Research article

# Spatial interaction between breast cancer and environmental pollution in the Monterrey Metropolitan Area

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## ARTICLE INFO

## ABSTRACT

This research examines the spatial structure of a sample of breast cancer (BC) cases and their spatial interaction with contaminated areas in the Monterrey Metropolitan Area (MMA). By applying spatial statistical techniques that treat the space as a continuum, degrees of spatial concentration were determined for the different study groups, highlighting their concentration pattern. The results indicate that 65 percent of the BC sample had exposure to more than 56 points of PM$_{10}$. Likewise, spatial clusters of BC cases of up to 39 cases were identified within a radius of 3.5 km, interacting spatially with environmental contamination sources, particularly with refineries, food processing plants, cement, and metals. This study can serve as a platform for other clinical research by identifying geographic clusters that can help focus health policy efforts.

## 1. Introduction

Breast cancer (BC) is considered the most common cancer in women and one of the leading causes of death in women worldwide, and the incidence has been increasing in the last three decades (Torre et al., 2015). Particularly, some researches identify the main risk factors associated with BC, including being a smoker (DiMarzio et al., 2018; Izano et al., 2015; Terry and Rohan, 2002), having some degree of obesity (Calle et al., 2003), mammographic density (DuPre et al., 2017), and other environmental and genetic factors have been suspected as risk factors for BC.

In this sense, BC is one of the most common neoplasms, involving different factors, both genetic and environmental, that changes according to the context in which it is analyzed. Some studies identify positive associations between lifestyle behaviors such as physical activity, diet, alcohol consumption habits, and tobacco smoking with some types of BC, particularly as the luminal A, luminal B, and HER2/neu+ (Ellingjord-Dale et al., 2018).

Regarding pollution, as a risk factor for BC, it has been widely studied in recent years. For example, Nie et al. (2007), in a case-control study,

found statistically significant evidence between traffic emissions and women in premenopausal periods; while Bonner et al. (2005) found evidence of the impact of aromatic pollutants and cancer risk in postmenopausal women, and White et al. (2016) reached similar results, finding an incidence of 30 percent in groups exposed to concentrations of aromatic pollutants.

Some studies had identified associations between different health problems and environmental pollution (Bravo and Bell, 2011; Csavina et al., 2014; O. and A., 2012). Some types of cancer, cardiovascular and respiratory diseases, and congenital malformations have been associated with different pollutants. Particularly, research on environmental pollution by PM$_{10}$ and PM$_{2.5}$ and other types of pollutants where the prevalence of BC and other types of cancer are significantly associated (Bentov et al., 2006; Desrosiers et al., 2012; Yu et al., 2019; Zhang and Tripathi, 2018).

Similarly, other studies establish associations between BC and various toxic agents such as heavy metals, PM$_{10}$, and PM$_{2.5}$ exposure (Crouse et al., 2010). PM$_{2.5}$ concentrations and BC have a positive relationship with more cases associated to high levels of PM$_{2.5}$ exposure (Hung et al., 2012). In a province of China, Huo et al. (2013) found that BC patients

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positive to estrogen receptor had variations in their tumor grade when exposed to higher levels of $PM_{10}$.

In this sense, recent studies corroborate the positive association between industrial process toxins and some cancer types, including breast cancer (Coudon et al., 2019). For a case in Canada (Crouse et al., 2010; Hystad et al., 2015) and Saudi Arabia (Al-Ahmadi and Al-Zahrani, 2013), there were empirical evidence between NO2 and breast cancer. Additionally, Reding et al. (2015) found positive associations between NO2 and BC estrogen receptor-positive.

A study by Hendryx et al. (2010) found significant correlations between cancer mortality and population exposure to mining activities in West Virginia. Fernández-Navarro et al. (2012) applied Bayesian regression models to determine the association between mining activity and cancer cases in Spain. Similar results report García-Pérez et al. (2013) about cancer mortality and proximity to hazardous waste incinerator facilities. In the same way, García-Pérez et al. (2016) and García-Pérez et al. (2018) confirm the association between BC and proximity to industrial facilities.

On the other hand, DuPre et al. (2017) carried out a study in which they associated pollution by $PM_{10}$ and $PM_{2.5}$, geographical distance from roads and mammographic density. Higher mammographic density was associated with some types of BC. Similarly, Yaghjyan et al. (2017) found significant associations between mammographic density and exposure to high levels of $PM_{2.5}$. In this regard, Shmuel et al. (2017) conducted a study in which they analyzed the proximity to major roads and cases of cancer, finding that the risk of suffering from BC increases with proximity to roads or where there is more density of them.

In a more recent study in China, Deng et al. (2019) analyzed the spatial distribution of heavy metals and found spatial interactions between high cadmium and zinc concentration and cancer cases. According to the authors, these high concentrations of heavy metals are from industrial and other anthropogenic activities. Other studies corroborate this (He et al., 2019).

The Monterrey Metropolitan Area (MMA), is one of the largest cities in Mexico and Latin America, with nearly 5 million people in 13 municipalities. From 1990 to 2018, MMA recorded 6,988 BC deaths. In 1990, the BC death rate in women treated in MMA had reported 9.61 deaths per 100,000 women. In the next decade, the death rate increased 25% during 1990–2000 (12.01 deaths per 100,000 women). Another increment of 13% occurred during 2000–2010 (13.67 deaths per 100,000 women), and during the 2010–2015 period, a quinquennial increment of 22%, 16.79 deaths per 100,000 women (INEGI, 2020) (See Figure 1b).

This metropolitan area is characterized by a robust industrial activity with highly polluting economic activities that include oil refining, the production of plastics and cardboard, metal and stone mining, engine manufacturing, and industrial machinery, among other highly polluting activities associated with some health problems for which there is empirical evidence (Monge et al., 2007; Zhou et al., 2018). In addition to this industrial intensity, the MMA concentrates more than 2 million vehicles, a situation that favors the concentration of large amounts of $PM_{10}$ and $PM_{2.5}$. (Hao and Liu, 2016). According to the World Health Organization, this situation makes this metropolitan area the most contaminated in Mexico and one of the most polluted in Latin America (Martínez-Cinco et al., 2016).

Similarly, some eating habits are practiced by the population living in the MMA, like the consumption of highly processed and industrialized foods and high consumption of grilled red meat. These habits may relate to some types of cancers. Several studies have shown the association between polycyclic aromatic hydrocarbons (PAHs), such as smoke from burning coal and breast cancer incidence (Gullett et al., 2003; White et al., 2014).

In this sense, the distribution of deaths due to BC in the MMA can be seen in Figure 1a. This Figure identifies the hot spots at the municipal level that account for the distribution and intensity of mortality from this disease. It can be seen that there is a higher incidence in the northern part of Mexico, where the MMA is found, identified in red in the same Figure. (The description of the Getis-Ord technique is developed in section 2.2.1).

Therefore, this research explores the spatial distribution of a sample of BC cases and their exposure to different environmental pollution degrees in the MMA. Spatial clusters of BC and companies are identified with records of polluting substances with their respective values distributed over continuous space. It seeks to know the degree of exposure of BC cases to pollutants. In particular, this study seeks to answer the following research questions: Does BC present a random distribution, or does it tend to concentrate on specific zones of the city? If so, what degrees of concentration does it present? Are the BC cases associated with the space with high values of pollution? The answers to these questions will contribute to identifying units of analysis of BC based on geographical location of cases and pollution, which aids in identifying the problem accurately.

The paper is structured as follows: first, a brief review of the literature was made, enunciating research that identifies the main risk factors for the BC, emphasizing the relation with environmental pollution ($PM_{10}$). Likewise, some studies addressing spatial distribution of some health problems, particularly BC, were reviewed. Then, the nature and processing of the database and the spatial statistical techniques are described. The results were analyzed and discussed.

## 2. Material and methods

This is an exploratory, ecological and transversal research aimed to analyze the spatial distribution of BC cases sample and their geographical association with pollution in the MMA. Although it does not establish causal relationships, it intends to find associations in space between the study groups to understand the exposure of the sample of BC cases to environmental pollution. In this study, various spatial statistics techniques are used, for example, the nearest neighbor index, seeks to identify the degrees in the agglomeration of BC cases, spatial scanning identifies risk areas and interpolation techniques distribute the pollution values over the study area.

This section describes the database used, as well as the spatial statistical techniques applied for cluster detection.

### 2.1. Data

A sample of 349 women with diagnosis of BC were ascertained. Latitude - longitude coordinates were obtained using the addresses of each of the cases. Their continuous residence in the georeferenced address were recorded too. These data were selected to know the exposure of the cases to the environmental pollution interpolated in the city.

The patients were recruited at the San Jose Hospital's Breast Cancer Center, Tecnologico de Monterrey, as part of a program where patients from public and private institutions receive treatment. The data was collected from 2014, which has been monitored until 2020. Only the records of patients with a clinical-stage between 0 - 4 were analyzed. 100% of the patients were women with an average age of 50 years (26–88).

The corresponding geographical coordinates were processed with the Crimestat 3.2 software Version 3.2, and the calculations were then projected in ArcGIS 10.4 to produce the maps. With Crimestat software, the Nearest Neighbor Index (NNI) techniques were used to determine BC cases, industry, and pollutants' degrees of concentration. In order to identify spatial clusters of the units of analysis, we used the Nearest Neighbor with Hierarchical Clusters (NNHC) technique. These techniques are described and explained in section 2.2.

