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Residential proximity to industrial pollution sources and colorectal cancer risk: A multicase-control study (MCC-Spain)

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Abbreviations: PM_{10}, Particulate matter with a diameter between 2.5 and 10 µm; POPs, Persistent organic pollutants; BHA, Basic health area; IPPC, Integrated Pollution Prevention and Control; E-PRTR, European Pollutant Release and Transfer Register; ORs, Odds ratios; 95%CIs, 95% confidence intervals; PAHs, Polycyclic aromatic hydrocarbons; IARC, International Agency for Research on Cancer; PACs, Polycyclic aromatic chemicals; Non-HPCs, Non-halogenated phenolic chemicals; VOCs, Volatile organic compounds; METS, Metabolic equivalent units; *p*-BH, *p*-value adjusted by Benjamini & Hochbergs's method; *p*-BY, *p*-value adjusted by Benjamini & Yekutieli's method

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ABSTRACT

Background: Colorectal cancer is the third most frequent tumor in males and the second in females worldwide. In Spain, it is an important and growing health problem, and epidemiologic research focused on potential risk factors, such as environmental exposures, is necessary.

Objectives: To analyze the association between colorectal cancer risk and residential proximity to industries, according to pollution discharge route, industrial groups, categories of carcinogens and other toxic substances, and specific pollutants released, in the context of a population-based multicase-control study of incident cancer carried out in Spain (MCC-Spain).

Methods: MCC-Spain included 557 colorectal cancer cases and 2948 controls in 11 provinces, frequency matched by sex, age, and region of residence. Distances were computed from subjects' residences to each of the 134 industries located in the study area. 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 industrial facilities, adjusting for matching variables and other confounders.

Results: Excess risk (OR; 95%CI) of colorectal cancer was detected near industries overall for all distances analyzed, from 1 km (2.03; 1.44–2.87) to 3 km (1.26; 1.00–1.59). In general, industries releasing pollutants to air showed higher excess risks than facilities releasing pollution to water. By industrial sector, excess risk (OR; 95%CI) was found near (≤3 km) production of metals (2.66; 1.77–4.00), surface treatment of metals (1.48; 1.08–2.02), glass and mineral fibers (2.06; 1.39–3.07), organic chemical industry (4.80; 3.20–7.20), inorganic chemical industry (6.74; 4.38–10.36), food/beverage sector (3.34; 2.38–4.68), and surface treatment using organic solvents (6.16; 4.06–9.36). By pollutants, the main excess risks (OR; 95%CI) were found near (≤3 km) industries releasing nonylphenol (9.19; 5.91–14.28), antimony (5.30; 3.45–8.15), naphthalene (3.11; 2.16–4.49), organotin compounds (2.64; 1.76–3.98), manganese (2.53; 1.63–3.93), dichloromethane (2.52; 1.74–3.66), and vanadium (2.49; 1.59–3.91).

Conclusions: Our results support the hypothesis that residing in the proximity of industries may be a risk factor for colorectal cancer.

1. Introduction

Colorectal cancer is the third most frequent tumor in males and second in females worldwide, with 1.03 and 0.82 million new cases in 2018, respectively (Ferlay et al., 2019). In the same year, in Spain, 37,172 new cases of colorectal cancer were estimated in both sexes, accounting for 13.7% of all cancer sites (International Agency for Research on Cancer, 2020). The temporal evolution of colorectal cancer incidence in Spain has shown a gradual increase in the last decades, probably ascribed to the increase in the prevalence of known modifiable risk factors, such as unhealthy dietary patterns (high consumption of processed and red meat, and low consumption of fiber), smoking and excessive alcohol consumption, obesity, and sedentary lifestyle (Brenner et al., 2014; Center et al., 2009; World Cancer Research Fund and American Institute for Cancer Research, 2018). This cancer is an important and growing health problem in Spain (and in the most industrialized countries) and, on the other hand, the above-mentioned risk factors account for between 45% and 58% of all colorectal cancer cases (Gu et al., 2018; Islami et al., 2018; Whiteman et al., 2015). Therefore, epidemiologic research focused on other potential risk factors that may explain the remaining variation, such as environmental exposures, is necessary.

In relation to industrial pollution, populations living close to facilities are exposed to a high number of carcinogens and toxic substances, some of them potentially related to colorectal cancer, such as some polychlorinated biphenyls, arsenic, particulate matter with a diameter between 2.5 and 10 µm (PM_{10}), persistent organic pollutants (POPs), and metalworking fluids (Friesen et al., 2012; Howsam et al., 2004; Kim et al., 2018; Lee et al., 2018; Núñez et al., 2016). Therefore, all these evidences support the need to carry out epidemiological studies to ascertain whether to reside near industrial pollution sources might have an influence on the incidence of colorectal cancer.

The present study analyzed the association between colorectal cancer risk and residential proximity to industrial plants, according to pollution discharge route, industrial groups, categories of carcinogens and other toxic substances, and certain industrial pollutants, in the context of a Spanish population-based multicase-control study of incident cancer (MCC-Spain).

2. Materials and methods

2.1. Subjects and study area

The design of the MCC-Spain study was previously described (Castaño-Vinyals et al., 2015), as well as the design and the methodology of a similar paper about the risk of breast cancer and proximity to industries (García-Pérez et al., 2018). Briefly, among the five types of cancers included in the MCC-Spain study (colorectal, breast, prostate, leukemias, and gastric), 2140 histologically confirmed colorectal cancer cases (International Classification of Diseases-10th: C18-C20, D01.0-D01.2), aged 20–85 years, were recruited from collaborating hospitals in 11 Spanish provinces (Asturias, Barcelona, Cantabria, Gipuzkoa, Granada, Huelva, Leon, Madrid, Murcia, Navarre, and Valencia) between 2008 and 2013. All of them resided in the hospitals' catchment areas for at least 6 months prior to recruitment.

Cases were identified, as soon as possible, after the diagnosis was made, through active search (by our research personnel) that included periodical visits to the collaborating hospital departments (oncology, gastroenterology, radiotherapy, pathology, and general surgery). Moreover, our research personnel reviewed the hospital admission registries weekly.

To facilitate the logistics of the study, 3950 population-based controls for the whole MCC-Spain study (common to the five types of tumors) were randomly selected from administrative records of specific primary care health centers selected for our study and located within hospitals' catchment areas, and were frequency matched to the overall distribution of all cases (colorectal cancer and other) by sex, region (province), and age (in 5-year age groups). Specifically, the selection process was as follows: a) Firstly, we made an initial estimate of the age-sex distribution that all combined cases would have in each province of the study, according to the cancers they recruited and to the incidence rates of cancer from the Spanish cancer registers; b) then, we applied these estimates to predefine the age-sex distribution of our population-based controls, which were selected randomly from the general practitioner lists of 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 needed in an attempt to ensure that each case had at least one control of the same 5-year age interval and sex in each province.

On the other hand, the Spanish territorial framework in relation to the primary care health is divided into health areas, which contain a hospital of reference. Every health area is divided into several basic health areas (BHAs) and every BHA may contain one or more primary care health centers. Whereas the cases were recruited in complete health areas (which cover many primary care health centers), the controls were selected in specific BHAs (which cover few primary care health centers). Taking into account that the study area of the controls (specific primary care health centers) was smaller than the study area of the cases (hospitals' catchment areas, which correspond to entire health areas), the present paper was restricted to those zones with controls and cases residing in BAHs of the specific (selected) primary care health centers. Therefore, those zones with only cases (and no controls), as well as small administrative divisions (municipal districts or *"pedanías"*) where there were only controls (without cases), were excluded.

Supplementary Data, Figure S1 shows a flow chart displaying the selection process of cases and controls.

2.2. Data collection

Information about family history of colorectal cancer, medical history, sociodemographic factors, physical activity, diet, and lifestyle was collected in a structured computerized questionnaire administered by interviewers in a face-to-face interview, with an average duration of 70 min (range: 30–130). In order to reduce the interviewer bias, professional interviewers with experience (most of them sociologists or nurses) were trained to adhere to the question and answer format strictly, with the same degree of questioning for both controls and cases. The *ad hoc* epidemiological questionnaire was made by the researchers participating in the project after discussing and reaching consensus on the main questions to achieve the MCC-Spain objectives. In many instances, questions were based on questionnaires used in previous studies by the research team. Controls were initially contacted via telephone and those who agreed to participate in the study were scheduled for a personal interview. All interviews of the participants were carried out within the collaborating hospitals. Dietary information in the year before diagnosis was obtained through a food-frequency questionnaire provided to each participant at the interview for self-fulfillment and returned by mail. Missing values on specific questions and relevant variables were completed through subsequent telephone contact. Moreover, hip and waist circumference, weight, and height were measured during the interview.

