Risk of gastric cancer in the environs of industrial facilities in the MCC-Spain study

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Abbreviations:

EDCs: Endocrine disrupting chemicals
PM: Particulate matter
PAHs: Polycyclic aromatic hydrocarbons

ORs: Odds ratios

95%CIs: 95% confidence intervals

p-BH: *p*-value adjusted by Benjamini & Hochberg’s method

p-BY: *p*-value adjusted by Benjamini & Yekutieli’s method

Abstract

Background: Gastric cancer is the fifth most frequent tumor worldwide. In Spain, it presents a large geographic variability in incidence, suggesting a possible role of environmental factors in its etiology. Therefore, epidemiologic research focused on environmental exposures is necessary.
Objectives: To assess the association between risk of gastric cancer (by histological type and tumor site) and residential proximity to industrial installations, according to categories of industrial groups and specific pollutants released, in the context of a population-based multicase-control study of incident cancer conducted in Spain (MCC-Spain).
Methods: In this study, 2664 controls and 137 gastric cancer cases from 9 provinces, frequency matched by province of residence, age, and sex were included. Distances from the individuals' residences to the 106 industries located in the study areas were computed. Logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (95%CIs) for categories of distance (from 1 km to 3 km) to industries, adjusting for matching variables and potential confounders.
Results: Overall, no excess risk of gastric cancer was observed in people living close to the industrial installations, with ORs ranging from 0.73 (at ≤2.5 km) to 0.93 (at ≤1.5 km). However, by industrial sector, excess risks (OR; 95%CI) were found near organic chemical industry (3.51; 1.42-8.69 at ≤2 km), inorganic chemical industry (3.33; 1.12-9.85 at ≤2 km), food/beverage sector (2.48; 1.12-5.50 at ≤2 km), and surface treatment using organic solvents (3.59; 1.40-9.22 at ≤3 km). By specific pollutant, a statistically significant excess risk (OR; 95%CI) was found near (≤3 km) industries releasing nonylphenol (6.43; 2.30-17.97) and antimony (4.82; 1.94-12.01).
Conclusions: The results suggest no association between risk of gastric cancer and living in the proximity to the industrial facilities as a whole. However, a few associations were detected near some industrial sectors and installations releasing specific pollutants.

Capsule:

Our results suggest no association between risk of gastric cancer and living in the proximity to the industrial facilities as a whole, although a few associations were detected near specific industries.

Key Words: gastric cancer; industrial pollution; risk factor; case-control study; residential proximity; MCC-Spain

1. Introduction

Gastric cancer is the fourth leading cause of cancer death and the fifth most frequent cancer worldwide, with 1.09 million new cases in both sexes in 2020 (International Agency for Research on Cancer, 2020). In Spain, 6981 new cases of gastric cancer were estimated in the same year (2.5% of all malignant tumors) (International Agency for Research on Cancer, 2020). Gastric cancer incidence has been decreasing during the last decades in Spain (Galceran et al., 2017); however, survival rates are still among the lowest of all cancer sites, with an estimated age-standardized 5-year net survival for the period 2010-2014 of 27.6% (Allemani et al., 2018). Moreover, this tumor presents a marked geographic variability in its incidence, both worldwide and among Spanish regions (Galceran et al., 2017).

With respect to the etiology of gastric cancer, the strongest risk factor for the most frequent type (the non-cardia gastric cancer) is the infection with the bacterium *Helicobacter pylori* (De Martel and Parsonnet, 2018a; Fernández de Larrea-Baz et al., 2017). Apart from genetic predisposition, other suggested or alleged risk factors include the Epstein-Barr virus, smoking, alcohol consumption, consumption of salt-preserved foods, low fruit and vegetable intake, obesity, and ionizing radiation (Aragonés et al., 2019; De Martel and Parsonnet, 2018b; Poorolajal et al., 2020; Rawla and Barsouk, 2019; WCRF/AICR, 2018), although they account for up to 3/4 of all cases (Charafeddine et al., 2017; Ko et al., 2018; Parkin et al., 2011; Poirier et al., 2019). Therefore, epidemiologic research focused on other potential risk factors, especially environmental causes, seems to be advisable.

With regard to environmental exposures, some authors have found associations between exposure to certain endocrine disrupting chemicals (EDCs), such as organophosphate esters (Li et al., 2020) or phthalate plasticizers (Wong et al., 2019), and gastrointestinal cancers. On the other hand, recent studies have suggested associations between air pollution and risk of gastric cancer, both incidence and mortality, due to particulate matter (PM), such as $PM_{2.5}$ and PM_{10} (Ethan et al., 2020;

Guo et al., 2020; Nagel et al., 2018; Weinmayr et al., 2018; Yin et al., 2020). PM is released by industrial installations, which also emit numerous potential carcinogens suspected of being related to gastric cancer, such as some heavy metals (e.g.: arsenic and lead) and polycyclic aromatic hydrocarbons (PAHs) (Deng et al., 2019; Liao et al., 2014; Núñez et al., 2016; Zhao et al., 2014). A recent systematic review of ecological studies revealed positive associations between proximity to certain industrial facilities and stomach cancer mortality and incidence (Khazaei et al., 2020). Moreover, industrial facilities generate hazardous waste, including metalworking fluids and materials containing asbestos, which have also been associated with gastric cancer risk (Di Ciaula, 2017; Park, 2001; Peng et al., 2015; Zhao et al., 2005). Accordingly, it is necessary to carry out epidemiological studies to ascertain whether residing close to industrial pollution sources might increase the incidence of gastric cancer.

The aim of the present paper was to assess the possible association between gastric cancer risk (by histological type and tumor site) and residential proximity to industrial installations, according to categories of industrial groups and specific pollutants released by the plants, in the context of a population-based multicase-control study of common tumors in Spain (MCC-Spain). Our study presents the novelty of being able to analyze the risk of gastric cancer associated with the proximity to industrial pollution sources using individual data, an area of research that has been deserted for many years in relation to gastric cancer. The results of the paper will allow to identify the existence, or not, of potential industrial sectors and specific pollutants possibly related to an increased risk of gastric cancer.

2. Materials and methods

2.1 Study population and data collection

The design of the MCC-Spain study and the overall methodology carried out to analyze the proposed objectives have been previously described (Castaño-Vinyals et al., 2015; García-Pérez et al., 2018). In brief, among the five types of tumors (breast, colorectal, leukemias, prostate, and gastric) included in the MCC-Spain study, a total of 459 histologically confirmed incident gastric cancer cases (codes C15.5, C16, and D00.2, according to the International Classification of Diseases-10th), between 20 and 85 years old, were recruited in in the period 2008-2013 in nine provinces of Spain (Valencia, Navarre, Madrid, Leon, Huelva, Granada, Cantabria, Barcelona, and Asturias) in the period 2008-2013. All of them had resided in the hospitals' catchment areas for at least 6 months prior to recruitment. Tumors were classified as cardia or non-cardia, according to their location (tumor site), and intestinal or diffuse, according to their morphology (histological type) following Lauren's classification (Lauren, 1965; Laurén and Nevalainen, 1993).

To facilitate the logistics of the study, population-based controls (n=3440) for the entire MCC-Spain study (common to the five types of cancers) were randomly selected from the administrative records of the primary health care centers located within hospitals' catchment areas, and were frequency matched to the overall distribution of all of the cases (gastric cancer and the others) by age (in 5-year age groups), province of residence, and sex. Specifically, the selection process was as follows: a) Firstly, we made an initial estimate of the age-sex distribution that all of the combined cases would have in each province, according to the tumors they had recruited and the cancer incidence rates from the Spanish cancer registers; b) secondly, we applied these estimates to predefine the age-sex distribution of our population-based controls, which were randomly selected from the general practitioner lists of primary health care centers in each hospital's catchment area; and, c) finally, when the recruitment of cases finished, we compared again the age-sex distribution of controls and cases and recruited new participants if necessary in an attempt to ensure that each case had at least one control of its 5-year age interval and sex in each province.

Information on family history of gastric cancer, sociodemographic factors, medical history, and lifestyle was collected through a structured questionnaire administered face-to-face by trained interviewers, with an average duration of 70 min. In order to reduce interviewer bias, experienced professional interviewers were instructed to adhere to the question and answer format strictly and equally for both, controls and cases interviews. The ad hoc epidemiological questionnaire was designed by the researchers participating in the project after discussing and agreeing about the main questions to achieve the MCC-Spain objectives. In many instances, questions were based on questionnaires already used in previous studies by the research team. Controls were initially contacted by phone and those who agreed to participate in the study were scheduled for a personal interview. The interviews were carried out in the collaborating hospitals and primary health care centers. Dietary information in the year prior to diagnosis (or prior to the interview for controls) was obtained through a food-frequency questionnaire provided to each participant during the interview for self-fulfillment and returned by mail. Missing values in specific questions and relevant variables were completed through subsequent telephone contact.

2.2 Residential locations

A total of 3890 participants' domiciles (3432 controls and 458 cases) could be geocoded into ED50/UTM zone 30N (EPSG:23030) coordinates using Google Earth Pro. Subsequently, these coordinates were individually checked using the National Cadastre and the "street-view" application of Google Earth Pro to ensure their exact location. Taking into account the selection process of the population-based controls (García-Pérez et al., 2020, 2018), only cases and controls residing in the area of influence of the corresponding primary health care centers and with complete information about the variables of interest were included in the present study. Consequently, 748 controls and 318 cases were excluded because they were located outside these areas.

2.3 Industrial installation locations

Data on industries (geographic locations of the installations and pollutant emissions released by them) were obtained from the facilities governed by the Integrated Pollution Prevention and Control Directive and installations included in the European Pollutant Release and Transfer Register, corresponding to 2009. Taking into account a minimum induction period of 10 years for gastric cancer development (in line with estimations for solid tumors (Armenian and Lilienfeld, 1974)), the facilities that had come into operation prior to 10 years before the mid-year of the recruitment period of each province were identified (n=106). These industries – whose coordinates had been previously geocoded into ED50/UTM zone 30N (EPSG:23030) and subsequently validated (García-Pérez et al., 2019, 2008) – were classified into one of the following 20 industrial groups: combustion installations; production and processing of metals; galvanization; surface treatment of metals and plastic; mining industry; cement and lime; glass and mineral fibers; ceramic; organic chemical industry; inorganic chemical industry; fertilizers; pharmaceutical products; hazardous waste; non-hazardous waste; disposal or recycling of animal waste; urban waste-water treatment plants; paper and wood production; food and beverage sector; surface treatment using organic solvents; and, ship building.

2.4 Statistical analyses

Differences in the distribution of sociodemographic characteristics and risk factors between gastric cancer cases and controls were tested using the two-sided Chi-square test and the Mann-Whitney U-test, where appropriate.

The shortest distance between each participant's domicile and each of the 106 industrial installations was calculated (industrial distance*).* To estimate odds ratios (ORs) and 95% confidence intervals (95%CIs) of gastric cancer in the environs of industrial facilities, four statistical analyses, using mixed multiple unconditional logistic regression models, were performed. Matching factors (age, sex, and province of residence as a random effect term), as well as potential confounders (family history of gastric cancer (none, second degree only, one first degree, and more than one first degree), tobacco smoking (never, former smoker, and current smoker), and education (less than primary school, primary school completed, secondary school, and university)) were included in all of the models.

