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Residential proximity to industrial pollution and mammographic density

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RESEARCH HIGHLIGHTS:

- First paper analyzing mammographic density (MD) and proximity to industries
- No association between MD and proximity to all industries as a whole
- Increased MD near urban waste-water treatment plants at all distances
- Increased MD near (≤2 km) plants releasing ammonia and dichloromethane

Abstract

Background: Mammographic density (MD), expressed as percentage of fibroglandular breast tissue, is an important risk factor for breast cancer. Our objective is to investigate the relationship between MD and residential proximity to pollutant industries in premenopausal Spanish women.

Methods: A cross-sectional study was carried out in a sample of 1225 women extracted from the DDM-Madrid study. Multiple linear regression models were used to assess the association of MD percentage (and their 95% confidence intervals (95%CIs)) and proximity (between 1 km and 3 km) to industries included in the European Pollutant Release and Transfer Register.

Results: Although no association was found between MD and distance to all industries as a whole, several industrial sectors showed significant association for some distances: "surface treatment of metals and plastic" (β=4.98, 95%CI=(0.85; 9.12) at ≤1.5 km, and β=3.00 (0.26; 5.73) at ≤2.5 km), "organic chemical industry" (β=6.73 (0.50; 12.97) at ≤1.5 km), "pharmaceutical products" (β=4.14 (0.58; 7.70) at ≤2 km; β=3.55 (0.49; 6.60) at ≤2.5 km; and β=3.11, 95%CI=(0.20; 6.01) at ≤3 km), and "urban waste-water treatment plants" (β=8.06, 95%CI=(0.82; 15.30) at ≤1 km; β=5.28; 95%CI=(0.49; 10.06) at ≤1.5 km; β=4.30, 95%CI=(0.03; 8.57) at ≤2 km; β=5.26, 95%CI=(1.83; 8.68) at ≤2.5 km; and β=3.19, 95%CI=(0.46; 5.92) at ≤3 km). Moreover, significant increased MD was observed in women close to industries releasing specific pollutants: ammonia (β=4.55, 95%CI=(0.26; 8.83) at ≤ 1.5 km; and β=3.81, 95%CI=(0.49; 7.14) at ≤ 2 km), dichloromethane (β=3.86, 95%CI=(0.00; 7.71) at ≤ 2 km), ethylbenzene (β=8.96, 95%CI=(0.57; 17.35) at ≤ 3 km), and phenols (β=2.60, 95%CI=(0.21; 5.00) at ≤ 2.5 km).

Conclusions: Our results suggest no statistically significant relationship between MD and proximity to industries as a whole, although we detected associations with various industrial sectors and some specific pollutants, which suggests that MD could have a mediating role in breast carcinogenesis.

Key Words: Breast cancer; Breast density; Industries; Pollutants; Residential proximity; DDM-Madrid

Abbreviations: MD, Mammographic density; BMI, Body mass index; EDCs, Endocrine disrupting chemicals; IARC, International Agency for Research on Cancer; $PM_{2.5}$, Particulate matter <2.5 µm; E-PRTR, European Pollutant Release and Transfer Register; 95%CI, 95% confidence interval; UTM, Universal Transverse Mercator; IQRs, Interquartile ranges; SDs, Standard deviations; PACs, Polycyclic aromatic chemicals; POPs, Persistent organic pollutants; SSH, spatial stratified heterogeneity; *p*-int, *p*-value of the interaction; *p*-BHs, *p*-values adjusted by Benjamini & Hochberg's method; PAHs, Polycyclic aromatic hydrocarbons; VOCs, Volatile organic compounds; PM_{10}, Particulate matter with a diameter between 2.5 and 10 µm.

1. Introduction

Breast cancer is a priority public health problem, since it is the most diagnosed tumor both worldwide (Sung et al., 2021) and in Spain, where 34,088 new cases were estimated in 2020 (12% of all cancer cases) (Ferlay J. et al., 2020). It also represents the leading cause of cancer death in Spanish women, with 6355 confirmed deaths in 2019 (15% of all cancer deaths) (Instituto de Salud Carlos III (ISCIII), 2019).

Percent mammographic density (MD), defined as the percentage of mammography occupied by radiologically dense fibroglandular tissue, is one of the main risk factors for breast cancer (Boyd et al., 2007). In fact, an increase of 13% in breast cancer risk has been estimated for every 10% increase in MD percentage, according to the meta-analysis published by Bond-Smith and Stone (Bond-Smith and Stone, 2019).

Although MD has a strong non-modifiable genetic component, several studies have observed that this phenotype is also influenced by several non-genetic factors, many of them hormone-related. Specifically, MD decreases with age, with body mass index (BMI), with parity, and with menopause transition, while the use of hormone replacement therapy, particularly treatments that combine estrogen and progesterone, seems to increase density (Assi et al., 2012; Huo et al., 2014).

Environmental influences (including physical environmental exposures, air pollution, or exposure to toxic substances, such as carcinogens, endocrine disrupting chemicals (EDCs), and other pollutants) can lead to breast cancer development (Assi et al., 2012; Huo et al., 2014; Namin et al., 2021; Vieira et al., 2020; Wu et al., 2021). Particularly, EDCs produce alterations in the endocrine system through diverse mechanisms and toxic effects occur with very low concentrations (Vilela et al., 2018). Many of these EDCs are estrogenic substances able to alter the development of the mammary glands and to increase the risk of having a higher MD (Gore et al., 2015; Siddique et al., 2016).

On the other hand, the International Agency for Research on Cancer (IARC) has classified outdoor air pollution as carcinogenic to humans (IARC group I) (International Agency for Research on Cancer, 2016; Loomis et al., 2013). The main sources of air pollution are transportation, power generation, industrial activity, biomass combustion, and domestic heating and cooking. These sources emit a wide variety of agents or mixtures classified as carcinogenic to humans by the IARC (International Agency for Research on Cancer, 2016). Despite the methodological limitations of epidemiological studies, there is evidence that long-term exposure to ambient air pollution may be associated with higher breast cancer risk (Andersen et al., 2017; Lemarchand et al., 2021; Zeinomar et al., 2020), but it is uncertain to what extent and whether this association could be mediated by MD. On the other hand, the possible role of outdoor air pollution on MD has been less studied, and the results are inconsistent: whereas some studies have not detected an association with exposure to traffic-related pollutants (DuPre et al., 2017; Huynh et al., 2015), other authors have reported an association with exposure to particulate matter <2.5 µm ($PM_{2.5}$), ozone, and airborne metals (White et al., 2019; Yaghjyan et al., 2017). Some air pollutants are known to exhibit endocrine-disrupting properties, including xenoestrogens capable of altering mammary gland development and increasing the risk of higher MD (Gore et al., 2015; Rodgers et al., 2018; Siddique et al., 2016). It has also been observed that certain outdoor air pollutants, such as $PM_{2.5}$, can reduce the involution of terminal duct lobular units of the normal breast and, as a consequence, increase MD (Niehoff et al., 2020).

Regarding industrial pollution in particular, living near these facilities involves daily exposure to potentially carcinogenic agents that could also alter MD. In fact, occupational exposure to some of these substances – such as pesticides, perchloroethylene, aliphatic / alicyclic hydrocarbon solvents, volatile sulfur compounds, gasoline or some heavy metals – has been associated with differences in MD in occupational studies previously published by our group (Jiménez et al., 2021; Lope et al., 2018). We have also previously reported an increased breast cancer risk among women living near specific industrial plants (García-Pérez et al., 2018).

In the EU, the European Pollutant Release and Transfer Register (E-PRTR) (European Environment Agency, 2022) provides information about industrial pollutants released to both air and water (Directive 2010/75/EU) making it possible to estimate the exposure to different industrial carcinogens (Slavik et al., 2018). This source of information has been already used in our context, showing higher cancer mortality in people living near industrial facilities compared to non-industrialized areas (Fernández-Navarro et al., 2017). However, to our knowledge, no epidemiologic studies have been conducted to evaluate the association between MD, an intermediate effect marker of breast cancer, and residential proximity to industrial exposures using individual data.

The present study aims to evaluate the association between residential proximity to pollutant industries and MD in Spanish premenopausal women.

2. Materials and methods

2.1 Study population and data collection

We designed a cross-sectional study using the population of the DDM-Madrid study (Lope et al., 2020, 2019). Briefly, from June 2013 to May 2015 a total of 1466 premenopausal women between 39 and 50 years were recruited from the Madrid Medical Diagnostic Center (*Madrid Salud*) in the context of their routine work medical checkups. The participation rate was 88%. After excluding 241 women with lack of information in some key covariates, the final sample size included 1225 participants. Women underwent mammograms and answered a standardized epidemiological questionnaire on sociodemographic data, lifestyle habits, personal and family medical history, gynecological, obstetric and work information, and residential history. Participants also completed a validated 117-item food frequency questionnaire that included eating habits during the previous 12 months (Vioque et al., 2013), and their height and weight were measured by the interviewers using a certified scale. DDM-Madrid study was conducted in accordance with the Declaration of Helsinki guidelines and was approved by the Ethics and Animal Welfare Committee of the Carlos III Institute of Health. All participants signed an informed consent form. Further details regarding the study design have been previously published (Lope et al., 2020, 2019).

The craniocaudal and mediolateral oblique views of the left and right breast mammograms of each participant were collected and anonymized, excluding analogical mammograms. MD percentage from the craniocaudal mammogram of the left breast was measured by an experienced radiologist using the DM-Scan computer tool, a free semi-automated software (https://www.iti.es/en/dmscan/) that quantifies MD in full-field digital images with high reproducibility and validity (Llobet et al., 2014; Pollán et al., 2013). To assess the internal consistency of the radiologist, a pilot study was carried out with 100 participants whose mammograms were duplicated, obtaining an intraclass correlation coefficient of 0.87 (95% confidence interval (95%CI)=(0.82; 0.92)) between the first and the second reading.

Data on industrial pollutant sources included in the E-PRTR were obtained from the Spanish Ministry for the Ecological Transition and the Demographic Challenge (Spanish Ministry for the Ecological Transition and the Demographic Challenge, 2022). For each industrial installation, we obtained information related to industrial activity, amounts of pollutant emissions, and geographical location, previously geocoded into Universal Transverse Mercator (UTM) ED50 zone 30N (EPSG:23030) and subsequently validated (García-Pérez et al., 2019). The 154 industries located in the study area (see Fig. 1) were classified into one of the 18 categories of industrial sectors (see Supplementary Data, Table S1).

The epidemiological questionnaire included information about each woman's last residence. Locations were geocoded into UTM ED50 zone 30N using Google Earth Pro.

2.2 Statistical analysis

Descriptive characteristics of the participants were presented with absolute values and percentages. MD, according to these characteristics, was described by medians and interquartile ranges (IQRs), and by arithmetic means, with their 95%CIs and standard deviations (SDs).

We used multivariable linear regression models to study the association of MD with proximity to industries and pollutants (including carcinogens and EDCs), in which the response variable was the percentage of MD. A total of five analyses, including these regression models, were performed to estimate β coefficients and 95%CIs. All models were adjusted for potential confounders at an individual level: age (continuous variable), energy intake (continuous), BMI (continuous), educational level (primary school or less, secondary school, university graduate), number of children (nulliparous, 1, 2, >2 children), family history of breast cancer (none, second degree only, first degree), previous breast biopsies (yes, no), alcohol consumption (never, <10 g/d, ≥10 g/d), smoking status (never, former smoker, current smoker), and use of oral contraceptives (never, past use, current use). These confounders were included because they are associated, with more or less evidence, with MD (Assi et al., 2012), could be related to proximity to industrial facilities (García-Pérez et al., 2018), and are common confounders in studies associating this biomarker with environmental exposures (García-Pérez et al., 2018; Jiménez et al., 2021).

