Risk of bone tumors in children and residential proximity to industrial and urban areas: New findings from a case-control study

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HIGHLIGHTS

• Excess risk of bone tumors was observed for children living near metal industries.

• Excess risk was detected near cement and combustion plants, and waste management.

• Excess risk of bone tumors in children was found near plants releasing pesticides.

• Excess risk was detected near facilities releasing persistent organic pollutants.

• Also, risk was found near industries releasing polycyclic aromatic chemicals.

GRAPHICAL ABSTRACT

abstract

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Abbreviations: RETI-SEHOP, Spanish Registry of Childhood Tumors; NSI, National Statistics Institute; E-PRTR, European Pollutant Release and Transfer Register; ORs, Odds ratios; 95% CIs, 95% confidence intervals; POPs, persistent organic pollutants; PACs, polycyclic aromatic chemicals; non-HPCs, non-halogenated phenolic chemicals; PAHs, polycyclic aromatic hydrocarbons.

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1. Introduction

Bone cancers in children account for approximately 4–6% of cancer cases among children <15 years of age (Larranaga et al., 2016; Ward et al., 2014), where Ewing tumor and osteosarcomas are the two main histologic types.

Little is known about the etiology of malignant bone tumors in children. Some evidence points to a genetic predisposition for Ewing tumor (Delattre et al., 1994; Linet et al., 2003; Ross and Spector, 2006), and a meta-analysis found some evidence of an association of this tumor with hermia (Valery et al., 2005). On the other hand, the incidence of osteosarcoma is increased among children with the hereditary form of retinoblastoma and Li-Fraumeni syndrome, as well as other genetic syndromes, but these conditions account for a few cases (Ross and Spector, 2006; Ward et al., 2014). Other risk factors, such as reproductive, perinatal, social, developmental, and dietary factors, have been explored with inconsistent findings, suggesting a probable role of gene-environment interactions in the etiology of bone tumors in children (Eyre et al., 2009; Ottaviani and Jaffe, 2009).

Insofar as environmental pollution exposures and bone tumors are concerned, there are few papers focused on pollution released by industrial plants or urban areas (Bovill et al., 1975; Pan et al., 1994). The diverse histologic types, clinical behaviors, and low numbers of cases limit the research in these rare cancers in children, and, therefore, epidemiologic science research is needed to ascertain whether residential proximity to environmental exposures might have an influence on the frequency of these tumors.

The present paper assessed the possible association between residential proximity to industrial facilities and urban areas, including different industrial groups, groups of carcinogenic and other toxic pollutants, and specific substances, and risk of bone tumors in children, in the context of the biggest population-based case-control study of incident childhood cancer carried out in Spain (García-Perez et al., 2016b; Ramis et al., 2015).

2. Materials and methods

2.1. Study area and subjects

A population-based case-control study of bone tumors in children (0–14 years) was carried out. Incident cases were obtained from the Spanish Registry of Childhood Tumors (RETI-SEHOP) for Autonomous Regions with a coverage of 100%: Catalonia, the Basque Country, Aragon, and Navarre (period 1996–2011), and Autonomous Region of Madrid (period 2000–2011). These cases corresponded to diseases coded as malignant bone tumors (code VIII of the International Classification of Diseases for Oncology, 3rd revision) (Stelinarova-Foucher et al., 2005). Six controls per case were selected, according to a simple random sampling from among all live births included in the Birth Registry of the Spanish National Statistics Institute (NSI) between 1996 and 2011, individually matched to cases by sex, year of birth, and autonomous region of residence.

2.2. Residential locations

Each subject’s last residence was geocoded using Google Map Javascript API and QGIS software (Open Source Geospatial Foundation, 2016), and the last digit of coordinates (X, Y) was assigned randomly in order to preserve their confidentiality.

The home address of the mother at birth for the controls (included in the Birth Registry of the NSI), and the home address of the cases at the moment of diagnosis (included in the RETI-SEHOP) were geocoded.