1) Analysis 1: risk of gastric cancer in the environs of industrial facilities as a whole. According to several industrial distances 'ID' (3, 2.5, 2, 1.5, and 1 km), the exposure variable for each participant was categorized as: a) "*exposed area*", if the participant lived at ≤'ID' km from any facility; b) "*intermediate area*", if it lived between 'ID' and 3 km from any facility; and, c) "*reference area*", if it lived at >3 km from any facility.
2) Analysis 2: risk of gastric cancer in the environs of industrial facilities according to categories of industrial groups (n=20). The exposure variable was analogous to the previous analysis, where the "*exposed area*" was defined as participants residing at ≤'ID' km from any installation belonging to the industrial group in question.
3) Analysis 3: risk of gastric cancer in the environs of industrial facilities, according to specific pollutants (n=43) released by them. The exposure variable was analogous to the first analysis,

where the "*exposed area*" was defined as participants residing at ≤'ID' km from any installation releasing the specific pollutant in question.

4) Analysis 4: assessment of the existence of radial effects near industrial facilities (risk gradient analysis): a) as a whole, b) by industrial group, and c) by specific pollutant. According to concentric rings (0-1 km, 1-1.5 km, 1.5-2 km, 2-2.5 km, 2.5-3 km, and using the 3-30 km ring as a reference), OR for each ring was estimated and the presence of radial effects (i.e., rise in OR with increasing proximity to facilities) was ascertained.

Given that matching conditions were applied taking into account the overall distribution of all of the cancer cases in each province included in the MCC-Spain study ("multicase-control", i.e., not individually), unconditional logistic regression models including the matched factors were used (Rothman et al., 2008). In the study of the association between proximity to industrial installations and risk of gastric cancer by histological type (intestinal or diffuse) and tumor site (cardia or non-cardia), the four abovementioned analyses were replicated using multinomial logistic regression models.

Moreover, with the aim of introducing robustness and controlling for potential biases in the analyses, only participants living in their last domiciles for at least 10 years (long-term residents) were considered in a sensitivity analysis carried out for the four analyses mentioned in the previous paragraphs.

Lastly, the issue of multiple comparisons was addressed by controlling for the false discovery rate (expected proportion of false positives) with *p*-values adjusted by the methods proposed by Benjamini & Hochberg (*p*-BH) (Benjamini and Hochberg, 1995) and Benjamini & Yekutieli (*p*-BY) (Benjamini and Yekutieli, 2001).

3. Results

3.1 Characteristics of the study population

The final study population (participants with no missing values in any of the potential confounders) comprised 2664 controls and 137 cases, whose main characteristics are listed in Table 1. In general, controls were slightly younger and had a higher educational level than cases.

3.2 Results of the analysis 1

ORs of gastric cancer, by histological type and tumor site, in the environs of industrial facilities as a whole are included in Table 2 (analysis with all of the individuals). No excess risk was observed for any of the industrial distances, with ORs ranging from 0.73 (at ≤2.5 km) to 0.93 (at ≤1.5 km). By histological type, ORs of intestinal tumors were slightly higher than those of diffuse tumors, at distances between 2.5 km and 3 km, and the opposite at distances between 1 km and 2 km. ORs of intestinal tumors were homogeneous for all of the industrial distances, between 0.89 (at ≤2.5 km) and 1.06 (at ≤3 km and ≤1.5 km); however, a non-statistically excess risk of diffuse tumors (OR=1.28) was found at ≤1.5 km of the industrial facilities. By tumor site, non-cardia tumors showed slightly higher ORs than those for cardia tumors for all of the distances (with the exception of 1 km). ORs of cardia and non-cardia tumors were lower than unity, except for 1 km for cardia tumors (OR=1.07) and 1.5 km for non-cardia tumors (OR=1.07).

The sensitivity analysis considering only long-term residents (Table 3) showed no excess risk for all of the industrial distances (with ORs ranging from 0.66 (at ≤2.5 km) to 0.95 (at ≤1.5 km)). The results of the sub-analysis by histological type were similar to the analysis with all of the individuals. ORs of intestinal tumors were very similar for all of the distances, varying between 0.80 (at ≤2.5 km) and 1.05 (at ≤1.5 km). For diffuse tumors, an OR of 1.17 was observed at a distance of 1.5 km, although non-statistically significant. By tumor site, ORs of non-cardia tumors were slightly higher than those of cardia tumors, at distances between 2.5 km and 3 km, and the opposite at distances between 1 km and 2 km. Non-statistically significant ORs of cardia tumors were found at distances of ≤1 km (OR=1.39) and ≤1.5 km (OR=1.16); in the case of non-cardia tumors, the only non-significant excess risk was observed at ≤1.5 km (OR=1.10).

3.3 Results of the analysis 2

The analyses by industrial groups did not reveal any excess risk for most of the industrial distances, with the exception of those shown in Figure 1 (A): 'Organic chemical industry' (analysis with all of the individuals: ORs=5.31 at 1.5 km, 3.51 at 2 km, and 2.70 at 3 km; sensitivity analysis with long-term residents: ORs=5.65 at 1.5 km, and 4.20 at 2 km), 'Inorganic chemical industry' (analysis with all of the individuals: ORs=3.33 at 2 km, and 2.46 at 2.5 km), 'Food and beverage sector' (analysis with all of the individuals: ORs=2.48 at 2 km, and 2.19 at 2.5 km), and 'Surface treatment using organic solvents' (analysis with all of the individuals: OR=3.59 at 3 km; sensitivity analysis with long-term residents: OR=3.49 at 3 km).

In relation to the problem of multiple comparisons, the following adjusted *p*-values (*p*-BH<0.200 and/or *p*-BY<0.200) should be stressed (data not shown): 'Organic chemical industry' (analysis with all of the individuals: *p*-BH=0.009, *p*-BY=0.029 at 1.5 km; and *p*-BH=0.119 at 2 km; / sensitivity analysis with long-term residents: *p*-BH=0.011, *p*-BY=0.038 at 1.5 km; and *p*-BH=0.100 at 2 km), 'Inorganic chemical industry' (analysis with all of the individuals: *p*-BH=0.170 at 2 km), 'Food and beverage sector' (analysis with all of the individuals: *p*-BH=0.170 at 2 km), and 'Surface treatment using organic solvents' (analysis with all of the individuals: *p*-BH=0.160 at 3 km).

On the other hand, with regard to the sub-analyses by histological type and tumor site, the following statistically significant excess risks of non-cardia tumors in the sub-analysis by tumor site (Figure 2 (A)) should be highlighted: ‘Organic chemical industry’ (analysis with all of the individuals: ORs=7.16 at 1.5 km, 4.37 at 2 km, 3.40 at 2.5 km, and 3.87 at 3 km; sensitivity analysis with long-term residents: ORs=9.76 at 1.5 km, 6.85 at 2 km,3.90 at 2.5 km, and 3.66 at 3 km), ‘Food and beverage sector’ (analysis with all of the individuals: OR=2.69 at 2 km), and ‘Surface treatment using organic solvents’ (analysis with all of the individuals: OR=4.45 at 3 km; sensitivity analysis with long-term residents: OR=5.26 at 3 km). The sub-analysis by histological type showed no significant excess risks (data not shown).

3.4 Results of the analysis 3

The only remarkable excess risks (statistically significant ORs and a number of controls and cases≥5) of gastric cancer in the environs of industrial facilities according to specific pollutants are shown in Figure 1 (B): ‘Nonylphenol and nonylphenol ethoxylates’ (analysis with all of the individuals: ORs=6.89 at 2.5 km, and 6.43 at 3 km; sensitivity analysis with long-term residents: ORs=5.88 at 2.5 km, and 6.25 at 3 km), ‘Phenols’ (sensitivity analysis with long-term residents: OR=2.91 at 1.5 km), and ‘Antimony’ (analysis with all of the individuals: ORs=6.18 at 1.5 km, 3.88 at 2 km, 5.01 at 2.5 km, and 4.82 at 3 km; sensitivity analysis with long-term residents: ORs=6.53 at 1.5 km, 4.36 at 2 km, 4.66 at 2.5 km, and 3.81 at 3 km).

As regards the problem of multiple comparisons, the following adjusted *p*-values (*p*-BH<0.200 and/or *p*-BY<0.200) should be highlighted (data not shown): ‘Nonylphenol and nonylphenol ethoxylates’ (analysis with all of the individuals: *p*-BH=0.015, *p*-BY=0.065 at 2.5 km; and *p*-BH=0.015, *p*-BY=0.065 at 3 km / sensitivity analysis with long-term residents: *p*-BH=0.056 at 2.5 km;

and *p*-BH=0.056 at 3 km), and ‘Antimony’ (analysis with all of the individuals: *p*-BH=0.009, *p*-BY=0.037 at 1.5 km; *p*-BH=0.015, *p*-BY=0.065 at 2.5 km; and *p*-BH=0.015, *p*-BY=0.065 at 3 km / sensitivity analysis with long-term residents: *p*-BH=0.019, *p*-BY=0.075 at 1.5 km; *p*-BH=0.056 at 2.5 km; and *p*-BH=0.110 at 3 km).

In relation to the sub-analyses by histological type and tumor site, the following statistically significant ORs of non-cardia tumors in the sub-analysis by tumor site are shown in Figure 2 (B): ‘Nonylphenol and nonylphenol ethoxylates’ (analysis with all of the individuals: ORs=8.65 at 2.5 km, and 9.66 at 3 km; sensitivity analysis with long-term residents: ORs=8.63 at 2.5 km, and 11.04 at 3 km), and ‘Antimony’ (analysis with all of the individuals: ORs=6.10 at 1.5 km, 4.70 at 2 km, 7.44 at 2.5 km, and 6.16 at 3 km; sensitivity analysis with long-term residents: ORs=8.18 at 1.5 km, 6.49 at 2 km, 7.85 at 2.5 km, and 5.10 at 3 km). The sub-analysis by histological type showed a high OR of diffuse tumors for industries releasing ‘Antimony’ at 3 km, in the analysis with all of the individuals (OR=12.28, 95%CI=1.96-77.05, data not shown).

3.5 Results of the analysis 4

Lastly, the risk gradient analysis detected positive radial effects (data not shown) associated with proximity to ‘Organic chemical industry’ (analysis with all of the individuals: *p*-trend=0.013, *p*-BH=0.117; sensitivity analysis with long-term residents: *p*-trend=0.023), ‘Inorganic chemical industry’ (analysis with all of the individuals: *p*-trend=0.022, *p*-BH=0.132), and industries releasing ‘Antimony’ (analysis with all of the individuals: *p*-trend=0.014; sensitivity analysis with long-term residents: *p*-trend=0.031).