2.3. Residential locations

Each participant's current residence was geocoded into Universal Transverse Mercator Zone 30 (ED50) coordinates using Google Earth Pro. Every single pair of coordinates was thoroughly checked using the National Cadastre and the "street-view" application of Google Earth Pro. Finally, 6069 individuals' residences (2128 cases and 3941 controls) were geocoded with valid coordinates. Taking into account the way in which population-based controls were selected (García-Pérez et al., 2018), only cases and controls residing in the area of influence of the corresponding primary care health centers and with complete

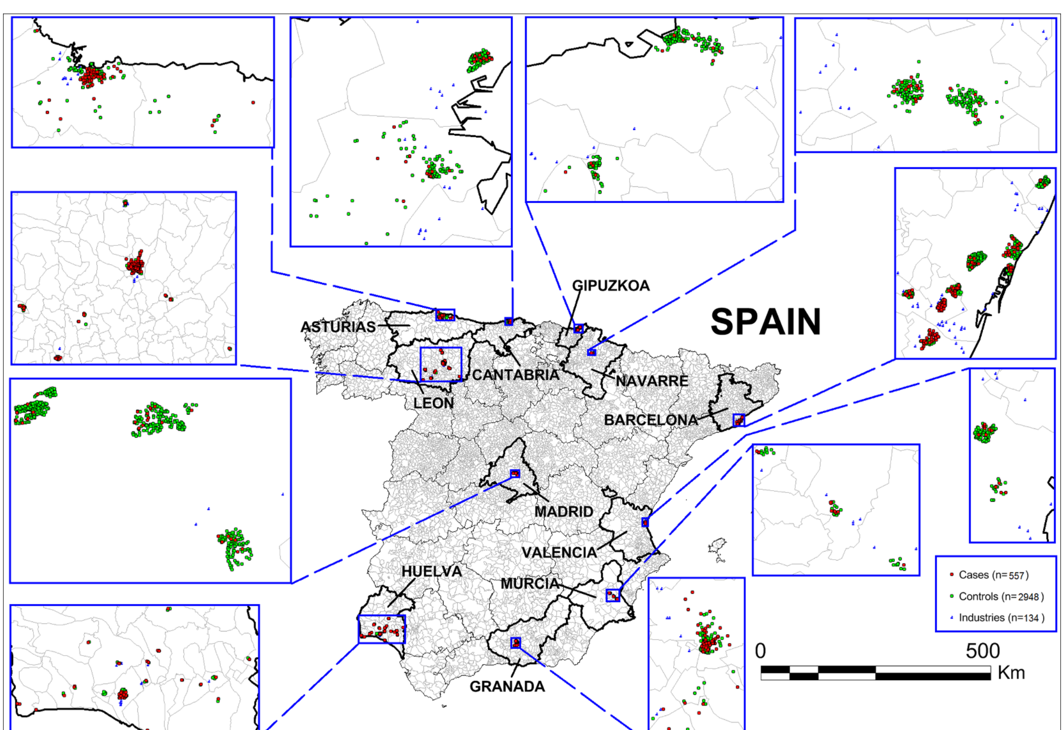

Fig. 1. Geographic distribution of cases, controls, and industries located in the study area.

information are included in the present study (see Supplementary Data, Figure S1).

2.4. Industrial facility locations

Industrial information about facilities governed by the Integrated Pollution Prevention and Control (IPPC) Directive and installations included in the European Pollutant Release and Transfer Register (E-PRTR), corresponding to 2009, was used. The IPPC is governed both Directive 2008/1/EC and by Act 16/2002 (which incorporates this Directive into the Spanish legal system), whereas the E-PRTR was passed by the European Commission in 2007 (European Environment Agency (EEA), 2020). Briefly, the member states of the EU have the obligation to declare all pollutant emissions to water (direct to water and indirect to water (via sewage treatment plants)), air, and soil that exceed the designated thresholds. The industrial information included in our paper was provided through the Spanish Ministry for the Ecological Transition (Spanish Ministry for the Ecological Transition, 2020).

Taking the minimum colorectal tumor induction period into account (generally 10 years for solid tumors), the facilities which came into operation prior to 10 years before the mid-year of the recruitment period of each province were selected. Supplementary Data, Figure S2 shows the distribution of the years of commencement of operations of the facilities studied, by category of industrial group, where the mean year of commencement of operations of the industries as a whole was 1962. The final database included information, previously validated (García-Pérez et al., 2019), about: a) the geographic coordinates of the 134 installations located in the study area (see Fig. 1), which were classified into one of the 22 industrial groups (according to E-PRTR categories) listed in Supplementary Data, Table S1; and, b) the types and amounts of pollutants released by these industrial plants to air and water.

2.5. Exposure coding and statistical analyses

The differences in the distribution between the characteristics of colorectal cancer cases and controls were tested using the two-sided Chi-square test (with Yates's correction for continuity) and Mann-Whitney *U* test (with continuity correction), where appropriate.

For each subject, the shortest distance between its residence and each industrial installation was calculated. Five types of statistical analysis, using mixed multiple unconditional logistic regression models, were performed to estimate odds ratios (ORs) and 95% confidence intervals (95%CIs) of the associations between colorectal cancer risk and various definitions of proximity to industrial installations (as a proxy of the real exposure to the industrial pollution). All models included matching factors (province of residence as a random effect, sex, and age), and potential confounders: body mass index one year prior the interview (continuous), family history of colorectal cancer (none, second degree only, one first degree, and more than one first degree), tobacco smoking (never, former smoker, and current smoker), educational level (less than primary school, primary school completed, secondary school, and university graduate), physical activity in leisure time (in metabolic equivalent units (METS)) (continuous), total energy intake (continuous), alcohol consumption (continuous), vegetable intake (continuous), and red and processed meat intake (continuous).

