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Mortality due to lung, laryngeal and bladder cancer in towns lying in the vicinity of combustion installations

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Abstract

Background: Installations that burn fossil fuels to generate power may represent a health problem due to the toxic substances which they release into the environment.

Objectives: To investigate whether there might be excess mortality due to tumors of lung, larynx and bladder in the population residing near Spanish combustion installations included in the European Pollutant Emission Register.

Methods: Ecologic study designed to model sex-specific standardized mortality ratios for the above three tumors in Spanish towns, over the period 1994-2003. Population exposure to pollution was estimated on the basis of distance from town of residence to pollution source. Using mixed Poisson regression models, we analyzed: risk of dying from cancer in a 5-kilometer zone around installations that commenced operations before 1990; effect of type of fuel used; and risk gradient within a 50-kilometer radius of such installations.

Results: Excess mortality (relative risk, 95% confidence interval) was detected in the vicinity of pre-1990 installations for lung cancer (1.066, 1.041-1.091 in the overall population; 1.084, 1.057–1.111 in men), and laryngeal cancer among men (1.067, 0.992–1.148). Lung cancer displayed excess mortality for all types of fuel used, whereas in laryngeal and bladder cancer, the excess was associated with coal-fired industries. There was a risk gradient effect in the proximity of a number of installations.

Conclusions: Our results could support the hypothesis of an association between risk of lung, laryngeal and bladder cancer mortality and proximity to Spanish combustion installations.

Key Words: Lung cancer, laryngeal cancer, bladder cancer, combustion installations, coal, relative risk.

Introduction

Residential proximity to fossil-fuel-fired (i.e., coal, oil, and natural gas) power plants might imply exposure to a considerable number of toxic substances. Recent studies have linked these emissions to respiratory problems (Karavus et al. 2002), pregnancy complications (Tang et al. 2008), and premature mortality (Hermann et al. 2004) among populations residing in its vicinity . It has been known for some time that these industries release known or suspected carcinogens (Natusch 1978), including metals such as chromium and nickel, radionuclides such as radon and uranium, and polycyclic organic matter such as benzo[a]pyrene (Samet and Cohen 2006). Great interest therefore lies in assessing the possible relationship between these installations and cancer. Among the tumors that can be associated with the above carcinogens are those of lung (Siemiatycki et al. 2004), larynx (Maier et al. 1991) and bladder (Boffetta et al. 1997).

In Spain, lung cancer is the leading neoplasm among men, and was responsible for 16,891 male and 2,638 female deaths in 2006. Spain, moreover, has the highest male laryngeal cancer mortality and incidence in Europe (Lopez-Abente et al. 2006b), with 1,482 deaths in 2006; in contrast, it is the country with the lowest female mortality and incidence rates, with only 59 deaths in the same year. Lastly, Spain also has one of the highest bladder cancer mortality and incidence rates in Europe: in 2006, there were 3,742 male deaths and 784 female deaths attributable to this cause. Not only does the geographic mortality pattern plotted by these tumors display points in common (Lopez-Abente et al. 2006b), but some risk factors also coincide, namely: smoking (Levi 1999; Olshan 2006; Silverman et al. 2006); occupational exposure to asbestos, aromatic amines and polycyclic aromatic hydrocarbons (PAHs) (Boffetta et al. 1997; Clapp et al. 2005; Kogevinas et al. 2003; Maier et al. 1991; Mastrangelo et al. 1996; Silverman et al. 2006; Spitz et al. 2006); and pollutant emissions from industrial installations (Benedetti et al. 2001; Biggeri et al. 1996; Clapp et al. 2005; Lee et al. 2002; Maier et al. 1991).

The European Pollutant Emission Register (EPER) (EPER 2008), a public inventory of industries set up by the European Commission under the terms of Directive 96/61/EC, constitutes a valuable resource for monitoring industrial pollution, and enables the possible influence of such pollution on geographic mortality patterns to be examined (Garcia-Perez et al. 2007). One of the

EPER industrial groups covers combustion installations, providing data on pollutants released and the geographic coordinates of the respective facilities.

This paper sought to ascertain whether there was excess lung, larynx and bladder cancer mortality among the population residing in the vicinity of Spanish combustion installations which report their emissions to the EPER.

Materials and methods

We designed an ecologic study that modeled standardized mortality ratios (SMRs) for lung, laryngeal and bladder tumors in Spain's 8073 towns, over the period 1994-2003. The analysis was performed separately for each sex (except in the case of laryngeal cancer, which was only studied among men, due to its low frequency among women).

SMRs were calculated as the ratio of observed to expected deaths, and exact methods were used to establish the 95% confidence intervals (95%CI). Observed municipal mortality data were drawn from the records of the National Statistics for the study period, and corresponded to deaths coded as: malignant neoplasm of trachea, bronchus, and lung -codes 162 (International Classification of Diseases/ICD-9) and C33-C34 (ICD-10); malignant neoplasm of larynx –codes 161 (ICD-9) and C32 (ICD-10); and malignant neoplasm of bladder –codes 188 (ICD-9) and C67 (ICD-10). Expected cases were calculated by multiplying the specific rates for Spain as a whole, broken down by age group (18 groups), sex, and five-year period (1994-1998, 1999-2003), by the person-years for each town, broken down by the same strata. For calculation of person-years, the two five-year periods were considered, with data corresponding to the 1996 voters roll and 2001 census being taken as the estimator of the population.

Population exposure to industrial pollution was estimated by reference to the distance from the centroid of town of residence to the pollution source. Data on industries were obtained from the EPER-Spain. We selected 57 combustion installations>50 MW (IPPC category 1.1) that reported their releases to air in 2001, along with the previously validated geographic coordinates of their respective locations (Garcia-Perez et al. 2008). Data on the date of commencement of industrial activity and type of fuel used were obtained from the official websites of the electric utility companies.

Initially, we conducted an exploratory "near vs. far" analysis to estimate the relative risks (RRs) of towns situated at a distance of less than 5 kilometers from combustion installations. The exposure variable was coded as a "dummy" with three levels:

1) exposed group ("near"): towns having their municipal centroid at a distance of less than 5 kilometers from a combustion installation;

2) intermediate group: towns at ≤5 kilometers from any industrial installation other than combustion; and,

3) unexposed group ("far"): towns having no industry within 5 kilometers of their municipal centroid (reference level).

RRs and their 95%CI were estimated on the basis of a Poisson regression model (Breslow and Day 1987), using expected cases as offset for the total population, men, and women, using Spanish rates as reference. Estimations were adjusted for the following standardized sociodemographic indicators, chosen for their availability at a municipal level: population size; percentages of illiteracy, farmers and unemployed; average persons per home according to the 1991 census; and, mean income as a measure of income level (Ayuso Orejana et al. 1993). In addition, mixed models were fitted (Gelman and Hill 2007), including province as a random effects term, to enable geographic variability to be taken into account and unexposed towns belonging to the same geographic setting to be considered as the reference level, something that is justified by the geographic differences observed in mortality attributable to these tumors (Lopez-Abente et al. 2006b; Lopez-Abente et al. 2006a).

In order to take the minimum tumor latency periods into account, the analysis was replicated, by confining the above model to industries that entered into operation prior to 1990. Furthermore, since there are areas where towns lie close to several industrial installations, including combustion, we conducted an analysis using "isolated" combustion installations, without any other industry nearby that might bias the risk estimator. Similarly, in order to obtain stratification of the risk according to the type of fuel used by this latter group of "isolated" installations, we created a variable of interest coded as a "dummy" with various levels:

1) group 1: towns having their municipal centroid at a distance of less than 5 kilometers from any combustion installation that solely used coal as fuel;

2) group 2: towns at ≤5 kilometers from any combustion installation that used fuel oil/gas oil/natural gas as fuel;

3) group 3: towns at ≤5 kilometers from any combustion installation that used coal in combination with other fuels;

4) intermediate group: towns at ≤5 kilometers from any industry other than combustion; and,

5) unexposed group: towns having no EPER-registered industry within a radius of 5 kilometers from the municipal centroid (reference level).

Finally, since the characteristics of the respective combustion installations vary, each combustion industry that commenced operations prior to 1990 was analyzed individually, and the analysis was restricted to an area of 50 kilometers surrounding each such installation, so as to have a local comparison group. To take into account the problem of multiple comparisons p-values were also suitably adjusted by controlling for the expected proportion of false positives (False Discovery Rate) as proposed by Benjamini (Benjamini and Hochberg 1995; Benjamini and Yekutieli 2001). The risk gradient in the vicinity of each facility was likewise studied, with distance from town to installation as an explanatory variable, categorized in concentric rings (0-5, 5-10, 10-20, 20-30, and 30-50 kilometers as reference). This was included in all models both as a categoric and as a continuous variable. Thus, it was possible, for the former, to estimate the effect for the respective distances and, for the latter, to ascertain the existence of radial effects (rise in RR with increasing proximity to an installation) and, by applying the likelihood ratio test, the statistical significance of such distance-related effects. RR estimates were adjusted for the abovementioned sociodemographic variables, and towns that had some industry other than combustion within a radius of 5 kilometers of the municipal centroid were excluded.

Results

From 1994 to 2003 there were 172,142 deaths due to lung cancer, 18,175 due to laryngeal cancer, and 38,396 due to bladder cancer in both sexes.

Figure 1 depicts the geographic distribution of the 57 combustion installations studied, along with their EPER codes and year of commencement of operations. In 2001, Spanish combustion installations reported releasing to air: 2,400 metric tons (mt) of CO; 94,200,000 mt of CO_2; 1,040 mt of N_2O; 291,000 mt of NO_2; 938,000 mt of SO_2; 2.08 mt of arsenic; 1.82 mt of cadmium; 5.87 mt of chrome; 4.61 mt of lead; 66.4 mt of nickel; 343 mt of chlorine; 831 mt of fluoride; 0.07 mt of PAHs; 29,300 mt of PM_{10}; and 0.13 kilograms of dioxins and furans.

Table 1 shows observed cases and SMRs of lung, laryngeal and bladder cancer for 85 Spanish towns, grouped by province, having one or more combustion installations at a distance of less than 5 kilometers. The highest lung cancer values were registered for Cadiz and Ciudad Real in men, and for Palencia, the Balearic Isles and Las Palmas in women. In laryngeal cancer Palencia and Burgos registered the highest values among men. Lastly, the highest bladder cancer values were registered by Burgos for men, and by Toledo, Corunna and Zaragoza for women.

