Industrial pollution and mortality from digestive cancers at the small area level in a Spanish industrialized province

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Abstract

The province of Cadiz, Spain, is a highly industrialized area with numerous registered industrial plants, which has led to major concern regarding the possible influence of these facilities on the high rate of cancer-related mortality observed. Our objective was to evaluate the association between digestive cancer mortality and proximity to industrial installations in the province of Cadiz over the period 1992-2014 and to analyse this risk according to different categories of carcinogenic substances. An ecological study at the census tract level was carried out. Mortality due to digestive cancer (involving the oral cavity, pharynx, oesophagus, stomach, liver, pancreas, gallbladder, colon and rectum) was analysed. Using the spatial Besag, York and Mollié (BYM) approach, we assessed the relative risk of dying from these cancers for people living between 500 m and 5 km from industrial installations. The models were adjusted to account for socioeconomic deprivation. We detected a significant, excess risk of dying due to cancer in the following organs (expressed as relative risk with 95% confidence intervals): colon/rectum (1.13; 1.04-1.22 at 4 km), stomach (1.13; 1.00-1.29 at 2 km), liver (1.28; 1.02-1.61 at 1 km), pancreas (1.19; 1.03-1.39 at 2 km), oral and pharyngeal (1.40; 1.08-1.82 at 1 km), oesophagus (2.05; 1.18-3.56 at 500 m) and gallbladder (2.80; 1.14-6.89 at 500 m) for men; and from colorectal (1.21; 1.00-1.46 at 1 km), stomach (1.15; 1.01-1.31 at 4 km) and liver (1.58; 1.20-2.07 at 1 km) cancers for women. The results support the hypothesis of an association between several digestive cancers and proximity to polluting industrial plants.

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Introduction

Digestive cancers include a group of malignant tumours that represent a significant burden on morbidity, mortality and use of healthcare services worldwide. Regarding the aetiology, different studies have shown that these cancers share a number of risk factors, such as type of diet or consumption of tobacco and alcohol, which in turn are influenced by the socioeconomic level of the population (Shibata and Parsonnet, 2006; Nagel *et al*., 2007; Uthman *et al*., 2013). However, part of the aetiology of these malignant tumours remains unknown and many studies focus on other environmental factors (Tomatis *et al*., 1990). One of these potentially harmful environmental factors is exposure to industrial pollution, since residential proximity to industrial installations that emit polluting substances into air or water is a potential source of exposure to known or suspected carcinogens. Although the evidence is limited, some publications relate mortality from digestive cancers with living close to polluting factories. For instance, García-Pérez *et al*. (2010) and López-Abente *et al*. (2012) found associations related to the risk of dying from colorectal and liver cancer in areas near industrial plants. Other studies have observed an increased risk of dying from cancers of the digestive system due to exposure to heavy metals, organic solvents, reactive chemicals and Particulate Matter (PM) (Blair and Kazerouni, 1997; Lynge *et al*., 1997; Landrigan *et al*., 2000; Siemiatycki *et al*., 2004, Clapp *et al*., 2005; Wong *et al*., 2016; Nyqvist *et al*., 2017). Similarly, associations between the risk of incidence of this type of cancers and occupational exposure to asbestos, mineral oils and fluids connected with metal work, have been described in the literature (Tolbert, 1997; Calvert *et al*., 1998; Aliyu *et al*., 2005).

According to Instituto Nacional de Estadística (INE), cancer is the leading cause of death for men and the second most common cause of death in women in Spain, (INE, 2017). Until the 1990s, total cancer mortality presented a spatial, differential pattern, with higher rates in the south of the country. This excess mortality mainly affected the western Andalusian provinces of Cadiz, Huelva and Seville (López-Abente *et al*., 2006). Despite showing a declining pattern in recent years, the cancer mortality rates in the province of Cadiz still lie above European and Spanish estimates for both sexes, for all cancers, and for certain digestive malignant tumour locations, such as colorectal and liver cancers (Ferlay *et al*., 2010; Benítez-Rodríguez *et al*., 2015). In Cadiz, as in the rest of Spain (INE, 2017), cancers of the digestive system (colorectal, stomach, liver, pancreas, oral cavity and pharyngeal, oesophagus and gallbladder) account for almost one third of all cancer-related deaths, whereby colorectal cancer is the third leading cause of death in men and the second in women (Benítez-Rodríguez *et al*., 2015).

The province of Cadiz, which has a population of 1.2 million, is a highly industrialized area, which has led to major concerns from both the population and government institutions about the possible effects of local industry on the high cancer-related mortality observed (European Parliament, 2010). This has led to the undertaking of research aimed at establishing a possible relationship between excess mortality from certain types of malignant tumours and residential proximity to these industrial installations. However, most of these studies had a limited scope focusing on the El Campo de Gibraltar District and not on the Cadiz Province as a whole (Benítez-Rodríguez, 2008; Grupo de Trabajo de la Sociedad Española de Epidemiología, 2013).

The Integrated Pollution Prevention and Control (IPPC) directive of the European Commission, approved in 2002 for industrial emissions, targets installations with a high polluting potential to control the effects derived from their industrial activity. The application of this measure led to the creation of the new European Pollutant Release and Transfer Register (E-PRTR, 2019), which makes it compulsory for all industrial plants to declare all emissions on a broad list of pollutants into the air, water or soil above the designated thresholds, as well as provide information on the geographical coordinates of the sites. This information makes it possible to study associations between industrial pollution and the local population's health status (Monge-Corella *et al*., 2008; Ramis *et al*., 2009).

In this context, the aims of this study were to evaluate the association between digestive cancer mortality and proximity to the industrial installations included in the E-PRTR and the IPPC at a census tract level in the Spanish province of Cadiz, and to analyse this risk according to the different categories of carcinogenic substances, while controlling for socioeconomic level.

Materials and Methods

We conducted a small area, cross-sectional study, with the census tract as the spatial analysis unit, for the period 1992-2014. The study includes the 819 census tracts of the province of Cadiz existing in the year 2001.

Mortality data

Mortality data by sex, age and year of death from the Andalusian Mortality Register were geocoded for the following causes of cancer, according to the International Classification of Diseases (10th rev.): Malignant neoplasm of oral cavity and pharynx (C00-14), malignant neoplasm of oesophagus (C15), malignant neoplasm of stomach (C16), malignant neoplasm of colon, rectum and anus (C18-C21), malignant neoplasm of liver (C22), malignant neoplasm of pancreas (C23-24) and malignant neoplasm of gallbladder (C25). In order to preserve the confidentiality of the data, the analyses were carried out at the census tract level. Thus, for each case we assigned the census tract corresponding to the domicile of the deceased using the Geocoder software from Junta de Andalucía. The cases that could not be coded using this tool were manually geocoded using Google Earth and the city street directory (INE, 2019). The total percentage of geocoded deaths was 95.57%.

