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Breast and prostate cancer mortality and industrial pollution

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Abbreviations:

PAHs: Polycyclic aromatic hydrocarbons

EDCs: Endocrine disrupting chemicals

NSI: National Statistics Institute

ICD: International Classification of Diseases

IPPC: Integrated Pollution Prevention and Control

E-PRTR: European Pollutant Release and Transfer Register

RRs: Relative risks

95%CrIs: 95% credible intervals

BYM: Besag, York and Mollié

INLAs: Integrated nested Laplace approximations

POPs: Persistent organic pollutants

Abstract

We investigated whether there might be an excess of breast and prostate cancer mortality among the population residing near Spanish industries, according to different categories of industrial groups. An ecologic study was designed to examine breast and prostate cancer mortality at a municipal level (period 1997-2006). Population exposure to pollution was estimated by means of distance from town of residence to industrial facilities. Using Besag-York-Mollié regression models with Integrated Nested Laplace approximations for Bayesian inference, we assessed the relative risk of dying from these tumors in 2-, 3-, 4-, and 5-kilometer zones around installations, and analyzed the effect of category of industrial group. For all sectors combined, no excess risk was detected. However, excess risk of breast cancer mortality (relative risk, 95% credible interval) was detected near mines (1.10, 1.00-1.21 at 4 km), ceramic industries (1.05, 1.00-1.09 at 5 km), and ship building (1.12, 1.00-1.26 at 5 km), and excess risk of prostate cancer was detected near aquaculture for all distances analyzed (from 2.42, 1.53-3.63 at 2 km to 1.63, 1.07-2.36 at 5 km). Our findings do not support that residing in the vicinity of pollutant industries as a whole (all industrial sectors combined) is a risk factor for breast and prostate cancer mortality. However, isolated statistical associations found in our study with respect to specific industrial groups warrant further investigation.

Capsule abstract:

Isolated associations were found in our study between breast cancer and mines, ceramic industries, and ship building, and prostate cancer in relation to aquaculture installations.

Key Words: Breast cancer; prostate cancer; industrial pollution; BYM model; INLA; PRTR register

1. Introduction

In 2012, breast cancer was the leading tumor, in terms of new cases and deaths, in women worldwide, whereas prostate cancer ranked second in incidence and fifth as cause of cancer death among men worldwide (Torre et al., 2015). In Spain, there were 6264 deaths due to breast cancer in 2012 (accounting for 15.4% of all female cancer-related deaths) and 6038 prostate cancer deaths in the same year (which accounts for 9.1% of all cancer-related deaths in men) (Carlos III Institute of Health, 2016).

Both tumors are “hormone-dependent cancers”, being influenced by steroid hormones that regulate the growth and development of both the mammary and prostate glands (Mokarram et al., 2016; Omoto and Iwase, 2015). They share similar characteristics, such as genetic abnormalities that could contribute to the acquisition of the malignant phenotype by both mammary and prostatic epithelial cells (Wu et al., 2015), and are both influenced by several lifestyle and environmental factors (Lopez-Abente et al., 2014b; Lopez-Otin and Diamandis, 1998; Risbridger et al., 2010).

With regard to industrial pollution, residential proximity to industries that release pollutants to air and water is a source of exposure to a high number of toxic substances, inasmuch as many types of industries release known or suspected carcinogens – such as dioxins, metals, and polycyclic aromatic hydrocarbons (PAHs), which have been related to breast and prostate cancer risk (Mitra and Faruque, 2004; Rybicki et al., 2006) –, as well as endocrine disrupting chemicals (EDCs), substances that alter functions of the endocrine system and are related with the increase in incidence of these tumors (Rachon, 2016; Sweeney et al., 2016). Also, industrial installations generate large amounts of toxic waste, such as metalworking fluids and mineral oils, related to prostate cancer risk (Agalliu et al., 2005; Rybicki et al., 2006). Accordingly, it would seem necessary to assess the relationship between industries and the frequency of breast and prostate cancer in their environs.

The aim of this study was to assess possible excess mortality due to breast and prostate cancer among the Spanish population residing in the environs of industrial installations.

2. Materials and methods

We designed an ecologic study to evaluate the association between breast and prostate cancer mortality and proximity to industrial installations at a municipal level (8,098 Spanish towns), over the period 1997-2006.

2.1 Mortality data

Observed municipal mortality data were drawn from the records of the National Statistics Institute (NSI) for the study period, and corresponded to deaths coded as: malignant neoplasm of female breast – codes 174 (International Classification of Diseases-9th/ICD-9) and C50 (ICD-10); and malignant neoplasm of prostate – codes 185 (ICD-9) and C61 (ICD-10). Expected cases were calculated by taking the specific rates for Spain as a whole, broken down by age group (18 groups) and five-year period (1997-2001, 2002-2006), and multiplying these by the person-years for each town, broken down by the same strata. Person-years for each quinquennium were calculated by multiplying the respective populations by 5 (with data corresponding to 1999 and 2004 being taken as the estimator of the population at the midpoint of the study period).

