Breast Cancer Period Prevalence in a Hazard-Exposed Cohort at Hermosillo, Sonora, Mexico: A Report from 2013-2019

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ABSTRACT

Breast cancer is the leading cause of female cancer-related deaths in Mexico. Residential exposure to industrial-derived hazards may increase cancer risk. Hermosillo is one municipality with high breast cancer prevalence in Sonora, Mexico. However, the relationship between breast cancer and hazards needs further investigation. This retrospective observational study evaluated the associations between breast cancer period prevalence (years 2013-2019) and residential exposure to potentially hazardous sites (PHS) in Hermosillo. Clinical data ($n=912$) of breast cancer cases were collected from 6-year-old files. Cluster analysis identified regions of period prevalence. Proximity analysis classified neighbourhoods by PHS-exposure, then calculated odds ratio (OR) for breast cancer risk. Age distribution analysis evaluated the risk for PHS-exposed vs non-PHS-exposed groups. Six neighbourhoods classified as high-high breast cancer clusters. Highly industrialized neighbourhoods (≥ 7 industries vs ≤ 6 industries) presented higher risk (crude OR = 1.69), as well as those in proximity to a gas power plant (≤ 4 km vs ≥ 4 km, crude OR = 1.55) or to a residual water site (≤ 3 km vs ≥ 3 km, crude OR = 1.45) (all p -values < 0.0001). Age distribution analysis showed an older population in the PHS-exposed group. Larger cohorts will confirm our findings.

KEYWORDS: Breast cancer risk; Environmental hazards; Observational studies

ABBREVIATIONS: PHS: Potentially Hazardous Sites; RWS: Residual Water Sites; HAPs: Hazardous Air Pollutants; GPP: Gas Power Plants

INTRODUCTION

Geography of Breast Cancer in Mexico

Breast cancer is considered the most common malignancy diagnosed in women worldwide and the leading cause of female cancer-related deaths in developing countries Ferlay et al. [1]. A population-based study conducted by the National Institute of Statistics and Geography (INEGI) indicated breast cancer as

the main cause of female morbidity in 2014 in Mexico INEGI [2]. Moreover, breast cancer represented the leading cause of cancer mortality in Mexican women from the period 2000-2013; Mohar-Betancourt et al. [3]. Studies by the Health Secretary of Mexico (SS) also showed breast cancer as the main cause of cancer-related deaths in 2002 [4]. The distribution of breast cancer prevalence, though, is not homogeneous in Mexico. There are sub-regional

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variations in breast cancer mortality across the country from the period 2001-2011, with a significant increase in mortality rates for the Southwest (annual percentage change, APC 2.7%, $p < 0.05$) and the Center-North regions of Mexico (APC 1.7%, $p < 0.05$) Soto-Perez-de-Celis et al. [5]. Another study showed twelve entities sustaining the highest breast cancer rates in the country. Among those, Sonora is reported with high rates of breast cancer morbidity and mortality Castrezana-Campos [6]. Furthermore, according to INEGI, Sonora revealed the highest breast cancer mortality rate in the country in 2015, with 16.25 deaths per 100,000 women INEGI [7]. More research is needed that aims at evaluating the associations of breast cancer rates and geographical regions in Sonora, specifically Hermosillo, Sonora.

Exposure to Hazardous Air Pollutants (HAPs) and Breast Cancer Risk

Epidemiological data indicates anthropogenic-derived air pollutants as potential human carcinogens Garcia et al. [8]. Two investigations conducted within the California Teacher's Study suggest a link between breast cancer risk and hazardous air pollutants (HAPs) in urban areas Garcia et al. [8]. Long-term exposure to specific chemicals such as acrylamide, benzidine, carbon tetrachloride, ethylidene dichloride, and vinyl chloride was related to an increased burden in hormone-responsive breast cancers Garcia et al. [8]. A higher risk of non-hormone responsive breast cancer was related to air pollution with benzene Garcia et al. [8]. Hormone receptor-negative breast cancers were related to cadmium exposure Liu et al. [9]. Other reports showed no associations between HAPs' exposure and breast cancer burden. A cross-sectional analysis within the Nurses' Health Study indicated no relationship between HAPs' exposure and breast cancer risk, neither to an overall increased incidence nor to specific breast cancer subtypes in the U.S.

