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Risk of breast cancer and residential proximity to industrial installations: new findings from a multicase-control study (MCC-Spain)

Authors:

Javier García-Pérez[a,b,*], Virginia Lope[a,b], Beatriz Pérez-Gómez[a,b], Antonio José Molina[c], Adonina Tardón[b,d], María Angustias Díaz Santos[e], Eva Ardanaz[b,f], Cristina O'Callaghan-Gordo[b,g,h], Jone M Altzibar[b,i], Inés Gómez-Acebo[b,j], Víctor Moreno[b,k,l,m], Rosana Peiró[b,n], Rafael Marcos-Gragera[o], Manolis Kogevinas[b,g,h,p], Nuria Aragonés[q,b], Gonzalo López-Abente[a,b], Marina Pollán[a,b]

Authors'affiliations:

[a]Cancer and Environmental Epidemiology Unit, National Center for Epidemiology, Carlos III Institute of Health, Avda. Monforte de Lemos 5, 28029, Madrid, Spain.

[b]Consortium for Biomedical Research in Epidemiology & Public Health (CIBER Epidemiología y Salud Pública - CIBERESP), Avda. Monforte de Lemos 3-5, Madrid, Spain.

[c]Research Group on Gene-Environment Interactions and Health, Institute of Biomedicine (IBIOMED), University of León, Campus Vegazana s/n, 24071, León, Spain.

[d]Instituto Universitario de Oncología (IUOPA), Universidad de Oviedo, Facultad de Medicina, Planta 7, Campus de El Cristo B, 33006, Oviedo, Spain.

[e]Centro de Investigación en Salud y Medio Ambiente (CYSMA), Universidad de Huelva, Campus Universitario de El Carmen, 21071, Huelva, Spain.

[f]Instituto de Salud Pública de Navarra, IdiSNA – Navarra Institute for Health Research, C/Leyre 15, 31003, Pamplona, Spain.

[g]ISGlobal, Center for Research in Environmental Epidemiology (CREAL), Carrer del Doctor Aiguader 88, 08003, Barcelona, Spain.

[h]Pompeu Fabra University (UPF), Plaça de la Mercè 10-12, 08002, Barcelona, Spain.

[i]Breast Cancer Screening Program, Osakidetza – Basque Health Service, Sancho el Sabio 35, 20010 San Sebastián, Spain.
[j]Universidad de Cantabria – IDIVAL, Avenida Cardenal Herrera Oria s/n, 39011 Santander, Spain.
[k]Cancer Prevention and Control Program, Catalan Institute of Oncology, Avinguda de la Granvia de l'Hospitalet 199-203, 08908, Hospitalet de Llobregat, Spain.
[l]Department of Clinical Sciences, Faculty of Medicine, University of Barcelona, Gran Via de les Corts Catalanes 585, 08007, Barcelona, Spain.
[m]Colorectal Cancer Group, Bellvitge Biomedical Research Institute (IDIBELL), Gran Via de l'Hospitalet 199, 08908, Hospitalet de Llobregat, Spain.
[n]Fundación para el Fomento de la Investigación Sanitaria y Biomédica de la Comunitat Valenciana FISABIO-Salud Pública − Foundation for the Promotion of Health and Biomedical Research of Valencian Region (FISABIO), Avda. de Catalunya 21, 46020, Valencia, Spain.
[o]Epidemiology Unit and Girona Cancer Registry (UERCG), Oncology Coordination Plan, Department of Health, Autonomous Government of Catalonia, Catalan Institute of Oncology (ICO), Girona Biomedical Research Institute (IDIBGI), University of Girona, Carrer del Sol 15, 17004 Girona, Spain.
[p]IMIM (Hospital del Mar Medical Research Institute), Dr. Aiguader 88, 08003, Barcelona, Spain.
[q]Epidemiology Section, Public Health Division, Department of Health of Madrid, C/ San Martín de Porres 6, 28035, Madrid, Spain.