2.2 Industrial pollution exposure data

Population exposure to industrial pollution was estimated by taking the distance from the centroid of town of residence to the industrial facility. 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. Bearing in mind the minimum induction period for solid tumors, generally 10 years (UNSCEAR, 2006), we selected the 1970 installations which released emissions into air, water, land, or generated toxic waste in 2009, and came into operation prior to 1993 (10 years before the mid-year of the study period). The year of commencement of the respective industrial activities was provided by the industries themselves and, owing to the presence of errors in the initial location of industries, their geographic coordinates were previously validated (Garcia-Perez et al., 2008; Garcia-Perez et al., 2013).

Finally, each of the installations was classified into one of the 27 categories of industrial groups created by us, on the basis of the similarity of their pollutant emission patterns.

2.3 Statistical analysis

Two types of analysis were performed to assess possible excess breast and prostate cancer mortality in towns lying near ("near") versus those lying far ("far") from pollutant industries, known as a "near vs. far" analysis. In all cases, several distances of 2, 3, 4 and 5 km were taken as the area of proximity ("exposure") to industrial installations:

1) in a first phase, we conducted a "near vs. far" analysis to estimate the relative risks (RRs) of towns situated at each one of the above-defined distances from industries as a whole (all sectors). The variable, "exposure", was coded as: a) exposed or proximity area ("near"): towns at ≤2, 3, 4 and 5 km from any facility; and, b) unexposed area ("far"): towns having no (IPPC+E-PRTR)-registered industry within each one of the above-defined distances of their municipal centroid (reference group); and,
2) lastly, we analyzed the risk according to the different categories of industrial groups. To this end, we created a variable of "exposure" for each industrial group in which the exposed area was stratified into the following levels: a) exposed or proximity area ("near"): towns at ≤2, 3, 4 and 5 km from any installation belonging to the industrial group in question; b) intermediate area: towns lying at the above-defined distances from any industrial installation other than the

group analyzed; and, c) unexposed area ("far"): towns having no (IPPC+E-PRTR)-registered industry within each one of the above-defined distances of their municipal centroid (reference group);

For the above analyses, RRs and their 95% credible intervals (95%CrIs) were estimated on the basis that the number of deaths per stratum followed a Poisson distribution, using a Bayesian conditional autoregressive model proposed by Besag, York and Mollié (BYM) (Besag et al., 1991), with explanatory variables:

$O_i \sim Poisson\ (\mu_i)$, with $\mu_i = E_i \lambda_i$

$$\log(\lambda_i) = \alpha Expos_i + \sum_j \beta_j Soc_{ij} + h_i + b_i \Rightarrow \log(\mu_i) = \log(E_i) + \alpha Expos_i + \sum_j \beta_j Soc_{ij} + h_i + b_i$$

$$Soc_{ij} = ps_i + ill_i + far_i + unem_i + pph_i + inc_i$$

$$i = 1, \dots, 8098\ towns, \quad j = 1, \dots, 6\ potential\ confounders$$

$h_i \sim Normal(\theta, \tau_h)$

$b_i \sim Car.Normal(\eta_i, \tau_b)$

$\tau_h \sim Gamma(1,0.01)$

$\tau_b \sim Gamma(1,0.001)$

with λ_i=RR in town i; O_i=number of observed deaths (dependent variable); and E_i=number of expected deaths (offset). All estimates for the variable of "exposure" ($\mathrm{Expos_i}$) were adjusted for the following standardized, sociodemographic indicators ($\mathrm{Soc_{ij}}$), chosen as potential confounders for their availability at a municipal level, potential explanatory ability vis-à-vis certain geographic mortality patterns (Lopez-Abente et al., 2014a) and because they have proven to be useful in other studies (Alavanja et al., 2005; Awadalla et al., 2007; Halbert et al., 2005; Shirley et al., 2014): population size (ps_i), percentage of illiteracy (ill_i), percentage of farmers (far_i), and percentage of unemployed ($unem_i$), and average persons per household (pph_i) according to the 1991 census; and mean income

(inc_i) as reported by the Spanish Market Yearbook (Ayuso Orejana et al., 1993). The variable of "exposure" and potential confounding covariates were fixed-effects terms in the models.