Pollution data was obtained from the Catalog of polluting companies and their emissions From *the Sistema Integral de Monitoreo Ambiental del Estado de Nuevo León* (SIMA) (Gobierno del Estado de Nuevo León, 2020). The catalog included 301 companies with records of polluting emissions, and the environmental pollution was obtained from reports of the nine

(a)



(b)
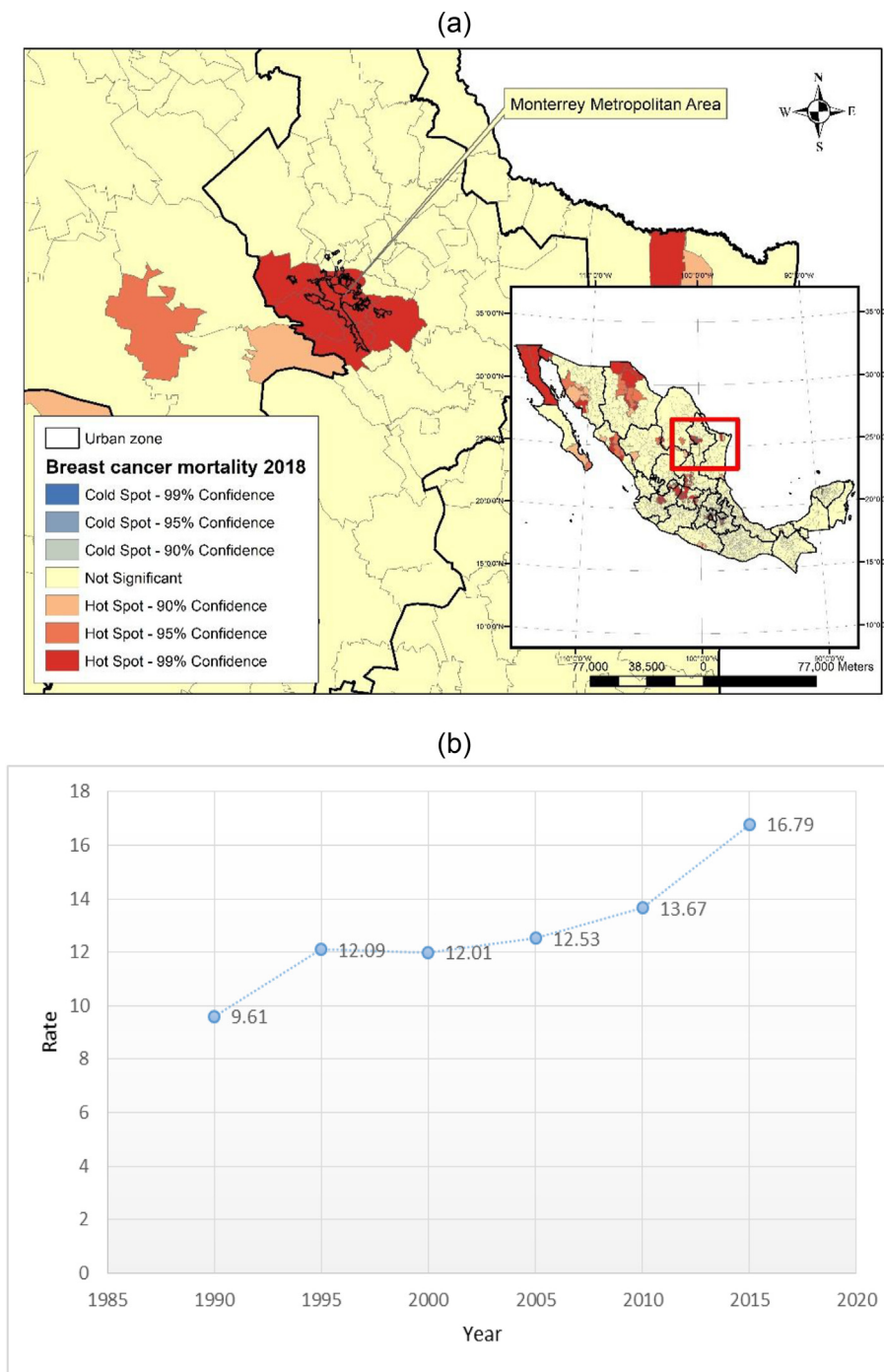


**Figure 1.** Getis-Ord Hot Spots of BC mortality at municipal level (a) and BC Mortality rate/100,000 women in MMA (b). (Source: From our authorship from data of National Institute of Statistics and Geography (INEGI, 2020).

state local monitoring stations in the MMA. An accumulation of substances for the period 2010–2015 was carried out by the company; subsequently, the urban space data were interpolated using interpolation by IDW, these techniques are explained in section 2.2.4. Figure 2 shows the information on polluting substances by chemical family and reported amounts from the 301 companies.

A cartographic database in shape format was also used for the 13 municipalities of the MMA, divided into 1,676 AGEB (Basic Geostatistical Area unit, It is a polygon that contains socioeconomic information and corresponds to the smallest territorial unit of the National Geostatistical framework.) that have information on population. For the estimation of corresponding pollutants values from the emitting industry sites and

from one of the nine State's air-monitoring stations to the patient address, we used ArcGIS 10.4 with the IDW and EBK techniques, both described in section 2.2.4.

The different spatial statistics techniques used for this research are described and explained below.

## 2.2. Spatial statics technique

Once the database of BC and environmental pollution settings were obtained, the CrimeStat program performed the Nearest Neighbor Index (NNI) and Nearest Neighbor Hierarchical Clustering (NNHC) analysis. The SaTScan software was used for statistical spatial scanning analysis.
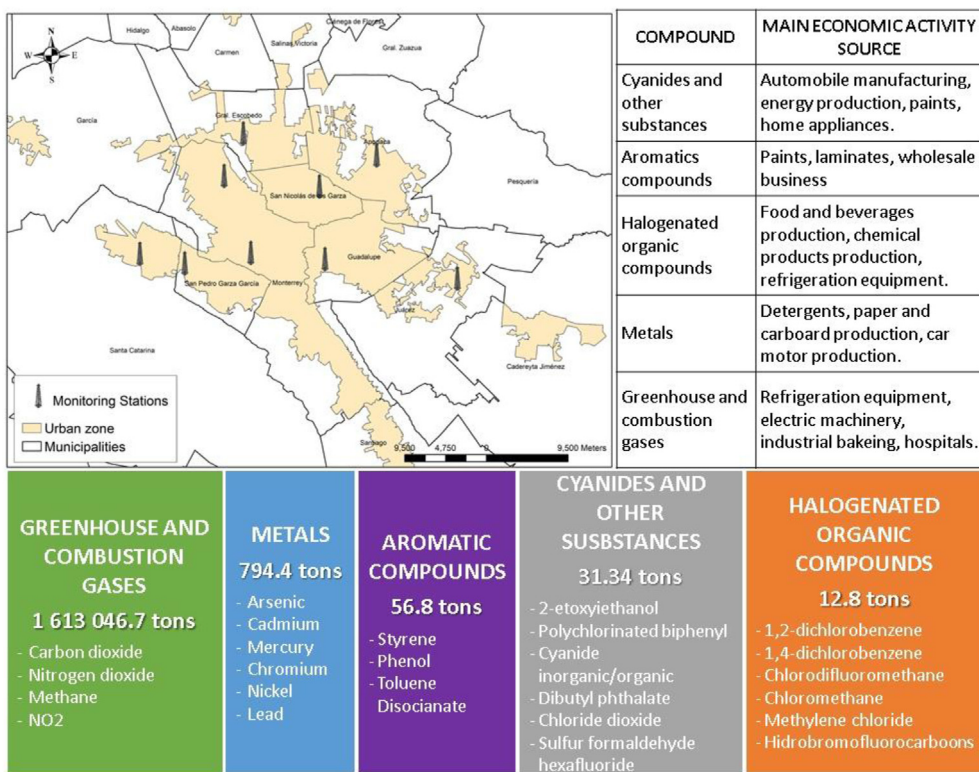
**Figure 2.** Map of the Monterrey Metropolitan Area with the location of the pollution monitoring stations with the classification and total production of pollutants emitted by companies in 2010–2015 (Source: Sistema Integral de Monitoreo Ambiental del Estado de Nuevo León (SIMA)).

We used interpolation techniques to estimate the values of contaminants emitted by the polluting companies and estimate $PM_{10}$ values from the environmental monitoring stations. Likewise, the Getis-Ord cluster analysis was used to generate hot spot maps.

### 2.2.1. Statistical Gi* Getis-Ord

The Getis-Ord statistic was used as a spatial statistical technique to identify significant concentrations of high and low values of the number of deaths associated with BC at the municipal level (Figure 1). This statistic is a local indicator of spatial autocorrelation that allows the identification and visualization of local patterns of association (hot spots) and local instabilities of the global spatial association (Anselin, 2010; Getis and Ord, 2010). The ArcGIS spatial statistics tools section for the implementation of this pattern analysis technique was used. This statistic is defined as follows:

$$G_i^* = \frac{\sum_{j=i}^{n} w_{ij}(d)x_{ij} - \overline{x} \sum_{j=i}^{n} w_{ij}(d)}{S\sqrt{\frac{n\sum_{j=i}^{n} w_{ij}^2(d) - \left(\sum_{j=i}^{n} w_{ij}(d)^2\right)}{n-1}}} \tag{1}$$

Equation 1. Spatial autocorrelation
where $x_j$ is the value of AGEB $j$, $w_{ij}$ $(d)$, is the spatial weighting between the value of AGEB $i$ and AGEB $j$, that is, the value of the same variable in another geographic unit, $n$ represents the total number of geographic areas. While $S$ is calculated as follows:

$$S = \sqrt{\frac{n\sum_{j=i}^{n} x_j^2}{n} - (\overline{x})^2} \tag{2}$$

Assuming $G_i^*$ has a normal distribution, the results can be interpreted as Z scores along a normal curve. In this sense, positive Z scores above 1.96 are statistically significant at significance levels of 0.05, which

indicates that the location of $i$ is surrounded by relatively high values, while the opposite occurs when $G_i^*$ is significant and negative, it is that is, the location of $i$ is surrounded by relatively low values.

### 2.2.2. Nearest Neighbor Index (NNI) analysis

After processing the information, the degree of concentration of the companies with information on polluting substances and BC cases was determined using the NNI proposed by Clark and Evans (1954). There are some investigations in which this technique was used to determine the degree of concentration of points over space and to identify clusters (Boix et al., 2015; Gasca-Sanchez et al., 2019; Meyer, 2006).

This technique consists of comparing the distance between the closest points, determining the average distance between neighbors, and comparing the expected average distance of a hypothetical random distribution. If the mean distance is less than the average of the random distribution, it can be determined that the distribution of points follows a pattern of agglomeration. (See Figure 3) On the other hand, if the mean distance is larger than the random distribution, the points are considered to follow a dispersion sequence (Levine, 2002).

The relationship of the distance to the nearest neighbor (NND, Neighbor Nearest Distance) is as follows:

$$\text{NND} = \frac{\overline{D}o}{\overline{D}a} \tag{3}$$

Equation 3. Neighbor Nearest Distance
where $\overline{D}o$ is the observed mean distance between each point and its nearest neighbor, and $\overline{D}a =$ is the expected mean distance for the points in a random distribution pattern calculated as:

$$\overline{D}a = 0.5\left(\frac{A}{N}\right) \tag{4}$$

Equation 4. Random distribution pattern
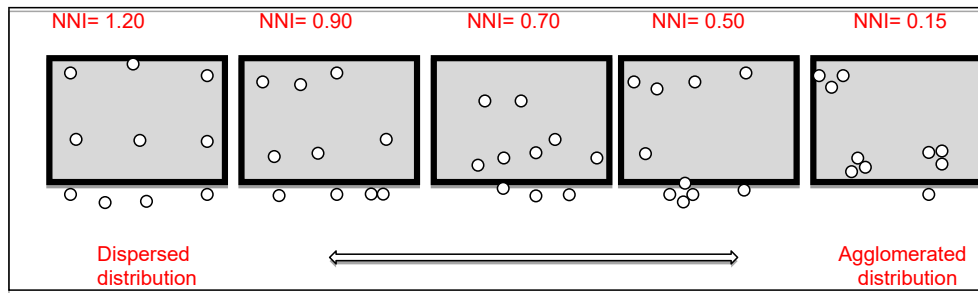
**Figure 3.** Example of an agglomerated or dispersed distribution of a number of BC cases with their respective NNI values. The NNI values show the intensity of the agglomeration of the points in space, it can be seen that the points with NNI values greater than 1 are more dispersed than the points with NNI values close to 0. Source: Authors' elaboration.

where A is the minimum area (square meters) enclosing a rectangle around all the points, and N is the number of points. In general terms, the NNI is the ratio of the distance from the nearest neighbor observed to the average random distance.

$$NNI = \frac{d\ (observed)}{d\ (random)} \qquad (5)$$

Equation 5. Nearest Neighbor Index

Consequently, if the result generates coefficients higher than 1, the points are considered dispersed, whereas they are agglomerated if it is less than 1. Coefficients closer to 0 indicate higher concentration in the point cloud.

