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RISK OF PROSTATE CANCER IN THE PROXIMITY OF INDUSTRIAL
INSTALLATIONS: A MULTICASE-CONTROL STUDY IN SPAIN (MCC-SPAIN)

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1 **Risk of prostate cancer in the proximity of industrial installations: a multicase-**
2 **control study in Spain (MCC-Spain)**

3
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1 **Abstract**

2 **Background:** Prostate cancer (PC) is the second most frequent tumor in men worldwide; however, its
3 etiology remains largely unknown, with the exception of age and family history. The wide variability
4 in incidence/mortality across countries suggests a certain role for environmental exposures that has not
5 yet been clarified.

6 **Objective:** To evaluate the association between risk of PC (by clinical profile) and residential proximity
7 to pollutant industrial installations (by industrial groups, groups of carcinogens, and specific pollutants
8 released), within the context of a Spanish population-based multicase-control study of incident cancer
9 (MCC-Spain).

10 **Methods:** This study included 1186 controls and 234 PC cases, frequency matched by age and province
11 of residence. Distances from participants' residences to the 58 industries located in the study area were
12 calculated and categorized into "near" (considering different limits between ≤ 1 km and ≤ 3 km) or "far"
13 (> 3 km). Odds ratios (ORs) and 95% confidence intervals (95% CIs) were estimated using mixed and
14 multinomial logistic regression models, adjusted for potential confounders and matching variables.

15 **Results:** No excess risk was detected near the overall industries, with ORs ranging from 0.66 (≤ 2 km)
16 to 1.11 (≤ 1 km). However, positive associations (OR; 95% CI) were found, by industrial group, near
17 (≤ 3 km) industries of ceramic (2.54; 1.28-5.07), food/beverage (2.18; 1.32-3.62), and
18 disposal/recycling of animal waste (2.67; 1.12-6.37); and, by specific pollutant, near plants releasing
19 fluorine (4.65; 1.45-14.91 at ≤ 1.5 km) and chlorine (5.21; 1.56-17.35 at ≤ 1 km). In contrast, inverse
20 associations were detected near industries releasing ammonia, methane, dioxins+furans, polycyclic
21 aromatic hydrocarbons, trichloroethylene, and vanadium to air.

22 **Conclusions:** The results suggest no association between risk of PC and proximity to the overall
23 industrial installations. However, some both positive and inverse associations were detected near
24 certain industrial groups and industries emitting specific pollutants.
25

26 **Key Words:** prostatic cancer; industrial pollution; risk factor; case-control study; residential proximity
27
28

29 **Abbreviations:** PC, Prostate cancer; POPs, Persistent organic pollutants; PCBs, Polychlorinated
30 biphenyls; EDCs, Endocrine disrupting chemicals; UTM, Universal Transverse Mercator; E-PRTR,
31 European Pollutant Release and Transfer Register, SIGPAC, Spanish Agricultural Plots Geographic
32 Information System; ISUP, International Society of Urological Pathology; PSA, Prostate-specific
33 antigen; AJCC, American Joint Committee on Cancer; IARC, International Agency for Research on
34 Cancer; PACs, Polycyclic aromatic chemicals; ORs, Odds ratios; RRRs, Relative risk ratios; 95% CIs,
35 95% confidence intervals; *p*-BHs, *p*-values adjusted by Benjamini & Hochberg's method; PAHs,

- 36 Polycyclic aromatic hydrocarbons; PM, Particulate matter; NO₂, Nitrogen dioxide; NPCSS, National
- 37 Priority Contaminated Sites

38 **1. Introduction**

39 Prostate cancer (PC) is the second most frequent tumor in men worldwide, with 1.47 million
40 new cases in 2022 (Ferlay et al., 2024). In Spain, it is the leading cause of cancer, with 32,967 new
41 cases estimated in the same year (Ferlay et al., 2024). The number of new cases of PC has increased in
42 the last decades, and its etiology remains largely unknown, with the exception of non-modifiable
43 factors, such as age, ethnicity, or family history. Therefore, it is important to evaluate the role of other
44 risk factors that can be intervened, such as environmental exposures.

45 Proximity to industrial installations is a source of exposure to known and suspected carcinogens
46 – such as heavy metals, and persistent organic pollutants (POPs), including polychlorinated biphenyls
47 (PCBs) –, which have been related to an increased risk of PC (Ali et al., 2016; Buñay et al., 2023; Lim
48 et al., 2017, 2019), as well as endocrine disrupting chemicals (EDCs), substances that produce
49 alterations in the endocrine system and are potentially able to increase the risk of PC (Lacouture et al.,
50 2022; Macedo et al., 2023). However, very few epidemiological studies exploring the risk of PC
51 associated with residing near industrial pollution sources have been conducted using individual data,
52 focusing on both PC mortality (Casella et al., 2005; Rava et al., 2009) and PC incidence (Kayyal-
53 Tarabeia et al., 2023; Onyije et al., 2021; Rottenberg et al., 2013). On the other hand, regarding the
54 tumor characteristics, some studies have detected possible associations between exposure to certain
55 pollutants, such as POPs or air cadmium, and more aggressive prostate tumors (Buñay et al., 2023;
56 Vijayakumar et al., 2021), whereas a French study observed an inverse relationship between mirex (an
57 organochlorine pesticide) concentration and aggressiveness features of PC in Caucasian patients
58 (Antignac et al., 2023).

59 Therefore, our paper aims to evaluate the possible association between risk of PC (by clinical
60 profile or tumor characteristics) and residing in the proximity to pollutant industrial installations, by

61 type of industrial groups and pollutants, in the context of the MCC-Spain project, the largest
62 population-based multicase-control study of incident cancer carried out in Spain.

63

64 **2. Materials and methods**

65 *2.1 Study population and data collection*

66 The design of the MCC-Spain study, as well as the methodology used in previous papers
67 analyzing the risk of other tumors in the environs of industrial facilities, have been previously published
68 (Castaño-Vinyals et al., 2015; Castelló et al., 2020; García-Pérez et al., 2021, 2020, 2018). Briefly,
69 among the five tumors included in the study (prostate, chronic leukemias, breast, gastric, and
70 colorectal), 1112 histologically confirmed PC cases (codes C61, D07.5, according to the International
71 Classification of Diseases, 10th revision), aged 20-85 years, were recruited between 2008 and 2013 in
72 seven Spanish provinces (Valencia, Madrid, Huelva, Granada, Cantabria, Barcelona, and Asturias). All
73 of them had resided in the hospitals' catchment areas for at least 6 months prior to recruitment. To
74 facilitate the logistics of the recruitment and interviewing of participants in MCC-Spain, population-
75 based controls for the entire study were randomly selected from administrative records of selected
76 primary care health centers located within the same hospitals' catchment areas. Controls were
77 frequency matched in each region to the overall distribution of all cancer cases (prostate cancer cases
78 and others) by sex, region (province of residence), and age (in 5-year age groups). More detailed
79 information on the selection process of the controls was previously published (García-Pérez et al.,
80 2021).

81 Information on family history of PC, sociodemographic factors, medical history, and lifestyle
82 was collected in a structured computerized questionnaire administered by trained interviewers in a face-

83 to-face interview (average duration: 70 min). Clinical data were collected by reviewing medical
84 records.

85

86 **2.2 Geocoding / validation of locations (strategies)**

87 The geographic coordinates of participants' residences (controls and cases) and industrial
88 installations were geocoded and validated as follows (see Figure 1 (A)):

89

90 **2.2.1 Residences (cases and controls)**

91 After excluding the participants with missing data in the domicile variable, a total of 2596 men's
92 residences (1489 controls and 1107 cases) could be geocoded with valid coordinates. Firstly, they were
93 geocoded into ED50/Universal Transverse Mercator (UTM) zone 30N (EPSG:23030) coordinates
94 using Google Earth Pro. Subsequently, these coordinates were thoroughly validated one by one using
95 the National Cadastre and the "street-view" application of Google Earth Pro to ensure their exact
96 locations. According to the selection process of the population-based controls (García-Pérez et al.,
97 2021, 2020), only controls and cases living in the zones of influence of the corresponding primary
98 health care centers (geographical areas whose limits are defined by the population that uses one or more
99 services of these centers) were included in our study. Therefore, 270 controls and 866 cases were
100 excluded because they lived outside these zones.

101

102 **2.2.2 Industrial installations**

103 Industrial information (geographic location of the industries and pollutants released by them in
104 2009) was obtained from the installations included in the European Pollutant Release and Transfer
105 Register (E-PRTR) and governed by the Integrated Pollution Prevention and Control Directive. The

106 original geographic location of the industries (longitude/latitude) was converted into ED50/UTM zone
107 30N (EPSG:23030) projection using R software (The R Foundation, 2024). Subsequently, these
108 coordinates were thoroughly validated one by one, to ensure their exact locations, applying the
109 following tools: a) Google Earth Pro (with its “street-view” application); b) the Google Maps server
110 (Google Maps, 2024); c) the Spanish Agricultural Plots Geographic Information System (SIGPAC)
111 viewer (Spanish Ministry of Agriculture, Fisheries and Food, 2024), which includes orthophotos and
112 topographic maps (showing the names of industries); d) the “Yellow pages” web page (which allows
113 for a search of industrial companies and their addresses); and, e) web pages of the industrial companies.
114 Finally, we considered those industries that released pollutants to air, excluding those installations that
115 reported to release pollutants only to water, since the most plausible hypothesis of a potential
116 association between industrial pollution exposure and prostate cancer risk is via the airborne route
117 (Goldberg et al., 2022; Youogo et al., 2022; Yuan et al., 2024).

118

119 ***2.3 Study variables: clinical profile (tumor characteristics), and types of industrial groups and*** 120 ***pollutants***

121 The clinical profile (tumor characteristics) of prostate cases was defined according to: a) tumor
122 aggressiveness, based on Gleason score at diagnosis (biopsy) (6: low grade vs. >6: intermediate/high
123 grade) (Epstein et al., 2016); b) tumor extension (cT1-cT2a: localized vs. cT2b-cT4: locally advanced)
124 (Buyyounouski et al., 2017); c) International Society of Urological Pathology (ISUP) grade group (1-
125 2 vs. 3-5) (Epstein et al., 2016); d) prostate-specific antigen (PSA) at diagnosis (<10 vs. ≥10); and, e)
126 American Joint Committee on Cancer (AJCC) stage (8th edition) (I-IIA vs. IIB-IV) (Buyyounouski et
127 al., 2017).

128 Considering a minimum induction period of 10 years for PC (in line with recommendations for
129 solid tumors), the industrial facilities that came into operation prior to 10 years before the mid-year of
130 the recruitment period of each province were included in our study (n=58), and classified into the
131 following 19 industrial groups: ‘Combustion installations’ (n=5); ‘Production and processing of
132 metals’ (n=6); ‘Galvanization’ (n=1); ‘Surface treatment of metals and plastics’ (n=14); ‘Cement and
133 lime’ (n=1); ‘Glass and mineral fibers’ (n=1); ‘Ceramic’ (n=6); ‘Organic chemical industry’ (n=1);
134 ‘Inorganic chemical industry’ (n=1); ‘Fertilizers’ (n=1); ‘Pharmaceutical products’ (n=2); ‘Explosives
135 and pyrotechnics’ (n=1); ‘Hazardous waste’ (n=5); ‘Disposal or recycling of animal waste’ (n=2);
136 ‘Urban waste-water treatment plants’ (n=2); ‘Paper and wood production’ (n=2); ‘Food and beverage
137 sector’ (n=4); ‘Surface treatment using organic solvents’ (n=1); and ‘Ship building’ (n=2). These
138 industrial groups were formed on the basis of their similarity of their pollutant emission patterns
139 (Fernández-Navarro et al., 2017; García-Pérez et al., 2016).

140 The carcinogens released by the facilities were classified as Group 2B (possibly carcinogenic),
141 Group 2A (probably carcinogenic), and Group 1 (carcinogenic to humans), according to the
142 International Agency for Research on Cancer (IARC) (IARC, 2024). On the other hand, the EDCs
143 released by them were classified as ‘Metals’, ‘PACs’ (polycyclic aromatic chemicals), ‘Plasticizers’,
144 ‘POPs’, and ‘Other solvents’, according to the World Health Organization and the United Nations
145 Environment Program (WHO/UNEP, 2013). Finally, a total of 37 specific pollutants were analyzed.

146

147 ***2.4 Statistical analyses (strategies)***

148 The differences in the distribution of characteristics and risk factors of controls and PC cases
149 were explored by calculating frequencies and percentages, and tested using the Mann-Witney *U* and
150 the two-sided Chi-square tests, where appropriate.

151 Euclidean distances between each man’s residence and each of the 58 industrial facilities
152 included in the study were calculated as a proxy of the real exposure to industrial pollution. To estimate
153 odds ratios (ORs)/relative risk ratios (RRRs) and 95% confidence intervals (95% CIs) of PC in the
154 proximity of industrial installations, two methodological approaches (“*near vs. far*” and “*risk*
155 *gradient*” analyses) were performed, using mixed multiple (for ORs) and multinomial (for RRRs)
156 unconditional logistic regression models (see Figure 1 (B)). Matching factors (age, and province of
157 residence as a random effect), as well as potential confounders (family history of PC, body mass index
158 one year prior to the interview, and educational level), were included in all models. These confounding
159 factors have been related to PC risk in previous studies (Kumsa et al., 2024; Shi et al., 2024; Wilson
160 and Mucci, 2018).

161 Three strategies of statistical analysis were implemented for each approach: 1) “*Joint*” analysis,
162 2) “*Stratified*” analysis, and 3) “*Individualized*” analysis.

163

164 **2.4.1 First methodological approach: “*near vs. far*” analyses**

165 Potential excess risk of PC in the participants residing close (“*near*”) to the industrial
166 installations versus those residing far (“*far*”) from industries was assessed, comparing the ratio

$$167 \frac{\text{no. cases}/\text{no. controls}(\text{"near"})}{\text{no. cases}/\text{no. controls}(\text{"far"})}$$

168 According to several predefined distances ‘D’ (3, 2.5, 2, 1.5, and 1 km), the exposure variable
169 for each man was categorized as: a) “*near*” or “*exposed*” area (industrial area), if the man lived at \leq ‘D’
170 km from the installations in study; b) “*intermediate area*”, if he lived between ‘D’ and 3 km from any
171 installation; and, c) “*far*” or “*reference*” area, if he lived at $>$ 3 km from any installation. The three
172 strategies of analyses used in the paper were (see Figure 1 (B)):

173 1) “*Joint*” analysis: relationship between risk of PC and proximity to all installations as a whole
174 (all industries jointly) was assessed. For each man, the minimum of the previously calculated
175 distances between his residence and the 58 industrial facilities was considered as his minimum
176 “industrial distance” to all installations jointly (for example, if the “industrial distance” is 1.8
177 km, that participant is categorized as “near” (≤ 2 km) all industries as a whole).