4. Discussion

To the best of our knowledge, this paper represents the first attempt to analyze the risk of gastric cancer, by histological type and tumor site, in the proximity of industrial facilities in Spain using individual data. Our results suggest no association between risk of this tumor and proximity to the industries as a whole. However, some specific statistically significant associations, especially with non-cardia tumors, have been found with proximity to industries belonging to the chemical sector (organic and inorganic chemical industries), food and beverage sector, and surface treatment using organic solvents, as well as industries releasing nonylphenol and nonylphenol ethoxylates, phenols, and antimony. These novel and remarkable results provide new hypotheses in the etiology of gastric cancer in relation to residential proximity to these industrial sectors and pollutants.

The hypothesis that the risk of gastric cancer could be related to residing in zones close to industrial areas is not new. Two studies showed indications of a potential association between risk of gastric cancer and exposure to industrial pollution as early as 1969: Winkelstein et al. (Winkelstein and Kantor, 1969) found higher mortality rates for gastric cancer in people living in an industrial area in the US with high suspended particulate air pollution, and Ashley (Ashley, 1969) found an association between gastric cancer mortality and residing in towns with coal mines and textile industries in counties of England and Wales. Moreover, in that same year, an experimental model that induced gastric tumors in mice fed on benzo(a)pyrene, provided emerging support for a possible role of airborne PM, obtained from a petrochemical area in the etiology of gastric cancer in air polluted areas (Neal and Rigdon, 1969). However, the subsequent literature about environmental exposures in the vicinity of industrial areas and risk of gastric cancer has been sparse. An ecologic study conducted in Croatia showed higher mortality rates of stomach cancer in an industrialized area compared to a non-industrialized region (Doričić et al., 2018). In Italy, Fantini et al. (Fantini et al., 2012) observed a statistically significant increased standardized mortality ratio for gastric cancer in men (but not in women) in an industrial zone.

With respect to the industrial sectors with some statistically significant results in our study, there are scarcely any studies on risk of gastric cancer and proximity to industries pertaining to the chemical sector. A Chinese study revealed that people residing in chemical industrial parks, who are exposed to higher levels of persistent toxic pollutants than those residing far from these industrial zones, presented a non-statistically significant excess risk of stomach cancer (OR=1.87, 95%CI=0.26-13.41) (Li et al., 2011). The remaining studies about the chemical industry are focused on occupational exposures, mainly in the rubber industry. Although in 1982, the International Agency for Research on Cancer determined that there was sufficient evidence of the relationship between working in the rubber manufacturing industry and increased risks of gastric tumors (International Agency for Research on Cancer, 1982), recent studies have shown inconsistent findings: a British cohort of rubber workers provided evidence of excess risks of gastric cancer (Hidajat et al., 2019; McElvenny et al., 2018), whereas a meta-analysis conducted in France (Mathieu Boniol et al., 2017) and two cohorts of rubber workers employed in Sweden and the United Kingdom (M. Boniol et al., 2017) showed no association between risk of this tumor and the rubber industry. Occupational studies about other types of chemical industries, in general, found no positive associations with gastric cancer risk (Bonneterre et al., 2012; Coggon et al., 2004; Marsh et al., 1999; Pasetto et al., 2012). In our study, ORs of gastric cancer in the environs of organic and inorganic chemical industries were high and statistically significant, ranging from 2.46 to 5.31. Both industrial sectors released known and suspected carcinogens (metals, PAHs, PM_{10}, benzene, or dioxins) (European Environment Agency (EEA), 2021) and, taking into account that the findings of occupational studies about the chemical sector and risk of gastric cancer are inconsistent, our results would support the hypothesis of a pathway of environmental exposure rather than an occupational one.

Our findings about the food and beverage sector (which includes slaughterhouses, treatment and processing intended for the production of food and beverage products, and treatment and processing of milk) revealed a possible association with the risk of gastric cancer in the environs around 2-2.5 km. To our knowledge, no epidemiologic studies have been conducted on people residing close to these industrial installations. As regards occupational studies, Johnson et al. (Johnson et al., 1997) observed a non-statistically significant elevated risk of gastric cancer mortality in workers of poultry slaughtering plants, albeit based on very few deaths. However, some studies about occupational exposures in the food industry have found statistically significant associations with incidence (Aragonés et al., 2002; Boffetta et al., 2000; Parent et al., 1998; Santibañez et al., 2012) and mortality (Johnson et al., 2011) of gastric cancer. Industries belonging to the food and beverage sector release carcinogens to both air and water, such as dioxins, PM, heavy metals, or naphthalene (European Environment Agency (EEA), 2021), and generate carcinogenic waste, such as asbestos-containing materials and mineral oils (European Environment Agency (EEA), 2021; Nunoo et al., 2018). Both asbestos (Fortunato and Rushton, 2015; Kang et al., 1997; Peng et al., 2015) and mineral oils (Zhao et al., 2005) have been associated with risk of gastric cancer, something that would be consistent with our finding of an excess risk in the vicinity of these facilities.

In relation to industries involved in the surface treatment using organic solvents, our results showed an increased risk of gastric cancer at ≤3 km of these plants, which include motor vehicle manufacturing, printing industry, optical manufacturing industry, or abrasive manufacturing plants. To our knowledge, no epidemiologic studies have been conducted on residents living near these industrial plants, even though they release known or suspected carcinogens such as lead, chromium, PAHs, dichloromethane, or PM_{10} (European Environment Agency (EEA), 2021). Although some occupational studies did not find associations with risk of gastric cancer in workers of these industries (Brown et al., 2002; Edling et al., 1987), most of them revealed positive associations (Chen and Seaton, 1998; Delzell et al., 2003; Jansson et al., 2006; Kvam et al., 2005; Wang et al., 1983).

In the analysis of gastric cancer risk according to specific pollutants released by the plants, statistically significant increased risks were detected for nonylphenol and nonylphenol ethoxylates, phenols, and antimony. Few studies in the literature have evaluated the gastric cancer risk and exposure to these substances. Regarding nonylphenol, Wu et al. (Wu et al., 2008) found that this EDC induced estrogenic activity in the stomach of female mice. Moreover, a role of estrogens and estrogen receptors' expression in the development of gastric cancer has been suggested by some authors (Ur Rahman and Cao, 2016), representing a possible mechanism by which exposure to EDCs released by surrounding industries could increase the risk of this tumor. In relation to phenols, a cohort of American workers exposed to these substances showed lower than expected mortality ratios of stomach cancer (Dosemeci et al., 1991). Finally, in relation to antimony, an Iranian study detected a high correlation between living in areas with mineral deposits of antimony and risk of gastric cancer (Eskandari et al., 2015).

Aside from the limitations inherent to this type of study, mention should also be made of the following: the non-inclusion of occupational exposures in the statistical models due to the lack of individual data; the possible recall bias linked to self-reported information about potential confounders (although this recall bias would be non-differential, which implies an attenuation of the studied effects); the potential source of uncontrolled bias derived from the differential distribution of cases and controls among the provinces of the study; the non-inclusion of potential factors that could be related to the exposure misclassification (e.g.: confounding by indoor air pollution or the time actually spent within the exposure areas); the loss of statistical power due to the exclusion of participants outside the study areas; the low number of cases in some sub-analyses referred to certain industrial groups and/or specific pollutants; and the assumption of an isotropic model using the distance as a proxy of the real exposure to the industrial pollution, which is dependent on geographic factors, such as landforms or prevailing winds.

Another aspect to consider is the non-inclusion of information about infection with *Helicobacter pylori*, an important risk factor for gastric cancer. In our study, the presence of antibodies to *Helicobacter pylori*, as a marker of infection, was determined in only a subsample of the participants and, more importantly, almost all of the participants in this subsample were seropositive (Fernández de Larrea-Baz et al., 2017). For these reasons, the inclusion of this variable in the analyses was discarded. Anyway, a sensitivity analysis including this information showed similar results to those presented here (data not shown).

With regard to the strengths of this paper, the robustness and completeness of the methodological approach used in the analyses (including stratification of the risk by industrial groups and specific substances), the use of adjusted *p*-values to control the problem of multiple comparisons, the detailed results by histological type and tumor site, and the inclusion of a sensitivity analysis (considering only long-term residents) for each type of analysis, have provided an exhaustive description of the association between industrial pollution and gastric cancer risk. The study included population-based controls and histologically confirmed incident cases, which adds specific value to our findings. Specifically, the recruitment of incident cases also served to prevent potential changes of address associated with the cancer diagnosis. Hence, if there were any bias affecting proximity to industrial facilities in the relevant periods of the participants' life, this bias would be non-differential, causing an underestimation of the estimated risk. Lastly, our paper is a multicenter case-control study carried out in nine provinces, representative of the general Spanish idiosyncrasy and located throughout the geography of Spain, covering both urban and rural settings. Our analyses included a random province-specific intercept term that accounted for unexplained heterogeneity in the models due to unmeasured factors in the different regions.

5. Conclusions

Our results suggest no association between the risk of gastric cancer and living in the proximity to the industrial facilities as a whole. However, some associations, especially with non-cardia tumors, have been found with proximity to a few industrial sectors (chemical, food/beverage, and surface treatment using organic solvents) and plants releasing specific pollutants (nonylphenol, phenols, and antimony). Further studies in the environs of industrial facilities are recommended to improve our understanding of the role of these pollutants in the etiology of gastric cancer.