To enable the positive spatial autocorrelation problem to be assessed (presence of geographic patterns in contiguous spatial data), this was estimated by applying Moran's I statistic to the Standardized Mortality Ratios at a municipal level (Bivand et al., 2013). The BYM Bayesian autoregressive model takes this problem into account, thanks to the inclusion of two random effects components: a spatial term containing municipal contiguities (b_i), and the municipal heterogeneity term (h_i). Integrated nested Laplace approximations (INLAs) (Rue et al., 2009) were used as a tool for Bayesian inference. For this purpose, we used R-INLA (The R-INLA project, 2016), with the option of “Gaussian” estimation of the parameters. A total of 8098 towns were included, and the spatial data on municipal contiguities were obtained by processing the official NSI maps.

3. Results and discussion

From 1997 to 2006 there were 57,830 and 55,772 deaths due to breast and prostate cancer, respectively, in Spain. Table 1 shows the RRs and 95%CrIs for breast and prostate cancer in towns near pollutant industries, by industrial group. Firstly, spatial autocorrelation in the distribution of breast (Moran’s I test statistic=0.018, *p*-value=0.041) and prostate (Moran’s I test statistic=0.024, *p*-value=0.006) cancer mortality was detected, and it thus seemed appropriate to use the BYM model in order to take this spatial autocorrelation into account. For all sectors combined, excess risk was not detected in any of the distances analyzed. Insofar as the specific industrial groups were concerned, there was a slight statistically significant excess risk of breast cancer near ‘Mining industry’ (RR=1.10; 95%CrI=1.00-1.21 at 4 km), ‘Ceramic’ (RR=1.05; 95%CrI=1.00-1.09 at 5 km), and ‘Ship building’ (RR=1.12; 95%CrI=1.00-1.26 at 5 km). For prostate cancer, however, a high excess risk was detected near ‘Aquaculture’ (RR=2.42, 95%CrI=1.53-3.63 at 2 km; RR=2.07, 95%CrI=1.33-3.07 at 3 km; RR=2.08, 95%CrI=1.33-3.08 at 4km; and RR=1.63, 95%CrI=1.07-2.36 at 5 km), although with only four installations.

In summary, our results indicate: a) a weak association between breast cancer mortality and proximity to mines (4 km), ceramic industries (5 km), and ship building (5 km); and, b) a strong association between prostate cancer mortality and proximity to aquaculture for all distances analyzed.

Ecologic studies, such as that reported here, are proposing new hypothesis and lines of research with respect to population exposure to industrial pollution, and industrial pollution emission registers, such as E-PRTR, afford a very useful tool for the surveillance and monitoring of the possible effects of industrial pollution on the health of neighboring populations (Wine et al., 2014).

3.1 Breast cancer

In relation to exposure to environmental pollution, some authors have found associations between breast cancer and ambient air pollution (Brody et al., 2007; Wei et al., 2012), traffic-related air pollution (Hystad et al., 2015), and exposure to environmental chemicals (Mitra and Faruque, 2004), specifically to cadmium (Gallagher et al., 2010), persistent organic pollutants (POPs) (Ghisari et al., 2014) or pesticides (Boada et al., 2012). However, Reding et al. (Reding et al., 2015) found no significant associations between air pollution and breast cancer risk overall. Regarding exposure to industrial pollution, literature about breast cancer and proximity to specific industrial sectors is sparse. Pan et al. (Pan et al., 2011) conducted a population-based case-control study in Canada, and their results suggested possible weak associations between breast cancer and proximity to steel mills, pulp mills, petroleum refineries, and thermal power plants. Lewis-Michl et al. (Lewis-Michl et al., 1996), in a case-control interview study in New York (USA), observed a significantly elevated risk of breast cancer among postmenopausal women who were ever potentially exposed to chemical facilities. Other studies have focused attention on waste management: whereas some authors have found associations between breast cancer and proximity to incinerators (Ranzi et al., 2011) and hazardous waste sites (Griffith et al., 1989; O'Leary et al., 2004), other authors did not find evidence of breast cancer risk near a solid waste landfill site in Montreal (Canada) (Goldberg et al., 1995).

With regard to the industrial groups with statistically significant results in our study, there are very few studies about breast cancer risk and proximity to mines, ceramic industries, or ship building, even though these facilities are known to release carcinogens and EDCs, such as asbestos, metals, particulate matter, benzene, and PAHs. Previous studies about cancer risk in the vicinity of mines did not support any statistically significant association (Fernandez-Navarro et al., 2012; Mueller et al., 2015). On the other hand, Cambra et al. (Cambra et al., 2011) found an excess risk of breast cancer near (≤2 km) mineral industries, including mines and ceramic industries. Our findings about these industrial sectors, with results bordering the limit of statistical significance, should be interpreted with caution, and support the need for more detailed exposure assessment and health risk analysis of certain toxic substances near these industrial facilities.