1) Analysis 1 (relationship between proximity to industrial installations as a whole and colorectal cancer risk). Taking into account several distances 'D' (1, 1.5, 2, 2.5, and 3 km) for the exposure variable, each subject was classified as resident in the industrial area, if it resided at ≤'D' km from any industry, or resident within the *"reference area"*, if it resided at > 3 km from any industry. With the purpose of analyzing the possible routes of exposure to the pollution released by the industries, a first sub-analysis stratifying the ORs by pollution discharge route (air and only water) was performed. Additionally, taking into account that the sex is a possible modifier of the associations between many exposures and diseases, a second sub-analysis stratifying the ORs by sex was performed.
2) Analysis 2 (relationship between proximity to installations by category of industrial group and colorectal cancer risk). Taking into account the 22 categories of industrial groups defined in Supplementary Data, Table S1, an exposure variable for each distance 'D' was created as follows: if the subject resided at ≤'D' km from any installation belonging to the industrial group analyzed, it was classified as resident near a specific *"industrial group"*, whereas if the subject resided at > 3 km from any industry, it was classified as resident in the *"reference area"*.
3) Analysis 3 (relationship between residential proximity to industries releasing groups of carcinogens and other toxic substances and colorectal cancer risk). For this purpose, the carcinogens were classified according to the International Agency for Research on Cancer (IARC) as: a) Group 1 carcinogenic to humans (arsenic and compounds, cadmium and compounds, chromium and compounds, nickel and compounds, lindane, dioxins + furans, pentachlorophenol, polychlorinated biphenyls, trichloroethylene, vinyl chloride, benzene, ethylene oxide, polycyclic aromatic hydrocarbons (PAHs), PM_{10}, total suspended particulate matter, and benzo(a)pyrene); b) Group 2A: probably carcinogenic to humans (lead and compounds, aldrin, DDT, dichloromethane, dieldrin, tetrachloroethylene, and hexabromobiphenyl); and, c) Group 2B: possibly carcinogenic to humans (chlordane, 1,2-dichloroethane, heptachlor, hexachlorobenzene, 1,2,3,4,5,6-hexachlorocyclohexane, mirex, tetrachloromethane, 1,1,2,2-tetrachloroethane, trichloromethane, ethyl benzene, naphthalene, di-(2-ethyl hexyl) phthalate, cobalt and compounds, benzo(b)fluoranthene, benzo(k) fluoranthene, and indeno(1,2,3-cd)pyrene).
   On the other hand, the toxic substances were classified in 9 groups: a) Metals (arsenic and compounds, cadmium and compounds, chromium and compounds, copper and compounds, mercury and compounds, nickel and compounds, lead and compounds, zinc and compounds, organotin compounds, tributyltin and compounds, triphenyltin and compounds, thallium, antimony, cobalt, manganese, and vanadium); b) Pesticides (alachlor, aldrin, atrazine, chlordane, chlorfenvinphos, chlorpyrifos, DDT, dieldrin, diuron, endosulfan, endrin, heptachlor, lindane, mirex, pentachlorobenzene, pentachlorophenol, simazine, tetrachloromethane, isoproturon, organotin compounds, tributyltin and compounds, triphenyltin and compounds, trifluralin, and isodrin); c) PACs: polycyclic aromatic chemicals (anthracene, ethylene oxide, naphthalene, PAHs, fluoranthene, benzo(g,h,i)perylene, benzo(a)pyrene, benzo(b) fluoranthene, benzo(k)fluoranthene, and indeno(1,2,3-cd)pyrene); d) Non-HPCs: non-halogenated phenolic chemicals (nonylphenol and nonylphenol ethoxylates, and octylphenols and octylphenol ethoxylates); e) Plasticizers (di-(2-ethyl hexyl) phthalate, and $C_{10\text{-}13}$-chloroalkanes); f) POPs (aldrin, chlordane, DDT, dieldrin, endosulfan, endrin, heptachlor, hexachlorobenzene, 1,2,3,4,5,6-hexachlorocyclohexane, lindane, mirex, dioxins + furans, pentachlorobenzene, polychlorinated biphenyls, brominated diphenylethers, organotin compounds, PAHs, hexabromobiphenyl, benzo(a)pyrene, benzo(b)fluoranthene, and benzo(k)fluoranthene); g) VOCs: volatile organic compounds (non-methane volatile organic compounds, 1,2-dichloroethane, dichloromethane, hexachlorobutadiene, tetrachloroethylene, trichlorobenzenes, 1,1,1-trichloroethane, trichloroethylene, trichloromethane, vinyl chloride, benzene, ethyl benzene, ethylene oxide, naphthalene, and toluene); h) Solvents (1,2-dichloroethane, dichloromethane, tetrachloroethylene, trichlorobenzenes, 1,1,1-trichloroethane, trichloroethylene, trichloromethane, benzene, ethyl benzene, toluene, and xylenes); and, i) Other (PM_{10}, and total suspended particulate matter). To this end, an exposure variable for each distance 'D' was

created, where each subject was categorized as resident near industries releasing the specific "*group of carcinogens or toxic substances"* or resident in the "*reference area"*, analogous to the previous analysis.

4) Analysis 4 (relationship between residential proximity to industries by specific industrial pollutants released by the facilities and colorectal cancer risk). To this end, an exposure variable for each distance 'D' was created, where each subject was categorized as resident near industries releasing the specific "*industrial pollutant"* or resident in the "*reference area"*, analogous to the previous analyses.
5) Analysis 5 (assessment of the existence of radial effects near industrial facilities). An analysis to assess the change in colorectal cancer risk with increasing proximity to industrial facilities (risk gradient) was performed (see Supplementary Data, Appendix A).

In addition, with the aim of introducing robustness in our analyses and controlling potential biases, only individuals living in their last residence for ≥ 10 years (long-term residents) were considered in a sensitivity analysis performed for the analyses mentioned in the previous paragraphs.

Given that, by design in the MCC-Spain study, matching conditions were applied taking the overall distribution of all cancer cases recruited in each province into account ("multicase-control"), unconditional logistic regression including the matched characteristics in the model was used (Rothman et al., 2008).

Lastly, adjusted *p*-values controlling for the false discovery rate (expected proportion of false positives) (Benjamini and Hochberg, 1995; Benjamini and Yekutieli, 2001) were used in our analyses to take the problem of multiple comparison into account.

3. Results

3.1. Characteristics of the study population

The final study population (individuals with no missing values in any of the selected confounders) comprised 557 cases and 2948 controls (see Supplementary Data, Figure S1), whose main characteristics are listed in Table 1 and their geographic distribution is depicted in Fig. 1.

In general, controls had a lower body mass index, higher educational level, and were slightly younger than cases. A sensitivity analysis, testing the distribution of the main characteristics between the included and excluded cases showed similar results, with the exception of tobacco consumption and province (see Supplementary Data, Table S2).

3.2. Results of the overall analysis (analysis 1)

ORs of colorectal cancer (considering all individuals) in the proximity to all industrial facilities (as a whole) (Table 2) were statistically significant for all distances analyzed in the multivariate analysis, from 1 km (OR = 2.03; 95%CI = 1.44–2.87) to 3 km (OR = 1.26; 95%CI = 1.00–1.59). On stratifying the ORs by pollution discharge route, the increased risks were higher and statistically significant in the proximity to installations releasing pollutants to air, from 1 km (OR = 2.12; 95%CI = 1.49–3.02) to 2 km (OR = 1.55; 95%CI = 1.19–2.02), and higher in the proximity to industries releasing pollutants to water (only) between 2.5 km and 3 km (although with very few individuals and non-statistically significant in the case of 2.5 km). The univariate analysis showed similar results. In the sensitivity analysis considering only long-term residents, the increased risks in the proximity to all installations were slightly lower between 3 km and 1.5 km, and slightly higher at 1 km, maintaining the statistical significance for all distances (with the exception of 3 km). The sub-analysis stratified by pollution discharge route showed similar results than in the sub-analysis with all individuals.

ORs of colorectal cancer stratified by sex are shown in Table 3. In general, the increased risks for women (with ORs ranging from 1.61 at 3 km to 3.08 at 1 km) were higher than for men (with ORs ranging from 1.13 at 3 km to 1.79 at 1 km), although the *p*-values for the interaction between the exposure variable (proximity to industries) and sex were not statistically significant (with the exception of 3 km: *p*-int = 0.043).

3.3. Results by industrial group (analysis 2)

ORs of colorectal cancer by industrial group (only industrial groups with a number of cases and controls ≥ 10) are shown in Fig. 2. Industrial sectors with statistically significant increased risks in this analysis correspond to the metal industry –'Production and processing of metals' (ORs = 1.91 at 2 km, 2.28 at 2.5 km, and 2.66 at 3 km) and 'Surface treatment of metals and plastic' (ORs = 5.45 at 1 km, 2.65 at 1.5 km, 2.10 at 2 km, 1.55 at 2.5 km, and 1.48 at 3 km)–, 'Glass and mineral fibers' (ORs = 4.24 at 2 km, 3.24 at 2.5 km, and 2.06 at 3 km), chemical industry –'Organic chemical industry' (ORs = 11.54 at 1 km, 5.78 at 1.5 km, 3.57 at 2 km, 4.70 at 2.5 km, and 4.80 at 3 km) and 'Inorganic chemical industry' (ORs = 10.77 at 2 km, 6.56 at 2.5 km,

Table 1
Characteristics of colorectal cancer cases and controls.