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References

Allemani, C., Matsuda, T., Di Carlo, V., Harewood, R., Matz, M., Nikšić, M., Bonaventure, A., Valkov, M., Johnson, C.J., Estève, J., Ogunbiyi, O.J., Azevedo e Silva, G., Chen, W.-Q., Eser, S., Engholm, G., Stiller, C.A., Monnereau, A., Woods, R.R., Visser, O., Lim, G.H., Aitken, J., Weir, H.K., Coleman, M.P., Bouzbid, S., Hamdi-Chérif, M., Zaidi, Z., Meguenni, K., Regagba, D., Bayo, S., Cheick Bougadari, T., Manraj, S.S., Bendahhou, K., Fabowale, A., Bradshaw, D., Somdyala, N.I.M., Kumcher, I., Moreno, F., Calabrano, G.H., Espinola, S.B., Carballo Quintero, B., Fita, R., Diumenjo, M.C., Laspada, W.D., Ibañez, S.G., Lima, C.A., De Souza, P.C.F., Del Pino, K., Laporte, C., Curado, M.P., de Oliveira, J.C., Veneziano, C.L.A., Veneziano, D.B., Latorre, M.R.D.O., Tanaka, L.F., Rebelo, M.S., Santos, M.O., Galaz, J.C., Aparicio Aravena, M., Sanhueza Monsalve, J., Herrmann, D.A., Vargas, S., Herrera, V.M., Uribe, C.J., Bravo, L.E., Garcia, L.S., Arias-Ortiz, N.E., Morantes, D., Jurado, D.M., Yépez Chamorro, M.C., Delgado, S., Ramirez, M., Galán Alvarez, Y.H., Torres, P., Martínez-Reyes, F., Jaramillo, L., Quinto, R., Castillo, J., Mendoza, M., Cueva, P., Yépez, J.G., Bhakkan, B., Deloumeaux, J., Joachim, C., Macni, J., Carrillo, R., Shalkow Klincovstein, J., Rivera Gomez, R., Poquioma, E., Tortolero-Luna, G., Zavala, D., Alonso, R., Barrios, E., Eckstrand, A., Nikiforuk, C., Noonan, G., Turner, D., Kumar, E., Zhang, B., McCrate, F.R., Ryan, S., MacIntyre, M., Saint-Jacques, N., Nishri, D.E., McClure, C.A., Vriends, K.A., Kozie, S., Stuart-Panko, H., Freeman, T., George, J.T., Brockhouse, J.T., O’Brien, D.K., Holt, A., Almon, L., Kwong, S., Morris, C., Rycroft, R., Mueller, L., Phillips, C.E., Brown, H., Cromartie, B., Schwartz, A.G., Vigneau, F., Levin, G.M., Wohler, B., Bayakly, R., Ward, K.C., Gomez, S.L., McKinley, M., Cress, R., Green, M.D., Miyagi, K., Ruppert, L.P., Lynch, C.F., Huang, B., Tucker, T.C., Deapen, D., Liu, L., Hsieh, M.C., Wu, X.C., Schwenn, M., Gershman, S.T., Knowlton, R.C., Alverson, G., Copeland, G.E., Bushhouse, S., Rogers, D.B., Jackson-Thompson, J., Lemons, D., Zimmerman, H.J., Hood, M., Roberts-Johnson, J., Rees, J.R., Riddle, B., Pawlish, K.S., Stroup, A., Key, C., Wiggins, C., Kahn, A.R., Schymura, M.J., Radhakrishnan, S., Rao, C., Giljahn, L.K., Slocumb, R.M., Espinoza, R.E., Khan, F., Aird, K.G., Beran, T., Rubertone, J.J., Slack, S.J., Garcia, L., Rousseau, D.L., Janes, T.A., Schwartz, S.M., Bolick, S.W., Hurley, D.M., Whiteside, M.A., Miller-Gianturco, P., Williams, M.A., Herget, K., Sweeney, C., Johnson, A.T., Keitheri Cheteri, M.B., Migliore Santiago, P., Blankenship, S.E., Farley, S., Borchers, R., Malicki, R., Espinoza, J.R., Grandpre, J., Wilson, R., Edwards, B.K., Mariotto, A., Lei, Y., Wang, N., Chen, J.S., Zhou, Y., He, Y.T., Song, G.H., Gu, X.P., Mei, D., Mu, H.J., Ge, H.M., Wu, T.H., Li, Y.Y., Zhao, D.L., Jin, F., Zhang, J.H., Zhu, F.D., Junhua, Q., Yang, Y.L., Jiang, C.X., Biao, W., Wang, J., Li, Q.L., Yi, H., Zhou, X., Dong, J., Li, W., Fu, F.X., Liu, S.Z., Chen, J.G., Zhu, J., Li, Y.H., Lu, Y.Q., Fan, M., Huang, S.Q., Guo, G.P., Zhaolai, H., Wei, K., Zeng, H., Demetriou, A.V., Mang, W.K., Ngan, K.C., Kataki, A.C., Krishnatreya, M., Jayalekshmi, P.A., Sebastian, P., Nandakumar, A., Malekzadeh, R., Roshandel, G., Keinan-Boker, L., Silverman, B.G., Ito, H., Nakagawa, H., Sato, M., Tobori, F., Nakata, I., Teramoto, N., Hattori, M., Kaizaki, Y., Moki, F., Sugiyama, H., Utada, M., Nishimura, M., Yoshida, K., Kurosawa, K., Nemoto, Y., Narimatsu, H., Sakaguchi, M., Kanemura, S., Naito, M., Narisawa, R., Miyashiro, I., Nakata, K., Sato, S., Yoshii, M., Oki, I., Fukushima, N., Shibata, A., Iwasa, K., Ono, C., Nimri, O., Jung, K.W., Won, Y.J., Alawadhi, E., Elbasmi, A., Ab Manan, A., Adam, F., Sanjaajmats, E., Tudev, U., Ochir, C., Al Khater, A.M., El Mistiri, M.M., Teo, Y.Y., Chiang, C.J., Lee, W.C., Buasom, R., Sangrajrang, S., Kamsa-ard, S., Wiangnon, S., Daoprasert, K., Pongnikorn, D., Leklob, A., Sangkitipaiboon, S., Geater, S.L., Sriplung, H., Ceylan, O., Kög, I., Dirican, O., Köse, T., Gurbuz, T., Karaşahin, F.E., Turhan, D., Aktaş, U., Halat, Y., Yakut, C.I., Altinisik, M., Cavusoglu, Y., Türkköylü, A., Üçüncü, N., Hackl, M., Zborovskaya, A.A., Aleinikova, O.V., Henau, K., Van Eycken, L., Valerianova, Z., Yordanova, M.R., Šekerija, M., Dušek, L., Zvolský, M., Storm, H., Innos, K., Mägi, M., Malila, N., Seppä, K., Jégu, J., Velten, M., Cornet, E., Troussard, X., Bouvier, A.M., Guizard, A.V., Bouvier, V., Launoy, G., Arveux, P., Maynadié, M., Mounier, M., Woronoff, A.S., Daoulas, M., Robaszkiewicz, M., Clavel, J., Goujon, S., Lacour, B., Baldi, I., Pouchieu, C., Amadeo, B., Coureau, G., Orazio, S., Preux, P.M., Rharbaoui, F., Marrer, E., Trétarre, B., Colonna, M., Delafosse, P., Ligier, K., Plouvier, S., Cowppli-Bony, A., Molinié, F., Bara, S., Ganry, O., Lapôtre-Ledoux, B., Grosclaude, P., Bossard, N., Uhry, Z., Bray, F., Piñeros, M., Stabenow, R., Wilsdorf-Köhler, H., Eberle, A., Luttmann, S., Löhden, I., Nennecke, A.L., Kieschke, J., Sirri, E., Emrich, K., Zeissig, S.R., Holleczek, B., Eisemann, N., Katalinic, A., Asquez, R.A., Kumar, V., Petridou, E., Ólafsdóttir, E.J., Tryggvadóttir, L., Clough-Gorr, K., Walsh, P.M., Sundseth, H., Mazzoleni, G., Vittadello, F., Coviello, E., Cuccaro, F., Galasso, R., Sampietro, G., Giacomin, A., Magoni, M., Ardizzone, A., D’Argenzio, A., Castaing, M., Grosso, G., Lavecchia, A.M., Sutera Sardo, A., Gola, G., Gatti, L., Ricci, P., Ferretti, S., Serraino, D., Zucchetto, A., Celesia, M.V., Filiberti, R.A., Pannozzo, F., Melcarne, A., Quarta, F., Russo, A.G., Carrozzi, G., Cirilli, C., Cavalieri d’Oro, L., Rognoni, M., Fusco, M., Vitale, M.F., Usala, M., Cusimano, R., Mazzucco, W., Michiara, M., Sgargi, P., Boschetti, L., Borciani, E., Seghini, P., Maule, M.M., Merletti, F., Tumino, R., Mancuso, P., Vicentini, M., Cassetti, T., Sassatelli, R., Falcini, F., Giorgetti, S., Caiazzo, A.L., Cavallo, R., Cesaraccio, R., Pirino, D.R., Contrino, M.L., Tisano, F., Fanetti, A.C., Maspero, S., Carone, S., Mincuzzi, A., Candela, G., Scuderi, T., Gentilini, M.A., Piffer, S., Rosso, S., Barchielli, A., Caldarella, A., Bianconi, F., Stracci, F., Contiero, P., Tagliabue, G., Rugge, M., Zorzi, M., Beggiato, S., Brustolin, A., Berrino, F., Gatta, G., Sant, M., Buzzoni, C., Mangone, L., Capocaccia, R., De Angelis, R., Zanetti, R., Maurina, A., Pildava, S., Lipunova, N., Vincerževskiené, I., Agius, D., Calleja, N., Siesling, S., Larønningen, S., Møller, B., Dyzmann-Sroka, A., Trojanowski, M., Góźdź, S., Mężyk, R., Mierzwa, T., Molong, L., Rachtan, J., Szewczyk, S., Błaszczyk, J., Kępska, K., Kościańska, B., Tarocińska, K., Zwierko, M., Drosik, K., Maksimowicz, K.M., Purwin-Porowska, E., Reca, E., Wójcik-Tomaszewska, J., Tukiendorf, A., Grądalska-Lampart, M., Radziszewska, A.U., Gos, A., Talerczyk, M., Wyborska, M., Didkowska, J.A., Wojciechowska, U., Bielska-Lasota, M., Forjaz de Lacerda, G., Rego, R.A., Bastos, J., Silva, M.A., Antunes, L., Laranja Pontes, J., Mayer-da-Silva, A., Miranda, A., Blaga, L.M., Coza, D., Gusenkova, L., Lazarevich, O., Prudnikova, O., Vjushkov, D.M., Egorova, A.G., Orlov, A.E., Kudyakov, L.A., Pikalova, L.V., Adamcik, J., Safaei Diba, C., Primic-Žakelj, M., Zadnik, V., Larrañaga, N., Lopez de Munain, A., Herrera, A.A., Redondas, R., Marcos-Gragera, R., Vilardell Gil, M.L., Molina, E., Sánchez Perez, M.J., Franch Sureda, P., Ramos Montserrat, M., Chirlaque, M.D., Navarro, C., Ardanaz, E.E., Guevara, M.M., Fernández-Delgado, R., Peris-Bonet, R., Carulla, M., Galceran, J., Alberich, C., Vicente-Raneda, M., Khan, S., Pettersson, D., Dickman, P., Avelina, I., Staehelin, K., Camey, B., Bouchardy, C., Schaffar, R., Frick, H., Herrmann, C., Bulliard, J.L., Maspoli-Conconi, M., Kuehni, C.E., Redmond, S.M., Bordoni, A., Ortelli, L., Chiolero, A., Konzelmann, I., Matthes, K.L., Rohrmann, S., Broggio, J., Rashbass, J., Fitzpatrick, D., Gavin, A., Clark, D.I., Deas, A.J., Huws, D.W., White, C., Montel, L., Rachet, B., Turculet, A.D., Stephens, R., Chalker, E., Phung, H., Walton, R., You, H., Guthridge, S., Johnson, F., Gordon, P., D’Onise, K., Priest, K., Stokes, B.C., Venn, A., Farrugia, H., Thursfield, V., Dowling, J., Currow, D., Hendrix, J., Lewis, C., 2018. Global surveillance of trends in cancer survival 2000–14 (CONCORD-3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. The Lancet 391, 1023–1075. https://doi.org/10.1016/S0140-6736(17)33326-3

Aragonés, N., Fernández de Larrea, N., Pastor-Barriuso, R., Michel, A., Romero, B., Pawlita, M., Mayorgas-Torralba, S., Martín, V., Moreno, V., Casabonne, D., Castilla, J., Fernandez-Tardón, G., Dierssen-Sotos, T., Capelo, R., Salas, D., Salcedo-Bellido, I., Chirlaque, M.D., Brenner, N., Pedraza, M., Bessa, X., Pérez-Gómez, B., Butt, J., Kogevinas, M., Del Campo, R., de Sanjosé, S., Waterboer, T., Pollán, M., 2019. Epstein Barr virus antibody reactivity and gastric cancer: A population-based case-control study. Cancer Epidemiol. 61, 79–88. https://doi.org/10.1016/j.canep.2019.05.008

Aragonés, N., Pollán, M., Gustavsson, P., 2002. Stomach cancer and occupation in Sweden: 1971-89. Occup. Environ. Med. 59, 329–337. https://doi.org/10.1136/oem.59.5.329

Armenian, H.K., Lilienfeld, A.M., 1974. The distribution of incubation periods of neoplastic diseases. Am. J. Epidemiol. 99, 92–100. https://doi.org/10.1093/oxfordjournals.aje.a121599

Ashley, D.J., 1969. Environmental factors in the aetiology of gastric cancer. Br. J. Prev. Soc. Med. 23, 187–189. https://doi.org/10.1136/jech.23.3.187

Benjamini, Y., Hochberg, Y., 1995. Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. J. R. Stat. Soc. Ser. B Methodol. 57, 289–300. https://doi.org/10.1111/j.2517-6161.1995.tb02031.x

Benjamini, Y., Yekutieli, D., 2001. The control of the false discovery rate in multiple testing under dependency. Ann Stat 29, 1165–1188.

