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Residential proximity to environmental pollution sources and risk of rare tumors in children

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ABSTRACT

Background: Few epidemiologic studies have explored risk factors for rare tumors in children, and the role of environmental factors needs to be assessed.
Objectives: To ascertain the effect of residential proximity to both industrial and urban areas on childhood cancer risk, taking industrial groups into account.
Methods: We conducted a population-based case-control study of five childhood cancers in Spain (retinoblastoma, hepatic tumors, soft tissue sarcomas, germ cell tumors, and other epithelial neoplasms/melanomas), including 557 incident cases from the Spanish Registry of Childhood Tumors (period 1996–2011), and 3342 controls individually matched by year of birth, sex, and region of residence. Distances were computed from the residences to the 1271 industries and the 30 urban areas with $\geq$75,000 inhabitants located in the study area. Using logistic regression, odds ratios (ORs) and 95% confidence intervals (95%CIs) for categories of distance to industrial and urban pollution sources were calculated, with adjustment for matching variables and socioeconomic confounders.
Results: Children living near industrial and urban areas as a whole showed no excess risk for any of the tumors analyzed. However, isolated statistical associations (OR; 95%CI) were found between retinoblastoma and proximity to industries involved in glass and mineral fibers (2.49; 1.01–6.12 at 3 km) and organic chemical industries (2.54; 1.10–5.90 at 2 km). Moreover, soft tissue sarcomas registered the lower risks in the environs of industries as a whole (0.59; 0.38–0.93 at 4 km).
Conclusions: We have found isolated statistical associations between retinoblastoma and proximity to industries involved in glass and mineral fibers and organic chemical industries.

1. Introduction

Childhood cancer is the main cause of disease-related death in childhood affecting both sexes in developed countries (National Cancer Institute, 2016; WHO, 2016). Although advances in diagnosis and treatment have improved 5-year survival rates for childhood cancer, which are now as high as 78–83% (Gatta et al., 2014; Howlader et al., 2015), children are at risk for short-and long-adverse effects of treatment: surgery-related complications, development of secondary tumors, and chronic health conditions (endocrine disorders and gonadal failure, orthopedic sequelae, cardiac disease and congestive heart failure, pulmonary complications, and neurosensory/neurologic adverse outcomes) (Diller

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; IARC, International Agency for Research on Cancer

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et al., 2009; Friedman et al., 2016; Kaste et al., 2008; Madenci et al., 2015; Marques et al., 2016; Meadows et al., 2009; Mulrooney et al., 2016; Oeffinger et al., 2006; Versluys and Bresters, 2016).

The causes of childhood cancer are largely unknown. Few risk factors have been established – including genetic factors, congenital anomalies or ionizing radiation – but they explain only a small proportion of childhood cancers (Ross and Spector, 2006; Ross and Swensen, 2000; Stiller, 2004; Wakeford et al., 2009). With respect to environmental exposures, several studies have analyzed the risk of frequent childhood cancers – such as leukemias, central nervous system or lymphomas – and exposure to toxic substances (Carlos-Wallace et al., 2016; Vinson et al., 2011; Whitworth et al., 2008) or in the environs of pollution sources (Danysh et al., 2015; Knox and Gilman, 1997; Weng et al., 2008). However, there are no epidemiologic studies about the risk of rare tumors in children (cancers with an incidence rate ≤ 2 per million per year (Bisogno et al., 2012), such as retinoblastoma, hepatoblastoma or germ cell tumors) in the proximity of environmental pollution sources, such as industrial plants and urban areas with air pollution from traffic. Some authors have focused attention on occupational exposures (Abdolahi et al., 2013; Buckley et al., 1989; Chen et al., 2005; Grufferman et al., 2014) but the diverse diagnostic groups, clinical behaviors, and low numbers of cases limit the research in these rare cancers (Brecht et al., 2014; Rodriguez-Galindo et al., 2013). Therefore, epidemiologic science research is needed to ascertain whether residential proximity to environmental exposures might have an influence on the frequency of these childhood cancers.

In this paper, we analyze the possible association between residential proximity to environmental pollution sources (industrial plants – including different industrial groups and groups of carcinogenic/toxic substances –, and urban areas) and risk of five groups of rare tumors in children (retinoblastoma, hepatic tumors, soft tissue sarcomas, germ cell tumors, and other epithelial neoplasms and melanomas), in the context of the biggest population-based case-control study of incident childhood cancer carried out in Spain (Garcia-Perez et al., 2015; Garcia-Perez et al., 2016; Ramis et al., 2015).

2. Materials and methods

2.1. Study area and subjects

We designed a population-based case-control study of childhood cancer in Spain. Cases were incident cases of rare tumors in children (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, according to the International Classification of Diseases for Oncology, 3rd revision, as retinoblastoma (code V), hepatic tumors (code VII), soft tissue and other extraosseous sarcomas (code IX), germ cell tumors, trophoblastic tumors, and neoplasms of gonads (code X), and other malignant epithelial neoplasms and malignant melanomas (code XI) (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 557 cases (139 of retinoblastoma, 58 of hepatic tumors, 200 of soft tissue sarcomas, 120 of germ cell tumors, and 40 of other epithelial neoplasms and melanomas) and 3342 controls.

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).

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., 2015), 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. Additionally, Supplementary Data, Fig. S1 shows the distribution of the years of commencement of operations of the installations studied, by industrial group. The mean year of commencement of operations for industries as a whole was 1974.

Finally, we considered as urban areas those towns with more than 75,000 inhabitants (named "big cities" by the Spanish Act 57/2003) according to the 2001 census, where a total of 30 towns were 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: the shortest Euclidean distance between the subject's residence and any of the 30 centroids of the towns.

Using the same methodology as in a previous paper of our group (Garcia-Perez et al., 2016), three 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); other potential confounders provided by the 2001 census at a census tract level (percentage of illiteracy, percentage of unemployed, and socio-economic status); and percentage of total crop surface in a 1-km buffer around each individual's last residence (GCI_{ij}) as a proxy of exposure to pesticides, described in detail in (Gomez-Barroso et al., 2016). The exposure variables, the matching factors year and sex, and potential confounding covariates were fixed-effects in the models, whereas autonomous region was a random effect.

1) Analysis 1 (relationship between childhood tumors and proximity to industrial installations and urban sites as a whole). Taking into account several industrial distances 'D' (5, 4, 3, and 2 km), each subject was classified into one of the following 4 categories of exposure variable for each tumor and distance 'D' (4 independent models for each tumor): a) residence in the *"industrial area (only)"*, defined in terms of proximity to industrial facilities, on the basis of the distance 'D'; b) residence in the *"urban area (only)"*, taking the areas defined by urban distances according to the size and spatial characteristics of the