***Corresponding author**:

Javier García-Pérez

Cancer and Environmental Epidemiology Unit

National Center for Epidemiology

Carlos III Institute of Health

Avda. Monforte de Lemos, 5, 28029 Madrid, Spain

Tel.: +34-918222643

E-mail: jgarcia@isciii.es

E-mail addresses:

JG-P: jgarcia@isciii.es

VL: vicarvajal@isciii.es

BP-G: bperez@isciii.es

AJM: ajmolt@unileon.es

AT: atardon@uniovi.es

MADS: mdiazsantos88@gmail.com

EA: me.ardanaz.aicua@cfnavarra.es

CO-G: cristina.ocallaghan@isglobal.org

JMA: JONEMIREN.ALTZIBARAROTZENA@osakidetza.eus

IG-A: ines.gomez@unican.es

VM: victor@morenoaguado.net

RP: peiro_ros@gva.es

RM-G: rmarcos@iconcologia.net

MK: manolis.kogevinas@isglobal.org

NA: nuria.aragones@salud.madrid.org

GL-A: glabente@isciii.es

MP: mpollan@isciii.es

Abbreviations:

EDCs: Endocrine disrupting chemicals

BHA: Basic health area

ORs: Odds ratios

95%CIs: 95% confidence intervals

BMI: Body mass index

IARC: International Agency for Research on Cancer

UNEP: United Nations Environment Program

WHO: World Health Organization

PACs: Polycyclic aromatic chemicals

Non-HPCs: Non-halogenated phenolic chemicals

POPs: Persistent organic pollutants

PM_{10}: Particulate matter

Abstract

Breast cancer is the most frequent tumor in women worldwide, although well-established risk factors account for 53%-55% of cases. Therefore, other risk factors, including environmental exposures, may explain the remaining variation. Our objective was to assess the relationship between risk of breast cancer and residential proximity to industries, according to categories of industrial groups and specific pollutants released, in the context of a population-based multicase-control study of incident cancer carried out in Spain (MCC-Spain). Using the current residence of cases and controls, this study was restricted to small administrative divisions, including both breast cancer cases (452) and controls (1511) in the 10 geographical areas recruiting breast cancer cases. Distances were calculated from the respective woman's residences to the 116 industries located in the study area. We used logistic regression to estimate odds ratios (ORs) and 95% confidence intervals (95%CIs) for categories of distance (between 1 km and 3 km) to industrial plants, adjusting for matching variables and other confounders. Excess risk (OR; 95%CI) of breast cancer was found near industries overall (1.30; 1.00-1.69 at 3 km), particularly organic chemical industry (2.12; 1.20-3.76 at 2.5 km), food/beverage sector (1.87; 1.26-2.78 at 3 km), ceramic (4.71; 1.62-13.66 at 1.5 km), surface treatment with organic solvents (2.00; 1.23-3.24 at 3 km), and surface treatment of plastic and metals (1.51; 1.06-2.14 at 3 km). By pollutants, the excess risk (OR; 95%CI) was detected near industries releasing pesticides (2.09; 1.14-3.82 at 2 km), and dichloromethane (2.09; 1.28-3.40 at 3 km). Our results suggest a possible increased risk of breast cancer in women living near specific industrial plants and support the need for more detailed exposure assessment of certain agents released by these plants.

Capsule:

Our results suggest a possible increased risk of breast cancer in women living near specific industrial plants and support the need for more detailed exposure assessment of certain industrial agents.

Key Words: breast cancer; case-control study; residential proximity; industrial pollution; pesticides; endocrine disrupting chemicals

1. Introduction

Breast cancer is the most frequent tumor in women worldwide (Torre et al., 2015). In Spain, 27,747 new cases were estimated in 2015 (Galceran et al., 2017). Insofar as the etiology of this tumor is concerned, well-established risk factors include genetic factors, age, family history of breast cancer, menstrual and reproductive history, high mammographic density, previous diagnosis of non-malignant breast diseases, obesity, alcohol intake, physical inactivity, and hormone replacement therapy use (Hankinson et al., 2004; Romieu et al., 2015; Vogel, 2008), although these factors account for between 53% and 55% of breast cancer cases (Engmann et al., 2017). Therefore, other risk factors, including environmental exposures, may explain the remaining variation.

In this sense, residential proximity to industrial installations that release toxic substances to the environment is a potential source of exposure to carcinogenic agents with sufficient or limited evidence in humans for breast cancer risk, such as ethylene oxide, polycyclic aromatic hydrocarbons, polychlorinated biphenyls, and environmental chemicals (Brody et al., 2007; IARC, 2017; Mitra and Faruque, 2004; Rodgers et al., 2018). Moreover, many of these agents are endocrine disrupting chemicals (EDCs), substances that alter the functions of the endocrine system and are related to an increase in incidence of breast cancer (Giulivo et al., 2016; Pastor-Barriuso et al., 2016; Rachon, 2015). Accordingly, it would seem necessary to ascertain whether the fact of living close to pollutant industries might have an influence on the frequency of breast cancer.