Shown in Table 2 are observed cases in towns with combustion installations at less than 5 kilometers, plus the RRs and 95%CI estimated by mixed Poisson regression models for the three tumors. In all the analyses there was a significant excess risk of lung cancer mortality in towns near such installations, both overall and among men, whilst in women the risk estimators obtained were less than unity. The results also suggest a greater risk of laryngeal cancer among men associated with proximity to combustion facilities, though the association ceased to be statistically significant when the analysis was confined to plants that had been operating the longest. Finally, while analysis of all facilities indicated significant excess mortality for bladder cancer among men, none of the estimators in pre-1990 facilities yielded significant excess risks for this tumor.

Table 3 shows the RRs, estimated by means of mixed Poisson regression models, for all three tumors in towns having an "isolated" combustion installation at less than 5 kilometers, according to the respective type of fuel used. For lung cancer, significant excess risk displayed a homogeneous distribution in each group in the overall population and among men, though it was more marked in industries that used coal+other fuels. In tumors of larynx and bladder, the risk was concentrated in the vicinity of installations that solely used coal. This analysis highlights a result that was concealed in the analysis of Table 2.

Table 4 shows the RRs for the area immediately surrounding (≤5 kilometers) from combustion facilities that commenced operations before 1990, and for concentric rings spaced at decreasing distances within a 50-kilometer radius of the installation. Data are listed for installations having a statistically significant excess risk in the "near vs. far" analysis and/or for those in which the test for trend proved to be significant in the risk gradient analysis, for one or more tumors studied. With respect to the first analysis, our results revealed excess risks of lung cancer in the proximity of facilities ‘1984' (Santa Cruz de Tenerife), ‘3518' (Corunna), ‘3588' (Asturias) and ‘3589' (Murcia). For laryngeal cancer in men, significant excess risk only appeared in the vicinity of industry ‘3588'. Finally, significant excess risks were found for bladder cancer near facilities ‘3381' (Leon), ‘3536' (Corunna), and `3588'. On analyzing the risk gradient, facility ‘3589' also displayed a significant effect for lung cancer among men, facility ‘2116' (Barcelona) showed elevated risks for laryngeal cancer in each band analyzed and facility ‘3536' also registered a significant effect for bladder cancer.

It has been estimated that, on studying the facilities on a one-by-one basis for α=0.05 random chance would account for 1 association (number of comparisons x percentage of statistically significant RR>1 expected under the null hypothesis) for each of the analyses by sex and by tumor, which is a number lower than that of the associations observed.

Analyses of the previous table were performed separately for each of the pre-1990 facilities, as were their respective corrections by means of multiple comparisons (see Supplemental Material).

Figure 2 depicts the geographic location of pre-1990 combustion installations having an excess risk of mortality in their environs for the tumors studied. Special mention should be made of facility ‘3536', which had fairly consistent corrected p-values for the overall population and for women. Accordingly, the p-values associated with Poisson regression model cannot be simply explained by random chance.

Figure 3 plots the geographic position of all pre-1990 combustion installations that had a statistically significant test for trend in the risk gradient analysis of mortality due to the three tumors.

Discussion

This is one of the first studies to use EPER-based information to explore the effects on cancer mortality of pollution emitted by a specific industrial sector. Our results indicate excess risk of dying of lung and laryngeal tumors among males in the proximity of Spanish combustion installations, for the industry as a whole and after elimination of the newest plants, whose possible influence is more debatable if minimum tumor latency periods are borne in mind. In the case of lung cancer, significant excess risks were found for facilities that used any type of fuel. In the case of laryngeal cancer, however, excess risks were limited to facilities that exclusively used coal as fuel; and, somewhat curiously, elevated risks of dying from bladder cancer were observed for these same plants.

In the individualized analysis, it must be stressed that, despite the lower statistical power and use of correction methods to minimize the possibility of spurious results, there were some industries which displayed excess risk in both the "near vs. far" and risk gradient analyses, for all three tumors studied, lung and bladder in particular.

Environmental and industrial pollution has a proven influence on lung cancer incidence and mortality (Benedetti et al. 2001; Biggeri et al. 1996; Enomoto et al. 2008), and some bladder cancer mortality excess risks could also be related to industrial emissions (Castano-Vinyals et al. 2008; Lopez-Abente et al. 2006a). While occupational studies serve to formulate hypotheses and guide research on many carcinogenic risk factors (Kogevinas et al. 2003; Lee et al. 2002; Maier et al. 1991; Mastrangelo et al. 1996), the association between industrial emissions and lung, laryngeal and bladder tumors in the population can also be studied by means of other types of designs, such as that presented here. It is likely, however, that the effect on the population by isolated environmental exposures deriving from specific industries may be small, thereby rendering detection of possible existing associations difficult. One advantage of the design chosen is precisely its high power, resulting from the inclusion of a greater number of subjects. Another advantage is that the analysis can be repeated in future with the purpose of monitoring and controlling the effects of environmental pollution.

This study also has limitations. Working with small areas means that the data evince wide random variability, which particularly affects women at these tumor sites, though a small-area study does minimize any possible ecological bias associated with the nature of the study *per se*.

One exposure that could confound the results is smoking, a recognized risk factor in the tumors studied but for which there is no information at a municipal level. We sought to minimize this problem by performing a separate analysis by sex in lung and bladder tumors, and adjusting for sociodemographic variables that could, in themselves, define subgroups with different proportions of smokers. Nevertheless, this adjustment was only indirect and partial, and there is thus a high likelihood of our results having been influenced by tobacco-related factors, as the fact that smoking habits are often strongly associated with socioeconomic factors, which may be associated with the distance from industrial facilities, due to the tendency of poor communities to live in polluted areas (Parodi et al. 2005). Nevertheless, we have adjusted for sociodemographic variables that take into account this concept. Occupational exposures may also have influenced the difference between men and women, something impossible to control for due to lack of data. Furthermore, risks associated with smoking habit could be magnified by interaction with industrial emissions ([Anonymous].1983).

Other possible biases that could be affecting our study are the migration bias and the tendency of occupationally exposed workers to live near their workplace, that might partly account for some trend in risk observed in males but not in females.

In order to reduce any possible biases deriving from confounding variables not considered in the study, mixed models were fitted with province as the random effects term, something that constitutes a more conservative option. A further point to be borne in mind is that some installations for which statistically significant RRs were observed, are situated in regions with numerous industries emitting into the air, which may pose a problem when it comes to interpreting the results. Accordingly, only "isolated" industries were analyzed, without any neighboring installation that might bias the estimation of risk. The choice of province as a random effects term, as well as limiting the analysis to a radius of 50 kilometers, partly solves this problem.

Assuming an isotropic model, this study uses distance to the pollutant source as a proxy of exposure, which in turn introduces a misclassification problem because real exposure is critically dependent on prevailing winds, geographic accidents, and releases into aquifers. Another possible bias in attribution of exposure stems from using centroids as coordinates for positioning a town's entire population, when, in reality, the population may be considerably dispersed. However, these problems would, at all events, affect the analysis by restricting the ability to find positive results, rather than invalidating the associations observed.

Another critical decision is the choice of radius in risk analysis of towns situated "near" pollutant foci. Our choice of a 5-kilometer ring encircling combustion installations coincides with the distance used by other authors (Karavus et al. 2002; Ranft et al. 2003) and is in line with the characteristics of these plants, which possess tall smokestacks so that the pollution released has a large radius of spread.

One aspect borne in mind in the analyses is that of multiple comparisons. We provide p-adjusted values, though from an epidemiologic point of view, we prefer to discuss the resulting RRs in the light of a series of factors, namely, the magnitude of risk *per se*, the consistency of the associations observed, and biologic plausibility.

Of all the industrial groups registered with the EPER-Spain, combustion installations are the main emitters to air of SO_2, PM_{10}, dioxins and furans, NO_2, CO, nickel, fluoride and arsenic. In other substances, such as cadmium, chrome and N_2O, they are the second leading emission group. Moreover, these industries are the leading industrial source of direct releases of lead into water, and the second leading industrial source of releases of cadmium, chrome and PAHs into water.

Although the industries analyzed in this study reported pollution data in 2001, we took the date on which combustion facilities commenced operations into account for analysis purposes (Figure 1); a large proportion began operating between the 1960s and 1980s, thereby making it possible for the surrounding populations to be exposed to their emissions for long periods of time, which is in line with the latency periods described for solid tumors.

It is necessary to underscore the fact that the presence of combustion installations is of enormous social interest from a public health point of view. Aside from these industries being one of the major sources responsible for air pollution and the greenhouse effect, some of the pollutants they release are, according to the International Agency for Research on Cancer (IARC): known carcinogens in humans, e.g., arsenic, cadmium, chrome and dioxins; or possible carcinogens, e.g., lead, nickel and furans (IARC 2008). Furthermore, emissions from coal-fired installations contain radioactive elements, principally uranium and thorium, as well as by-products deriving from the disintegration of these isotopes, such as radium, radon, polonium, bismuth, and lead (Gabbard 1993; Samet and Cohen 2006). In this regard, McBride et al. (1978) concluded that “Americans living near coal-fired power plants are exposed to higher radiation doses than those living near nuclear power plants that meet government regulations.” Comparing nuclear powered with coal-fired facilities, some reports reveal that the population effective dose equivalent from coal plants is 100 times that from nuclear plants (NCRP 1987). Other author states that the fact that coal-fired power plants throughout the world are the major sources of radioactive materials released to the environment has several implications. It suggests that coal combustion is more hazardous to health than nuclear power. Furthermore, radioactive elements released in coal ash and exhaust produced by coal combustion contain fissionable fuels and much larger quantities of fertile materials than can be bred into fuels by absorption of neutrons (Gabbard 1993). Coal ash is primarily composed of oxides of silicon, aluminum, calcium, magnesium, titanium, sodium, potassium, arsenic, mercury and sulfur, plus small quantities of uranium and thorium. It is important to stress that waste from fossil-fuel combustion implies potential risks to human health which may be compared to nuclear waste (Christensen et al. 1992).