3.2 Prostate cancer

Insofar as exposure to environmental and industrial pollution is concerned, the few studies existing in the literature about prostate cancer risk and proximity to industrial are inconsistent. Whereas some authors have found evidence of associations between prostate cancer and proximity to metal industries (Ramis et al., 2011) or a municipal solid waste landfill site (Goldberg et al., 1995) in specific geographic areas, a French study did not find any association between this tumor and exposure to pesticides, metals or pollutants from industry (Multigner et al., 2008).

With regard to the industrial groups with excess risk in our study, the growth of aquaculture sector over the past few years has been accompanied by some practices potentially damaging to human health, which include intensive use of antibiotics (Cabello, 2004; Cabello, 2006; Mo et al., 2015), misuse of antimicrobial agents (Heuer et al., 2009), inappropriate fish discards management with high concentration of POPs (Antelo et al., 2012), and chemical wastes produced by intentional and unintentional use of many chemicals (Haya et al., 2001). Regarding the use antibiotics in aquaculture, they have been used mainly for therapeutic purposes and as prophylactic agents, and these substances released into the environment may have a serious ecological impact, since their residues may contaminate surface waters, groundwaters, sediments, and biota (Kummerer, 2009; Pereira et al., 2015). Moreover, antibiotics are leached from the food and feces and, diffused into the sediment, they can be washed by currents to distant sites (Cabello, 2006). Some antibiotics and antimicrobial agents authorized for use in aquaculture, such as sulfonamides, macrolides, and quinolones, had been associated with an increased risk of prostate cancer (Boursi et al., 2015; Tamim et al., 2010), something that could be related to the significant excess risk of this tumor detected by our study in the proximity of aquaculture installations. On the other hand, some studies have found high levels of arsenic in aquacultural ponds (Huang et al., 2014; Kar et al., 2011), a carcinogen related to prostate cancer risk (Hong et al., 2014).

Aside from the limitations inherent in all ecologic studies, in our case mention should also be made of the following: the non-inclusion of possible confounding factors that might be associated with distance (though adjustment for socioeconomic variables goes some way to mitigating this lack of information, since many life-style-related risk factors, such as smoking, alcohol consumption or type of diet, show a distribution correlated with socioeconomic status (Prattala et al., 2009; Woitas-Slubowska et al., 2010)); the use of distance from town to industrial facilities as a "proxy" of population exposure to industrial pollution, based on the assumption of an isotropic model, since real exposure may depend on prevailing wind patterns or geographical landforms (though this would limit the capacity for detecting positive results, without invalidating the associations found); the use of mortality rather than incidence data, due to the absence of a national population-based incidence register; and the non-inclusion in the analysis of possible clusters of morbidity in some regions, which might indicate high risk of exposure.

One of the principal strengths of our study resides in the completeness of its exploratory analysis, which consisted of an in-depth examination of breast and prostate cancer mortality with reference to 27 industrial groups. Another strength is the use of a Bayesian hierarchical methodological approach to perform the statistical analysis, in which the use of spatial terms, not only meant that it was less susceptible to the presence of the ecological fallacy (Clayton et al., 1993), but also ensured that the geographic heterogeneity of the distribution of mortality was taken into account. On the other hand, the method of estimation afforded by INLA amounts to a qualitative leap in the use of hierarchical models with explanatory variables (Rue et al., 2009). Further advantages of the study are: its high statistical power, thanks to the inclusion of a great number of reported deaths, a factor that enables it to identify excess mortality of a lower magnitude, in line with the expected effects of environmental exposures; the good quality of the information in terms both of diagnostic accuracy of cause of death (Perez-Gomez et al., 2006) and validity of geographic coordinates of the industries (Garcia-Perez et al., 2008; Garcia-Perez et al., 2013); and elimination for study purposes of those installations that had come into operation more recently, and whose possible influence on tumor development is debatable if the minimum latency period is taken into account.

4. Conclusion

Our findings do not support that residing in the vicinity of pollutant industries as a whole (all industrial sectors combined) is a risk factor for breast and prostate cancer mortality. However, isolated statistical associations between breast cancer risk and mines, ceramic industries, and ship building, and prostate cancer risk and aquaculture, need to be confirmed by other type of studies that improve exposure assessment. For example, it would be of great interest to analyze cancer incidence – which was not included in this study – and clusters of cases and/or deaths close to the industrial installations using spatial clustering techniques, and to assess the possibility of using better exposure markers for studying what is happening in the environs of each specific installation. Despite the above-mentioned limitations, the design of the present study could be a useful tool for studying point-source environmental pollution and cancer.

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