### 2.2.3. Nearest Neighbor Analysis with Hierarchical Clusters (NNHC)

This technique identifies groups of points that are spatially close. It compares the distance between pairs of points with the expected distance of a hypothetical random distribution in a given area and clusters the groups of unusually close pairs (Levine, 2002). This generates first-order clusters; then, the analysis applied to first-order clusters to enclose in circles clusters that are unusually close, generating second-order clusters. This procedure continues until more levels of clusters are generated until they can no longer be found. Normally, the hierarchical clustering procedure generates groups up to third order. In order to generate first-order clusters, the software selected that each cluster would significantly cluster a minimum of five or more cases.

### 2.2.4. Interpolation by Inverse Distance Weighted (IDW), Empirical Bayesian Kriging (EBK), and Kernel Density Approach

The technique to analyze the spatial distribution of pollutants in the sample of companies was IDW; this technique assumes that things that are close to others are more similar than others that are far away, so to predict a value in space takes as a reference to their nearest neighbors in a given radius. There is empirical evidence on the use of interpolation techniques applied to environmental pollution, using both IDW and Kriging Density Approach (Dhiman and Singh Sandhu, 2017; Duc et al., 2000; Shi et al., 2013). According to Cañada (2008), the spatial interpolation by IDW is developed as follows:

$$Z(s_0) = \sum_{j=i}^{n} \lambda * Z(s_i) \qquad (6)$$

Equation 6. Spatial interpolation by IDW

where $Z(s_0)$ is the value that predict the location $(s_0)$, $n$ is the total sample points (pollutant firms) near the point to be predicted, $\lambda$ is the weighted value assigned to each point and it will be used for the prediction of values. The point values diminish with the distance, were $Z(s_i)$ is the value observed in the location $s_i$. Although there are other interpolation methods such as Kiriging, the IDW interpolation is the one that best fits the database of polluting companies in this research, since the distribution of the points generated greater errors with other techniques.

On the other hand, the interpolation by Empirical Kriging Bayesian was used to distribute the $PM_{10}$ values of the nine monitoring stations,

employing the ArcGIS Geostatistical Analyst 10.4.1, since it presents a better adjustment to distribute the air pollution over continuous space. With a structure similar to the previous formula, the results were generalized by calculating the mean squared error of interpolation (RMSR) is described as follows:

$$RMSR = \sqrt{\sum_{i=1}^{n} \frac{\widehat{Z}\ (x_i)\ -\ Z\ (x_i)^2}{n}} \qquad (7)$$

Equation 7. Mean squared error of Interpolation

where $(x_i)$ is the value after interpolation and $Z\ (x_i)$ is the measured value in point $(x_i)$. In the case of $PM_{10}$ contamination interpolation, the EBK was chosen because with this technique the mean error was considerably reduced (.6530) in relation to the IDW technique (1.314). In Figure 4, the fit of the data is shown by means of the semivariogram.

Similarly, Kernel Density was used to identify the areas of the MMA where BC cases are intensified, which according to Kelsall & Diggle (1995) is denoted as follows:

$$g(xj) = \sum_{i=1}^{N} \left[ KW_i I_i \frac{1}{h^2 2\pi} e^{\frac{d_{ij}^2}{2h^2}} \right] \qquad (8)$$

Equation 8. Kernel density

where $g(xj)$ is the density of cell $j$, $d_{ij}^2$ is the distance between cell $j$ and a location of a BC case $i$, $h$ is the standard deviation of the normal distribution, $K$ is a constant, $W_i$ is a weight in the location of a BC case and $I_i$ is an intensity of the location of a BC case. The density of BC cases provides assistance in identifying areas where the sample is intensified, as well as helping to identify spatial patterns.

### 2.2.5. Spatial scanning statistical analysis

Kulldorff (1997) spatial scan statistical analysis was used to identify risk areas for BC cases, using information on the population of each AGEB. This method has been widely used in health research as a tool to identify groupings of phenomena associated with health and
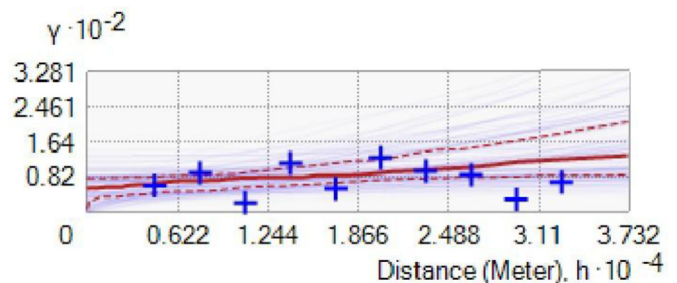


**Figure 4.** Semivariogram for EBK interpolation of monitoring stations showing $PM_{10}$ values.

sociodemographic (Kihal-Talantikite et al., 2013; Kulldorff and Nagar-walla, 1995; Rao et al., 2017). Statistical scanning was performed using a discrete Poisson model, identifying high-risk groups of BC cases in the AGEBS, in relation to their population. The expected number of BC cases in each AGEB is calculated as:

$$E[c] = p*C/P \qquad (9)$$

Equation 9. Discrete Poisson Model for high-risk groups

where c is the observed number of BC cases, p is the AGEB population, and C and P are the total number of BC cases and population, respectively. A relative risk of BC cases for each AGEB is calculated by dividing the observed number of BC cases by the expected number of BC cases. The alternative hypothesis is that there is a high risk of BC cases within the exploration cluster compared to what happens outside it.

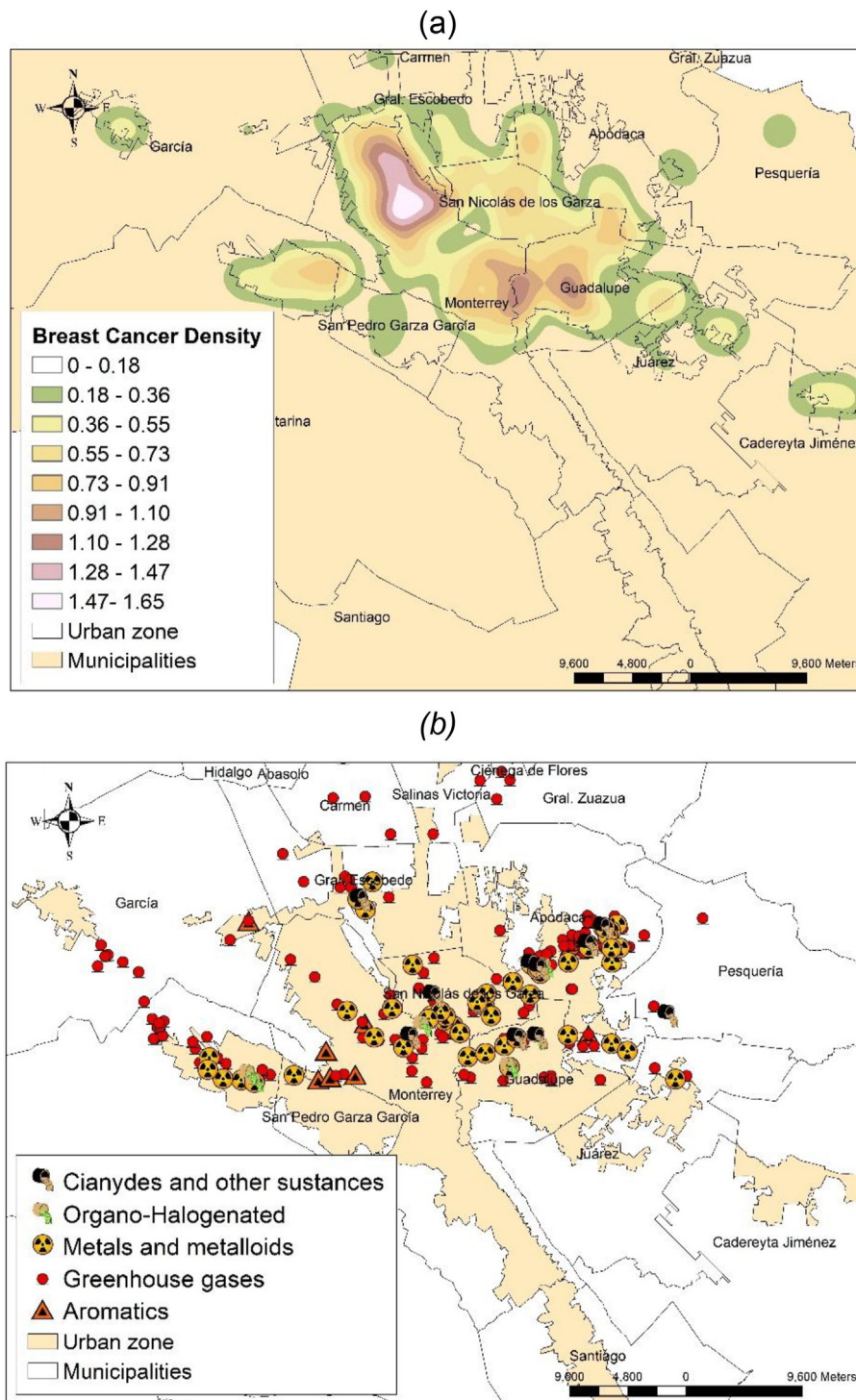Under the Poisson assumption, the likelihood function for a specific window is proportional to:

(a)



(b)



**Figure 5.** Spatial distribution of breast cancer cases with Kernel density technique (a), and polluting firms' location according to the type of pollutant they emit (b). (Source: From our authorship from data of the National Institute of Statistics and Geography (INEGI, 2020), Sistema Integral de Monitoreo Ambiental del Estado de Nuevo León (SIMA), and our database of BC cases.).