Industrial pollution exposure data

Exposure to industrial pollution was estimated by the distance measured from the centroid of the census tract to each of the facilities. First, the geometric centroid of each census tract was calculated; if the centroid was located in a sparsely populated or depopulated area, it was moved to the area with the largest population.

The locations of the industrial plants were obtained by the E-PRTR and IPPC registers for 2010 available from the Ministry of Agriculture, Food and Environment. Taking into account the latency of cancer development, generally considered to be 10 years for solid cancers (UNSCEAR, 2006), we selected the 26 industries that had started their activities before 1994, 10 years before the midpoint of the study period, and were generating emissions to air or water (directly or indirectly) in 2010. The E-PRTR register does not include the starting date of the industrial activities, so these data (year) were provided by the installations themselves. Figure 1 shows their locations.

In order to avoid errors in the initial industry locations recorded in the 2010 IPCC and E-PRTR databases, each of the coordinates was validated using Google Earth, the Spanish Agricultural Plots Geographic Information System (Spanish Ministry of Agriculture and Food and Environment, 2019), the telephone

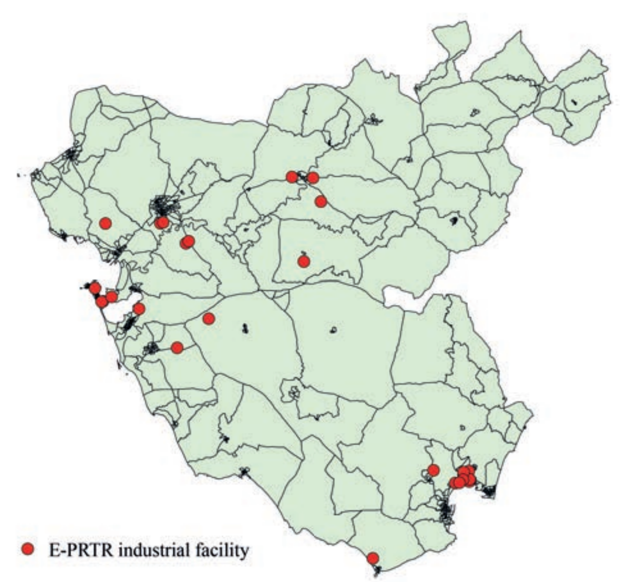

Figure 1. Geographic distribution of the 26 polluting industrial installations analysed.

directory and the web pages of the industries themselves (García-Pérez *et al*., 2008, 2013).

Socioeconomic level

For our study, we used a deprivation index by census tract (Ruíz-Ramos *et al*., 2006) elaborated from three variables corresponding to the Census of Population and Housing of Andalusia of the year 2001, namely i) percentage of people with a low level of education; ii) percentage of unemployed people and iii) percentage of unskilled workers. Using a principal component analysis, a summary index was constructed that classified all the census tracts in the province into five levels of deprivation according to the quintiles of the distribution of the respective factorial scores, assigning level 1 to the census tracts with the least deprivation and level 5 to those most deprived. We used level 1 (less deprived) as a reference level.

Statistical analysis

The expected number of cases was calculated by multiplying the specific rates for each cause for the whole province by the number of person-years, both by age group (17 five-year groups from 0 to 84 years and one group with those aged ≥85 years). The population by census tract, sex and age for the entire period was calculated by multiplying the population of the 2001 Census of the National Statistics Institute by the total number of years analysed.

In order to estimate the possible effect on cancer mortality of living near industrial installations versus living far away, three types of analyses were carried out:

i) In the first phase, we conducted a "near *vs*. far" analysis to estimate the relative risks (RRs) of mortality associated with distance to industrial plants, creating exposure variables at 0.5, 1, 2, 3, 4 and 5 km. For each cut-off point, we considered those census tracts with a centroid lying at a shorter distance from at least one industrial plant as being an exposed or proximity area ("near"). In the same way, unexposed areas ("far") consisted of census tracts with no (IPPC+E-PRTR) registered industry within the considered cut-off point. Using linear regression models, trends between RRs obtained at different distances were computed to evaluate the potential increase/decrease in RRs with increasing distance from the industrial installations.

ii) In the second analysis, the relationship between mortality by digestive cancer and proximity to industrial installations releasing substances classified by the IARC as carcinogenic (Group 1) and possibly carcinogenic (Group 2A) as a whole was studied. For this purpose, the exposure variables were created for the different groups using the same methodology as in phase 1 of the analysis. We also computed trend tests.

iii) Finally, separate analyses were carried out according to specific carcinogenic pollutants, all of which belong to Groups 1 and 2A of the IARC. A total of 10 different carcinogens in Group 1 as well as 2 carcinogens in Group 2A were included. The exposure variables were created in a similar way to the previous phases.

To carry out all the above analyses, the conditional autoregressive model of Besag, York and Mollié (BYM) (1991) was used to calculate the RRs and their corresponding 95% credibility intervals. In addition to including industrial exposure variables in the models, the deprivation index of the census tract was included as covariate. The model was defined as follows:

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

$$\log(\lambda_i) = \alpha Expos_i + \beta Soc_i + h_i + b_i \Rightarrow \log(\mu_i) = \log(E_i) = \alpha Expos_i + \beta Soc_i + h_i + b_i$$

