

Supplementary Data

Title of the manuscript: “Risk of breast cancer and residential proximity to industrial installations: new findings from a multicase-control study (MCC-Spain)”.

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

- a) Appendix A, showing the description of the risk gradient analysis.
- b) Table S1, showing the list of industrial groups, together with their E-PRTR categories, and number of installations by industrial group and autonomous region.
- c) Table S2, showing the odds ratios of breast cancer by industrial distance and groups of carcinogens.
- d) Table S3, showing the odds ratios of breast cancer for ever-decreasing radiuses within a 30-kilometer area surrounding each facility, both overall and by industrial group (risk gradient analysis, with categorical and continuous variables).

Fifth analysis: Risk gradient analysis

The risk gradient analysis in the vicinity of installations was confined to an area of 30 km surrounding each installation, and the ORs were estimated using mixed multiple unconditional logistic regression models, as follows:

- a) *All industries as a whole (all sectors)*: for each woman, we calculated a new variable, “*minimum distance_i*”, defined as:

$$\text{minimum distance}_i = \min\{\text{industrial distance}_{ij}\}_j$$
$$i=1, \dots, 1963 \text{ women, } j=1, \dots, 116 \text{ facilities}$$

where *industrial distance_{ij}* is the distance between woman *i* and facility *j*. This new explanatory variable was categorized in concentric rings (0-1, 1-1.5, 1.5-2, 2-2.5, 2-3, and 3-30 km as reference). This was included in the models as both a categorical and a continuous variable, thereby making it possible for: the effect of the respective distances to be estimated by the former; the existence of radial effects to be ascertained by the latter (rise in OR with increasing proximity to an installation); and, by applying the likelihood ratio test, the statistical significance of such minimum distance-related effects to be computed.

- b) *By industrial group*: for each woman and industrial group, we calculated 21 new variables, “*minimum distance_industrial group_{ik}*”, defined as:

$$\text{minimum distance_industrial group}_{ik} = \min\{\text{industrial group distance}_{ij}\}_j$$

$i=1, \dots, 1963$ women, $k=1, \dots, 21$ industrial groups, $j=1, \dots$, no. of facilities of industrial group *k*, where *industrial group distance_{ij}* is the distance between woman *i* and facility *j* belonging to industrial group *k*. These new explanatory variables were categorized in concentric rings (0-1, 1-1.5, 1.5-2, 2-2.5, 2-3, and 3-30 km as reference). These were included in the models as categorical and continuous variables, and women that had some industry other than the group analyzed at ≤ 3 km were excluded.

Supplementary Data, Table S1: list of industrial groups, together with their E-PRTR categories, and number of installations by industrial group and autonomous region.

Industrial group	E-PRTR category	Provinces										TOTAL
		Asturias	Barcelona	Cantabria	Girona	Gipuzkoa	Huelva	Leon	Madrid	Navarre	Valencia	
Combustion installations	1.c	1	0	0	1	1	2	1	0	0	0	6
Production and processing of metals	2.a, 2.b, 2.c.i, 2.c.ii, 2.d, 2.e	1	3	4	0	2	1	0	0	2	0	13
Galvanization	2.c.iii	2	0	0	0	0	0	0	0	0	0	2
Surface treatment of metals and plastic	2.f	2	8	6	0	2	0	0	1	4	1	24
Mining industry	3.a, 3.b	0	0	0	0	0	0	1	0	0	0	1
Cement and lime	3.c, 3.d	1	0	0	1	1	1	1	0	0	0	5
Glass and mineral fibers	3.e, 3.f	0	2	0	0	0	1	0	0	0	0	3
Ceramic	3.g	1	0	1	0	0	1	0	0	0	0	3
Organic chemical industry	4.a	0	9	0	0	0	0	0	0	1	0	10
Inorganic chemical industry	4.b	0	1	0	0	0	1	0	0	0	0	2
Fertilizers	4.c	0	0	0	0	0	1	0	0	0	0	1
Pharmaceutical products	4.e	0	1	0	0	0	0	1	1	0	0	3
Explosives and pyrotechnics	4.f	0	0	0	0	0	1	0	0	0	0	1
Hazardous waste	5.a, 5.b	0	1	4	2	0	1	0	0	0	0	8
Non-hazardous waste	5.c, 5.d	0	0	1	0	1	0	0	0	0	0	2
Disposal or recycling of animal waste	5.e	0	1	0	0	0	0	0	0	0	1	2
Urban waste-water treatment plants	5.f, 5.g	0	1	1	0	0	0	1	0	0	0	3
Paper and wood production	6.a, 6.b, 6.c	0	0	0	1	0	1	0	0	1	0	3
Food and beverage sector	8.a, 8.b, 8.c	0	4	0	2	0	0	5	1	2	1	15
Surface treatment using organic solvents	9.c	0	1	0	2	0	0	0	0	3	1	7
Ship building	9.e	1	0	1	0	0	0	0	0	0	0	2
TOTAL		9	32	18	9	7	11	10	3	13	4	116

Supplementary Material, Table S2: Odds ratios of breast cancer by industrial distance and groups of carcinogens.