In Mexico, scarce studies are evaluating HAPs' exposure by geographical regions. A report in 2010 by the Commission for Environmental Cooperation (CCA) indicated high emissions of nitric dioxide (range 16.4- 61.8 thousand metric tons) and sulphur dioxide (range 65,000-130,000 metric tons) in several localities in the state of Sonora [10]. However, few studies aimed to assess the relationship between industrialized areas and the breast cancer burden in Mexico, where highly industrialized municipalities across the country also showed a high burden of this disease. We need more investigations that aim at evaluating the relationship between HAPs and breast cancer rates in Sonora [11-13].

Contaminated Water Sources (CWS) and Breast Cancer Risk

Drinking water from sources impacted by wastewater, run-off from agricultural lands, or contaminated wells present a potential pathway of human exposure to hazardous chemicals Kuch et al. [14]; Rudel et al. [15]. Improper disposal from industrial operations and small businesses can also contribute to chemical exposure Moran et al. [16]. Specific hazards, like tetrachloroethylene (PCE) and organic solvents found in contaminated drinking water can accumulate in mammary tissue and may increase breast cancer risk Labreche et al. [17]. Some case-control studies indicate slightly to moderate increases in breast cancer burden with high PCE exposure Aschengrau et al. [18]; Gallagher et al. [19]. However, other studies show inconsistent associations between chemical hazards in drinking waters and breast cancer rates Brody et al. [20]. Discrepancies in findings can be due to regional variations in

hazardous exposure by water supply, methodological limitations for exposure assessment, and difficulties to retrospectively collect information about potentially affected individuals.

In Mexico, few studies evaluated geographical exposure to CWS and breast cancer burden. The CONAGUA (National Water Commission) identified distinct geographical areas across the country with CWS CONAGUA [21]. In the state of Sonora, Hermosillo municipality figures as a region of interest CONAGUA. Previous studies by the SINA (National Water Information System) identified high concentrations (≥ 45 mg/l) of hazardous chemicals in several wells within the Hermosillo municipality SINA [22]. Among the hazards found by SINA were nitrates, benzene, aromatic compounds, DDT, iron, magnesium, and arsenic. Exposure to these has been related to breast cancer development Hiatt et al. [23]. The preceding results suggest the need to evaluate possible associations between these elements and breast cancer in Hermosillo, Sonora.

Innovation and Objectives

Hermosillo municipality is a geographical region with high breast cancer prevalence in Sonora, Mexico. The potential associations of breast cancer burden with residential exposure to environmental hazards, though, remains to be elucidated. This observational retrospective study aims to evaluate statistical associations between breast cancer prevalence and residential exposure to hazardous pollutants (number of industries, gas power plants (GPP), and residual water sites (RWS)) from the period 2013 to 2019. For this aim, we set the following goals: (1) to create a database of female breast cancer cases as reported in hospital files from the period 2013 to 2019, (2) to geolocalize potentially hazardous sites (PHS) using reports from government databases INEGI [24] and (3) to evaluate potential associations between residential exposure to PHS and breast cancer period prevalence by using a statistical approach. In this study we seek to provide evidence of a potential link between hazardous pollutants and breast cancer period prevalence at Hermosillo municipality. Future studies derived from the present investigation may focus on breast cancer prevention policies in high-risk populations.