178 2) “*Stratified*” analysis:

179 2.a) With the aim of analyzing the relationship between excess risk of PC and proximity to
180 industries by type of industrial groups and pollutants, a first sub-analysis was performed, where
181 the previous ORs were stratified by: i) categories of the previously defined 19 industrial groups,
182 ii) groups of pollutants (IARC-carcinogens and EDCs), and iii) specific pollutants released to
183 air by the industries.

184 2.b) With the purpose of identifying differences in the risk of PC according to the clinical
185 profile, a second sub-analysis was performed considering tumor aggressiveness, tumor local
186 extension, ISUP grade group, PSA at diagnosis, and AJCC stage (8th edition). This sub-analysis
187 was applied to the “*joint*” analysis and the “*stratified*” analysis by type of industrial groups and
188 pollutants.

189 3) “*Individualized*” analysis: relationship between risk of PC and proximity to each one of the 58
190 industrial installations was assessed.

191

192 **2.4.2 Second methodological approach: “*risk gradient*” analyses**

193 To assess the existence of radial effects around industrial installations, i.e., rise in OR with
194 increasing proximity to installations (“*risk gradient*”), the exposure variable for each man was
195 categorized according to concentric rings (0-1 km, 1-1.5 km, 1.5-2 km, 2-2.5 km, 2.5-3 km, and 3-30

196 km as reference), and included in the models as a continuous variable. These analyses were confined
197 to an area of 30 km surrounding each industry. The three strategies of analyses used were:

- 198 1) “*Joint*” analysis: considering all installations as a whole.
- 199 2) “*Stratified*” analysis: considering: i) categories of industrial groups, ii) groups of IARC-
200 carcinogens and EDCs, and iii) specific pollutants released by the industries.
- 201 3) “*Individualized*” analysis: rise in OR with increasing proximity to each of the industrial
202 installations individually.

203 Given that frequency matching was applied, taking into account the overall distribution of all
204 cancer cases included in the MCC-Spain study in each province instead of individual matching
205 (“multicase-control”), unconditional logistic regression including the matching factors was used (Lash
206 and Rothman, 2021). All the above-mentioned analyses used mixed multiple logistic regression
207 models, with the exception of the clinical profile analysis, which used mixed multinomial logistic
208 regression models.

209

210 **2.5 Robustness (strategies)**

211 With the purpose of introducing robustness and controlling potential biases in the different
212 analyses and methodological approaches, the following two strategies were implemented (see Figure 1
213 (C)):

214

215 **2.5.1 Sensitivity analysis**

216 A sensitivity analysis including only men living in their last residence for ≥ 10 years (long-term
217 residents) was conducted for all the previous analyses.

218

219 **2.5.2 Multiple comparisons**

220 The problem of multiple comparisons, that is, the possibility of finding falsely positive or
221 inverse associations by random chance, was addressed by controlling for the false discovery rate, which
222 is the expected proportion of false associations. This was achieved by the calculation of p-values
223 adjusted by the Benjamini & Hochberg method (*p*-BHs) (Benjamini and Hochberg, 1995), as applied
224 in those analyses with a high number of comparisons.

225

226 **2.6 Ethics**

227 The MCC-Spain study was conducted in conformity with the Declaration of Helsinki
228 guidelines, was formally approved by the Ethics Committee of each collaborating institution, and all
229 participants were informed about the objectives and signed an informed consent. Personal identifiers
230 were removed from the datasets in order to secure the confidentiality of the participants. Researchers
231 were asked to sign a confidentiality agreement. The database was recorded in the Spanish Agency for
232 Data Protection (Number: 2102672171).

233

234 **3. Results**

235 **3.1 Characteristics of the study population**

236 After excluding 7 cases and 33 controls with missing data on covariates (potential confounders),
237 the final study population comprised 1186 controls and 234 PC cases, whose main characteristics are
238 shown in Table 1. Barcelona and Madrid were the provinces that recruited the largest number of
239 controls and cases, and, in general, controls had a higher educational level and had been living longer
240 in their last residence than cases. On the other hand, in relation to the different distances (exposure
241 areas), the percentage of participants (cases and controls) with university studies was higher among

242 those living at >3 km from any industry than among those living close to industries. Moreover, the
243 number of cases with high-grade tumors (Gleason>6) was higher in those residing in zones close to
244 industries.

245

246 **3.2 First methodological approach: “near vs. far” analyses**

247 **3.2.1 “Joint” analysis (strategy 1)**

248 Numbers and percentages of controls and cases, and ORs of PC by distance in the environs of
249 all industrial installations as a whole (analysis including all the participants), were presented in Table
250 2A. No excess risk was detected for any of the distances, where the ORs (95% CIs) ranged from 0.66
251 (0.40-1.07) (with 326 controls and 67 cases, at ≤ 2 km) to 1.11 (0.51-2.40) (54 controls and 14 cases, at
252 ≤ 1 km). The sensitivity analysis considering only men living in their last domicile for ≥ 10 years (Table
253 2B) yielded slightly higher, although not statistically significant, ORs (95% CIs) than the previous
254 analysis, ranging from 0.72 (0.42-1.23) (286 controls and 55 cases, at ≤ 2 km) to 1.51 (0.64-3.55) (37
255 controls and 12 cases, at ≤ 1 km).

256

257 **3.2.2 “Stratified” analysis by industrial group (strategy 2.a.i)**

258 The analysis with all the individuals (Figure 2A) showed statistically significant increased risks
259 (OR (95% CI)) of PC in the proximity to industries belonging to the ‘Ceramic’ sector (4.56 (1.85-11.21)
260 at ≤ 1.5 km, 2.27 (1.08-4.78) at ≤ 2 km, 2.26 (1.12-4.55) at 2.5 km, and 2.54 (1.28-5.07) at ≤ 3 km),
261 ‘Disposal or recycling of animal waste’ (2.67 (1.12-6.37) at ≤ 3 km), and ‘Food and beverage sector’
262 (2.18 (1.32-3.62) at ≤ 3 km). Similar results were detected in the sensitivity analysis with long-term
263 residents (Figure 2B), with the exception of ‘Disposal or recycling of animal waste’, where the
264 statistical significance was disappeared.

265

266 **3.2.3 “Stratified” analysis by groups of pollutants (strategy 2.a.ii)**

267 There was no excess risk of PC in the proximity to industries releasing known or suspected
268 carcinogens, and EDCs to air (Table 3A) for any of the distances analyzed. Indeed, there were some
269 statistically significant decreased risks for industries releasing Group 2B-carcinogens (at ≤ 2 km), and
270 PACs and POPs (at $\leq 2, 2.5$ and 3 km), suggesting an inverse association between proximity to
271 industries releasing these groups of pollutants and risk of PC. In the sensitivity analysis restricted to
272 long-term residents (Table 3B), the results were very similar to the previous analysis, although the
273 statistically significant decreased risks were detected in the environs of industries releasing Group 2B-
274 carcinogens, PACs, and POPs, only at ≤ 2 km.

275

276 **3.2.4 “Stratified” analysis by specific pollutant (strategy 2.a.iii)**

277 When analyzing the potential relationship between risk of PC in the environs of installations
278 that release specific pollutants to air (Supplementary Data, Table S1), no excess risk was detected for
279 any of the pollutants and distances studied (in fact, the majority of the ORs were lower than unity, some
280 of them statistically significant). The only statistically significant excess risk was revealed for
281 industries releasing ‘Fluorine and inorganic compounds’ at ≤ 1.5 km (OR=3.46), although the p -
282 BH=0.400 indicates that this result could be due to chance. The sensitivity analysis including only
283 individuals living in their last residence for ≥ 10 years (Supplementary Data, Table S2) shows similar
284 results, including the statistically significant increased risk at ≤ 1.5 km from industries releasing
285 ‘Fluorine and inorganic compounds’ to air (OR=4.65, p -BH=0.274). In addition, a new statistically
286 significant OR was detected in men living at ≤ 1 km from industries releasing ‘Chlorine and inorganic
287 compounds’ to air (OR=5.21, p -BH=0.151). On the contrary, some pollutants showed significant

288 inverse associations with risk of PC, especially ‘Ammonia’ (OR=0.14, p -BH=0.004 at ≤ 2 km),
289 ‘Methane’ (OR=0.18, p -BH=0.008 at ≤ 2 km), ‘PCDD+PCDF (dioxins+furans)’ (OR=0.16, p -
290 BH=0.004 at ≤ 2 km), ‘Polycyclic aromatic hydrocarbons’ (PAHs) (OR=0.13, p -BH=0.004 at ≤ 2 km),
291 ‘Trichloroethylene’ (OR=0.22, p -BH=0.037 at ≤ 3 km), and ‘Vanadium’ (OR=0.14, p -BH=0.004 at ≤ 2
292 km).

293

294 ***3.2.5 “Stratified” analysis by clinical profile (strategy 2.b) applied to the analysis of all installations*** 295 ***as a whole***

296 The results for the analysis with all the individuals are shown in Table 4A, whereas the
297 corresponding sensitivity analysis with only participants residing in their last residence for ≥ 10 years
298 are shown in Table 4B. By tumor aggressiveness, non-statistically significant RRRs of prostate tumors
299 with Gleason >6 were higher than those of Gleason=6 for all distances, ranging from 0.93 (at ≤ 2 km) to
300 1.21 (at ≤ 3 km). The corresponding sensitivity analysis detected that RRRs of prostate tumors with
301 Gleason >6 were higher than those with Gleason=6 for distances between ≤ 2 and ≤ 3 km, and the
302 opposite for distances of ≤ 1 and ≤ 1.5 km, although none of them reached the statistical significance.

303 By tumor extension, RRRs of locally advanced tumors (cT2b-cT4) were higher than those of
304 localized tumors (cT1-cT2a) for all distances (with the exception of ≤ 3 km), being statistically
305 significant in the case of ≤ 1 km (RRR=2.81, 95%CI=1.00-7.90). The sensitivity analysis revealed an
306 increased risk of locally advanced tumors (cT2b-cT4) in men living at ≤ 1 km from industries
307 (RRR=3.55, 95%CI=1.15-10.96).

308 By ISUP grade group, RRRs of prostate tumors with ISUP ≤ 2 were higher, although not
309 statistically significant, than those of ISUP >2 for all distances (with the exception of ≤ 3 km), ranging

310 from 0.78 (at ≤ 2 km) to 1.36 (at ≤ 1 km). Similar results were found in the sensitivity analysis with
311 long-term residents.

312 The sub-analysis by PSA at diagnosis detected higher RRRs, although not statistically
313 significant, of prostate tumors with $\text{PSA} \geq 10$ than those with $\text{PSA} < 10$ for distances between ≤ 2 and ≤ 3
314 km, and the opposite for distances of ≤ 1 and ≤ 1.5 km. Similar results were shown in the sensitivity
315 analysis.

316 Lastly, by AJCC stage, RRRs of prostate tumors in stages IIB-IV were higher, although not
317 statistically significant, than those in stages I-IIA, for all distances. The sensitivity analysis revealed
318 similar results, with the exception of ≤ 1 km.

319

320 ***3.2.6 “Stratified” analysis by clinical profile (strategy 2.b) applied to the analysis by industrial group***

321 The results for the analysis with all the individuals are shown in Figure 3, whereas the
322 corresponding sensitivity analysis with only individuals living in their last domicile for ≥ 10 years are
323 shown in Supplementary Data, Figure S1. By tumor aggressiveness, intermediate-high grade tumors
324 (Gleason > 6) showed higher RRRs than low-grade tumors (Gleason 6), highlighting the following
325 statistically significant increased risks: ‘Ceramic’ (Gleason 6: $\text{RRR} = 3.81$ at ≤ 1.5 km; Gleason > 6 :
326 $\text{RRRs} = 6.30$ at ≤ 1.5 km, 3.06 at ≤ 2 km, 2.86 at ≤ 2.5 km, and 3.19 at ≤ 3 km), and ‘Food and beverage
327 sector’ (Gleason > 6 : $\text{RRR} = 2.93$ at ≤ 3 km). The sensitivity analysis detected the following significant
328 results: ‘Ceramic’ (Gleason 6: $\text{RRR} = 3.64$ at ≤ 3 km; Gleason > 6 : $\text{RRRs} = 6.09$ at ≤ 1.5 km, and 3.11 at
329 ≤ 2 km), ‘Hazardous waste’ (Gleason 6: $\text{RRRs} = 5.41$ at ≤ 1.5 km, and 5.60 at ≤ 2 km), and ‘Food and
330 beverage sector’ (Gleason > 6 : $\text{RRR} = 2.66$ at ≤ 3 km).

331 By tumor local extension, the RRRs of locally advanced tumors (cT2b-cT4) were higher than
332 those of localized tumors (cT1-cT2a), emphasizing the following results: ‘Production and processing

333 of metals' (cT2b-cT4: RRR=3.63 at ≤ 2.5 km), 'Ceramic' (cT1-cT2a: RRRs=3.32 at ≤ 1.5 km, and 2.18
334 at ≤ 3 km; cT2b-cT4: RRRs=10.40 at ≤ 1.5 km, 5.20 at ≤ 2 km, 4.11 at ≤ 2.5 km, and 4.17 at ≤ 3 km),
335 'Hazardous waste' (cT2b-cT4: RRR=3.47 at ≤ 1.5 km, and 4.55 at ≤ 2 km), 'Disposal or recycling of
336 animal waste' (cT1-cT2a: RRR=2.95 at ≤ 3 km), and 'Food and beverage sector' (cT1-cT2a: RRR=2.34
337 at ≤ 3 km). The associated sensitivity analysis revealed statistically significant results for the following
338 sectors: 'Production and processing of metals' (cT2b-cT4: RRR=3.62 at ≤ 2.5 km), 'Ceramic' (cT1-
339 cT2a: RRR=4.79 at ≤ 1.5 km; cT2b-cT4: RRRs=6.57 at ≤ 2 km, 4.88 at ≤ 2.5 km, and 4.93 at ≤ 3 km),
340 'Hazardous waste' (cT2b-cT4: RRRs=4.97 at ≤ 1.5 km, and 4.20 at ≤ 2 km), and 'Food and beverage
341 sector' (cT1-cT2a: RRR=2.29 at ≤ 3 km).