2.3. Industrial facility and urban locations

We used industrial information about industries governed by the Integrated Pollution Prevention and Control Directive and facilities included in the European Pollutant Release and Transfer Register (E-PRTR), provided by the Spanish Ministry for Agriculture, Food & Environment in 2009. This industrial database included information, previously validated, about the geographic position and pollution emissions of the 1271 facilities located in the study area that reported their releases to air and water. These industries were classified into one of the 25 categories of industrial groups listed in Table 1. Additionally, Supplementary Data, Fig. S1 shows the distribution of the years of commencement of operations of the facilities studied, by industrial group. The mean year of commencement of operations for industries as a whole was 1974.

Finally, we considered as urban areas the 30 municipalities ≥ 75,000 inhabitants (”big cities” according to the Spanish Act 57/2003) included in the 2001 census, and located in the study area.

2.4. Exposure coding and statistical analysis

For each individual, the following distances were calculated: a) industrial distance: the shortest distance between the individual’s residence and any of the 1271 industrial facilities; and b) urban distance: the shortest distance between the individual’s residence and any of the 30 centroids of the towns.

Using the same methodology as in a previous paper of our group (García-Perez et al., 2016a), five types of statistical analysis, including mixed multiple unconditional logistic regression models, were performed to estimate odds ratios (ORs) and 95% confidence intervals (95% CIs):
Y is the case−control status (1 = case, 0 = control), i = 1, ..., 798 children

All models included: matching factors (year of birth (year), sex (sex), and autonomous region of residence (ri)); other potential confounders provided by the 2001 census at a census tract level (percentage of illiteracy (ill)), percentage of unemployed (unem), and socioeconomic status (SES)); and percentage of total crop surface in a 1-km buffer around each subject’s last residence (GCI) as a measure of exposure to pesticides (Gomez-Barros et al., 2016). The exposure variable, the matching factors year, sex, and potential confounding factors were fixed-effects in the models, whereas ri was a random effect.

1) Analysis 1 (relationship between bone tumors in children and proximity to industrial installations and urban areas as a whole). Taking into account several industrial distances (D (3, 2.5, 2, 1.5, and 1 km), each subject was classified into one of the following 4 categories of the exposure variable (ExpoVariable) for each distance ‘D’ (5 independent models): a) residence in the “industrial area (only)”, if it resides at ≤D km from any industrial facility; b) residence in the “urban area (only)”, taking the zones defined by urban distances according to the spatial characteristics and size of the municipalities in Spain; c) residence in the intersection between industrial and urban areas (“both”); and, d) residence within the “reference area”: zones with children having no industries within 3 km of their residences and far from urban zones.

2) Analysis 2 (relationship between bone tumors in children and proximity to facilities by category of industrial groups). Taking into account the 25 categories of industrial groups defined in Table 1, we created an exposure variable (ExpoVariable) for each distance ‘D’ (25 independent models), in which the subject was classified as resident near a specific “industrial group”, if it resides at ≤D km from any installation belonging to the industrial group in question, and resident in the “reference area”, if it resides at > 3 km from any industry and far from urban areas.

3) Analysis 3 (relationship between bone tumors in children and residential proximity to industries releasing groups of carcinogens according to the International Agency for Research on Cancer, and other toxic substances). To this end, an exposure variable (ExpoVariable) for each distance ‘D’ (12 independent models) was created, where each subject was categorized as resident near
industries releasing the specific “group of carcinogens or toxic substances” or resident in the “reference area”, analogous to the previous analysis.

4) Analysis 4 (relationship between bone tumors in children and residential proximity to industries by specific industrial pollutants released by the facilities). To this end, an exposure variable (ExpoVariable) for each distance ‘D’ (72 independent models) was created, where each subject was categorized as resident near industries releasing the specific “industrial pollutant” or resident in the “reference area”, analogous to the previous analyses.

5) Analysis 5 (assessment of the existence of radial effects near industries). To this end, we perform an analysis to analyze the risk gradient in the proximity of industrial installations, described in Supplementary Data, Appendix A.

Additionally, with the aim of introducing robustness in our analysis and controlling potential biases, two sensitivity analyses were performed for the analyses 1–4: a) a first sensitivity analysis with only individuals of the autonomous regions with the highest proportion of cases and controls; and, b) a second sensitivity analysis including only cases with the same address at the time of birth and at the moment of diagnosis. For this purpose, a matching strategy to find children with the addresses on the Birth Registry of the NSI matched to the addresses on RETI-SEHOP was used.