The shortest distances between women's residences and industrial facilities were calculated and, for the first four analyses, we took into account several distances 'd' (between 1 and 3 km increasing every 0.5 km) for the proximity ("exposure") variable (women living at ≤'d' km), with the same reference area for all the models, consisting in women living at >3 km from any industry:

1) First analysis: relationship between MD and proximity to all industries as a whole (an independent model for each distance).
2) Second analysis: MD and proximity to industries by categories of industrial sectors (an independent model for each industrial sector and distance).
3) Third analysis: MD and proximity to industries releasing groups of carcinogens and EDCs. Carcinogens were classified by IARC as carcinogenic (group 1), probably carcinogenic (group 2A) and possibly carcinogenic (group 2B) to humans. EDCs were classified according to the United Nations Environment Program and World Health Organization as pesticides, metals, polycyclic aromatic chemicals (PACs), persistent organic pollutants (POPs), plasticizers, and other solvents (an independent model for each group of pollutants (carcinogens and EDCs) and distance).
4) Fourth analysis: MD and proximity to industries releasing specific pollutants (including EDCs, carcinogens, and other toxic substances) (an independent model for each specific pollutant and distance).

In brief, each distance and type of analysis (all industries as a whole, industrial sector, group of pollutants or specific pollutant) corresponded to a single exposure variable categorized into two categories or strata: "near", if the women lived at ≤'d' km of the industrial facility belonging to the analysis of interest, and "far" or reference, if the women lived at >3 km of any industry.

For the fifth analysis, we studied the risk gradient (assessment of the existence of radial effects near industrial installations), a) for all industries as a whole (a single model), b) by industrial sector (an independent model for each industrial sector), c) by groups of carcinogens and EDCs (and independent model for each group of pollutants (carcinogens and EDCs)), and d) by specific pollutant (an independent model for each pollutant). With the purpose of assessing the existence of radial effects near industrial plants (rise in β coefficient of the model with increasing proximity to industries), the proximity ("exposure") variable was categorized in concentric rings – [0-1 km], (1-1.5 km], (1.5-2 km], (2-2.5 km], (2.5-3 km], and (3-30 km] as a reference –, and included in the models as a continuous variable.

Moreover, we adjusted *p*-values by controlling the expected proportion of false positives (False Discovery Rate) to take into account the problem of multiple comparisons (Benjamini and Hochberg, 1995).

Finally, possible effect modifications between covariates were tested using the Likelihood Ratio Test to compare the final model with a model that also included an interaction term between the exposure variable for each distance and the corresponding explanatory variable.

All analyses were performed using R 3.3.2 software.

2.3 Factor detector method

With the purpose of measuring the possible spatial stratified heterogeneity (SSH) of the MD explained by the proximity ("exposure") variable and the potential confounders included in the models, we used the factor detector *q*-statistic proposed by Wang et al. (Wang et al., 2010, 2016)), and implemented in the package 'geodetector' (version 1.0-4) in the R software (The Comprehensive R Archive Network, 2020). SSH is a concept referred to the fact that within-strata variance of a variable is lower than the between-strata variance, and the *q*-statistic value is within the [0-1] interval (0, if a spatial stratification of heterogeneity is not statistically significant, and 1, if there is a perfect spatial stratification of heterogeneity).

3. Results

3.1 Characteristics of the study population

Results obtained are based on 1225 women, whose geographic distribution is shown in Figure 1 and main characteristics are presented in Table 1. Mean age of the participants was 44 years. Most of them attended university (61.4%) and had two children or more (52.1%). 31.4% of the participants were obese or overweight, 10.8% had previous biopsies, 7.1% had at least one first-degree relative with breast cancer, and 3.1% were taking oral contraceptives. The average caloric consumption was 1981.23 kcal/day. Finally, 39.4% of the participants never smoked and 20.2% never drank. Mean MD was 34.82% (95%CI=(33.85; 35.79)) and median MD was 32.70% (IQR=24.78), being particularly higher in women with lower BMI, nulliparous, with previous breast biopsies, and in women who never used oral contraceptives.

3.2 MD and proximity to all industries as a whole

Participants living closer to any facility showed higher MD, with β coefficients that ranged from 1.04 (at ≤3 km) to 1.95 (at ≤1.5 km), although the results were not statistically significant (Table 2).

Interactions between the exposure variable for each distance and potential confounders were tested (see Supplementary Data, Table S2), showing no statistically significant *p*-values of the interaction (*p*-int), with the exception of 'Family history of breast cancer' at ≤1.5 km (*p*-int=0.043) and ≤3 km (*p*-int=0.020): in the case of 1.5 km, MD displayed different effects in women who had no family history of breast cancer (β=3.14, 95%CI=(0.38; 5.90)), second degree only (β=-3.58, 95%CI=(-10.09; 2.92)), and first degree (β=2.27, 95%CI=(-7.64; 12.18)); and in the case of 3 km, MD also displayed different effects in women who had no family history of breast cancer (β=2.36, 95%CI=(0.33; 4.38)), second degree only (β=-2.46, 95%CI=(-7.37; 2.46)), and first degree (β=-3.64, 95%CI=(-10.71; 3.43)) (data not shown).

3.3 MD and proximity to industries by industrial sector

Regarding the exposure to each industrial sector, we observed a statistically significant (*p*-value<0.05) increased MD in women living near installations belonging to the following sectors (see Fig. 2): "surface treatment of metals and plastic" (β=4.98, 95%CI=(0.85; 9.12) at ≤1.5 km; and β=3.00, 95%CI=(0.26; 5.73) at ≤2.5 km), "organic chemical industry" (β=6.73, 95%CI=(0.50; 12.97) at ≤1.5 km), "pharmaceutical products" (β=4.14, 95%CI=(0.58; 7.70) at ≤2 km; β=3.55, 95%CI=(0.49; 6.60) at ≤2.5 km; and β=3.11, 95%CI=(0.20; 6.01) at ≤3 km), and "urban waste-water treatment plants" (β=8.06, 95%CI=(0.82; 15.30) at ≤1 km; β=5.28; 95%CI=(0.49; 10.06) at ≤1.5 km; β=4.30, 95%CI=(0.03; 8.57) at ≤2 km; β=5.26, 95%CI=(1.83; 8.68) at ≤2.5 km; and β=3.19, 95%CI=(0.46; 5.92) at ≤3 km).

Other results of interest, for *p*-value<0.1, are referred to the following sectors (see Supplementary Data, Table S1): "surface treatment of metals and plastic" at ≤2 km (β=3.22) and ≤3 km (β=2.10), "mining industry" at ≤2.5 km (β=10.55), "ceramic" at ≤3 km (β=6.45), "organic chemical industry" at ≤2.5 km (β=3.26) and ≤3 km (β=3.00), and "hazardous waste" at ≤3 km (β=5.65). When we observed the *p*-values adjusted by Benjamini & Hochberg's method (*p*-BHs), the sectors that showed *p*-BH<0.2 were the following: 'surface treatment of metals and plastic' (at ≤1.5 km and ≤2.5 km), 'organic chemical industry' (at ≤1.5 km), 'pharmaceutical products' (at ≤2.5 km), and 'urban waste-water treatment plants' (at ≤1.5 km and ≤2.5 km).

3.4 MD and proximity to industries by groups of carcinogens and EDCs

In the analysis of the association between MD and industries releasing groups of IARC-carcinogens and EDCs (Table 3), no statistically significant increased MD was detected, for *p*-value<0.05, although most of the point estimates showed positive associations, except for plasticizers. When considering *p*-value<0.1 as the limit for statistical significance, women exposed to group 2B carcinogens showed an increased MD (β=2.59, 95%CI=(-0.02; 5.20) at ≤2.5 km; and β=2.15, 95%CI=(-0.24; 4.54) at ≤3 km). Detailed information about amounts of carcinogens and EDCs discharged by each industrial sector is provided in Supplementary Data, Table S3.

3.5. MD and proximity to industries by specific pollutant

When analyzing the relationship between MD and proximity to industries that release specific pollutants (Fig. 3) we found a statistical association in women living close to industries releasing ammonia (β=4.55, 95%CI=(0.26; 8.83) at ≤ 1.5 km); and β=3.81, 95%CI=(0.49; 7.14) at ≤ 2 km), dichloromethane (β=3.86, 95%CI=(0.00; 7.71) at ≤ 2 km), ethylbenzene (β=8.96, 95%CI=(0.57; 17.35) at ≤ 3 km), and phenols (β=2.60, 95%CI=(0.21; 5.00) at ≤ 2.5 km).

Other results of interest, for *p*-value<0.1, are referred to the following specific pollutants (see Supplementary Data, Table S4): chemical oxygen demand at ≤1.5 km (β=2.25); cyanides at ≤3 km (β=2.46); dichloromethane at ≤2.5 km (β=3.18) and at ≤3 km (β=2.85); ethylbenzene at ≤2.5 km (β=8.53); ethylene oxide at ≤1.5 km (β=6.40); halogenated organic compounds at ≤2.5 km (β=1.95); nitrous oxide at ≤2.5 km (β=2.57); phenols at ≤2 km (β=2.48); sulfur hexafluoride at ≤1.5 km (β=6.40); toluene at ≤2 km (β=3.22), at ≤2.5 km (β=2.73), and at ≤3 km (β=2.37); total organic carbon at ≤1.5 km (β=2.21); total organic carbon (air) at ≤2 km (β=2.31); total phosphorus at ≤1.5 km (β=2.21), at ≤2.5 km (β=1.97), and at ≤3 km (β=1.56); trichloromethane at ≤2.5 km (β=2.91) and at ≤3 km (β=2.76); and xylenes at ≤3 km (β=5.68).

3.6. Risk gradient analysis

Finally, risk gradient analysis (Supplementary Data, Table S5) showed an increased MD with increasing proximity to facilities (for *p*-trend <0.05) in the sectors of “surface treatment of metals and plastic” (*p*-trend=0.043), and “urban waste-water treatment plants” (p-trend= 0.009). Moreover, for *p*-trend <0.1, the industrial sectors of “organic chemical industry” (*p*-trend=0.052), and “pharmaceutical products” (*p*-trend=0.052), and facilities releasing ammonia (*p*-trend=0.073), dichloromethane (*p*-trend=0.096), and ethylbenzene (*p*-trend=0.068) showed positive radial effects.

3.7. SSH test (factor detector method)

The factor detector showed no statistically significant SSH between MD and the exposure variable for all the distances. In the analysis between MD and proximity to all industries as a whole, the *q*-statistic values were: 0.00319 (p-value=0.289) at ≤1 km, 0.00161 (p-value=0.299) at ≤1.5 km, 0.00153 (p-value=0.232) at ≤2 km, 0.00061 (p-value=0.420) at ≤2.5 km, and 0.00103 (p-value=0.284) at ≤3 km. In the risk gradient analysis for all industries as a whole, with the exposure variable categorized in concentric rings and included in the model as a continuous variable, the SSH test yielded a *q*-statistic value of 0.00344 (p-value=0.679) (data not shown).

Regarding the potential confounders, the factor detector revealed statistically significant SSH of the MD for the following distances and covariates (see Supplementary data, Table S6), where the contribution of each variable to the variability of MD was ranked by the *q*-statistic (*p*-value<0.05) as follows: a) for distance ≤1 km: BMI (23.72%) > Previous breast biopsies (2.62%); b) for distance ≤1.5 km: BMI (23.40%) > Previous breast biopsies (2.20%); c) for distance ≤2 km: BMI (23.71%) > Previous breast biopsies (2.78%); d) for distance ≤2.5 km: BMI (23.55%) > Previous breast biopsies (2.47%) > Number of children (1.35%); and e) for distance ≤3 km: BMI (23.66%) > Previous breast biopsies (2.17%) > Number of children (1.48%). These results suggest that BMI, previous breast biopsies, and number of children could explain the SSH of the MD.