Characteristic	n (%) or mean (SD) Controls (n = 2948)	n (%) or mean (SD) Cases (n = 557)	*p*-value[a]
Age, mean (SD)	63.1 (11.4)	67.2 (10.0)	< 0.001
Sex, n (%)			
Men	1535 (52.1)	352 (63.2)	
Women	1413 (47.9)	205 (36.8)	< 0.001
Province, n (%)			
Asturias	157 (5.3)	62 (11.1)	
Barcelona	790 (26.8)	130 (23.3)	
Cantabria	251 (8.5)	18 (3.2)	
Gipuzkoa	274 (9.3)	9 (1.6)	
Granada	140 (4.7)	44 (7.9)	
Huelva	79 (2.7)	32 (5.8)	
Leon	323 (11.0)	199 (35.7)	
Madrid	604 (20.5)	27 (4.9)	
Murcia	33 (1.1)	10 (1.8)	
Navarre	207 (7.0)	14 (2.5)	
Valencia	90 (3.1)	12 (2.2)	< 0.001
Body mass index (kg/m^2), mean (SD)	26.6 (4.4)	27.6 (4.6)	< 0.001
Family history of colorectal cancer, n (%)			
None	2594 (88.0)	442 (79.4)	
Second degree only	94 (3.2)	20 (3.6)	
1 first degree	241 (8.2)	81 (14.5)	
> 1 first degree	19 (0.6)	14 (2.5)	< 0.001
Tobacco smoking, n (%)			
Never	1271 (43.1)	210 (37.7)	
Former smoker	1055 (35.8)	251 (45.1)	
Current smoker	622 (21.1)	96 (17.2)	< 0.001
Educational level, n (%)			
Less than primary school	497 (16.9)	159 (28.5)	
Primary school completed	941 (31.9)	215 (38.6)	
Secondary school	878 (29.8)	124 (22.3)	
University graduate	632 (21.4)	59 (10.6)	< 0.001
Physical activity in leisure time (METS), mean (SD)	157.3 (247.9)	155.4 (272.1)	0.003
Total energy intake (kcal/day), mean (SD)	1905.6 (577.1)	1980.8 (605.6)	0.011
Alcohol consumption (g/day), mean (SD)	17.7 (27.2)	22.8 (32.8)	0.025
Vegetable intake (g/day), mean (SD)	189.3 (120.0)	173.5 (111.8)	< 0.001
Red/processed meat intake (g/day), mean (SD)	62.7 (38.6)	71.9 (43.7)	< 0.001
Living in their current residence for ≥ 10 years, n (%)	2463 (83.5)	451 (81.0)	0.153

[a] Two-sided Chi-square test (with Yates's correction for continuity), and Mann-Whitney *U* test (with continuity correction) test where appropriate.

Table 2
Odds ratios of colorectal cancer by industrial distance and pollution discharge route.

		Analysis with all individuals				Sensitivity analysis with only individuals living in their current residence for ≥ 10 years			
		n (%)		Univariate analysis	Multivariate analysis	n (%)		Univariate analysis	Multivariate analysis
Distance	Pollution discharge route	Controls (n = 2948)	Cases (n = 557)	OR (95%CI)[a]	OR (95%CI)[b]	Controls (n = 2463)	Cases (n = 451)	OR (95%CI)[a]	OR (95%CI)[b]
Reference (> 3 km)		1215 (41.2)	167 (30.0)	1.00	1.00	999 (40.6)	136 (30.2)	1.00	1.00
≤3 Km	All installations	1733 (58.8)	390 (70.0)	1.25 (1.00–1.57)	1.26 (1.00–1.59)	1464 (59.4)	315 (69.8)	1.19 (0.93–1.53)	1.20 (0.92–1.56)
	Air	1732 (58.8)	386 (69.3)	1.24 (0.99–1.56)	1.25 (0.99–1.58)	1464 (59.4)	313 (69.4)	1.18 (0.92–1.52)	1.20 (0.92–1.55)
	Water (only)	1 (0.0)	4 (0.7)	12.75 (1.31–123.77)	11.93 (1.23–115.76)	0 (0.0)	2 (0.4)	inf (0-inf)	inf (0-inf)
≤2.5 Km	All installations	1354 (45.9)	325 (58.3)	1.38 (1.09–1.74)	1.39 (1.09–1.77)	1130 (45.9)	262 (58.1)	1.33 (1.03–1.73)	1.35 (1.03–1.77)
	Air	1344 (45.6)	320 (57.4)	1.38 (1.09–1.74)	1.39 (1.09–1.77)	1127 (45.8)	258 (57.2)	1.31 (1.01–1.71)	1.33 (1.01–1.75)
	Water (only)	10 (0.3)	5 (0.9)	1.56 (0.51–4.81)	1.48 (0.46–4.70)	3 (0.1)	4 (0.9)	6.29 (1.31–30.06)	5.67 (1.12–28.79)
≤2 Km	All installations	1015 (34.4)	235 (42.2)	1.52 (1.19–1.96)	1.51 (1.16–1.96)	852 (34.6)	193 (42.8)	1.51 (1.14–2.00)	1.51 (1.13–2.02)
	Air	981 (33.3)	225 (40.4)	1.56 (1.21–2.01)	1.55 (1.19–2.02)	825 (33.5)	188 (41.7)	1.57 (1.19–2.08)	1.56 (1.16–2.10)
	Water (only)	34 (1.1)	10 (1.8)	0.96 (0.44–2.07)	0.91 (0.41–2.03)	27 (1.1)	5 (1.1)	0.63 (0.23–1.73)	0.62 (0.21–1.80)
≤1.5 Km	All installations	560 (19.0)	157 (28.2)	1.95 (1.48–2.56)	1.96 (1.47–2.61)	466 (18.9)	128 (28.4)	1.89 (1.39–2.56)	1.91 (1.38–2.62)
	Air	521 (17.7)	146 (26.2)	1.98 (1.49–2.62)	1.98 (1.48–2.65)	435 (17.7)	122 (27.1)	1.95 (1.43–2.66)	1.97 (1.42–2.72)
	Water (only)	39 (1.3)	11 (2.0)	1.64 (0.79–3.40)	1.73 (0.82–3.68)	31 (1.2)	6 (1.3)	1.15 (0.46–2.91)	1.18 (0.45–3.08)
≤1 Km	All installations	295 (10.0)	86 (15.4)	2.12 (1.52–2.94)	2.03 (1.44–2.87)	239 (9.7)	75 (16.6)	2.27 (1.58–3.26)	2.26 (1.54–3.30)
	Air	277 (9.4)	80 (14.3)	2.21 (1.58–3.12)	2.12 (1.49–3.02)	226 (9.2)	70 (15.5)	2.36 (1.63–3.43)	2.31 (1.57–3.41)
	Water (only)	18 (0.6)	6 (1.1)	1.32 (0.50–3.49)	1.31 (0.48–3.56)	13 (0.5)	5 (1.1)	1.47 (0.50–4.35)	1.69 (0.54–5.23)

[a] ORs were adjusted by age, sex, and province of residence (as a random effect).
[b] ORs were estimated from various mixed multiple logistic regression models (an independent model for each industrial distance), that included age, sex, body mass index 1-year before the interview, family history of colorectal cancer, tobacco smoking, educational level, physical activity, total energy intake, alcohol consumption, vegetable intake, red/processed meat intake, and province of residence (as a random effect).

Table 3
Odds ratios of colorectal cancer by industrial distance and sex.

Distance	Analysis with all individuals			Men			Women			
	n (%)			n (%)			n (%)			
	Controls (n = 2948)	Cases (n = 557)	OR (95%CI)[a]	Controls (n = 1535)	Cases (n = 352)	OR (95%CI)[a]	Controls (n = 1413)	Cases (n = 205)	OR (95%CI)[a]	p-int[b]
Reference (> 3 km)	1215 (41.2)	167 (30.0)	1.00	596 (38.8)	110 (31.3)	1.00	619 (43.8)	57 (27.8)	1.00	–
≤3 Km	1733 (58.8)	390 (70.0)	1.26 (1.00–1.59)	939 (61.2)	242 (68.7)	1.13 (0.83–1.54)	794 (56.2)	148 (72.2)	1.61 (1.11–2.35)	0.043
≤2.5 Km	1354 (45.9)	325 (58.3)	1.39 (1.09–1.77)	723 (47.1)	201 (57.1)	1.28 (0.93–1.75)	631 (44.7)	124 (60.5)	1.76 (1.19–2.60)	0.133
≤2 Km	1015 (34.4)	235 (42.2)	1.51 (1.16–1.96)	523 (34.1)	147 (41.8)	1.46 (1.04–2.06)	492 (34.8)	88 (42.9)	1.78 (1.17–2.71)	0.102
≤1.5 Km	560 (19.0)	157 (28.2)	1.96 (1.47–2.61)	280 (18.2)	95 (27.0)	1.86 (1.27–2.72)	280 (19.8)	62 (30.2)	2.39 (1.52–3.77)	0.143
≤1 Km	295 (10.0)	86 (15.4)	2.03 (1.44–2.87)	140 (9.1)	53 (15.1)	1.79 (1.14–2.81)	155 (11.0)	33 (16.1)	3.08 (1.75–5.42)	0.123