342 By ISUP grade group, the following sectors are highlighted: 'Ceramic' (1-2: RRRs=4.28 at ≤ 1.5
343 km, 2.39 at ≤ 2 km, 2.25 at ≤ 2.5 km, and 2.65 at ≤ 3 km; 3-5: RRR=7.60 at ≤ 1.5 km), 'Disposal or
344 recycling of animal waste' (3-5: RRR=4.07 at ≤ 3 km), 'Food and beverage sector' (1-2: RRR=2.00 at
345 ≤ 3 km; 3-5: RRR=3.00 at ≤ 3 km), and 'Surface treatment using organic solvents' (3-5: RRR=3.71 at
346 ≤ 3 km). The sensitivity analysis detected significant results in 'Ceramic', 'Hazardous waste', and 'Food
347 and beverage sector'.

348 The sub-analysis by PSA at diagnosis detected remarkable results in the environs of industries
349 pertaining to 'Ceramic' (PSA<10: RRRs=4.72 at ≤ 1.5 km, 2.24 at ≤ 2.5 km, and 2.63 at ≤ 3 km),
350 'Disposal or recycling of animal waste' (PSA ≥ 10 : RRR=3.56 at ≤ 3 km), and 'Food and beverage
351 sector' (PSA<10: RRR=2.47 at ≤ 3 km). The associated sensitivity analysis detected statistically
352 significant excess risks in the proximity of installations belonging to 'Ceramic', and 'Food and
353 beverage sector'.

354 Finally, in the analysis by AJCC stage, attention should be drawn to the results detected in men
355 living close to 'Ceramic' industries (I-IIA: RRR=3.54 at ≤ 1.5 km; IIB-IV: RRRs=7.09 at ≤ 1.5 km, 3.36

356 at ≤ 2 km, 3.18 at ≤ 2.5 km, and 3.51 at ≤ 3 km), and installations belonging to 'Food and beverage
357 sector' (IIB-IV: RRR=3.03 at ≤ 3 km). The sensitivity analysis detected remarkable increased risks in
358 the following sectors: 'Ceramic', 'Hazardous waste', 'Disposal or recycling of animal waste', and
359 'Food and beverage sector'.

360

361 ***3.2.7 "Stratified" analysis by clinical profile (strategy 2.b) applied to the analysis by groups of*** 362 ***pollutants***

363 The results of the sub-analyses by the several clinical classifications applied to the IARC and
364 EDCs groups of pollutants showed no statistically significant excess risks of PC (data not shown).

365

366 ***3.2.8 "Stratified" analysis by clinical profile (strategy 2.b) applied to the analysis by specific pollutant***

367 By tumor aggressiveness (data not shown), the only remarkable excess risk (statistically
368 significant RRR and a number of controls and cases ≥ 5) was found in men with low-grade tumors
369 (Gleason=6) living at ≤ 1.5 km of industrial facilities releasing 'Fluorine and inorganic compounds'
370 (RRR=4.73, 95%CI=1.49-15.04). In the sub-analysis by tumor local extension (data not shown), the
371 most remarkable results (RRR (95%CI)) were found in men with locally advanced tumors (cT2b-cT4)
372 close to industries releasing the following pollutants: 'Carbon monoxide' (3.31 (1.16-9.46) at ≤ 1 km),
373 'Nitrogen oxides' (3.31 (1.16-9.46) at ≤ 1 km), 'Non-methane volatile organic compounds' (3.47 (1.21-
374 9.97) at ≤ 1 km), 'Sulfur oxides' (3.43 (1.20-9.82) at ≤ 1 km), and 'Total organic carbon (air)' (2.67
375 (1.04-6.88) at ≤ 2.5 km). In relation to the remaining clinical classifications (data not shown), the only
376 significant excess risks were detected at ≤ 1 km of industries releasing 'Chlorine and inorganic
377 compounds' for cases with ISUP grade group=1-2 (RRR=2.95, 95%CI=1.01-8.65) and PSA<10
378 (RRR=3.03, 95%CI=1.04-8.87), and at ≤ 1.5 km of industries releasing 'Fluorine and inorganic

379 compounds' for cases with ISUP grade group=1-2 (RRR=4.75, 95%CI=1.67-13.48), PSA<10
380 (RRR=4.76, 95%CI=1.68-13.48), and AJCC stage=I-IIA (RRR=3.97, 95%CI=1.27-12.46).

381

382 **3.2.9 “Individualized” analysis (strategy 3)**

383 The four specific installations with ORs>1 in the “*near vs. far*” analysis”, for a distance of ≤3
384 km, are shown in Table 5. The ‘3498’ facility (belonging to the food/beverage sector and located in
385 Barcelona) was the only one that showed a significant increase in the risk of PC in its environs
386 (OR=3.14, 95%CI=1.11-8.93), with this excess risk being higher in participants with high-grade tumors
387 (Gleason>6) (RRR=3.91, 95%CI=1.04-14.55, data not shown).

388

389 **3.3 Second methodological approach: “risk gradient” analyses**

390 For the following strategies, the results for the analyses with all the individuals are shown in
391 Supplementary Data, Table S3A, whereas the corresponding sensitivity analyses with only participants
392 residing in their last residence for ≥10 years are shown in Supplementary Data, Table S3B.

393 **a) “Joint” analysis (strategy 1):** no positive radial effects were detected for all industries as a
394 whole, neither on the analysis with of all the individuals nor in the sensitivity analysis.

395 **b) “Stratified” analysis by industrial group (strategy 2.a.i):** Significant positive radial effects
396 (ORs>1) were detected in the proximity of ‘Hazardous waste’ (*p*-trend=0.016) and ‘Food and
397 beverage sector’ (*p*-trend=0.001) industries, whereas significant inverse radial effects (ORs<1)
398 were found in the environs of ‘Glass and mineral fibers’ (*p*-trend=0.010) and ‘Organic chemical
399 industry’ (*p*-trend<0.001). Their respective corrections by multiple comparisons showed *p*-BHs
400 for trend<0.100 in all the above cases. Similar results were yielded by the sensitivity analysis.

- 401 c) **“Stratified” analysis by groups of pollutants (strategy 2.a.ii):** this analysis only yielded radial
402 effects for industries releasing PACs and POPs, with an inverse association, both in the analysis
403 with all the individuals and the sensitivity analysis.
- 404 d) **“Stratified” analysis by specific pollutant (strategy 2.a.iii):** the “*risk gradient*” analysis by
405 specific pollutant did not show any positive radial effects. However, statistically significant
406 radial effects in the opposite direction were found near industries releasing ‘Ammonia’,
407 ‘Methane’, ‘Dioxins+furans’, ‘PAHs’, ‘Trichloroethylene’, and ‘Vanadium’. Similar results
408 were found in the sensitivity analysis.
- 409 e) **“Individualized” analysis (strategy 3):** table 5 shows the “*risk gradient*” analysis for the
410 specific installations that showed ORs>1 in the “*near vs. far*” analysis. Again, installation
411 ‘3498’ showed the only significant positive radial effect (p -trend=0.045).

412

413 **4. Discussion**

414 **4.1 Summary**

415 To our knowledge, this is the first paper analyzing thoroughly the risk of developing PC in the
416 proximity of Spanish industrial installations using individual data, and applying several methodological
417 approaches and robustness strategies in the statistical analyses. In summary, our results suggest no
418 association between risk of this cancer and proximity to the overall installations.

419 However, the following potential positive associations with some industrial groups and
420 pollutants released to air, at specific distances, were identified: a) ‘Ceramic’ and all prostate tumors
421 (all distances); b) ‘Food and beverage sector’ and all prostate tumors, especially high-grade tumors,
422 localized tumors, with PSA<10, or tumors in stage IIB-IV (≤ 3 km); c) ‘Disposal or recycling of animal
423 waste’ and all prostate tumors (≤ 3 km); d) ‘Hazardous waste’ and locally advanced tumors (≤ 1.5 and

424 ≤ 2 km); e) ‘Surface treatment using organic solvents’ and tumors with ISUP grade group=3-5 (≤ 3 km);
425 f) ‘Production and processing of metals’ and locally advanced tumors (≤ 2.5 km); g) ‘Fluorine and
426 inorganic compounds’ and all prostate tumors (≤ 1.5 km); and, h) ‘Chlorine and inorganic compounds’
427 and all prostate tumors (≤ 1 km).

428 These novel results could provide new research hypotheses about the etiology of PC in relation to
429 proximity to environmental pollutant sources, such as the abovementioned industrial groups and
430 pollutants.

431 On the contrary, surprisingly, some inverse associations were found between risk of PC and
432 proximity to industries releasing ‘Ammonia’, ‘Methane’, ‘Dioxins+furans’, ‘PAHs’,
433 ‘Trichloroethylene’, and ‘Vanadium’ to air. The fact that these industrial zones “*near*” industries
434 emitting these substances (“exposed” areas) have lower risks than those areas “*far*” from any industry
435 (“non-exposed” areas) could reflect the presence of uncontrolled potential risk factors of PC in the
436 analyses, or possible inverse causation.

437 In 2016, an ecological study analyzing PC mortality at a municipal level and its relationship
438 with industrial pollution that was published by our group (García-Pérez et al., 2016) did not support
439 that residing in the environs of industrial facilities as a whole was a risk factor for PC mortality. In the
440 present paper, we have improved the study design including individual data on several PC risk factors,
441 which have been controlled in the analyses.

442

443 ***4.2 Discussion of results in relation to other studies***

444 In relation to environmental exposures and risk of PC, two studies conducted in the US in the
445 1960s suggested that PC mortality rates were higher in zones with a high level of air pollution
446 (Hagstrom et al., 1967; Winkelstein and Kantor, 1969). More recently, some authors have found

447 positive associations between PC incidence rates (at a county level) and poor environmental quality
448 (based on variables referred to hazardous air pollutants) (Jagai et al., 2017), or higher risks of PC in
449 men exposed to traffic-related air pollution (Cohen et al., 2018), to ambient ultrafine particles
450 (Weichenthal et al., 2017), and to particulate matter (PM), such as PM_{2.5} (Yu et al., 2022) and PM₁₀
451 (Datzmann et al., 2018). Moreover, a retrospective population-based study conducted in Shanghai
452 (China) suggested that ambient air pollution from waste gas emissions was associated with PC
453 incidence (Cong, 2018). Recently, a case-control study conducted in Canada found positive
454 associations between exposure to ambient air pollution (mainly due to PM and nitrogen dioxide (NO₂))
455 and PC (Youogo et al., 2022).

456 On the other hand, an Italian ecological study detected significant excess risk of PC in six
457 National Priority Contaminated Sites (NPCSs) and significant lower risk in four NPCSs (Benedetti et
458 al., 2017). These findings are in line with our results, showing both positive and inverse associations
459 between risk of PC and proximity to specific industrial installations. This reflects the apparently
460 contradictory nature of this tumor, whose etiology remains still largely unknown, and very few risk
461 factors are well established.

462

463 ***4.2.1 Studies about industrial groups***

464 To the best of our knowledge, there is hardly any research on PC risk in populations close to
465 industrial installations belonging to specific sectors. In relation to PC incidence and proximity to
466 specific industrial sites, a Swedish study reported a significant increased risk of PC in a population
467 cohort that resided close to metal-contaminated glasswork sites (Nyqvist et al., 2017). However, our
468 results showed an inverse association with proximity to the only factory pertaining to the ‘Glass and
469 mineral fibers’ sector in the “*risk gradient*” analysis (p -trend=0.010), although the low number of cases

470 and controls living close to this installation and the fact that this estimate was based on only one factory
471 could make this result due to chance.

472 With regard to PC mortality and industrial groups, two Italian studies found an increased risk
473 in populations exposed to emissions in an industrial district with presence of wooden furniture factories
474 (Rava et al., 2009), and living near a steel plant (Casella et al., 2005). In relation to the metal industry,
475 Ramis et al. (Ramis et al., 2011) found some evidence of an association between the spatial distribution
476 of PC mortality at a census tract level and proximity to metal installations. In our study, with incident
477 cases of PC, we have found an increased risk of PC in men with locally advanced tumors living close
478 (≤ 2.5 km) to installations of ‘Production and processing of metals’ (OR=3.63), something that would
479 need to be confirmed in further studies.

480 On the contrary, some studies have found significant decreased risks of PC associated with
481 proximity to specific industrial groups, or inconsistent associations. For example, with regard to
482 residential proximity to mining sites, Mueller et al. (Mueller et al., 2015) found an association between
483 residential proximity to coal mines in Illinois (US) and PC mortality at a county level. However, another
484 ecological study conducted in Spain revealed both positive and inverse associations, depending on the
485 type of mining activity, between proximity to specific mines and PC mortality at a municipal level
486 (Fernández-Navarro et al., 2012), whereas a systematic review found no increased risk of PC among
487 exposed populations (Cortes-Ramirez et al., 2018). In our study, there were no mining sites in the study
488 area.

489

490 ***4.2.2 Studies about pollutants***

491 Environmental exposures to arsenic and cadmium have been associated with an increased risk
492 of PC in industrialized countries (McDonald et al., 2022; Mezynska and Brzóska, 2018; Mukherjee and

493 Gopalakrishnan, 2024; Nyqvist et al., 2017; Tyagi et al., 2023; Vijayakumar et al., 2021; Yang et al.,
494 2022), although some studies have shown inconsistent associations in the case of cadmium exposure
495 (Chen et al., 2016; Nishijo et al., 2018). The results shown in our paper suggest no association between
496 PC and residential proximity to industries releasing these two pollutants (see Supplementary Data,
497 Tables S1 and S2).

498 With regard to exposure to POPs, some authors have found some evidence of associations
499 between body and serum concentrations of POPs and increased risks of PC, including dose-response
500 relationships (Lim et al., 2017, 2019). However, our findings about this group of pollutants are in the
501 opposite direction: decreased risks of PC in men living close to industries releasing POPs in the “*near*
502 *vs. far*” analysis and inverse radial effects in the “*risk gradient*” analysis.