As we have considered a frequency matched study, given that matching conditions 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 in cases with the same address at the time of birth and at the moment of diagnosis. For this purpose, a matching strategy to find children with the addresses on the Birth Registry of the NSI matched to the addresses on RETI-SEHOP was used.

3. Results

3.1. Characteristics of the study population

The final study population comprised 114 cases and 684 controls. The main characteristics of subjects included in the analyses were depicted in Table 2. Catalonia and Madrid Region were the autonomous regions with the highest proportion of individuals (48.3% and 29.8%, respectively), so these two regions were used in the first sensitivity analysis above mentioned. Histologically, Ewing tumor was the main type of bone cancer in children (63.1% of cases).

3.2. Results of the analysis 1

Estimated ORs of childhood cancers associated with residential proximity to industrial and urban areas, using several industrial distances, are shown in Table 3. Children close to industrial areas (only) registered excess risks of bone cancer for all industrial distances analyzed in the analysis with all individuals, statistically significant in the case of 3 km (OR = 2.33; 95%CI = 1.17–4.63) and 2.5 km (OR = 2.19; 95%CI = 1.10–4.39). However, when the two sensitivity analyses were applied, the statistical significance disappeared, and all risk estimates decreased for all distances analyzed. On the other hand, children living near urban areas (only) registered high and statistically significant excess risks for all industrial distances in the case of the analysis with all individuals –with ORs ranged between 4.01 (95%CI = 1.77–9.06) (at 1 km) and 4.43 (95%CI = 1.80–10.92) (at 3 km)– and the sensitivity analysis with only individuals of Catalonia and Madrid Region –with ORs ranged between 2.77 (95%CI = 1.19–6.44) (at 1 km) and 3.24 (95%CI = 1.29–8.10) (at 3 km)–. The second sensitivity analysis registered non-statistically significant excess risks of bone tumors near urban areas (only). Lastly, for the intersection area between industrial and urban zones, there were statistically significant excess risks of bone tumors for all industrial distances (with the exception of 1.5 km) in the analysis with all individuals, ranged from 3 km (OR = 3.66; 95%CI = 1.53–8.75) to 1 km (OR = 4.39; 95%CI = 1.19–16.23). However, only the second sensitivity analysis showed statistically significant excess risks in the case of 2.5 km (OR = 4.10; 95%CI = 1.07–15.68) and 2 km (OR = 5.89; 95%CI = 1.51–22.98).

3.3. Results of the analysis 2

The most noteworthy results for the analysis of proximity to facilities by categories of industrial groups are shown in Fig. 1. Attention should be drawn to the increased risks found for the following industrial groups and distances: ‘Surface treatment of metals and plastic’ at 2 km (OR = 2.50; 95%CI = 1.13–5.56 in the analysis with all individuals, and OR = 3.43; 95%CI = 1.06–11.12 in the second sensitivity analysis); ‘Production and processing of metals’ at 2.5 km (OR = 3.30; 95%CI = 1.41–7.77 in the analysis with all individuals, and OR = 3.58; 95%CI = 1.03–12.40 in the second sensitivity analysis); ‘Urban waste-water treatment plants’ at 2 km (OR = 4.41; 95%CI = 1.62–11.98 in the analysis with all individuals, and OR = 3.51; 95%CI = 1.26–9.82 in the first sensitivity analysis); ‘Hazardous waste’ at 2 km (OR = 4.63; 95%CI = 1.37–15.61 in the analysis with all individuals, and OR = 3.93; 95%CI = 1.13–13.90 in the first sensitivity analysis); ‘Disposal or recycling of animal waste’ at 2 km (OR = 4.73; 95%CI = 1.40–15.57 in the analysis with all individuals, and OR = 3.97; 95%CI = 1.13–13.90 in the first sensitivity analysis); ‘Cement and lime’ at 2.5 km (OR = 3.89; 95%CI = 1.19–12.77 in the analysis with all individuals, and OR = 3.45; 95%CI = 1.22–11.18 in the first sensitivity analysis).