4. Discussion

In summary, our results suggest no association between an increased MD in the environs of all the industries as a whole. However, in the analysis by industrial sector, an association between higher MD and proximity to urban waste-water treatment plants was found for all distances, including the risk gradient analysis. Moreover, some potential associations with industrial sectors and pollutants have been detected in relation to specific distances:

a) industrial facilities belonging to “surface treatment of metals and plastic” (1.5 and 2.5 km), “organic chemical industry” (1.5 km), and “pharmaceutical industry” (2, 2.5, and 3 km); and,
b) industrial facilities releasing ammonia (1.5 km), dichloromethane (2 km), ethylbenzene (3 km), and phenols (2.5 km).

To our knowledge, this is the first study that analyses the proximity to industrial facilities by industrial sector, groups of carcinogens and EDCs, and individual pollutants and its relation with MD. These novel results represent a good source of new hypotheses about the possible biological mechanisms that mediate the relationship, as yet unknown, between industrial pollution and breast cancer risk. Industrial pollution is particularly important inasmuch as several studies have found some evidence that industrial emissions have a detrimental impact on human health, in relation to increased death rates, decreased life expectancy, induction of neurodegenerative and neurological diseases, mortality non-accidental and cardiac diseases, and a higher incidence and mortality from cancers in adult population and children (Bauleo et al., 2019; Fernández-Navarro et al., 2017; Ortega-García et al., 2017; Peters et al., 2021; Rahman et al., 2021; Rajagopalan and Landrigan, 2021; Siddique and Kiani, 2020).

Some previous studies have assessed the relationship between proximity to industrial installations and risk of breast cancer (García-Pérez et al., 2018; Pan et al., 2011; VoPham et al., 2020). With respect to MD, to date, the only studies that have evaluated environmental exposures have focused on air pollution in general (not specifically industrial pollution), with inconsistent results: some authors found an increased MD in women living in urbanized areas (Emaus et al., 2014) or in women exposed to ambient air pollutants, such as $PM_{2.5}$ (Yaghjyan et al., 2017), or to certain metals, such as lead and cobalt (White et al., 2019). Conversely, other authors did not find any relationship between MD and traffic-related air pollution exposure (DuPre et al., 2017; Huynh et al., 2015).

4.1 Results about industrial sectors

The relationship between industries and MD has not been previously studied, but their relation with breast cancer is growing today. With respect to industries pertaining to the "surface treatment of metals and plastic" sector, they use metalworking fluids and mineral oils, many of them carcinogens and/or EDCs, which have been related to an increased risk of breast cancer in several occupational studies (Brophy et al., 2012; Thompson et al., 2005). In our study, we found a higher MD in women living close to these installations, as well as a positive radial effect in the gradient analysis. Moreover, taking into account that our participants did not work in the metal industry (Jiménez et al., 2021), this result could support the hypothesis of an environmental exposure pathway in relation to MD, rather than an occupational one.

Regarding "urban waste-water treatment plants", there are no epidemiological studies analyzing breast cancer risk in women residing near this type of installations. Only a Tunisian study, focused on hospital wastewaters (as a proxy of urban waste-water), found that wastewater samples containing EDCs induced proliferation of the human breast cancer cell line MDA-231 (Nasri et al., 2017), which could be related to risk of breast cancer. Our results in relation to MD were consistent, since all the distances explored in the analysis by industrial sector as well as the gradient analysis showed statistically significant increased MD. Although, according to the E-PRTR information, the plants in our study belonging to this sector did not emit carcinogens or EDCs (see Supplementary Data, Table S3), it is known that the effluents of municipal sewage treatment plants may contain potential carcinogens and EDCs (Schilirò et al., 2009; Torretta, 2012; Wang et al., 2003).

In connection with the pharmaceutical industrial sector, to our knowledge, there are not epidemiological studies about incidence of breast cancer in women living near to these industries. However, we found an increased MD in women living at least 2 km away from the "pharmaceutical products" industry, the industrial sector with the highest amounts of Group 2A and 2B-carcinogens, and other solvents released to air and water in our study. In this sense, a recent Swiss study concluded that pharmaceutical production is a relevant emission source of a wide variety of unknown chemical compounds (Anliker et al., 2020), and supports the need for more detailed exposure assessment of effluents and emissions released by these installations.

A relationship between risk of breast cancer and organic chemical industries was previously described by our group (Garcia-Pérez et al., 2018), detecting an excess risk of breast cancer near (≤2.5 km) this type of installations. In the present study, an increased MD has been detected in women living at a distance of up to 3 km. Lewis-Michl et al. (Lewis-Michl et al., 1996) detected a high risk of breast cancer among American women residing near chemical industries although, unlike our study, the increased risk was only observed in postmenopausal women. On the other hand, in a Chinese study that characterized and evaluated the soil and groundwater contamination at an organic chemical plant, the authors found a high cancer risk, due to the metals, polycyclic aromatic hydrocarbons (PAHs) or volatile organic compounds (VOCs) detected in its surroundings (Liu et al., 2016).

Lastly, in relation to other industrial sectors associated with MD in our study, mining and ceramic industries were also associated with an excess of breast cancer mortality in women who were living close to these industries (García-Pérez et al., 2016). An American study showed that women living in a mining region with high rates of breast cancer had higher urinary arsenic levels than the national average, as well as higher levels of cadmium in older women with long-term exposure (Von Behren et al., 2019).

With respect to the “hazardous waste” sector (which includes incinerators and plants for the disposal or recovery of hazardous waste), a nested case-control study of breast cancer found an increased risk of this tumor in women who lived near (<1 mile) hazardous waste sites (O’Leary et al., 2004). Moreover, it was reported an increased rate of hospitalization for breast cancer in urban areas near hazardous waste sites with VOCs (Lu et al., 2014). However, a systematic review found limited evidence about exposure to hazardous waste sites and its relationship with breast cancer (Fazzo et al., 2017). In the case of incinerators, Ranzi et al. (Ranzi et al., 2011) found an excess of breast cancer in women living (≤3.5 km) close to these installations, whereas VoPham et al. (VoPham et al., 2020) also found increased breast cancer risks in women residing within 10 km and 5 km of any municipal solid waste incinerator. In our study, the increased MD was detected in participants residing at ≤3 km from hazardous waste plants.

4.2 Results about industrial pollutants

Concerning specific industrial pollutants, our results about exposure to dichloromethane and MD can be approached those of the literature concerning breast cancer, tumor associated with exposure to this substance in previous studies (Cooper et al., 2011; Niehoff et al., 2019). Dichloromethane is a mutagenic industrial solvent (Group 2A by the IARC) widely used in a variety of products. In *in vitro* and *in vivo* studies, it induces chromosomal aberrations, micronuclei, and DNA damage that correlated with tissue and/or species availability of functional glutathione *S*-transferase (GST) metabolic activity, the key activation pathway for dichloromethane-induced cancer (Schlosser et al., 2015). The key enzyme in this pathway (the glutathione-S transferase-theta 1, GSTT1) has been detected in the normal human mammary gland (Lehmann and Wagner, 2008).

With regard to ammonia exposure, Mitra et al. (Mitra et al., 2004) published a study carried out in the state of Mississippi (US) about incidence of breast cancer at a county level, and they observed a relationship between maximum emissions of industrial ammonia and breast cancer incidence.

Our study shows an association between living near installations releasing industrial ammonia (at distances of ≤1.5 and ≤2 km) and higher MD. Although the potential biological mechanism involved is not known, Spinelli et al. (Spinelli et al., 2017), observed that metabolic recycling of ammonia stimulates growth and proliferation in breast cancer cells.

Although the evidence on phenols and breast cancer risk is scarce, Parada et al., in a case-control analysis, found an association between high levels of phenol biomarkers and higher risk of breast cancer, specifically in women with lower BMI (<25 kg/m^2) (Parada et al., 2019). In our study, where the majority of participants had a BMI <25 kg/m^2 (68.6%, see Table 1), the increased MD was observed in the environs of industries releasing phenols at distances of 2 and 2.5 km. One previous study also reported greater percent breast density associated with exposure to phenols, particularly bisphenol-A (Sprague et al., 2013).

4.3 Limitations and strengths

One of the main limitations of our study is the cross-sectional nature of the study, limiting the possibility to assess changes in MD patterns across time and prevent from drawing interpretations of causality between proximity to industrial pollution and MD. Another limitation was the non-inclusion of time living in the last residence or their completed residential history, since many participants did not report this information. On the other hand, some adjustment covariates were self-reported and, therefore, susceptible to a possible recall bias. With respect to the variable of interest (proximity), the use of the distance as a proxy of the real exposure to the pollution sources (which depends on geographic landforms or prevailing winds) could lead to a problem of misclassification. Several radiuses between 1 and 3 km were chosen, in line with the distances used in studies with individual data (case-control studies) regarding breast cancer risk and proximity to industrial pollutants (García-Pérez et al., 2018; Pan et al., 2011) and based on dispersion modeling studies, where the maximum concentrations in the environment of specific pollutants released by industries have been found between 0 and 3 km from the pollution sources (Bertazzon et al., 2021; Hodgson et al., 2006; Tuygun et al., 2017; Yarandi et al., 2021).

The main strength of our study is its novelty, since it is the first approach to the study of the residential proximity to industrial pollution sources and MD. To do this, we have taken into account the industries and their emissions included in the E-PRTR, the public inventory of industries in the EU. In addition, we must highlight the completeness and robustness of the methodology used in the different analyses, which include stratification of the results by industrial sector, groups of carcinogens and EDCs, specific pollutants, and a gradient analysis, providing a comprehensive description of the possible relationship between MD and industrial pollution exposure. Another strength is the high participation rate. In addition, a single professional reader, who showed high internal consistency, measured the MD on a continuous scale using a validated computer-assisted method. Lastly, the problem of multiple comparisons was addressed, including adjusted *p*-values by Benjamini’s method.

5. Conclusions

To our knowledge, this is the first study assessing the potential relationship between residential proximity to industrial pollution and MD. In general, our results suggest no association between residing in the environs of all the industrial installations as a whole and an increased MD. However, we have detected possible associations with certain industrial sectors (surface treatment of metals and plastic, organic chemical industry, pharmaceutical industry, and urban waste-treatment plants) and facilities releasing specific pollutants (ammonia, dichloromethane, ethylbenzene, and phenols). Given the long latency period of breast cancer, the use of intermediate-effect markers, such as MD, are of great interest, being able to provide additional information on the underlying biological mechanisms of this tumor. More studies are necessary to confirm these associations.

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Figure legends

Figure 1. Map with the geographic distribution of industries and women’s residences.

Figure 2. Association between mammographic density and residential proximity to industries by categories of industrial sectors, with statistically significant results and a number of women ≥5.

Figure 3. Association between mammographic density and residential proximity to industries releasing specific pollutants, with statistically significant results and a number of women ≥5.

Table 1. Descriptive characteristics of the participants and mammographic density percentage according to women's characteristics.