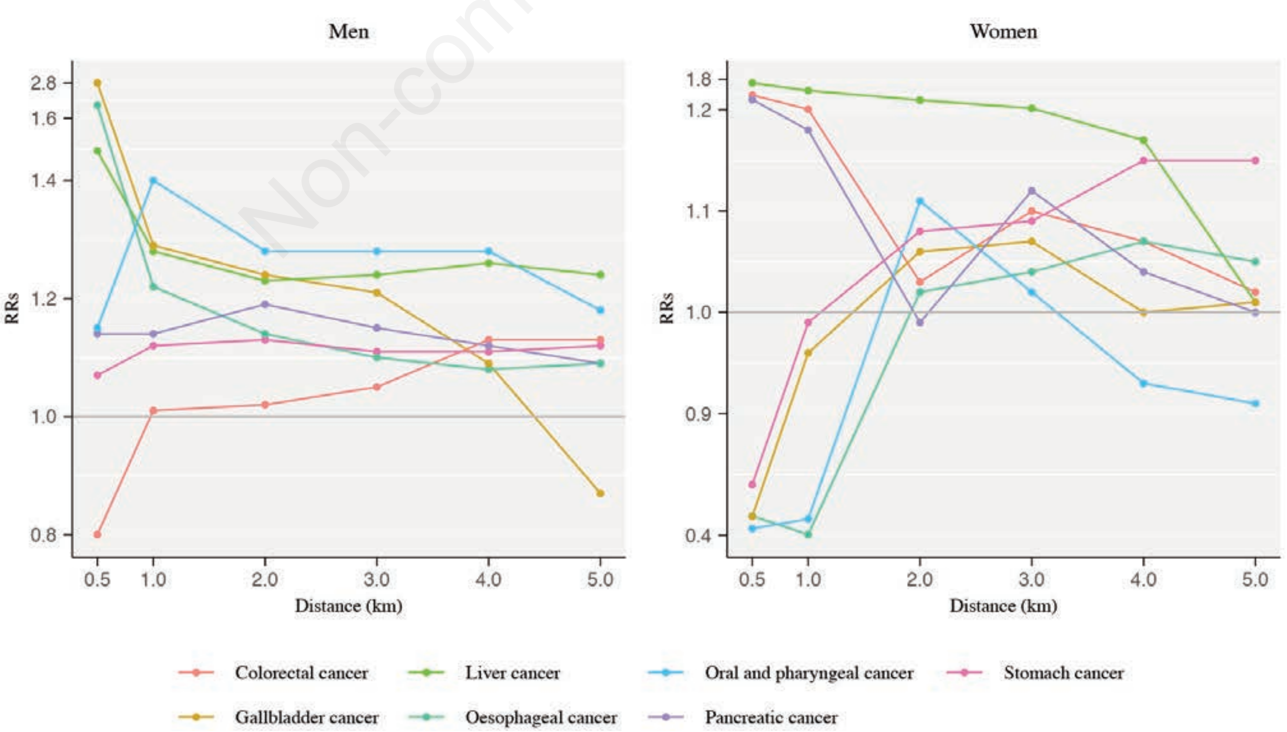

Figure 2. Trends for the relative risks of dying from digestive cancers in census tracts situated near polluting industry.

where i represents 1,…,819 census tracts; *Expos* the exposure variable; *Soc* the socioeconomic level, O_i the cases observed in the census tract i; E_i the expected cases; λ_i the relative risk; α and β estimators of effects associated with each covariate; h_i the non-spatial random effect and b_i the spatial random effect.

Exposure variables and socioeconomic level were considered in the models as fixed effects. The tool used for the Bayesian inference of subsequent marginal distributions was Integrated Nested Laplace Approximations (INLA) (Rue *et al.*, 2009). For this purpose, we used the R-INLA library available in the R statistical package (The R-INLA project, 2018).

Results

During the period 1992-2014, there were 16,446 deaths from cancers of the digestive system in the province of Cadiz, of which 9,910 (60.26%) were in men and 6,536 (39.74%) in women. During the same period, there were 6,000 deaths due to colorectal cancer, 3,416 (56.93%) in men and 2,584 (43.07%) in women; 2,786 due to stomach cancer, 1,745 (62.63%) in men and 1,041 (37.37%) in women; 2,549 due to liver cancer, 1,668 (65.44%) in men and 881 (34.56%) in women; 2,020 due to pancreatic cancer, 1,110 (54.95%) in men and 910 (45.05%) in women; 1,300 due to oral cavity and pharyngeal cancer, 698 (53.69%) in men and 602 (46.31%) in women; 1,073 due to malignant neoplasm of the oesophagus, 904 (84.25%) in men and 169 (15.75%) in women and 718 due to gallbladder cancer, 369 (51.39%) in men and 349 (48.61%) in women.

Table 1 shows the RRs and their corresponding 95% credibility intervals for all distances considered, as well as their trends, estimated according to the BYM model. The red (downward trend) and blue (upward trend) triangles accompanying the trends represent the sign of the corresponding estimator in the linear regression. In men, excess mortality RRs are observed for all digestive cancers, and they are observed for colorectal, stomach and liver cancers in women. The values of RRs obtained at 500 m for oesophagus (RR=2.05) and gallbladder (RR=2.80) cancers in men and for liver cancer at 1 km in women (RR=1.58) stand out. Figure

Table 1. Relative risks of dying from digestive cancers adjusted for deprivation index in census tracts situated near polluting industrial installations.

	1 km Exposed CT=46			2 km Exposed CT=151			3 km Exposed CT=224			4 km Exposed CT=297			5 km Exposed CT=413		
CAUSE	n	RR	95%CI	n	RR	95%CI	n	RR	95%CI	n	RR	95%CI	n	RR	95%CI
Colorectal cancer															
Men	181	1.01	0.85-1.19	647	1.02	0.93-1.13	964	1.05	0.97-1.15	1308	**1.13**	1.04-1.22	1793	**1.13**	1.05-1.23
Women	176	**1.21**	1.00-1.46	541	1.03	0.92-1.16	812	1.10	0.99-1.21	1049	1.07	0.97-1.18	1393	1.02	0.92-1.12
Stomach cancer															
Men	97	1.12	0.89-1.39	350	**1.13**	1.00-1.29	501	1.11	0.99-1.24	651	**1.11**	1.00-1.23	894	**1.12**	1.01-1.24
Women	57	0.99	0.75-1.31	223	1.08	0.93-1.26	319	1.09	0.95-1.25	431	**1.15**	1.01-1.31	580	**1.15**	1.01-1.31
Liver cancer															
Men	109	**1.28**	1.02-1.61	361	**1.23**	1.07-1.40	524	**1.24**	1.11-1.40	679	**1.26**	1.13-1.41	904	**1.24**	1.11-1.39
Women	75	**1.58**	1.20-2.07	230	**1.39**	1.18-1.65	294	**1.23**	1.05-1.44	368	**1.17**	1.00-1.36	462	1.01	0.86-1.17
Pancreatic cancer															
Men	66	1.14	0.88-1.47	237	**1.19**	1.03-1.39	333	**1.15**	1.00-1.31	426	1.12	0.99-1.28	577	1.09	0.96-1.24
Women	61	1.18	0.90-1.56	185	0.99	0.84-1.18	286	1.12	0.96-1.29	360	1.04	0.91-1.20	483	1.00	0.87-1.15
Oral and pharyngeal cancer															
Men	73	**1.40**	1.08-1.82	236	**1.28**	1.10-1.50	332	**1.28**	1.11-1.47	425	**1.28**	1.12-1.46	550	**1.18**	1.03-1.35
Women	9	0.72	0.37-1.41	48	1.11	0.80-1.53	65	1.02	0.76-1.37	81	0.93	0.70-1.23	112	0.91	0.69-1.20
Oesophageal cancer															
Men	53	1.22	0.91-1.63	180	1.14	0.96-1.35	252	1.10	0.94-1.28	324	1.08	0.93-1.25	445	1.09	0.94-1.25
Women	4	0.41	0.15-1.11	35	1.02	0.70-1.48	51	1.04	0.75-1.45	69	1.07	0.78-1.46	93	1.05	0.77-1.44
Gallbladder cancer															
Men	15	1.29	0.76-2.20	50	1.24	0.91-1.70	70	1.21	0.91-1.62	85	1.09	0.83-1.43	105	0.87	0.67-1.15
Women	26	0.96	0.63-1.46	104	1.06	0.84-1.33	148	1.07	0.87-1.30	187	1.00	0.83-1.22	257	1.01	0.83-1.22
Lung cancer															
Men	581	**1.24**	1.08-1.41	1934	**1.14**	1.05-1.24	2762	**1.12**	1.04-1.20	3589	**1.11**	1.04-1.19	4885	**1.09**	1.02-1.16
Women	71	1.18	0.91-1.54	197	0.95	0.80-1.13	278	0.92	0.79-1.08	367	0.92	0.80-1.07	486	0.88	0.77-1.01
Laryngeal cancer															
Men	64	1.19	0.88-1.59	211	1.07	0.89-1.28	318	1.11	0.95-1.31	422	1.13	0.98-1.31	562	1.09	0.95-1.25
Women	2	1.67	0.36-7.78	6	1.48	0.53-4.14	11	1.89	0.78-4.55	13	1.72	0.73-4.02	21	1.99	0.91-4.37
Bladder cancer															
Men	141	**1.32**	1.08-1.60	458	**1.18**	1.05-1.34	669	**1.18**	1.06-1.31	848	**1.14**	1.03-1.26	1141	**1.11**	1.01-1.22
Women	31	**1.91**	1.28-2.86	81	**1.37**	1.03-1.82	114	**1.36**	1.05-1.76	147	**1.32**	1.04-1.69	190	1.24	0.98-1.57
Kidney cancer															
Men	43	**1.55**	1.12-2.17	122	1.23	0.99-1.54	172	1.18	0.97-1.44	226	1.18	0.98-1.42	303	1.14	0.95-1.35
Women	24	**1.59**	1.02-2.50	69	1.27	0.94-1.72	89	1.13	0.85-1.50	123	1.18	0.91-1.53	174	1.20	0.94-1.53