METHODS

Breast Cancer Database

Source population and subject selection criteria: This is an observational retrospective study that collected breast cancer cases (new and pre-existing) reported from the period of January 1st, 2013 to September 20th, 2019. The REDCap platform Harris [25] was used to create the breast cancer database. Clinical files were transcribed from physical records registered in private hospitals CIMA, Hospital San José, and Clínica del Noroeste; and public hospitals Hospital General del Estado de Sonora Ernesto Ramos Bours (HGE) and Centro Estatal de Oncología Dr. Ernesto Rivera Claisse (CEO). The participating hospitals are located in Hermosillo, Sonora, Mexico. The breast cancer database had the following inclusion criteria:

Female breast cancer cases (current/survivor/deceased) available at hospital archives from the period of January 1st, 2013 to September 20th, 2019.

Patients who were current Hermosillo residents; (3) patients had an ID-verifiable residential address (as registered at the National Electoral Institute (INE) or their medical insurance card).

The database had the following exclusion criteria:

Male breast cancer cases.

Former Hermosillo residents.

Non-Hermosillo residents.

Unavailable or non-verifiable residential address.

Non-cancer patients.

Patients diagnosed with neoplasia(s) other than breast cancer. The sample size included all breast cancer cases in compliance with the inclusion criteria ($n=949$ for Hermosillo municipality) as reported by local hospitals. Given the small sample size for rural communities, this study focused on breast cancer cases from Hermosillo city ($n=912$).

Variables of Breast Cancer Database: The breast cancer database collected information from clinical files available in hospital archives. For this database, the Safe Harbor Approach was used to remove 18 potential identifiers HHS [26] to comply with national LFM [27]; DOF [28] and international regulations for the protection and privacy of human subjects.

Variables related to residential information included the following: zip code of current and former residence(s), neighbourhood of current and former residence(s), current location of residence, and former location of residence. In cases of move-outs, the analysis was based on the oldest residential information (residence location ≥ 10 years old) available from clinical files. This last consideration was done based due to time-latency for tumour development in adulthood, as previously indicated in environmental proximity analyses Brender [29]. This study did not collect private addresses and was limited to register neighbourhoods and zip codes-only.

Variables related to breast cancer information included the following: age at the time of diagnosis, familiar history of cancer, personal history of cancer, breast cancer type, classification of tumour by SBR (Scarff-Bloom-Richardson), classification of tumour by TNM, tumour grade, breast density by mammography (BI-RADS classification), current treatment (chemotherapy, radiotherapy, surgery, breast implants, port-a-cath), and current diagnosis. Breast cancer cases older than January 1st, 2013 were not available to be part of the sample.

Other variables of breast cancer database: Each patient record was assigned a unique ID number to prevent duplicity. Database included information of the following potential confounders: highest degree of education (elementary school, junior high school, high school, technical career, university); religion (atheist, Catholic, Christian, Mormon, Jehovah Witness, other); occupation (homemaker, employee, teaching, engineer, accountant, own business, retired, other); alcohol consumption (former/non-consumer/social consumer (< 7 drinks per week)/alcoholism (> 7 drinks per week) and tobacco (former/non-consumer/passive smoker/current smoker/not-included); weekly red meat consumption (non-consumer/from 1-2 times/from 3-4 times/from 5 times or more/not included); BMI, exercise habits (yes/no/not-included), number of live births, age at menarche, menopausal status (premenopausal, peri-menopausal, menopause, postmenopausal, non-included), use of hormonal contraception (yes/no/not included), use of hormonal replacement therapy (yes/no/not included), elements of metabolic syndrome as defined by the NCEP ATP III criteria Huang [30], prior chronic illnesses other

than neoplasia, prior malignancies other than breast cancer, and red blood type. The variables of race and ethnicity were not collected, as the population at Hermosillo municipality is constituted by Hispanics, considering it as a homogenous population.