Boffetta, P., Gridley, G., Gustavsson, P., Brennan, P., Blair, A., Ekström, A.M., Fraumeni, J.F., 2000. Employment as butcher and cancer risk in a record-linkage study from Sweden. Cancer Causes Control CCC 11, 627–633. https://doi.org/10.1023/a:1008947531573

Boniol, Mathieu, Koechlin, A., Boyle, P., 2017. Meta-analysis of occupational exposures in the rubber manufacturing industry and risk of cancer. Int. J. Epidemiol. 46, 1940–1947. https://doi.org/10.1093/ije/dyx146

Boniol, M., Koechlin, A., Sorahan, T., Jakobsson, K., Boyle, P., 2017. Cancer incidence in cohorts of workers in the rubber manufacturing industry first employed since 1975 in the UK and Sweden. Occup. Environ. Med. 74, 417–421. https://doi.org/10.1136/oemed-2016-103989

Bonneterre, V., Mathern, G., Pelen, O., Balthazard, A.-L., Delafosse, P., Mitton, N., Colonna, M., 2012. Cancer incidence in a chlorochemical plant in Isère, France: an occupational cohort study, 1979-2002. Am. J. Ind. Med. 55, 756–767. https://doi.org/10.1002/ajim.22069

Brown, L.M., Moradi, T., Gridley, G., Plato, N., Dosemeci, M., Fraumeni, J.F., 2002. Exposures in the painting trades and paint manufacturing industry and risk of cancer among men and women in Sweden. J. Occup. Environ. Med. 44, 258–264. https://doi.org/10.1097/00043764-200203000-00013

Castaño-Vinyals, G., Aragonés, N., Pérez-Gómez, B., Martín, V., Llorca, J., Moreno, V., Altzibar, J.M., Ardanaz, E., de Sanjosé, S., Jiménez-Moleón, J.J., Tardón, A., Alguacil, J., Peiró, R., Marcos-Gragera, R., Navarro, C., Pollán, M., Kogevinas, M., 2015. Population-based multicase-control study in common tumors in Spain (MCC-Spain): rationale and study design. Gac. Sanit. 29, 308–315. https://doi.org/10.1016/j.gaceta.2014.12.003

Charafeddine, M.A., Olson, S.H., Mukherji, D., Temraz, S.N., Abou-Alfa, G.K., Shamseddine, A.I., 2017. Proportion of cancer in a Middle eastern country attributable to established risk factors. BMC Cancer 17, 337. https://doi.org/10.1186/s12885-017-3304-7

Chen, R., Seaton, A., 1998. A meta-analysis of painting exposure and cancer mortality. Cancer Detect. Prev. 22, 533–539. https://doi.org/10.1046/j.1525-1500.1998.00a47.x

Coggon, D., Harris, E.C., Poole, J., Palmer, K.T., 2004. Mortality of workers exposed to ethylene oxide: extended follow up of a British cohort. Occup. Environ. Med. 61, 358–362. https://doi.org/10.1136/oem.2003.008268

De Martel, C., Parsonnet, J., 2018a. Stomach cancer, in: Thun, M.J., Linet, M.S., Cerhan, J.R., Haiman, C.A., Schottenfeld, D. (Eds.), Schottenfeld and Fraumeni. Cancer Epidemiology and Prevention. Fourth Edition. Oxford University Press, Oxford, pp. 593–610.

De Martel, C., Parsonnet, J., 2018b. Stomach cancer, in: Thun, M.J., Linet, M.S., Cerhan, J.R., Haiman, C.A., Schottenfeld, D. (Eds.), Schottenfeld and Fraumeni. Cancer Epidemiology and Prevention. Fourth Edition. Oxford University Press, Oxford, pp. 593–610.

Delzell, E., Brown, D.A., Matthews, R., 2003. Mortality among hourly motor vehicle manufacturing workers. J. Occup. Environ. Med. 45, 813–830. https://doi.org/10.1097/01.jom.0000079092.95532.49

Deng, Y., Wang, M., Tian, T., Lin, S., Xu, P., Zhou, L., Dai, C., Hao, Q., Wu, Y., Zhai, Z., Zhu, Y., Zhuang, G., Dai, Z., 2019. The Effect of Hexavalent Chromium on the Incidence and Mortality of Human Cancers: A Meta-Analysis Based on Published Epidemiological Cohort Studies. Front. Oncol. 9, 24. https://doi.org/10.3389/fonc.2019.00024

Di Ciaula, A., 2017. Asbestos ingestion and gastrointestinal cancer: a possible underestimated hazard. Expert Rev. Gastroenterol. Hepatol. 11, 419–425. https://doi.org/10.1080/17474124.2017.1300528

Doričić, R., Ćorić, T., Tomljenović, M., Lakošeljac, D., Muzur, A., Kolarić, B., 2018. Mortality Characteristics of Two Populations in the Northern Mediterranean (Croatia) in the Period 1960⁻2012: An Ecological Study. Int. J. Environ. Res. Public. Health 15. https://doi.org/10.3390/ijerph15112591

Dosemeci, M., Blair, A., Stewart, P.A., Chandler, J., Trush, M.A., 1991. Mortality among industrial workers exposed to phenol. Epidemiol. Camb. Mass 2, 188–193. https://doi.org/10.1097/00001648-199105000-00005

Edling, C., Järvholm, B., Andersson, L., Axelson, O., 1987. Mortality and cancer incidence among workers in an abrasive manufacturing industry. Br. J. Ind. Med. 44, 57–59. https://doi.org/10.1136/oem.44.1.57

Eskandari, O., Ghias, M., Fatehizadeh, A., Zare, M., Amin, M., Kazemi, A., 2015. Geographical distribution of stomach cancer related to heavy metals in Kurdistan, Iran. Int. J. Environ. Health Eng. 4, 12. https://doi.org/10.4103/2277-9183.157700

Ethan, C.J., Mokoena, K.K., Yu, Y., Shale, K., Fan, Y., Rong, J., Liu, F., 2020. Association between PM2.5 and mortality of stomach and colorectal cancer in Xi'an: a time-series study. Environ. Sci. Pollut. Res. Int. 27, 22353–22363. https://doi.org/10.1007/s11356-020-08628-0

European Environment Agency (EEA), 2021. The European Pollutant Release and Transfer Register (E-PRTR) [WWW Document]. URL https://prtr.eea.europa.eu/#/home (accessed 2.23.21).

Fantini, F., Porta, D., Fano, V., De Felip, E., Senofonte, O., Abballe, A., D'Ilio, S., Ingelido, A.M., Mataloni, F., Narduzzi, S., Blasetti, F., Forastiere, F., 2012. [Epidemiologic studies on the health status of the population living in the Sacco River Valley]. Epidemiol. Prev. 36, 44–52.

Fernández de Larrea-Baz, N., Pérez-Gómez, B., Michel, A., Romero, B., Lope, V., Pawlita, M., Fernández-Villa, T., Moreno, V., Martín, V., Willhauck-Fleckenstein, M., López-Abente, G., Castilla, J., Fernández-Tardón, G., Dierssen-Sotos, T., Santibáñez, M., Peiró, R., Jiménez-Moleón, J.J., Navarro, C., Castaño-Vinyals, G., Kogevinas, M., Pollán, M., de Sanjosé, S., Del Campo, R., Waterboer, T., Aragonés, N., 2017. Helicobacter pylori serological biomarkers of gastric cancer risk in the MCC-Spain case-control Study. Cancer Epidemiol. 50, 76–84. https://doi.org/10.1016/j.canep.2017.08.002

Fortunato, L., Rushton, L., 2015. Stomach cancer and occupational exposure to asbestos: a meta-analysis of occupational cohort studies. Br. J. Cancer 112, 1805–1815. https://doi.org/10.1038/bjc.2014.599

Galceran, J., Ameijide, A., Carulla, M., Mateos, A., Quirós, J.R., Rojas, D., Alemán, A., Torrella, A., Chico, M., Vicente, M., Díaz, J.M., Larrañaga, N., Marcos-Gragera, R., Sánchez, M.J., Perucha, J., Franch, P., Navarro, C., Ardanaz, E., Bigorra, J., Rodrigo, P., Bonet, R.P., REDECAN Working Group, 2017. Cancer incidence in Spain, 2015. Clin. Transl. Oncol. Off. Publ. Fed. Span. Oncol. Soc. Natl. Cancer Inst. Mex. 19, 799–825. https://doi.org/10.1007/s12094-016-1607-9

García-Pérez, J., Boldo, E., Ramis, R., Vidal, E., Aragonés, N., Pérez-Gómez, B., Pollán, M., López-Abente, G., 2008. Validation of the geographic position of EPER-Spain industries. Int. J. Health Geogr. 7, 1. https://doi.org/10.1186/1476-072X-7-1

García-Pérez, J., Fernández de Larrea-Baz, N., Lope, V., Molina, A.J., O'Callaghan-Gordo, C., Alonso, M.H., Rodríguez-Suárez, M.M., Mirón-Pozo, B., Alguacil, J., Gómez-Acebo, I., Ascunce, N., Vanaclocha-Espi, M., Amiano, P., Chirlaque, M.D., Simó, V., Jiménez-Moleón, J.J., Tardón, A., Moreno, V., Castaño-Vinyals, G., Martín, V., Aragonés, N., Pérez-Gómez, B., Kogevinas, M., Pollán, M., 2020. Residential proximity to industrial pollution sources and colorectal cancer risk: A multicase-control study (MCC-Spain). Environ. Int. 144, 106055. https://doi.org/10.1016/j.envint.2020.106055

García-Pérez, J., Gómez-Barroso, D., Tamayo-Uria, I., Ramis, R., 2019. Methodological approaches to the study of cancer risk in the vicinity of pollution sources: the experience of a population-based case-control study of childhood cancer. Int. J. Health Geogr. 18, 12. https://doi.org/10.1186/s12942-019-0176-x

García-Pérez, J., Lope, V., Pérez-Gómez, B., Molina, A.J., Tardón, A., Díaz Santos, M.A., Ardanaz, E., O'Callaghan-Gordo, C., Altzibar, J.M., Gómez-Acebo, I., Moreno, V., Peiró, R., Marcos-Gragera, R., Kogevinas, M., Aragonés, N., López-Abente, G., Pollán, M., 2018. Risk of breast cancer and residential proximity to industrial installations: New findings from a multicase-control study (MCC-Spain). Environ. Pollut. 237, 559–568. https://doi.org/10.1016/j.envpol.2018.02.065

Guo, C., Chan, T.-C., Teng, Y.-C., Lin, C., Bo, Y., Chang, L.-Y., Lau, A.K.H., Tam, T., Wong, M.C.S., Qian Lao, X., 2020. Long-term exposure to ambient fine particles and gastrointestinal cancer mortality in Taiwan: A cohort study. Environ. Int. 138, 105640. https://doi.org/10.1016/j.envint.2020.105640

Hidajat, M., McElvenny, D.M., Ritchie, P., Darnton, A., Mueller, W., van Tongeren, M., Agius, R.M., Cherrie, J.W., de Vocht, F., 2019. Lifetime exposure to rubber dusts, fumes and N-nitrosamines and cancer mortality in a cohort of British rubber workers with 49 years follow-up. Occup. Environ. Med. 76, 250–258. https://doi.org/10.1136/oemed-2018-105181

International Agency for Research on Cancer, 2020. Global Cancer Observatory. Cancer Today [WWW Document]. URL https://gco.iarc.fr/today/home (accessed 2.23.21).