Detailed information on emission amounts by groups of substances released by the industrial groups analyzed is provided in Table 1.

3.4. Results of the analysis 3

In relation to the analysis of proximity to facilities by categories of groups of carcinogens and other toxic pollutants released by the facilities, the results showed statistically significant excess risks in children living near industries releasing carcinogens to humans (data not
shown), for industrial distances of 2 km (OR = 2.09; 95%CI = 1.01–4.33), 2.5 km (OR = 2.28; 95%CI = 1.13–4.62), and 3 km (OR = 2.25; 95%CI = 1.12–4.52). The two sensitivity analyses also showed excess risks, although non-statistically significant. The most remarkable results of bone tumors in children refer to groups of other toxic chemical substances released by facilities are shown in Fig. 2. The results showed high and statistically significant excess risks in children living close to industrial facilities releasing: ‘Pesticides’ at 2, 2.5, and 3 km; ‘persistent organic pollutants’ (POPs) at 2, 2.5, and 3 km; ‘polycyclic aromatic chemicals’ (PACs) at 2 km; and, ‘non-halogenated phenolic chemicals’ (non-HPCs) at 2 km.

3.5. Results of the analysis 4

The most remarkable ORs of bone tumors in children living near industries releasing specific substances are shown in Fig. 3. Attention should be drawn to the significant excess risks found in the analysis and confirmed by the two sensitivity analyses, for the following pollutants and distances: ‘Dioxins + furans’ at 2 and 2.5 km; ‘Polycyclic aromatic hydrocarbons’ (PAHs) at 2 km; ‘Benzene’ at 3 km; ‘1,2-dichloroethane’ at 2.5 and 3 km; and, ‘simazine’ at 3 km.

3.6. Results of the analysis 5

Finally, the risk gradient analysis showed in Supplementary Data, Table S1 detected positive radial effects (rise in OR with increasing proximity to facilities of a specific sector) for ‘Urban waste-water treatment plants’ (OR = 1.72, p-trend = 0.029), ‘Surface treatment using organic solvents’ (OR = 1.92, p-trend = 0.034), ‘Disposal or recycling of animal waste’ (OR = 2.11, p-trend = 0.057), and ‘cement and lime’ (OR = 2.19, p-trend = 0.065).

4. Discussion

4.1. Summary

To our knowledge, this is the first study that analyzes the risk of bone tumors in children in the vicinity of environmental pollution sources, as industrial installations and urban areas, according to different industrial groups, groups of carcinogens and other toxic pollutants, and specific industrial pollutants. Our results could suggest a possible association between residential proximity to certain industries –especially between 2 and 3 km– and urban sites and risk of bone tumors in children. However, the two sensitivity analyses –carried out with the aim of introducing robustness in our initial analyses– restricted the statistical significance to the following industrial groups and toxic substances: metal industry (surface treatment of metals and plastic, and production and processing of metals), waste management industries (urban and waste-water treatment plants, hazardous waste, and disposal or recycling of animal waste), cement and lime industries, and energy sector (combustion installations); and facilities releasing pesticides, POPs, PACs, and non-HPCs.

In the case of industrial areas, the ORs decrease gradually when the industrial distances decrease for all analyses, with the loss of the statistical significance in the analysis with all individuals. This is probably due to the fact that the proportion of cases vs. controls decreases when the industrial distance decreases. However, in the case of urban areas, the ORs are statistically significant for all distances analyzed, in the analyses with all individual and the sensitivity analysis with only individuals of Catalonia and Madrid Region. This association is more robust, probably due to the fact that the proportion of cases vs. controls is more or less constant when the industrial distance decreases.
4.2. Results in relation to other studies