Exposed CT=number of census tracts at a distance less than that considered, n=number of observed deaths.

Table 2. Relative risks of dying from digestive cancers adjusted for deprivation index in census tracts situated near polluting industry that release substances of the IARC Groups 1 and 2A.

CAUSE	500 m RR	500 m 95%CI	1 km RR	1 km 95%CI	2 km RR	2 km 95%CI	3 km RR	3 km 95%CI	4 km RR	4 km 95%CI	5 km RR	5 km 95%CI	Trend p-value	
IARC Group 1*														
Colorectal cancer														
Men	0.80	0.51-1.26	1.01	0.85-1.19	1.04	0.94-1.15	**1.09**	1.00-1.19	**1.13**	1.05-1.23	**1.14**	1.05-1.23	0.17	▲
Women	1.49	0.94-2.34	1.21	1.00-1.46	1.04	0.93-1.17	**1.12**	1.01-1.24	1.07	0.97-1.18	1.03	0.93-1.13	**0.04**	▼
Stomach cancer														
Men	1.07	0.62-1.84	1.12	0.89-1.39	**1.13**	1.00-1.29	**1.12**	1.00-1.26	**1.12**	1.01-1.25	**1.11**	1.00-1.24	0.32	▼
Women	0.83	0.38-1.78	0.99	0.75-1.31	1.13	0.97-1.32	1.14	0.99-1.30	**1.17**	1.03-1.33	**1.15**	1.01-1.31	0.26	▲
Liver cancer														
Men	1.45	0.86-2.45	**1.28**	1.02-1.61	**1.23**	1.07-1.41	**1.24**	1.10-1.40	**1.25**	1.12-1.40	**1.22**	1.10-1.37	**0.02**	▼
Women	1.73	0.88-3.40	**1.58**	1.2-02.07	**1.46**	1.23-1.73	**1.27**	1.08-1.49	**1.17**	1.01-1.36	1.01	0.87-1.18	**0.00**	▼
Pancreatic cancer														
Men	1.14	0.61-2.12	1.14	0.88-1.47	**1.19**	1.02-1.38	**1.16**	1.01-1.33	1.11	0.98-1.27	1.09	0.96-1.23	0.04	▼
Women	1.40	0.72-2.72	1.18	0.90-1.56	1.01	0.85-1.20	1.14	0.98-1.32	1.07	0.93-1.23	0.99	0.86-1.14	0.04	▼
Oral and pharyngeal cancer														
Men	1.15	0.60-2.21	**1.40**	1.08-1.82	**1.30**	1.11-1.52	**1.29**	1.12-1.48	**1.26**	1.10-1.44	**1.19**	1.05-1.36	0.15	▼
Women	0.53	0.07-3.80	0.72	0.37-1.41	1.15	0.83-1.59	1.05	0.78-1.42	0.95	0.72-1.26	0.92	0.70-1.21	0.20	▲
Oesophageal cancer														
Men	**2.05**	1.18-3.56	1.22	0.91-1.63	1.13	0.95-1.34	1.12	0.96-1.31	1.10	0.95-1.27	1.10	0.96-1.27	0.09	▼
Women	0.78	0.11-5.62	0.41	0.15-1.11	0.99	0.67-1.45	1.05	0.75-1.47	1.10	0.81-1.51	1.11	0.81-1.52	0.09	▲
Gallbladder cancer														
Men	**2.80**	1.14-6.89	1.29	0.76-2.20	1.30	0.95-1.78	1.25	0.94-1.67	1.12	0.85-1.47	0.91	0.69-1.19	0.07	▼
Women	0.77	0.24-2.49	0.96	0.63-1.46	1.08	0.86-1.36	1.13	0.92-1.38	1.01	0.83-1.23	1.01	0.83-1.23	0.33	▲
IARC Group 2**														
CAUSE	500 m RR	500 m 95%CI	1 km RR	1 km 95%CI	2 km RR	2 km 95%CI	3 km RR	3 km 95%CI	4 km RR	4 km 95%CI	5 km RR	5 km 95%CI	Trend p-value	
Colorectal cancer														
Men	0.80	0.48-1.32	1.07	0.86-1.32	1.03	0.91-1.16	**1.10**	1.00-1.21	**1.16**	1.07-1.26	1.16	1.07-1.25	0.23	▲
Women	**1.66**	1.03-2.68	1.17	0.91-1.50	0.97	0.83-1.12	1.09	0.97-1.22	1.05	0.95-1.16	1.03	0.94-1.14	0.11	▼
Stomach cancer														
Men	1.17	0.66-2.08	1.12	0.85-1.48	1.13	0.96-1.32	1.11	0.98-1.26	**1.12**	1.00-1.25	**1.12**	1.01-1.24	**0.05**	▼
Women	0.96	0.44-2.07	1.01	0.70-1.45	**1.21**	1.00-1.47	1.15	0.98-1.34	**1.18**	1.03-1.35	**1.17**	1.02-1.33	0.55	▲
Liver cancer														
Men	1.20	0.65-2.21	1.13	0.83-1.52	1.08	0.91-1.28	**1.16**	1.01-1.32	**1.20**	1.07-1.35	**1.26**	1.13-1.41	0.70	▼
Women	1.84	0.90-3.76	**1.51**	1.04-2.17	**1.37**	1.10-1.69	**1.21**	1.01-1.44	1.13	0.96-1.32	1.02	0.88-1.19	**0.00**	▼
Pancreatic cancer														
Men	1.26	0.65-2.42	1.16	0.84-1.60	1.07	0.89-1.30	1.07	0.92-1.25	1.02	0.89-1.17	1.06	0.94-1.21	**0.01**	▼
Women	1.00	0.43-2.32	1.26	0.89-1.80	0.99	0.80-1.24	**1.20**	1.02-1.41	1.10	0.95-1.28	1.02	0.89-1.17	0.51	▼
Oral and pharyngeal cancer														
Men	1.16	0.58-2.31	1.32	0.95-1.85	1.19	0.98-1.45	1.15	0.97-1.35	**1.21**	1.05-1.39	**1.22**	1.07-1.39	0.19	▼
Women	0.62	0.09-4.45	0.84	0.37-1.90	1.10	0.73-1.65	1.06	0.76-1.47	0.94	0.70-1.27	0.99	0.75-1.31	0.19	▲
Oesophageal cancer														
Men	**2.16**	1.21-3.84	1.23	0.85-1.77	1.06	0.86-1.32	1.08	0.91-1.29	1.10	0.95-1.28	**1.15**	1.00-1.33	0.13	▼
Women	0.92	0.13-6.66	0.58	0.18-1.82	1.09	0.68-1.75	1.02	0.70-1.50	1.06	0.76-1.47	1.21	0.88-1.66	0.16	▲
Gallbladder cancer														
Men	**3.42**	1.38-8.46	**1.98**	1.12-3.48	1.19	0.80-1.77	1.14	0.82-1.58	1.06	0.79-1.41	0.96	0.73-1.27	**0.45**	▼
Women	0.29	0.04-2.13	0.80	0.44-1.46	1.05	0.78-1.41	1.13	0.90-1.42	0.99	0.81-1.22	1.03	0.85-1.25	0.13	▲