Groups of carcinogens (no. industries)	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		
	Controls (n)	Cases (n)	OR (95%CI) ^a	Controls (n)	Cases (n)	OR (95%CI) ^a	Controls (n)	Cases (n)	OR (95%CI) ^a	Controls (n)	Cases (n)	OR (95%CI) ^a	Controls (n)	Cases (n)	OR (95%CI) ^a
Reference	677	167	-	677	167	-	677	167	-	677	167	-	677	167	-
<i>IARC groups^b</i>															
Group 1 (81)	153	39	1.18 (0.75-1.87)	263	66	1.23 (0.84-1.80)	462	125	1.24 (0.90-1.70)	612	185	1.23 (0.92-1.63)	743	246	1.25 (0.95-1.64)
Group 2A (40)	72	15	0.92 (0.45-1.88)	131	24	0.94 (0.51-1.74)	256	49	1.01 (0.63-1.62)	352	65	0.88 (0.59-1.30)	465	102	1.09 (0.78-1.52)
Group 2B (12)	55	10	0.83 (0.37-1.87)	81	19	1.23 (0.66-2.28)	137	34	1.45 (0.91-2.30)	175	39	1.20 (0.78-1.84)	213	47	1.19 (0.80-1.78)

^aORs were estimated from various mixed multiple logistic regression models (an independent model for each of the categories of industrial distance), that included age, study level, BMI 1-year prior the interview, age at first birth, previous biopsies, family history of breast cancer, age at menarche, and province of residence (as a random effect).

^bIARC carcinogenic classification: Group 1: carcinogens to humans (arsenic and compounds, cadmium and compounds, chromium and compounds, nickel and compounds, lindane, dioxins+furans, polychlorinated biphenyls, trichloroethylene, vinyl chloride, benzene, ethylene oxide, polycyclic aromatic hydrocarbons, particulate matter (PM₁₀), total suspended particulate matter, benzo(a)pyrene, and pentachlorophenol); Group 2A: probably carcinogenic to humans (lead and compounds, dichloromethane, tetrachloroethylene, DDT, and hexabromobiphenyl); Group 2B: possibly carcinogenic to humans (chlordane, 1,2-dichloroethane, heptachlor, hexachlorobenzene, 1,2,3,4,5,6-hexachlorocyclohexane, mirex, tetrachloromethane, trichloromethane, ethyl benzene, naphthalene, di-(2-ethyl hexyl) phthalate, cobalt and compounds, benzo(b)fluoranthene, benzo(k)fluoranthene, and indeno(1,2,3-cd)pyrene).

Supplementary Data, Table S3: Odds ratios of breast cancer for ever-decreasing radiuses within a 30-kilometer area surrounding each facility, both overall and by industrial group (risk gradient analysis, with categorical and continuous variables).