[a] ORs were estimated from various mixed multiple logistic regression models (an independent model for each industrial distance), that included age, sex, body mass index 1-year before the interview, family history of colorectal cancer, tobacco smoking, educational level, physical activity, total energy intake, alcohol consumption, vegetable intake, red/processed meat intake, and province of residence (as a random effect).
[b] p-values for the interaction between the exposure variable and sex.

and 6.74 at 3 km)–, and others –'Food and beverage sector' (ORs = 3.47 at 1 km, 5.38 at 1.5 km, 4.93 at 2 km, 5.89 at 2.5 km, and 3.34 at 3 km) and 'Surface treatment using organic solvents' (ORs = 4.28 at 2 km, 6.62 at 2.5 km, and 6.16 at 3 km)–. The analyses performed separately for each of the 22 categories of industrial groups are shown in Supplementary Data, Table S3, where the *p*-values adjusted by Benjamini & Hochbergs's method (*p*-BH) and Benjamini & Yekutieli's method (*p*-BY) are included. In this sense, the following results (*p*-BH < 0.100 and/or *p*-BY < 0.100) should be highlighted: 'Production and processing of metals' (*p*-BH = 0.023, *p*-BY = 0.081 at 2 km; *p*-BH < 0.001, *p*-BY < 0.001 at 2.5 km; and *p*-BH < 0.001, *p*-BY < 0.001 at 3 km), 'Surface treatment of metals and plastic' (*p*-BH < 0.001, *p*-BY < 0.001 at 1 km, 1.5 km, and 2 km; *p*-BH = 0.023, *p*-BY = 0.084 at 2.5 km; and *p*-BH = 0.028 at 3 km), 'Glass and mineral fibers' (*p*-BH < 0.001, *p*-BY < 0.001 at 2 km, 2.5 km, and 3 km), 'Organic chemical industry' (*p*-BH < 0.001, *p*-BY < 0.001 for all distances), 'Inorganic chemical industry' (*p*-BH < 0.001, *p*-BY < 0.001 at 2 km, 2.5 km, and 3 km), 'Food and beverage sector' (*p*-BH = 0.020, *p*-BY = 0.066 at 1 km; and *p*-BH < 0.001, *p*-BY < 0.001 at 1.5 km, 2 km, 2.5 km, and 3 km), and 'Surface treatment using organic solvents' (*p*-BH < 0.001, *p*-BY < 0.001 at 2 km, 2.5 km, and 3 km).

Similar results to the previous paragraph were obtained in the sensitivity analysis considering only long-term residents (see Supplementary Data, Table S4).

Detailed information on type of specific pollutants that can be released by the industrial groups of our study, as well as emission amounts by categories of carcinogens and other toxic substances, is provided in Supplementary Data, Tables S5 and S6, respectively.

3.4. Results by groups of carcinogens and other toxic substances (analysis 3)

In relation to residential proximity to industries releasing groups of carcinogens and other toxic substances and colorectal cancer risk (Fig. 3), the three IARC groups showed statistically significant increased risks for all industrial distances (with ORs ranging from 1.29 at 3 km to 2.01 at 1 km in the case of Group 1, from 1.39 at 3 km to 1.58 at 1.5 km in Group 2A, and from 1.44 at 3 km to 1.73 at 1.5 km in Group 2B), with the exception of Groups 2A and 2B at the distance of 1 km, which showed ORs close to the unit.

With respect to groups of toxic substances, the main results (only groups with a number of cases and controls ≥ 10) are focused on the excess risk of colorectal cancer in the environs of industries releasing: 'Metals' at all distances; 'Pesticides' and 'Other' at distances between 1 km and 2.5 km; 'PACs' at distances between 1.5 km and 2.5 km; 'VOCs' at distances between 1.5 km and 3 km; 'Non-HPCs' at distances between 2 km and 3 km; 'Solvents' at 2.5 km and 3 km; and 'POPs' at 1.5 km.

Finally, similar results were obtained in the sensitivity analysis considering only long-term residents (see Supplementary Data, Figure S3).

3.5. Results by specific pollutants (analysis 4)

The most remarkable results (statistically significant ORs and a number of cases and controls ≥ 10) for the analysis of proximity to industries releasing specific pollutants are depicted in Fig. 4. Attention should be drawn to the excess risks registered in individuals with residence close to industries releasing: 'Antimony' (ORs = 5.05 at 1 km, 4.37 at 1.5 km, 4.15 at 2 km, 6.36 at 2.5 km, and 5.30 at 3 km), 'Arsenic and compounds' (OR = 1.46 at 2.5 km), 'Cadmium and compounds' (ORs = 1.70 at 1.5 km, and 1.53 at 2.5 km), 'Chromium and compounds' (ORs = 1.75 at 1 km, 1.71 at 1.5 km, and 1.49 at 2.5 km), 'Copper and compounds' (OR = 1.68 at 1.5 km), 'Dichloromethane' (ORs = 3.32 at 2 km, 3.18 at 2.5 km, and 2.52 at 3 km), 'Lead and

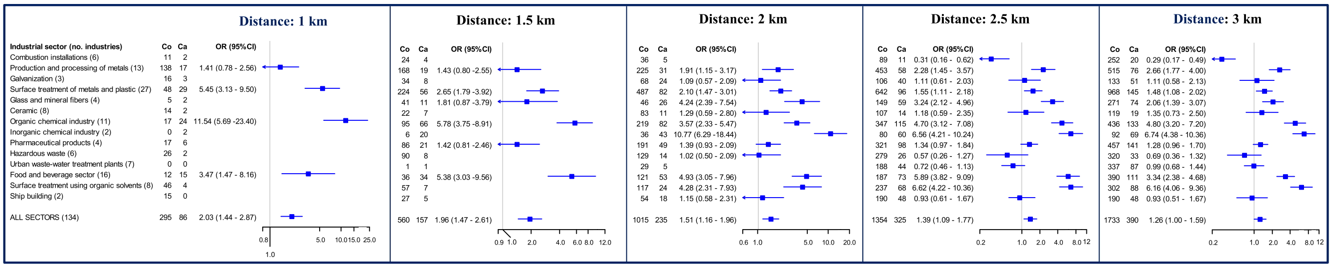

Fig. 2. Odds ratios of colorectal cancer with a number of cases and controls ≥ 10 for the analysis of proximity to industries by industrial group. X-axis is plotted in logarithmic scale.

compounds' (ORs = 1.58 at 1.5 km, 1.49 at 2 km, 1.57 at 2.5 km, and 1.35 at 3 km), 'Manganese and compounds' (ORs = 2.52 at 2.5 km, and 2.53 at 3 km), 'Naphthalene' (ORs = 2.81 at 1.5 km, 4.17 at 2 km, 3.76 at 2.5 km, and 3.11 at 3 km), 'Nickel and compounds' (ORs = 1.45 at 1.5 km, 1.34 at 2.5 km, and 1.27 at 3 km), 'Non-methane volatile organic compounds' (ORs = 1.84 at 1.5 km, 1.53 at 2 km, 1.47 at 2.5 km, and 1.30 at 3 km), 'Nonylphenol and nonylphenol ethoxylates' (ORs = 14.42 at 2 km, 12.46 at 2.5 km, and 9.19 at 3 km), 'Organotin compounds' (ORs = 2.69 at 1 km, 3.46 at 1.5 km, 2.75 at 2 km, 2.91 at 2.5 km, and 2.64 at 3 km), 'Particulate matter (PM_{10})' (ORs = 2.36 at 1 km, 2.26 at 1.5 km, 1.68 at 2 km, 1.66 at 2.5 km, and 1.55 at 3 km), 'Total suspended particulate matter' (ORs = 2.39 at 1 km, 4.18 at 1.5 km, 4.05 at 2 km, 2.23 at 2.5 km, and 1.53 at 3 km), 'Vanadium' (ORs = 2.46 at 2.5 km, and 2.49 at 3 km), and 'Zinc and compounds' (ORs = 1.85 at 1.5 km, 1.43 at 2 km, 1.45 at 2.5 km, and 1.29 at 3 km). Similar results were obtained in the sensitivity analysis considering only long-term residents (see Supplementary Data, Figure S4).