* Analysed substances belonging to IARC Group 1 carcinogens: Arsenic and compounds, benzene, benzo(a)pyrene, cadmium and compounds, polycyclic aromatic hydrocarbons, nickel and compounds, PCDD+PCDF (dioxins+furans), particulate matter (PM_{10}) and trichloroethylene. ** Analysed substances belonging to IARC Group 2A possible carcinogens: Lead and compounds and tetrachloroethylene.

2 shows the trend in mortality RRs as the distance increases. In men, the observed results are highlighted at different distances for oesophageal (RR=2.05 at 500 m vs. RR=1.09 at 5 km) and gallbladder cancers (RR=2.80 at 500 m vs. RR=0.87 at 5 km), with a downward trend in mortality RRs. However, these trends are not statistically significant. Significant downward trends were only observed for liver and pancreatic cancers. For women, we observed significant downward trends in colorectal cancer (RR=1.49 at 500 m vs RR=1.02 at 5 km) and liver cancer (RR=1.73 at 500 m vs. RR=1.01 at 5 km).

Table 2 shows the RRs and 95% credibility intervals for facilities that release substances classified by the IARC as carcinogenic (Group 1) and possibly carcinogenic (Group 2A). Of the total of 26 industrial installations analysed, 21 released substances belonging to Group 1 and 11 released those belonging to Group 2A. For Group 1 carcinogens, the results are very similar to those found for the general results, which take into account all the industrial plants present in the province; this is possibly due to the fact that, except for 5 of them, all emit some substance belonging to this group. With respect to Group 2A possible carcinogens, excess risks are observed in men at different exposure distances for colorectal, stomach, liver, oral and pharyngeal, oesophageal and gallbladder cancers, with special reference to oesophageal cancer and gallbladder cancer, with excess risks of 2.16 and 3.42, respectively, at 500 m from a facility. In addition, for gallbladder cancer there is a significant negative gradient in the RR trend. Although the results do not show a clear gradient, a significant negative trend is observed for stomach and pancreatic cancers. For women, in Group 2A there is an excess risk associated with colorectal, stomach, liver and pancreatic cancers. The significant negative gradient observed in liver cancer stands out, with a RR of 1.84 at 500 meters vs. a RR of 1.02 at 5 km. Discriminating by the type of substance, Table S1 of the Supplementary Data shows the RRs of dying from digestive cancers in census tracts situated near IPCC+E-PRTR polluting facilities that release carcinogenic pollutants.

Discussion

For men, the results of the analyses suggest a significant excess risk of dying from all digestive cancers analysed for the population living in the proximity of IPPC+E-PRTR registered industrial facilities, after adjusting for socioeconomic deprivation. For women, there is an excess risk of colorectal, stomach and liver cancers, which is more pronounced for liver cancer. Similar results are obtained for Group 1 by stratifying the analysis according to the IARC categories. With respect to Group 2A, the excess risk obtained in men for colorectal, stomach, liver, oral and pharyngeal, oesophageal and gallbladder cancers stands out, as does the excess risk for women associated with colorectal, stomach, liver and pancreatic cancer.

The industrial installations registered in IPPC+E-PRTR emit a complex combination of toxic substances recognized as carcinogens and possible carcinogens by IARC (2019). Thus, in our analysis carried out according to the type of substance, we observed differentiated mortality risks results for arsenic, polycyclic aromatic hydrocarbons and leads and compounds. The remaining substances for which excess risk was found show a similar distribution of risks according to cause and level of exposure, probably due to the fact that the industrial facilities that emit them are almost the same. These substances are released into the air and water (directly and indirectly), causing on the one hand the exposure of the population to polluted air and, on the other hand, the incorporation of various substances into the food chain, which could be an explanation for the results associated with cancers of the digestive system (Vromman *et al*., 2008; Granata *et al*., 2011).