Industrial group	Categorical variables															Continuous variables			
	[0-1 km]			[1-1.5 km]			[1.5-2 km]			[2-2.5 km]			[2.5-3 km]			Reference: [3-30 km]		OR	p-trend
	Co ^a	Ca ^b	OR (95%CI)	Co ^a	Ca ^b	OR (95%CI)	Co ^a	Ca ^b	OR (95%CI)	Co ^a	Ca ^b	OR (95%CI)	Co ^a	Ca ^b	OR (95%CI)	Co ^a	Ca ^b		
All sectors	154	41	1.23 (0.78-1.94)	134	31	0.94 (0.58-1.53)	225	68	1.33 (0.91-1.93)	149	67	1.23 (0.84-1.81)	172	78	1.70 (1.17-2.48)	676	175	1.02	0.623
Combustion installations	3	0	0 (0-inf)	5	1	0.23 (0.03-2.18)	11	7	0.89 (0.28-2.88)	18	7	0.41 (0.14-1.20)	40	12	0.33 (0.13-0.83)	216	95	0.73	0.021
Production and processing of metals	78	12	1.29 (0.57-2.93)	29	9	2.65 (1.00-7.02)	48	5	0.56 (0.18-1.75)	149	28	1.09 (0.54-2.21)	35	11	0.78 (0.34-1.78)	322	63	1.07	0.397
Galvanization	12	4	0.57 (0.13-2.52)	9	9	2.00 (0.53-7.61)	15	13	1.82 (0.55-6.03)	23	12	0.82 (0.26-2.53)	14	11	1.65 (0.48-5.74)	17	12	1.00	0.998
Surface treatment of metals and plastic	12	5	2.85 (0.87-9.32)	88	8	0.71 (0.31-1.61)	139	22	1.17 (0.65-2.11)	58	20	2.38 (1.25-4.54)	169	58	2.87 (1.73-4.79)	588	79	1.04	0.592
Mining industry	9	1	0.061 (0.01-0.80)	1	0	0 (0-inf)	0	0	-	0	0	-	0	0	-	51	49	0.39	0.781
Cement and lime	7	0	0 (0-inf)	6	1	0.18 (0.02-2.05)	5	0	0 (0-inf)	29	1	0.41 (0.05-3.51)	52	11	1.43 (0.51-4.00)	215	94	0.61	0.013
Glass and mineral fibers	1	0	0 (0-inf)	7	0	0 (0-inf)	3	0	0 (0-inf)	15	6	2.99 (0.89-10.04)	10	2	0.87 (0.16-4.72)	198	66	0.89	0.569
Ceramic	7	5	0.70 (0.12-4.21)	5	5	1.13 (0.15-8.83)	37	6	0.12 (0.03-0.53)	16	2	0.18 (0.02-1.35)	8	7	1.26 (0.28-5.62)	22	13	0.84	0.408
Organic chemical industry	8	3	2.30 (0.51-10.32)	16	7	4.33 (1.35-13.96)	39	11	2.48 (0.97-6.33)	52	15	2.03 (0.88-4.70)	39	4	1.00 (0.30-3.30)	155	18	1.33	0.005
Inorganic chemical industry	0	0	-	2	4	9.54 (1.34-67.72)	17	4	0.55 (0.15-1.93)	18	6	0.82 (0.26-2.60)	6	10	1.80 (0.51-6.38)	159	41	1.09	0.529
Fertilizers	0	0	-	0	0	-	0	0	-	0	0	-	13	3	0.25 (0.03-1.95)	17	25	0.25	0.186
Pharmaceutical products	5	0	0 (0-inf)	23	1	0.23 (0.03-1.77)	60	22	1.21 (0.67-2.21)	45	27	1.49 (0.81-2.74)	32	27	1.54 (0.81-2.92)	465	106	0.97	0.730
Explosives and pyrotechnics	0	0	-	0	0	-	0	0	-	0	0	-	1	1	NE ^c	2	2	NE ^c	NE ^c
Hazardous waste	19	5	1.28 (0.32-5.21)	41	9	0.58 (0.20-1.68)	25	8	0.58 (0.19-1.81)	90	20	0.58 (0.23-1.48)	25	14	1.33 (0.50-3.54)	162	41	0.94	0.570
Non-hazardous waste	0	0	-	1	0	0 (0-inf)	1	1	64.98 (1.12-3756.48)	10	1	NE ^c	41	9	2.72 (0.74-9.96)	133	8	1.91	0.127
Disposal or recycling of animal waste	0	0	-	0	0	-	0	0	-	6	2	3.70 (0.54-25.28)	30	5	1.75 (0.49-6.31)	158	17	1.86	0.141
Urban waste-water treatment plants	0	0	-	0	0	-	7	0	0 (0-inf)	41	10	0.50 (0.21-1.17)	68	16	1.01 (0.45-2.27)	201	66	0.71	0.083
Paper and wood production	0	0	-	0	1	inf (0-inf)	0	0	-	5	2	0.70 (0.06-8.34)	16	3	0.53 (0.04-6.89)	30	25	1.43	0.438
Food and beverage sector	4	7	4.44 (1.14-17.28)	19	6	1.26 (0.41-3.87)	63	18	2.87 (1.16-7.10)	38	13	2.48 (1.06-5.80)	107	26	1.50 (0.86-2.64)	506	118	1.27	0.005
Surface treatment using organic solvents	47	9	2.29 (0.80-7.18)	8	2	3.40 (0.58-19.96)	46	12	2.70 (1.14-6.39)	61	16	2.75 (1.29-5.89)	33	12	3.42 (1.46-8.02)	301	27	1.28	0.005
Ship building	11	2	0.28 (0.05-1.64)	5	8	4.73 (1.03-21.68)	16	12	1.44 (0.44-4.69)	43	19	0.89 (0.32-2.49)	40	19	1.83 (0.60-5.54)	20	12	0.96	0.739

^aNumber of controls.

^bNumber of cases.

^cNot estimated: risk could not be estimated.