503 In our study, we found a significant increased risk of locally advanced PC near (≤ 1 km)
504 industries releasing ‘Nitrogen oxides’ (data not shown). This finding is in line with that found in a case-
505 control study conducted in Montreal (Canada), in which the authors concluded that exposure to ambient
506 concentrations of NO₂ at the current address was linked to an increased risk of PC (Parent et al., 2013).
507 On the other hand, in a cohort of patients with myocardial infarction living in a predominantly urban
508 area, the authors found a strong association between exposure to long-term residential nitrogen oxides
509 levels and a higher incidence of PC (together with other cancers) (Cohen et al., 2019, 2017). Moreover,
510 a recent study conducted in China revealed a positive correlation between NO₂ concentration values
511 and PC incidence and mortality (Zhang et al., 2023). Our novel finding, in relation to proximity to
512 industrial sources releasing ‘Nitrogen oxides’, requires replication.

513 Lastly, exposure to pesticides could be related to an increased risk of PC (Belpomme, 2009;
514 Cockburn et al., 2011; Pardo et al., 2020; Remigio et al., 2024). However, in our study, there were no
515 industries releasing pesticides to air in the study area. Another group of pollutants related to risk of PC,

516 including both positive (Ali et al., 2016) and inverse (Emeville et al., 2015) associations, are PCBs. In
517 our study, however, there were no cases close to the industrial installations releasing these substances.

518

519 ***4.3 Limitations and strengths***

520 The use of the Euclidean distance to the industrial installations as a proxy of the real exposure
521 to industrial pollution is one of the main limitations of our study because this could lead to a problem
522 of misclassification of the exposure, which is dependent on geographic factors (for example, prevailing
523 winds). In this sense, we have used several distances in our analyses, between 1 and 3 km, in line with
524 the distances chosen by other authors in studies about proximity to industrial pollution sources and
525 cancer risk involving individual data (De Roos et al., 2010; García-Pérez et al., 2021; Rodríguez-
526 Villamizar et al., 2020), and based on industrial pollution dispersion modeling studies (Bergstra et al.,
527 2022; Leogrande et al., 2019; Paolucci et al., 2020; Yarandi et al., 2021). Moreover, we only had
528 information on the place of residence, but people move during the day and expend a substantial part of
529 the day at work or in other places. It is important to note that our study has no individual measures of
530 exposure to substances and pollutants released by the industrial plants, since it is an exploratory study
531 used as a generator of etiological hypotheses on PC risk.

532 On the other hand, we could have selected other approaches to measure pollution exposure,
533 such as the amounts of pollutants released by the industries or the duration of exposure. In relation to
534 the intensity of exposure to the industrial pollution, the E-PRTR contains information on the amounts
535 of pollutants released by the industrial facilities; however, this information was not included in our
536 analyses because it was not reliable, as it has not been checked or validated by the official organizations
537 (European Environment Agency and the Spanish Ministry for the Ecological Transition and
538 Demographic Challenge). In relation to the duration of exposure to the industrial pollution, we do not

539 have information on how long the participants were exposed to the pollution; however, we were able
540 to palliate this lack of information using a robustness strategy in the analyses including only those
541 individuals living in their last residence ≥ 10 years. Moreover, we have included industrial installations
542 that came into operation prior to 10 years before the mid-year of the recruitment period of each
543 province, excluding recent industries with less than 10 years of operation.

544 Another limitation is referred to the fact that some of the potential confounders are self-reported
545 and subject to a possible recall bias; however, this hypothetical recall bias would probably be non-
546 differential with respect to the distance to the industries, implying an attenuation of the effects found
547 in our study. One aspect to consider is the problem of multiple comparisons, due to the large number
548 of analyses carried out; this was palliated using a robustness strategy in the analyses including adjusted
549 p -values to control the expected proportion of false associations. Other limitations include: the loss of
550 statistical power due to the exclusion of the participants outside the study areas; the low number of
551 cases and controls in some “*stratified*” sub-analyses; and the lack of information on other factors that
552 could be involved in a misclassification of the exposure (such as occupational exposures, indoor air
553 pollution, information on wind roses and prevailing winds, exposure to other sources of known or
554 suspected carcinogens (including tap water or diet), or the time actually spent inside the exposure
555 zones).

556 One of the main strengths in our paper is the exhaustiveness and completeness of the analyses,
557 implying two methodological approaches, three strategies of statistical analysis, and two strategies of
558 robustness, that allowed us to provide a very detailed description of PC risk in relation to exposure to
559 industrial pollution. Moreover, our analyses included a random province-specific intercept term that
560 accounted for unexplained heterogeneity in the models due to unmeasured factors across the different
561 provinces. These seven representative provinces were located throughout the geography of Spain, being

562 representative of the general idiosyncrasy in Spain, and covered both urban and rural settings. Another
563 strength refers to the fact that our study included histologically confirmed incident cancer cases and
564 population-based controls, which provides added value to our findings. Particularly, the recruitment of
565 incident cases contributed to preventing potential changes of address associated with the PC diagnosis.
566 Hence, if there were any bias affecting proximity to industrial installations in relevant periods of the
567 participants' life, this would be a non-differential bias, causing an underestimation of the ORs/RRRs.

568

569 **5. Conclusions**

570 Our results suggest no association between risk of PC and proximity to the overall industrial
571 installations. However, some positive associations were detected in the environs of installations
572 belonging to specific industrial groups (ceramic, food/beverage, disposal/recycling of animal waste,
573 hazardous waste, surface treatment using organic solvents, and production/processing of metals) and
574 installations releasing specific pollutants to air (fluorine and chlorine). On the contrary, some inverse
575 associations were found with the proximity of industries releasing ammonia, methane, dioxins+furans,
576 PAHs, trichloroethylene, and vanadium to air. These novel findings could provide new research
577 hypotheses on the etiology of PC in relation to proximity to environmental pollutant sources and should
578 to be replicated.

579

580 **Declaration of competing interest:**

581 The authors declare that they have no conflicts of interest. This article presents independent
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584

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603

604

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875 **Figure legends**

876 Figure 1. Diagram of the strategies for geocoding/validation of locations (A), statistical analyses (B),
877 and robustness (C) used in the present paper. SIGPAC: Spanish Agricultural Plot Geographic
878 Information System.

879 Figure 2. Statistically significant odds ratios (ORs) and their 95% confidence intervals (95% CIs) of
880 prostate cancer at different distances to industries, based on a number of controls (Co) and cases (Ca)
881 ≥ 5 , for the “*stratified*” analysis by industrial group. X-axis is plotted on a logarithmic scale. Analysis
882 with all the individuals (A), and sensitivity analysis with only individuals living in their last residence
883 for ≥ 10 years (B).

884 Figure 3. Statistically significant relative risk ratios (RRRs) and their 95% confidence intervals
885 (95% CIs) of prostate cancer at different distances to industries (analysis with all the individuals), based
886 on a number of controls (Co) and cases (Ca) ≥ 5 , for the “*stratified*” analysis by clinical profile applied
887 to the analysis by industrial group. X-axis is plotted in logarithmic scale.

Table 1. Characteristics of controls and prostate cancer cases.

Characteristic	All men		p-value ^a	Men living at ≤1 km from any industry		Men living at ≤1.5 km from any industry		Men living at ≤2 km from any industry		Men living at ≤2.5 km from any industry		Men living at ≤3 km from any industry		Men living at >3 km from any industry	
	Controls (n=1186)	Cases (n=234)		Controls (n=54)	Cases (n=14)	Controls (n=144)	Cases (n=36)	Controls (n=326)	Cases (n=67)	Controls (n=490)	Cases (n=95)	Controls (n=661)	Cases (n=140)	Controls (n=525)	Cases (n=94)
Age, mean (SD)	66.4 (8.5)	66.4 (7.6)	0.860	66.2 (10.3)	67.1 (6.4)	68.5 (9.6)	65.9 (6.8)	67.8 (8.2)	65.4 (7.0)	67.3 (8.5)	66.3 (7.2)	66.9 (8.4)	66.9 (7.5)	65.7 (8.6)	65.6 (7.7)
Province, n (%)			<0.001												
Asturias	69 (5.8)	15 (6.4)		5 (9.3)	0 (0.0)	14 (9.7)	2 (5.5)	26 (8.0)	5 (7.5)	45 (9.2)	9 (9.5)	54 (8.1)	12 (8.6)	15 (2.9)	3 (3.2)
Barcelona	417 (35.2)	46 (19.7)		0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	8 (2.4)	0 (0.0)	115 (23.5)	8 (8.4)	234 (35.4)	29 (20.7)	183 (34.9)	17 (18.1)
Cantabria	143 (12.1)	35 (15.0)		47 (87.0)	13 (92.9)	76 (52.8)	23 (63.9)	138 (42.3)	34 (50.7)	138 (28.2)	35 (36.8)	138 (20.9)	35 (25.0)	5 (0.9)	0 (0.0)
Granada	109 (9.2)	28 (11.9)		0 (0.0)	0 (0.0)	27 (18.7)	1 (2.8)	89 (27.3)	10 (14.9)	99 (20.2)	19 (20.0)	105 (15.9)	25 (17.9)	4 (0.8)	3 (3.2)
Huelva	62 (5.2)	35 (15.0)		2 (3.7)	1 (7.1)	3 (2.1)	6 (16.7)	11 (3.4)	6 (9.0)	26 (5.3)	11 (11.6)	35 (5.3)	17 (12.1)	27 (5.1)	18 (19.1)
Madrid	323 (27.2)	63 (26.9)		0 (0.0)	0 (0.0)	24 (16.7)	4 (11.1)	54 (16.6)	12 (17.9)	61 (12.4)	12 (12.6)	62 (9.4)	12 (8.6)	261 (49.7)	51 (54.3)
Valencia	63 (5.3)	12 (5.1)		0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	6 (1.2)	1 (1.1)	33 (5.0)	10 (7.1)	30 (5.7)	2 (2.1)
Family history of prostate cancer, n (%)			<0.001												
None	1108 (93.4)	183 (78.2)		52 (96.3)	12 (85.7)	136 (94.4)	32 (88.9)	304 (93.3)	54 (80.6)	461 (94.1)	75 (79.0)	617 (93.3)	110 (78.6)	491 (93.5)	73 (77.7)
Second degree only	13 (1.1)	6 (2.6)		0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	2 (0.6)	1 (1.5)	2 (0.4)	2 (2.1)	6 (0.9)	2 (1.4)	7 (1.3)	4 (4.2)
≥1 first degree	65 (5.5)	45 (19.2)		2 (3.7)	2 (14.3)	7 (4.9)	4 (11.1)	20 (6.1)	12 (17.9)	27 (5.5)	18 (18.9)	38 (5.8)	28 (20.0)	27 (5.2)	17 (18.1)
Body mass index, mean (SD)	27.5 (3.8)	27.4 (3.4)	0.726	27.7 (3.7)	27.8 (3.2)	27.7 (3.4)	28.0 (4.2)	27.6 (3.4)	27.7 (3.8)	27.7 (3.5)	27.8 (3.6)	27.7 (3.6)	27.6 (3.5)	27.3 (4.0)	27.2 (3.4)
Educational level, n (%)			0.031												
Less than primary school	214 (18.0)	46 (19.7)		12 (22.2)	4 (28.6)	36 (25.0)	5 (13.9)	65 (19.9)	11 (16.4)	110 (22.4)	18 (18.9)	153 (23.2)	30 (21.4)	61 (11.6)	16 (17.0)
Primary school completed	376 (31.7)	92 (39.3)		23 (42.6)	2 (14.3)	55 (38.2)	16 (44.5)	123 (37.7)	30 (44.8)	186 (38.0)	43 (45.3)	248 (37.5)	61 (43.6)	128 (24.4)	31 (33.0)
Secondary school	320 (27.0)	59 (25.2)		15 (27.8)	6 (42.8)	40 (27.8)	12 (33.3)	86 (26.4)	19 (28.4)	128 (26.1)	23 (24.2)	172 (26.0)	32 (22.9)	148 (28.2)	27 (28.7)
University graduate	276 (23.3)	37 (15.8)		4 (7.4)	2 (14.3)	13 (9.0)	3 (8.3)	52 (16.0)	7 (10.4)	66 (13.5)	11 (11.6)	88 (13.3)	17 (12.1)	188 (35.8)	20 (21.3)
Living in their last residence for ≥10 years, n (%)	1043 (87.9)	192 (82.1)	0.019	37 (68.5)	12 (85.7)	121 (84.0)	31 (86.1)	286 (87.7)	55 (82.1)	433 (88.4)	80 (84.2)	590 (89.3)	116 (82.9)	453 (86.3)	76 (80.6)
Tumor aggressiveness, n (%)															
Gleason = 6	-	98 (41.9)		-	6 (42.9)	-	14 (38.9)	-	25 (37.3)	-	39 (41.0)	-	59 (42.2)	-	49 (52.1)
Gleason > 6	-	120 (51.3)		-	7 (50.0)	-	21 (58.3)	-	41 (61.2)	-	53 (55.8)	-	78 (55.7)	-	42 (44.7)
Unknown	-	16 (6.8)		-	1 (7.1)	-	1 (2.8)	-	1 (1.5)	-	3 (3.2)	-	3 (2.1)	-	3 (3.2)
Tumor local extension, n (%)															
cT1-cT2a	-	169 (72.2)		-	6 (42.9)	-	21 (58.3)	-	44 (65.7)	-	69 (72.6)	-	102 (72.9)	-	67 (71.3)
cT2b-cT4	-	42 (18.0)		-	7 (50.0)	-	11 (30.6)	-	19 (28.3)	-	20 (21.1)	-	25 (17.8)	-	17 (18.1)
Other / Unknown	-	23 (9.8)		-	1 (7.1)	-	4 (11.1)	-	4 (6.0)	-	6 (6.3)	-	13 (9.3)	-	10 (10.6)
ISUP grade group, n (%)															
1-2	-	157 (67.1)		-	11 (78.6)	-	28 (77.8)	-	48 (71.6)	-	69 (72.6)	-	95 (67.9)	-	62 (65.9)
3-5	-	61 (26.1)		-	2 (14.3)	-	7 (19.4)	-	17 (25.4)	-	21 (22.1)	-	38 (27.1)	-	23 (24.5)
Other / Unknown	-	16 (6.8)		-	1 (7.1)	-	1 (2.8)	-	2 (3.0)	-	5 (5.3)	-	7 (5.0)	-	9 (9.6)
PSA at diagnosis (ng/ml), n (%)															
<10	-	155 (66.3)		-	11 (78.6)	-	26 (72.2)	-	47 (70.1)	-	64 (67.4)	-	91 (65.0)	-	64 (68.1)
≥10	-	78 (33.3)		-	3 (21.4)	-	10 (27.8)	-	20 (29.9)	-	31 (32.6)	-	49 (35.0)	-	29 (30.8)
Other / Unknown	-	1 (0.4)		-	0 (0.0)	-	0 (0.0)	-	0 (0.0)	-	0 (0.0)	-	0 (0.0)	-	1 (1.1)
AJCC stage (8 th edition), n (%)															
I-IIA	-	106 (45.3)		-	7 (50.0)	-	14 (38.9)	-	24 (35.8)	-	37 (39.0)	-	56 (40.0)	-	50 (53.2)
IIB-IV	-	118 (50.4)		-	7 (50.0)	-	21 (58.3)	-	42 (62.7)	-	54 (56.8)	-	79 (56.4)	-	39 (41.5)
Other / Unknown	-	10 (4.3)		-	0 (0.0)	-	1 (2.8)	-	1 (1.5)	-	4 (4.2)	-	5 (3.6)	-	5 (5.3)

^a Two-sided Chi-square and Mann-Whitney U tests, where appropriate.