Insofar as environmental pollution exposures and bone tumors in children are concerned, there are few papers focused on pollution released by industries or urban areas. A Taiwanese study found a higher mortality of bone cancer in children aged 0–19 years in the petrochemical industrial districts than in the reference areas (Pan et al., 1994). In our study, the organic chemical industry showed statistically significant excess risks of bone cancer at 2.5 km (OR = 3.07; 95%CI = 1.23–7.62) and 3 km (OR = 2.92; 95%CI = 1.21–7.03) (data not shown).
In relation to urban pollution, two ecological analyses suggested a higher incidence of bone tumors in urban areas (Bovill et al., 1975; Larsson and Lorentzon, 1974), whereas another study showed upward trends in childhood bone cancer in males in urban Shanghai (China) (Bao et al., 2010), a finding that concurs with our results found in children living near urban sites. However, other authors showed no excess risks of malignant bone tumors in the urban counties of Texas (US) (Thompson et al., 2008). Traffic exhaust is a major cause of children’s exposure to air toxics, including PAHs, metals, and particulate material (Belpomme et al., 2007; Garcia-Algar et al., 2015), and several studies have found associations between some childhood tumors and air pollutants (Filippini et al., 2015; Raaschou-Nielsen and Reynolds, 2006). In our study, we have found high and robust excess risks of bone tumors in children living in urban areas, especially in the two regions with the biggest number of big cities with high levels of traffic exposure (Madrid Region and Catalonia). It is possible that exposure to PAHs and metals released from motor vehicle exhaust relates to these high increased risks. Moreover, some authors have reported higher levels of DNA adducts in children living in urban areas compared to referents living in rural areas (Neri et al., 2006b).

With regard to proximity to other pollution sources, such as crop fields as a proxy of exposure to pesticides, a previous paper of our group found an association between proximity to cultivated land and bone cancer in children (Gomez-Barroso et al., 2016), although another study of childhood cancer in Texas (US) did not confirm any association between risk of bone cancer in children and proximity of birth residence to agricultural use land (Carozza et al., 2009).

In relation to the industrial groups with statistically significant ORs of our study, the metal sector (surface treatment of metals and plastic, and production/processing of metals) releases known or suspected carcinogens (metals, dioxins, PAHs, and solvents), generate great amounts of toxic waste (gear and lubricating oils, mineral-based non-chlorinated engine, oil filters, solvents, and lead batteries), and their effluents are genotoxic: they induce mutations, cytogenetic damage, and DNA damage in the repair process (Houk, 1992; Katic et al., 2010). This group is the leading polluter of metals, PACs, and POPs in air and water, and the second-leading polluter of pesticides in water (see Table 1), substances which are known or suspected carcinogens. In this sense, a Swedish study about cancer incidence for children born in a smelting community found 13 childhood cancers vs. 6.7 cases expected in the neighborhood of the smelter (Wulff et al., 1996). On the other hand, some authors have found radioactive elements in the production processes and effluents of the metal industry (Bahari et al., 2007; Soflic et al., 2006). Radiation is a mutagen, carcinogen, and an initiator as well as a promoter of cancer. Moreover, exposure to ionizing radiation is a recognized cause of bone cancer in the general population (Clapp et al., 2005), and the findings of an American study showed that bone cancer occurred more frequently among children of fathers in all facilities with moderate potential ionizing radiation exposure (Hicks et al., 1984). This fact could be related to the high excess risks found by us in the environs of this type of installations. In this case, exposure to radioactive materials from these industries, such as radium and strontium, can cause bone cancer because these minerals build up in bones (American Cancer Society, 2016; IARC, 2001; IARC, 2012).

Another important result of our study is the increased risk of bone cancer found in children living near urban waste-water treatment plants (OR = 4.41 at 2 km), as well as a risk gradient (p-trend = 0.0289). This industrial group was the leading polluter of pesticides in water and the second-leading polluter of metals in air and water (see Table 1). Furthermore, high residual concentrations of radionuclides were identified in material derived from these installations (Kleinschmidt and Akber, 2008). In this sense, some studies have found that people living near these installations or exposed to soil treated with waste-water/sewage treatment plant sludge were potentially exposed to cancer risks (Eschenroeder et al., 1986; Yang et al., 2014).