This paper assessed the association between residential proximity to industrial installations and risk of breast cancer, according to different categories of industrial groups, groups of carcinogens and EDCs, and specific pollutants, in the context of a multicase-control study of incident cancer carried out in Spain (MCC-Spain).

2. Materials and methods

2.1 Study area and subjects

The present study is part of the MCC-Spain study (MCC-Spain, 2018), a population-based multicase-control study that evaluates genetic and environmental factors associated with the risk of frequent tumors (breast, colorectal, gastric, and prostate cancer) and chronic lymphocytic leukemia in Spain. The design has been previously described (Castano-Vinyals et al., 2015). Briefly, between 2008 and 2013 we recruited 1738 histologically confirmed incident breast cancer cases (International Classification of Diseases-10th: C50, D05.1, D05.7) in women aged 20-85 who resided in the hospitals' catchment areas for at least 6 months prior to recruitment in 10 provinces (Asturias, Barcelona, Cantabria, Girona, Gipuzkoa, Huelva, Leon, Madrid, Navarre, and Valencia). To facilitate the logistics of the study, population-based controls for the whole study were randomly selected from administrative records of selected primary care health centers located within hospitals' catchment areas, and frequency matched to the overall distribution of cases (breast cancer and other) by sex, age (in 5-year age groups), and region (province). The study protocol was approved by the Ethics Committee from each participating center, and all participants signed an informed consent before recruitment. The response rate was 54% among female controls and 69% among breast cancer cases.

In Spain, the territorial framework for the primary health care is divided into health areas, which contain a hospital of reference. Every health area is divided into several basic health areas (BHAs) and every BHA may contain one or more primary care health centers. Whereas the cases were recruited in complete health areas, the controls were selected in specific BHAs. Taking into account that the study area of controls (BHAs covered by the selected primary care health centers) was smaller than the study area of cases (hospitals' catchment areas), the present study was restricted to cases and controls living in BAHs of the selected primary care health centers, excluding those zones with only cases (and no controls). Furthermore, we also excluded small administrative divisions (municipal districts or "*pedanías*") where there were only controls without breast cancer cases. Figure 1 represents a flow chart showing the selection process of breast cancer cases and controls.

2.2 Data collection

Trained interviewers administered a structured computerized epidemiological questionnaire in a face-to-face interview, including: personal and family history of breast cancer; medical, gynecologic, and obstetric history; physical activity; self-reported weight and height one year prior to the interview; socioeconomic data; smoking; and occupational and residential history.

2.3 Residential locations

Each woman's last residence was geocoded into UTM Zone 30 (ED50) coordinates, and individually checked using Google Earth Pro (with the "street-view" application) and the National Cadastre. Of the 3648 participants interviewed (1738 cases and 1910 controls), 3633 individuals' residences (1725 cases and 1908 controls) were finally geocoded with valid coordinates. Subsequently, a total of 1218 cases and 186 controls were excluded because they were located outside the BHAs of the primary care health centers.

2.4 Industrial facility locations

Information about industries included in the European Pollutant Release and Transfer Register and governed by the Integrated Pollution Prevention and Control Directive, corresponding to 2009, was used. Taking the minimum breast cancer induction period into account, about 10 years, we selected those installations that were already in operation 10 years before the mid-year of the recruitment period of each province. This industrial database included information, previously validated, about the location and pollutant emissions of the 116 facilities located in the study area (see Figure 2) that reported their releases to water and air, classified into one of 21 categories of industrial groups (see Supplementary Data, Table S1).

2.5 Exposure coding and statistical analysis

For each woman, the shortest distance between the individual's residence and any of the 116 industrial facilities was calculated. A total of five statistical analyses were performed to estimate odds ratios (ORs) and 95% confidence intervals (95%CIs). These analyses included mixed multiple unconditional logistic regression models, which included matching factors (age (continuous), and province of residence (categorized into 10 provinces) as a random effect), and other potential confounders: family history of breast cancer (none, second degree only, one first degree, and more than one first degree), previous biopsies (yes/no), age at menarche (<12 years, 12-13 years, and >13 years), educational level (less than primary school, primary school completed, secondary school, and university graduate), body mass index (BMI) one year prior the interview (continuous), age at first birth (nulliparous, <20 years, 20-24 years, 25-29 years, and >29 years), and menopausal status (premenopausal/peri-postmenopausal). These confounding variables have been strongly related to breast cancer risk in previous studies (Crujeiras et al., 2012; Hankinson et al., 2004; Vogel, 2008).