Ethics Statement: This study was reviewed and approved by the Institutional Review Board (IRB) from public (HGE, CEO) and private health institutions (CIMA, Hospital San José, Clínica del Noroeste) participating in this study, as well as from the IRB of University of Sonora, and the Secretary of Health of Sonora. The national regulations in Mexico as established by the General Law in Health for Clinical Research and according to Article #17, considered this study as without risk for the individual SSA [31].

Exposure Assessment to Potentially Hazardous Sites (PHS)

Location of PHS: The coordinates (latitude and longitude) of active industries, gas power plants (GPP), contaminated water sources (CWS), and garbage disposals at Hermosillo municipality were obtained through the INEGI Census 2010 and projected onto a map by conversion to Universal Transverse Mercator System (UTM) zone 12 N (12 N).

The coordinates (latitude and longitude) of agricultural lands contaminated with organochloride pesticides (OCPs) were obtained from Leal-Soto and collaborators Leal-Soto et al. [32]. The coordinates converted to UTM zone 12 N for their projection onto a map (ArcGIS version 10.7.1). Sampling methods and OCPs' analyses were conducted as previously described Leal-Soto et al. [32]. Briefly, OCPs were collected and analysed from active, in-rest, or abandoned agricultural lands located at La Costa de Hermosillo. Field selection criteria included the recent historical use of OCPs (1950-2000), qualifying them as potentially contaminated by its former use. Farmers applied OCPs in a dose concentration of 3 to 8 kg ha⁻¹ twice per month, per crop cycle. This dosage is superior to that recommended in the official guidelines (0.5 to 1.5 kg ha⁻¹) CCGRS [33]; SARH [34]. The selected fields included cotton, wheat, safflower, corn, and citric crops. Field owners authorized the soil sampling of their lands ($n=20$) following regulations as established by the National System of Environmental Monitoring INECC-CCA [35]. Five samples were (1.5 kg each one) collected from each field (at surface-level and 60 cm underground) following the EPA guidelines EPA [36] for the zigzag scheme or squared sampling method. Soil samples were stored in brown paper bags and kept at -20 °C until their extraction by matrix solid-phase dispersion (MSDD) and analysis by gas chromatography Leal-Soto et al. [32].

Moreover, the coordinates (latitude and longitude) of heavy metals in urban dust were obtained from available research studies Garcia-Rico et al. [37] and projected onto a map by conversion to UTM zone 12 N. Methodology for sampling and heavy metal analysis are described by Garcia-Rico et al. [37]. Briefly, sampling of dust was collected from urban streets and parks (particle size < 325 (-44 mm). The total concentration of heavy metals was determined with fluorescence ray-X portable equipment, using a portable analyzer NITTON XLt3 of Thermo Scientific Garcia-Rico et al. [37].

The coordinates (latitude and longitude) of contaminated wells and residual water sites (RWS) were obtained from INEGI Census 2010 and of previous investigations conducted by Gomez-Alvarez et al. [38]; Gomez-Alvarez et al. [39]. Reported wells with metals and RWS were projected onto a map by conversion to UTM zone 12 N. The methodological approach for wells' sampling and chemical analysis are described fully by García-Rico et al. [40]. Concisely,

surface water samples were collected at distinct locations of the Sonora River, using polyethylene of 1 L bottles previously conditioned (rinsed with 0.2 M nitric acid, HNO₃). Once in the laboratory, samples were filtered (polycarbonate 0.4 mm filters, Nucleopore, Whatman), and added 2 mL of 14 M HNO₃ for metals' analysis which was performed in Inductivity Coupled Plasma-Optic Emission Spectrophotometry (ICP-OES VARIAN 730-ES) according to the manufacturer's specifications Calderon [41].

Industries considered as potential sources of chemical hazards, are the following: production of industrial laminates, furniture, coolers and AC, dental laboratories, production of pesticides and fungicides, manufacturers of orthopedic materials, candle production, chemical laboratories, metal production, automobile assembly, manufacturers of agricultural products, technology machinery production and assembly, manufacturers of cleaning products, electronics production and assembly, production of dyes and construction materials, iron foundries, printer suppliers, welding shops, production of toys and jewelry, manufacturers of chemical products, aquaculture products, polymer and plastic production, clinical hospital products, mechatronics and electrics, and other related industrial manufacturers.