With regard to hazardous waste, our results showed statistically significant increased risks at 2 km. In a previous ecological study about cancer mortality in the vicinity of this type of installations, we found excess risks for bone cancer in the general population near four specific installations (Garcia-Perez et al., 2013), three of them located in the
present study (two incinerators in Catalonia, and one installation for the regeneration of spent baths in the Basque Country). These installations generate recognized and suspected carcinogenic substances, such as arsenic, dioxins, benzene, chromium, PAHs, lead, cadmium, tetrachloroethylene, nickel, hexachlorobenzene, and naphthalene (European Commission, 2006), and their effluents represent a serious environmental problem, as they are a type of waste that contains fluorides, nitrates, heavy metals, and acids (Singhal et al., 2006; Vijay and Sihorwala, 2003). In this sense, some authors have explored childhood cancer incidence (White and Aldrich, 1999) and chromosomal anomalies in offspring (Brender et al., 2008) near hazardous waste sites, and did not find any association. However, a Chinese study found that childhood lead exposure affected both physical development and increased bone resorption of children of an electronic waste processing area (Yang et al., 2013). On the other hand, treatment of wastes gives rise to exposure to radioactive materials among workers at these plants and populations in their environs (Donzella et al., 2007; Lubenau and Yusko, 1998; Parmaksiz et al., 2015; Vearrier et al., 2009).

The cement industry has been identified as one of the main sources of hazardous air pollutants' emissions, including, dioxins, metals, PAHs, benzene, particulate material, and polychlorinated biphenyls (European Commission, 2010; Schuhmacher et al., 2004; Sidhu et al., 2001). Some experiments in laboratory with animals exposed to dust cement showed that the chemical components of the cement dust particles inhaled by animals are accumulated in their bones (Meo, 2004; Reichrrota, 1986). Moreover, some authors have found radiation hazards in the cement industry (Aslam et al., 2012; El Bahi, 2004; El Taher et al., 2010), which could be related to the increased risk of bone cancer found in our study.

The energy sector (combustion installations) release carcinogens into the environment (metals, dioxins, PAHs, and benzene), and this industrial group was the second-leading polluter of PACs and POPs in air and water (see Table 1). In addition, emissions from coal-fired installations contain radioactive elements, principally thorium and uranium, as well as by-products deriving from the disintegration of these isotopes, such as radon, radium, bismuth, polonium, and lead (Gabbard, 1993; Samet and Cohen, 2006), a finding that could be related to the excess risk of bone cancer found by us in the proximity of these facilities.

With regard to specific pollutants, the studies existing in the literature focused on parental exposure to pesticides and Ewing sarcoma: whereas some papers have found increased risks of this tumor for children whose fathers had occupational exposure to fertilizers, pesticides, or herbicides (Holly et al., 1992; Valery et al., 2002; Vinson et al., 2011; Zahm and Ward, 1998), other studies did not find evidence of risk of Ewing tumor and parental exposure to pesticides (Belpomme et al., 2007; Flower et al., 2004; Moore et al., 2005; Pearce et al., 2006). In our study, statistically significant excess risks for children close to industries releasing pesticides were found for all distances analyzed. In this case, exposure to the parents can lead to effects in the child in several potential ways: parental exposures prior to pregnancy could result in transmissible genetic effects that could cause childhood bone cancer; maternal exposures during pregnancy could result in in utero exposure to the developing infant; and maternal exposures prenatally or during the neonatal period could result in transmission of exposures in breast milk, affecting to the child's bones (Moya et al., 2004; Peters and Preston-Martin, 1984). In relation to other specific pollutants, some authors have provided molecular and genetic evidence of links between exposure to PAHs and increased fetal susceptibility. Moreover, prenatal exposure to PAHs affects epigenetic patterning by altering DNA methylation, and this has been shown to play a role in cancer (Perera, 2011; Perera et al., 1999). Insofar as exposure to metals are concerned, lead is a heavy metal that bioaccumulates in bone, more in children's bones doubling between infancy and the late ten years (Bearer, 1995). In our study, statistically significant excess risks were found for children close to industries releasing PAHs and lead at 2 km.

Lastly, children interact with the physical environment differently than adults, and are uniquely susceptible to environmental pollutants. Routes of absorption, distribution, metabolism, and target organ toxicities vary as children grow and develop (Falck et al., 2015; Neri et al., 2006a).