For the first four analyses, we took into account several distances 'D' (3, 2.5, 2, 1.5, and 1 km) for the exposure variable, and each woman was classified as: a) resident in the industrial area ("exposed area"), if she resided at ≤'D' km from any industrial facility; b) resident in the intermediate area, if she resided between 'D' and 3 km from any industry; and, c) resident within the reference area ("unexposed area"), if she resided at >3 km from any industry, being this reference category the same for the four analyses. Figures 3 (A), 3 (B), and 3 (C) depict three examples of the above-defined areas, for distances of 1, 2, and 3 km, respectively, in the province of Asturias:

1) First analysis: relationship between breast cancer and proximity to industries as a whole

2) Second analysis: breast cancer and proximity to industries by category of industrial group, taking into account the 21 categories of industrial groups defined in Supplementary Data, Table S1.
3) Third analysis: breast cancer and proximity to facilities releasing groups of carcinogens and EDCs. The carcinogens were classified by the International Agency for Research on Cancer (IARC) as carcinogenic, probably carcinogenic, and possibly carcinogenic to humans. And the EDCs were classified according to the United Nations Environment Program and the World Health Organization (WHO/UNEP, 2013) as 'Pesticides', 'Metals', 'Non-HPCs' (non-halogenated phenolic chemicals), 'PACs' (polycyclic aromatic chemicals), 'POPs' (persistent organic pollutants), 'Plasticizers', 'Other persistent', and 'Other solvents'.
4) Fourth analysis: breast cancer and proximity to industries releasing specific pollutants released.

For the fifth analysis, we assessed the existence of radial effects near industries. To this end, we performed an analysis to study the risk gradient in the proximity of industrial installations, described in Supplementary Data, Appendix A.

Additionally, with the aim of controlling potential biases and introducing robustness in our analyses, a sensitivity analysis considering only long-term residents (individuals living in their last residence for more than 10 years) was performed for the above-mentioned five analyses.

In all instances, since matching conditions were applied considering the overall distribution of all cancer cases in each region included in the MCC-Spain study, we used unconditional logistic regression including the matched characteristics in the model.

Finally, the problem of multiple comparisons was addressed by controlling for the expected proportion of false positives (False Discovery Rate) with adjusted *p*-values (Benjamini and Hochberg, 1995).

3. Results

3.1 Characteristics of the study population

Results presented in this manuscript are based on participants with no missing values in any of the selected confounders (see Figure 1). Thus, the final study population comprised 452 cases and 1511 controls, whose geographic distribution is depicted in Figure 2 and main characteristics are shown in Table 1. Leon and Madrid were the provinces that recruited more cases and controls respectively, and, in general, cases were slightly younger and had higher BMI than controls. A sensitivity analysis, testing the distribution of these main characteristics in excluded cases and controls, showed similar results to those obtained here (data not shown).

3.2 Analysis 1: breast cancer and proximity to industries as a whole

ORs of breast cancer associated with proximity to industrial installations overall are shown in Table 2. Women close to industries registered excess risks of breast cancer for all distances analyzed, statistically significant in the case of 3 km (OR=1.30, 95%CI=1.00-1.69 considering all individuals; and, OR=1.36, 95%CI=1.01-1.85 considering only long-term residents).

3.3 Analysis 2: breast cancer and proximity to industries by category of industrial group

The analysis of proximity to facilities by categories of industrial group, as well as their respective corrections by multiple comparisons, is shown in Table 3. The most noteworthy results are the following: 'Organic chemical industry' (OR=3.08; 95%CI=1.33-7.15 at 1.5 km, OR=2.19; 95%CI=1.18-4.07 at 2 km, and OR=2.12; 95%CI=1.20-3.76 at 2.5 km), 'Beverage and food sector' (OR=1.85; 95%CI=1.05-3.26 at 2 km, OR=2.04; 95%CI=1.22-3.42 at 2.5 km, and OR=1.87; 95%CI=1.26-2.78 at 3 km), 'Ceramic' (OR=4.19; 95%CI=1.00-17.52 at 1 km, and OR=4.71; 95%CI=1.62-13.66 at 1.5 km), 'Surface treatment with organic solvents' (OR=2.00; 95%CI=1.23-3.24 at 3 km), and 'Surface treatment of plastic and metals' (OR=1.51; 95%CI=1.06-2.14 at 3 km). On the other hand, the sensitivity analysis with only long-term residents yielded similar results (data not shown).