Criteria for Assessment of Residential Exposure to PHS

Potentially hazardous sites (PHS) per neighbourhood: In this study, neighbourhoods are considered as a geographical unit. Residential exposure will be evaluated in terms of the variables: number of industries, GPP, and RWS. The cut-offs for highly industrialized neighbourhoods and low-industrialized locations will be defined using regression analysis. The cut-offs for GPP and RWS-exposure will be defined by proximity analysis where neighbourhoods within the established cut-off values are considered as exposed, and locations beyond them are classified as non-exposed.

Proximity analysis: The literature reports distinct environmental proximity analyses to assess PHS residential exposure, where the most common approach is distance-based analysis as defined by buffer Brender et al. [29]. In this study, geographical information software (ArcGIS version 10.7.1) was used to calculate the radial distances (in km) between PHS and neighbourhoods. According to radial distances (in km) to one or more PHS, neighbourhoods with reported breast cancer cases classified as PHS-exposed or non-PHS exposed. Buffer analyses defined cut-off values for radial distances to PHS (in km). In detail, a PHS of interest was the origin of multiple ring buffers, with a buffer unit of 1 km. The cut-off values defined for PHS exposure distance-based analyses were the following: $X \leq 4$ km for GPP or industries, $X \leq 4$ km for RWS, and $X \leq 1$ km for garbage disposals, where X represents the core of the neighbourhood of interest. Neighbourhoods located beyond the cut-off values to PHS were considered non-exposed.

Potential Sources of Bias

In this study, we considered the following variables as potential sources of bias:

Time of residence: The database included women with ID-verified address of 10 years or more. In general, tumour screening detects cancer that was on development for a minimum of 10 years Brender et al. [29]. For this reason, residential exposure to hazards needs to consider the location of a minimum of 10 years.

Access to media and information: Prior demographic analysis

of breast cancer patients considered accessibility to information through the internet and communication media (TV, radio, cell phone, landline phone). Neighbourhoods with reported breast cancer cases and those without them showed no difference in communication media and access to information.

Socioeconomic status: Neighbourhoods with breast cancer cases were compared to those without them. Prior demographic analysis indicated no differences for the following variables:

Women economically active.

Women non-economically active.

Women with completed high school or some college.

Statistical Methods

In this study, cluster analysis identified geographical patterns of breast cancer period prevalence (years 2013-2019). The odds ratio (OR) was used to give evidence of an association between hazards and breast cancer in Hermosillo residents. Breast cancer patients were compared in terms of age distribution and hazard exposure using neighbourhood as the geographical unit. Data available from INEGI of non-breast cancer patients included only age by range, here defined as the number of women equal or older than 18 years old. For this reason, partial or total adjustment for ORs could not be made.

Breast cancer database (Years 2013-2019): The breast cancer database created in this study served to provide the number of cases per neighbourhood, as reported in hospital files from the period of January 1st, 2013 to September 20th, 2019. The sample size for the present study included all the cases collected from the public and private health institutions that agreed to collaborate in this investigation. No sampling strategy was employed in this case, as the intent was to collect all the breast cancer cases available in hospital files. The hospitals granted IRB approval to acquire data from the patient's file in full extent, with the agreement to de-identify 18 potential personal identifiers by the Safe Harbor approach for data analysis.

This study created a unique breast cancer database in cloud format using the REDCap platform. There is no data linkage with other electronic databases. For this reason, there are no methods for data linkage in this investigation.

Geographical patterns of breast cancer period prevalence (Years 2013-2019): The cluster analysis approach was used to detect geographical patterns of breast cancer prevalence from the period 2013-2019. To this end, the number of the female population (women ≥ 18 years old) by neighbourhood was obtained according to INEGI Demographic Census 2010.