		Mammographic density (%)		
Characteristic	**n (%)**	**Median (IQR[a])**	**Mean (95%CI)**	**SD[b]**
Total	1225 (100.0)	32.70 (24.78)	34.82 (33.85; 35.79)	17.28
Age (years)				
<45	654 (53.4)	34.47 (25.43)	36.14 (34.82; 37.46)	17.22
≥45	571 (46.6)	31.27 (24.25)	33.30 (31.89; 34.72)	17.24
Education				
Primary school or less	52 (4.2)	30.51 (30.46)	31.33 (26.42; 36.24)	18.05
Secondary school	421 (34.4)	31.85 (24.95)	33.40 (31.82; 34.99)	16.61
University graduate	752 (61.4)	34.23 (24.98)	35.85 (34.60; 37.11)	17.54
Body mass index (kg/m^2)				
<18.5	20 (1.6)	42.51 (20.61)	41.74 (33.84; 49.64)	18.03
18.5-24.9	821 (67.0)	37.87 (24.67)	39.12 (37.98; 40.26)	16.64
25-29.9	278 (22.7)	25.93 (19.48)	27.53 (25.84; 29.23)	14.41
≥30	106 (8.7)	18.12 (16.10)	19.35 (16.80; 21.89)	13.37
Number of children				
0	306 (25.0)	36.40 (27.90)	37.86 (35.82; 39.90)	18.20
1	280 (22.9)	33.50 (25.67)	35.81 (33.68; 37.95)	18.23
2	576 (47.0)	31.93 (22.94)	33.00 (31.67; 34.33)	16.26
>2	63 (5.1)	30.00 (18.45)	32.32 (28.55; 36.10)	15.29
Previous breast biopsies				
No	1093 (89.2)	31.82 (23.92)	33.94 (32.93; 34.95)	17.07
Yes	132 (10.8)	41.22 (26.77)	42.14 (39.17; 45.10)	17.41
Family history of breast cancer				
None	946 (77.2)	33.05 (25.07)	35.00 (33.91; 36.08)	17.07
Second degree only	192 (15.7)	32.03 (23.60)	34.73 (32.15; 37.31)	18.27
First degree	87 (7.1)	32.57 (24.48)	33.11 (29.43; 36.78)	17.48
Energy intake (Kcal/day)[c]				
<1674.8	408 (33.3)	31.23 (24.96)	33.68 (31.98; 35.37)	17.47
1674.8-2151.1	409 (33.4)	34.61 (23.42)	35.74 (34.07; 37.40)	17.18
>2151.1	408 (33.3)	32.62 (26.13)	35.04 (33.38; 36.71)	17.18
Use of oral contraceptives				
Never	473 (38.6)	35.50 (26.38)	36.70 (35.08; 38.31)	17.92
Past use	714 (58.3)	32.15 (24.37)	33.79 (32.55; 35.02)	16.82
Current use	38 (3.1)	29.72 (14.75)	30.89 (25.82; 35.96)	15.94
Tobacco consumption				
Never	483 (39.4)	33.30 (25.67)	35.54 (33.96; 37.13)	17.74
Former smoker	429 (35.0)	33.33 (23.99)	34.57 (32.99; 36.16)	16.74
Current smoker	313 (25.6)	31.46 (25.07)	34.04 (32.13; 35.96)	17.31
Alcohol consumption (g/day)				
Never	248 (20.2)	32.05 (25.54)	34.07 (31.89; 36.26)	17.56
<10	802 (65.5)	32.81 (24.72)	34.98 (33.79; 36.18)	17.30
≥10	175 (14.3)	33.58 (25.18)	35.14 (32.64; 37.63)	16.87

[a] Interquartile range.
[b] Standard deviation.
[c] Variable in tertiles.

Table 2. Association between mammographic density and distance to all industries as a whole.

Distance	**n**	**β[a]**	**95%CI**
Reference (>3 km)	499	-	-
≤3 km	726	1.04	(-0.74; 2.82)
≤2.5 km	606	1.29	(-0.58; 3.17)
≤2 km	439	1.34	(-0.70; 3.38)
≤1.5 km	270	1.95	(-0.43; 4.34)
≤1 km	120	1.87	(-1.35; 5.08)

[a] β coefficients estimated from various multiple linear regression models (an independent model for each distance), adjusted for age, education, body mass index, number of children, oral contraceptives use, previous breast biopsies, family history of breast cancer, smoking, energy intake, and alcohol consumption.

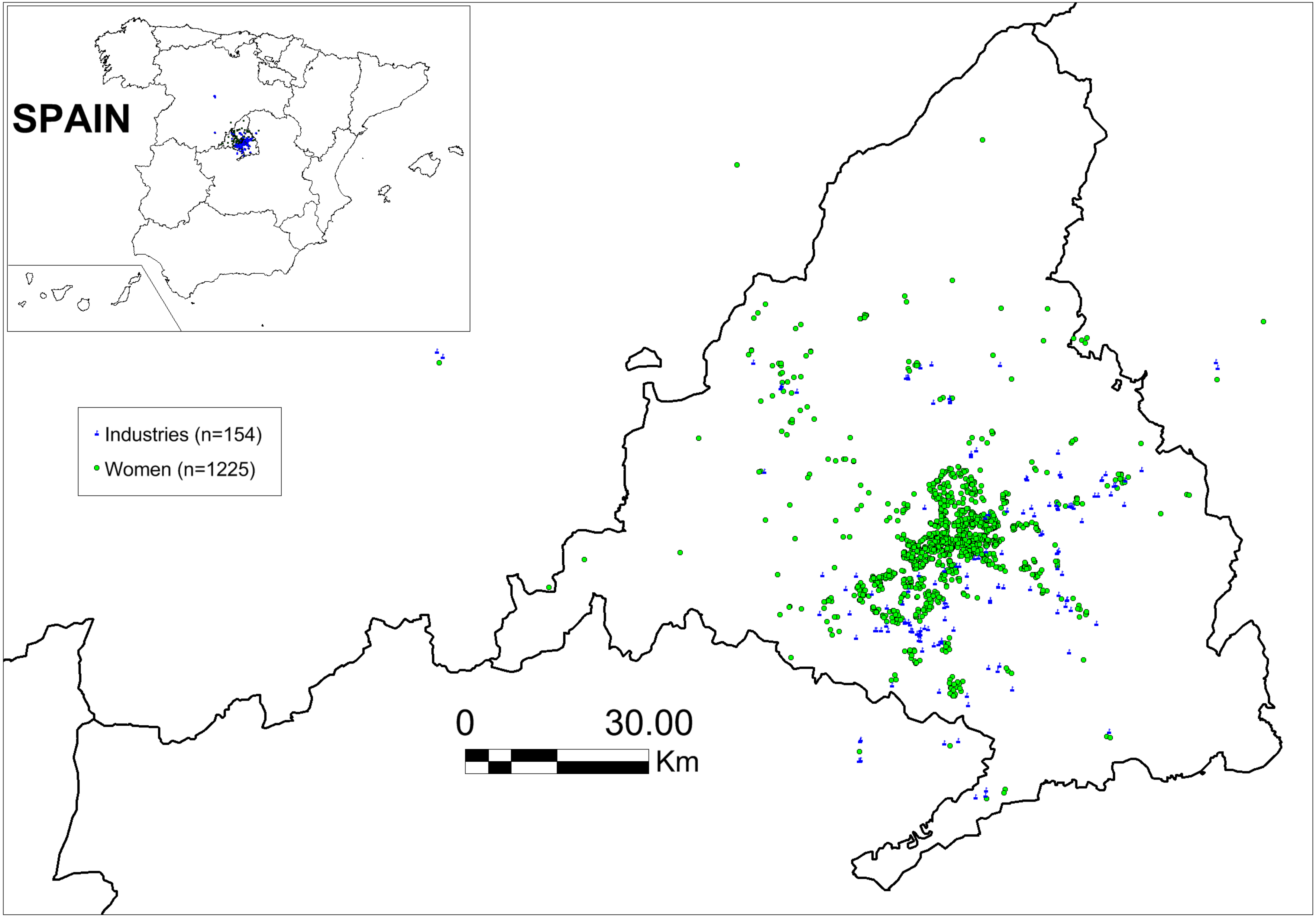
Table 3. Association between mammographic density and residential proximity to industries releasing groups of carcinogens and EDCs.

	Women residing at ≤1 km			Women residing at ≤1.5 km			Women residing at ≤2 km			Women residing at ≤2.5 km			Women residing at ≤3 km		
Groups of pollutants (no. industries)	**n**	**β[a]**	**95%CI**	**n**	**β[a]**	**95%CI**	**n**	**β[a]**	**95%CI**	**n**	**β[a]**	**95%CI**	**n**	**β[a]**	**95%CI**
IARC groups[b]															
Group 1 (98)	81	1.62	(-2.15; 5.39)	212	1.47	(-1.10; 4.04)	375	1.50	(-0.63; 3.64)	544	1.11	(-0.80; 3.03)	646	1.01	(-0.82; 2.84)
Group 2A (37)	44	0.51	(-4.38; 5.40)	102	1.43	(-2.01; 4.86)	194	1.65	(-1.00; 4.30)	306	1.24	(-1.04; 3.52)	370	1.21	(-0.96; 3.39)
Group 2B (24)	38	-1.10	(-6.28; 4.08)	82	1.68	(-2.01; 5.37)	139	2.44	(-0.54; 5.41)	203	2.59	(-0.02; 5.20)	257	2.15	(-0.24; 4.54)
EDCs groups[c]															
Metals (50)	35	3.64	(-1.89; 9.18)	84	1.46	(-2.28; 5.20)	172	0.73	(-2.04; 3.51)	274	0.87	(-1.48; 3.22)	362	0.98	(-1.21; 3.16)
Pesticides (2)	0	-	-	1	8.26	(-22.48;38.99)	3	0.85	(-17.24; 18.94)	9	3.15	(-7.20; 13.49)	16	1.25	(-6.54; 9.04)
PACs (20)	26	1.74	(-4.50; 7.97)	72	2.87	(-1.03; 6.77)	133	1.07	(-1.94; 4.09)	202	1.88	(-0.72; 4.48)	291	1.50	(-0.81; 3.80)
Plasticizers (3)	2	-7.13	(-28.85; 14.58)	5	0.95	(-13.11; 15.00)	8	-3.43	(-14.61; 7.74)	16	-3.86	(-11.89; 4.17)	25	-1.86	(-8.26; 4.55)
POPs (26)	17	2.20	(-5.44; 9.85)	42	1.93	(-3.06; 6.93)	96	0.34	(-3.09; 3.77)	160	0.71	(-2.12; 3.54)	236	0.56	(-1.92; 3.03)
Other solvents (19)	31	0.60	(-5.12; 6.33)	76	1.93	(-1.95; 5.80)	131	2.20	(-0.86; 5.27)	204	2.02	(-0.58; 4.61)	250	1.83	(-0.59; 4.25)

[a] β coefficients estimated from various multiple linear regression models (an independent model for each group of pollutants and distance), adjusted for age, education, body mass index, number of children, oral contraceptives use, previous breast biopsies, family history of breast cancer, smoking, energy intake, and alcohol consumption.

[b] IARC carcinogenic classification: Group 1: carcinogenic to humans (arsenic and compounds, cadmium and compounds, chromium and compounds, nickel and compounds, PCDD+PCDF (dioxins+furans), polychlorinated biphenyls, benzene, ethylene oxide, polycyclic aromatic hydrocarbons (PAHs), particulate matter (PM_{10}), total suspended particulate matter, and benzo(a)pyrene); Group 2A: probably carcinogenic to humans (lead and compounds, and dichloromethane); Group 2B: possibly carcinogenic to humans (hexachlorobenzene, trichloromethane, ethylbenzene, naphthalene, di-(2-ethyl hexyl) phthalate, cobalt and compounds, benzo(b)fluoranthene, benzo(k)fluoranthene, and indeno(1,2,3-cd)pyrene).