International Agency for Research on Cancer, 1982. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 28: the rubber industry [WWW Document]. URL http://publications.iarc.fr/46

Jansson, C., Plato, N., Johansson, A.L.V., Nyrén, O., Lagergren, J., 2006. Airborne occupational exposures and risk of oesophageal and cardia adenocarcinoma. Occup. Environ. Med. 63, 107–112. https://doi.org/10.1136/oem.2005.022467

Johnson, E.S., Faramawi, M.F., Sall, M., Choi, K.-M., 2011. Cancer and noncancer mortality among American seafood workers. J. Epidemiol. 21, 204–210. https://doi.org/10.2188/jea.je20100147

Johnson, E.S., Shorter, C., Rider, B., Jiles, R., 1997. Mortality from cancer and other diseases in poultry slaughtering/processing plants. Int. J. Epidemiol. 26, 1142–1150. https://doi.org/10.1093/ije/26.6.1142

Kang, S.K., Burnett, C.A., Freund, E., Walker, J., Lalich, N., Sestito, J., 1997. Gastrointestinal cancer mortality of workers in occupations with high asbestos exposures. Am. J. Ind. Med. 31, 713–718. https://doi.org/10.1002/(sici)1097-0274(199706)31:6<713::aid-ajim7>3.0.co;2-r

Khazaei, S., Mohammadbeigi, A., Jenabi, E., Asgarian, A., Heidari, H., Saghafipour, A., Arsang-Jang, S., Ansari, H., 2020. Environmental and ecological factors of stomach cancer incidence and mortality: a systematic review study on ecological studies. Rev. Environ. Health. https://doi.org/10.1515/reveh-2020-0022

Ko, K.-P., Shin, A., Cho, S., Park, S.K., Yoo, K.-Y., 2018. Environmental contributions to gastrointestinal and liver cancer in the Asia-Pacific region. J. Gastroenterol. Hepatol. 33, 111–120. https://doi.org/10.1111/jgh.14005

Kvam, B.M.N., Romundstad, P.R., Boffetta, P., Andersen, A., 2005. Cancer in the Norwegian printing industry. Scand. J. Work. Environ. Health 31, 36–43. https://doi.org/10.5271/sjweh.846

Lauren, P., 1965. THE TWO HISTOLOGICAL MAIN TYPES OF GASTRIC CARCINOMA: DIFFUSE AND SO-CALLED INTESTINAL-TYPE CARCINOMA. AN ATTEMPT AT A HISTO-CLINICAL CLASSIFICATION. Acta Pathol. Microbiol. Scand. 64, 31–49. https://doi.org/10.1111/apm.1965.64.1.31

Laurén, P.A., Nevalainen, T.J., 1993. Epidemiology of intestinal and diffuse types of gastric carcinoma. A time-trend study in Finland with comparison between studies from high- and low-risk areas. Cancer 71, 2926–2933. https://doi.org/10.1002/1097-0142(19930515)71:10<2926::aid-cncr2820711007>3.0.co;2-x

Li, J., Lu, Y., Shi, Y., Wang, T., Wang, G., Luo, W., Jiao, W., Chen, C., Yan, F., 2011. Environmental pollution by persistent toxic substances and health risk in an industrial area of China. J. Environ. Sci. China 23, 1359–1367. https://doi.org/10.1016/s1001-0742(10)60554-2

Li, Y., Fu, Y., Hu, K., Zhang, Y., Chen, J., Zhang, S., Zhang, B., Liu, Y., 2020. Positive correlation between human exposure to organophosphate esters and gastrointestinal cancer in patients from Wuhan, China. Ecotoxicol. Environ. Saf. 196, 110548. https://doi.org/10.1016/j.ecoenv.2020.110548

Liao, L.M., Hofmann, J.N., Kamangar, F., Strickland, P.T., Ji, B.-T., Yang, G., Li, H.-L., Rothman, N., Zheng, W., Chow, W.-H., Gao, Y.-T., Shu, X.-O., 2014. Polycyclic aromatic hydrocarbons and risk of gastric cancer in the Shanghai Women’s Health Study. Int. J. Mol. Epidemiol. Genet. 5, 140–144.

Marsh, G.M., Gula, M.J., Youk, A.O., Schall, L.C., 1999. Mortality among chemical plant workers exposed to acrylonitrile and other substances. Am. J. Ind. Med. 36, 423–436. https://doi.org/10.1002/(sici)1097-0274(199910)36:4<423::aid-ajim3>3.0.co;2-m

McElvenny, D.M., Mueller, W., Ritchie, P., Cherrie, J.W., Hidajat, M., Darnton, A.J., Agius, R.M., de Vocht, F., 2018. British rubber and cable industry cohort: 49-year mortality follow-up. Occup. Environ. Med. 75, 848–855. https://doi.org/10.1136/oemed-2017-104834

Nagel, G., Stafoggia, M., Pedersen, M., Andersen, Z.J., Galassi, C., Munkenast, J., Jaensch, A., Sommar, J., Forsberg, B., Olsson, D., Oftedal, B., Krog, N.H., Aamodt, G., Pyko, A., Pershagen, G., Korek, M., De Faire, U., Pedersen, N.L., Östenson, C.-G., Fratiglioni, L., Sørensen, M., Tjønneland, A., Peeters, P.H., Bueno-de-Mesquita, B., Vermeulen, R., Eeftens, M., Plusquin, M., Key, T.J., Concin, H., Lang, A., Wang, M., Tsai, M.-Y., Grioni, S., Marcon, A., Krogh, V., Ricceri, F., Sacerdote, C., Ranzi, A., Cesaroni, G., Forastiere, F., Tamayo-Uria, I., Amiano, P., Dorronsoro, M., de Hoogh, K., Beelen, R., Vineis, P., Brunekreef, B., Hoek, G., Raaschou-Nielsen, O., Weinmayr, G., 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, 1632–1643. https://doi.org/10.1002/ijc.31564

Neal, J., Rigdon, R.H., 1969. Stomach cancer and air pollution: an experimental study in a petrochemical area. Tex. Rep. Biol. Med. 27, 787–793.

Núñez, O., Fernández-Navarro, P., Martín-Méndez, I., Bel-Lan, A., Locutura, J.F., López-Abente, G., 2016. Arsenic and chromium topsoil levels and cancer mortality in Spain. Environ. Sci. Pollut. Res. Int. 23, 17664–17675. https://doi.org/10.1007/s11356-016-6806-y

Nunoo, E.K., Panin, A., Essien, B., 2018. Environmental health risk assessment of asbestos-containing materials in the brewing industry in Ghana. J Env. Res 2, 1–11.

Parent, M.E., Siemiatycki, J., Fritschi, L., 1998. Occupational exposures and gastric cancer. Epidemiol. Camb. Mass 9, 48–55.

Park, R.M., 2001. Mortality at an Automotive Engine Foundry and Machining Complex: J. Occup. Environ. Med. 43, 483–493. https://doi.org/10.1097/00043764-200105000-00009

Parkin, D.M., Boyd, L., Walker, L.C., 2011. 16. The fraction of cancer attributable to lifestyle and environmental factors in the UK in 2010. Br. J. Cancer 105 Suppl 2, S77-81. https://doi.org/10.1038/bjc.2011.489

Pasetto, R., Zona, A., Pirastu, R., Cernigliaro, A., Dardanoni, G., Addario, S.P., Scondotto, S., Comba, P., 2012. Mortality and morbidity study of petrochemical employees in a polluted site. Environ. Health Glob. Access Sci. Source 11, 34. https://doi.org/10.1186/1476-069X-11-34

Peng, W., Jia, X., Wei, B., Yang, L., Yu, Y., Zhang, L., 2015. Stomach cancer mortality among workers exposed to asbestos: a meta-analysis. J. Cancer Res. Clin. Oncol. 141, 1141–1149. https://doi.org/10.1007/s00432-014-1791-3

Poirier, A.E., Ruan, Y., Volesky, K.D., King, W.D., O'Sullivan, D.E., Gogna, P., Walter, S.D., Villeneuve, P.J., Friedenreich, C.M., Brenner, D.R., ComPARe Study Team, 2019. The current and future burden of cancer attributable to modifiable risk factors in Canada: Summary of results. Prev. Med. 122, 140–147. https://doi.org/10.1016/j.ypmed.2019.04.007

Poorolajal, J., Moradi, L., Mohammadi, Y., Cheraghi, Z., Gohari-Ensaf, F., 2020. Risk factors for stomach cancer: a systematic review and meta-analysis. Epidemiol. Health 42, e2020004. https://doi.org/10.4178/epih.e2020004

Rawla, P., Barsouk, A., 2019. Epidemiology of gastric cancer: global trends, risk factors and prevention. Gastroenterol. Rev. 14, 26–38. https://doi.org/10.5114/pg.2018.80001

Rothman, K.J., Greenland, S., Lash, T.L., 2008. Case-control studies, in: Rothman, K.J., Greenland, S., Lash, T.L. (Eds.), Modern Epidemiology, Third Edition. Lippincott Williams & Wilkins, Philadelphia, PA, USA.

Santibañez, M., Alguacil, J., de la Hera, M.G., Navarrete-Muñoz, E.M., Llorca, J., Aragonés, N., Kauppinen, T., Vioque, J., PANESOES Study Group, 2012. Occupational exposures and risk of stomach cancer by histological type. Occup. Environ. Med. 69, 268–275. https://doi.org/10.1136/oemed-2011-100071

Ur Rahman, M.S., Cao, J., 2016. Estrogen receptors in gastric cancer: Advances and perspectives. World J. Gastroenterol. 22, 2475–2482. https://doi.org/10.3748/wjg.v22.i8.2475

Wang, J.D., Wegman, D.H., Smith, T.J., 1983. Cancer risks in the optical manufacturing industry. Br. J. Ind. Med. 40, 177–181. https://doi.org/10.1136/oem.40.2.177

WCRF/AICR, 2018. World Cancer Research Fund/American Institute for Cancer Research. Continuous Update Project Report: Diet, nutrition, physical activity and stomach cancer. [WWW Document]. URL https://www.wcrf.org/sites/default/files/Stomach-cancer-report.pdf (accessed 2.23.21).

