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Central nervous system (CNS) cancer in children and young people in the European Union and its involvements with socio-economic and environmental factors

Agustín Llopis-González [a,b,c], Teresa Alcaide Capilla [a], Unai Chenlo Alonso [a], Nuria Rubio-López [a,b,c], Antoni Alegre-Martinez [d], María Morales Suárez-Varela [a,b,c,*]

[a] Public Health and Environmental Care Unit, Department of Preventive Medicine, University of Valencia, Valencia, Spain
[b] CIBER Epidemiologia y Salud Pública (CIBERESP), Spain
[c] Center for Advanced Research in Public Health, CSISP-FISABIO, Valencia, Spain
[d] Biomedical Sciences Department, Universidad Cardenal Herrera CEU, Valencia, Spain

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ABSTRACT

Malignant central nervous system (CNS) tumors are the leading cause of death by cancer in children and the second commonest pediatric cancer type. Despite several decades of epidemiologic research, the etiology of childhood CNS tumors is still largely unknown. A few genetic syndromes and therapeutic ionizing radiation are thought to account for 5–10% of childhood cancer, but the etiology of other cases remains unknown. Nongenetic causes, like environmental agents, are thought to explain them. However, as very few epidemiologic studies have been conducted, it is not surprising that nongenetic risk factors have not been detected. The biggest difference between cancers for which there are good etiologic clues and those for which there are none could be the number of relevant studies.

This study, which covers the 1980–2011 period, identified links between CNS cancer evolution and the socio-economic and environmental indicators in the same space and time limits in the European Union.

1. Introduction

Cancer ranks second as a global cause of death [1]. The latest statistics have revealed an increase in the number of cases, which does not seem to be exclusively due to a better and more accurate diagnosis. It is, therefore, urgent to discover the risk factors and to treat them with appropriate preventive measures. According to the International Agency for Research on Cancer (IARC), cancer caused 7.6 million deaths (approximately 13% of all deaths) in 2008 [2].

The etiology of cancer indicates that genetic and environmental factors are interrelated [3]. There are different hypotheses about the causes that produce cancer based on changes that occur to different populations. Thus a relationship appears between certain agents and cancer development. The IARC classifies these agents according to scientific evidence and informs us of carcinogenic agents, but not all substances have been assessed.

Specifically, central nervous system (CNS) cancer is the second commonest pediatric cancer type that causes more deaths in childhood [4]. In Europe, it is estimated that 140 per million for children (0–14 years) and 157 per million for children (0–19 years) will develop cancer each year [5]. The etiology of CNS cancer is not well-defined, but has been described to between 5% and 10% of cases with known risk factors and genetic factors, such as therapeutic ionizing radiation. It is believed that environmental factors play a key role in the remaining cases, and that the roots of the remaining 90–95% lie in the environment and lifestyle. Lifestyle factors include cigarette smoking, diet (fried foods, red meat), alcohol, sun exposure, environmental pollutants, infections, stress, obesity, and physical inactivity. There is evidence to indicate that of all cancer-related deaths, almost 25–30% are due to tobacco, as many as 30–35% are linked to diet, about 15–20% are owing to infections, and the remaining percentage is due to other factors: radiation, stress, physical activity, environmental pollutants, etc. [6], although the results obtained so far are contradictory.

Many potential carcinogenics are liposolubles and are, therefore, bio-accumulative in fatty tissues [6]. The brain is a tissue with a high

Abbreviations: CNS, Central nervous system; CO_2, Carbon dioxide; EU, European Union; GDP, Gross Domestic Product; IARC, International Agency for Research of Cancer; ICD, international classification of diseases; ISIC, International Standard Industrial Classification; WHO, World Health Organization.

* Corresponding author at: Public Health and Environmental Care Unit, Department of Preventive Medicine, University of Valencia, Avda. Vicente Andrés Estellés s/n, 46100 Burjasot, Valencia, Spain.
E-mail address: maria.m.morales@uv.es (M. Morales Suárez-Varela).

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fat concentration, which makes it more vulnerable to toxics due to its high lipophilicity [7].

Cancer is classified in the international classification of diseases (ICD 10) from heading C00 to D48, and according to anatomical and histological criteria. In this classification, CNS cancer occupies header C72. As shown in Table 1, CNS cancer is classified into different subtypes according to the function of the cellular structure [8].

Studies that have been carried out on the role of potential environmental agents in the etiology of CNS cancer in children and young people have spark considerable controversy, probably because the environmental conditions in which these studies were performed differed from each other or belonged to distinct times where pollution levels varied and were higher in the last study years. Therefore, our objective was to know CNS cancer evolution in children and young people in a given area, Europe Union (EU) countries in our case, and its possible involvements with environmental and socio-economic factors, to shed some light on its prevention.