[c] Metals (arsenic and compounds, cadmium and compounds, mercury and compounds, lead and compounds, organotin compounds, and manganese); Pesticides (organotin compounds); PACs: polycyclic aromatic chemicals (anthracene, ethylene oxide, naphthalene, PAHs, fluoranthene, benzo(g,h,i)perylene, benzo(a)pyrene, benzo(b)fluoranthene, benzo(k)fluoranthene, and indeno(1,2,3-cd)pyrene); Plasticizers (C_{10-13}-chloroalkanes, and di-(2-ethyl hexyl) phthalate); POPs: persistent organic pollutants (hexachlorobenzene, PCDD+PCDF (dioxins+furans), polychlorinated biphenyls, organotin compounds, PAHs, benzo(a)pyrene, benzo(b)fluoranthene, and benzo(k)fluoranthene); Other solvents (dichloromethane, benzene, ethylbenzene, toluene, xylenes, *p*-xylene, *o*-xylene, and *m*-xylene).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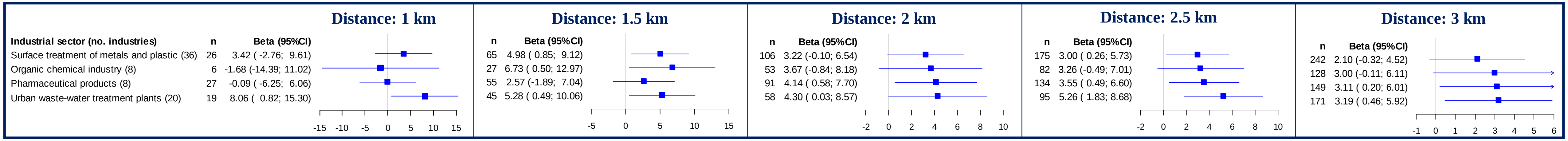
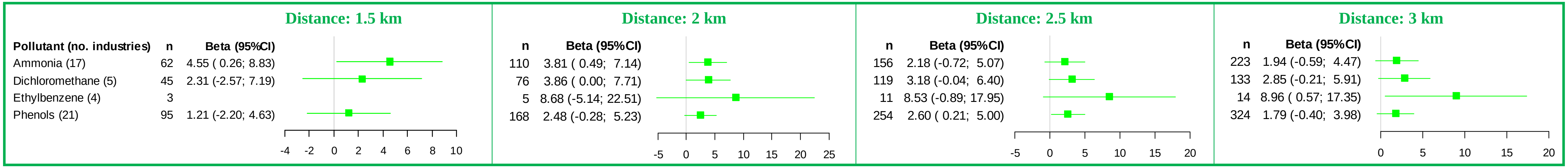


	Distance: 1 km		Distance: 1.5 km		Distance: 2 km		Distance: 2.5 km		Distance: 3 km	
Industrial sector (no. industries)	**n**	**Beta (95%CI)**	**n**	**Beta (95%CI)**	**n**	**Beta (95%CI)**	**n**	**Beta (95%CI)**	**n**	**Beta (95%CI)**
Surface treatment of metals and plastic (36)	26	3.42 (-2.76; 9.61)	65	4.98 (0.85; 9.12)	106	3.22 (-0.10; 6.54)	175	3.00 (0.26; 5.73)	242	2.10 (-0.32; 4.52)
Organic chemical industry (8)	6	-1.68 (-14.39; 11.02)	27	6.73 (0.50; 12.97)	53	3.67 (-0.84; 8.18)	82	3.26 (-0.49; 7.01)	128	3.00 (-0.11; 6.11)
Pharmaceutical products (8)	27	-0.09 (-6.25; 6.06)	55	2.57 (-1.89; 7.04)	91	4.14 (0.58; 7.70)	134	3.55 (0.49; 6.60)	149	3.11 (0.20; 6.01)
Urban waste-water treatment plants (20)	19	8.06 (0.82; 15.30)	45	5.28 (0.49; 10.06)	58	4.30 (0.03; 8.57)	95	5.26 (1.83; 8.68)	171	3.19 (0.46; 5.92)



	Distance: 1.5 km		Distance: 2 km		Distance: 2.5 km		Distance: 3 km	
Pollutant (no. industries)	**n**	**Beta (95%CI)**	**n**	**Beta (95%CI)**	**n**	**Beta (95%CI)**	**n**	**Beta (95%CI)**
Ammonia (17)	62	4.55 (0.26; 8.83)	110	3.81 (0.49; 7.14)	156	2.18 (-0.72; 5.07)	223	1.94 (-0.59; 4.47)
Dichloromethane (5)	45	2.31 (-2.57; 7.19)	76	3.86 (0.00; 7.71)	119	3.18 (-0.04; 6.40)	133	2.85 (-0.21; 5.91)
Ethylbenzene (4)	3		5	8.68 (-5.14; 22.51)	11	8.53 (-0.89; 17.95)	14	8.96 (0.57; 17.35)
Phenols (21)	95	1.21 (-2.20; 4.63)	168	2.48 (-0.28; 5.23)	254	2.60 (0.21; 5.00)	324	1.79 (-0.40; 3.98)

Residential proximity to industrial pollution and mammographic density

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Supplementary Data

Title of the manuscript: “Residential proximity to industrial pollution and mammographic density”.

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

a) Table S1, showing the association between mammographic density and proximity to industrial sectors.

b) Table S2, showing the *p*-values for the interactions between the exposure variable for each distance and potential confounders, in the first analysis (MD and proximity to all industries as a whole).

c) Table S3, showing the amounts (in kg) of carcinogens (IARC classification) and EDCs released by the facilities in the study area in 2009, grouped by industrial sector.

d) Table S4, showing the association between mammographic density and proximity to industries releasing specific pollutants.

e) Table S5, showing the risk gradient analysis a) for all industries as a whole, b) by industrial sector, c) by groups of carcinogens and EDCs, and d) by specific pollutant.

f) Table S6, showing the contribution of each characteristic (covariate) to the spatial stratified heterogeneity (SSH) of the MD (*q*-statistic values and their corresponding *p*-values).

Supplementary Data, Table S1: Association between mammographic density and residential proximity to industrial sectors.

	Women residing at ≤1 km					**Women residing at ≤1.5 km**					**Women residing at ≤2 km**					**Women residing at ≤2.5 km**					**Women residing at ≤3 km**				
Industrial sector (no. industries)	**n**	**β[a]**	**95%CI**	***p*-value**	***p-BH*[b]**	**n**	**β[a]**	**95%CI**	***p*-value**	***p-BH*[b]**	**n**	**β[a]**	**95%CI**	***p*-value**	***p-BH*[b]**	**n**	**β[a]**	**95%CI**	***p*-value**	***p-BH*[b]**	**n**	**β[a]**	**95%CI**	***p*-value**	***p-BH*[b]**
Combustion installations (6)	-	-	-	-	-	3	-1.99	(-19.84; 15.86)	0.827	0.975	18	-2.88	(-10.37; 4.61)	0.451	0.677	40	-1.32	(-6.45; 3.80)	0.612	0.726	69	-0.23	(-4.28; 3.82)	0.910	0.964
Production and processing of metals (10)	16	5.53	(-2.56; 13.62)	0.181	0.871	46	3.18	(-1.71; 8.06)	0.203	0.557	113	1.38	(-1.93; 4.70)	0.414	0.677	196	0.10	(-2.57; 2.76)	0.944	0.944	252	-0.05	(-2.50; 2.41)	0.971	0.971
Galvanization (6)	11	1.62	(-7.98; 11.22)	0.741	0.934	29	0.19	(-5.81; 6.20)	0.950	0.975	54	1.02	(-3.56; 5.60)	0.662	0.764	79	1.63	(-2.28; 5.53)	0.414	0.677	101	1.04	(-2.45; 4.54)	0.558	0.717
Surface treatment of metals and plastic (36)	26	3.42	(-2.76; 9.61)	0.278	0.871	65	4.98	(0.85; 9.12)	0.019	0.175	106	3.22	(-0.10; 6.54)	0.058	0.290	175	3.00	(0.26; 5.73)	0.032	0.192	242	2.10	(-0.32; 4.52)	0.089	0.255
Mining industry (3)	-	-	-	-	-	1	-11.88	(-42.63; 18.87)	0.449	0.748	4	8.01	(-7.61; 23.63)	0.315	0.677	7	10.55	(-1.20; 22.31)	0.079	0.267	8	7.89	(-3.10; 18.88)	0.160	0.360
Cement and lime (5)	2	-7.13	(-28.85; 14.58)	0.520	0.934	3	-8.70	(-26.45; 9.05)	0.337	0.632	4	-4.21	(-19.64; 11.21)	0.592	0.764	7	4.44	(-7.42; 16.30)	0.464	0.696	15	4.63	(-3.69; 12.96)	0.276	0.552
Glass and mineral fibers (1)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	28.53	(-2.74; 59.80)	0.074	0.267	1	28.53	(-2.74; 59.80)	0.074	0.255
Ceramic (8)	4	1.50	(-13.97; 16.97)	0.849	0.934	10	1.87	(-8.04; 11.78)	0.712	0.971	14	5.17	(-3.29; 13.63)	0.232	0.677	16	6.11	(-1.79; 14.01)	0.130	0.334	17	6.45	(-1.21; 14.11)	0.099	0.255
Organic chemical industry (8)	6	-1.68	(-14.39; 11.02)	0.795	0.934	27	6.73	(0.50; 12.97)	0.035	0.175	53	3.67	(-0.84; 8.18)	0.112	0.420	82	3.26	(-0.49; 7.01)	0.089	0.267	128	3.00	(-0.11; 6.11)	0.059	0.255
Inorganic chemical industry (2)	-	-	-	-	-	4	9.13	(-6.31; 24.58)	0.247	0.557	7	4.56	(-7.21; 16.34)	0.448	0.677	15	2.05	(-6.19; 10.28)	0.626	0.726	20	1.57	(-5.60; 8.74)	0.668	0.802
Pharmaceutical products (8)	27	-0.09	(-6.25; 6.06)	0.977	0.977	55	2.57	(-1.89; 7.04)	0.260	0.557	91	4.14	(0.58; 7.70)	0.023	0.290	134	3.55	(0.49; 6.60)	0.023	0.192	149	3.11	(0.20; 6.01)	0.037	0.255
Hazardous waste (5)	1	13.42	(-17.57; 44.40)	0.396	0.871	4	-4.83	(-20.35; 10.69)	0.542	0.813	6	0.49	(-12.26; 13.23)	0.940	0.940	12	4.65	(-4.53; 13.82)	0.321	0.677	27	5.65	(-0.57; 11.86)	0.076	0.255
Non-hazardous waste (4)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	3	-4.21	(-22.12; 13.71)	0.645	0.726	6	5.16	(-7.55; 17.87)	0.427	0.699
Disposal or recycling of animal waste (1)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	13.42	(-17.57; 44.40)	0.396	0.677	1	13.42	(-17.57; 44.40)	0.396	0.699
Urban waste-water treatment plants (20)	19	8.06	(0.82; 15.30)	0.030	0.330	45	5.28	(0.49; 10.06)	0.031	0.175	58	4.30	(0.03; 8.57)	0.049	0.290	95	5.26	(1.83; 8.68)	0.003	0.054	171	3.19	(0.46; 5.92)	0.022	0.255
Paper and wood production (2)	-	-	-	-	-	1	-20.62	(-53.14; 11.89)	0.214	0.557	2	-11.09	(-33.60; 11.42)	0.335	0.677	9	-3.29	(-13.87; 7.29)	0.543	0.726	20	-1.19	(-8.35; 5.97)	0.744	0.837
Food and beverage sector (15)	22	1.19	(-5.75; 8.12)	0.737	0.934	72	0.07	(-3.99; 4.13)	0.975	0.975	134	0.52	(-2.58; 3.62)	0.741	0.794	194	0.35	(-2.33; 3.03)	0.797	0.844	280	0.79	(-1.57; 3.15)	0.511	0.708
Surface treatment using organic solvents (13)	18	-3.58	(-10.97; 3.81)	0.343	0.871	50	-0.08	(-4.60; 4.45)	0.974	0.975	93	0.87	(-2.62; 4.36)	0.626	0.764	127	1.37	(-1.72; 4.45)	0.386	0.677	167	1.02	(-1.73; 3.78)	0.467	0.701

[a] β coefficients estimated from various multiple linear regression models (an independent model for each industrial sector and distance), adjusted for age, education, body mass index, number of children, oral contraceptives use, previous breast biopsies, family history of breast cancer, smoking, energy intake, and alcohol consumption.

[b] *p*-value adjusted by Benjamini & Hochberg's method.

Supplementary Data, Table S2: *p*-values for the interactions between the exposure variable for each distance and potential confounders, in the first analysis (MD and proximity to all industries as a whole).