Cancer mortality in the province of Cadiz has been subject to several studies that have tried to disentangle a possible relationship to exposure to industrial pollution. In part, those studies were motivated by a concern for the population (European Parliament, 2010) regarding the cancer over-mortality observed in the province and the possible environmental and health consequences of the industrial hub of El Campo de Gibraltar, located in areas close to several urban centres and in which numerous industrial facilities dedicated to the chemical, energy and steel sectors are located. However, the studies carried out to date do not show conclusive results that relate the presence of industry to the high mortality rate due to cancer observed (Grupo de Trabajo de la Sociedad Española de Epidemiología, 2013). The study of Benítez-Rodríguez (2008) analysed cancer mortality by census tract in relation to industrial pollution in four municipalities of El Campo de Gibraltar. In men, after adjusting for deprivation and lung cancer, no relationship was found between proximity to industrial facilities and the risk of death from cancer. In women, a statistically significant increased risk of death was identified for only one of the 11 industrial facilities analysed. The differences to the results obtained in our research may be due to a shorter study period, to the analysis of global mortality due to cancer and not according to the causes, to the study of each of the polluting facilities individually instead of a multisource, and to a smaller territorial extension.

Colorectal cancer

The results obtained for colorectal cancer show excess mortality risks for both sexes in relation to industrial proximity. Other authors have found associations between mortality due to colorectal cancer and exposure to environmental pollution and significant associations between colorectal cancer and different types of industrial facilities are described in the literature (García-Pérez *et al*., 2010, 2013; López-Abente *et al*., 2012). The magnitude of the RRs is similar to that found in our study at 5 km, in the results involving all industrial facilities. It should be noted that in our study, the RRs found in women are close to statistical significance at some distances of exposure, probably due to the low number of cases in the exposed areas, which reduces the power to find significant associations. The RRs for this cause show a significant downward trend with increasing distance in women, while in men we observe the opposite direction, which could indicate possible sex and gender-associated differences in exposure to different risk factors, such as diet (Kim *et al*., 2015).

Regarding the province of Cadiz, in the study by Fernández-Navarro *et al*. (2012), an association was found between residing less than 5 km from three quarries located in Cadiz and a higher mortality from colorectal cancer for both sexes. Associations have also been found between colorectal cancer mortality in men and one of the metal casting plants in El Campo de Gibraltar (García-Pérez *et al*., 2010).

Stomach cancer

The excesses of risk observed for stomach cancer mortality for both sexes are not very relevant, whereby we highlight those obtained in women at distances of 4 and 5 km, with increases of risks of around 15%. However, the literature describes results with higher excess risks, in some cases with magnitudes greater than 1.5 (Nagel *et al*., 2018; Fernández-Navarro *et al*., 2012).

Liver cancer

Liver cancer is the only type for which we find excess risk for both sexes, with significant downward trends, which could indicate a possible effect related to environmental pollution. This same result can be found described in the literature (García-Pérez *et al*., 2010), where when stratifying by way of pollution discharge (air or water) there are significant excess risks only in facilities that released a type of pollutant into the air. When analysing all industrial facilities together, our results highlight the negative gradient observed in women, which shows a high risk at close distances and a moderate risk as distance from the source increases. In all analyses, we can observe a downward trend in mortality RRs, significant for both sexes for the overall analysis and Group 1, and for Group 2A for women. This may be a consequence of the use of a very small area, *i.e*., the census tract, as the spatial analysis unit in this study, which allows us to better discriminate trends in RRs compared to research using larger study units.

Pancreatic cancer

Currently, evidence regarding the relationship between pancreatic cancer mortality and exposure to industrial pollution is limited. In our study, we only found slight excesses of risk in men at distances of 2 and 3 km, nevertheless, the trend in RRs is downward and significant. However, by stratifying the analysis by type of industrial activity, other authors have found some significant associations between mortality from pancreatic cancer and residing in towns at distances of less than 5 km from installations for the production of cement, scrap metal and end-of-life vehicles, physico-chemical treatment, industrial waste, and waste not otherwise specified (García-Pérez et al., 2013, 2015).

Oral and pharyngeal cancer

Existing literature does not show clear evidence between oral and pharyngeal cancer mortality and proximity to industrial plants. Some associations have been found in relation to incinerators, hazardous waste treatment, cement and lime installations (García-Pérez *et al*., 2013, 2015). The significant results in this study relate solely to men. The gender differences observed in the relative mortality risks may be due to the small number of cases observed in women, differences in lifestyles, possible occupational-exposure pathways, or increased tobacco use in men (Elwood *et al*., 1984).

Oesophageal cancer

Previous studies have found associations between oesophageal cancer mortality and proximity to mining and metal industrial plants (Wang *et al*., 2011; García-Pérez *et al*., 2012) as well as for incinerators and hazardous waste treatment installations (García-Pérez *et al*., 2013). Our results highlight the values obtained for men at exposure distances of 500 meters, both in the general analysis and by IARC group.

Gallbladder cancer

Associations between mortality from gallbladder cancer and residential proximity to certain types of installations have been described in the literature (Fernández-Navarro *et al*., 2012; García-Pérez *et al*., 2013). These findings were only observed in men. This is in agreement with the results we obtained for men at a distance less than 500 meters, similar to what we observed in the case of oesophageal cancer. In both cases, this association could be indicative of a possible source of occupational exposure.

Strengths and limitations

This is the first study in Spain to analyse the relationship between the spatial distribution of mortality due to digestive cancer and exposure to industrial pollution at the census tract level over a long period. It should be borne in mind that previous studies did not use census tracts as the spatial unit to be studied, but rather the municipality. The province of Cadiz has a total of 44 municipalities, each with a population ranging from less than 500 to more than 200,000 inhabitants. However, the 819 census tracts analysed in our study have a homogeneous size between 1,000 and 2,500 inhabitants, unless the corresponding municipality has a smaller population. Considering a greater number of units to be studied enables a better estimation of exposure, which provides greater precision in locating the population and allows risks to be detected at smaller exposure distances. In addition, the use of a greater number of spatial units for study provides us with a better estimate of the effects of exposure. On the other hand, the use of small spatial units could be a drawback as it reduces the study population in each of the areas, which would also imply a reduction in the number of death cases. However, this is partially compensated for by the long-term study period used.

Importantly, this exploratory study is exhaustive as it analyses the mortality from seven types of digestive cancers in relation to all industrial installations in the province as well as the carcinogenic substances they emit. The long study period provides high power, owing to the inclusion of a great number of reported deaths. Another advantage, besides the quality of the inventory of polluting industry and validation of their geographical coordinates (García-Pérez *et al*., 2008), is the exclusion of those installations that were started recently (after the midpoint of the study period) and whose possible influence on cancer development is debatable if we take into account the minimum latency periods of the analysed cancers.