Table 2. Odds ratios (ORs) of prostate cancer at different distances to all the industrial installations as a whole. Analysis with all the individuals (A), and sensitivity analysis with only individuals living in their last residence for ≥ 10 years (B).

Distance	A) Analysis with all the individuals			B) Sensitivity analysis with only individuals living in their last residence for ≥ 10 years		
	n (%)		OR (95%CI) ^a	n (%)		OR (95%CI) ^a
	Controls (n=1186)	Cases (n=234)		Controls (n=1043)	Cases (n=192)	
Reference (>3 km)	525 (43.9)	94 (39.5)	1.00	453 (43.1)	76 (38.8)	1.00
≤ 3 Km	661 (55.3)	140 (58.8)	1.00 (0.70-1.43)	590 (56.1)	116 (59.2)	1.09 (0.73-1.63)
≤ 2.5 Km	490 (41.0)	95 (39.9)	0.76 (0.51-1.15)	433 (41.2)	80 (40.8)	0.88 (0.56-1.38)
≤ 2 Km	326 (27.3)	67 (28.1)	0.66 (0.40-1.07)	286 (27.2)	55 (28.1)	0.72 (0.42-1.23)
≤ 1.5 Km	144 (12.0)	36 (15.1)	1.06 (0.62-1.80)	121 (11.5)	31 (15.8)	1.19 (0.67-2.11)
≤ 1 Km	54 (4.5)	14 (5.9)	1.11 (0.51-2.40)	37 (3.5)	12 (6.1)	1.51 (0.64-3.55)

^a ORs were estimated from various mixed multiple logistic regression models (an independent model for each distance), adjusted for age, education, family history of prostate cancer, body mass index, and province of residence (the latter as a random effect term).

Table 3. Odds ratios (ORs) of prostate cancer at different distances to industries releasing groups of carcinogens (according to the IARC classification) and endocrine disrupting chemicals (EDCs). Analysis with all the individuals (A), and sensitivity analysis with only individuals living in their last residence for ≥ 10 years (B).

A) Analysis with all the individuals															
Groups of pollutants (no. industries)	Residing at ≤ 1 km			Residing at ≤ 1.5 km			Residing at ≤ 2 km			Residing at ≤ 2.5 km			Residing at ≤ 3 km		
	Co ^a	Ca ^b	OR (95%CI) ^c	Co ^a	Ca ^b	OR (95%CI) ^c	Co ^a	Ca ^b	OR (95%CI) ^c	Co ^a	Ca ^b	OR (95%CI) ^c	Co ^a	Ca ^b	OR (95%CI) ^c
Reference (residing at >3 km)	525	94	-	525	94	-	525	94	-	525	94	-	525	94	-
<i>IARC groups^d</i>															
Group 1 (41)	40	10	0.98 (0.41-2.32)	102	25	1.00 (0.56-1.77)	215	46	0.77 (0.48-1.24)	409	80	0.74 (0.48-1.14)	565	105	0.75 (0.50-1.11)
Group 2A (23)	38	9	0.89 (0.36-2.17)	94	22	0.92 (0.50-1.68)	198	44	0.83 (0.51-1.34)	293	60	0.86 (0.56-1.34)	522	92	0.75 (0.50-1.11)
Group 2B (10)	2	1	1.22 (0.10-14.28)	32	5	0.49 (0.17-1.40)	97	15	0.33 (0.15-0.77)	108	24	0.65 (0.28-1.49)	130	31	0.88 (0.42-1.82)
<i>EDCs groups^e</i>															
Metals (23)	38	9	0.89 (0.36-2.17)	76	20	1.01 (0.52-1.95)	144	32	0.75 (0.41-1.39)	198	47	0.98 (0.57-1.69)	460	80	0.67 (0.42-1.05)
PACs (12)	1	0	0 (0-inf)	31	0	0 (0-inf)	101	11	0.19 (0.07-0.47)	196	32	0.52 (0.28-0.95)	451	75	0.61 (0.39-0.96)
Plasticizers (1)	0	0	-	2	0	0 (0-inf)	4	0	0 (0-inf)	4	0	0 (0-inf)	5	0	0 (0-inf)
POPs (17)	1	0	0 (0-inf)	32	0	0 (0-inf)	116	13	0.23 (0.10-0.53)	271	48	0.48 (0.26-0.88)	481	78	0.55 (0.34-0.88)
Other solvents (16)	9	4	2.07 (0.58-7.38)	60	16	1.12 (0.58-2.14)	187	42	0.85 (0.52-1.38)	282	57	0.85 (0.55-1.32)	416	75	0.84 (0.56-1.25)
B) Sensitivity analysis with only individuals living in their last residence for ≥ 10 years															
Groups of pollutants (no. industries)	Residing at ≤ 1 km			Residing at ≤ 1.5 km			Residing at ≤ 2 km			Residing at ≤ 2.5 km			Residing at ≤ 3 km		
	Co ^a	Ca ^b	OR (95%CI) ^c	Co ^a	Ca ^b	OR (95%CI) ^c	Co ^a	Ca ^b	OR (95%CI) ^c	Co ^a	Ca ^b	OR (95%CI) ^c	Co ^a	Ca ^b	OR (95%CI) ^c
Reference (residing at >3 km)	453	76	-	453	76	-	453	76	-	453	76	-	453	76	-
<i>IARC groups^d</i>															
Group 1 (41)	30	8	1.05 (0.40-2.77)	83	22	1.17 (0.63-2.17)	186	37	0.84 (0.49-1.43)	356	67	0.87 (0.54-1.39)	504	88	0.85 (0.55-1.32)
Group 2A (23)	28	7	0.92 (0.33-2.54)	77	19	1.06 (0.55-2.03)	174	36	0.89 (0.53-1.52)	260	50	0.98 (0.61-1.59)	465	76	0.84 (0.54-1.31)
Group 2B (10)	2	1	1.10 (0.09-13.12)	32	5	0.57 (0.20-1.68)	97	12	0.33 (0.14-0.83)	107	20	0.72 (0.30-1.72)	129	26	0.97 (0.44-2.11)
<i>EDCs groups^e</i>															
Metals (23)	28	7	0.92 (0.33-2.54)	61	17	1.17 (0.57-2.42)	128	26	0.82 (0.42-1.63)	178	39	1.13 (0.62-2.08)	416	66	0.75 (0.45-1.23)
PACs (12)	1	0	0 (0-inf)	30	0	0 (0-inf)	97	7	0.13 (0.05-0.40)	176	26	0.60 (0.31-1.18)	406	61	0.67 (0.41-1.11)
Plasticizers (1)	0	0	-	2	0	0 (0-inf)	4	0	0 (0-inf)	4	0	0 (0-inf)	5	0	0 (0-inf)
POPs (17)	1	0	0 (0-inf)	30	0	0 (0-inf)	110	8	0.15 (0.06-0.43)	242	39	0.55 (0.28-1.07)	436	64	0.60 (0.36-1.00)
Other solvents (16)	7	3	1.95 (0.45-8.46)	53	14	1.23 (0.61-2.48)	165	35	0.94 (0.55-1.61)	251	48	0.98 (0.60-1.58)	374	63	0.94 (0.61-1.47)

^a Number of controls.

^b Number of cases.

^c ORs were estimated from various mixed multiple logistic regression models (an independent model for each group of pollutants and distance), adjusted for age, education, family history of prostate cancer, body mass index, and province of residence (the latter as a random effect term).

^d IARC carcinogenicity classification: Group 1: carcinogenic to humans (arsenic and compounds, cadmium and compounds, chromium and compounds, nickel and compounds, PCDD+PCDF (dioxins+furans), polychlorinated biphenyls, trichloroethylene, benzene, polycyclic aromatic hydrocarbons (PAHs), particulate matter (PM₁₀), and total suspended particulate matter); Group 2A: probably carcinogenic to humans (lead and compounds, and dichloromethane); Group 2B: possibly carcinogenic to humans (hexachlorobenzene, naphthalene, di-(2-ethyl hexyl) phthalate, and cobalt and compounds).

^e Metals (arsenic and compounds, cadmium and compounds, mercury and compounds, lead and compounds, and manganese); PACs: polycyclic aromatic chemicals (anthracene, naphthalene, and PAHs); Plasticizers (di-(2-ethyl hexyl) phthalate); POPs: persistent organic pollutants (hexachlorobenzene, PCDD+PCDF (dioxins+furans), polychlorinated biphenyls, and PAHs); Other solvents (dichloromethane, trichloroethylene, and benzene).

Table 4. Relative risk ratios (RRRs) of prostate cancer at different distances to all the industrial installations as a whole, by clinical profile (tumor characteristics).

Analysis with all the individuals (A), and sensitivity analysis with only individuals living in their last residence for ≥ 10 years (B).

A) Analysis with all the individuals

Distance	Controls (n=1186)	Analysis by tumor aggressiveness				Analysis by tumor extension				ISUP grade group				PSA at diagnosis				AJCC stage (8 th ed)			
		Gleason = 6 (98 cases)		Gleason > 6 (120 cases)		cT1-cT2a (169 cases)		cT2b-cT4 (42 cases)		1-2 (157 cases)		3-5 (61 cases)		<10 (155 cases)		≥ 10 (78 cases)		I-IIA (106 cases)		IIB-IV (118 cases)	
		Ca ^a	RRR (95%CI) ^b	Ca ^a	RRR (95%CI) ^b	Ca ^a	RRR (95%CI) ^b	Ca ^a	RRR (95%CI) ^b	Ca ^a	RRR (95%CI) ^b	Ca ^a	RRR (95%CI) ^b	Ca ^a	RRR (95%CI) ^b	Ca ^a	RRR (95%CI) ^b	Ca ^a	RRR (95%CI) ^b	Ca ^a	RRR (95%CI) ^b
Reference (>3 km)	525	43	1.00	42	1.00	67	1.00	17	1.00	62	1.00	23	1.00	64	1.00	29	1.00	50	1.00	39	1.00
≤ 3 Km	661	55	0.93 (0.58-1.50)	78	1.21 (0.77-1.90)	102	1.03 (0.69-1.54)	25	0.95 (0.48-1.86)	95	1.08 (0.72-1.61)	38	1.11 (0.62-1.99)	91	0.95 (0.64-1.43)	49	1.15 (0.68-1.95)	56	0.79 (0.50-1.26)	79	1.28 (0.81-2.02)
≤ 2.5 Km	490	37	0.71 (0.42-1.22)	53	0.94 (0.57-1.55)	69	0.79 (0.50-1.25)	20	0.81 (0.39-1.67)	69	0.90 (0.57-1.41)	21	0.69 (0.35-1.34)	64	0.76 (0.48-1.20)	31	0.81 (0.45-1.47)	37	0.59 (0.34-0.99)	54	0.98 (0.59-1.64)
≤ 2 Km	326	24	0.58 (0.31-1.08)	41	0.93 (0.52-1.63)	44	0.58 (0.34-1.02)	19	0.82 (0.38-1.77)	48	0.78 (0.46-1.33)	17	0.71 (0.34-1.49)	47	0.68 (0.40-1.16)	20	0.65 (0.33-1.28)	24	0.46 (0.25-0.86)	42	0.95 (0.53-1.69)
≤ 1.5 Km	144	14	0.83 (0.41-1.69)	21	1.12 (0.60-2.13)	21	0.86 (0.46-1.60)	11	1.34 (0.57-3.14)	28	1.13 (0.63-2.00)	7	0.69 (0.27-1.74)	26	1.14 (0.63-2.07)	10	0.80 (0.36-1.78)	14	0.83 (0.41-1.67)	21	1.18 (0.62-2.24)
≤ 1 Km	54	6	1.10 (0.40-3.02)	7	1.15 (0.44-3.01)	6	0.65 (0.24-1.75)	7	2.81 (1.00-7.90)	11	1.36 (0.59-3.14)	2	0.62 (0.13-2.90)	11	1.26 (0.55-2.92)	3	0.76 (0.21-2.78)	7	1.09 (0.42-2.84)	7	1.21 (0.46-3.17)

B) Sensitivity analysis with only individuals living in their last residence for ≥ 10 years

Distance	Controls (n=1043)	Analysis by tumor aggressiveness				Analysis by tumor extension				ISUP grade group				PSA at diagnosis				AJCC stage (8 th ed)			
		Gleason = 6 (81 cases)		Gleason > 6 (99 cases)		cT1-cT2a (139 cases)		cT2b-cT4 (34 cases)		1-2 (125 cases)		3-5 (55 cases)		<10 (122 cases)		≥ 10 (69 cases)		I-IIA (86 cases)		IIB-IV (97 cases)	
		Ca ^a	RRR (95%CI) ^b	Ca ^a	RRR (95%CI) ^b	Ca ^a	RRR (95%CI) ^b	Ca ^a	RRR (95%CI) ^b	Ca ^a	RRR (95%CI) ^b	Ca ^a	RRR (95%CI) ^b	Ca ^a	RRR (95%CI) ^b	Ca ^a	RRR (95%CI) ^b	Ca ^a	RRR (95%CI) ^b	Ca ^a	RRR (95%CI) ^b
Reference (>3 km)	453	34	1.00	36	1.00	54	1.00	15	1.00	49	1.00	21	1.00	49	1.00	26	1.00	39	1.00	33	1.00
≤ 3 Km	590	47	1.12 (0.61-2.07)	63	1.17 (0.68-2.04)	85	1.12 (0.72-1.76)	19	0.86 (0.41-1.82)	76	1.16 (0.73-1.83)	34	1.10 (0.59-2.05)	73	1.04 (0.66-1.66)	43	1.22 (0.69-2.14)	47	0.90 (0.49-1.65)	64	1.33 (0.75-2.34)
≤ 2.5 Km	433	31	0.83 (0.41-1.67)	45	0.99 (0.54-1.83)	58	0.90 (0.54-1.50)	16	0.81 (0.37-1.78)	56	1.01 (0.61-1.69)	20	0.76 (0.38-1.54)	50	0.84 (0.50-1.41)	30	0.98 (0.53-1.83)	30	0.60 (0.29-1.23)	46	1.12 (0.60-2.10)
≤ 2 Km	286	19	0.54 (0.23-1.25)	34	1.05 (0.52-2.13)	36	0.64 (0.35-1.17)	15	0.82 (0.36-1.88)	37	0.82 (0.45-1.48)	16	0.77 (0.36-1.67)	36	0.73 (0.40-1.32)	19	0.75 (0.36-1.53)	19	0.39 (0.16-0.91)	35	1.13 (0.56-2.29)
≤ 1.5 Km	121	13	1.19 (0.52-2.74)	17	1.04 (0.48-2.23)	19	1.05 (0.54-2.05)	8	1.23 (0.47-3.19)	24	1.37 (0.73-2.56)	6	0.68 (0.25-1.84)	21	1.26 (0.66-2.43)	10	1.00 (0.44-2.28)	13	1.10 (0.47-2.55)	17	1.13 (0.52-2.44)
≤ 1 Km	37	6	2.86 (0.84-9.78)	5	0.82 (0.25-2.71)	5	0.87 (0.29-2.62)	6	3.55 (1.15-10.96)	10	2.08 (0.84-5.17)	1	0.38 (0.05-3.16)	9	1.66 (0.65-4.26)	3	1.14 (0.30-4.30)	7	2.65 (0.80-8.76)	5	0.93 (0.28-3.08)

^a Number of cases.