There are some studies that have examined and characterized emissions from combustion installations ([Anonymous].1983; Aytekin et al. 2007; Ito et al. 2006), and others that have analyzed exposure to arsenic from coal-burning power plants (Pesch et al. 2002; Ranft et al. 2003). In addition, some authors have assessed the impact on health (Lopez et al. 2005; Mukhopadhyay and Forssell 2005) and the environment (Hao et al. 2007) of emissions from combustion installations. Moreover, a study covering worker cohorts from the Italian power utility, ENEL, reported that a general increase in SMRs suggested an association with occupational exposure to carcinogenic substances and lung cancer (Crosignani et al. 1995).

One of the compounds with highest emissions in these industries is SO_2, the inhalation of which can cause serious respiratory problems. Although the IARC has recognized it as being a noncarcinogen in humans, its carcinogenicity has been demonstrated in a number of animal models (Ohyama et al. 1999). In addition, the IARC has classified strong sulfuric acid aerosol (produced as secondary pollutants resulting from the combustion of fossil fuels) as a known human carcinogen, based on epidemiologic findings of increased lung and laryngeal cancer in heavily exposed occupational groups (Samet and Cohen 2006). Epidemiologic studies have not only reported that occupational exposure to SO_2 in the paper, pulp and board industry could increase the risk of lung cancer (Lee et al. 2002), but have also described an increase in the frequency of chromosomal aberrations among groups of workers exposed to SO_2 (Meng and Zhang 1990) and possible interactions that would raise the risk of lung damage in the presence of PAHs (Lee et al. 2002; Natusch 1978). This is important, bearing in mind that combustion installations also emit PAHs. In reports on emissions to air by large-sized combustion plants that use fossil fuels in Europe, 18 Spanish industries are listed among the 100 top-ranked SO_2-emitting installations in the 25 European Union (EU) Member States, headed by facility ‘3536' (Barret 2004).

One of the most noteworthy results of our study is the elevated bladder cancer mortality observed, particularly among women, in the proximity of facility ‘3536'. This industry ranks first in the classification of the 200 most harmful combustion installations for EU citizens, in terms of reduced life expectancy and premature deaths per annum (Holland 2006). Some authors have analyzed the fate of its industrial emissions during the coal-combustion process (Otero-Rey et al. 2003), with high concentrations of noxious substances, such as arsenic, mercury or selenium, being detected.

Conclusion

The results of this study could support the hypothesis that residence in towns in the vicinity of combustion installations in Spain is associated with excess risk in lung, laryngeal and bladder cancer mortality, since the effect estimators obtained are statistically significant, not merely for analysis of the industry as a whole, but also for individualized analysis of specific facilities. Furthermore, increased risk with proximity was observed in the environs of a number of installations. Risk levels could be linked to the type of fuel used. Moreover, the absence of certain relevant information and the study's ecologic nature hinders interpretation of the results of association in terms of cause and effect.

The study of cancer mortality in areas surrounding pollutant foci is a useful tool for environmental surveillance, and serves to highlight areas of interest susceptible to being investigated by "*ad hoc*" studies and more accurate ways of assessing exposure. Hence, despite present limitations, recognition is due to the advance represented by publication of the EPER.

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Figure legends

Figure 1: Geographic distribution of Spanish combustion installations.

Figure 2: Geographic location of pre-1990 combustion installations with statistically significant excess mortality in their vicinity. Tumors of lung, larynx and bladder.

Figure 3: Geographic location of pre-1990 combustion installations with statistically significant test for trend in the risk gradient analysis of mortality. Tumors of lung, larynx and bladder.

Table 1: Provinces with towns at a distance of less than 5 kilometers from combustion installations. Observed cases, SMRs and 95%CI. Tumors of lung, larynx and bladder.

			LUNG						LARYNX			BLADDER					
PROVINCE	T[a]	INHAB[b]	MEN			WOMEN			MEN			MEN			WOMEN		
			Obs[c]	SMR	95%CI	Obs[c]	SMR	95%CI	Obs[c]	SMR	95%CI	Obs[c]	SMR	95%CI	Obs[c]	SMR	95%CI
Alava	4	215799	643	0.82	0.76-0.89	90	1.02	0.82-1.25	93	1.02	0.82-1.25	166	1.12	0.95-1.30	51	1.59	1.18-2.09
Albacete	1	22163	92	1.10	0.89-1.35	7	0.77	0.31-1.58	10	1.06	0.51-1.96	15	0.91	0.51-1.50	3	0.91	0.19-2.66
Almeria	1	6212	19	1.13	0.68-1.77	2	1.18	0.14-4.25	3	1.52	0.31-4.38	1	0.34	0.01-1.86	0	--	--
Asturias	4	107029	594	1.27	1.17-1.37	53	0.95	0.71-1.24	76	1.45	1.14-1.81	115	1.25	1.03-1.50	17	0.79	0.46-1.27
Balearic Isles	4	67337	266	1.15	1.02-1.30	38	1.46	1.03-2.00	24	0.90	0.58-1.34	55	1.21	0.91-1.57	11	1.17	0.58-2.09
Barcelona	12	853007	3623	1.20	1.16-1.24	297	0.88	0.78-0.99	354	1.00	0.90-1.11	582	1.05	0.96-1.13	123	1.06	0.88-1.26
Burgos	1	35506	134	0.86	0.72-1.02	20	1.21	0.74-1.86	33	1.89	1.30-2.65	59	1.87	1.42-2.41	9	1.43	0.65-2.71
Cadiz	2	81460	347	1.37	1.23-1.52	24	0.81	0.52-1.20	46	1.56	1.14-2.07	57	1.21	0.92-1.57	8	0.77	0.33-1.52
Cantabria	2	61854	250	1.04	0.92-1.18	29	1.03	0.69-1.48	43	1.57	1.14-2.11	69	1.43	1.11-1.81	7	0.65	0.26-1.35
Castellon	1	135732	562	1.12	1.03-1.22	68	1.19	0.92-1.51	68	1.18	0.92-1.49	112	1.13	0.93-1.36	23	1.12	0.71-1.68
Ciudad Real	2	51578	266	1.37	1.21-1.54	15	0.69	0.39-1.14	19	0.86	0.52-1.34	41	1.07	0.77-1.46	5	0.63	0.21-1.48
Cordoba	1	628	2	0.56	0.07-2.01	0	--	--	0	--	--	0	--	--	0	--	--
Granada	9	348642	1168	1.03	0.97-1.09	136	0.96	0.81-1.14	164	1.26	1.07-1.47	248	1.13	0.99-1.28	61	1.23	0.94-1.58
Guipuzcoa	4	71588	301	1.14	1.02-1.28	27	0.90	0.59-1.30	48	1.57	1.15-2.07	65	1.33	1.03-1.70	11	1.03	0.51-1.84
Huelva	5	177908	676	1.29	1.20-1.40	52	0.83	0.62-1.08	67	1.10	0.85-1.39	133	1.39	1.16-1.65	27	1.27	0.84-1.84
Corunna	2	33561	128	1.08	0.90-1.28	11	0.88	0.44-1.57	14	1.02	0.55-1.70	26	1.12	0.73-1.64	11	2.48	1.25-4.47
Las Palmas	2	57121	150	1.15	0.97-1.34	21	1.47	0.91-2.24	22	1.40	0.88-2.12	36	1.55	1.09-2.15	6	1.42	0.52-3.11
Leon	4	10489	40	0.86	0.61-1.17	1	0.19	0.00-1.07	6	1.14	0.42-2.46	6	0.63	0.23-1.37	1	0.49	0.01-2.79
Murcia	1	170485	718	1.20	1.11-1.29	77	1.13	0.89-1.42	69	1.00	0.78-1.27	128	1.11	0.93-1.32	36	1.51	1.06-2.09
Palencia	2	10756	33	0.80	0.55-1.12	10	2.19	1.04-4.00	12	2.56	1.32-4.46	4	0.48	0.13-1.23	1	0.58	0.01-3.28
Sta. Cruz de Tenerife	5	243303	841	1.12	1.05-1.20	137	1.51	1.27-1.78	86	0.99	0.79-1.22	204	1.40	1.22-1.61	43	1.36	0.98-1.83
Tarragona	1	4242	14	0.62	0.34-1.04	1	0.48	0.01-2.65	2	0.77	0.09-2.78	2	0.52	0.06-1.90	1	1.56	0.04-9.29
Teruel	3	6189	24	0.96	0.61-1.42	2	0.78	0.09-2.78	1	0.35	0.01-1.92	3	0.60	0.12-1.75	0	--	--
Toledo	1	1573	8	1.08	0.47-2.13	1	1.37	0.04-7.96	1	1.22	0.03-6.96	0	--	--	1	3.29	0.08-18.57
Vizcaya	8	258113	1006	1.06	0.99-1.12	130	1.16	0.97-1.38	139	1.26	1.06-1.49	195	1.09	0.94-1.25	33	0.82	0.57-1.15
Zaragoza	3	3010	16	0.80	0.46-1.31	2	1.02	0.12-3.61	2	0.92	0.11-3.28	4	0.85	0.23-2.18	2	2.35	0.27-8.03

[a]Number of towns. [b]Number of inhabitants. [c]Observed.

Table 2: Observed cases, RR, 95%CI, of towns at a distance of less than 5 kilometers from combustion installations, estimated using mixed Poisson regression models. Tumors of lung, larynx and bladder.

	INSTALLATIONS COMBUSTION (ALL)			PRE-1990 INSTALLATIONS			PRE-1990 INSTALLATIONS (ISOLATED)		
	Observed	RR	95%CI	Observed	RR	95%CI	Observed	RR	95%CI
				LUNG CANCER					
TOTAL	13172	1.070	1.048-1.093	9501	1.066	1.041-1.091	3134	1.121	1.080-1.164
MEN	11921	1.087	1.063-1.112	8675	1.084	1.057-1.111	2859	1.144	1.100-1.189
WOMEN	1251	0.925	0.866-0.989	826	0.912	0.843-0.985	275	0.932	0.823-1.055
				LARYNGEAL CANCER					
MEN	1402	1.077	1.010-1.149	990	1.067	0.992-1.148	323	1.121	0.998-1.258
				BLADDER CANCER					
TOTAL	2817	1.045	1.000-1.093	1879	1.006	0.955-1.060	632	1.050	0.967-1.141
MEN	2326	1.055	1.004-1.108	1568	1.017	0.961-1.076	526	1.062	0.970-1.162
WOMEN	491	1.026	0.926-1.138	311	0.958	0.847-1.084	106	0.998	0.818-1.216

Table 3: Observed cases, RR, 95%CI, of towns at a distance of less than 5 kilometers from "isolated" combustion installations, estimated using mixed Poisson regression models, according to type of fuel used. Tumors of lung, larynx and bladder.