(a)



(b)
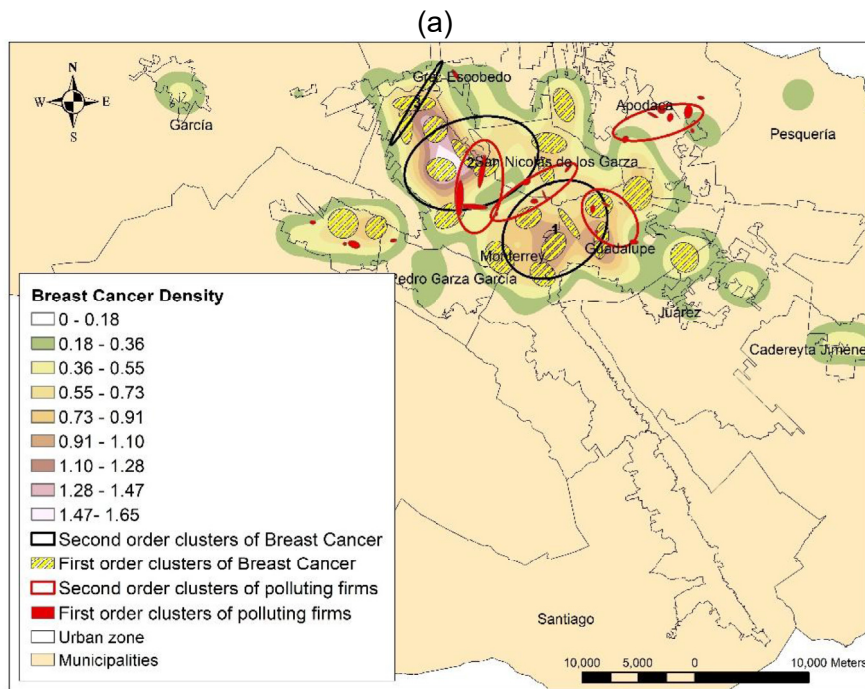
| Chemical type | Sample | First order Clusters | Mean Nearest Neighbor Distance (m) | Expected Nearest Neighbor Distance (m) | Nearest Neighbor Index (NNI) | p-value |
|---|---|---|---|---|---|---|
| Breast cancer | 349 | 22 | 716.1179 | 1435.3215 | 0.50 | 0.00 |
| Total Polluting firms | 312 | 23 | 438.8 | 1125.2 | 0.4 | 0.00 |
| Firms emiting Greenhouse gases | 228 | 7 | 537.93 | 1292.84 | 0.42 | 0.00 |
| Firms emiting aromatics | 10 | 0 | 4787.16 | 3031.97 | 1.58 | 0.01 |
| Firms emiting Organic-Halogenated | 8 | 0 | 4942.43 | 5018.51 | 0.98 | 0.96 |
| Firms emiting Metals and metalloids | 56 | 2 | 1471.95 | 2289.19 | 0.64 | 0.05 |
| Firms emiting Cyanides and other pollutants | 10 | 0 | 3523.61 | 2701.33 | 1.30 | 0.05 |

**Figure 6.** Breast cancer spatial clusters and polluting firms (a), Nearest Neighbor Index (NNI) for breast cancer and polluting firms (b). (Source: From our authorship from data of the National Institute of Statistics and Geography (INEGI, 2020), Sistema Integral de Monitoreo Ambiental del Estado de Nuevo León (SIMA), and our database of BC cases.).

$$\left(\frac{c}{E[c]}\right)^c \left(\frac{C-c}{C-E[c]}\right)^{c-c} I() \qquad (10)$$

Equation 10. Relative risk for high-risk groups

where $C$ is the total number of BC cases, $c$ is the observed number of BC cases within the window, and y $E[c]$ is the expected number of BC cases within the window under the null hypothesis that there is no difference. Because the analysis is conditioned on the total number of observed cases, $C- E[c]$, is the expected number of cases outside the window. $I()$ is an indicator function, with $I() = 1$, is when the window has more cases than expected under the null hypothesis and 0 otherwise The Most likely

cluster was determined through a maximum LLR (Log Likelihood Ratio), generating 999 Monte Carlo simulations to determine the statistical significance for the identified clusters.

## 3. Results

### 3.1. Spatial localization of BC cases and polluting firms

In order to identify the spatial distribution of the sample of cases of BC, several interpolation techniques were used to know the intensity of

the phenomena in the urban space. Figure 5(a) shows the Kernel density distribution of BC cases, and Figure 5(b) shows the spatial distribution and registry of firms with types of pollutants.

## 3.2. Nearest Neighbor Analysis

The density analysis (Figure 5a) showed the BC cases spatial behavior and intensity in the urban space, but failed to show significant agglomeration. To illustrate this association, we used the Nearest Neighbor Analysis with Hierarchical Clusters. Figure 6 shows 22 first-order clusters in yellow color; each of these clusters agglomerates at least 5 BC cases in the MMA. The first order cluster showed coincidence with the intensity of the Kernel analysis. This Figure also shows 3 second-order BC clusters with a black color line, each numbered, representing agglomeration hierarchy. The second-order cluster number 1 agglomerates more clusters (7 first-order clusters) than second-order cluster number 2 (5 first-order clusters) and second-order cluster number 3 (3 first-order clusters). Also, the first and second-order clusters with a registry of polluting substances were pointed in red. Figure 6 (a) showed the spatial interaction of second-order clusters of BC and polluting firms, demonstrating a non-random distribution with a spatial interaction between them.

In order to quantitatively show this interaction, the Nearest Neighbor Analysis produces a coefficient. The closest the coefficient is to 0, it is more agglomerated (See data in Figure 6 b). This datum shows the analysis by the BC cases and the polluting firms. The firms that emit greenhouse gases are the majority, with 228 out of 312, and the organic/halogenated polluter's firms are only 8. The third column shows the number of first-order clusters of both BC and Polluting firms, 22 and 23, respectively. The fourth and fifth columns show the near neighbor coefficients. By the NNI values, in the sixth column, the firms emitting greenhouse gases tend to have some degree of agglomeration, while firms emitting aromatics and cyanides showed spatial dispersion.

## 3.3. Spatial interaction of BC cases by polluting type

Figure 7 shows the spatial interaction of BC cases with different types of pollutants. Each pollutant may produce different patterns; for example, greenhouse gases spatial distribution (7a) was more heterogeneous compared with other pollutants with a more centripetal distribution like aromatics (7b) and cyanides (7e) located in the northern urban zones.

Figure 8 shows the BC cases at different ranges of concentration of pollutants. For the analysis, the value of concentration for each pollutant was encoded in 10 ranges. Datum presented were expressed in metric tons (mean values). Figure 8 (a) greenhouse gases, showed that 79.7% of BC cases were in the range 5 and 6; this sample showed a significant spatial interaction with this pollutant up to 16,000 metric tons. A similar situation is present with the halogenated compounds where most BC cases lie in the intermediate ranges, and most the cases were in range 7. In the case of metals, the ranges 4 and 5 accumulate the majority of cases (55.9%). Aromatic and cyanide compounds tend to accumulate in the higher ranges.

Figure 7(f) shows the different $PM_{10}$ concentration ranges, from 42 to 68 $\mu g/m^3$. The BC first-order clusters are in yellow, and BC second-order clusters in black. There are 12 first-order clusters with clear interaction with the $PM_{10}$ higher levels, as well as second-order clusters number 2 and number 3. There are 9 first-order clusters and 1 second-order cluster associated with $PM_{10}$ at medium range levels in a zone with a significant polluting industry like food processing plants and cement industry. Figure 8(f) shows the localization of BC cases associated with the different $PM_{10}$ concentration ranges. Range 8 agglomerates the highest number of cases, 65 (18.6%). In summarize, 65% of BC cases had exposure to $PM_{10}$ concentration of 56 $\mu g/m^{3)}$ or more.

## 3.4. BC cluster identification by spatial scan statistics

In Figure 9, 5 clusters of BC cases can be observed generated by the spatial statistical scan, all of them with significant values at least at 10 percent. Similarly, it can be observed that these clusters have close geographic proximity to some sources of environmental pollution, such as food processing plants, cement, metal products, among others. Particular attention is generated by secondary cluster 5, which is close to an oil refinery, a source of contamination with strong empirical evidence on the incidence of many diseases, including BC.

Particular attention is generated by the most likely cluster located in the central part of the urban space; this cluster is located in a residential area of the city that has a high population density (202,855 inhabitants) in a radius of 3.59 km with 39 observed cases of BC.

Likewise, in the most likely cluster, many industries that generate various pollutants associated with multiple cancer types are agglomerated. Illustratively, Figure 9 shows only the large food processing plants, other industrial products and some sources of environmental pollution. However, other small and medium-sized companies also generate environmental pollution. In this way, it is shown that this metropolitan area is characterized by a strong interaction between the population and polluting industry, as can be seen in the picture in appendix 1.

The most likely cluster presents a relative risk of 2.67; that is, this cluster presents a BC excess risk rate of 1.67 higher than what could be found outside of it. This is generated by a randomization process with high levels of significance. Similarly, secondary cluster 5, located in the lower right part of Figure 9 and close to an oil refinery, agglomerates 22 cases of BC in a radius of 3.53 km with a population of 229,771 inhabitants and a relative risk of 2.18. The secondary clusters could be read similarly.

## 4. Discussion

Breast cancer is one of the leading causes of death in women older than 30 years. Since 1990 there is a record of 126,276 deaths nationwide and 6,988 deaths in the MMA, attributed to BC (INEGI, 2020). In South Korea, breast cancer has annually increased by 6.1% from 1999 to 2014, that represented 91.5% in 15 years (Jung et al., 2017). In Mexico, the death rate of BC in women was increased by 174.7% in 15 years (1990–2015) (INEGI, 2020). This high mortality rate makes the MMA a good study case. The MMA represents an urban area with various ambient elements (eating patterns, air pollution, type of polluting industry, and others) that might act as disease triggers, particularly in the BC generation.

In order to understand the BC neogenesis, we can rely on geographical patterns. Still, it is necessary to build up a link to a physio-pathological mechanism if we considered that less than 30% of BC cases has heritable causes. Most cases resulting as the sum of several acquired risk factors during a life-course. In this paper, we discuss only the environmental risk factors.