^b RRRs were estimated from various mixed multinomial logistic regression models (an independent model for each distance), adjusted for age, education, family history of prostate cancer, body mass index, and province of residence (the latter as a random effect term).

Table 5. Odds ratios (ORs) of prostate cancer (near (≤ 3 km) vs. far and risk gradient analyses) for specific industrial installations with ORs >1 in the near vs. far analysis.

PRTR code	Industrial group	Province	Reference: [3-30 km] ^a		Near (≤ 3 km) vs. far analysis			Risk gradient analysis	
			Controls	Cases	Controls	Cases	OR (95%CI)	OR	<i>p</i> -trend
415	Disposal or recycling of animal waste	Barcelona	183	17	8	5	2.33 (0.52-10.50)	1.09	0.888
3498	Food and beverage sector	Barcelona	183	17	28	12	3.14 (1.11-8.93)	2.75	0.045
3558	Food and beverage sector	Madrid	261	51	38	12	1.28 (0.60-2.74)	1.27	0.459
7489	Urban waste-water treatment plants	Barcelona	183	17	36	12	1.78 (0.63-5.08)	0.99	0.975

^a Reference area for both "near (≤ 3 km) vs. far" and "risk gradient" analyses.

Distance: 1.5 km

Distance: 2 km

Distance: 2.5 km

Distance: 3 km

A) Analysis with all the individuals

INDUSTRIAL GROUP (no. industries)	Co	Ca	OR (95%CI)		Co	Ca	OR (95%CI)		Co	Ca	OR (95%CI)		Co	Ca	OR (95%CI)	
Ceramic (6)	13	13	4.56 (1.85 - 11.21)		38	19	2.27 (1.08 - 4.78)		47	23	2.26 (1.12 - 4.55)		48	25	2.54 (1.28 - 5.07)	
Disposal or recycling of animal waste (2)													34	13	2.67 (1.12 - 6.37)	
Food and beverage sector (4)													82	31	2.18 (1.32 - 3.62)	

B) Sensitivity analysis with long-term residents

INDUSTRIAL GROUP (no. industries)	Co	Ca	OR (95%CI)		Co	Ca	OR (95%CI)		Co	Ca	OR (95%CI)		Co	Ca	OR (95%CI)	
Ceramic (5)	8	11	6.15 (2.13 - 17.72)		25	17	3.22 (1.40 - 7.41)		32	19	2.76 (1.25 - 6.08)		33	20	2.97 (1.35 - 6.52)	
Disposal or recycling of animal waste (2)													30	9	2.34 (0.87 - 6.34)	
Food and beverage sector (4)													69	23	2.09 (1.18 - 3.70)	

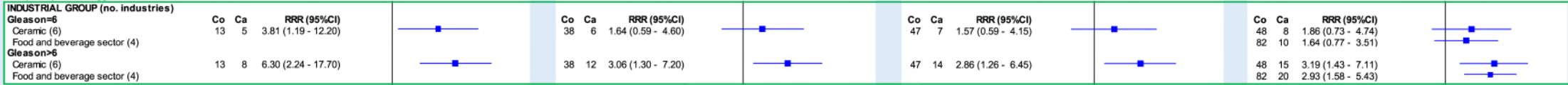
Distance: 1.5 km

Distance: 2 km

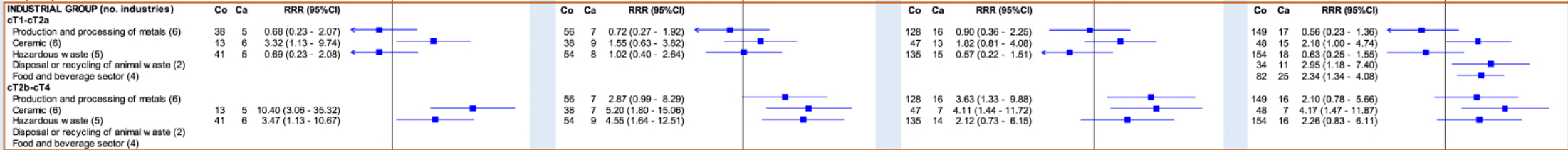
Distance: 2.5 km

Distance: 3 km

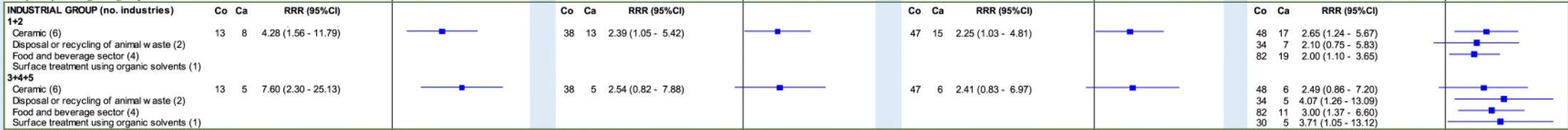
Analysis by tumor aggressiveness



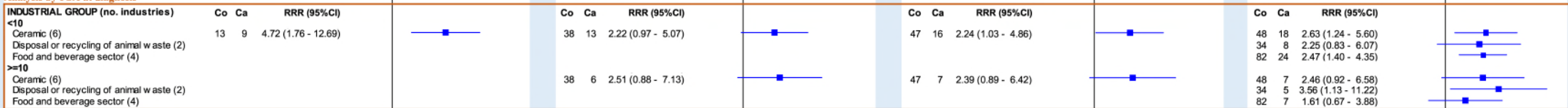
Analysis by tumor extension



Analysis by ISUP grade group



Analysis by PSA at diagnosis



Analysis by AJCC stage (8th ed)



0.3 1.0 10.0 20.0 40.0

0.3 1.0 5.0 10.0 20.0

0.3 1.0 2.0 4.0 6.0 10.0 14.0

0.25 1.0 2.0 4.0 8.00 14.00

Supplementary Data

Title of the manuscript: “Risk of prostate cancer in the proximity of industrial installations: a multicase-control study in Spain (MCC-Spain)”.

This document is available as supplementary data for inclusion as online documentation. It includes:

- a) Table S1, showing the odds ratios of prostate cancer at different distances to industries by specific pollutants released to air (analysis with all the individuals).
- b) Table S2, showing the odds ratios of prostate cancer at different distances to industries by specific pollutants released to air (sensitivity analysis including only individuals living in their last residence for ≥ 10 years).
- c) Table S3, showing the “*risk gradient*” analysis: 1) for all industries as a whole; 2) by industrial group; 3) by groups of carcinogens (according to the IARC classification) and endocrine disrupting chemicals (EDCs); and 4) by specific pollutant. Analysis with all the individuals (A), and sensitivity analysis with only individuals living in their last residence for ≥ 10 years (B).
- d) Figure S1, showing the statistically significant relative risk ratios (RRRs) and their 95% confidence intervals (95% CIs) of prostate cancer at different distances to industries (sensitivity analysis with only individuals living in their last residence for ≥ 10 years), based on a number of controls (Co) and cases (Ca) ≥ 5 , for the “*stratified*” analysis by clinical profile applied to the analysis by industrial group. X-axis is plotted in logarithmic scale. NE*: not estimated.

Supplementary Data, Table S1. Odds ratios (ORs) of prostate cancer at different distances to industries, by specific pollutants released to air (analysis with all the individuals).

Industrial pollutant	Individuals residing at ≤1 km					Individuals residing at ≤1.5 km					Individuals residing at ≤2 km					Individuals residing at ≤2.5 km					Individuals residing at ≤3 km				
	Co ^a	Ca ^b	OR (95%CI) ^c	p ^d	p-BH ^e	Co ^a	Ca ^b	OR (95%CI) ^c	p ^d	p-BH ^e	Co ^a	Ca ^b	OR (95%CI) ^c	p ^d	p-BH ^e	Co ^a	Ca ^b	OR (95%CI) ^c	p ^d	p-BH ^e	Co ^a	Ca ^b	OR (95%CI) ^c	p ^d	p-BH ^e
Reference	525	94	-	-	-	525	94	-	-	-	525	94	-	-	-	525	94	-	-	-	525	94	-	-	-
1,1,1-trichloroethane (1)	0	0	-	-	-	0	0	-	-	-	0	0	-	-	-	0	0	-	-	-	26	8	2.00 (0.66-6.01)	0.219	0.309
Ammonia (10)	0	0	-	-	-	30	0	0 (0-inf)	0.966	0.997	95	10	0.16 (0.06-0.42)	0.000	0.004	123	21	0.39 (0.17-0.88)	0.024	0.178	167	35	0.65 (0.35-1.23)	0.188	0.278
Antimony / Cobalt / Manganese (8)	2	1	1.22 (0.10-14.28)	0.876	0.994	30	5	0.51 (0.18-1.47)	0.210	0.997	92	15	0.35 (0.15-0.82)	0.016	0.075	102	24	0.72 (0.31-1.70)	0.455	0.723	121	30	0.97 (0.45-2.07)	0.933	0.933
Arsenic and compounds / Mercury and compounds (22)	38	9	0.89 (0.36-2.17)	0.795	0.994	76	20	1.01 (0.52-1.95)	0.986	0.997	144	32	0.75 (0.41-1.39)	0.364	0.573	198	47	0.98 (0.57-1.69)	0.940	0.987	460	80	0.67 (0.42-1.05)	0.081	0.180
Benzene (13)	9	4	2.07 (0.58-7.38)	0.264	0.994	42	14	1.36 (0.65-2.83)	0.412	0.997	133	30	0.79 (0.42-1.47)	0.450	0.622	185	43	0.95 (0.55-1.67)	0.868	0.987	350	62	0.83 (0.52-1.30)	0.409	0.528
Cadmium and compounds (21)	37	9	0.91 (0.37-2.23)	0.835	0.994	75	20	1.02 (0.53-1.97)	0.957	0.997	144	32	0.75 (0.41-1.39)	0.364	0.573	198	47	0.98 (0.57-1.69)	0.940	0.987	460	80	0.67 (0.42-1.05)	0.081	0.180
Carbon dioxide (40)	43	9	0.78 (0.32-1.88)	0.574	0.994	135	34	1.05 (0.61-1.81)	0.862	0.997	301	63	0.66 (0.39-1.09)	0.104	0.300	426	81	0.68 (0.44-1.06)	0.086	0.320	624	125	0.91 (0.63-1.32)	0.626	0.746
Carbon monoxide (44)	50	14	1.23 (0.56-2.70)	0.613	0.994	135	34	1.05 (0.61-1.81)	0.862	0.997	299	63	0.68 (0.41-1.13)	0.132	0.331	426	81	0.69 (0.44-1.07)	0.096	0.320	593	108	0.74 (0.50-1.09)	0.129	0.227
Chlorine and inorganic compounds (20)	17	7	2.32 (0.84-6.38)	0.105	0.994	73	13	0.65 (0.31-1.38)	0.260	0.997	157	27	0.50 (0.26-0.96)	0.037	0.154	322	54	0.45 (0.23-0.86)	0.016	0.178	474	72	0.47 (0.28-0.78)	0.004	0.036
Chromium and compounds (25)	38	9	0.89 (0.36-2.17)	0.795	0.994	77	20	0.99 (0.51-1.91)	0.976	0.997	144	32	0.75 (0.41-1.39)	0.364	0.573	206	47	0.94 (0.55-1.62)	0.828	0.987	453	80	0.70 (0.45-1.11)	0.131	0.227
Copper and compounds (25)	38	9	0.89 (0.36-2.17)	0.795	0.994	100	24	0.98 (0.55-1.74)	0.934	0.997	194	44	0.84 (0.52-1.37)	0.482	0.636	302	60	0.85 (0.55-1.31)	0.458	0.723	525	92	0.74 (0.50-1.11)	0.146	0.227
Dichloromethane (2)	0	0	-	-	-	18	2	0.53 (0.12-2.43)	0.417	0.997	54	12	0.90 (0.43-1.85)	0.765	0.853	116	14	0.62 (0.33-1.16)	0.132	0.359	184	16	0.47 (0.26-0.85)	0.013	0.057
Fluorine and inorganic compounds (14)	8	3	2.20 (0.53-9.09)	0.275	0.994	14	8	3.46 (1.28-9.32)	0.014	0.400	53	15	1.15 (0.54-2.44)	0.712	0.853	78	21	0.93 (0.48-1.80)	0.828	0.987	203	50	0.96 (0.55-1.66)	0.883	0.933
Hexachlorobenzene (1)	0	0	-	-	-	0	0	-	-	-	1	0	0 (0-inf)	0.986	0.987	2	0	0 (0-inf)	0.987	0.987	6	1	0.61 (0.06-5.87)	0.670	0.769
Hydrogen cyanide (3)	0	0	-	-	-	26	4	0.80 (0.27-2.43)	0.697	0.997	54	12	0.89 (0.43-1.83)	0.754	0.853	141	14	0.54 (0.29-1.00)	0.050	0.251	237	17	0.38 (0.22-0.68)	0.001	0.017
Lead and compounds (21)	38	9	0.89 (0.36-2.17)	0.795	0.994	76	20	1.01 (0.52-1.95)	0.986	0.997	144	32	0.75 (0.41-1.39)	0.364	0.573	198	47	0.98 (0.57-1.69)	0.940	0.987	460	80	0.67 (0.42-1.05)	0.081	0.180
Methane (10)	1	0	0 (0-inf)	0.994	0.994	30	1	0.12 (0.02-0.90)	0.039	0.550	95	11	0.19 (0.08-0.49)	0.001	0.004	145	21	0.39 (0.18-0.85)	0.018	0.178	310	40	0.50 (0.29-0.85)	0.011	0.056
Nickel and compounds (27)	31	6	0.62 (0.22-1.74)	0.366	0.994	95	19	0.77 (0.42-1.42)	0.394	0.997	191	41	0.78 (0.48-1.28)	0.327	0.573	301	59	0.84 (0.54-1.30)	0.433	0.723	524	91	0.74 (0.50-1.11)	0.144	0.227
Nitrogen oxides (51)	50	14	1.23 (0.56-2.70)	0.613	0.994	135	34	1.05 (0.61-1.81)	0.862	0.997	302	63	0.65 (0.39-1.09)	0.102	0.300	433	82	0.68 (0.44-1.06)	0.090	0.320	624	125	0.91 (0.63-1.32)	0.626	0.746
Nitrous oxide (13)	1	0	0 (0-inf)	0.994	0.994	3	1	1.59 (0.15-16.61)	0.699	0.997	12	3	0.86 (0.22-3.32)	0.829	0.890	65	9	0.59 (0.26-1.31)	0.191	0.410	235	29	0.62 (0.37-1.02)	0.062	0.180
Non-methane volatile organic compounds (30)	49	14	1.25 (0.57-2.78)	0.576	0.994	125	31	0.99 (0.56-1.75)	0.976	0.997	297	62	0.68 (0.41-1.13)	0.137	0.331	415	83	0.82 (0.54-1.26)	0.368	0.690	563	108	0.85 (0.58-1.24)	0.400	0.528
Particulate matter (PM ₁₀) (30)	40	10	0.98 (0.41-2.32)	0.958	0.994	77	21	1.05 (0.55-2.02)	0.878	0.997	150	32	0.69 (0.38-1.25)	0.218	0.485	191	50	0.91 (0.53-1.56)	0.727	0.987	322	86	1.07 (0.65-1.74)	0.802	0.887
PCDD+PCDF (dioxins+furans) (11)	0	0	-	-	-	31	0	0 (0-inf)	0.997	0.997	112	13	0.24 (0.10-0.56)	0.001	0.006	236	42	0.61 (0.34-1.12)	0.111	0.334	454	67	0.48 (0.29-0.80)	0.005	0.036
Polychlorinated biphenyls / Anthracene / Naphthalene / Di-(2-ethyl hexyl) phthalate (1)	0	0	-	-	-	2	0	0 (0-inf)	0.989	0.997	4	0	0 (0-inf)	0.987	0.987	4	0	0 (0-inf)	0.987	0.987	5	0	0 (0-inf)	0.924	0.933
Polycyclic aromatic hydrocarbons (12)	1	0	0 (0-inf)	0.994	0.994	31	0	0 (0-inf)	0.911	0.997	101	11	0.19 (0.07-0.47)	0.000	0.004	196	32	0.52 (0.28-0.95)	0.033	0.200	451	75	0.61 (0.39-0.96)	0.034	0.133
Sulfur oxides (37)	48	13	1.14 (0.51-2.55)	0.743	0.994	127	32	1.02 (0.58-1.80)	0.936	0.997	296	62	0.64 (0.38-1.08)	0.094	0.300	369	79	0.73 (0.46-1.16)	0.180	0.410	568	105	0.75 (0.50-1.11)	0.146	0.227
Total organic carbon (air) (5)	1	0	0 (0-inf)	0.959	0.994	3	1	0.56 (0.05-6.62)	0.647	0.997	17	3	0.59 (0.15-2.28)	0.444	0.622	93	21	0.94 (0.46-1.96)	0.876	0.987	223	30	0.60 (0.33-1.06)	0.079	0.180
Total suspended particulate matter (12)	0	0	-	-	-	26	4	0.80 (0.27-2.42)	0.693	0.997	72	15	0.84 (0.44-1.58)	0.578	0.729	256	40	0.71 (0.44-1.13)	0.145	0.362	408	56	0.55 (0.35-0.86)	0.009	0.055
Trichloroethylene (2)	0	0	-	-	-	0	0	-	-	-	0	0	-	-	-	35	2	0.42 (0.10-1.84)	0.249	0.498	171	6	0.18 (0.07-0.45)	0.000	0.006
Vanadium (4)	0	0	-	-	-	27	0	0 (0-inf)	0.985	0.997	89	10	0.16 (0.06-0.44)	0.000	0.004	98	16	0.24 (0.09-0.68)	0.007	0.178	117	22	0.41 (0.15-1.12)	0.081	0.180
Zinc and compounds (22)	37	9	0.91 (0.37-2.23)	0.835	0.994	101	24	0.96 (0.54-1.71)	0.894	0.997	206	45	0.80 (0.49-1.31)	0.375	0.573	332	73	0.85 (0.53-1.35)	0.491	0.736	521	92	0.72 (0.48-1.08)	0.113	0.227