The breast cancer period prevalence was calculated as follows: $100X = [(\text{number of breast cancer cases reported in years 2013-2019}) / (\text{number of women} \geq 18 \text{ years old})]$. Statistically significant hot spots, cold spots, and spatial outliers were detected using Anselin Local Moran's I. Spatial relationships among features were defined by contiguity edges-only, with a number of permutations of 499 (ArcGIS version 10.7.1.).

Estimation of breast cancer risk by PHS exposure: The odds ratio (OR) and 95% of confidence intervals (95% CI) estimated the likelihood of breast cancer risk through comparison between PHS-exposed and non-PHS-exposed neighbourhoods previously reported with breast cancer cases (SAS Institute, Inc., Cary, N.C.).

Additionally, distribution analysis by age was conducted between breast cancer cases located in PHS-exposed neighbourhoods versus their non-PHS-exposed counterparts. The aim was to observe differences in age distribution by PHS exposure.

The objective of the statistical analysis is to verify a possible decrease in the influence of the risk factor as distance to the core increases. Given a PHS location, three subpopulations were defined by their radial distance (in km) to the PHS of interest. The cut-off values for this radial distance to PHS were the following: $0 \leq X < 2$ km (subpopulation 1), $2 \text{ km} \leq X < 4$ km (subpopulation 2), and $X > 4$ km (subpopulation 3), where X represents a PHS of interest. The subpopulations were compared by OR with 95 % CI to estimate the likelihood of breast cancer risk.

The three subpopulations give a total of six comparisons. To evaluate if the influence of environmental hazards is affected by radial distance, subpopulation 1 was compared with subpopulation 2 and with subpopulation 3. Additionally, subpopulation 2 was compared with subpopulation 3. This analysis assessed if the effect of hazardous exposure decreases with radial distance (in km).

Age distribution and PHS exposure: The analysis compared the age distribution of breast cancer patients residentially exposed to all three PHS (highly industrialized neighbourhoods, GPP-exposed, and RWS-exposed) versus their non-exposed counterparts. The aim was to characterize the exposed subpopulation in terms of age, considering aging as a risk factor for cancer development.

Key Assumptions and Limitations

This research considers the female subpopulation (≥ 18 years old) residing in a neighbourhood as a unit of analysis. The measure of effect for each unit is given by the odds ratio comparing the likelihood of breast cancer in PHS-exposed neighbourhoods

versus their non-PHS-exposed counterparts. This ecological study estimated breast cancer likelihood at the unit level (neighbourhood), not for an individual with or without breast cancer.

RESULTS

Characteristics of the Study Population in the Hermosillo Municipality

The INEGI Census 2010 reports 281,267 women equal or older than eighteen residing at the Hermosillo municipality. Such population is distributed by neighbourhoods; therefore, the information on the number of women by neighbourhood is available. The previous information allowed us to determine the density of cases in each neighbourhood.

The breast cancer database included 1,916 cases reported in hospital archives (CIMA, Clínica del Noroeste, Hospital San José, HGE, CEO) from the period of January 1st, 2013 to September 20th, 2019. 967 breast cancer cases were not included as those women reported to reside outside of Hermosillo municipality. The remaining 949 breast cancer cases were current Hermosillo residents, which correspond to the 0.34% of the female population equal or older than 18 years.

The present analysis included 947 breast cancer cases, as two individuals had no verifiable residential address by ID or medical insurance card. From those 947 breast cancer cases, 912 cases (96.3 %) were from Hermosillo city, 22 cases (2.31 %) were from Miguel Aleman, and 14 cases (1.48 %) were from rural communities at Hermosillo municipality (Bahia de Kino, El Choyudo, El Triunfo, La Yesca, Mesa del Seri, Real del Alamito, San Pedro El Saucito, Zamora); (Figure 1). Due to the small number of cases reported in rural communities, the present study focused on the analysis for Hermosillo city-only.