In these paper we showed that the most likely cluster produced one of the largest RR to the largest population (RR = 2.67 to 202, 855 inhabitants). In this setting high population density coincide with high vehicle density and industrial emissions (locally produced and carried by city's winds) from food processing plants, cement industry, chemical industry, oil refinery and others. Secondary clusters 2 and 3 had a higher RR (8.5 and 5.6, respectively) but to a relative smaller population. These findings in probably represented an accumulation of city's pollutants that cross the city to the north-west direction and stop between the mounts El Mirador and Sierra Madre. No single ambient pollutant showed a dose-response trend, but several picks in the middle concentration range of cyanides, aromatic greenhouse gases and metals, pointed to a synergy mechanism. Also we are not accounting to daily, temporal picks, but to daily averages or annual average, and one of these picks might cause the cancer initiation process. So, ambient conditions associated with persona
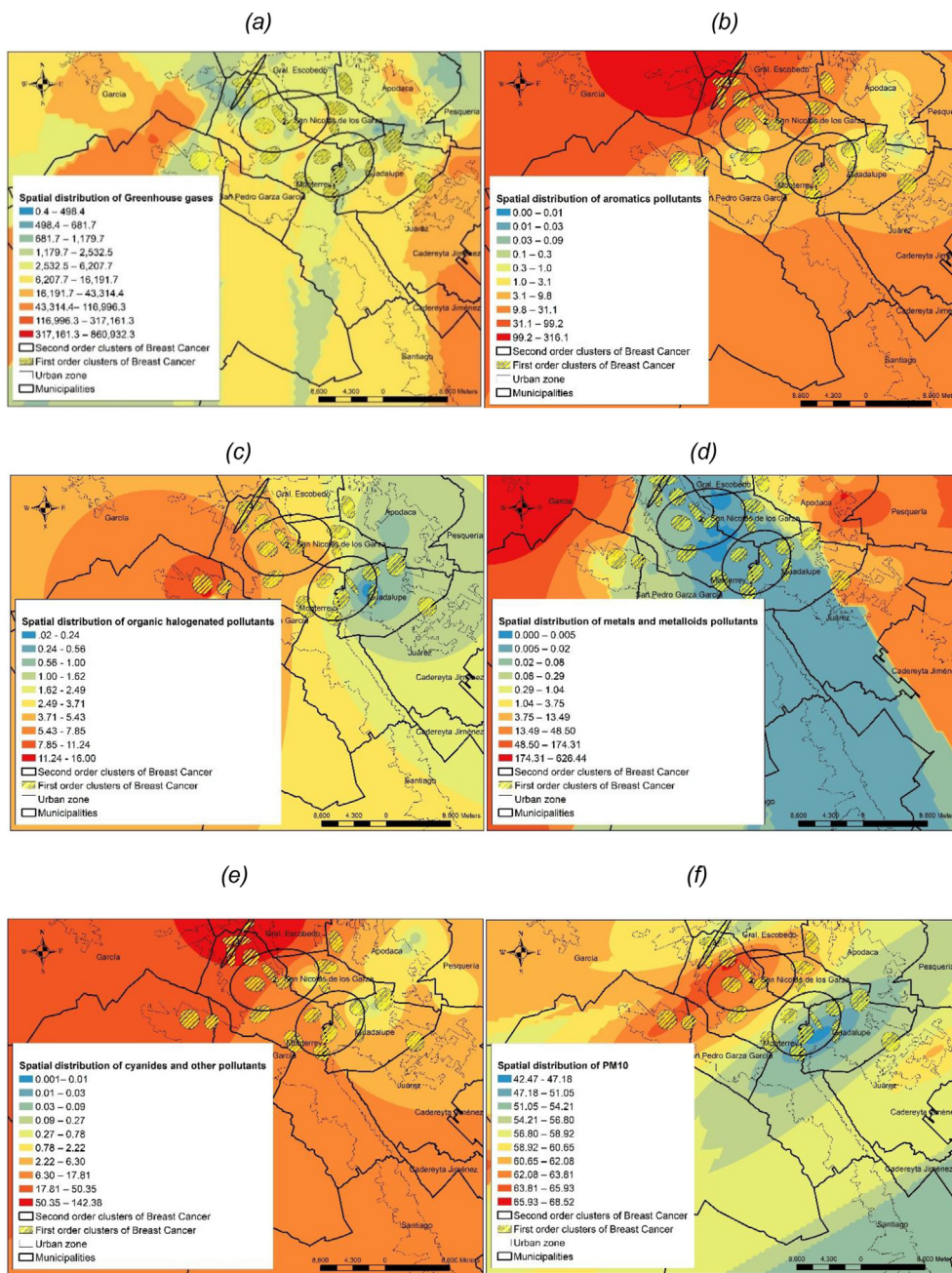
**Figure 7.** Spatial interpolation of industry's pollutants by type using IDW technique. Greenhouse gases (a); aromatic pollutants (b); organic-halogenated pollutants (c); metals and metalloids (d); cyanides (e) and $PM_{10}$ (f). First order clusters as shown in yellow color and second order clusters are in black color. (Source: From our authorship from data of the National Institute of Statistics and Geography (INEGI, 2020), Sistema Integral de Monitoreo Ambiental del Estado de Nuevo León (SIMA), and our database of BC cases.).

habits impose the highest risks, in the presence of a synergic effects of ambient pollutants. The spatial statistical techniques help us to understand these complex risk relationships with a non-aleatory spatial distribution of the variables.

In the epidemiology perspective the presence of industrial activity is associated to BC. For example in the city of Kemerovo, a socioeconomic crisis shut down a whole industrial setting composed of mining, chemical, metallurgical, and power sectors. After ten years of industrial cessation and ecological improvements in the same area, a cancer trend tended to decrease and behave more like a rural setting instead of an urban setting. This research pointed to the environmental toxicity associated with urban industrial environments (Kutikhin et al., 2012). In the last decade MMA had an opposite direction with a growing trend in population density, a projected industrial land use 63.1% with a

consequent increase in industrial production and a 40% increment of BC mortality rate (Garza-Villarreal, 1998).

Other example is the endocrine disruption produced by alteration in hormone synthesis, blockage of hormone binding sites in target tissues, change the hormone secretion pattern, change in target tissues, change in the cascade signaling, or alter the hormone metabolism (Macon and Fenton, 2013) that might lead to BC. A frequent endocrine disruptor is dioxin, a bypoduct of internal combustion motors and machinery (Soto and Sonnenschein, 2010). These are probably present in many of the city locations.

BC has also been linked to air pollution, especially to nitrogen oxides, fine particulate matter ($PM_{10}$ and $PM_{2.5}$), and PAHs (Hwang et al., 2020). There are other reports of the association between exposure to the higher levels of $PM_{10}$ and BC. (Andersen et al., 2017; Bonner et al., 2005; Hwang

### (a) Greenhouse gases

| range | values | Breast cancer cases | Percentage |
|---|---|---|---|
| 1 | 0.4 – 498.4 | 0 | 0 |
| 2 | 498.4 – 681.7 | 0 | 0 |
| 3 | 681.7 – 1,179.7 | 0 | 0 |
| 4 | 1,179.7 – 2,532.5 | 9 | 2.58 |
| 5 | 2,532.5 – 6,207.7 | 126 | 36.10 |
| 6 | 6,207.7 – 16,191.7 | 152 | 43.55 |
| 7 | 16,191.7 – 43,314.4 | 53 | 15.19 |
| 8 | 43,314.4– 116,996.3 | 9 | 2.58 |
| 9 | 116,996.3 – 317,161.3 | 0 | 0 |
| 10 | 317,161.3 – 860,932.3 | 0 | 0 |

### (b) Aromatics

| range | values | Breast cancer cases | Percentage |
|---|---|---|---|
| 1 | 0.00 – 0.001 | 0 | 0.00 |
| 2 | 0.001 – 0.03 | 0 | 0.00 |
| 3 | 0.03 – 0.09 | 0 | 0.00 |
| 4 | 0.09 – 0.30 | 2 | 0.57 |
| 5 | 0.30 – 0.96 | 6 | 1.72 |
| 6 | 0.96 – 3.06 | 33 | 9.46 |
| 7 | 3.06 – 9.76 | 166 | 47.56 |
| 8 | 9.76 – 31.11 | 87 | 24.93 |
| 9 | 31.11 – 99.16 | 35 | 10.03 |
| 10 | 99.16 – 316.1 | 20 | 5.73 |

### (c) Organic-halogenated

| range | values | Breast cancer cases | Percentage |
|---|---|---|---|
| 1 | .02 - 0.24 | 3 | 0.86 |
| 2 | 0.24 - 0.56 | 8 | 2.29 |
| 3 | 0.56 - 1.00 | 38 | 10.89 |
| 4 | 1.00 - 1.62 | 56 | 16.05 |
| 5 | 1.62 - 2.49 | 52 | 14.90 |
| 6 | 2.49 - 3.71 | 57 | 16.33 |
| 7 | 3.71 - 5.43 | 100 | 28.65 |
| 8 | 5.43 - 7.85 | 17 | 4.87 |
| 9 | 7.85 - 11.24 | 17 | 4.87 |
| 10 | 11.24 - 16.00 | 1 | 0.29 |

### (d) Metal and metalloids

| range | values | Breast cancer cases | Percentage |
|---|---|---|---|
| 1 | 0.000 – 0.005 | 1 | 0.29 |
| 2 | 0.005 – 0.02 | 1 | 0.29 |
| 3 | 0.02 – 0.08 | 7 | 2.01 |
| 4 | 0.08 – 0.29 | 94 | 26.93 |
| 5 | 0.29 – 1.04 | 101 | 28.94 |
| 6 | 1.04 – 3.75 | 61 | 17.48 |
| 7 | 3.75 – 13.49 | 44 | 12.61 |
| 8 | 13.49 – 48.50 | 21 | 6.02 |
| 9 | 48.50 – 174.31 | 18 | 5.16 |
| 10 | 174.31 – 626.44 | 1 | 0.29 |

### (e) Cyanides

| range | values | Breast cancer cases | Percentage |
|---|---|---|---|
| 1 | 0.001– 0.01 | 0 | 0.00 |
| 2 | 0.01 – 0.03 | 0 | 0.00 |
| 3 | 0.03 – 0.09 | 0 | 0.00 |
| 4 | 0.09 – 0.27 | 3 | 0.86 |
| 5 | 0.27 – 0.78 | 5 | 1.43 |
| 6 | 0.78 – 2.22 | 33 | 9.46 |
| 7 | 2.22 – 6.30 | 90 | 25.79 |
| 8 | 6.30 – 17.81 | 97 | 27.79 |
| 9 | 17.81 – 50.35 | 77 | 22.06 |
| 10 | 50.35 – 142.38 | 44 | 12.61 |

### (f) PM$_{10}$

| range | values | Breast cancer cases | Percentage |
|---|---|---|---|
| 1 | 42.47 - 47.18 | 4 | 1.15 |
| 2 | 47.18 – 51.05 | 33 | 9.46 |
| 3 | 51.05 – 54.21 | 44 | 12.61 |
| 4 | 54.21 – 56.80 | 39 | 11.17 |
| 5 | 56.80 – 58.92 | 53 | 15.19 |
| 6 | 58.92 – 60.65 | 37 | 10.6 |
| 7 | 60.65 – 62.08 | 41 | 11.75 |
| 8 | 62.08 – 63.81 | 65 | 18.62 |
| 9 | 63.81 – 65.93 | 28 | 8.02 |
| 10 | 65.93 – 68.52 | 5 | 1.43 |

**Figure 8.** BC cases by concentrations of the pollutant type. (a) Greenhouse gases; (b) Aromatic pollutants; (c) Organic-halogenated pollutants; (d) Metals and metalloids; (e) Cyanides (f) PM$_{10}$. (Source: From our authorship from data of the National Institute of Statistics and Geography (INEGI, 2020), Sistema Integral de Monitoreo Ambiental del Estado de Nuevo León (SIMA), and our database of BC cases.).