	TOTAL			MEN			WOMEN		
	Observed	RR	95%CI	Observed	RR	95%CI	Observed	RR	95%CI
				LUNG CANCER					
GROUP1[a]	809	1.096	1.019-1.177	743	1.128	1.046-1.216	66	0.826	0.644-1.059
GROUP2[b]	1997	1.110	1.059-1.162	1812	1.127	1.073-1.183	185	0.969	0.833-1.126
GROUP3[c]	328	1.279	1.140-1.435	304	1.308	1.160-1.474	24	0.981	0.647-1.488
				LARYNGEAL CANCER					
GROUP1[a]				117	1.461	1.207-1.770			
GROUP2[b]				184	1.004	0.863-1.168			
GROUP3[c]				22	0.875	0.566-1.352			
				BLADDER CANCER					
GROUP1[a]	181	1.180	1.013-1.373	153	1.218	1.033-1.438	28	0.971	0.664-1.420
GROUP2[b]	401	1.024	0.924-1.135	329	1.022	0.912-1.145	72	1.059	0.832-1.348
GROUP3[c]	50	0.874	0.655-1.165	44	0.911	0.670-1.239	6	0.628	0.278-1.420

[a] Combustion installations that solely use coal as fuel. [b] Combustion installations that use fuel oil/gas oil/natural gas as fuel. [c] Combustion installations that use a combination of coal+other fuels.

Table 4: Observed cases, RR, 95%CI, of towns at a distance of less than 5 kilometers from pre-1990 combustion installations with statistically significant excess risk in the "near vs. far" analysis and/or risk gradient analysis. Tumors of lung, larynx and bladder.

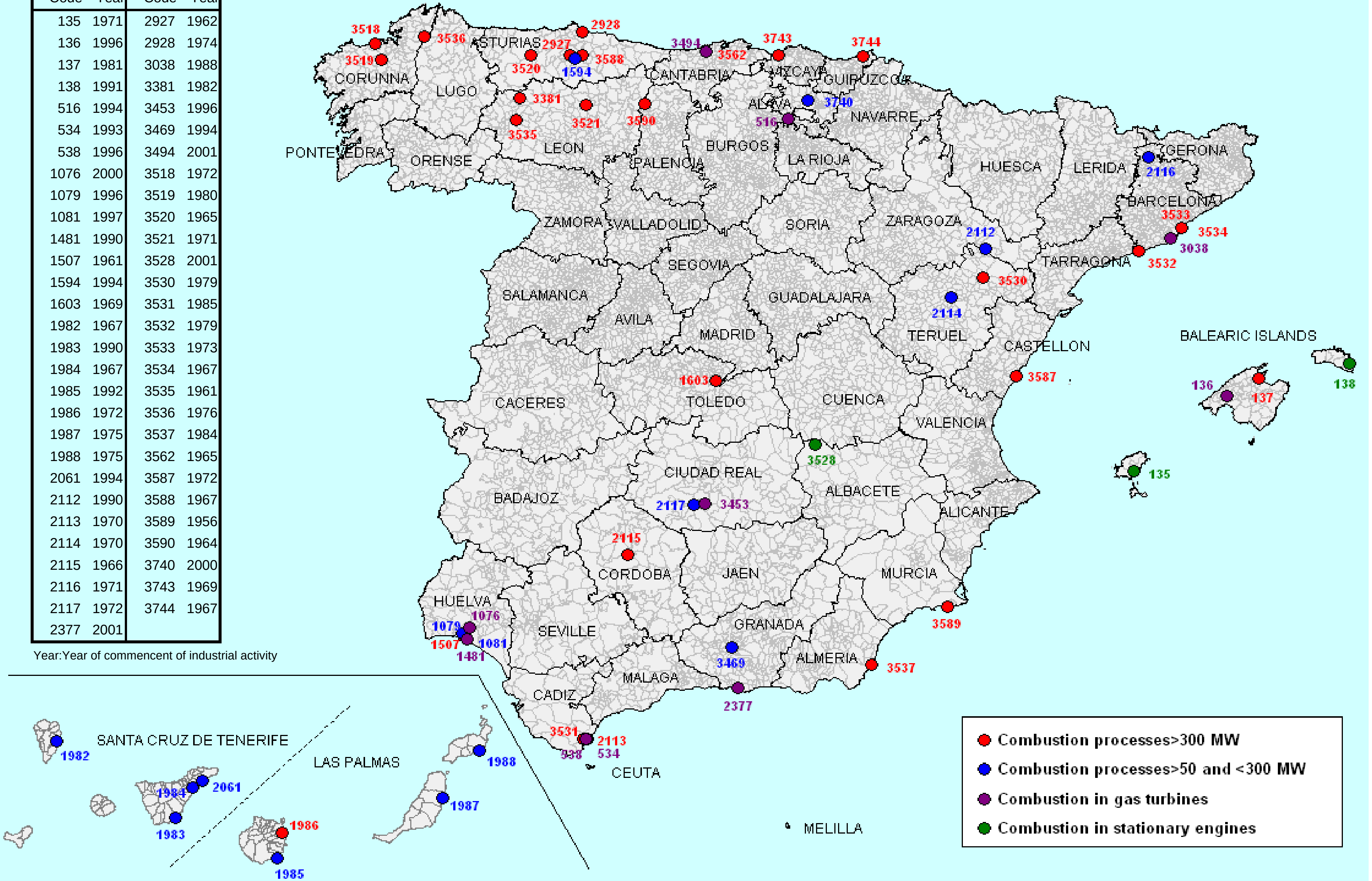
	NEAR VS FAR ANALYSIS		RISK GRADIENT ANALYSIS									
			[0-5 Km)		[5-10 Km)		[10-20 Km)		[20-30 Km)		[30-50 Km]^a	
EPER CODE	RR	95%CI	Observed	RR	Observed	RR	Observed	RR	Observed	RR	Observed	p trend
					LUNG							
1603												
TOTAL	1.235	0.630-2.422	9	1.25	20	0.99	365	1.18	187	0.98	1842	0.02
MEN	1.237	0.606-2.525	8	1.29	19	1.04	331	1.20	174	1.02	1656	0.01
WOMEN	1.239	0.164-9.378	1	1.01	1	0.53	34	1.10	13	0.65	186	0.93
1984												
TOTAL	1.060	0.765-1.470	44	1.18	85	0.93	790	1.16	136	1.17	415	0.37
MEN	0.867	0.594-1.264	32	1.00	76	0.99	664	1.19	120	1.27	343	0.49
WOMEN	2.557	1.303-5.018	12	2.28	9	0.62	126	1.01	16	0.72	72	0.61
1986												
TOTAL	--	--	0	--	1356	1.30	457	1.26	198	1.13	42	0.20
MEN	--	--	0	--	1168	1.44	399	1.35	167	1.12	34	0.05
WOMEN	--	--	0	--	188	0.76	58	0.95	31	1.18	8	0.15
2113												
TOTAL	1.115	0.945-1.315	371	1.16	0	--	12	1.04	208	1.31	657	0.06
MEN	1.178	0.992-1.399	347	1.23	0	--	12	1.10	193	1.33	600	0.01
WOMEN	0.612	0.331-1.132	24	0.65	0	--	0	0.00	15	1.16	57	0.13
2117												
TOTAL	0.976	0.748-1.275	281	1.24	101	1.84	15	1.28	29	0.90	440	0.03
MEN	1.004	0.762-1.323	266	1.34	97	2.04	13	1.16	26	0.87	387	0.01
WOMEN	0.814	0.273-2.430	15	0.46	4	0.58	2	7.22	3	1.63	53	0.77
3038												
TOTAL	1.052	0.990-1.119	2194	1.07	17	1.70	8662	1.11	1341	1.02	1404	0.03
MEN	1.057	0.991-1.127	2024	1.07	12	1.37	7460	1.09	1217	1.02	1258	0.06
WOMEN	1.013	0.820-1.251	170	1.08	5	4.10	1202	1.17	124	1.02	146	0.21
3518												
TOTAL	1.254	1.000-1.573	88	1.30	0	--	304	1.01	1064	1.09	462	0.16
MEN	1.258	0.993-1.593	81	1.35	0	--	279	1.04	943	1.12	410	0.12
WOMEN	1.185	0.537-2.615	7	0.95	0	--	25	0.71	121	0.90	52	0.70
3533												
TOTAL	1.065	0.991-1.146	1688	1.05	8762	1.05	278	0.99	1442	0.96	1039	0.01
MEN	1.068	0.990-1.152	1563	1.05	7550	1.04	249	1.00	1307	0.96	922	0.02
WOMEN	1.023	0.795-1.317	125	1.08	1212	1.12	29	0.93	135	0.99	117	0.34
3534												
TOTAL	1.064	0.990-1.145	1688	1.05	8762	1.06	254	0.99	1395	0.96	1069	0.01
MEN	1.067	0.989-1.151	1563	1.04	7550	1.04	228	1.00	1262	0.95	949	0.03
WOMEN	1.024	0.795-1.318	125	1.16	1212	1.13	26	0.93	133	1.05	120	0.30
3537												
TOTAL	1.499	0.879-2.557	21	1.73	0	--	24	1.09	169	1.32	181	0.01
MEN	1.550	0.885-2.715	19	1.85	0	--	19	0.91	162	1.38	167	0.01
WOMEN	1.276	0.209-7.812	2	0.50	0	--	5	21.04	7	0.39	14	0.90

