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Risk of neuroblastoma and residential proximity to industrial and urban sites: A case-control study

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ABSTRACT

Background: Neuroblastoma is the most common extracranial solid tumor in children but its etiology is not clearly understood. While a small fraction of cases might be attributable to genetic factors, the role of environmental pollution factors needs to be assessed.
Objectives: To ascertain the effect of residential proximity to both industrial and urban areas on neuroblastoma risk, taking into account industrial groups and toxic substances released.
Methods: We conducted a population-based case-control study of neuroblastoma in Spain, including 398 incident cases gathered from the Spanish Registry of Childhood Tumors (period 1996–2011), and 2388 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 and the 30 urban areas with ≥75,000 inhabitants located in the study area. Using logistic regression, odds ratios (ORs) and 95% confidence intervals (95%CIs) for categories of distance (from 1 km to 5 km) to industrial and urban pollution sources were calculated, with adjustment for matching variables and socioeconomic confounders.
Results: Excess risk (OR; 95%CI) of neuroblastoma was detected for the intersection between industrial and urban areas: (2.52; 1.20–5.30) for industrial distance of 1 km, and (1.99; 1.17–3.37) for industrial distance of 2 km. By industrial groups, excess risks were observed near 'Production of metals' (OR = 2.05; 95%CI = 1.16–3.64 at 1.5 km), 'Surface treatment of metals' (OR = 1.89; 95%CI = 1.10–3.28 at 1 km), 'Mines' (OR = 5.82; 95%CI = 1.04–32.43 at 1.5 km), 'Explosives/pyrotechnics' (OR = 4.04; 95%CI = 1.31–12.42 at 4 km), and 'Urban wastewater treatment plants' (OR = 2.14; 95%CI = 1.08–4.27 at 1.5 km).
Conclusions: These findings support the need for more detailed exposure assessment of certain substances released by these industries.

1. Introduction

Neuroblastoma is the most common extracranial solid tumor in children – accounting for 8–10% of all childhood cancers (Colon and Chung, 2011; Park et al., 2010) – and the most common tumor diagnosed during the first year of life in developed countries (Ries et al., 1999), with an estimated annual incidence of 10.9 cases per million children (<15 years of age) in Europe and 10.2 cases/million in the US (Maris, 2010; Spix et al., 2006).

The etiology of neuroblastoma is not clearly understood: whereas known genetic factors, including mutations of the anaplastic lymphoma kinase oncogene, account for 7–8% of cases, the high incidence in early childhood would suggest that factors occurring in pregnancy are likely

Abbreviations: RETI-SEHOP, Spanish Registry of Childhood Tumors; NSI, National Statistics Institute; IPPC, Integrated Pollution Prevention and Control; E-PRTR, European Pollutant Release and Transfer Register; ORs, Odds ratios; 95%CIs, 95% confidence intervals; PAHs, Polycyclic aromatic hydrocarbons; EDCs, Endocrine disrupting chemicals.

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important in its development (Azarova et al., 2011; Esiashvili et al., 2009). However, studies existing in the literature provide inconsistent and/or inconclusive results: although several factors – including birth weight, maternal smoking or alcohol consumption during pregnancy, prenatal hormone exposure, maternal medication use during pregnancy, and hair dye – have been explored as potential risk factors associated with neuroblastoma (Heck et al., 2009; Mullassery et al., 2009; Parodi et al., 2014; Ross and Spector, 2006), little is known about their mechanisms involved in neuroblastoma's etiopathogenesis and the role of such factors in the etiology of this cancer (Zhu et al., 2010). With regard to environmental and parental occupational exposures, several authors have analyzed the risk of neuroblastoma and exposure to pesticides (Daniels et al., 2001), different types of chemicals – such as metals or hydrocarbons (De Roos et al., 2001; Parodi et al., 2014) –, and ambient air toxics (Heck et al., 2013a, 2013b), with findings that need to be confirmed with other studies.

In this paper, we examine the effects of exposure to pollutant industries and urban areas, including different industrial groups and specific toxic substances, on neuroblastoma risk, in the context of an ongoing population-based case-control study of incident childhood cancer in Spain (Garcia-Perez et al., 2015b, 2016; Ramis et al., 2015).

2. Materials and methods

2.1. Study area and subjects

We designed a population-based case-control study of neuroblastoma in Spain. Cases were incident cases of neuroblastoma (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 neuroblastoma and other peripheral nervous cell tumors – code IV (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 live births registered in the Birth Registry of the Spanish National Statistics Institute (NSI) between 1996 and 2011, individually matched to cases by year of birth, sex, and autonomous region of residence. The final study population comprised 398 cases and 2388 controls, and both cases and controls were ethnically homogeneous.

2.2. Residential locations

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

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

With respect to the cases, we successfully validated 98% of their addresses. The remaining 2% of cases were fairly uniformly distributed through the different regions and, therefore, we concluded that data were not biased in this sense. With respect to the controls, only 2% of controls did not have valid coordinates. Given that this number of failures was small, 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 and urban 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 Pollutant Release and Transfer Register (E-PRTR) – provided by the Spanish Ministry for Agriculture, Food & Environment in 2009, which includes information on the geographic location, previously validated (Garcia-Perez et al., 2015b), and industrial pollution emissions of all industrial plants in Spain. We selected the 1271 industries that reported their releases to air and water in 2009, classified into one of the 25 categories of industrial groups listed in Supplementary Data, Table S1.

Finally, for the purposes of this study, we considered as urban areas the 30 towns with >75,000 inhabitants (big cities, according to the Spanish Act 57/2003) identified in the areas under study.

2.4. Exposure coding and statistical analysis

For each subject, we calculated: a) industrial distance: the shortest Euclidean distance between the subject's residence and any of the 1271 industrial installations; and b) urban distance: Euclidean distance between the subject's residence and the centroid of the town in which it resides.

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)), other potential confounders provided by the 2001 census at a census tract level (percentage of illiteracy, percentage of unemployed, and socioeconomic status), and percentage of total crop surface as a proxy of exposure to pesticides, described in detail in (Gomez-Barroso et al., in press). In a first phase, we evaluated the relationship between neuroblastoma 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) and urban sites (7 independent models). 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*)", 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 and spatial characteristics of the municipalities in Spain: 8 km (for towns ≥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 (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. In a second phase, we evaluated the relationship between neuroblastoma and residential proximity to industries by categories of industrial groups defined in Supplementary Data, Table S1 (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 ≤'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. Lastly, we assessed the relationship between neuroblastoma and residential proximity to industries, according to specific industrial pollutants released by the facilities (72 independent models). To this end, we created and exposure variable for each model, analogous to the previous analysis.

Since 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 including the matched characteristics in the model.

Finally, to take into account the problem of multiple comparisons or multiple testing (which occurs when a set of statistical inferences is