerea Fernández de Larrea-Baz:** Investigation, Writing – review & editing. **David Lora-Pablos:** Writing – review & editing. **Dolores Salas-Trejo:** Writing – review & editing. **Rafael Llobet:** Writing – review & editing. **Inmaculada Martínez:** Writing – review & editing. **Marina Nieves Pino:** Writing – review & editing. **Mercedes Martínez-Cortés:** Writing – review & editing. **Beatriz Pérez-Gómez:** Writing – review & editing. **Virgina Lope:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation, Visualization, Supervision, Funding acquisition, Project administration, Writing – review & editing. **Javier García-Pérez:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation, Visualization, Supervision, Project administration, Writing – review & editing.

Data availability

The data that has been used is confidential.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2023.162768.

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