In addition to the limitations of any ecological study, we must mention the non-inclusion of possible confounding factors that could be related to distance, although the adjustment made by the socioeconomic level of the census tract reduces this bias, since lifestyles, which constitute risk factors for digestive cancers, are intimately related to the socioeconomic level of the population (Prattala *et al*., 2009). Another point to bear in mind is that the census tracts with the highest level of deprivation are found in areas neighbouring industrial plants found by some studies (Cambra *et al*., 2012). Another limitation is the use of the centroid to locate the entire population, which in reality may be dispersed; this could bias the results if there is a substantial variation in the risk within the entire area being considered (Diggle and Elliott, 1995). This bias has been limited by moving the geometric centroids to the most populated area of the census tract. On the other hand, the magnitude of this bias is likely to be small, considering that the estimated effects of exposure extend over several kilometres while the average area of a census tract is 0.36 km^2. In addition, the use of the BYM model, which takes into account the use of spatial terms in small areas, also considers the geographic heterogeneity of the mortality distribution, reducing the risk of ecological fallacy (Clayton *et al*., 1993). 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).

The following should also be mentioned as limitations: The use of distance to determine exposures without taking into account that the actual exposure depends on other factors, such as wind or geographical forms of the terrain, and the use of address data to determine exposure without taking into account possible movements or migrations of the population. However, while these factors could lead to a limitation in finding associations, they do not invalidate those found.

Our results show differences in the excess risk observed for each cause according to sex that could highlight lifestyles or occupational exposures. In this sense, some studies have described associations between cancers of the digestive system and occupational exposure (Firth *et al*., 1999). Due to the lack of data, it has been impossible for us to control for the effect of occupational exposure, which could be causing the possible similarities or differences found by sex in the different causes of cancer mortality analysed in our study.

Conclusions

This is one of the first studies to analyse the association between mortality from digestive cancers and industrial proximity by census tract over a long period, adjusting for socioeconomic level. The findings support the need for a more detailed exposure assessment and health risk analysis of certain carcinogenic substances in populations near industrial installations. The limitations due to the exploratory nature of this study notwithstanding, our results support the hypothesis of an association between mortality from some cancers of the digestive system and proximity at the census tract level to pollutant substances from IPCC+E-PRTR-registered industrial plants. Specifically, excess mortality risks have been found in both sexes for colorectal, stomach and liver cancers as well as for pancreatic, oral cavity and pharyngeal, oesophagus and gallbladder cancers in men.

References

Aliyu OA, Cullen MR, Barnett MJ, Balmes JR, Cartmel B, Redlich CA, et al., 2005. Evidence for excess colorectal cancer incidence among asbestos exposed men in the Beta-Carotene and Retinol Efficacy Trial. Am J Epidemiol 162:868-78.

Benítez-Rodríguez E, 2008. Análisis espacial de la mortalidad por cáncer en la provincia de Cádiz, 1992-2002: Factores ambientales y socio-económicos.

Benítez-Rodríguez E, Sanz-García MJ, Mejías-Márquez C, Vilches-Campos ML, Doménech-Torrejón R, Machado-Ruguero MA, et al., 2015. Situación del cáncer en la provincia de Cádiz. Periodo 2007-2009. In: Córdoba Doña JA, Martínez Nieto JM, Almenara Barrios J, editors. La salud en Cádiz y sus determinantes. Cádiz: Editorial UCA. Servicio de Publicaciones de la Universidad de Cádiz, pp. 245-62.

Besag J, York J, Mollié A, 1991. Bayesian image restoration with two applications in spatial statistics. Ann Inst Stat Math 43:1-59.

Blair A, Kazerouni N. Reactive chemicals and cancer, 1997. Cancer Causes Control 8:473-90.

Calvert GM, Ward E, Schnorr TM, Fine LJ, 1998. Cancer risks among workers exposed to metalworking fluids: a systematic review. Am J Ind Med 33:282-92.

Cambra K, Martínez-Rueda T, Alonso-Fustel E, Cirarda FB, Audicana C, Esnaola S, et al., 2012. Association of proximity to polluting industries, deprivation and mortality in small areas of the Basque Country (Spain). Eur J Public Health 231:171-6.

Clapp RW, Howe GK, Jacobs MM, 2005. Environmental and occupational causes of cancer. A review of recent scientific literature. Lowell Center for Sustainable Production.

Clayton DG, Bernardinelli L, Montomoli C, 1993. Spatial correlation in ecological analysis. Int J Epidemiol 22:1193-202.

Diggle PJ, Elliott P, 1995. Disease risk near point sources: statistical issues for analyses using individual or spatially aggregated data. J Epidemiol Community Health 49:20-7.

Elwood JM, Pearson JCG, Skippen DH, Jackson SM, 1984. Alcohol, smoking, social and occupational factors in the aetiology of cancer of the oral cavity, pharynx and larynx. Int J Cancer 34:603-12.

EPER. European Pollutant Emission Register; 2019. Available from: https://prtr.eea.europa.eu/#/home. Accessed: 6 October 2018.

European Parliament. Committee on Petitions. Petition 1098/2007 by Juan Antonio Carrasco Ragel (Spanish), on behalf of Plataforma Por El Estudio Epidemologico, on the conduct of an integrated epidemiologic study for the inhabitants of both Gibraltar County (Andalucia, Spain) and Gibraltar (United Kingdom); 2010. Available from: http://www.europarl.europa.eu/meetdocs/2009_2014/documents/peti/cm/802/802727/802727en.pdf. Accessed 23 January 2019.

Ferlay J, Parkin DM, Steliarova-Foucher E, 2010. Estimates of cancer incidence and mortality in Europe in 2008. Eur J Cancer 46:765-81.

Fernández-Navarro P, García Pérez J, Ramis R, Boldo E, López-Abente G, 2012. Proximity to mining industry and cancer mortality. Sci Total Environ 435-436:66-73.

Firth HM, Elwood JM, Cox B, Herbison GP, 1999. Historical cohort study of a New Zealand foundry and heavy engineering plant. Occup Environ Med 56:134-8.

Garcia-Perez J, Boldo E, Ramis R, Vidal E, Aragonés N, Perez-Gomez B, et al., 2008. Validation of the geographic position of EPER-Spain industries. Int J Health Geogr 7:1.

Garcia-Perez J, Fernandez-Navarro P, Castello A, Lopez-Cima MF, Ramis R, Boldo E, et al., 2013. Cancer mortality in towns in the vicinity of incinerators and installations for the recovery or disposal of hazardous waste. Enviro Int 51:31-44.

García-Pérez J, López-Abente G, Castelló A, González-Sánchez M, Fernández-Navarro P, 2015. Cancer mortality in towns in the vicinity of installations for the production of cement, lime, plaster, and magnesium oxide. Chemosphere 128:103-10.