Weinmayr, G., Pedersen, M., Stafoggia, M., Andersen, Z.J., Galassi, C., Munkenast, J., Jaensch, A., Oftedal, B., Krog, N.H., Aamodt, G., Pyko, A., Pershagen, G., Korek, M., De Faire, U., Pedersen, N.L., Östenson, C.-G., Rizzuto, D., Sørensen, M., Tjønneland, A., Bueno-de-Mesquita, B., Vermeulen, R., Eeftens, M., Concin, H., Lang, A., Wang, M., Tsai, M.-Y., Ricceri, F., Sacerdote, C., Ranzi, A., Cesaroni, G., Forastiere, F., de Hoogh, K., Beelen, R., Vineis, P., Kooter, I., Sokhi, R., Brunekreef, B., Hoek, G., Raaschou-Nielsen, O., Nagel, G., 2018. Particulate matter air pollution components and incidence of cancers of the stomach and the upper aerodigestive tract in the European Study of Cohorts of Air Pollution Effects (ESCAPE). Environ. Int. 120, 163–171. https://doi.org/10.1016/j.envint.2018.07.030

Winkelstein, W., Kantor, S., 1969. Stomach cancer. Positive association with suspended particulate air pollution. Arch. Environ. Health 18, 544–547. https://doi.org/10.1080/00039896.1969.10665450

Wong, J.-H., Wang, Y.-S., Nam, S., Ho, K.-H., Chang, C.-M., Chen, K.-C., Chen, Y.-F., Chang, W.-C., 2019. Phthalate plasticizer di(2-ethyl-hexyl) phthalate induces cyclooxygenase-2 expression in gastric adenocarcinoma cells. Environ. Toxicol. 34, 1191–1198. https://doi.org/10.1002/tox.22820

Wu, F., Xu, R., Kim, K., Martin, J., Safe, S., 2008. In vivo profiling of estrogen receptor/specificity protein-dependent transactivation. Endocrinology 149, 5696–5705. https://doi.org/10.1210/en.2008-0720

Yin, J., Wu, X., Li, S., Li, C., Guo, Z., 2020. Impact of environmental factors on gastric cancer: A review of the scientific evidence, human prevention and adaptation. J. Environ. Sci. China 89, 65–79. https://doi.org/10.1016/j.jes.2019.09.025

Zhao, Q., Wang, Y., Cao, Y., Chen, A., Ren, M., Ge, Y., Yu, Z., Wan, S., Hu, A., Bo, Q., Ruan, L., Chen, H., Qin, S., Chen, W., Hu, C., Tao, F., Xu, D., Xu, J., Wen, L., Li, L., 2014. Potential health risks of heavy metals in cultivated topsoil and grain, including correlations with human primary liver, lung and gastric cancer, in Anhui province, Eastern China. Sci. Total Environ. 470–471, 340–347. https://doi.org/10.1016/j.scitotenv.2013.09.086

Zhao, Y., Krishnadasan, A., Kennedy, N., Morgenstern, H., Ritz, B., 2005. Estimated effects of solvents and mineral oils on cancer incidence and mortality in a cohort of aerospace workers. Am. J. Ind. Med. 48, 249–258. https://doi.org/10.1002/ajim.20216

Figure legends

Figure 1: odds ratios of gastric cancer with statistically significant results and based on a number of controls and cases ≥5 for the analysis of proximity to industrial facilities by category of industrial group (A), and for the analysis of proximity to industries releasing specific pollutants (B). X-axis is plotted in logarithmic scale.

Figure 2: odds ratios of non-cardia tumors with statistically significant results and based on a number of controls and cases ≥5 for the analysis of proximity to industrial facilities by category of industrial group (A), and for the analysis of proximity to industries releasing specific pollutants (B). X-axis is plotted in logarithmic scale.

Table 1: Characteristics of gastric cancer cases and controls.

Characteristic	Controls (n=2664)	Cases (n=137)	*p*-value[a]
Age, mean (SD)	63.9 (11.5)	67.7 (11.3)	<0.001
Sex, n (%)			
Men	1422 (53.4)	79 (57.7)	
Women	1242 (46.6)	58 (42.3)	0.372
Province, n (%)			
Asturias	149 (5.6)	14 (10.2)	
Barcelona	714 (26.8)	16 (11.7)	
Cantabria	295 (11.1)	1 (0.7)	
Granada	110 (4.1)	2 (1.5)	
Huelva	101 (3.8)	13 (9.5)	
Leon	320 (12.0)	72 (52.6)	
Madrid	708 (26.6)	11 (8.0)	
Navarre	251 (9.4)	7 (5.1)	
Valencia	16 (0.6)	1 (0.7)	<0.001
Family history of gastric cancer, n (%)			
None	2362 (88.7)	111 (81.0)	
Second degree only	131 (4.9)	5 (3.6)	
1 first degree	163 (6.1)	19 (13.9)	
>1 first degree	8 (0.3)	2 (1.5)	<0.001
Tobacco smoking, n (%)			
Never	1185 (44.5)	70 (51.1)	
Former smoker	918 (34.5)	38 (27.7)	
Current smoker	561 (21.0)	29 (21.2)	0.223
Educational level, n (%)			
Less than primary school	540 (20.3)	32 (23.4)	
Primary school completed	932 (35.0)	59 (43.1)	
Secondary school	721 (27.0)	32 (23.4)	
University	471 (17.7)	14 (10.2)	0.049
Individuals living in their current residence for ≥10 years, n (%)	2249 (84.4)	109 (79.6)	0.161
Histological type, n (%)			
Intestinal	-	65 (47.4)	
Diffuse	-	29 (21.2)	
Other / not classified	-	43 (31.4)	
Tumor site, n (%)			
Cardia	-	19 (13.9)	
Non-cardia	-	107 (78.1)	
Other / not classified	-	11 (8.0)	

[a] Two-sided Chi-square test and Mann-Whitney U-test, where appropriate.

Table 2: Odds ratios of gastric cancer by distance to the industrial installations as a whole (all individuals), by histological type, and by tumor site.

	All of the individuals			Analysis by histological type				Analysis by tumor site			
	n (%)			Intestinal (65 cases)		Diffuse (29 cases)		Cardia (19 cases)		Non-cardia (107 cases)	
Industrial distance	Controls (n=2664)	Cases (n=137)	OR (95%CI)[a]	Cases (n)	OR (95%CI)[b]	Cases (n)	OR (95%CI)[b]	Cases (n)	OR (95%CI)[b]	Cases (n)	OR (95%CI)[b]
Reference (>3 km)	870 (32.7)	50 (36.5)	1.00	20	1.00	11	1.00	9	1.00	35	1.00
≤3 Km	1794 (67.3)	87 (63.5)	0.81 (0.54-1.22)	45	1.06 (0.58-1.93)	18	0.79 (0.34-1.83)	10	0.70 (0.25-1.97)	72	0.96 (0.60-1.54)
≤2.5 Km	1423 (53.4)	60 (43.8)	0.73 (0.47-1.13)	28	0.89 (0.47-1.70)	12	0.66 (0.27-1.65)	9	0.78 (0.27-2.23)	47	0.83 (0.50-1.37)
≤2 Km	1080 (40.5)	45 (32.8)	0.84 (0.53-1.34)	18	0.95 (0.47-1.91)	12	1.05 (0.42-2.61)	7	0.95 (0.31-2.91)	35	0.96 (0.57-1.63)
≤1.5 Km	587 (22.0)	28 (20.4)	0.93 (0.55-1.58)	12	1.06 (0.48-2.33)	8	1.28 (0.47-3.48)	4	0.98 (0.27-3.58)	22	1.07 (0.59-1.95)
≤1 Km	296 (11.1)	14 (10.2)	0.79 (0.41-1.54)	7	0.93 (0.36-2.40)	3	1.06 (0.27-4.23)	3	1.07 (0.25-4.61)	9	0.76 (0.34-1.69)

[a] ORs were estimated from various mixed multiple logistic regression models (an independent model for each of the categories of industrial distance), including age, sex, education, family history of gastric cancer, tobacco smoking, and province of residence (the latter as a random effect term).

[b] ORs were estimated from various multinomial logistic regression models (an independent model for each of the categories of industrial distance), including age, sex, education, family history of gastric cancer, tobacco smoking, and province of residence.

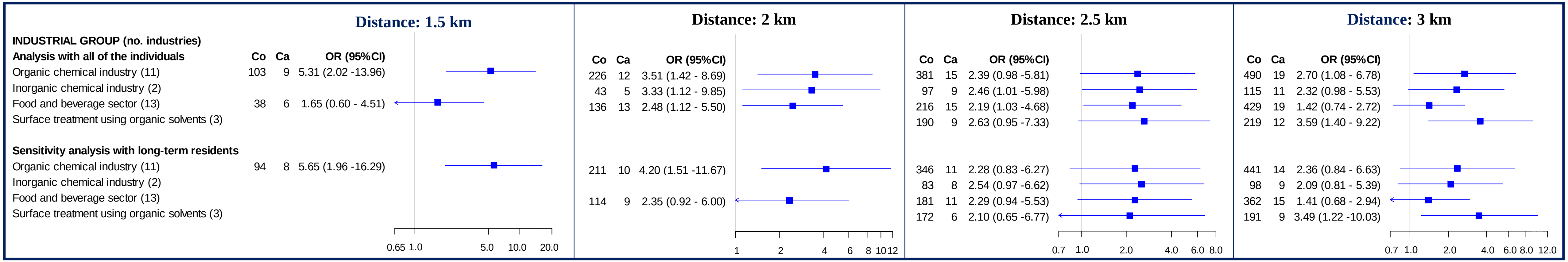
Table 3: Odds ratios of gastric cancer by distance to the industrial installations as a whole (individuals living in their current residence for ≥10 years), by histological type, and by tumor site.