	Distance				
Characteristic	**≤1 km**	**≤1.5 km**	**≤2 km**	**≤2.5 km**	**≤3 km**
Age	0.992	0.758	0.667	0.257	0.242
Education	0.978	0.717	0.647	0.176	0.275
BMI	0.193	0.356	0.182	0.240	0.355
Number of children	0.086	0.067	0.137	0.144	0.201
Previous breast biopsies	0.987	0.783	0.476	0.478	0.620
Family history of breast cancer	0.546	0.043	0.063	0.095	0.020
Energy intake	0.300	0.798	0.865	0.624	0.945
Use of oral contraceptives	0.600	0.301	0.562	0.336	0.431
Tobacco consumption	0.974	0.461	0.398	0.253	0.406
Alcohol consumption	0.539	0.659	0.364	0.341	0.335

Supplementary Data, Table S3: Amounts (in kg) of carcinogens (IARC classification) and EDCs released by the facilities in the study area in 2009, grouped by industrial sector.

		IARC groups[a]			EDCs groups[b]					
Industrial sector	E-PRTR category	Group 1	Group 2A	Group 2B	Metals	Pesticides	PACs	Plasticizers	POPs	Other solvents
Combustion installations	1.c	44,100	86	0	86	0	17	0	17	0
Production and processing of metals	2.a, 2.b, 2.c.i, 2.c.ii, 2.d, 2.e	116,003	6,992	4	7,129	0	672	0	676	3,810
Galvanization	2.c.iii	2,945	8	0	8	0	0	0	0.0000004	0
Surface treatment of metals and plastic	2.f	5,555	9	6	11	0.005	6	28	0.02	0.3
Mining industry	3.a, 3.b	38,204	0	0	0	0	0	0	0	0
Cement and lime	3.c, 3.d	105,361	0.2	1.5	0.5	0	1.4	0.08	0.0004	13
Glass and mineral fibers	3.e, 3.f	10,890	0	3	2	0	0	0	0	79
Ceramic	3.g	44,400	100	0.3	137	0	0.01	0	0.0000002	49
Organic chemical industry	4.a	333	86	0.001	1.1	0	0.05	0	0.0002	0
Inorganic chemical industry	4.b	0	0	0	0	0	0	0	0	0
Pharmaceutical products	4.e	51	269,271	91,704	7	0.00	0.01	0	0.01	269,281
Hazardous waste	5.a, 5.b	2,975	26	0.3	29	0.004	88	0	88	0.9
Non-hazardous waste	5.c, 5.d	7,962	6	0.03	8	0	0	0	0.00001	0
Disposal or recycling of animal waste	5.e	256	0	0	0	0	0.6	0	0.6	0
Urban waste-water treatment plants	5.f, 5.g	0	0	0	0	0	0	0	0	0
Paper and wood production	6.a, 6.b, 6.c	0	0	0	0	0	0	0	0	0
Food and beverage sector	8.a, 8.b, 8.c	830	1.0	0.01	8	0	0.05	0	0.01	0.3
Surface treatment using organic solvents	9.c	14,273	122	201	0.1	0	200	0	0.01	122
TOTAL		**394,139**	**276,706**	**91,920**	**7,427**	**0**	**985**	**28**	**781**	**273,356**

[a] IARC carcinogenic classification: Group 1: carcinogenic to humans (arsenic and compounds, cadmium and compounds, chromium and compounds, nickel and compounds, PCDD+PCDF (dioxins+furans), polychlorinated biphenyls, benzene, ethylene oxide, polycyclic aromatic hydrocarbons (PAHs), particulate matter (PM_{10}), total suspended particulate matter, and benzo(a)pyrene); Group 2A: probably carcinogenic to humans (lead and compounds, and dichloromethane); Group 2B: possibly carcinogenic to humans (hexachlorobenzene, trichloromethane, ethylbenzene, naphthalene, di-(2-ethyl hexyl) phthalate, cobalt and compounds, benzo(b)fluoranthene, benzo(k)fluoranthene, and indeno(1,2,3-cd)pyrene).

[b] Metals (arsenic and compounds, cadmium and compounds, mercury and compounds, lead and compounds, organotin compounds, and manganese); Pesticides (organotin compounds); PACs: polycyclic aromatic chemicals (anthracene, ethylene oxide, naphthalene, PAHs, fluoranthene, benzo(g,h,i)perylene, benzo(a)pyrene, benzo(b)fluoranthene, benzo(k)fluoranthene, and indeno(1,2,3-cd)pyrene); Plasticizers ($C_{10\text{-}13}$-chloroalkanes, and di-(2-ethyl hexyl) phthalate); POPs: persistent organic pollutants (hexachlorobenzene, PCDD+PCDF (dioxins+furans), polychlorinated biphenyls, organotin compounds, PAHs, benzo(a)pyrene, benzo(b)fluoranthene, and benzo(k)fluoranthene); Other solvents (dichloromethane, benzene, ethylbenzene, toluene, xylenes, *p*-xylene, *o*-xylene, and *m*-xylene).

Supplementary Data, Table S4: Association between mammographic density and residential proximity to industries releasing specific pollutants.