3.4 Analysis 3: breast cancer and proximity to industries releasing groups of carcinogens and EDCs

With respect to the analysis of proximity to facilities releasing groups of carcinogens, the results showed no statistically significant excess risks (see Supplementary Data, Table S2). However, the analysis by categories of EDCs (see Figure 4) showed statistically significant excess risks in women living close to industries releasing pesticides (OR=2.50; 95%CI=1.00-6.22 at 1 km, OR=2.23; 95%CI=1.16-4.29 at 1.5 km, and OR=2.09; 95%CI=1.14-3.82 at 2 km), and other solvents (OR=1.48; 95%CI=1.02-2.16 at 2.5 km, and OR=1.56; 95%CI=1.10-2.22 at 3 km). The sensitivity analysis with only women living in their last residence for more than 10 years yielded similar results (data not shown) and, moreover, a new statistically significant OR in the vicinity of industries releasing Non-HPCs (OR=2.34; 95%CI=1.18-4.65 at 3 km) was found.

3.5 Analysis 4: breast cancer and proximity to industries by specific pollutants

The most remarkable ORs of breast cancer in women living close to industries releasing specific substances are depicted in Figure 5: 'Hydrofluorocarbons' (ORs=4.18 at 2 km, 3.07 at 2.5 km, and 3.94 at 3 km), 'Nonylphenol and nonylphenol ethoxylates' (ORs=4.18 at 2 km, 2.92 at 2.5 km, and 3.66 at 3 km), 'Organotin compounds' (ORs=2.50 at 1 km, 2.23 at 1.5 km, 2.32 at 2 km, 2.38 at 2.5 km, and 2.29 at 3 km), 'Halogenated organic compounds' (ORs=1.58 at 2 km, 1.56 at 2.5 km, and 1.69 at 3 km), 'Antimony' (ORs=3.83 at 1.5 km, 4.03 at 2 km, and 3.14 at 2.5 km), '1,2-dichloroethane' (OR=2.49 at 3 km), 'Particulate matter (PM_{10})' (OR=1.66 at 1.5 km), and 'Dichloromethane' (OR=2.09 at 3 km). Of these substances, the IARC classifies PM_{10} as carcinogen (Group 1), dichloromethane as probably carcinogenic (Group 2A), and 1-2-dichloroethane as possibly carcinogenic (Group 2B) to humans. And in relation to EDCs, the UNEP and WHO classify nonylphenol and nonylphenol ethoxylates as non-HPCs, organotin compounds as pesticides, and dichloromethane as other solvents.

The sensitivity analysis with only women living in their last residence ≥10 years yielded similar results (data not shown) and, moreover, new statistically significant ORs in the vicinity of installations releasing trichloroethylene (OR=3.50 at 3 km), trichloromethane (OR=2.17 at 3 km), and fluoranthene (OR=2.11 at 3 km) were found. Trichloromethane and trichloromethane are carcinogen and possibly carcinogenic to humans, respectively, whereas fluoranthene is a PAC.

3.6 Analysis 5: risk gradient analysis

Finally, the risk gradient analysis (see Supplementary Data, Table S3) detected positive radial effects (rise in OR with increasing proximity to facilities of a specific sector) for ‘Organic chemical industry’ (*p*-trend=0.005), ‘Surface treatment using organic solvents’ (OR=1.28, *p*-trend=0.005), and ‘Food and beverage sector’ (*p*-trend=0.005). The sensitivity analysis with only long-term residents yielded similar results (data not shown).

4. Discussion

4.1 Summary

This is the first attempt to assess the influence of industrial pollution on breast cancer in our country using individual data. In summary, our results suggest a possible association between risk of breast cancer and residential proximity to:

a) plants involved in the organic chemical industry, food and beverage sector, ceramic, surface treatment using organic solvents, and surface treatment of metals and plastic; and,

b) facilities releasing specific EDCs (organotin compounds, and nonylphenol and nonylphenol ethoxylates), known or suspected carcinogens (PM_{10}, dichloromethane, and 1-2-dichloroethane), and other toxic substances (hydrofluorocarbons, halogenated organic compounds, and antimony).