	Individuals living in their current residence for ≥10 years			Analysis by histological type				Analysis by tumor site			
	n (%)			Intestinal (51 cases)		Diffuse (26 cases)		Cardia (17 cases)		Non-cardia (84 cases)	
Industrial distance	Controls (n=2249)	Cases (n=109)	OR (95%CI)[a]	Cases (n)	OR (95%CI)[b]	Cases (n)	OR (95%CI)[b]	Cases (n)	OR (95%CI)[b]	Cases (n)	OR (95%CI)[b]
Reference (>3 km)	728 (32.4)	41 (37.6)	1.00	16	1.00	10	1.00	8	1.00	29	1.00
≤3 Km	1521 (67.6)	68 (62.4)	0.73 (0.46-1.17)	35	0.93 (0.47-1.84)	16	0.79 (0.32-1.95)	9	0.63 (0.20-1.93)	55	0.86 (0.50-1.46)
≤2.5 Km	1192 (53.0)	46 (42.2)	0.66 (0.40-1.08)	22	0.80 (0.39-1.67)	10	0.63 (0.23-1.69)	8	0.72 (0.23-2.26)	35	0.74 (0.42-1.30)
≤2 Km	901 (40.1)	37 (33.9)	0.86 (0.51-1.45)	15	0.94 (0.43-2.07)	10	1.04 (0.39-2.80)	7	1.07 (0.33-3.42)	28	0.97 (0.54-1.76)
≤1.5 Km	480 (21.3)	23 (21.1)	0.95 (0.53-1.72)	10	1.05 (0.44-2.52)	6	1.17 (0.38-3.57)	4	1.16 (0.30-4.46)	18	1.10 (0.56-2.15)
≤1 Km	237 (10.5)	11 (10.1)	0.80 (0.38-1.70)	5	0.81 (0.27-2.44)	2	0.84 (0.16-4.30)	3	1.39 (0.32-6.17)	7	0.76 (0.31-1.91)

[a] ORs were estimated from various mixed multiple logistic regression models (an independent model for each of the categories of industrial distance), including age, sex, education, family history of gastric cancer, tobacco smoking, and province of residence (the latter as a random effect term).

[b] ORs were estimated from various multinomial logistic regression models (an independent model for each of the categories of industrial distance), including age, sex, education, family history of gastric cancer, tobacco smoking, and province of residence.

A) CATEGORIES OF INDUSTRIAL SECTORS



Distance: 1.5 km

INDUSTRIAL GROUP (no. industries)	Co	Ca	OR (95%CI)
Analysis with all of the individuals			
Organic chemical industry (11)	103	9	5.31 (2.02 -13.96)
Inorganic chemical industry (2)			
Food and beverage sector (13)	38	6	1.65 (0.60 - 4.51)
Surface treatment using organic solvents (3)			
Sensitivity analysis with long-term residents			
Organic chemical industry (11)	94	8	5.65 (1.96 -16.29)
Inorganic chemical industry (2)			
Food and beverage sector (13)			
Surface treatment using organic solvents (3)			

Distance: 2 km

Co	Ca	OR (95%CI)
226	12	3.51 (1.42 - 8.69)
43	5	3.33 (1.12 - 9.85)
136	13	2.48 (1.12 - 5.50)
211	10	4.20 (1.51 -11.67)
114	9	2.35 (0.92 - 6.00)

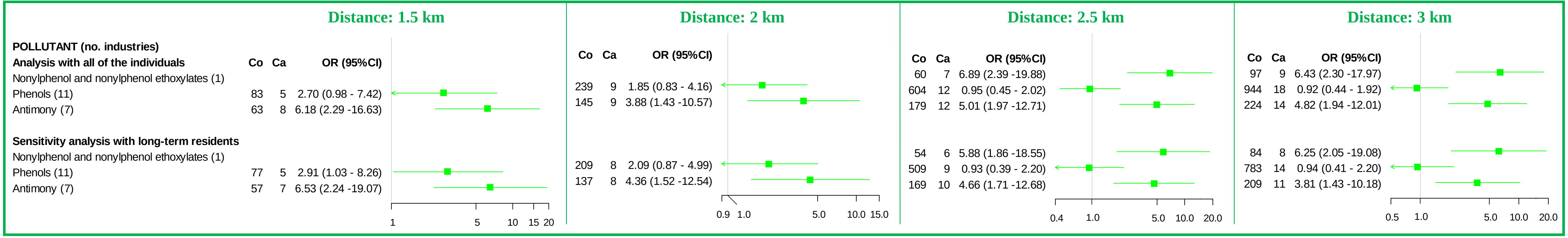
Distance: 2.5 km

Co	Ca	OR (95%CI)
381	15	2.39 (0.98 -5.81)
97	9	2.46 (1.01 -5.98)
216	15	2.19 (1.03 -4.68)
190	9	2.63 (0.95 -7.33)
346	11	2.28 (0.83 -6.27)
83	8	2.54 (0.97 -6.62)
181	11	2.29 (0.94 -5.53)
172	6	2.10 (0.65 -6.77)

Distance: 3 km

Co	Ca	OR (95%CI)
490	19	2.70 (1.08 - 6.78)
115	11	2.32 (0.98 - 5.53)
429	19	1.42 (0.74 - 2.72)
219	12	3.59 (1.40 - 9.22)
441	14	2.36 (0.84 - 6.63)
98	9	2.09 (0.81 - 5.39)
362	15	1.41 (0.68 - 2.94)
191	9	3.49 (1.22 -10.03)

B) SPECIFIC POLLUTANTS



Distance: 1.5 km

POLLUTANT (no. industries)	Co	Ca	OR (95%CI)
Analysis with all of the individuals			
Nonylphenol and nonylphenol ethoxylates (1)			
Phenols (11)	83	5	2.70 (0.98 - 7.42)
Antimony (7)	63	8	6.18 (2.29 -16.63)
Sensitivity analysis with long-term residents			
Nonylphenol and nonylphenol ethoxylates (1)			
Phenols (11)	77	5	2.91 (1.03 - 8.26)
Antimony (7)	57	7	6.53 (2.24 -19.07)

Distance: 2 km

Co	Ca	OR (95%CI)
239	9	1.85 (0.83 - 4.16)
145	9	3.88 (1.43 -10.57)
209	8	2.09 (0.87 - 4.99)
137	8	4.36 (1.52 -12.54)

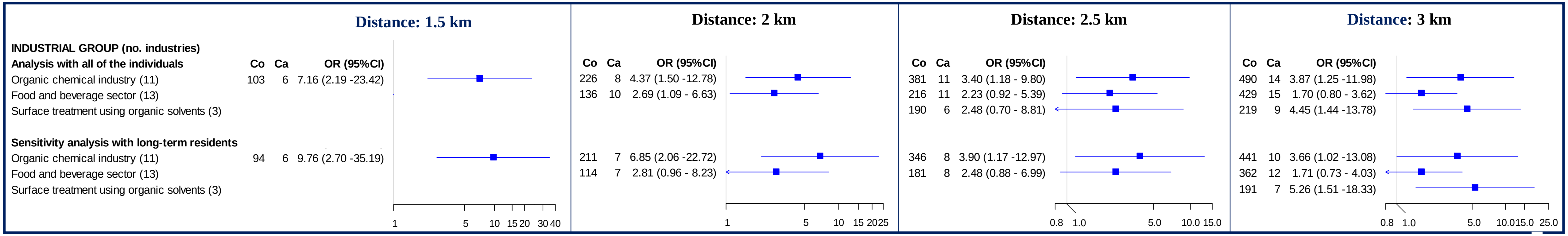
Distance: 2.5 km

Co	Ca	OR (95%CI)
60	7	6.89 (2.39 -19.88)
604	12	0.95 (0.45 - 2.02)
179	12	5.01 (1.97 -12.71)
54	6	5.88 (1.86 -18.55)
509	9	0.93 (0.39 - 2.20)
169	10	4.66 (1.71 -12.68)

Distance: 3 km

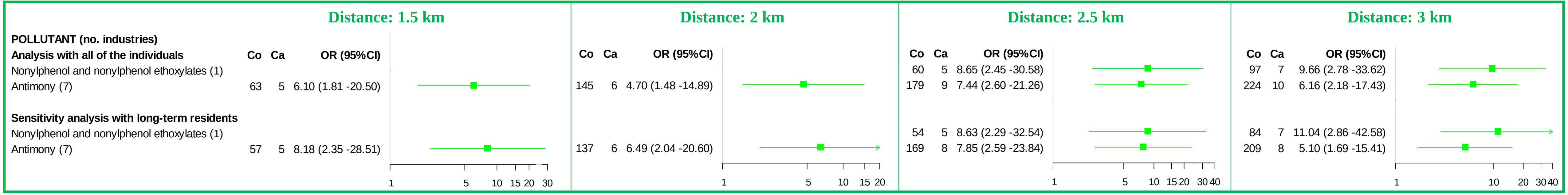
Co	Ca	OR (95%CI)
97	9	6.43 (2.30 -17.97)
944	18	0.92 (0.44 - 1.92)
224	14	4.82 (1.94 -12.01)
84	8	6.25 (2.05 -19.08)
783	14	0.94 (0.41 - 2.20)
209	11	3.81 (1.43 -10.18)

A) CATEGORIES OF INDUSTRIAL SECTORS



	Distance: 1.5 km			Distance: 2 km			Distance: 2.5 km			Distance: 3 km		
INDUSTRIAL GROUP (no. industries)												
Analysis with all of the individuals	**Co**	**Ca**	**OR (95%CI)**	**Co**	**Ca**	**OR (95%CI)**	**Co**	**Ca**	**OR (95%CI)**	**Co**	**Ca**	**OR (95%CI)**
Organic chemical industry (11)	103	6	7.16 (2.19 -23.42)	226	8	4.37 (1.50 -12.78)	381	11	3.40 (1.18 - 9.80)	490	14	3.87 (1.25 -11.98)
Food and beverage sector (13)				136	10	2.69 (1.09 - 6.63)	216	11	2.23 (0.92 - 5.39)	429	15	1.70 (0.80 - 3.62)
Surface treatment using organic solvents (3)							190	6	2.48 (0.70 - 8.81)	219	9	4.45 (1.44 -13.78)
Sensitivity analysis with long-term residents												
Organic chemical industry (11)	94	6	9.76 (2.70 -35.19)	211	7	6.85 (2.06 -22.72)	346	8	3.90 (1.17 -12.97)	441	10	3.66 (1.02 -13.08)
Food and beverage sector (13)				114	7	2.81 (0.96 - 8.23)	181	8	2.48 (0.88 - 6.99)	362	12	1.71 (0.73 - 4.03)
Surface treatment using organic solvents (3)										191	7	5.26 (1.51 -18.33)

B) SPECIFIC POLLUTANTS



	Distance: 1.5 km			Distance: 2 km			Distance: 2.5 km			Distance: 3 km		
POLLUTANT (no. industries)												
Analysis with all of the individuals	**Co**	**Ca**	**OR (95%CI)**	**Co**	**Ca**	**OR (95%CI)**	**Co**	**Ca**	**OR (95%CI)**	**Co**	**Ca**	**OR (95%CI)**
Nonylphenol and nonylphenol ethoxylates (1)							60	5	8.65 (2.45 -30.58)	97	7	9.66 (2.78 -33.62)
Antimony (7)	63	5	6.10 (1.81 -20.50)	145	6	4.70 (1.48 -14.89)	179	9	7.44 (2.60 -21.26)	224	10	6.16 (2.18 -17.43)
Sensitivity analysis with long-term residents												
Nonylphenol and nonylphenol ethoxylates (1)							54	5	8.63 (2.29 -32.54)	84	7	11.04 (2.86 -42.58)
Antimony (7)	57	5	8.18 (2.35 -28.51)	137	6	6.49 (2.04 -20.60)	169	8	7.85 (2.59 -23.84)	209	8	5.10 (1.69 -15.41)