^a Number of controls.

^b Number of cases.

^c ORs were estimated from various mixed multiple logistic regression models (an independent model for each specific pollutant and distance), adjusted for age, education, family history of prostate cancer, body mass index, and province of residence (the latter as a random effect term).

^d p-value associated with hypothesis test for the mixed multiple logistic regression model.

^e p-value adjusted by Benjamini & Hochberg's method.

Supplementary Data, Table S2. Odds ratios (ORs) of prostate cancer at different distances to industries by specific pollutants released to air (sensitivity analysis including only individuals living in their last residence for ≥ 10 years).

Industrial pollutant	Individuals residing at ≤ 1 km					Individuals residing at ≤ 1.5 km					Individuals residing at ≤ 2 km					Individuals residing at ≤ 2.5 km					Individuals residing at ≤ 3 km									
	Co ^a	Ca ^b	OR (95%CI) ^c	p ^d	p-BH ^e	Co ^a	Ca ^b	OR (95%CI) ^c	p ^d	p-BH ^e	Co ^a	Ca ^b	OR (95%CI) ^c	p ^d	p-BH ^e	Co ^a	Ca ^b	OR (95%CI) ^c	p ^d	p-BH ^e	Co ^a	Ca ^b	OR (95%CI) ^c	p ^d	p-BH ^e	Co ^a	Ca ^b	OR (95%CI) ^c	p ^d	p-BH ^e
Reference	453	76	-	-	-	453	76	-	-	-	453	76	-	-	-	453	76	-	-	-	453	76	-	-	-	453	76	-	-	-
1,1,1-trichloroethane (1)	0	0	-	-	-	0	0	-	-	-	0	0	-	-	-	0	0	-	-	-	23	6	1.73 (0.51-5.80)	0.379	0.672	152	29	0.80 (0.40-1.61)	0.530	0.747
Ammonia (10)	0	0	-	-	-	30	0	0 (0-inf)	0.986	0.987	95	7	0.14 (0.05-0.41)	0.000	0.004	119	17	0.41 (0.17-1.01)	0.052	0.560	152	29	0.80 (0.40-1.61)	0.530	0.747	120	25	1.09 (0.48-2.49)	0.845	0.933
Antimony / Cobalt / Manganese (8)	2	1	1.10 (0.09-13.12)	0.939	0.952	30	5	0.60 (0.20-1.78)	0.355	0.987	92	12	0.35 (0.14-0.88)	0.026	0.123	101	20	0.81 (0.33-2.00)	0.651	0.925	120	25	1.09 (0.48-2.49)	0.845	0.933	416	66	0.75 (0.45-1.23)	0.255	0.564
Arsenic and compounds / Mercury and compounds (22)	28	7	0.92 (0.33-2.54)	0.874	0.952	61	17	1.17 (0.57-2.42)	0.667	0.987	128	26	0.82 (0.42-1.63)	0.576	0.759	178	39	1.13 (0.62-2.08)	0.690	0.925	416	66	0.75 (0.45-1.23)	0.255	0.564	321	52	0.94 (0.56-1.56)	0.801	0.933
Benzene (13)	7	3	1.95 (0.45-8.46)	0.374	0.952	37	12	1.50 (0.67-3.36)	0.324	0.987	119	25	0.91 (0.46-1.81)	0.785	0.898	167	36	1.13 (0.61-2.10)	0.704	0.925	321	52	0.94 (0.56-1.56)	0.801	0.933	416	66	0.75 (0.45-1.23)	0.255	0.564
Cadmium and compounds (21)	27	7	0.95 (0.34-2.62)	0.913	0.952	60	17	1.19 (0.57-2.46)	0.640	0.987	128	26	0.82 (0.42-1.63)	0.576	0.759	178	39	1.13 (0.62-2.08)	0.690	0.925	416	66	0.75 (0.45-1.23)	0.255	0.564	321	52	0.94 (0.56-1.56)	0.801	0.933
Carbon dioxide (40)	31	7	0.84 (0.31-2.29)	0.729	0.952	112	29	1.20 (0.67-2.16)	0.545	0.987	262	51	0.71 (0.41-1.24)	0.225	0.571	373	68	0.80 (0.49-1.30)	0.364	0.925	555	102	0.98 (0.65-1.47)	0.902	0.933	555	102	0.98 (0.65-1.47)	0.902	0.933
Carbon monoxide (44)	33	12	1.75 (0.73-4.23)	0.212	0.952	112	29	1.20 (0.67-2.16)	0.545	0.987	262	51	0.72 (0.41-1.25)	0.236	0.571	372	68	0.81 (0.50-1.32)	0.398	0.925	530	91	0.84 (0.55-1.29)	0.432	0.672	530	91	0.84 (0.55-1.29)	0.432	0.672
Chlorine and inorganic compounds (20)	8	6	5.21 (1.56-17.35)	0.007	0.151	57	11	0.82 (0.36-1.90)	0.649	0.987	140	20	0.47 (0.22-0.99)	0.047	0.196	290	44	0.51 (0.25-1.02)	0.056	0.560	430	59	0.52 (0.30-0.90)	0.019	0.198	430	59	0.52 (0.30-0.90)	0.019	0.198
Chromium and compounds (25)	28	7	0.92 (0.33-2.54)	0.874	0.952	62	17	1.15 (0.56-2.38)	0.705	0.987	128	26	0.82 (0.42-1.63)	0.576	0.759	186	39	1.08 (0.59-1.97)	0.797	0.929	413	66	0.77 (0.46-1.27)	0.300	0.619	413	66	0.77 (0.46-1.27)	0.300	0.619
Copper and compounds (25)	28	7	0.92 (0.33-2.54)	0.874	0.952	82	21	1.13 (0.61-2.11)	0.696	0.987	171	36	0.91 (0.53-1.55)	0.716	0.898	266	50	0.97 (0.60-1.56)	0.888	0.929	467	76	0.84 (0.54-1.30)	0.434	0.672	467	76	0.84 (0.54-1.30)	0.434	0.672
Dichloromethane (2)	0	0	-	-	-	16	2	0.63 (0.14-2.91)	0.551	0.987	46	10	0.93 (0.43-2.03)	0.856	0.920	103	12	0.71 (0.36-1.39)	0.315	0.925	163	14	0.56 (0.30-1.06)	0.076	0.387	163	14	0.56 (0.30-1.06)	0.076	0.387
Fluorine and inorganic compounds (14)	6	2	2.24 (0.41-12.21)	0.351	0.952	9	6	4.65 (1.45-14.91)	0.010	0.274	34	12	1.64 (0.69-3.92)	0.262	0.585	55	17	1.13 (0.54-2.39)	0.740	0.925	167	40	1.00 (0.54-1.84)	0.997	0.997	167	40	1.00 (0.54-1.84)	0.997	0.997
Hexachlorobenzene (1)	0	0	-	-	-	0	0	-	-	-	1	0	0 (0-inf)	0.986	0.986	2	0	0 (0-inf)	0.929	0.929	6	1	0.65 (0.07-6.37)	0.712	0.920	6	1	0.65 (0.07-6.37)	0.712	0.920
Hydrogen cyanide (3)	0	0	-	-	-	23	4	0.94 (0.31-2.90)	0.916	0.987	47	10	0.91 (0.42-1.97)	0.805	0.898	125	12	0.61 (0.31-1.20)	0.154	0.771	215	15	0.45 (0.24-0.84)	0.012	0.183	215	15	0.45 (0.24-0.84)	0.012	0.183
Lead and compounds (21)	28	7	0.92 (0.33-2.54)	0.874	0.952	61	17	1.17 (0.57-2.42)	0.667	0.987	128	26	0.82 (0.42-1.63)	0.576	0.759	178	39	1.13 (0.62-2.08)	0.690	0.925	416	66	0.75 (0.45-1.23)	0.255	0.564	416	66	0.75 (0.45-1.23)	0.255	0.564
Methane (10)	1	0	0 (0-inf)	0.940	0.952	30	1	0.15 (0.02-1.16)	0.068	0.958	94	8	0.18 (0.06-0.51)	0.001	0.008	141	18	0.49 (0.22-1.13)	0.093	0.697	296	34	0.57 (0.32-1.00)	0.051	0.316	296	34	0.57 (0.32-1.00)	0.051	0.316
Nickel and compounds (27)	23	5	0.68 (0.22-2.12)	0.507	0.952	78	18	0.97 (0.51-1.86)	0.925	0.987	169	34	0.83 (0.50-1.47)	0.573	0.759	265	49	0.96 (0.59-1.55)	0.851	0.929	466	75	0.84 (0.54-1.30)	0.425	0.672	466	75	0.84 (0.54-1.30)	0.425	0.672
Nitrogen oxides (51)	33	12	1.75 (0.73-4.23)	0.212	0.952	112	29	1.20 (0.67-2.16)	0.545	0.987	263	51	0.71 (0.41-1.23)	0.221	0.571	379	69	0.81 (0.50-1.30)	0.383	0.925	555	102	0.98 (0.65-1.47)	0.902	0.933	555	102	0.98 (0.65-1.47)	0.902	0.933
Nitrous oxide (13)	1	0	0 (0-inf)	0.940	0.952	3	1	1.65 (0.15-17.80)	0.679	0.987	7	2	1.26 (0.24-6.65)	0.789	0.898	56	8	0.73 (0.31-1.73)	0.468	0.925	214	24	0.65 (0.37-1.15)	0.136	0.423	214	24	0.65 (0.37-1.15)	0.136	0.423
Non-methane volatile organic compounds (30)	32	12	1.81 (0.74-4.41)	0.191	0.952	103	26	1.12 (0.61-2.08)	0.714	0.987	262	50	0.70 (0.40-1.23)	0.217	0.571	370	68	0.90 (0.56-1.45)	0.676	0.925	503	89	0.94 (0.62-1.44)	0.787	0.933	503	89	0.94 (0.62-1.44)	0.787	0.933
Particulate matter (PM ₁₀) (30)	30	8	1.05 (0.40-2.77)	0.924	0.952	62	18	1.23 (0.60-2.51)	0.568	0.987	130	26	0.79 (0.40-1.56)	0.501	0.759	164	42	1.11 (0.61-2.02)	0.724	0.925	283	71	1.16 (0.68-1.99)	0.583	0.785	283	71	1.16 (0.68-1.99)	0.583	0.785
PCDD+PCDF (dioxins+furans) (11)	0	0	-	-	-	29	0	0 (0-inf)	0.904	0.987	108	8	0.16 (0.06-0.44)	0.000	0.004	216	34	0.68 (0.35-1.32)	0.252	0.925	416	56	0.55 (0.32-0.94)	0.029	0.227	416	56	0.55 (0.32-0.94)	0.029	0.227
Polychlorinated biphenyls / Anthracene / Naphthalene / Di-(2-ethyl hexyl) phthalate (1)	0	0	-	-	-	2	0	0 (0-inf)	0.952	0.987	4	0	0 (0-inf)	0.917	0.949	4	0	0 (0-inf)	0.917	0.929	5	0	0 (0-inf)	0.903	0.933	5	0	0 (0-inf)	0.903	0.933
Polycyclic aromatic hydrocarbons (12)	1	0	0 (0-inf)	0.940	0.952	30	0	0 (0-inf)	0.966	0.987	97	7	0.13 (0.05-0.40)	0.000	0.004	176	26	0.60 (0.31-1.18)	0.138	0.771	406	61	0.67 (0.41-1.11)	0.120	0.420	406	61	0.67 (0.41-1.11)	0.120	0.420
Sulfur oxides (37)	31	11	1.62 (0.66-3.99)	0.296	0.952	105	27	1.17 (0.63-2.15)	0.623	0.987	257	50	0.69 (0.39-1.22)	0.205	0.571	321	66	0.86 (0.53-1.42)	0.564	0.925	507	88	0.85 (0.55-1.32)	0.473	0.699	507	88	0.85 (0.55-1.32)	0.473	0.699
Total organic carbon (air) (5)	1	0	0 (0-inf)	0.952	0.952	2	1	0.67 (0.05-8.96)	0.759	0.987	14	2	0.46 (0.09-2.34)	0.352	0.729	81	16	0.83 (0.37-1.89)	0.661	0.925	200	24	0.60 (0.31-1.15)	0.122	0.420	200	24	0.60 (0.31-1.15)	0.122	0.420
Total suspended particulate matter (12)	0	0	-	-	-	21	4	1.03 (0.33-3.21)	0.961	0.987	59	11	0.80 (0.38-1.65)	0.538	0.759	216	33	0.81 (0.48-1.36)	0.426	0.925	353	48	0.65 (0.39-1.07)	0.087	0.387	353	48	0.65 (0.39-1.07)	0.087	0.387
Trichloroethylene (2)	0	0	-	-	-	0	0	-	-	-	0	0	-	-	-	35	2	0.47 (0.10-2.11)	0.323	0.925	163	6	0.22 (0.09-0.55)	0.001	0.037	163	6	0.22 (0.09-0.55)	0.001	0.037
Vanadium (4)	0	0	-	-	-	27	0	0 (0-inf)	0.987	0.987	89	7	0.14 (0.05-0.43)	0.001	0.004	97	13	0.29 (0.10-0.90)	0.031	0.560	116	18	0.51 (0.18-1.44)	0.203	0.564	116	18	0.51 (0.18-1.44)	0.203	0.564
Zinc and compounds (22)	27	7	0.95 (0.34-2.62)	0.913	0.952	82	21	1.13 (0.61-2.11)	0.703	0.987	182	36	0.84 (0.49-1.43)	0.512	0.759	293	60	0.94 (0.57-1.56)	0.807	0.929	465	76	0.80 (0.51-1.26)	0.340	0.659	465	76	0.80 (0.51-1.26)	0.340	0.659

