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

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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 PM10. 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 PM10 and PM2.5 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, PM10, and PM2.5 exposure (Crouse et al., 2010). PM2.5 concentrations and BC have a positive relationship with more cases associated to high levels of PM2.5 exposure (Hung et al., 2012). In a province of China, Huo et al. (2013) found that BC patients...
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-Navaoro 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, Du Pré 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 6,986 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 degree 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, elucidating 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 Leon (SIMA) (Gobierno del Estado de Nuevo Leon, 2020). The catalog included 301 companies with records of polluting emissions, and the environmental pollution was obtained from reports of the nine
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.
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:

$$G_{i}^{*} = \frac{\sum_{j=1}^{n} w_{ij} (d) x_{j} - \bar{x} \sum_{j=1}^{n} w_{ij} (d)}{S \sqrt{\sum_{j=1}^{n} w_{ij}^2 (d) - \sum_{j=1}^{n} w_{ij}^2 (d)^2}}$$

Equation 1. Spatial autocorrelation

where $x_j$ is the value of AGEB $i$, $w_{ij} (d)$, 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:

$$S = \sqrt{\frac{n \sum_{j=1}^{n} x_j^2}{n} - (\bar{x})^2}$$

Equation 2. Random distribution pattern

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:

$$NND = \frac{D_0}{D_a}$$

Equation 3. Neighbor Nearest Distance

where $D_0$ is the observed mean distance between each point and its nearest neighbor, and $D_a = ...$ is the expected mean distance for the points in a random distribution pattern calculated as:

$$D_a = 0.5 \left( \frac{A}{N} \right)$$

Equation 4. Random distribution pattern
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.

\[
\text{NNI} = \frac{d_{\text{observed}}}{d_{\text{random}}} \quad (5)
\]

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., 2018). According to Canada (2008), the spatial interpolation by IDW is developed as follows:

\[
Z(s_i) = \sum_{j=1}^{n} \lambda_i Z(s_j) \quad (6)
\]

Equation 6. Spatial interpolation by IDW

where \(Z(s_j)\) is the value that predict the location \(s_0\), n is the total sample points (pollutant firms) near the point to be predicted, \(\lambda_i\) 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 Kriging, 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:

\[
\text{RMSR} = \sqrt{\frac{1}{n} \sum_{i=1}^{n} (Z(x_i) - Z(x_i'))^2} \quad (7)
\]

Equation 7. Mean squared error of Interpolation

where \(Z(x_i)\) 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:

\[
g(x) = \sum_{i=1}^{N} \frac{KW_i}{h^{d+2}d!} e^{-\frac{d^2}{2h^2d!}} \quad (8)
\]

Equation 8. Kernel density

where \(g(x)\) is the density of cell j, \(d^2\) 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 \(d\) 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...
sociodemographic (Khal-Talantikite et al., 2013; Kulldorff and Nagarwalla, 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:

\[ E[c] = \frac{p^*C}{P} \]  

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:

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.)
Equation 10. Relative risk for high-risk groups

\[
\left( \frac{c}{E[c]} \right) \times \left( \frac{C - c}{C - E[c]} \right)^{c-e} I() \tag{10}
\]

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 PM10 concentration ranges, from 42 to 68 μg/m3. 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 PM10 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 PM10 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 PM10 concentration ranges. Range 8 agglomerates the highest number of cases, 65 (18.6%). In summarize, 65% of BC cases had exposure to PM10 concentration of 56 μg/m3 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 the most likely 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 polluant 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
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 byproduct of internal combustion motors and machinery (Soto and Sönnschein, 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 (PM10 and PM2.5), and PAHs (Hwang et al., 2020). There are other reports of the association between exposure to the higher levels of PM10 and BC. (Andersen et al., 2017; Bonner et al., 2005; Hwang et al., 2008).
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 Leon (SIMA), and our database of BC cases.).

(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     | 0.02 - 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       |
In this paper, two-thirds (65%) of cases are exposed to PM$_{10}$ concentration of 56 $\mu$g/m$^3$ or more. As a reference, the Mexican mean annual concentration for PM$_{10}$, set as a normal limit, is 40 $\mu$g/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).

Eating chargrilled meats can also impose a BC risk. This cooking style is very popular in the MMA. In this cooking 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 aacenaphthylene, pyrene, benzo(a)
anthracene, chrysene, benzo(k)fluoranthene + benzo(b)fluoranthene, benzo(a)pyrene + benzo(e)pyrene, perylene, indeno(123cd)pyrene, benzo(g,h,i)perylene, dibenz(a)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 burning, re...
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.
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