2. Material and methods

2.1. Design

This ecological study was conducted during the 1980–2011 period in EU countries.

2.2. Study unit

EU countries were the study area (except Cyprus because it had no available data). The CNS tumors (rubric C72) rate that corresponds to children and young people (aged 0–19 years) has been identified. To perform this comparative study among EU countries, age-standardized mortality rates were used by an indirect method, and by taking the World Health Organization (WHO) population in 1996 as a reference.

2.3. Study variables

The selected socio-economic and environmental indicators were: Gross Domestic Product per capita (current US$), which indicates a country's development level; industrialization level (% of GDP), which comprises the value added in mining, manufacturing, construction, electricity, water and gas [9]; carbon dioxide (CO_2) emissions (metric tons per capita); electricity consumed (kWh per capita); fossil fuel energy consumed (% of total); nuclear power energy production (% of total energy use); PM10 (micrograms per cubic meter, particulate matter concentrations refer to fine suspended particulates less than 10 μm in diameter, the state of a country's technology and pollution controls are an important determinant of particulate matter concentrations); use of chemical products (% of the value added in manufacturing); use of fertilizers (kilograms per hectare of arable land). All these data were collected for each studied country. The sources resorted to were the WHO (World Health Organization Statistical Information System) and the World Bank, with high data accuracy.

The variables were selected by considering the relationship between them and the association of socio-economic and environmental exposure with its effect on CNS tumors in youngsters aged 0–19 years. Both socio-economic and environmental variables were integrated into the CNS mortality rates.

As this study is of an ecological type, it is not without its weak points and is, therefore, subject to ecological deceit. Thus specific studies on the obtained results are needed to confirm these findings. This study also has its strong points as it collected data from countries under the same information conditions (both exposure and effect), which increases its internal validity. Moreover, the evaluation made of environmental exposure allows some research hypotheses to be put forward.

(http://datos.bancomundial.org/indicador).

2.4. Statistical analysis

With this information, a database was created using countries as a unit of ecological analyses with standardized age and sex rates. To know the correlation between death by CNS cancer and the socio-economic and environmental factors, a Pearson's correlation analysis was used. A comparison was made between the death rates of a specific year and the factors of the previous year due to the lag period that cancer has [10], which we considered to be at least 1 year. Correlations were taken as significant if p-values were below 0.05.

The clustering process is a statistical exploration technique that performs the partitioning of a data set into subsets (called clusters) so that the data in each subset share some common trait (most often the proximity according to some defined similarity measure). Clustering is used in many fields, including image analysis and bioinformatics [11,12].

Data clustering algorithms can be hierarchical or partitional [13]. The hierarchical cluster analysis (HCA) was used in this paper, whereas partitional algorithms determine all the clusters at once. The traditional representation of the hierarchical approach is a tree, called a dendrogram, with the different types of energy use in each country in the EU. Clustering is based on a matrix that contains the "distances" (dissimilarities) between multivariate observations.

We used a multivariate comparison of death by CNS cancer in childhood in the EU by a cluster analysis-comparison of the different uses of energies (use of chemical products, CO_2 emissions, fossil fuel energy consumed, industrialization level and nuclear energy) and GDP (Gross Domestic Product) in each EU country.

Finally, in order to know the relation between the two variables from another perspective, a linear multiple regression analysis was used to assess the socio-economic and environmental factors as a whole. Regarding mortality, we identified the weight of each one with a saturated repeated model by introducing steps. In this way, the factors that better explained the evolution of CNS tumors in children and young people in the EU were selected. Data were analyzed by the Statistical Product and Service Solutions software (SPSS).

Table 1
Classification of childhood CNS cancer and its frequency.

Histological subtypes	% of all CNS tumors[a]
Ependymomas	10
Astrocytomas	40–50
Primitive neuroectodermal tumors/medulloblastomas	25
Other gliomas	10
Other specified and nonspecified CNS	8–13

[a] Proportions vary according to different case series.

Table 2
Pearson's correlation of GDP per capita with mortality by CNS tumors in children and its p-value in EU countries.

Year	Pearson's product	p-Value
1981–1982	−0.520	0.032
1993–1994	−0.615	0.002
1994–1995	−0.589	0.003
1995–1996	−0.434	0.030
1996–1997	−0.469	0.018
1997–1998	−0.480	0.015
1998–1999	−0.394	0.042
2000–2001	−0.460	0.018
2001–2002	−0.609	0.001
2008–2009	−0.450	0.018