This paper is part of the MCC-Spain study, the largest population-based case-control study of incident cancer carried out in Spain. Recently, our group published a paper that analyzed breast cancer mortality and industrial pollution using an ecological approach (Garcia-Perez et al., 2016). Now, the study design of the present work guarantees the availability of individual information on breast cancer risk factors, which can be taken into account in the analyses.

In relation to proximity to industrial facilities, our measures were based on individuals' last-reported residence. In this sense, our study population proved to be quite stable, with 86.3 % of cases and 92.1 % of controls having lived in their last residence ≥5 years, and 71.9 % of cases and 79.0 % of controls having lived there ≥10 years. Moreover, a sensitivity analysis considering only long-term residents (≥10 years) was conducted and yielded similar results.

4.2 Results in relation to other studies

In relation to industrial pollution, literature about incidence of breast cancer and residential proximity to industrial plants is sparse. Recently, an Italian study registered high incidence of breast cancer between 1999 and 2006 in contaminated sites located in Sicily (Fazzo et al., 2016). With respect to specific industrial groups, preliminary results about a population-based case-control study conducted in Canada by Pan et al. (Pan et al., 2011) suggested possible weak associations between breast cancer risk and proximity (≤3.2 km) to pulp mills, steel mills, combustion installations, and petroleum refineries. In our study, however, we found no associations with these industrial groups (see Table 3). Other studies have focused attention on waste management industries and breast cancer incidence, with inconsistent results: some authors have found increased risks for breast cancer in women living within

1 mile of hazardous waste sites (O'Leary et al., 2004), whereas other authors did not find associations with proximity to incinerators (Ranzi et al., 2011) or solid waste landfill sites (Goldberg et al., 1995). In this sense, our results about the waste management sector did not show excess risks of breast cancer (see Table 3).

In relation to the industrial groups with statistically significant results in our study, a case-control study conducted in the USA showed a significant excess risk of breast cancer among postmenopausal women living in counties with one or more chemical facilities (Lewis-Michl et al., 1996). In our study, the significant excess risks were found in the proximity of organic chemical industries, which release carcinogens and EDCs into the environment, such as metals, dioxins, pesticides, PACs, non-HPCs, and POPs (European Environment Agency (EEA), 2018). With respect to the other industrial groups, to our knowledge, no epidemiologic studies about incidence of breast cancer have been conducted on women living near food and beverage industries, ceramic plants, industries involved in surface treatment using organic solvents, or surface treatment of metals and plastic. However, installations for surface treatment of metals and plastic materials (many of which belong to the automobile sector) use metalworking fluids, a range of mineral oils and other chemical substances used to cool and/or lubricate metal workpieces, which have been associated with increased risk of breast cancer (Thompson et al., 2005).

With regard to specific pollutants of our study, our results about pesticides are consistent with the literature, where some authors have found an association between exposure to pesticides, especially organochlorine, and risk of breast cancer (Arrebola et al., 2015; Boada et al., 2012; Eldakroory et al., 2017; He et al., 2017; O'Leary et al., 2004; Rodgers et al., 2018). In our paper, the statistically significant ORs of pesticides are due, principally, to proximity to industries releasing organotin compounds (see Figure 5).

In relation to exposure to particulate matter and breast cancer risk, the findings are not solid: whereas some authors showed increased risks of breast cancer mortality associated with $PM_{2.5}$ exposure (Tagliabue et al., 2016), other studies did not suggest increased risks of breast cancer with increasing exposures to particulate matter air pollution (Andersen et al., 2017; Hart et al., 2016). Our results only showed a statistically significant OR at a distance of 1.5 km from industries releasing PM_{10}.

With regard to dichloromethane exposure, some authors have found weak associations between this pollutant and risk of breast cancer, based on occupational (Dell et al., 1999) and ecologic (Coyle et al., 2005) studies. In 2011, a review of dichloromethane exposure and cancer risk revealed limited associations between this substance and breast cancer (Cooper et al., 2011), a finding that could be related to the excess risk observed by us in the proximity industries with emissions of this pollutant (statistically significant excess risks at a distance of 3 km, but not in other).

Our results about excess risk found in the environs of industries releasing trichloroethylene (only in the sensitivity analysis considering long-term residents) are consistent with other studies, where the authors have found associations between exposure to trichloroethylene and risk of female (Coyle et al., 2005; Rodgers et al., 2018; Sung et al., 2007) and male (Ruckart et al., 2015) breast cancer.

