Residential proximity to industrial pollution and mammographic density

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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; PAHs, Polycyclic aromatic hydrocarbons; E-PRTR, European Pollutant Release and Transfer Register; 95%CI: 95% confidence interval; UTM, Universal Transverse Mercator; PACs, Polycyclic aromatic chemicals; POPs, Persistent organic pollutants; PM_{10}, Particulate matter with a diameter between 2.5 and 10 μm; VOCs, volatile organic compounds.

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 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. Linear regression models were used to assess the association of mean MD values (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, 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). 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 could have a mediating role in breast carcinogenesis.

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

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, with 34,088 new cases estimated in 2020 (12% of all cancer cases) (Ferlay J., Ervik, M., Lam, F., Colombet, M., Mery, L., Piñeros, M., Znaor, A., Soerjomataram, I., Bray, F., 2020). It also represents the leading cause of cancer death in Spanish women, with 6355 confirmed deaths in 2019 (Instituto de Salud Carlos III (ISCIII), 2019).

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, women with a MD greater than 75% have an almost 4 times higher risk of developing breast cancer, 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 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 (Namin et al., 2021; Vieira et al., 2020; Wu et al., 2021). Particularly, EDCs produce alterations in the endocrine system through diverse mechanisms and toxics 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). In relation to MD, 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 between MD and 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 disrupting mammary gland development and increase 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., 2019).

Regarding industrial pollution in particular, a previous study of our group showed an increased breast cancer risk among women living near specific industrial plants (García-Pérez et al., 2018). 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 a higher or lower MD in studies previously published by our group (Jiménez et al., 2021; Lope et al., 2018).

In the EU, the European Pollutant Release and Transfer Register (E-PRTR) (European Environment Agency, 2021) provides information about industrial pollutants released to both air and water (Directive 2010/75/EU) making it possible to know the exposure to different industrial carcinogens (Slavik et al., 2018). In addition, the emissions reported by this register in the Spanish context have been related to an increase in cancer mortality in those who reside near the sources of industrial compared to those who live in non-industrialized areas (Fernández-Navarro et al., 2017). However, to our knowledge, no epidemiologic studies have conducted to evaluate the association between MD, an intermediate effect marker of breast cancer, and industrial exposures.

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. 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*). 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 completed an epidemiological standardized 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 they were measured and weighed 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. MD percentage from the craniocaudal mammogram of the left breast was estimated 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, 2021). For each industrial installation, we obtained information related to industrial activity, amounts of pollutant emissions, and geographical location of the installation, 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. Mean MD values and their corresponding 95%CIs were also calculated.

We used multivariable linear regression models to study the association of MD with proximity to industries and pollutants (including carcinogens and EDCs). A total of five models were performed, in which the response variable was the percentage of MD. All models were adjusted for 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).

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 a reference area consisting in women living at >3 km from any industry:

1) First analysis: relationship between MD and proximity to all industries as a whole.
2) Second analysis: MD and proximity to industries by categories of industrial sectors.
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.
4) Fourth analysis: MD and proximity to industries releasing specific pollutants (including EDCs, carcinogens, and other toxic substances).

   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, b) by industrial sector, c) by groups of carcinogens and EDCs, and d) by specific 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).

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).

All analysis were performed using R 3.3.2 software.

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. Women of our study presented a mean MD of 34.82%, and a mean age of 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. MD was 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

Table 2 shows the association between MD and distance to industries as a whole. Although the participants showed higher MD in closer distances to the facilities, with β coefficients that ranged from 1.04 (at ≤3 km) to 1.95 (at ≤1.5 km), the results were not statistically significant.

3.3 MD and proximity to industries by industrial sector

Regarding the exposure to each industrial sector (Fig. 2), we observed a statistically significant ($p<0.05$) increased MD in women living near installations belonging to the following sectors: "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).

Another 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 at ≤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 at ≤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 $p<0.05$. However, for $p<0.1$, 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 S2.

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 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).

Another results of interest, for *p*-value<0.1, are referred to the following specific pollutants (see Supplementary Data, Table S3): 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 S4) 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 the specific pollutants concerning of ammonia (*p*-trend=0.073), dichloromethane (*p*-trend= 0.096), and ethylbenzene (*p*-trend=0.068) showed positive radial effects.

4. Discussion

In summary, our results suggest a possible association between higher MD and proximity to:

a) industrial facilities belonging to “surface treatment of metals and plastic”, “organic chemical industry”, “pharmaceutical industry”, and “urban waste-treatment plants”; and,
b) industrial facilities releasing ammonia, dichloromethane, ethylbenzene, and phenols.

To our knowledge, this is the first study that analyses the proximity to industrial groups, groups of carcinogens and EDCs, and individual pollutants and its relation with a higher MD. These remarkable and novel results provide new evidence on the possible biological mechanisms that mediate the relationship, as yet unknown, between industrial pollution and breast cancer risk.

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 (not specifically in 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 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 the proliferation of human breast cancer cell line MDA-231 (Nasri et al., 2017), which could be related with the risk of breast cancer. Our results in relation to MD were consistent, since all distances analyzed in the analysis by industrial sector and in the gradient analysis showed statistically significant increased MD. Although the plants in our study belonging to this sector did not emit carcinogens or EDCs (see Supplementary Data, Table S2), it is known that the effluents of municipal sewage treatment plants 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. Moreover, a cohort study among women employed detected a higher risk of breast cancer among pharmacists (Pollán and Gustavsson, 1999).

The 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 founded a high cancer risk, due to the metals, 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 arsenic levels than women in the national sample, 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) to hazardous waste sites (O’Leary et al., 2004). Moreover, it was reported an increased rate of hospitalization for breast cancer in urban areas near to 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 approach to 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. 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 $\leq$1.5 and $\leq$2 km) and higher MD. Although we do not know the biological mechanism involved, 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 BMI <25kg/m^2 (68.6%, see Table 1), the increased MD was observed in the environs of industries releasing phenols at distances at 2 and 2.5 km. Regarding MD, one previous study 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 limitations of our study was that the effect of changes in density patterns over time could not be assessed, due the cross-sectional nature of the study. Another limitation was the non-inclusion of time living in the last residence, 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, 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.

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 UE. 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 more comprehensive description of the possible relationship between MD and industrial pollution exposure. Another strength is the high participation rate. In addition, MD was measured on a continuous scale using a validated computer-assisted method, by a single professional reader who showed high internal consistency. 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 paper 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 industrial installations 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 women's residences and industries.

Figure 2. Association between mammographic density and 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 specific pollutants, with statistically significant results and a number of women ≥5.