NEAR VS FAR ANALYSIS			RISK GRADIENT ANALYSIS									
			[0-5 Km)		[5-10 Km)		[10-20 Km)		[20-30 Km)		[30-50 Km]^a	
EPER CODE	RR	95%CI	Observed	RR	Observed	RR	Observed	RR	Observed	RR	Observed	p trend
						LUNG						
3588												
TOTAL	1.177	1.009-1.373	304	1.09	124	0.80	1627	0.96	206	0.92	629	0.91
MEN	1.239	1.054-1.455	284	1.15	114	0.82	1439	0.94	179	0.89	562	0.66
WOMEN	0.688	0.400-1.182	20	0.64	10	0.64	188	1.13	27	1.17	67	0.30
3589												
TOTAL	1.325	1.066-1.648	795	1.22	54	0.27	55	1.13	113	2.14	1417	0.09
MEN	1.388	1.105-1.744	718	1.29	48	0.24	53	1.25	106	2.39	1281	0.03
WOMEN	0.721	0.301-1.725	77	1.6E+03	6	2.6E+22	2	0.00	7	0.00	136	0.19
						LARYNX (MEN)						
2116	1.546	0.191-12.475	1	2.47	9	1.84	5	1.95	20	1.61	68	0.05
3588	1.676	1.089-2.579	47	1.02	14	0.56	178	0.77	27	1.10	75	0.80
						BLADDER						
3381												
TOTAL	4.565	1.228-16.964	3	3.59	1	0.56	10	0.83	23	1.00	63	0.73
MEN	5.813	1.513-22.327	3	3.88	1	0.61	7	0.55	19	0.73	57	0.91
WOMEN	0	0-Inf	0	0.00	0	0.00	3	9.17	4	7.76	6	0.32
3536												
TOTAL	2.423	1.476-3.976	22	2.45	0	--	14	0.72	100	1.03	349	0.01
MEN	1.852	1.033-3.321	15	1.85	0	--	12	0.71	80	1.01	290	0.21
WOMEN	6.840	2.532-18.477	7	7.71	0	--	2	0.74	20	1.10	59	0.00
3588												
TOTAL	1.459	1.034-2.059	64	1.29	24	0.88	294	0.93	67	1.49	123	0.11
MEN	1.503	1.034-2.186	55	1.21	19	0.83	216	0.80	54	1.48	102	0.14
WOMEN	1.413	0.581-3.437	9	1.70	5	1.09	78	1.55	13	1.56	21	0.41

[a] Reference group in the risk gradient analysis.

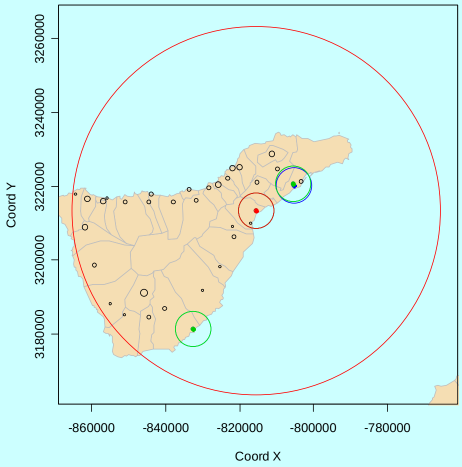
EPER Code	Year	EPER Code	Year
135	1971	2927	1962
136	1996	2928	1974
137	1981	3038	1988
138	1991	3381	1982
516	1994	3453	1996
534	1993	3469	1994
538	1996	3494	2001
1076	2000	3518	1972
1079	1996	3519	1980
1081	1997	3520	1965
1481	1990	3521	1971
1507	1961	3528	2001
1594	1994	3530	1979
1603	1969	3531	1985
1982	1967	3532	1979
1983	1990	3533	1973
1984	1967	3534	1967
1985	1992	3535	1961
1986	1972	3536	1976
1987	1975	3537	1984
1988	1975	3562	1965
2061	1994	3587	1972
2112	1990	3588	1967
2113	1970	3589	1956
2114	1970	3590	1964
2115	1966	3740	2000
2116	1971	3743	1969
2117	1972	3744	1967
2377	2001		

Year:Year of commencent of industrial activity



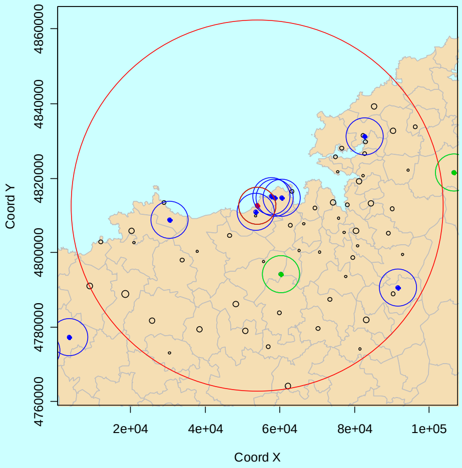
LUNG CANCER

Facility 1984
(CANDELARIA - Santa Cruz de Tenerife)



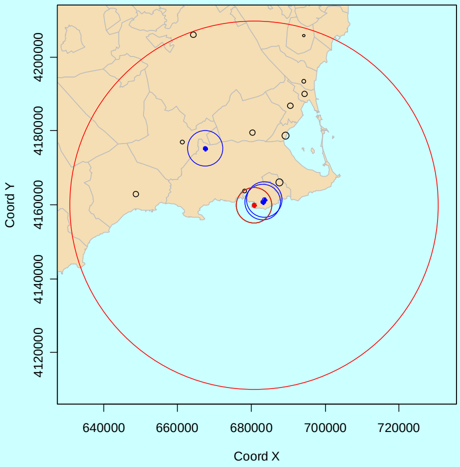
p(women)=0.00640 pBH(women)=0.18560

Facility 3518
(ARTEIXO -Corunna)



p(total)=0.04980 pBH(total)=0.32944

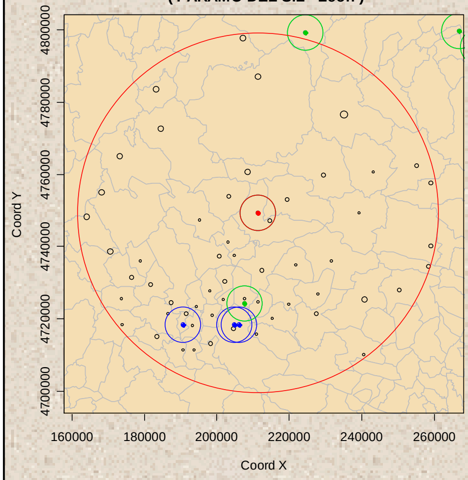
Facility 3589
(CARTAGENA - Murcia)



p(total)=0.01140 pBH(total)=0.32944
p(men)=0.00490 pBH(men)=0.13344

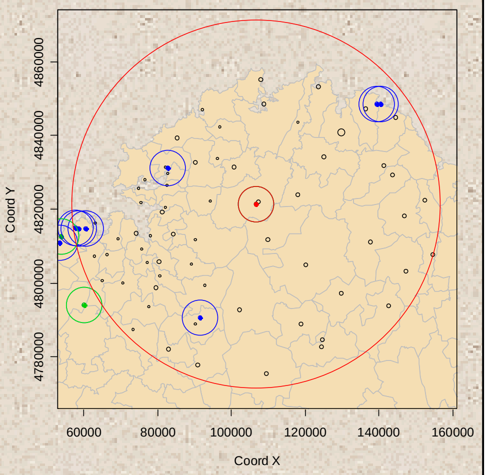
BLADDER CANCER

Facility 3381
(PARAMO DEL SIL - Leon)



p(total)=0.02340 pBH(total)=0.22620
p(men)=0.01040 pBH(men)=0.27985

Facility 3536
(AS PONTES DE GARCIA RODRIGUEZ-Corunna)

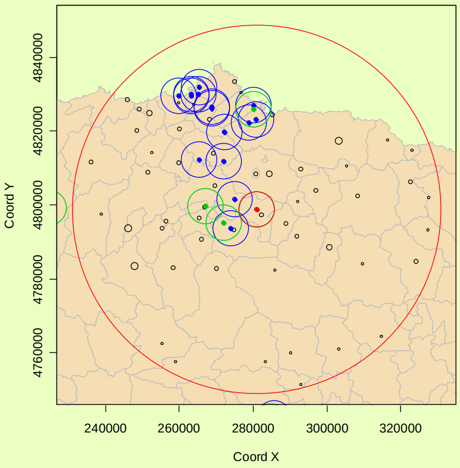


p(total)=0.00050 pBH(total)=0.01450
p(men)=0.03860 pBH(men)=0.27985
p(women)=0.00010 pBH(women)=0.00290

pBY(total)=0.05744
pBY(men)=1
pBY(women)=0.01149

LUNG, LARYNGEAL AND BLADDER CANCER

Facility 3588
(LANGREO - Asturias)



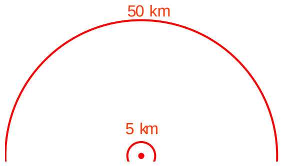
LUNG
p(total)=0.03790
p(men)=0.00920
pBH(total)=0.32944
pBH(men)=0.13340

LARYNX
p(men)=0.01880
pBH(men)=0.54520

BLADDER
p(total)=0.03140 pBH(total)=0.22765
p(men)=0.03280 pBH(men)=0.27985

p=p-value associated with hypothesis test for the Poisson regression model
pBH=p-value adjusted by Benjamini & Hochberg's method
pBY=p-value adjusted by Benjamini & Yekutieli's method