3.6. Results of the risk gradient analysis (analysis 5)

Positive radial effects (a rise in the ORs with increasing proximity to an industry) were detected (Table 4) for all sectors as a whole (OR = 1.15, p-trend < 0.001), especially in 'Production and processing of metals' (OR = 1.15, p-trend = 0.033), 'Surface treatment of metals and plastic' (OR = 1.29, p-trend < 0.001), 'Glass and mineral fibers' (OR = 1.59, p-trend < 0.001), 'Organic chemical industry' (OR = 1.53, p-trend < 0.001), 'Inorganic chemical industry' (OR = 2.06, p-trend < 0.001), 'Non-hazardous waste' (OR = 2.90, p-trend = 0.006), 'Food and beverage sector' (OR = 1.51, p-trend < 0.001), and 'Surface treatment using organic solvents' (OR = 2.18, p-trend < 0.001). Similar results were yielded by the sensitivity analysis considering only long-term residents (see Supplementary Data, Table S7).

4. Discussion

4.1. Summary

To our knowledge, this is the first paper analyzing the relationship between proximity to industrial pollution sources and colorectal cancer using individual data. In brief, the results of our study indicate an association between colorectal cancer risk and proximity to industrial facilities (with higher excess risks in the environs of industries releasing pollutants to air than industries releasing pollution only to water), especially:

a) facilities belonging to the metal industry (production and processing of metals, and surface treatment of metals and plastic), the industry of the manufacture of glass and mineral fibers, chemical industry (organic and inorganic chemical industries), food and beverage sector, and the industry of surface treatment using organic solvents; and,
b) plants releasing known or suspected carcinogens (arsenic, cadmium, chromium, nickel, dichloromethane, lead, PM_{10}, and total suspended particulate matter), and other toxic substances, such as metals (antimony, copper, manganese, organotin compounds, vanadium, and zinc), VOCs (naphthalene, and non-methane volatile organic compounds), and non-HPCs (nonylphenol and nonylphenol ethoxylates).

In 2012, our group published the results of a study that investigated the association between colorectal cancer mortality and industrial pollution in Spain, applying an ecological approach at a municipal level, and showing that industrial emissions could be a risk factor for colorectal cancer (López-Abente et al., 2012). In the present paper, the study design guarantees the availability of individual data on several colorectal cancer risk factors, which have been controlled in the statistical analyses.

4.2. Results in relation to other studies about industrial pollution

Insofar as exposure to industrial pollution is concerned, the number of studies available in the literature regarding proximity to industries and colorectal cancer risk is limited. In Italy, some authors have found an increased risk of colorectal cancer in contaminated sites with presence of industrial activities, in relation to both incidence (Comba et al., 2014; Zona et al., 2019) and mortality (Salerno et al., 2014). The findings of studies from other countries, such as Russia, Brazil, and China, point to an increase in the incidence and mortality of this tumor in specific industrial regions (Kutikhin et al., 2012; Li et al., 2017; Medrado-Faria et al., 2001).

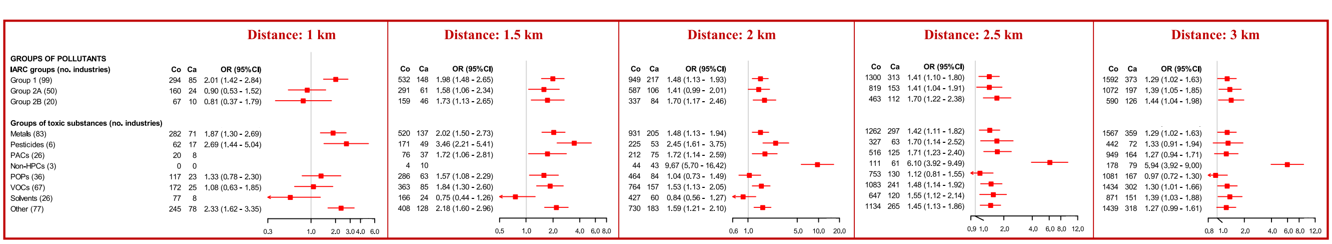

Fig. 3. Odds ratios of colorectal cancer with a number of cases and controls ≥ 10 for the analysis of proximity to industries by groups of carcinogens and other toxic substances. X-axis is plotted in logarithmic scale.

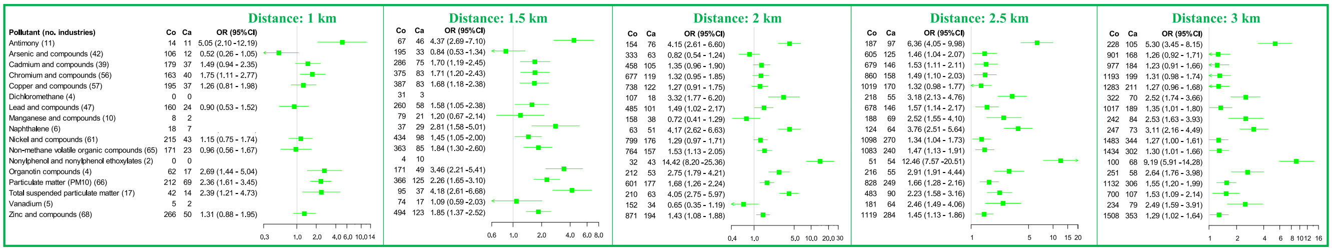

Fig. 4. Odds ratios of colorectal cancer with statistically significant results and a number of cases and controls ≥ 10 for the analysis of proximity to industries releasing specific pollutants. X-axis is plotted in logarithmic scale.

4.3. Results in relation to other studies about industrial groups

4.3.1. Metal industry

In 2010, our group published an ecological study about mortality due to cancers of the digestive system in towns close to the Spanish metal industry, and we found excess colorectal cancer mortality at ≤ 5 km from different groups of metal installations (García-Pérez et al., 2010). With regard to the industries involved in the production and processing of metals, an Italian study found a higher colorectal cancer mortality among women living near a steel plant (Casella et al., 2005). In our study, the statistically significant excess risks were found between 2 and 3 km around these types of industries, which release large amounts of carcinogens, such as dioxins, heavy metals, benzene or PAHs (Cusano et al., 2017; Remus et al., 2013). In relation to the industries involved in the surface treatment of metals and plastic (another sector related to the metal industry), our data revealed increased risks for all distances analyzed. To our knowledge, no epidemiologic studies about proximity to these types of industries and colorectal cancer incidence have been conducted. However, these industrial facilities are known to use mineral oils and metalworking fluids, a range of toxic chemical substances used to lubricate and/or cool metal workpieces, which have been related to increased risks of colon and rectal cancers in several occupational studies (Friesen et al., 2012; Gerosa et al., 2013; Mark S. Goldberg et al., 2001a; Malloy et al., 2006).

4.3.2. Manufacture of glass and mineral fibers

An investigation carried out in Sweden showed statistically significant increased risks of colon and rectum cancers in a population cohort residing at ≤ 2 km from glassworks sites (Nyqvist et al., 2017), with standardized incidence ratios ranging from 1.18 to 1.34. These types of installations release known and suspected carcinogens, mainly metals (arsenic, cadmium, lead, chromium), dioxins, benzene, and PM_{10} (Scalet et al., 2013), which could be related with colorectal cancer risk. In our study, the OR of colorectal cancer at a distance of 2 km around industries belonging to the production of glass and mineral fibers was very high (OR = 4.24).

4.3.3. Chemical industry

Our findings about organic and inorganic chemical industry are in line with those of a recent study published by our group that found a relationship between colorectal cancer mortality and proximity (≤5 km) to industrial chemical plants in Spain (Ayuso-Álvarez et al., 2020). Both industrial sectors released known and suspected carcinogens (metals, PAHs, PM_{10}, benzene, or dioxins, see Supplementary Data, Table S5) and the organic chemical industry is the leading polluter in PACs and the second-leading polluter in non-HPCs (see Supplementary Data, Table S6).

4.3.4. Others

With regard to colorectal cancer risk and proximity to installations belonging to the remaining industrial sectors with significant results in our study, the few papers existing in the literature are focused on occupational exposures. In relation to the food and beverage sector (one of the most noteworthy sector in our study, with high ORs near these types of industries for all distances analyzed and a positive radial effect in the risk gradient analysis), two Canadian studies found an association for workers employed in the food processing industries and colon (M. S. Goldberg et al., 2001b) and colorectal (Sritharan et al., 2014) cancers. Moreover, a *meta*-analysis by Oddone et al. (Oddone et al., 2014) showed increased risks of colorectal cancers in workers occupied in the manufacture of beverages. Aside from occupational exposures, these types of industries release a wide variety of harmful substances to both air and water, which could be related to the excess risk of colorectal cancer found in our study, such as heavy metals, dioxins, particulate matter or naphthalene (see Supplementary Data, Table S5).