4.3. Limitations and strengths

Similarly to other case-control studies, our study has some limitations: the small sample size; the low statistical power in the case of the two sensitivity analyses carried out; the use of distances to the pollution sources, according to an isotropic model, as a proxy of exposure, something that could introduce a problem of misclassification, since real exposure is dependent on prevailing winds or geographic landforms; and the non-inclusion of information about parental occupational exposures for their unavailability at an individual level. Moreover, we could not include possible confounders that might be associated with the distance (sociodemographic variables or life-style-related factors), for their unavailability at an individual level. However, we included some socioeconomic variables at a census tract level, so we assigned to every subject the information of the corresponding census tract, as other similar studies (Mezei et al., 2006).

On the other hand, we had the home address of the mother at birth for the controls, and the home address of the cases at the time of diagnosis. This difference could introduce some bias in the analyses. To control this bias, a sensitivity analysis including only cases with the same address at birth and at the moment of diagnosis was carried out. This reduces partially the problem of misclassification in the exposure due to the residential mobility of children, although it is possible that some controls had migrated after birth.

Although in Spain, there is a low rate of local migration between provinces (only around 1% of the children change their residence to another province (National Statistics Institute, 2016)), an important limitation is the possible residential mobility of individuals within the same province, something that could affect the accuracy of the exposure assessment. In this sense, we have no data on migration within each province. This fact would amount to a non-differential bias which would limit the capacity to find positive findings.

Another aspect is that the identification of the critical time window of exposure in children is problematic. The evidence for exposures occurring during the preconceptional period that have an association with bone tumors in children is equivocal. Moreover, the list of environmental exposures that occur during the perinatal/postnatal period with potential to increase the risk of childhood cancer is lengthening, but the evidence available to date is inconsistent or inconclusive (Anderson et al., 2000).

Strengths of the study include the completeness of the several methodological approaches used in the statistical analyses, and the robustness provided for the two sensitivity analyses carried out. The sensitivity analysis with only individuals of Catalonia and Madrid Region was justified because almost all cases of the reference area are located in these two autonomous regions (11 of 12, see Table 3). Another advantage is the large control group (6 controls per case), which should give a clear view of the spatial distribution of the population at risk and should have a similar risk of exposure as the cases (the null hypothesis of our study is that controls and cases have the same risk of exposure in industrial and urban zones). The matching strategy used accounts for the temporal and regional variation in the child population. Lastly, the stratification of the risk by industrial group and group of carcinogenic and toxic pollutants has provided a description more exhaustive of childhood cancer risk.

Lastly, the fact that potential risk factors in relation to risk of bone tumors in children have been explored with inconsistent findings (e.g.: dietary exposure) (Eyre et al., 2009) could reduce the impact of the aforementioned limitations.
4.4. Implications and future directions

The industrial registers, such as E-PRTR, afford a very useful tool for the monitoring and surveillance of possible effects of industrial pollution on the health of the children (Wine et al., 2014), such as bone tumors. In this sense, the main challenges and action points that the scientific community should take into account are: to assess robustness of current etiological hypotheses regarding “suspected” environmental carcinogens and toxic substances; to improve the measurement of children population exposure to environmental pollution; to monitor exposure to proven environmental carcinogens; to carry out epidemiological surveillance of clusters of childhood cancers; to investigate interaction gen-environment; and to establish new biomarkers of exposure, effect, and susceptibility that can be infused into future studies of environmental factors in the childhood cancer etiology (Linet et al., 2003; Massey-Stokes and Lanning, 2002; Ramis et al., 2015; Ross and Spector, 2006; Terracini, 2002).

5. Conclusions

Our results could suggest a possible association between residential proximity to certain industrial and urban sites, specifically, plants involved in the metal industry, waste management, cement and lime, and susceptibility that can be infused into future studies of environmental factors in the childhood cancer etiology (Linet et al., 2003; Massey-Stokes and Lanning, 2002; Ramis et al., 2015; Ross and Spector, 2006; Terracini, 2002).

These findings support the need for more detailed exposure assessment and health risk analysis of certain substances released by these types of industries.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.scitotenv.2016.11.131.

References