Combustion installation of interest

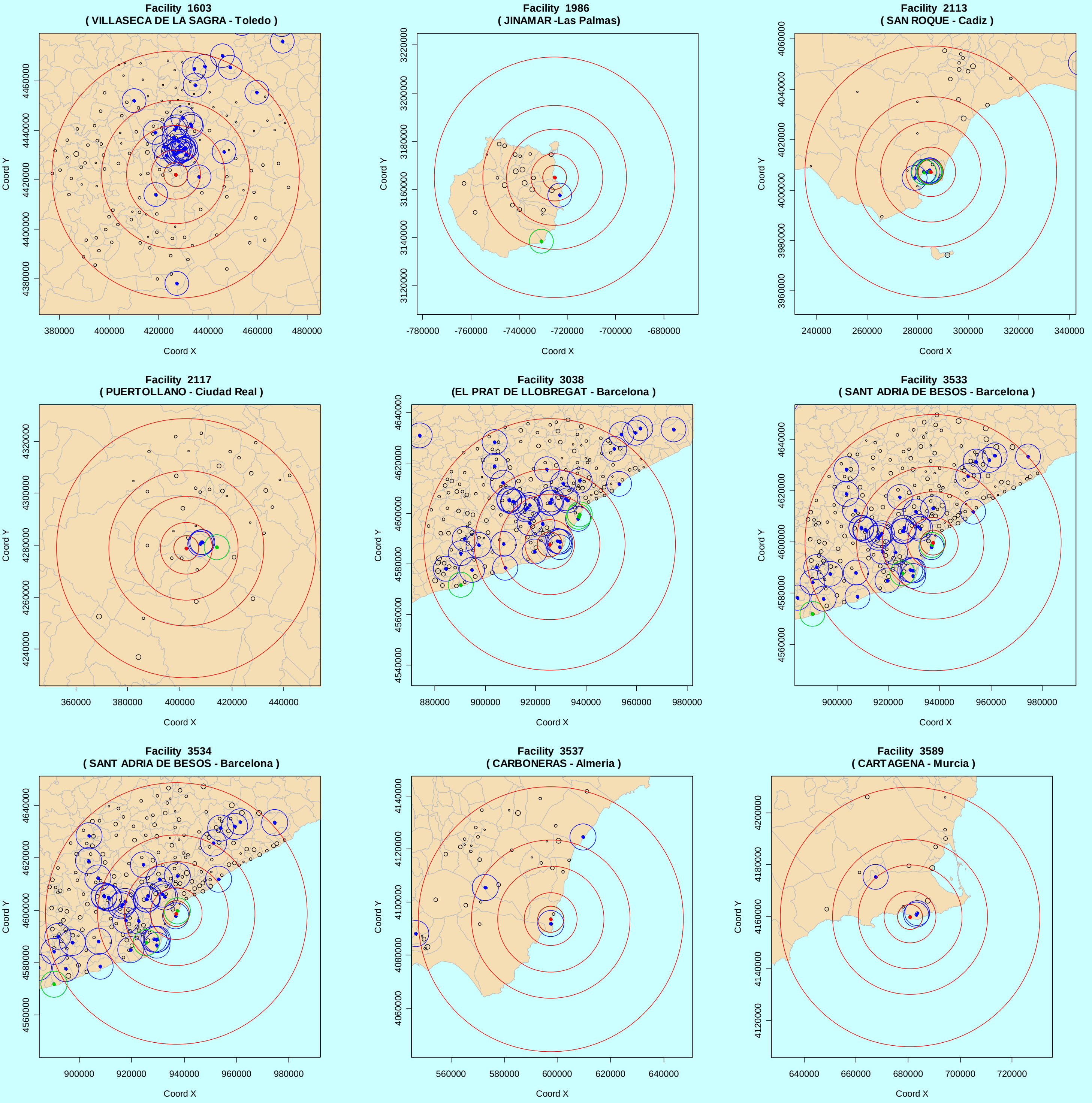


○ Situation of municipal centroids (circled are proportional to SMR values in men, except in facility '1984', which refers to women). In facility '3588' areas are proportional to SMRs for laryngeal cancer.

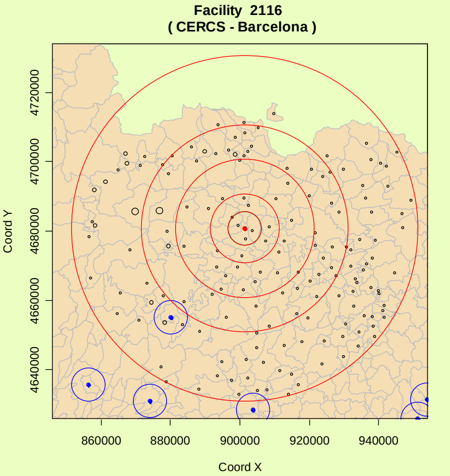
Other combustion installations

Remaining industries

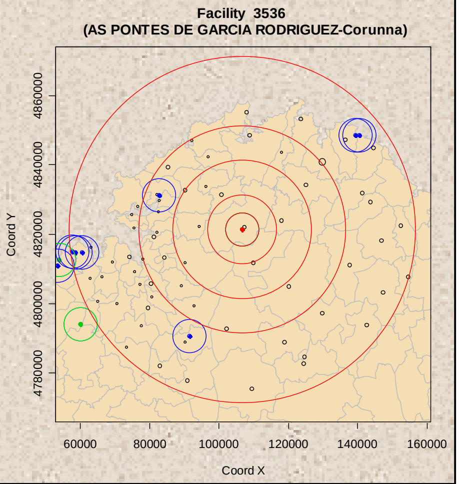
LUNG CANCER

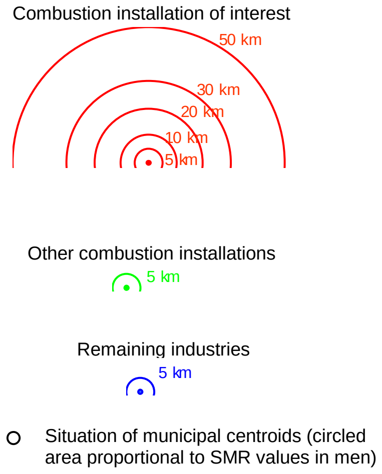


LARYNGEAL CANCER



BLADDER CANCER





Title of the manuscript:

Mortality due to lung, laryngeal and bladder cancer in towns lying in the vicinity of combustion installations

Supplemental Material:

This document is available as Supplemental Material for inclusion as online documentation. It includes Table 1, Table 2 and Table 3, that show observed and expected cases, RR, 95%CI, of towns at a distance of less than 5 kilometers from pre-1990 combustion installations in the “near vs. far” analysis and their respective corrections by means of multiple comparisons. Tumors of lung, larynx and bladder.

Supplemental Material, Table 1: Observed and expected cases, RR, 95%CI, of towns at a distance of less than 5 kilometers from pre-1990 combustion installations in the “near vs. far” analysis and their respective corrections by means of multiple comparisons. Tumor of lung.

EPER CODE	T[a]	Obs[b]	Exp[c]	RR	95%CI	p[d]	pBH[e]	pBY[f]
137	1							
TOTAL		47	35.4	0.820	0.557 - 1.207	0.3142000	0.6074533	1.0000000
MEN		38	32.0	0.741	0.488 - 1.127	0.1614000	0.3900500	1.0000000
WOMEN		9	3.4	1.433	0.476 - 4.312	0.5220000	0.9962000	1.0000000
1507	3							
TOTAL		666	523.0	1.122	0.886 - 1.420	0.3394000	0.6151625	1.0000000
MEN		620	466.1	1.140	0.892 - 1.456	0.2958000	0.5361375	1.0000000
WOMEN		46	56.9	0.901	0.370 - 2.194	0.8182000	0.9962000	1.0000000
1603	1							
TOTAL		9	8.1	1.235	0.630 - 2.422	0.5382000	0.8671000	1.0000000
MEN		8	7.4	1.237	0.606 - 2.525	0.5594000	0.8111300	1.0000000
WOMEN		1	0.7	1.239	0.164 - 9.378	0.8357000	0.9962000	1.0000000
1982	3							
TOTAL		84	101.1	0.966	0.569 - 1.641	0.8987000	0.9307964	1.0000000
MEN		75	90.1	0.962	0.551 - 1.681	0.8930000	0.9248929	1.0000000
WOMEN		9	10.9	1.034	0.178 - 6.003	0.9703000	0.9962000	1.0000000
1984	1							
TOTAL		44	46.9	1.060	0.765 - 1.470	0.7248000	0.9307964	1.0000000
MEN		32	42.6	0.867	0.594 - 1.264	0.4572000	0.7366000	1.0000000
WOMEN		12	4.3	2.557	1.303 - 5.018	0.0064000	0.1856000	0.7352830
2113	2							
TOTAL		371	283.8	1.115	0.945 - 1.315	0.1970000	0.4941154	1.0000000
MEN		347	254.0	1.178	0.992 - 1.399	0.0618000	0.2717300	1.0000000
WOMEN		24	29.8	0.612	0.331 - 1.132	0.1174000	0.9962000	1.0000000
2114	3							
TOTAL		26	27.6	1.072	0.654 - 1.756	0.7829000	0.9307964	1.0000000
MEN		24	25.1	1.037	0.621 - 1.731	0.8896000	0.9248929	1.0000000
WOMEN		2	2.6	1.777	0.273 - 11.553	0.5473000	0.9962000	1.0000000
2115	1							
TOTAL		2	3.9	0.407	0.097 - 1.718	0.2213000	0.4941154	1.0000000
MEN		2	3.6	0.448	0.106 - 1.898	0.2760000	0.5336000	1.0000000
WOMEN		0	0.4	0.000	0.000 - Inf	0.9962000	0.9962000	1.0000000
2116	4							
TOTAL		10	12.4	1.189	0.618 - 2.286	0.6039000	0.8769600	1.0000000
MEN		10	11.3	1.363	0.706 - 2.631	0.3558000	0.6069529	1.0000000
WOMEN		0	1.1	0.000	0.000 - Inf	0.9928000	0.9962000	1.0000000
2117	2							
TOTAL		281	216.4	0.976	0.748 - 1.275	0.8602000	0.9307964	1.0000000
MEN		266	194.7	1.004	0.762 - 1.323	0.9778000	0.9778000	1.0000000
WOMEN		15	21.7	0.814	0.273 - 2.430	0.7130000	0.9962000	1.0000000
2927	2							
TOTAL		24	28.8	0.624	0.403 - 0.965	0.0339000	0.3294400	1.0000000
MEN		21	26.1	0.566	0.355 - 0.901	0.0165000	0.1595000	0.6318838