	Women residing at ≤1 km					Women residing at ≤1.5 km					Women residing at ≤2 km					Women residing at ≤2.5 km					Women residing at ≤3 km				
Industrial pollutant (no. Industries)	**n**	**β[a]**	**95%CI**	***p*-value**	***p*-BH[b]**	**n**	**β[a]**	**95%CI**	***p*-value**	***p*-BH[b]**	**n**	**β[a]**	**95%CI**	***p*-value**	***p*-BH[b]**	**n**	**β[a]**	**95%CI**	***p*-value**	***p*-BH[b]**	**n**	**β[a]**	**95%CI**	***p*-value**	***p*-BH[b]**
Ammonia (17)	20	0.05	(-7.08; 7.19)	0.989	0.992	62	4.55	(0.26; 8.83)	0.038	0.685	110	3.81	(0.49; 7.14)	0.025	0.479	156	2.18	(-0.72; 5.07)	0.141	0.456	223	1.94	(-0.59; 4.47)	0.133	0.518
Anthracene (1)	2	-7.13	(-28.85; 14.58)	0.520	0.918	2	-7.13	(-28.85; 14.58)	0.520	0.889	2	-7.13	(-28.85; 14.58)	0.520	0.748	2	-7.13	(-28.85; 14.58)	0.520	0.650	2	-7.13	(-28.85; 14.58)	0.520	0.650
Antimony (3)	2	5.65	(-16.26; 27.57)	0.613	0.918	2	5.65	(-16.26; 27.57)	0.613	0.889	3	6.93	(-10.92; 24.78)	0.447	0.659	3	6.93	(-10.92; 24.78)	0.447	0.596	5	9.89	(-3.86; 23.65)	0.159	0.518
Arsenic and compounds (27)	25	2.84	(-3.62; 9.30)	0.389	0.918	62	0.57	(-3.69; 4.83)	0.794	0.938	126	-0.08	(-3.23; 3.06)	0.959	0.976	205	-0.14	(-2.75; 2.47)	0.915	0.931	263	0.36	(-2.08; 2.79)	0.774	0.787
Benzene (7)	6	-2.16	(-14.91; 10.58)	0.740	0.931	12	-2.73	(-11.83; 6.37)	0.557	0.889	28	-3.97	(-9.93; 2.00)	0.193	0.479	49	-2.26	(-6.90; 2.39)	0.342	0.526	64	-0.89	(-5.04; 3.27)	0.676	0.723
Benzo(a)pyrene (2)	7	8.15	(-3.66; 19.97)	0.177	0.918	14	0.55	(-7.86; 8.97)	0.898	0.938	17	-0.12	(-7.83; 7.59)	0.976	0.976	27	1.15	(-5.06; 7.35)	0.717	0.782	49	1.53	(-3.14; 6.20)	0.522	0.650
Benzo(b)fluoranthene (5)	7	8.15	(-3.66; 19.97)	0.177	0.918	15	0.99	(-7.17; 9.16)	0.811	0.938	26	0.46	(-5.82; 6.74)	0.886	0.967	43	3.11	(-1.87; 8.09)	0.222	0.456	76	2.36	(-1.47; 6.19)	0.228	0.518
Benzo(g,h,i)perylene (2)	2	10.60	(-11.26; 32.46)	0.343	0.918	8	-8.52	(-19.46; 2.43)	0.128	0.685	9	-8.68	(-18.98; 1.62)	0.099	0.479	19	-2.40	(-9.61; 4.81)	0.514	0.650	41	-0.02	(-5.02; 4.99)	0.994	0.994
Benzo(k)fluoranthene (1)	6	7.58	(-5.22; 20.38)	0.247	0.918	8	9.10	(-1.98; 20.18)	0.108	0.685	11	5.86	(-3.71; 15.43)	0.231	0.505	11	5.86	(-3.71; 15.43)	0.231	0.456	11	5.86	(-3.71; 15.43)	0.231	0.518
$C_{10\text{-}13}$-chloroalkanes (1)	-	-	-	-	-	1	-7.17	(-38.00; 23.65)	0.648	0.906	1	-7.17	(-38.00; 23.65)	0.648	0.850	1	-7.17	(-38.00; 23.65)	0.648	0.778	1	-7.17	(-38.00; 23.65)	0.648	0.706
Cadmium and compounds (26)	13	3.51	(-5.21; 12.22)	0.431	0.918	38	0.51	(-4.72; 5.74)	0.849	0.938	77	0.24	(-3.55; 4.03)	0.901	0.967	117	0.35	(-2.84; 3.54)	0.830	0.889	144	0.85	(-2.10; 3.80)	0.574	0.687
Carbon dioxide (111)	102	1.69	(-1.75; 5.13)	0.336	0.918	244	1.44	(-1.03; 3.90)	0.253	0.685	407	1.23	(-0.85; 3.32)	0.247	0.520	574	1.48	(-0.41; 3.38)	0.126	0.456	702	1.13	(-0.66; 2.92)	0.215	0.518
Carbon monoxide (104)	98	2.04	(-1.43; 5.52)	0.250	0.918	220	2.02	(-0.54; 4.58)	0.122	0.685	366	1.59	(-0.56; 3.73)	0.148	0.479	521	1.54	(-0.41; 3.48)	0.122	0.456	656	1.27	(-0.55; 3.09)	0.172	0.518
Chemical oxygen demand (COD) (79)	95	1.16	(-2.36; 4.68)	0.518	0.918	216	2.25	(-0.32; 4.81)	0.086	0.685	366	1.65	(-0.49; 3.79)	0.132	0.479	504	1.20	(-0.77; 3.18)	0.233	0.456	591	0.90	(-0.98; 2.78)	0.347	0.518
Chlorides (72)	83	1.61	(-2.14; 5.35)	0.401	0.918	203	1.79	(-0.84; 4.42)	0.183	0.685	355	1.54	(-0.62; 3.71)	0.163	0.479	494	1.37	(-0.59; 3.33)	0.172	0.456	600	1.20	(-0.65; 3.05)	0.204	0.518
Chlorine and inorganic compounds (33)	27	3.40	(-2.82; 9.62)	0.285	0.918	69	3.05	(-1.02; 7.12)	0.143	0.685	141	2.21	(-0.81; 5.23)	0.151	0.479	214	0.91	(-1.69; 3.51)	0.491	0.640	267	1.07	(-1.34; 3.47)	0.384	0.520
Chromium and compounds (47)	44	-1.08	(-6.00; 3.84)	0.667	0.918	146	0.43	(-2.48; 3.35)	0.771	0.938	260	1.29	(-1.09; 3.68)	0.287	0.564	384	1.33	(-0.80; 3.46)	0.220	0.456	464	1.06	(-0.94; 3.06)	0.299	0.518
Cobalt (4)	3	-1.60	(-19.55; 16.35)	0.862	0.964	3	-1.60	(-19.55; 16.35)	0.862	0.938	4	1.17	(-14.21; 16.64)	0.882	0.967	4	1.17	(-14.29; 16.64)	0.882	0.928	6	5.62	(-6.99; 18.23)	0.383	0.520
Copper and compounds (60)	72	0.02	(-3.90; 3.94)	0.992	0.992	186	1.00	(-1.68; 3.69)	0.464	0.868	323	0.90	(-1.31; 3.11)	0.425	0.655	444	1.11	(-0.91; 3.12)	0.282	0.483	546	0.92	(-0.99; 2.83)	0.343	0.518
Cyanides (15)	20	1.41	(-5.58; 8.41)	0.693	0.918	40	2.09	(-2.99; 7.17)	0.421	0.842	63	2.78	(-1.37; 6.92)	0.189	0.479	118	2.41	(-0.79; 5.61)	0.141	0.456	163	2.46	(-0.37; 5.28)	0.089	0.518
Di-(2-ethyl hexyl) phthalate (2)	2	-7.13	(-28.85; 14.58)	0.520	0.918	4	3.04	(-12.66; 18.74)	0.705	0.929	7	-2.83	(-14.80; 9.14)	0.643	0.850	15	-3.63	(-11.96; 4.69)	0.393	0.548	24	-1.64	(-8.18; 4.90)	0.623	0.691
Dichloromethane (5)	21	-1.74	(-8.61; 5.13)	0.619	0.918	45	2.31	(-2.57; 7.19)	0.354	0.750	76	3.86	(0.00; 7.71)	0.050	0.479	119	3.18	(-0.04; 6.40)	0.053	0.456	133	2.85	(-0.21; 5.91)	0.068	0.518
Ethylbenzene (4)	1	13.42	(-17.57; 44.40)	0.396	0.918	3	5.00	(-12.84; 22.84)	0.583	0.889	5	8.68	(-5.14; 22.51)	0.219	0.505	11	8.53	(-0.89; 17.95)	0.077	0.456	14	8.96	(0.57; 17.35)	0.037	0.518
Ethylene oxide (1)	3	0.13	(-17.83; 18.08)	0.989	0.992	19	6.40	(-0.89; 13.69)	0.086	0.685	32	3.88	(-1.82; 9.59)	0.182	0.479	51	3.22	(-1.38; 7.81)	0.171	0.456	67	3.35	(-0.73; 7.43)	0.108	0.518
Fluoranthene (4)	1	11.37	(-19.68; 42.42)	0.473	0.918	7	-7.90	(-19.65; 3.85)	0.188	0.685	15	-3.22	(-11.29; 4.84)	0.433	0.655	32	2.23	(-3.43; 7.88)	0.440	0.596	65	1.89	(-2.18; 5.96)	0.364	0.518
Fluorides (42)	54	1.70	(-2.76; 6.16)	0.456	0.918	143	1.71	(-1.25; 4.68)	0.258	0.685	249	1.09	(-1.31; 3.48)	0.373	0.611	377	1.35	(-0.75; 3.45)	0.209	0.456	476	1.33	(-0.66; 3.33)	0.189	0.518
Fluorine and inorganic compounds (15)	9	1.46	(-8.94; 11.87)	0.783	0.936	23	1.00	(-5.61; 7.61)	0.767	0.938	44	0.35	(-4.51; 5.21)	0.888	0.967	67	0.78	(-3.27; 4.82)	0.707	0.782	84	0.98	(-2.71; 4.67)	0.604	0.691
Halogenated organic compounds (39)	74	1.19	(-2.74; 5.11)	0.554	0.918	165	1.89	(-0.92; 4.71)	0.188	0.685	295	1.79	(-0.50; 4.08)	0.125	0.479	417	1.95	(-0.12; 4.03)	0.065	0.456	491	1.29	(-0.66; 3.25)	0.196	0.518
Hexachlorobenzene (2)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2	4.71	(-17.28; 26.69)	0.675	0.782	6	3.25	(-9.42; 15.91)	0.616	0.691
Hydrochlorofluorocarbons (2)	-	-	-	-	-	1	3.74	(-27.01; 34.50)	0.812	0.938	2	17.13	(-4.72; 38.98)	0.125	0.479	6	5.71	(-6.97; 18.39)	0.378	0.540	11	1.47	(-7.91; 10.86)	0.759	0.785
Hydrofluorocarbons (1)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-9.25	(-40.22; 21.71)	0.558	0.681
Hydrogen cyanide (4)	13	1.28	(-7.33; 9.90)	0.770	0.936	26	2.90	(-3.33; 9.14)	0.362	0.750	42	2.56	(-2.43; 7.55)	0.315	0.581	90	1.61	(-1.94; 5.16)	0.375	0.540	121	1.71	(-1.44; 4.86)	0.288	0.518
Indeno(1,2,3-cd)pyrene (1)	-	-	-	-	-	-	-	-	-	-	7	-0.22	(-11.95; 11.51)	0.971	0.976	13	5.64	(-3.10; 14.38)	0.207	0.456	19	2.59	(-4.69; 9.87)	0.486	0.631
Lead and compounds (33)	23	2.81	(-3.86; 9.48)	0.410	0.918	61	0.85	(-3.43; 5.14)	0.696	0.929	127	0.62	(-2.51; 3.75)	0.699	0.877	207	0.50	(-2.09; 3.09)	0.706	0.782	276	1.05	(-1.35; 3.44)	0.392	0.520
Manganese (7)	3	-1.60	(-19.55; 16.35)	0.862	0.964	4	1.60	(-13.96; 17.17)	0.840	0.938	8	4.47	(-6.53; 15.47)	0.426	0.655	14	6.00	(-2.30; 14.30)	0.157	0.456	23	4.21	(-2.30; 10.71)	0.205	0.518
Mercury and compounds (33)	17	4.42	(-3.32; 12.17)	0.264	0.918	41	1.42	(-3.68; 6.53)	0.585	0.889	83	0.82	(-2.90; 4.54)	0.667	0.856	138	1.41	(-1.64; 4.47)	0.365	0.540	181	1.38	(-1.37; 4.13)	0.325	0.518
Methane (41)	43	3.60	(-1.38; 8.59)	0.157	0.918	115	2.05	(-1.22; 5.33)	0.220	0.685	195	1.44	(-1.20; 4.07)	0.286	0.564	277	1.75	(-0.59; 4.09)	0.143	0.456	395	1.24	(-0.84; 3.32)	0.242	0.518
Naphthalene (12)	14	-1.85	(-10.19; 6.50)	0.665	0.918	36	0.27	(-5.06; 5.60)	0.922	0.938	64	0.54	(-3.58; 4.65)	0.798	0.961	89	2.52	(-1.11; 6.14)	0.175	0.456	130	2.56	(-0.52; 5.65)	0.104	0.518
Nickel and compounds (53)	42	1.24	(-3.76; 6.23)	0.628	0.918	126	1.22	(-1.85; 4.29)	0.437	0.845	227	1.88	(-0.58; 4.34)	0.135	0.479	333	1.72	(-0.46; 3.91)	0.123	0.456	417	1.49	(-0.55; 3.54)	0.152	0.518
Nitrogen oxides (116)	108	1.78	(-1.58; 5.15)	0.298	0.918	240	1.30	(-1.18; 3.78)	0.303	0.685	401	1.02	(-1.07; 3.12)	0.339	0.588	566	1.28	(-0.62; 3.18)	0.187	0.456	695	1.02	(-0.78; 2.81)	0.266	0.518
Nitrous oxide (31)	34	3.92	(-1.57; 9.41)	0.162	0.918	86	2.01	(-1.62; 5.63)	0.279	0.685	131	1.84	(-1.17; 4.85)	0.231	0.505	186	2.57	(-0.06; 5.19)	0.056	0.456	293	1.85	(-0.39; 4.09)	0.106	0.518
NMVOC[c] (36)	32	-2.13	(-7.70; 3.44)	0.454	0.918	93	2.13	(-1.36; 5.61)	0.232	0.685	175	1.94	(-0.75; 4.63)	0.158	0.479	280	1.38	(-0.93; 3.70)	0.242	0.456	340	1.57	(-0.59; 3.74)	0.155	0.518
Organotin compounds (2)	-	-	-	-	-	1	8.26	(-22.48; 38.99)	0.599	0.889	3	0.85	(-17.24; 18.94)	0.927	0.976	9	3.15	(-7.20; 13.49)	0.551	0.675	16	1.25	(-6.54; 9.04)	0.754	0.785
Particulate matter (PM_{10}) (28)	19	4.77	(-2.50; 12.04)	0.199	0.918	57	1.00	(-3.40; 5.40)	0.656	0.906	119	0.46	(-2.76; 3.68)	0.781	0.960	185	1.45	(-1.26; 4.16)	0.296	0.485	258	1.13	(-1.29; 3.54)	0.362	0.518
PCDD+PCDF (dioxins+furans) (16)	8	0.88	(-10.14; 11.90)	0.876	0.964	28	3.16	(-2.88; 9.20)	0.306	0.685	74	1.10	(-2.77; 4.97)	0.578	0.812	121	0.64	(-2.53; 3.81)	0.691	0.782	164	0.72	(-2.12; 3.56)	0.621	0.691
Phenols (21)	36	-2.44	(-7.77; 2.88)	0.369	0.918	95	1.21	(-2.20; 4.63)	0.487	0.883	168	2.48	(-0.28; 5.23)	0.078	0.479	254	2.60	(0.21; 5.00)	0.033	0.456	324	1.79	(-0.40; 3.98)	0.109	0.518
Polychlorinated biphenyls (1)	1	7.52	(-24.78; 39.82)	0.648	0.918	5	-0.82	(-15.12; 13.47)	0.910	0.938	7	-3.19	(-15.23; 8.86)	0.604	0.829	16	-0.49	(-8.38; 7.40)	0.903	0.931	27	-2.96	(-9.16; 3.25)	0.351	0.518
Polycyclic aromatic hydrocarbons (14)	13	2.44	(-6.27; 11.16)	0.583	0.918	30	-0.38	(-6.23; 5.47)	0.899	0.938	65	0.43	(-3.74; 4.59)	0.841	0.967	118	2.26	(-0.95; 5.46)	0.168	0.456	186	1.25	(-1.44; 3.94)	0.363	0.518
p-xylene / *o*-xylene / *m*-xylene (1)	1	-16.22	(-47.32; 14.89)	0.307	0.918	1	-16.22	(-47.32; 14.89)	0.307	0.685	1	-16.22	(-47.32; 14.89)	0.307	0.581	1	-16.22	(-47.32; 14.89)	0.307	0.485	1	-16.22	(-47.32; 14.89)	0.307	0.518
Sulfur hexafluoride (1)	3	0.13	(-17.83; 18.08)	0.989	0.992	19	6.40	(-0.89; 13.69)	0.086	0.685	32	3.88	(-1.82; 9.59)	0.182	0.479	51	3.22	(-1.38; 7.81)	0.171	0.456	67	3.35	(-0.73; 7.43)	0.108	0.518
Sulfur oxides (64)	76	-0.09	(-3.95; 3.77)	0.963	0.992	185	1.81	(-0.91; 4.54)	0.193	0.685	319	1.48	(-0.76; 3.72)	0.195	0.479	461	1.19	(-0.81; 3.19)	0.243	0.456	571	1.13	(-0.77; 3.02)	0.244	0.518
Toluene (10)	20	-1.53	(-8.61; 5.55)	0.671	0.918	54	1.20	(-3.29; 5.69)	0.600	0.889	86	3.22	(-0.45; 6.89)	0.086	0.479	136	2.73	(-0.30; 5.76)	0.077	0.456	170	2.37	(-0.39; 5.13)	0.093	0.518
Total nitrogen (74)	84	1.10	(-2.65; 4.85)	0.565	0.918	207	1.62	(-1.00; 4.24)	0.226	0.685	361	1.50	(-0.67; 3.66)	0.176	0.479	497	1.47	(-0.50; 3.45)	0.143	0.456	605	1.36	(-0.50; 3.21)	0.152	0.518
Total organic carbon (99)	105	1.26	(-2.13; 4.66)	0.466	0.918	245	2.21	(-0.26; 4.68)	0.080	0.685	413	1.38	(-0.70; 3.47)	0.193	0.479	560	1.11	(-0.81; 3.02)	0.258	0.469	667	1.16	(-0.66; 2.99)	0.212	0.518
Total organic carbon (air) (39)	39	0.87	(-4.34; 6.07)	0.745	0.931	96	2.80	(-0.64; 6.23)	0.111	0.685	173	2.31	(-0.40; 5.02)	0.095	0.479	240	1.89	(-0.52; 4.29)	0.124	0.456	284	1.09	(-1.18; 3.36)	0.346	0.518
Total phosphorus (74)	88	2.24	(-1.41; 5.89)	0.230	0.918	212	2.21	(-0.37; 4.79)	0.094	0.685	340	1.64	(-0.55; 3.83)	0.143	0.479	489	1.97	(-0.02; 3.95)	0.052	0.456	630	1.56	(-0.27; 3.40)	0.095	0.518
Total suspended particulate matter (53)	42	3.13	(-1.95; 8.22)	0.228	0.918	111	0.87	(-2.45; 4.19)	0.607	0.889	213	1.20	(-1.39; 3.79)	0.364	0.611	364	1.22	(-0.95; 3.38)	0.271	0.478	468	1.04	(-0.99; 3.06)	0.317	0.518
Trichloromethane (6)	24	-5.21	(-11.62; 1.20)	0.111	0.918	55	0.12	(-4.20; 4.54)	0.939	0.939	96	2.56	(-0.90; 6.02)	0.147	0.479	139	2.91	(-0.10; 5.91)	0.058	0.456	162	2.76	(-0.07; 5.59)	0.057	0.518
Vanadium (3)	1	2.94	(-28.05; 33.92)	0.853	0.964	1	2.94	(-28.05; 33.92)	0.853	0.938	1	2.94	(-28.05; 33.92)	0.853	0.967	4	-0.17	(-15.61; 15.28)	0.983	0.983	11	4.38	(-5.09; 13.85)	0.365	0.518
Xylenes (6)	8	5.28	(-5.81; 16.38)	0.351	0.918	12	5.97	(-3.13; 15.07)	0.199	0.685	17	5.24	(-2.43; 12.91)	0.181	0.479	22	5.01	(-1.80; 11.81)	0.150	0.456	25	5.68	(-0.76; 12.11)	0.084	0.518
Zinc and compounds (80)	85	0.72	(-2.96; 4.40)	0.701	0.918	209	1.35	(-1.24; 3.94)	0.307	0.685	365	1.05	(-1.09; 3.19)	0.335	0.588	504	1.02	(-0.93; 2.97)	0.306	0.485	596	1.06	(-0.79; 2.92)	0.262	0.518