Lastly, for installations belonging to the ‘Surface treatment using organic solvents’ sector, high significant ORs have been found in our study for distances between 2 and 3 km, as well as a positive radial effect in the risk gradient analysis. Despite the fact that these industries emit known or suspected carcinogens, such as chromium, lead, dichloromethane, PM_{10} or PAHs (see Supplementary Data, Table S5), to our knowledge, no epidemiologic studies have been carried out in people close to these facilities, although a Norwegian cohort of workers in the printing industry showed significantly elevated risk of colon cancer between 1953 and 1998 (Kvam et al., 2005).

4.4. Results in relation to other studies about pollutants

Focusing on groups of pollutants, our findings about pesticides could be related to those of other authors, which suggest that pesticide exposure could be a risk factor for colorectal cancers (El-Tawil, 2010; Martin et al., 2018). With respect to proximity to industries releasing POPs, only a statistically significant excess risk of colorectal cancer was found in our study at a distance of 1.5 km. However, there are indications in the literature that this group of pollutants could be related to colorectal cancer: a recent case-control study conducted in Korea showed that chronic exposure to low-dose POPs could be associated with an increased risk of colorectal polyps and cancer (Lee et al., 2018), and other authors have shown that a mixture of POPs caused increased intestinal tumorigenesis in mice (Hansen et al., 2019).

With regard to the specific pollutants studied in our paper, one of the most noteworthy results is referred to industries releasing nonylphenol and nonylphenol ethoxylates (the highest ORs found in our study, with values ranging between 9.19 and 14.42). Nonylphenol is an endocrine-disrupting chemical that can be released to water by plants involved in the production and processing of metals, organic chemical industry, non-hazardous waste, and urban waste-water treatment (see Supplementary Data, Table S5). Recently, some authors have found that this substance promotes the proliferation of colorectal cancer (Xie et al., 2019; Yang et al., 2019, 2017), and it is possible that the nonylphenol released to water by the industries can pass into the aquifers and soils, and then, into the trophic chain, affecting the population living near these industries.

Insofar as exposure to particulate matter is concerned, our results showed increased risks of colorectal cancer at all distances analyzed. In this sense, Buggiano et al. (Buggiano et al., 2015) have suggested that

Table 4
Odds ratios of colorectal cancer for ever-decreasing radiuses within a 30-kilometer area surrounding each industrial installations, both overall and by industrial group (risk gradient analysis, with categorical and continuous variables).

	Categorical variables																	Continuous variables	
	[0–1 km)			[1–1.5 km)			[1.5–2 km)			[2–2.5 km)			[2.5–3 km)			Reference: [3–30 km]			
Industrial group	Co[a]	Ca[b]	OR (95%CI)	Co[a]	Ca[b]	OR (95%CI)	Co[a]	Ca[b]	OR (95%CI)	Co[a]	Ca[b]	OR (95%CI)	Co[a]	Ca[b]	OR (95%CI)	Co[a]	Ca[b]	OR	*p*-trend
All sectors	295	86	2.08 (1.47–2.93)	265	71	1.84 (1.29–2.64)	455	78	0.96 (0.67–1.36)	339	90	1.17 (0.85–1.61)	379	65	0.84 (0.59–1.20)	1212	65	1.16	< 0.001
Combustion installations	11	2	0.19 (0.04–0.92)	13	2	0.19 (0.04–0.93)	12	1	0.11 (0.01–1.01)	53	6	0.39 (0.15–1.07)	163	9	0.37 (0.17–0.82)	639	120	0.63	< 0.001
Production and processing of metals	138	17	1.82 (0.91–3.63)	30	2	2.82 (0.58–13.87)	57	12	4.74 (1.98–11.37)	228	27	2.80 (1.43–5.47)	62	18	4.12 (2.05–8.27)	564	50	1.15	0.033
Galvanization	16	3	0.57 (0.12–2.81)	18	5	0.55 (0.15–2.03)	34	16	0.94 (0.37–2.40)	38	16	0.83 (0.32–2.14)	27	11	1.13 (0.40–3.19)	33	15	0.90	0.325
Surface treatment of metals and plastic	48	29	6.82 (3.73–12.49)	176	27	1.98 (1.17–3.36)	263	26	1.49 (0.86–2.58)	155	14	0.84 (0.43–1.64)	326	49	1.61 (1.00–2.60)	1057	66	1.29	< 0.001
Mining industry	23	4	0.19 (0.05–0.68)	3	0	0 (0-inf)	0	0	–	0	0	–	0	0	–	92	67	0.69	0.004
Cement and lime	17	3	0.15 (0.04–0.61)	11	1	0.08 (0.01–0.75)	3	0	0 (0-inf)	18	0	0 (0-inf)	35	3	1.99 (0.43–9.29)	323	85	0.64	0.001
Glass and mineral fibers	5	2	4.47 (0.76–26.30)	36	9	3.06 (1.23–7.64)	5	15	42.02 (12.61–139.97)	103	33	3.98 (2.10–7.53)	122	15	1.32 (0.63–2.76)	395	91	1.59	< 0.001
Ceramic	14	2	0.16 (0.03–0.95)	8	5	1.31 (0.34–5.00)	61	4	0.10 (0.03–0.38)	24	3	0.22 (0.05–0.92)	12	5	0.63 (0.17–2.34)	69	31	0.86	0.268
Organic chemical industry	17	24	14.04 (6.36–30.98)	78	42	5.31 (2.82–10.00)	124	16	1.31 (0.57–3.01)	128	33	3.39 (1.76–6.51)	89	18	2.45 (1.23–4.87)	312	26	1.53	< 0.001
Inorganic chemical industry	0	2	inf (0-inf)	6	18	26.37 (9.07–76.65)	30	23	6.61 (3.16–13.82)	44	17	3.28 (1.53–7.04)	12	9	8.65 (2.96–25.32)	309	30	2.06	< 0.001
Fertilizers	0	0	–	0	0	–	0	0	–	0	0	–	23	4	0.02 (0.00–3.13)	39	15	0.02	0.133
Biocides	0	0	–	0	0	–	0	0	–	6	2	NE[c]	4	2	NE[c]	1	0	NE[c]	NE[c]
Pharmaceutical products	17	6	1.05 (0.37–3.00)	69	15	1.98 (1.02–3.83)	105	28	1.37 (0.77–2.41)	130	49	1.27 (0.52–1.98)	136	43	1.26 (0.79–2.02)	873	112	1.11	0.067
Explosives and pyrotechnics	0	0	–	0	0	–	3	0	0 (0-inf)	9	2	0.24 (0.01–7.00)	5	0	0 (0-inf)	10	7	0.37	0.221
Hazardous waste	26	2	0.34 (0.06–2.08)	64	6	0.49 (0.14–1.66)	39	6	0.85 (0.26–2.79)	150	12	0.49 (0.17–1.45)	41	7	0.92 (0.34–2.50)	317	30	0.87	0.283
Non-hazardous waste	0	0	–	2	1	49.25 (1.36–1783.43)	0	0	–	23	4	13.16 (1.66–104.22)	59	3	6.25 (0.86–45.32)	207	3	2.90	0.006
Disposal or recycling of animal waste	0	0	–	0	0	–	0	0	–	11	0	0 (0-inf)	55	9	2.86 (1.17–7.00)	317	21	1.71	0.167
Urban waste-water treatment plants	0	0	–	1	1	1.69 (0.09–32.36)	28	4	0.45 (0.14–1.44)	159	39	0.96 (0.57–1.63)	149	43	1.54 (0.90–2.61)	459	106	0.93	0.521
Paper and wood production	0	0	–	0	0	–	2	0	0 (0-inf)	7	0	0 (0-inf)	94	2	0.08 (0.02–0.43)	324	33	0.08	0.003
Food and beverage sector	12	15	3.73 (1.53–9.13)	24	19	9.08 (4.11–20.03)	85	19	5.70 (2.62–12.41)	66	20	7.32 (3.60–14.88)	203	38	1.76 (1.08–2.88)	948	131	1.55	< 0.001
Surface treatment using organic solvents	46	4	5.31 (1.18–23.77)	11	3	24.16 (4.91–118.75)	60	17	13.12 (5.39–31.95)	120	44	11.02 (5.70–21.31)	65	20	6.09 (2.82–13.14)	533	26	2.18	< 0.001
Ship building	15	0	0 (0-inf)	12	5	0.71 (0.18–2.76)	27	13	0.98 (0.36–2.70)	74	17	0.64 (0.27–1.56)	62	13	0.95 (0.34–2.61)	40	15	0.84	0.144

[a] Number of controls.
[b] Number of cases.
[c] Not estimated: risk could not be estimated.

exposure to particulate matter, especially PM_{10}, could contribute to the onset of colon cell proliferation *in vitro*. However, a recent *meta*-analysis found no association between colorectal cancer mortality and PM_{10} exposure (Kim et al., 2018). In the case of $PM_{2.5}$, some authors suggest a possible association with colorectal cancer mortality (Kim et al., 2018; Turner et al., 2017).