(a)

(b)

| Cluster | Latitude | Longitude | Radius (km) | Number of AGEBS | LLR | Observed | Expected | Relative Risk | Population | P value |
|---------|----------|-----------|-------------|-----------------|-----|----------|----------|---------------|-----------|---------|
| Most likely cluster | 25.669175 | -100.275703 | 3.59 | 89 | 12.94 | 39 | 15.82 | 2.67 | 202,855 | 0.00 |
| Secondary cluster 2 | 25.604946 | -100.029031 | 2.84 | 63 | 8.62 | 6 | 0.58 | 8.48 | 67,501 | 0.07 |
| Secondary cluster 3 | 25.73001 | -100.374018 | 0.78 | 4 | 6.25 | 7 | 1.27 | 5.60 | 16,341 | 0.08 |
| Secondary cluster 4 | 25.777321 | -100.377697 | 2.51 | 49 | 6.10 | 30 | 15.07 | 2.10 | 193,279 | 0.05 |
| Secondary cluster 5 | 25.683218 | -100.456075 | 3.53 | 79 | 4.18 | 22 | 10.08 | 2.18 | 229,771 | 0.05 |

et al., 2020; Hystad et al., 2015). In this paper, two-thirds (65%) of cases are exposed to $PM_{10}$ concentration of 56 μg/m$^{3)}$ or more. As a reference, the Mexican mean annual concentration for $PM_{10}$, set as a normal limit, is 40 μg/m$^3$ (NOM-025-SSA1-2014). This exposure puts the MMA in constant risk. Most of the pollution scenarios are above the normal limit, but the annual average does not show the spikes, lower or higher, that might occur during the year. Some of the higher spikes might also have a profound effect on the BC neo-genesis.

Another issue is the window of susceptibility for BC that can be located in the prenatal, puberty, pregnancy, and menopausal period. Here is where many of the endocrine disruptors like PAHs, perfluorinated compounds, polybrominated diphenyl ethers, phenols and metals can act, some of them may increase the risk for BC at any age, including the prenatal period. (Bonner et al., 2005; Terry et al., 2019). An example of the relationship between polluting industries and BC cases is Pan et al. (2011), they found an association of BC in premenopausal women, that lived near steel mills (0.8–3.2 km) or

thermal power plants (<0.8 km). For postmenopausal women, BC cases were associated with living near petroleum refinery (0.8–3.2 km) and pulp mills (0.8–3.2 km). Also, BC was also associated with living for ten or more years near thermal power plants within a distance of 0.8 km.

Eating chargrilled meats can also impose a BC risk. This cooking style is very popular in the MMA. In this cocking process, especially in the well-done level, PAHs like 2-amino-1-methyl-6-phenylimidazo pyridine (PhIP), a carcinogenic compound, can contaminate the food (Zheng et al., 1998). The food cooking byproducts had been linked to cancer, but also the meat processing. Johnson (2011) showed an excess of death from several cancers, including BC, in meat processing industry workers from slaughters, butchers, meat cutters, and meat processors. Processed meat may also constitute a risk for BC and this products are highly consumed by the study population.

Mancilla et al. (2016) characterized $PM_{2.5}$ content and found twelve PAH compounds – fluoranthene acephenanthrylene, pyrene, benzo(a)

anthracene, chrysene, benzo(k)fluoranthene + benzo(b)fluoranthene, benzo(a)pyrene + benzo(e)pyrene, perylene, indeno(123cd)pyrene, benzo(ghi)perylene, dibenz(ah)anthracene and coronene. The concentration of this compounds vary with year-season and daytime/night periods. Many of this compounds came from industrial, domestic combustion sources and gasoline or diesel-powered vehicles. The chemical mass balance contribution to the MMA's ambient PM2.5 was described as Diesel 45.3%, Gasoline 18.6%, Meat cooking 30.9%, fuel oil 2.9% and biomass burning 0.5%.

Even that most of our cases derived from urban communities, some organochlorine compounds commonly used as domestic and agricultural pesticides might impact breast tissue (Kleanthi and Andreas, 2009). Other possible contaminants are cyanides; for example, hydrogen cyanide could be emitted into the air as a combustion exhaust from vehicles, burnings, refineries, and other elements present in the MMA. Hydrogen cyanide has been linked to BC cases (Jaszczak et al., 2017). The plastic industry might produce bisphenols, an environmental pollutant with carcinogenic activity (Nair et al., 2020). We did not measure some of this compounds, but we expect their presence in the MMA as well.

Metals and metalloids may produce estrogenic effects and oxidative stress that may act as inductors of cancer in mammary cells (White et al., 2018). Antimonium, cobalt, and mercury, also present in the local industry, may have estrogenic effects that increase the risk of BC (Kresovich et al., 2019). Martínez-Cinco et al. (2016) characterized mean concentration and elemental analysis of PM2.5 found in ambient air of MMA. The particle content included Aluminum, silicon, sulfur, chorine, potassium, calcium, thallium, vanadium, chromium, manganese, iron, nickel, cuprum, zinc, bromide, lead, chromium, $NO_3^-$, $SO_4^-$, $NH_4^-$, potassium, sodium, organic carbon, BC, and total carbon. In this article the estimated source contribution to the mass of PM2.5 was vehicle emission (36.7–46.7%) secondary aerosols (17.4–32.4%), geological material (20.4–23.4%) industry (1.0–2.3%) and cooking (4.5–16.9%), depending on the season of the year. Some of these compounds easily travel to the pulmonary alveolus and might produce carcinogenic effects.

Regarding the sample of this study, the patients have an average age of 51 (range 26–88), 100% were female, and the body mass index average of 29.3 (range 17.9–48.6). 1.5% of the patients were underweight, 21% normal BMI, 35.7% overweight, 26.3% obesity grade I, 10.8% obesity grade II and 4.7% obesity grade III at the moment of the diagnosis, a situation that, together with the exposure of environmental pollution, could favor the appearance of breast cancer. Regarding immunohistochemistry diagnosis, 2.1% had an undifferentiated luminal type, 14% were HER2-enriched, 24.1 % were triple-negative, 28.1% were luminal B, and 31.7% were luminal A subtype, in particular, the HER2 and triple negative types have the worst prognosis since they often do not respond to chemotherapies.

According to the clinical stage classification, 0.6% patients had a clinical-stage 0, 7.7% clinical-stage I, 20.3% clinical-stage IIA, 24.7% clinical-stage IIB, 21.5% clinical-stage IIIA, 14.1% clinical-stage IIIB, 3.5% clinical-stage IIIC, 7.6% clinical-stage IV and 0.6% patients had a clinical-stage VI, of which those belonging to clinical-stage IV present invasion in different areas of the body. Regarding the age of the sample, 51% are patients younger than 50 years and 49% older than 50 years, a risk factor for the presence of breast cancer. The spatial grouping in relation to age can be observed in appendix 6.2, in which the differences in the location of patients older and younger than 50 years can be observed.

Once we observed the non-aleatory spatial distribution of BC cases in the urban space, we need more studies to determine how specific exposures of several pollutants might increase the risk of BC.

### 4.1. Limitations

One of the limitations of this research is that it uses a no probabilistic sample-size of BC cases, since accessibility to obtain information at such a disaggregated level is very complicated in Mexico, both due to confidentiality criteria and the quality of the data from government agencies. In this sense, it was possible to have access to data from a specialized center in BC, for which an effort was made to leave empirical evidence on studies associated with health that treat the space as continuous.

## 5. Conclusions

This exploratory and ecological investigation aimed to identify distribution patterns and spatial associations between BC cases and environmental pollution sources. Employing spatial statistical techniques that treat the space as continuous and spatial scanning, which identified high incidence areas, it was determined that BC does not present a random distribution but tends to concentrate in certain city spaces.

The Satscan analysis detected the most polluted cluster with more abundant BC cases in a disaggregated manner that may serve public policymakers to focus on health issues. The NNHC analysis showed the association of BC cases with metals and carcinogens like cyanides. Also, more than half of the BC clusters were associated with $PM_{10}$ levels of 60 $\mu g/m^3$ or more.

This research was intended as an exploratory analysis of a sample of BC cases to identify their spatial behavior and proximity to pollution sources. The BC cases do not show an aleatory spatial distribution in the urban space. The BC clusters were associated with environmental pollution, particularly with food processing plants, cement industry, chemical industry, and oil refinery. These industries emit large amounts of either cyanides or greenhouse gases that could be related to the BC cases.

BC have a complex scenario with many possible factors that contribute to the neogenesis. The environment and geographical proximity have an important role in BC cases that needs further studies and more consideration from the health policymakers.

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### Declarations

#### Author contribution statement

Jesús Santos-Guzman, Francisco Manuel Gasca-Sanchez, Sandra Karina Santuario-Facio, Rocío Ortiz-López, Augusto Rojas-Martinez, Erick Meinardo Garza-Perez, Gerardo Manuel Mejía-Velázquez: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

José Ascención Hernández-Hernández, Servando Cardona-Huerta & Rosa del Carmen López-Sánchez: Conceived and designed the experiments; Contributed reagents, materials, analysis tools or data.

#### Data availability statement

The data that has been used is confidential.

#### Declaration of interests statement

The authors declare no conflict of interest.

#### Additional information

No additional information is available for this paper.

## Appendix

*Geographic proximity between food processing plant and population in the Most Likely Cluster of Breast Cancer*



Figure 10. Geographic proximity between food processing plant and population in the Most Likely Cluster of Breast Cancer.

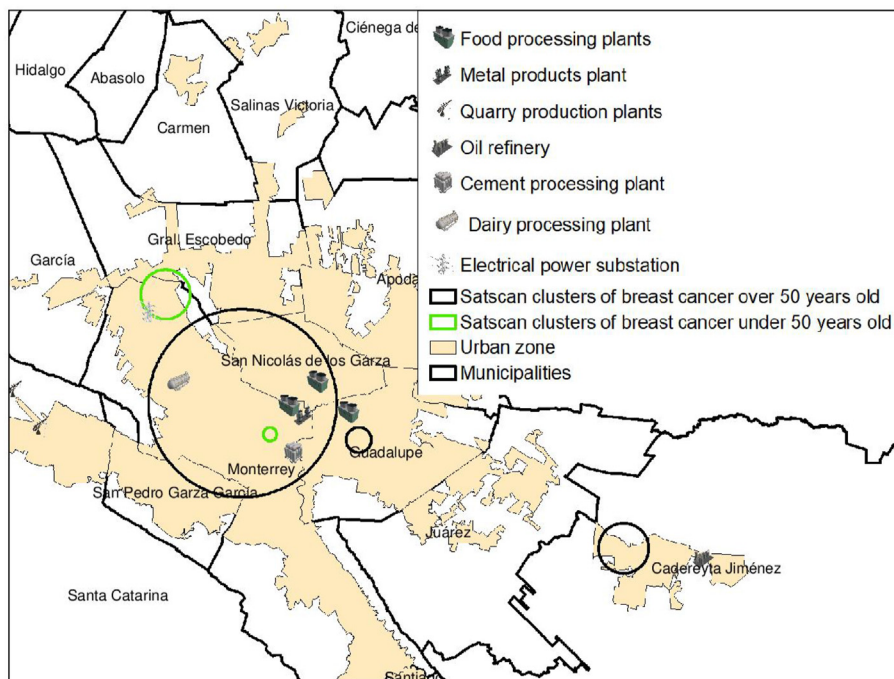*Satscan clusters of breast cancer cases by age group*



Figure 11. Satscan clusters of breast cancer cases classified by under and over 50 years.