García-Pérez J, López-Cima MF, Pérez-Gómez B, Aragonés N, Pollán M, Vidal E, et al., 2010. Mortality due to tumours of the digestive system in towns lying in the vicinity of metal production and processing installations. Sci Total Environ 408:3102-112.

García-Pérez J, López-Cima MF, Pollán M, Pérez-Gómez B, Aragonés N, Fernández-Navarro P, et al., 2012. Risk of dying of cancer in the vicinity of multiple pollutant sources associated with the metal industry. Environ Int 40:116-12.

Granata T, Alfa M, Giuffrida D, Rando R, Dugo G, 2011. Contamination of the food products by lead, cadmium and copper in the area at risk of Gela (Sicily). Epidemiol Prev 35:94-100.

Grupo de Trabajo de la Sociedad Española de Epidemiología. Dictamen realizado por encargo del Defensor del Pueblo Andaluz sobre El exceso de mortalidad y morbilidad detectado en varias investigaciones en El Campo de Gibraltar, 2013. Available from: https://www.seepidemiologia.es/documents/

dummy/DICTAMEN_CampoGibraltar-Definitiva.pdf. Accessed: 7 March 2019.

IARC, 2019. Monographs on the evaluation of carcinogenic risks to humans. Available from: https://monographs.iarc.fr/agents-classified-by-the-iarc/. Accessed: 14 September 2018.

INE, 2017. Instituto Nacional de Estadística. Defunciones según la Causa de Muerte. Available from: https://www.ine.es/dynt3/inebase/es/index.htm?padre=5449&capsel=5450. Accessed: 16 January 2019.

Kim SE, Paik HY, Yoon H, Lee JE, Kim N, Sung MK, 2015. Sex and gender-specific disparities in colorectal cancer risk. World J Gastroenterol 21:5167-75.

Landrigan PJ, Boffetta P, Apostoli P, 2000. The reproductive toxicity and carcinogenicity of lead: a critical review. Am J Ind Med 38:231-43.

López-Abente G, García-Pérez J, Fernández-Navarro P, Boldo E, Ramis R, 2012. Colorectal cancer mortality and industrial pollution in Spain. BMC Public Health 12:589.

López-Abente G, Ramis R, Pollán M, Aragonés N, Pérez-Gómez B, Gómez-Barroso D, et al., 2006. Atlas Municipal de Mortalidad Por Cáncer En España, 1989-1998. Madrid: Instituto de Salud Carlos III.

Lynge E, Anttila A, Hemminki K, 1997. Organic solvents and cancer. Cancer Causes Control 8:406-19.

Monge-Corella S, García-Pérez J, Aragonés N, Pollán M, Pérez-Gómez B, López-Abente G, 2008. Lung cancer mortality in towns near paper, pulp and board industries in Spain: a point source pollution study. BMC Public Health 8:288.

Nagel G, Linseisen J, Boshuisen HC, Pera G, Del Giudice G, Westert GP, et al., 2007. Socioeconomic position and the risk of gastric and oesophageal cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC-EURGAST). Int J Epidemiol 36:66-76.

Nagel G, Stafoggia M, Pedersen M, Andersen ZJ, Galassi C, Munkenast J, et al., 2018. Air pollution and incidence of cancers of the stomach and the upper aerodigestive tract in the European Study of Cohorts for Air Pollution Effects (ESCAPE). Int J Cancer 143:1632-43.

Nyqvist F, Helmfrid I, Augustsson A, Wingren G, 2017. Increased cancer incidence in the local population around metal-contaminated glassworks sites. J Occup Environ Med 59:e84-e90.

Prattala R, Hakala S, Roskam AJ, Roos E, Helmert U, Klumbiene J, et al., 2009. Association between educational level and vegetable use in nine European countries. Public Health Nutr 12:2174-82.

Ramis R, Vidal E, García-Pérez J, Lope V, Aragonés N, Pérez-Gómez B, et al., Study of non-Hodgkin's lymphoma mortality associated with industrial pollution in Spain, using Poisson models. BMC Public Health 9:26.

Rue H, Martino S, Chopin N, 2009. Approximate Bayesian inference for latent Gaussian models using integrated nested Laplace approximations (with discussion). J R Stat Soc Series B 71:319-92.

Ruiz-Ramos M, Escolar-Pujolar A, Sánchez Perea J, Garrucho Rivero G, 2006. Evolución de las desigualdades sociales en la mortalidad general de la ciudad de Sevilla (1994-2002). Gac Sanit 20:303-10.

Shibata A, Parsonnet J, 2006. Stomach cancer. In: Schottenfeld D, Fraumeni JF Jr, editors. Cancer Epidemiology and Prevention. New York: Oxford University Press, pp. 707-20.

Siemiatycki J, Richardson L, Straif K, Latreille B, Lakhani R, Campbell S, et al., 2004. Listing occupational carcinogens. Environ Health Perspect 112:1447-59.

Spanish Ministry of Agriculture and Food and Environment, 2019. SIGPAC. Available from: http://sigpac.mapa.es/fega/visor/. Accessed: 17 January 2019.

Spiegelhalter DJ, Best NG, Carlin BP, van der Linde A, 2002. Bayesian measures of model complexity and fit. J R Stat Soc Series B Stat Methodol 64:583-616.

The R-INLA project. Available from: http://www.r-inla.org/. Accessed: 22 November 2018.

Tolbert PE, 1997. Oils and cancer. Cancer Causes Control 8:386-405.

Tomatis L, Aitio A, Day N, 1990. Cancer: causes, occurrence and control. Lyon: IARC Scientific Publications. International Agency for Research on Cancer (IARC).

UNSCEAR, 2006. UNSCEAR 2006 Report: Volume I Annex A: Epidemiological Studies of Radiation and cancer. Available from: http://www.unscear.org/unscear/en/publications.html. Accessed: 10 December 2018.

Uthman OA, Jadidi E, Moradi T, 2013. Socioeconomic position and incidence of gastric cancer: a systematic review and meta-analysis. J Epidemiol Community Health 67:854-60.

Vromman V, Saegerman C, Pussemier L, Huyghebaert A, De Temmerman L, Pizzolon JC, et al., 2008. Cadmium in the food chain near non-ferrous metal production sites. Food Addit Contam Part A. Chem Anal Control Expo Risk Assess 25:293-301.

Wang M, Song H, ChenWQ, Lu C, Hu Q, Ren Z, et al., 2011. Cancer mortality in a Chinese population surrounding a multi-metal sulphide mine in Guangdong province: an ecologic study. BMC Public Health 11:319.

Wong CM, Tsang H, Lai HK, Thomas GN, Lam KB, Chan KP, et al., 2016. Cancer mortality risks from long-term exposure to ambient fine particle. Cancer Epidemiol Biomarkers Prev 25:839-45.