EPER CODE	T[a]	Obs[b]	Exp[c]	RR	95%CI	p[d]	pBH[e]	pBY[f]
WOMEN		3	2.8	1.407	0.405 - 4.886	0.5910000	0.9962000	1.0000000
3038	4							
TOTAL		2194	1936.5	1.052	0.990 - 1.119	0.1040000	0.3351111	1.0000000
MEN		2024	1742.9	1.057	0.991 - 1.127	0.0913000	0.2717300	1.0000000
WOMEN		170	193.5	1.013	0.820 - 1.251	0.9035000	0.9962000	1.0000000
3381	1							
TOTAL		8	9.7	1.221	0.573 - 2.602	0.6048000	0.8769600	1.0000000
MEN		8	8.7	1.537	0.713 - 3.313	0.2727000	0.5336000	1.0000000
WOMEN		0	1.0	0.000	0.000 - Inf	0.9937000	0.9962000	1.0000000
3518	1							
TOTAL		88	78.7	1.254	1.000 - 1.573	0.0498000	0.3294400	1.0000000
MEN		81	71.0	1.258	0.993 - 1.593	0.0569000	0.2717300	1.0000000
WOMEN		7	7.7	1.185	0.537 - 2.615	0.6737000	0.9962000	1.0000000
3521	1							
TOTAL		20	23.0	1.019	0.636 - 1.633	0.9365000	0.9365000	1.0000000
MEN		19	20.7	1.057	0.650 - 1.719	0.8224000	0.9248929	1.0000000
WOMEN		1	2.3	0.582	0.076 - 4.427	0.6007000	0.9962000	1.0000000
3531	1							
TOTAL		100	75.7	1.035	0.820 - 1.307	0.7711000	0.9307964	1.0000000
MEN		92	68.3	1.079	0.845 - 1.377	0.5429000	0.8111300	1.0000000
WOMEN		8	7.4	0.738	0.333 - 1.635	0.4548000	0.9962000	1.0000000
3532	2							
TOTAL		43	49.9	0.896	0.651 - 1.232	0.4985000	0.8503824	1.0000000
MEN		40	45.2	0.938	0.673 - 1.308	0.7073000	0.9248929	1.0000000
WOMEN		3	4.6	0.573	0.177 - 1.863	0.3549000	0.9962000	1.0000000
3533	3							
TOTAL		1688	1377.2	1.065	0.991 - 1.146	0.0884000	0.3342250	1.0000000
MEN		1563	1237.5	1.068	0.990 - 1.152	0.0891000	0.2717300	1.0000000
WOMEN		125	139.7	1.023	0.795 - 1.317	0.8576000	0.9962000	1.0000000
3534	3							
TOTAL		1688	1377.2	1.064	0.990 - 1.145	0.0922000	0.3342250	1.0000000
MEN		1563	1237.5	1.067	0.989 - 1.151	0.0937000	0.2717300	1.0000000
WOMEN		125	139.7	1.024	0.795 - 1.318	0.8544000	0.9962000	1.0000000
3535	2							
TOTAL		13	19.2	0.954	0.529 - 1.720	0.8744000	0.9307964	1.0000000
MEN		13	17.3	1.092	0.601 - 1.986	0.7725000	0.9248929	1.0000000
WOMEN		0	1.9	0.000	0.000 - Inf	0.9944000	0.9962000	1.0000000
3536	1							
TOTAL		51	52.7	1.026	0.759 - 1.386	0.8675000	0.9307964	1.0000000
MEN		47	47.8	1.037	0.758 - 1.420	0.8185000	0.9248929	1.0000000
WOMEN		4	4.8	0.909	0.319 - 2.592	0.8581000	0.9962000	1.0000000
3537	1							
TOTAL		21	18.5	1.499	0.879 - 2.557	0.1375000	0.3987500	1.0000000
MEN		19	16.8	1.550	0.885 - 2.715	0.1254000	0.3306000	1.0000000
WOMEN		2	1.7	1.276	0.209 - 7.812	0.7918000	0.9962000	1.0000000
3562	2							
TOTAL		279	268.6	0.812	0.656 - 1.006	0.0568000	0.3294400	1.0000000
MEN		250	240.4	0.816	0.653 - 1.021	0.0752000	0.2717300	1.0000000
WOMEN		29	28.2	0.688	0.324 - 1.460	0.3298000	0.9962000	1.0000000

EPER CODE	T[a]	Obs[b]	Exp[c]	RR	95%CI	p[d]	pBH[e]	pBY[f]
3587	1							
TOTAL		630	559.3	1.012	0.867 - 1.181	0.8809000	0.9307964	1.0000000
MEN		562	502.0	0.985	0.838 - 1.159	0.8572000	0.9248929	1.0000000
WOMEN		68	57.2	1.305	0.772 - 2.207	0.3195000	0.9962000	1.0000000
3588	1							
TOTAL		304	240.3	1.177	1.009 - 1.373	0.0379000	0.3294400	1.0000000
MEN		284	214.2	1.239	1.054 - 1.455	0.0092000	0.1334000	0.5284846
WOMEN		20	26.1	0.688	0.400 - 1.182	0.1757000	0.9962000	1.0000000
3589	1							
TOTAL		795	667.9	1.325	1.066 - 1.648	0.0114000	0.3294400	1.0000000
MEN		718	600.0	1.388	1.105 - 1.744	0.0049000	0.1334000	0.5284846
WOMEN		77	67.9	0.721	0.301 - 1.725	0.4627000	0.9962000	1.0000000
3590	2							
TOTAL		43	45.9	1.268	0.867 - 1.856	0.2215000	0.4941154	1.0000000
MEN		33	41.3	1.120	0.732 - 1.715	0.6009000	0.8298143	1.0000000
WOMEN		10	4.6	2.442	0.998 - 5.974	0.0505000	0.7322500	1.0000000
3743	8							
TOTAL		1136	1063.9	0.883	0.771 - 1.011	0.0708000	0.3342250	1.0000000
MEN		1006	952.0	0.870	0.754 - 1.005	0.0576000	0.2717300	1.0000000
WOMEN		130	111.9	0.939	0.622 - 1.417	0.7634000	0.9962000	1.0000000
3744	4							
TOTAL		328	293.2	1.087	0.925 - 1.277	0.3122000	0.6074533	1.0000000
MEN		301	263.1	1.124	0.948 - 1.332	0.1785000	0.3981923	1.0000000
WOMEN		27	30.2	0.804	0.476 - 1.358	0.4154000	0.9962000	1.0000000

[a]Number of towns. [b]Observed. [c]Expected. [d]p-value associated with hypothesis test for the Poisson regression model. [e]p-value adjusted by Benjamini & Hochberg's method. [f]p-value adjusted by Benjamini & Yekutieli's method.

Supplemental Material, Table 2: Observed and expected cases, RR, 95%CI, of towns at a distance of less than 5 kilometers from pre-1990 combustion installations in the “near vs. far” analysis and their respective corrections by means of multiple comparisons. Tumor of larynx.

EPER CODE	T[a]	Obs[b]	Exp[c]	RR	95%CI	p[d]	pBH[e]	pBY[f]
137	1	3	3.8	1.170	0.264 - 5.181	0.8363000	0.9701080	1.0000000
1507	3	62	54.5	0.699	0.328 - 1.488	0.3529000	0.7186562	1.0000000
1603	1	1	0.8	2.103	0.274 - 16.138	0.4747000	0.7647944	1.0000000
1982	3	13	10.4	0.172	0.021 - 1.404	0.1004000	0.5823200	1.0000000
1984	1	3	5.0	0.594	0.178 - 1.979	0.3965000	0.7186562	1.0000000
2113	2	46	29.6	1.319	0.836 - 2.079	0.2337000	0.7065455	1.0000000
2114	3	1	2.9	0.409	0.041 - 4.097	0.4472000	0.7628706	1.0000000
2115	1	0	0.4	0	0 - Inf	0.9961000	0.9961000	1.0000000
2116	4	1	1.3	1.546	0.191 - 12.475	0.6828000	0.9429143	1.0000000
2117	2	19	22.1	0.672	0.273 - 1.653	0.3867000	0.7186562	1.0000000
2927	2	1	2.9	0.180	0.024 - 1.369	0.0976000	0.5823200	1.0000000
3038	4	192	203.8	0.972	0.792 - 1.193	0.7869000	0.9508375	1.0000000
3381	1	0	1.0	0	0 - Inf	0.9939000	0.9961000	1.0000000
3518	1	10	8.3	1.550	0.790 - 3.041	0.2022000	0.7065455	1.0000000
3521	1	3	2.3	1.259	0.360 - 4.407	0.7188000	0.9475091	1.0000000
3531	1	12	8.0	1.528	0.761 - 3.069	0.2336000	0.7065455	1.0000000
3532	2	4	5.2	0.734	0.256 - 2.103	0.5645000	0.8185250	1.0000000
3533	3	159	145.2	1.128	0.888 - 1.432	0.3240000	0.7186562	1.0000000
3534	3	159	145.2	1.130	0.890 - 1.435	0.3141000	0.7186562	1.0000000
3535	2	3	1.9	1.487	0.388 - 5.701	0.5632000	0.8185250	1.0000000
3536	1	4	5.5	0.848	0.295 - 2.435	0.7593000	0.9508375	1.0000000
3537	1	3	2.0	1.028	0.267 - 3.954	0.9676000	0.9961000	1.0000000
3562	2	43	27.4	1.391	0.779 - 2.483	0.2649000	0.7065455	1.0000000
3587	1	68	57.7	1.316	0.809 - 2.140	0.2680000	0.7065455	1.0000000
3588	1	47	24.1	1.676	1.089 - 2.579	0.0188000	0.5452000	1.0000000
3589	1	69	68.8	0.569	0.296 - 1.093	0.0906000	0.5823200	1.0000000
3590	2	12	4.7	1.975	0.888 - 4.392	0.0950000	0.5823200	1.0000000
3743	8	139	110.3	1.269	0.851 - 1.893	0.2421000	0.7065455	1.0000000
3744	4	48	30.7	1.005	0.643 - 1.569	0.9833000	0.9961000	1.0000000

[a] Number of towns. [b] Observed. [c] Expected. [d] p-value associated with hypothesis test for the Poisson regression model. [e] p-value adjusted by Benjamini & Hochberg’s method. [f] p-value adjusted by Benjamini & Yekutieli’s method.

Supplemental Material, Table 3: Observed and expected cases, RR, 95%CI, of towns at a distance of less than 5 kilometers from pre-1990 combustion installations in the “near vs. far” analysis and their respective corrections by means of multiple comparisons. Tumor of bladder.