In Figure 11, most of the patients had ages less than 50 years old and most of the clustered in the middle of the city and near the petrochemical plant.

# References

Al-Ahmadi, K., Al-Zahrani, A., 2013. NO2 and cancer incidence in Saudi Arabia. Int. J. Environ. Res. Publ. Health 10, 5844–5862.

Andersen, Z.J., Stafoggia, M., Weinmayr, G., Pedersen, M., Galassi, C., Jørgensen, J.T., Oudin, A., Forsberg, B., Olsson, D., Oftedal, B., Marit Aasvang, G., Aamodt, G., Pyko, A., Pershagen, G., Korek, M., De Faire, U., Pedersen, N.L., Östenson, C.-G., Fratiglioni, L., Eriksen, K.T., Tjønneland, A., Peeters, P.H., Bueno-de-Mesquita, B., Plusquin, M., Key, T.J., Jaensch, A., Nagel, G., Lang, A., Wang, M., Tsai, M.-Y., Fournier, A., Boutron-Ruault, M.-C., Baglietto, L., Grioni, S., Marcon, A., Krogh, V., Ricceri, F., Sacerdote, C., Migliore, E., Tamayo-Uria, I., Amiano, P., Dorronsoro, M., Vermeulen, R., Sokhi, R., Keuken, M., de Hoogh, K., Beelen, R., Vineis, P., Cesaroni, G., Brunekreef, B., Hoek, G., Raaschou-Nielsen, O., 2017. Long-term exposure to ambient air pollution and incidence of postmenopausal breast cancer in 15 European cohorts within the ESCAPE project. Environ. Health Perspect. 125, 107005.

Anselin, L., 2010. Local indicators of spatial association-LISA. Geogr. Anal. 27, 93–115.

Bentov, Y., Kordysh, E., Hershkovitz, R., Belmaker, I., Polyakov, M., Bilenko, N., Sarov, B., 2006. Major congenital malformations and residential proximity to a regional industrial park including a national toxic waste site: an ecological study. Environ. Health 5, 8.

Boix, R., Hervás-Oliver, J.L., De Miguel-Molina, B., 2015. Micro-geographies of creative industries clusters in Europe: from hot spots to assemblages: micro-geographies of creative industries clusters. Pap. Reg. Sci. 94, 753–772.

Bonner, M.R., Han, D., Nie, J., Rogerson, P., Vena, J.E., Muti, P., Trevisan, M., Edge, S.B., Freudenheim, J.L., 2005. Breast cancer risk and exposure in early life to polycyclic aromatic hydrocarbons using total suspended particulates as a proxy measure. Cancer Epidemiol. Biomark. Prev. Publ. Am. Assoc. Cancer Res. Cosponsored Am. Soc. Prev. Oncol. 14, 53–60.

Bravo, M.A., Bell, M.L., 2011. Spatial heterogeneity of $PM_{10}$ and $O_3$ in são paulo, Brazil, and implications for human health studies. J. Air Waste Manag. Assoc. 61, 69–77.

Calle, E.E., Rodriguez, C., Walker-Thurmond, K., Thun, M.J., 2003. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of. U.S. Adults. N. Engl. J. Med. 348, 1625–1638.

Cañada, R., 2008. Técnicas de interpolación espacial deterministas y exactas: media ponderada por el inverso de la distancia y funciones de base radial. In: En: Moreno, A. Coordinador. *Sistemas y Análisis de la Información Geográfica. Manual de autoaprendizaje con ArcGis*. Segunda Edición. México: Alfa y Omega- Ra Ma.

Clark, P.J., Evans, F.C., 1954. Distance to nearest neighbor as a measure of spatial relationships in populations. Ecology 35, 445–453.

Coudon, T., Danjou, A.M.N., Faure, E., Praud, D., Severi, G., Mancini, F.R., Salizzoni, P., Fervers, B., 2019. Development and performance evaluation of a GIS-based metric to assess exposure to airborne pollutant emissions from industrial sources. Environ. Health 18, 8.

Crouse, D.L., Goldberg, M.S., Ross, N.A., Chen, H., Labrèche, F., 2010. Postmenopausal breast cancer is associated with exposure to traffic-related air pollution in montreal, Canada: a case–control study. Environ. Health Perspect. 118, 1578–1583.

Csavina, J., Taylor, M.P., Félix, O., Rine, K.P., Eduardo Sáez, A., Betterton, E.A., 2014. Size-resolved dust and aerosol contaminants associated with copper and lead smelting emissions: implications for emission management and human health. Sci. Total Environ. 493, 750–756.

Deng, Y., Jiang, L., Xu, L., Hao, X., Zhang, S., Xu, M., Zhu, P., Fu, S., Liang, Y., Yin, H., Liu, X., Bai, L., Jiang, H., Liu, H., 2019. Spatial distribution and risk assessment of heavy metals in contaminated paddy fields – a case study in Xiangtan City, southern China. Ecotoxicol. Environ. Saf. 171, 281–289.

Desrosiers, T.A., Lawson, C.C., Meyer, R.E., Richardson, D.B., Daniels, J.L., Waters, M.A., van Wijngaarden, E., Langlois, P.H., Romitti, P.A., Correa, A., Olshan, A., National Birth Defects Prevention Study, 2012. Maternal occupational exposure to organic solvents during early pregnancy and risks of neural tube defects and orofacial clefts. Occup. Environ. Med. 69, 493–499.

Dhiman, S., Singh Sandhu, H.A., 2017. Spatial distribution of ambient air pollution using air quality index in Himachal Pradesh- A case study. Int. J. Res. Appl. Sci. Eng. Technol. 5.

DiMarzio, P., Peila, R., Dowling, O., Timony, D.M., Balgobind, A., Lee, L.N., Kostroff, K.M., Ho, G.Y.F., 2018. Smoking and alcohol drinking effect on radiotherapy associated risk of second primary cancer and mortality among breast cancer patients. Cancer Epidemiol. 57, 97–103.

Duc, H., Shannon, I., Azzi, M., 2000. Spatial distribution characteristics of some air pollutants in Sydney. Math. Comput. Simul. 54, 1–21.

DuPre, N.C., Hart, J.E., Bertrand, K.A., Kraft, P., Laden, F., Tamimi, R.M., 2017. Residential particulate matter and distance to roadways in relation to mammographic density: results from the Nurses' Health Studies. Breast Cancer Res 19, 124.

Ellingjord-Dale, M., Vos, L., Vik Hjerkind, K., Hjartåker, A., Russnes, H.G., Tretli, S., Hofvind, S., dos-Santos-Silva, I., Ursin, G., 2018. Number of risky lifestyle behaviors and breast cancer risk. JNCI Cancer Spectr. 2, pky030.

Fernández-Navarro, P., García-Pérez, J., Ramis, R., Boldo, E., López-Abente, G., 2012. Proximity to mining industry and cancer mortality. Sci. Total Environ. 435–436, 66–73.

García-Pérez, J., Fernández-Navarro, P., Castelló, A., López-Cima, M.F., Ramis, R., Boldo, E., López-Abente, G., 2013. Cancer mortality in towns in the vicinity of incinerators and installations for the recovery or disposal of hazardous waste. Environ. Int. 51, 31–44.

García-Pérez, J., Lope, V., Pérez-Gómez, B., Molina, A.J., Tardón, A., Díaz Santos, M.A., Ardanaz, E., O'Callaghan-Gordo, C., Altzibar, J.M., Gómez-Acebo, I., Moreno, V., Peiró, R., Marcos-Gragera, R., Kogevinas, M., Aragonés, N., López-Abente, G., Pollán, M., 2018. Risk of breast cancer and residential proximity to industrial installations: new findings from a multicase-control study (MCC-Spain). Environ. Pollut. 237, 559–568.

García-Pérez, J., Pérez-Abad, N., Lope, V., Castelló, A., Pollán, M., González-Sánchez, M., Valencia, J.L., López-Abente, G., Fernández-Navarro, P., 2016. Breast and prostate cancer mortality and industrial pollution. Environ. Pollut. 214, 394–399.

Garza-Villarreal, G., 1998. El área metropolitana de Monterrey en el año 2020, p. 3.

Gasca-Sanchez, F.M., Santos-Guzman, J., Elizondo-Dueñaz, R., Mejia-Velazquez, G.M., Ruiz-Pacheco, C., Reyes-Rodriguez, D., Vazquez-Camacho, E., Hernandez-Hernandez, J.A., Lopez-Sanchez, R., del, C., Ortiz-Lopez, R., Olvera-Posada, D., Rojas-Martinez, A., 2019. Spatial clusters of children with cleft lip and palate and their association with polluted zones in the Monterrey Metropolitan Area. Int. J. Environ. Res. Publ. Health 16, 2488.

Getis, A., Ord, J.K., 2010. The analysis of spatial association by use of distance statistics. Geogr. Anal. 24, 189–206.

Gobierno del Estado de Nuevo León, 2020. Sistema Integral de Monitoreo Ambiental (SIMA) [WWW Document]. Sist. Integral Monit. Ambient. SIMA Nuevo Ón. URL. http://aire.nl.gob.mx/.

Gullett, B.K., Touati, A., Hays, M.D., 2003. PCDD/F, PCB, HxCBz, PAH, and PM emission factors for fireplace and woodstove combustion in the San Francisco Bay region. Environ. Sci. Technol. 37, 1758–1765.

Hao, Y., Liu, Y.-M., 2016. The influential factors of urban PM2.5 concentrations in China: a spatial econometric analysis. J. Clean. Prod. 112, 1443–1453.

He, J., Ding, S., Liu, D., 2019. Exploring the spatiotemporal pattern of PM2.5 distribution and its determinants in Chinese cities based on a multilevel analysis approach. Sci. Total Environ. 659, 1513–1525.