[a] β coefficients estimated from various multiple linear regression models (an independent model for each specific pollutant and distance), adjusted for age, education, body mass index, number of children, oral contraceptives use, previous breast biopsies, family history of breast cancer, smoking, energy intake, and alcohol consumption.

[b] *p*-value adjusted by Benjamini & Hochberg's method.

[c] Non-methane volatile organic compounds.

Supplementary Data, Table S5: Risk gradient analysis a) for all industries as a whole, b) by industrial sector, c) by groups of carcinogens and EDCs, and d) by specific pollutant.

a) RISK GRADIENT ANALYSIS FOR ALL INDUSTRIES AS A WHOLE		
Industries (no. industries)	**β^{a}**	***p*-trend**
All industries (154)	0.34	0.178

b) RISK GRADIENT ANALYSIS BY INDUSTRIAL SECTOR			
Industrial sector (no. industries)	**β^{b}**	***p*-trend**	***p*-BH^{e}**
Combustion installations (6)	-0.41	0.681	0.839
Production and processing of metals (10)	0.18	0.682	0.839
Galvanization (6)	0.29	0.622	0.839
Surface treatment of metals and plastic (36)	0.84	0.043	0.208
Mining industry (3)	2.94	0.174	0.557
Cement and lime (5)	0.11	0.946	0.946
Ceramic (8)	1.22	0.247	0.659
Organic chemical industry (8)	1.15	0.052	0.208
Inorganic chemical industry (2)	1.06	0.471	0.837
Pharmaceutical products (8)	0.86	0.052	0.208
Hazardous waste (5)	1.48	0.309	0.706
Non-hazardous waste (4)	1.27	0.761	0.870
Urban waste-water treatment plants (20)	1.30	0.009	0.144
Paper and wood production (2)	-1.88	0.372	0.744
Food and beverage sector (15)	0.07	0.869	0.927
Surface treatment using organic solvents (13)	0.21	0.649	0.839

c) RISK GRADIENT ANALYSIS BY GROUPS OF CARCINOGENS AND ECDs			
Groups of pollutants (no. industries)	**β^{c}**	***p*-trend**	***p*-BH^{e}**
IARC groups			
Group 1 (98)	0.28	0.302	0.449
Group 2A (37)	0.26	0.449	0.449
Group 2B (24)	0.49	0.195	0.449
EDCs groups			
Metals (50)	0.16	0.660	0.660
Pesticides (2)	0.95	0.634	0.660
PACs (20)	0.48	0.226	0.660
Plasticizers (3)	-0.94	0.467	0.660
POPs (26)	0.21	0.650	0.660
Other solvents (19)	0.53	0.175	0.660

d) RISK GRADIENT ANALYSIS BY SPECIFIC POLLUTANT			
Industrial pollutant (no. industries)	**β^{d}**	***p*-trend**	***p*-BH^{e}**
Ammonia (17)	0.77	0.073	0.661
Antimony (3)	1.87	0.366	0.673
Arsenic and compounds (27)	-0.04	0.920	0.920
Benzene (7)	-0.64	0.410	0.684
Benzo(a)pyrene (2)	0.47	0.586	0.722
Benzo(b)fluoranthene (5)	0.71	0.345	0.661
Benzo(g,h,i)perylene (2)	-0.74	0.508	0.684
Benzo(k)fluoranthene (1)	1.27	0.263	0.661
Cadmium and compounds (26)	0.13	0.797	0.826
Carbon dioxide (111)	0.30	0.252	0.661
Carbon monoxide (104)	0.33	0.214	0.661
Chemical oxygen demand (COD) (79)	0.38	0.157	0.661
Chlorides (72)	0.33	0.224	0.661
Chlorine and inorganic compounds (33)	0.41	0.299	0.661
Chromium and compounds (47)	0.15	0.633	0.723
Cobalt (4)	0.46	0.794	0.826
Copper and compounds (60)	0.18	0.528	0.684
Cyanides (15)	0.62	0.211	0.661
Di-(2-ethyl hexyl) phthalate (2)	-0.87	0.524	0.684
Dichloromethane (5)	0.81	0.096	0.661
Ethylbenzene (4)	2.95	0.068	0.661
Ethylene oxide (1)	1.11	0.135	0.661
Fluoranthene (4)	0.25	0.794	0.826
Fluorides (42)	0.24	0.443	0.684
Fluorine and inorganic compounds (15)	0.21	0.738	0.809
Halogenated organic compounds (39)	0.47	0.103	0.661
Hexachlorobenzene (2)	2.22	0.634	0.723
Hydrochlorofluorocarbons (2)	1.85	0.437	0.684
Hydrogen cyanide (4)	0.57	0.329	0.661
Indeno(1,2,3-cd)pyrene (1)	1.11	0.516	0.684
Lead and compounds (33)	0.09	0.827	0.842
Manganese (7)	1.42	0.269	0.661
Mercury and compounds (33)	0.34	0.478	0.684
Methane (41)	0.42	0.205	0.661
Naphthalene (12)	0.43	0.414	0.684
Nickel and compounds (53)	0.37	0.253	0.661
Nitrogen oxides (116)	0.24	0.347	0.661
Nitrous oxide (31)	0.55	0.138	0.661
Non-methane volatile organic compounds (36)	0.33	0.348	0.661
Organotin compounds (2)	0.95	0.634	0.723
Particulate matter (PM_{10}) (28)	0.32	0.455	0.684
PCDD+PCDF (dioxins+furans) (16)	0.29	0.585	0.722
Phenols (21)	0.50	0.158	0.661
Polychlorinated biphenyls (1)	-0.72	0.595	0.722
Polycyclic aromatic hydrocarbons (14)	0.44	0.400	0.684
Sulfur hexafluoride (1)	1.11	0.135	0.661
Sulfur oxides (64)	0.27	0.340	0.661
Toluene (10)	0.69	0.127	0.661
Total nitrogen (74)	0.29	0.290	0.661
Total organic carbon (99)	0.30	0.243	0.661
Total organic carbon (air) (39)	0.54	0.124	0.661
Total phosphorus (74)	0.38	0.161	0.661
Total suspended particulate matter (53)	0.24	0.478	0.684
Trichloromethane (6)	0.48	0.282	0.661
Vanadium (3)	1.06	0.663	0.741
Xylenes (6)	1.40	0.125	0.661
Zinc and compounds (80)	0.19	0.493	0.684

[a] β coefficient estimated from a single multiple linear regression model, adjusted for age, education, body mass index, number of children, oral contraceptives use, previous breast biopsies, family history of breast cancer, smoking, energy intake, and alcohol consumption.

[b] β coefficients estimated from various multiple linear regression models (an independent model for each industrial sector), adjusted for age, education, body mass index, number of children, oral contraceptives use, previous breast biopsies, family history of breast cancer, smoking, energy intake, and alcohol consumption.

[c] β coefficients estimated from various multiple linear regression models (an independent model for each group of pollutants), adjusted for age, education, body mass index, number of children, oral contraceptives use, previous breast biopsies, family history of breast cancer, smoking, energy intake, and alcohol consumption.

[d] β coefficients estimated from various multiple linear regression models (an independent model for each specific pollutant), adjusted for age, education, body mass index, number of children, oral contraceptives use, previous breast biopsies, family history of breast cancer, smoking, energy intake, and alcohol consumption.

[e] *p*-trend adjusted by Benjamini & Hochberg's method.

Supplementary Data, Table S6: Contribution of each characteristic (covariate) to the spatial stratified heterogeneity (SSH) of the MD (*q*-statistic values and their corresponding *p*-values).

	Distance									
	≤1 km		**≤1.5 km**		**≤2 km**		**≤2.5 km**		**≤3 km**	
Characteristic	***q*-statistic**	***p*-value**	***q*-statistic**	***p*-value**	***q*-statistic**	***p*-value**	***q*-statistic**	***p*-value**	***q*-statistic**	***p*-value**
Age	0.02354	0.617	0.01737	0.700	0.01621	0.489	0.01086	0.686	0.01312	0.429
Education	0.01336	0.124	0.01186	0.074	0.01054	0.051	0.00610	0.129	0.00624	0.104
Body mass index (BMI)	0.23724	<0.001	0.23396	<0.001	0.23713	<0.001	0.23552	<0.001	0.23660	<0.001
Number of children	0.00483	0.620	0.00833	0.267	0.01052	0.080	0.01354	0.015	0.01479	0.005
Previous breast biopsies	0.02620	0.008	0.02197	0.006	0.02778	<0.001	0.02471	<0.001	0.02165	<0.001
Family history of breast cancer	0.00170	0.861	0.00052	0.947	0.00004	0.994	0.00039	0.936	0.00078	0.845
Energy intake	0.00156	0.620	0.00101	0.681	0.00176	0.440	0.00259	0.242	0.00246	0.223
Use of oral contraceptives	0.01443	0.077	0.00928	0.147	0.00891	0.095	0.00613	0.166	0.00826	0.053
Tobacco consumption	0.00467	0.246	0.00170	0.533	0.00242	0.336	0.00144	0.466	0.00128	0.469
Alcohol consumption	0.00094	0.854	0.00055	0.891	0.00099	0.773	0.00095	0.750	0.00048	0.852