To our knowledge, no epidemiologic papers about colorectal cancer risk in the proximity of installations releasing specific metals have been carried out. In relation to cadmium exposure, a hospital-based case-control study conducted in the Southeast China suggested an association between blood cadmium levels among the participants and colorectal cancer risk (Lin et al., 2018); however, a prospective cohort study carried out in American Indians did not find an increased risk of mortality from colon and rectum cancers (García-Esquinas et al., 2014). Our results suggest an excess risk in the environs of industries releasing cadmium at distances of 1.5 and 2.5 km, but not in the remaining distances. On the other hand, our results showed an increased risk of colorectal cancer at 2.5 around industries releasing arsenic. Arsenic released to water can be seeped in soils, affecting the aquifers. In this sense, two ecological studies revealed associations of soil arsenic concentrations with colorectal cancer mortality rates (Chen et al., 2015; Núñez et al., 2016). In relation to antimony exposure (the metal with the highest ORs found in our study, for all distances analyzed), Wingren et al. (Wingren and Axelson, 1993) observed an increasing trend in colon cancer risk with increasing use of antimony in workers in the glass industry, an industrial sector that already showed an excess risk in our study. In the case of lead exposure, the studies obtained in the literature are focused on occupational exposures and rectal cancers, suggesting positive associations (Barry and Steenland, 2019; Fayerweather et al., 1997; Steenland et al., 2019). With regard to manganese, our study showed increased risks for colorectal cancer at 2.5 and 3 km; however, the only study found in the literature about environmental manganese and population-level colon cancer mortality showed an inverse relationship between air manganese and colon cancer death rates (Spangler and Reid, 2010). In relation to chromium exposure, the occupational studies existing in the literature are inconsistent: whereas a Finnish study showed an increased risk of rectal cancer in women occupationally exposed to chromium (Weiderpass et al., 2003), other authors did not find any association between exposure to chromium compounds and risk of colorectal and rectal cancers (Gatto et al., 2010; Sciannameo et al., 2019). With respect to nickel exposure, a study conducted on Italian electroplaters (which belong to the 'Surface treatment of metals and plastic' industrial group) suggested that exposure to nickel significantly increased mortality from rectal cancer (Sciannameo et al., 2019). In our study, both this industrial group and this pollutant presented significant ORs. Finally, in relation to other metals, some authors have found significant concentrations of zinc and copper in colorectal tumors (Juloski et al., 2020; Kucharzewski et al., 2003; Rinaldi et al., 2015; Sohrabi et al., 2018), a finding that could be related to the increased ORs observed by us in the proximity of industries releasing these pollutants.

Lastly, insofar as exposure to other toxic substances is concerned, increased ORs of colorectal cancer were found in our study in the environs (between 1.5 and 3 km) of facilities releasing naphthalene, a pollutant possibly carcinogenic to humans and released, principally, from industrial use and fossil-fuel combustion. In the literature, case reports of colorectal cancer and naphthalene exposure are limited and inadequate for evaluating human cancer risk (Jeffrey Lewis, 2012).

4.5. Limitations and strengths

Aside from the limitations inherent to all case-control studies, in our case attention should also be drawn from the following: the non-inclusion of potential factors that could be related to the misclassification of the exposure (e.g.: indoor air pollution or the time actually spent inside the exposure zones); 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 geographic landforms or prevailing winds; the non-inclusion of occupations and high-risk occupational exposures related to colorectal cancer and time working in high-risk occupations, due to lack of individual data; the loss of statistical power due to the exclusion of participants out of the study areas (90.1% of the total excluded cases is due to this reason), as well as the exclusion of the participants with missing data on key covariates (65.0% of the total excluded controls is due to this reason) (see Supplementary Data, Figure S1); and the possible recall bias affecting self-reported information about potential confounders (although this recall bias would be non-differential, which implies an attenuation of the studied effects). In relation to the strengths of our paper, the study included population-based controls and histologically confirmed incident cases, which add specific value to our findings. Specifically, the recruitment of incident cases also served to prevent potential changes of residence associated with the cancer diagnosis. Hence, if there were any bias affecting proximity to industrial facilities in relevant periods of the participants' life, this bias would be non-differential, causing an underestimation of the risk. On the other hand, this is a multicenter case-control study carried out in 11 provinces, representative of the general idiosyncrasy of Spain and located throughout the Spanish geography covering both rural and urban settings. Our analyses included a random province-specific intercept that accounted for unexplained heterogeneity in the models due to unmeasured factors across different zones. Lastly, the completeness and robustness of the methodological approach used in the analyses, which include the stratification of the risk (by pollution discharge route, sex, industrial groups, groups of carcinogens and other toxic pollutants, and specific substances), the inclusion of a sensitivity analysis (considering only long-term residents) for each type of analysis, a sensitivity analysis testing the distribution of the main characteristics between the included and excluded cases, and the use of adjusted *p*-values controlling the problem of multiple comparisons, have provided a very exhaustive description of colorectal cancer risk.

5. Conclusions

Our study supports the hypothesis that residing in the proximity of certain industrial areas may be a risk factor for colorectal cancer. A more detailed exposure assessment of specific toxic substances emitted by these facilities is necessary to confirm this hypothesis.

CRediT authorship contribution statement

Javier García-Pérez: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Data curation, Software, Writing - original draft, Writing - review & editing, Visualization, Supervision, Project administration, Funding acquisition. **Nerea Fernández Larrea-Baz:** Conceptualization, Validation, Investigation, Writing - review & editing, Visualization. **Virginia Lope:** Conceptualization, Validation, Investigation, Writing - review & editing, Visualization. **Antonio J. Molina:** Validation, Writing - review & editing. **Cristina O'Callaghan-Gordo:** Validation, Writing - review & editing. **María Henar Alonso:** Writing - review & editing. **Marta María Rodríguez-Suárez:** Writing - review & editing. **Benito Mirón-Pozo:** Writing - review & editing. **Juan Alguacil:** Resources, Writing - review & editing, Funding acquisition. **Inés Gómez-Acebo:** Resources, Writing - review & editing, Funding acquisition. **Nieves Ascunce:** Resources, Writing - review & editing, Funding acquisition. **Mercedes Vanaclocha-Espi:** Validation, Resources, Writing - review & editing, Funding acquisition. **Pilar Amiano:** Validation, Resources, Writing - review & editing, Funding acquisition. **María Dolores Chirlaque:** Resources, Writing - review & editing, Funding acquisition. **Vicente Simó:** Writing - review & editing. **José J. Jiménez-Moleón:** Validation, Resources, Writing - review & editing, Funding acquisition. **Adonina Tardón:** Resources, Writing -

review & editing, Funding acquisition. **Víctor Moreno:** Resources, Writing - review & editing, Funding acquisition. **Gemma-Castaño-Vinyals:** Resources, Writing - review & editing, Funding acquisition. **Vicente Martín:** Resources, Writing - review & editing, Funding acquisition. **Nuria Aragonés:** Resources, Writing - review & editing, Funding acquisition. **Beatriz Pérez-Gómez:** Resources, Writing - review & editing, Funding acquisition. **Manolis Kogevinas:** Resources, Writing - review & editing, Project administration, Funding acquisition. **Marina Pollán:** Conceptualization, Formal analysis, Investigation, Resources, Writing - review & editing, Visualization, Supervision, Project administration, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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