Hendryx, M., Fedorko, E., Anesetti-Rothermel, A., 2010. A geographical information system-based analysis of cancer mortality and population exposure to coal mining activities in West Virginia, United States of America. Geospatial Health 4, 243.

Hung, L.-J., Tsai, S.-S., Chen, P.-S., Yang, Y.-H., Liou, S.-H., Wu, T.-N., Yang, C.-Y., 2012. Traffic air pollution and risk of death from breast cancer in taiwan: fine particulate matter (PM2.5) as a proxy marker. Aerosol Air Qual. Res. 12, 275–282.

Huo, Q., Zhang, N., Wang, X., Jiang, L., Ma, T., Yang, Q., 2013. Effects of ambient particulate matter on human breast cancer: is xenogenesis responsible? PLoS ONE 8, e76609.

Hwang, J., Bae, H., Choi, S., Yi, H., Ko, B., Kim, N., 2020. Impact of air pollution on breast cancer incidence and mortality: a nationwide analysis in South Korea. Sci. Rep. 10, 5392.

Hystad, P., Villeneuve, P.J., Goldberg, M.S., Crouse, D.L., Johnson, K., 2015. Exposure to traffic-related air pollution and the risk of developing breast cancer among women in eight Canadian provinces: a case–control study. Environ. Int. 74, 240–248.

INEGI, 2020. Mortalidad [WWW document]. Natl. Inst. Stat. Geogr. URL. https://www.inegi.org.mx/programas/mortalidad/.

Izano, M., Satariano, W.A., Hiatt, R.A., Braithwaite, D., 2015. Smoking and mortality after breast cancer diagnosis: the health and functioning in women study. Cancer Med. 4, 315–324.

Jaszczak, E., Polkowska, Ż., Narkowicz, S., Namieśnik, J., 2017. Cyanides in the environment—analysis—problems and challenges. Environ. Sci. Pollut. Res. 24, 15929–15948.

Johnson, E.S., 2011. Cancer mortality in workers employed in cattle, pigs, and sheep slaughtering and processing plants. Environ. Int. 37, 950–959.

Jung, K.-W., Won, Y.-J., Oh, C.-M., Kong, H.-J., Lee, D.H., Lee, K.H., The community of population-based regional cancer registries, 2017. cancer statistics in Korea: incidence, mortality, survival, and prevalence in 2014. Cancer Res. Treat. 49, 292–305.

Kelsall, Julia E., Diggle, Peter J., March 1995. Kernel estimation of relative risk. Bernoulli 1 (1–2), 3–16. In this issue.

Kihal-Talantikite, W., Padilla, C.M., Lalloue, B., Rougier, C., Defrance, J., Zmirou-Navier, D., Deguen, S., 2013. An exploratory spatial analysis to assess the relationship between deprivation, noise and infant mortality: an ecological study. Environ. Health 12, 109.

Kleanthi, G., Andreas, L., 2009. Burden of organochlorine substances as a risk factor of breast cancer. Health Sci. J. 3, 10–31.

Kresovich, J.K., Erdal, S., Chen, H.Y., Gann, P.H., Argos, M., Rauscher, G.H., 2019. Metallic air pollutants and breast cancer heterogeneity. Environ. Res. 177, 108639.

Kulldorff, M., 1997. A spatial scan statistic. Commun. Stat. - Theory Methods 26, 1481–1496.

Kulldorff, M., Nagarwalla, N., 1995. Spatial disease clusters: detection and inference. Stat. Med. 14, 799–810.

Kutikhin, A.G., Yuzhalin, A.E., Brailovskiy, V.V., Zhivotovskiy, A.S., Magarill, Y.A., Brusina, E.B., 2012. Analysis of cancer incidence and mortality in the industrial region of south-East siberia from 1991 through 2010. Asian Pac. J. Cancer Prev. 13, 5189–5193.

Levine, N., 2002. A Spatial Statistics Program for the Analysis of Crime Incident Locations (Version 3.3). Ned Levine & Associates, Houston, Texas, and the National Institute of Justice, Washington, D.C.

Macon, M.B., Fenton, S.E., 2013. Endocrine disruptors and the breast: early life effects and later life disease. J. Mammary Gland Biol. Neoplasia 18, 43–61.

Mancilla, Y., Mendoza, A., Fraser, M.P., Herckes, P., 2016. Organic composition and source apportionment of fine aerosol at Monterrey, Mexico, based on organic markers. Atmospheric Chem. Phys. 16, 953–970.

Martínez-Cinco, M., Santos-Guzmán, J., Mejía-Velázquez, G., 2016. Source apportionment of $PM_{2.5}$ for supporting control strategies in the Monterrey Metropolitan Area, Mexico. J. Air Waste Manag. Assoc. 66, 631–642.

Meyer, S.P., 2006. A spatial analysis of small- and medium-sized information technology firms in Canada and the importance of local connections to institutions of higher education. Can. Geogr. Geographe Can. 50, 114–134.

Monge, P., Wesseling, C., Guardado, J., Lundberg, I., Ahlbom, A., Cantor, K.P., Weiderpass, E., Partanen, T., 2007. Parental occupational exposure to pesticides and the risk of childhood leukemia in Costa Rica. Scand. J. Work. Environ. Health 33, 293–303.

Nair, V.A., Valo, S., Peltomäki, P., Bajbouj, K., Abdel-Rahman, W.M., 2020. Oncogenic potential of bisphenol A and common environmental contaminants in human mammary epithelial cells. Int. J. Mol. Sci. 21, 3735.

Nie, J., Beyea, J., Bonner, M.R., Han, D., Vena, J.E., Rogerson, P., Vito, D., Muti, P., Trevisan, M., Edge, S.B., Freudenheim, J.L., 2007. Exposure to traffic emissions throughout life and risk of breast cancer: the Western New York Exposures and Breast Cancer (WEB) study. Cancer Causes Control 18, 947–955.

O, A., A, J., 2012. Particulate matter and cardiovascular health effects. In: Khare, M. (Ed.), Air Pollution - Monitoring, Modelling and Health. InTech.

Pan, S.Y., Morrison, H., Gibbons, L., Zhou, J., Wen, S.W., DesMeules, M., Mao, Y., 2011. Breast cancer risk associated with residential proximity to industrial plants in Canada. J. Occup. Environ. Med. 53, 522–529.

Rao, H., Shi, X., Zhang, X., 2017. Using the Kulldorff`s scan statistical analysis to detect spatio-temporal clusters of tuberculosis in Qinghai Province, China, 2009–2016. BMC Infect. Dis. 17, 578.

Reding, K.W., Young, M.T., Szpiro, A.A., Han, C.J., DeRoo, L.A., Weinberg, C., Kaufman, J.D., Sandler, D.P., 2015. Breast cancer risk in relation to ambient air pollution exposure at residences in the sister study cohort. Cancer Epidemiol. Biomarkers Prev 24, 1907–1909.

Shi, X., Miller, S., Mwenda, K., Onda, A., Rees, J., Onega, T., Gui, J., Karagas, M., Demidenko, E., Moeschler, J., 2013. Mapping disease at an approximated individual level using aggregate data: a case study of mapping New Hampshire birth defects. Int. J. Environ. Res. Publ. Health 10, 4161–4174.

Shmuel, S., White, A.J., Sandler, D.P., 2017. Residential exposure to vehicular traffic-related air pollution during childhood and breast cancer risk. Environ. Res. 159, 257–263.

Soto, A.M., Sonnenschein, C., 2010. Environmental causes of cancer: endocrine disruptors as carcinogens. Nat. Rev. Endocrinol. 6, 363–370.

Terry, M.B., Michels, K.B., Brody, J.G., Byrne, C., Chen, S., Jerry, D.J., Malecki, K.M.C., Martin, M.B., Miller, R.L., Neuhausen, S.L., Silk, K., Trentham-Dietz, A., 2019. Environmental exposures during windows of susceptibility for breast cancer: a framework for prevention research. Breast Cancer Res. 21, 96.

Terry, P.D., Rohan, T.E., 2002. Cigarette smoking and the risk of breast cancer in women: a review of the literature. Cancer Epidemiol. Biomark. Prev. Publ. Am. Assoc. Cancer Res. Cosponsored Am. Soc. Prev. Oncol. 11, 953–971.

Torre, L.A., Bray, F., Siegel, R.L., Ferlay, J., Lortet-Tieulent, J., Jemal, A., 2015. Global cancer statistics, 2012: global cancer statistics, 2012. CA. Cancer J. Clin. 65, 87–108.

White, A.J., Bradshaw, P.T., Hamra, G.B., 2018. Air pollution and breast cancer: a review. Curr. Epidemiol. Rep. 5, 92–100.

White, A.J., Bradshaw, P.T., Herring, A.H., Teitelbaum, S.L., Beyea, J., Stellman, S.D., Steck, S.E., Mordukhovich, I., Eng, S.M., Engel, L.S., Conway, K., Hatch, M., Neugut, A.I., Santella, R.M., Gammon, M.D., 2016. Exposure to multiple sources of polycyclic aromatic hydrocarbons and breast cancer incidence. Environ. Int. 89–90, 185–192.

White, A.J., Teitelbaum, S.L., Stellman, S.D., Beyea, J., Steck, S.E., Mordukhovich, I., McCarty, K.M., Ahn, J., Rossner, P., Santella, R.M., Gammon, M.D., 2014. Indoor air pollution exposure from use of indoor stoves and fireplaces in association with breast cancer: a case-control study. Environ. Health 13, 108.

Yaghjyan, L., Arao, R., Brokamp, C., O'Meara, E.S., Sprague, B.L., Ghita, G., Ryan, P., 2017. Association between air pollution and mammographic breast density in the Breast Cancer Surveillance Consortium. Breast Cancer Res. 19, 36.

Yu, S.Y., Liu, W.J., Xu, Y.S., Zhao, Y.Z., Cai, C.Y., Liu, Y., Wang, X., Xiong, G.N., Tao, S., Liu, W.X., 2019. Organochlorine pesticides in ambient air from the littoral cities of northern China: spatial distribution, seasonal variation, source apportionment and cancer risk assessment. Sci. Total Environ. 652, 163–176.

Zhang, H., Tripathi, N.K., 2018. Geospatial hot spot analysis of lung cancer patients correlated to fine particulate matter (PM2.5) and industrial wind in Eastern Thailand. J. Clean. Prod. 170, 407–424.

Zheng, W., Gustafson, D.R., Moore, D., Hong, C.-P., Anderson, K.E., Kushi, L.H., Sellers, T.A., Folsom, A.R., Sinha, R., Cerhan, J.R., 1998. Well-done meat intake and the risk of breast cancer. JNCI J. Natl. Cancer Inst. 90, 1724–1729.

Zhou, C., Chen, J., Wang, S., 2018. Examining the effects of socioeconomic development on fine particulate matter (PM2.5) in China's cities using spatial regression and the geographical detector technique. Sci. Total Environ. 619–620, 436–445.