EPER CODE	T[a]	Obs[b]	Exp[c]	RR	95%CI	p[d]	pBH[e]	pBY[f]
137	1							
TOTAL		4	7.2	0.623	0.197 - 1.973	0.4214000	0.8147067	1.0000000
MEN		3	6.1	0.611	0.165 - 2.262	0.4605000	0.8779750	1.0000000
WOMEN		1	1.1	0.597	0.048 - 7.370	0.6876000	1.0000000	1.0000000
1507	3							
TOTAL		143	104.9	0.732	0.441 - 1.215	0.2278000	0.5693667	1.0000000
MEN		117	85.6	0.643	0.367 - 1.125	0.1214000	0.5029429	1.0000000
WOMEN		26	19.3	1.302	0.402 - 4.218	0.6596000	1.0000000	1.0000000
1603	1							
TOTAL		1	1.8	0.498	0.068 - 3.630	0.4918000	0.8389529	1.0000000
MEN		0	1.5	0	0 - Inf	0.9901000	0.9958000	1.0000000
WOMEN		1	0.3	4.910	0.572 - 42.128	0.1468000	1.0000000	1.0000000
1982	3							
TOTAL		23	22.9	0.952	0.343 - 2.644	0.9252000	0.9948000	1.0000000
MEN		21	18.6	1.257	0.411 - 3.840	0.6882000	0.9958000	1.0000000
WOMEN		2	4.3	1.1E+05	0 - Inf	1.0000000	1.0000000	1.0000000
1984	1							
TOTAL		8	9.3	0.882	0.416 - 1.871	0.7439000	0.9948000	1.0000000
MEN		7	8.0	0.963	0.428 - 2.165	0.9273000	0.9958000	1.0000000
WOMEN		1	1.3	0.591	0.075 - 4.672	0.6179000	1.0000000	1.0000000
2113	2							
TOTAL		65	57.4	1.016	0.689 - 1.499	0.9363000	0.9948000	1.0000000
MEN		57	47.0	1.299	0.851 - 1.983	0.2252000	0.6778091	1.0000000
WOMEN		8	10.4	0.304	0.106 - 0.873	0.0270000	0.3915000	1.0000000
2114	3							
TOTAL		3	6.0	0.469	0.134 - 1.639	0.2356000	0.5693667	1.0000000
MEN		3	5.0	0.543	0.150 - 1.967	0.3520000	0.7291429	1.0000000
WOMEN		0	1.0	0	0 - Inf	0.9933000	1.0000000	1.0000000
2115	1							
TOTAL		0	0.9	0	0 - Inf	0.9939000	0.9948000	1.0000000
MEN		0	0.8	0	0 - Inf	0.9939000	0.9958000	1.0000000
WOMEN		0	0.1	0	0 - Inf	0.9949000	1.0000000	1.0000000
2116	4							
TOTAL		3	2.9	0.730	0.225 - 2.363	0.5995000	0.9658611	1.0000000
MEN		3	2.5	0.884	0.271 - 2.888	0.8387000	0.9958000	1.0000000
WOMEN		0	0.4	0	0 - Inf	0.9914000	1.0000000	1.0000000
2117	2							
TOTAL		46	46.1	1.109	0.601 - 2.049	0.7403000	0.9948000	1.0000000
MEN		41	38.2	1.265	0.654 - 2.446	0.4844000	0.8779750	1.0000000
WOMEN		5	7.9	0.535	0.090 - 3.176	0.4914000	1.0000000	1.0000000
2927	2							
TOTAL		5	6.5	0.704	0.271 - 1.832	0.4723000	0.8389529	1.0000000
MEN		5	5.4	0.804	0.303 - 2.129	0.6602000	0.9958000	1.0000000

EPER CODE	T[a]	Obs[b]	Exp[c]	RR	95%CI	p[d]	pBH[e]	pBY[f]
WOMEN		0	1.1	0	0 - Inf	0.9944000	1.0000000	1.0000000
3038	4							
TOTAL		407	389.3	1.125	0.977 - 1.295	0.1023000	0.4878444	1.0000000
MEN		339	322.5	1.133	0.970 - 1.323	0.1145000	0.5029429	1.0000000
WOMEN		68	66.8	1.089	0.776 - 1.529	0.6204000	1.0000000	1.0000000
3381	1							
TOTAL		3	2.1	4.565	1.228 - 16.964	0.0234000	0.2262000	0.8961261
MEN		3	1.7	5.813	1.513 - 22.327	0.0104000	0.2798500	1.0000000
WOMEN		0	0.4	0	0 - Inf	0.9945000	1.0000000	1.0000000
3518	1							
TOTAL		15	16.4	1.044	0.607 - 1.795	0.8757000	0.9948000	1.0000000
MEN		11	13.7	0.899	0.480 - 1.685	0.7401000	0.9958000	1.0000000
WOMEN		4	2.7	1.903	0.641 - 5.650	0.2464000	1.0000000	1.0000000
3521	1							
TOTAL		4	5.0	1.195	0.416 - 3.435	0.7411000	0.9948000	1.0000000
MEN		3	4.2	1.178	0.349 - 3.978	0.7915000	0.9958000	1.0000000
WOMEN		1	0.8	1.297	0.154 - 10.920	0.8107000	1.0000000	1.0000000
3531	1							
TOTAL		20	15.0	1.039	0.619 - 1.745	0.8844000	0.9948000	1.0000000
MEN		15	12.6	1.002	0.553 - 1.813	0.9958000	0.9958000	1.0000000
WOMEN		5	2.4	1.268	0.416 - 3.865	0.6763000	1.0000000	1.0000000
3532	2							
TOTAL		10	9.7	0.924	0.476 - 1.793	0.8149000	0.9948000	1.0000000
MEN		7	8.2	0.805	0.367 - 1.768	0.5889000	0.9487833	1.0000000
WOMEN		3	1.6	1.431	0.412 - 4.973	0.5730000	1.0000000	1.0000000
3533	3							
TOTAL		288	275.6	1.132	0.955 - 1.342	0.1514000	0.4878444	1.0000000
MEN		235	227.6	1.115	0.924 - 1.346	0.2571000	0.6778091	1.0000000
WOMEN		53	48.0	1.221	0.822 - 1.813	0.3224000	1.0000000	1.0000000
3534	3							
TOTAL		288	275.6	1.133	0.956 - 1.343	0.1493000	0.4878444	1.0000000
MEN		235	227.6	1.117	0.925 - 1.349	0.2487000	0.6778091	1.0000000
WOMEN		53	48.0	1.216	0.819 - 1.805	0.3334000	1.0000000	1.0000000
3535	2							
TOTAL		0	4.4	0	0 - Inf	0.9910000	0.9948000	1.0000000
MEN		0	3.6	0	0 - Inf	0.9910000	0.9958000	1.0000000
WOMEN		0	0.8	0	0 - Inf	0.9948000	1.0000000	1.0000000
3536	1							
TOTAL		22	11.4	2.423	1.476 - 3.976	0.0005000	0.0145000	0.0574440
MEN		15	9.6	1.852	1.033 - 3.321	0.0386000	0.2798500	1.0000000
WOMEN		7	1.7	6.840	2.532 - 18.477	0.0001000	0.0029000	0.0114888
3537	1							
TOTAL		1	3.4	0.287	0.037 - 2.226	0.2325000	0.5693667	1.0000000
MEN		1	3.0	0.332	0.042 - 2.608	0.2943000	0.7112250	1.0000000
WOMEN		0	0.5	0	0 - Inf	0.9962000	1.0000000	1.0000000
3562	2							
TOTAL		76	58.9	0.998	0.630 - 1.581	0.9948000	0.9948000	1.0000000
MEN		69	48.2	1.074	0.661 - 1.744	0.7738000	0.9958000	1.0000000
WOMEN		7	10.7	0.476	0.106 - 2.130	0.3317000	1.0000000	1.0000000

EPER CODE	T[a]	Obs[b]	Exp[c]	RR	95%CI	p[d]	pBH[e]	pBY[f]
3587	1							
TOTAL		135	119.9	0.745	0.535 - 1.037	0.0811000	0.4703800	1.0000000
MEN		112	99.4	0.710	0.497 - 1.014	0.0597000	0.3462600	1.0000000
WOMEN		23	20.6	1.015	0.414 - 2.489	0.9743000	1.0000000	1.0000000
3588	1							
TOTAL		64	51.9	1.459	1.034 - 2.059	0.0314000	0.2276500	0.9018705
MEN		55	41.9	1.503	1.034 - 2.186	0.0328000	0.2798500	1.0000000
WOMEN		9	10.0	1.413	0.581 - 3.437	0.4455000	1.0000000	1.0000000
3589	1							
TOTAL		164	139.0	0.563	0.352 - 0.903	0.0170000	0.2262000	0.8961261
MEN		128	115.1	0.552	0.321 - 0.948	0.0314000	0.2798500	1.0000000
WOMEN		36	23.8	0.785	0.269 - 2.291	0.6584000	1.0000000	1.0000000
3590	2							
TOTAL		5	10.0	0.463	0.173 - 1.238	0.1250000	0.4878444	1.0000000
MEN		4	8.3	0.446	0.149 - 1.337	0.1496000	0.5423000	1.0000000
WOMEN		1	1.7	0.589	0.064 - 5.452	0.6413000	1.0000000	1.0000000
3743	8							
TOTAL		228	219.0	0.852	0.637 - 1.139	0.2783000	0.5764786	1.0000000
MEN		195	178.8	0.906	0.660 - 1.243	0.5405000	0.9220294	1.0000000
WOMEN		33	40.2	0.564	0.272 - 1.168	0.1231000	1.0000000	1.0000000
3744	4							
TOTAL		76	59.5	1.214	0.869 - 1.697	0.2554000	0.5697385	1.0000000
MEN		65	48.8	1.192	0.828 - 1.716	0.3447000	0.7291429	1.0000000
WOMEN		11	10.7	1.409	0.598 - 3.319	0.4326000	1.0000000	1.0000000

[a] Number of towns. [b] Observed. [c] Expected. [d] p-value associated with hypothesis test for the Poisson regression model. [e] p-value adjusted by Benjamini & Hochberg's method. [f] p-value adjusted by Benjamini & Yekutieli's method.