Figure 1: Consort diagram of breast cancer study population at Hermosillo municipality.

Geographical Patterns of Breast Cancer Period Prevalence (Years 2013-2019) in Hermosillo Municipality

Geographical patterns of breast cancer period prevalence (Years 2013 to 2019) in Hermosillo city: In this study, Local Anselin Moran's I detected H-H clusters of breast cancer period prevalence (January 1st, 2013 to September 20th, 2019) for six neighbourhoods (all $p \leq 0.05$) across Hermosillo municipality. All of them are located in Hermosillo, the capital of the state of Sonora.

The west area of Hermosillo city contains three H-H neighbourhoods, all of them at a radial distance of ≤ 3 km from inactive residual water sites. From those three, two of them are contiguous (zone 12 N, 499,870.370 m E/ 3,216,269.563 m N; and 499,914.414 m E/3,216,842.126 m N) and are within the same zip code (83245). The third neighbourhood (zone 12 N, 497,315.856

m E/ 3,217,238.516 m N) is within a radial distance of < 3 km from the other two sharing the same zip code. The northwest side contains one H-H neighbourhood (zone 12 N, 497,007.553 m E/ 3,221,422.635 m N), located at a radial distance of ≤ 1 km from a garbage disposal site (zone 12 N, 498,030.990 m E/ 3,221,208.504 m N). The southeast of Hermosillo city contains two H-H clusters, and those neighbourhoods are reported to contain heavy metals in samples taken from urban dust from streets and parks (Neighbourhood "A" with Mn = 625 mg/kg, and Pb = 78.82 mg/kg; neighbourhood "B" with Cr = 183.79 mg/kg, and Pb = 142.79 mg/kg). Those two neighbourhoods are within a radial distance ≤ 2 km from each other (zone 12 N, 504,538.965 m E/ 3,213,010.355 m N for Neighbourhood "A"; and 506,036.439 m E/ 3,212,922.268 m N for Neighbourhood "B"); (Figure 2).

Figure 2: Spatial clusters (Local Anselin Moran's I) of breast cancer period prevalence (January 1st, 2013 to September 20th, 2019) at Hermosillo city. source: INEGI census 2010, clinical databases from hospitals HGE, CEO, clínica del noroeste, Hospital San José, and CIMA. projected coordinate system: WGS84 UTM 12 N. Geographic coordinate system: WGS84.

An additional geographical pattern of breast cancer period prevalence indicates cold spots (L-L clusters) for seven neighbourhoods across Hermosillo municipality (all p-values < 0.05). From those cold spots, four of them belong to Hermosillo city. Two of those L-L clusters are located in the southwest area (zone 12 N, 499,465.172 m E/ 3,213,979.309 m N; and 500,486.977 m E/ 3,213,054.398 m N) and are within a radial distance ≤ 2 km from each other. Also, those cold spots are close to two high-low (H-L) outliers (< 3 km) (zone 12 N, 500,381.725 m E/ 3,213,508.400 m N; and 500,980.263 m E/ 3,211,583.351 m N).

A third cold spot is located in the southeast area of Hermosillo city (zone 12 N, 506,476.873 m E/ 3,209,328.331 m N) and it is within a radial distance < 1.7 km from two L-H outliers (zone 12 N, 505,525.536 m E/ 3,211,442.412 m N; 508,908.065 m E/ 3,211,548.116 m N; and 508,094.383 m E/ 3,208,714.818 m N). The remaining L-L cluster of the city locates in the northeast (zone 12 N, 504,805.865 m E/ 3,221,979.748 m N) and is within a radial distance of < 2 km from three H-L outliers (zone 12 N, 504,714.700

m E/ 3,223,193.458 m N; 504,179.552 m E/ 3,222,989.419 m N;
and 504,781.238 m E/ 3,222,616.564 m N).