^a Number of controls.

^b Number of cases.

^c ORs were estimated from various mixed multiple logistic regression models (an independent model for each specific pollutant and distance), adjusted for age, education, family history of prostate cancer, body mass index, and province of residence (the latter as a random effect term).

^d p-value associated with hypothesis test for the mixed multiple logistic regression model.

^e p-value adjusted by Benjamini & Hochberg's method.

Supplementary Data, Table S3. “Risk gradient” analysis: 1) for all industries as a whole; 2) by industrial group; 3) by groups of carcinogens (according to the IARC classification) and endocrine disrupting chemicals (EDCs); and 4) by specific pollutant. Analysis with all the individuals (A), and sensitivity analysis with only individuals living in their last residence for ≥ 10 years (B).

A) Analysis with all the individuals														
1) ALL INDUSTRIES AS A WHOLE			2) BY INDUSTRIAL GROUP			3) BY GROUPS OF CARCINOGENS AND ECDs			4) BY SPECIFIC POLLUTANT					
Industries (no. industries)	OR	p-trend	Industrial sector (no. industries)	OR	p-trend	p-BH ^a	Groups of pollutants (no. industries)	OR	p-trend	p-BH ^a	Industrial pollutant (no. industries)	OR	p-trend	p-BH ^a
All industries (58)	0.93	0.242	Combustion installations (5)	0.75	0.143	0.270	<i>IARC groups</i>				1,1,1-trichloroethane (1)	10.02	0.057	0.207
			Production and processing of metals (6)	0.96	0.650	0.812	Group 1 (41)	0.91	0.167	0.250	Ammonia (10)	0.48	<0.001	0.003
			Galvanization (1)	0.98	0.984	0.994	Group 2A (23)	0.94	0.382	0.382	Antimony / Cobalt / Manganese (8)	0.74	0.055	0.207
			Surface treatment of metals and plastics (14)	0.88	0.180	0.305	Group 2B (10)	0.75	0.053	0.160	Arsenic and compounds / Mercury and compounds (22)	0.97	0.675	0.738
			Cement and lime (1)	NE ^b	-	-					Benzene (13)	0.97	0.764	0.791
			Glass and mineral fibers (1)	0.29	0.010	0.055	<i>EDCs groups</i>				Cadmium and compounds (21)	0.97	0.687	0.738
			Ceramic (6)	1.31	0.078	0.189	Metals (23)	0.97	0.675	0.675	Carbon dioxide (40)	0.90	0.137	0.361
			Organic chemical industry (1)	0.38	<0.001	0.001	PACs (12)	0.64	0.002	0.004	Carbon monoxide (44)	0.91	0.174	0.361
			Inorganic chemical industry (1)	0.53	0.075	0.189	Plasticizers (1)	NE ^b	-	-	Chlorine and inorganic compounds (20)	0.82	0.081	0.260
			Fertilizers (1)	NE ^b	-	-	POPs (17)	0.62	0.001	0.002	Chromium and compounds (25)	0.98	0.814	0.814
			Pharmaceutical products (2)	0.87	0.240	0.371	Other solvents (16)	0.94	0.441	0.588	Copper and compounds (25)	0.95	0.418	0.526
			Explosives and pyrotechnics (1)	0.52	0.495	0.702					Dichloromethane (2)	0.87	0.240	0.387
			Hazardous waste (5)	1.27	0.016	0.067					Fluorine and inorganic compounds (14)	1.18	0.167	0.361
			Disposal or recycling of animal waste (2)	2.20	0.066	0.189					Hexachlorobenzene (1)	NE ^b	-	-
			Urban waste-water treatment plants (2)	1.00	0.994	0.994					Hydrogen cyanide (3)	0.87	0.201	0.364
			Paper and wood production (2)	1.04	0.906	0.994					Lead and compounds (21)	0.97	0.675	0.738
			Food and beverage sector (4)	1.98	0.001	0.012					Methane (10)	0.63	0.007	0.039
			Surface treatment using organic solvents (1)	3.75	0.100	0.213					Nickel and compounds (27)	0.92	0.215	0.366
			Ship building (2)	1.09	0.669	0.812					Nitrogen oxides (51)	0.92	0.199	0.364
											Nitrous oxide (13)	0.85	0.332	0.481
											Non-methane volatile organic compounds (30)	0.94	0.386	0.509
											Particulate matter (PM10) (30)	0.96	0.613	0.738
											PCDD+PCDF (dioxins+furans) (11)	0.67	0.010	0.050
											Polychlorinated biphenyls / Anthracene / Naphthalene / Di-(2-ethyl hexyl) phthalate (1)	NE ^b	-	-
											Polycyclic aromatic hydrocarbons (12)	0.64	0.002	0.017
											Sulfur oxides (37)	0.90	0.150	0.361
											Total organic carbon (air) (5)	0.81	0.307	0.468
											Total suspended particulate matter (12)	0.88	0.174	0.361
											Trichloroethylene (2)	0.28	0.007	0.039
											Vanadium (4)	0.38	0.000	0.003
											Zinc and compounds (22)	0.94	0.348	0.481

B) Sensitivity analysis with only individuals living in their last residence for ≥ 10 years														
1) ALL INDUSTRIES AS A WHOLE			2) BY INDUSTRIAL SECTOR			3) BY GROUPS OF CARCINOGENS AND ECDs			4) BY SPECIFIC POLLUTANT					
Industries (no. industries)	OR	p-trend	Industrial sector (no. industries)	OR	p-trend	p-BH ^a	Groups of pollutants (no. industries)	OR	p-trend	p-BH ^a	Industrial pollutant (no. industries)	OR	p-trend	p-BH ^a
All industries (56)	0.96	0.964	Combustion installations (5)	0.84	0.431	0.666	<i>IARC groups</i>				1,1,1-trichloroethane (1)	5.84	0.151	0.547
			Production and processing of metals (6)	0.97	0.813	0.921	Group 1 (40)	0.96	0.532	0.760	Ammonia (10)	0.46	0.001	0.010
			Galvanization (1)	1.48	0.686	0.832	Group 2A (22)	0.98	0.760	0.760	Antimony / Cobalt / Manganese (7)	0.83	0.253	0.735
			Surface treatment of metals and plastics (13)	0.91	0.350	0.661	Group 2B (9)	0.82	0.226	0.678	Arsenic and compounds / Mercury and compounds (21)	1.02	0.877	0.880
			Cement and lime (1)	NE ^b	-	-					Benzene (12)	1.04	0.745	0.880
			Glass and mineral fibers (1)	0.33	0.031	0.130	<i>EDCs groups</i>				Cadmium and compounds (20)	1.02	0.860	0.880
			Ceramic (5)	1.34	0.112	0.382	Metals (22)	1.02	0.877	0.877	Carbon dioxide (39)	0.94	0.395	0.764
			Organic chemical industry (1)	0.39	0.001	0.019	PACs (11)	0.65	0.009	0.019	Carbon monoxide (43)	0.96	0.592	0.880
			Inorganic chemical industry (1)	0.56	0.169	0.479	Plasticizers (1)	NE ^b	-	-	Chlorine and inorganic compounds (20)	0.86	0.249	0.735
			Fertilizers (1)	NE ^b	-	-	POPs (16)	0.61	0.002	0.019	Chromium and compounds (24)	1.04	0.696	0.880
			Pharmaceutical products (2)	0.90	0.900	0.956	Other solvents (15)	0.98	0.825	0.877	Copper and compounds (24)	0.98	0.816	0.880
			Explosives and pyrotechnics (1)	0.62	0.627	0.832					Dichloromethane (2)	0.90	0.392	0.764
			Hazardous waste (5)	1.39	0.006	0.048					Fluorine and inorganic compounds (14)	1.25	0.110	0.455
			Disposal or recycling of animal waste (2)	1.66	0.303	0.644					Hexachlorobenzene (1)	NE ^b	-	-
			Urban waste-water treatment plants (2)	0.91	0.649	0.832					Hydrogen cyanide (3)	0.90	0.355	0.764
			Paper and wood production (2)	1.36	0.395	0.666					Lead and compounds (20)	1.02	0.877	0.880
			Food and beverage sector (4)	1.94	0.011	0.063					Methane (10)	0.68	0.044	0.212
			Surface treatment using organic solvents (1)	3.33	0.217	0.526					Nickel and compounds (26)	0.96	0.610	0.880
			Ship building (2)	1.00	0.985	0.985					Nitrogen oxides (49)	0.96	0.579	0.880
											Nitrous oxide (13)	0.94	0.741	0.880
											Non-methane volatile organic compounds (29)	0.98	0.750	0.880
											Particulate matter (PM10) (29)	1.01	0.880	0.880
											PCDD+PCDF (dioxins+furans) (11)	0.64	0.014	0.104
											Polychlorinated biphenyls / Anthracene / Naphthalene / Di-(2-ethyl hexyl) phthalate (1)	NE ^b	-	-
											Polycyclic aromatic hydrocarbons (11)	0.65	0.009	0.091
											Sulfur oxides (36)	0.95	0.540	0.880
											Total organic carbon (air) (4)	0.77	0.284	0.749
											Total suspended particulate matter (12)	0.90	0.323	0.764
											Trichloroethylene (2)	0.32	0.027	0.154
											Vanadium (3)	0.34	0.000	0.009
											Zinc and compounds (21)	0.97	0.664	0.880

^a p-BH for trend.

^b Not estimated: risk could not be estimated.

Supplementary Data, Figure S1. Statistically significant relative risk ratios (RRRs) and their 95% confidence intervals (95% CIs) of prostate cancer at different distances to industries (sensitivity analysis with only individuals living in their last residence for ≥ 10 years), based on a number of controls (Co) and cases (Ca) ≥ 5 , for the “stratified” analysis by clinical profile applied to the analysis by industrial group. X-axis is plotted in logarithmic scale. NE*: not estimated.