Finally, we have found surprising results in relation to industries releasing hydroflurocarbons, and nonylphenol and nonylphenol ethoxylates, with statistically significant excess risks for all distances analyzed, and antimony for distances between 1.5 km and 2.5 km. To our knowledge, there is no epidemiologic study about breast cancer risk and its possible relationship with these substances. Therefore, these results are novel and noteworthy, and our paper provides new hypotheses in the etiology of breast cancer in relation to residential proximity to these pollutants.

4.3 Limitations and strengths

We stress the following limitations: the use of the Euclidean distance as a proxy of exposure to the industrial sources, something that could lead to a problem of misclassification, since real exposure is dependent on prevailing winds or geographic landforms; the loss of statistical power due to the exclusion of individuals out of the study areas; the non-inclusion of some factors that could be potentially related to the misclassification of the exposure, such as the time actually spent inside the exposure areas and confounding by indoor air pollution; and the non-inclusion of information about occupational exposures due to lack of data. Moreover, some potential confounders are self-reported and so they are subject to possible recall bias. However, if recall bias exists, it would probably be non-differential, thus implying an underestimation of the effects studied.

One aspect addressed in the analysis of the industrial groups is the problem of multiple comparisons. In Table 3, we have provided adjusted *p*-values, although we have preferred to discuss the results from an epidemiologic standpoint, taking into account the biologic plausibility, the consistency of the associations observed, and the magnitude of risk per se.

This study uses distance to the industrial facility as a proxy of the real exposure to the pollutants released by the industries, using several distances, something that could be a critical decision. We decided to select several radiuses between 1 and 3 km, in line with the distance used by other authors in similar case-control studies (Pan et al., 2011), and based on dispersion modeling studies, where the maximum concentrations in the environment of specific pollutants released by the facilities have been found between 0 and 3 km from the pollution sources (Hodgson et al., 2007; Llanos et al., 2011; Ranzi et al., 2011; Tuygun et al., 2017; Yu et al., 2011).

Insofar as the strengths of this paper are concerned, this is a multicenter case-control study carried out in 10 representative Spanish provinces located throughout the Spanish geography covering rural and urban settings. Moreover, we have histologically confirmed incident cases and population-based controls, which add specific value to our results. In this sense, the recruitment of incident cases also served to prevent possible changes of address associated with a diagnosis of cancer. Hence, if there were any bias affecting proximity to industrial pollution sources in relevant periods of life, this bias would be non-differential, causing an attenuation of the estimated risk. On the other hand, the statistical models included a random province-specific intercept term which accounted for unexplained heterogeneity due to unmeasured factors across different regions. Finally, the inclusion of sensitivity analysis considering only women living in their last residence for more than 10 years, and the stratification of the results by industrial group, groups of carcinogens and EDCs, and specific pollutants, have provided a more comprehensive description of breast cancer risk.

5. Conclusions

Our results suggest a possible increased risk of breast cancer in women living near certain industrial plants and pollutants released. This supports the need for more detailed exposure assessment of certain toxics released by these industries.

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Figure legends

Figure 1: Flow chart displaying the selection process of breast cancer cases and controls.

Figure 2: Geographic distribution of cases, controls, and industrial installations located in the study area.

Figure 3: Examples of exposure areas to industrial installations for distances of 1 (A), 2 (B), and 3 km (C), in the province of Asturias.

Figure 4: Odds ratios of breast cancer with statistically significant results and a number of cases and controls ≥5 for the analysis of proximity to industries by groups of endocrine disrupting chemicals. Co=number of controls. Ca=number of cases. Pesticides: alachlor, aldrin, atrazine, chlordane, chlorfenvinphos, chlorpyrifos, DDT, dieldrin, diuron, endosulfan, endrin, heptachlor, lindane, mirex, pentachlorobenzene, pentachlorophenol, simazine, isoproturon, organotin compounds, tributyltin and compounds, triphenyltin and compounds, trifluralin, and isodrin. Other solvents: dichloromethane, tetrachloroethylene, trichloroethylene, benzene, ethyl benzene, toluene, and xylenes. Y-axis is plotted in logarithmic scale.

Figure 5: Odds ratios of breast cancer with statistically significant results and a number of cases and controls ≥5 for the analysis of proximity to industries releasing specific pollutants. Y-axis is plotted in logarithmic scale. Co=number of controls. Ca=number of cases.