This analysis identified fifty-eight spatial outliers (24 neighbourhoods with H-L clusters, and 32 L-H clusters) in Hermosillo city. Most of the low-high (L-H) outliers are close to the H-H spatial clusters. With the exception of the previously mentioned three H-L outliers, the majority locates close to the high-high area and the L-H outliers.

Geographical patterns of breast cancer period prevalence (Years 2013 to 2019) at other communities of Hermosillo municipality: For the town Miguel Aleman, cluster analysis identified three cold spots and no hot spots (Figure 3). Those L-L clusters located in the west area of Miguel Aleman (zone 12 N, 450,619.036 m E/ 3,191,110.215 m N; 450,416.466 m E/ 3,190,537.430 m N; and 451,394.391 m E/ 3,190,537.430 m N). Other rural communities (Bahia de Kino, El Choyudo, El Triunfo, La Yesca, Mesa del Seri, Real del Alamito, San Pedro El Saucito, Zamora)

communities, 14 cases) for locations other than Hermosillo city, those communities were not further analysed.

Residential Exposure to PHS and Breast Cancer Risk in Hermosillo City

industries. The response variable keeps growing (for all cases except for 11 industries) when the number of industries was ≥ 8 , with at least one outlier for 21 industries. This implies that 7 industries could be a reasonable choice as a cut-off for high and low industrialized neighbourhoods. A neighbourhood is defined as a highly industrialized if its number is ≥ 7 .

Residential exposure according to the number of industries and breast cancer risk: The aim is to compare two subpopulations, high and low industrialized neighbourhoods for breast cancer risk assessment. The resulting odds ratio is 1.69 (1.41, 2.02) (p -value < 0.0001); (Figure 4).

Figure 4: Comparison of the female population living in high and low industrialized neighbourhoods. OR = 1.69 (1.41, 2.02) (p -value < 0.0001).

Residential exposure by proximity to GPP and breast cancer risk: Two GPPs were reported by INEGI Census 2010, where the first (GPP1) located on the west side (zone 12 N, 493,612.626 m E/ 3,219,141.024 m N) of the city. The second one (GPP2) was located at the east side downtown (zone 12 N, 502,995.056 m E/ 3,217,038.065 m N). First, GPP1 is analysed using a radial distance of 2km and after the effect of GPP1 and GPP2 together (GGP) is calculated.

The odds ratio was calculated for breast cancer risk per neighbourhood exposed to GPP1 at distinct radial distances X. The cut-off values are defined for radial distance to GPP1: 0 km $\leq$ X $\leq$ 2 km (subpopulation 1), 2 km $<$ X $\leq$ 4 km (subpopulation 2), 4 km $<$ X $\leq$ 6 km (subpopulation 3), and 6 km $<$ X $\leq$ 8 km (subpopulation 4).

4).The following comparisons were performed: Subpopulation 1 is compared with subpopulation 2 and the following OR = 0.62 (0.52, 0.74) (p -value $<$ 0.00001) was obtained; comparison between subpopulation 1 and subpopulation 3 produced an OR = 0.39 (0.32, 0.47) (p -value $<$ 0.00001), and comparison between subpopulation 1 and 4 an OR = 0.41 (0.33, 0.51) (p -value $<$ 0.00001); (Table 1).

Demographic data from INEGI Census 2010 served to estimate the number of breast cancer cases per 100,000 women for both GPP1-exposed and GPP1-nonexposed locations. The number of breast cancer cases per 100,000 women was the highest for subpopulation 1 ($n=606$), followed by subpopulation 2 ($n=382$), and for subpopulations 3 and 4 ($n=239$) and ($n=254$) which are very similar (Table 1).

Table 1: Comparison of the female population living in neighbourhoods at distinct radial distances (in km) to GPP1.

Radial Distance to GPP1 (km)	Number of Women Without Breast Cancer B	Number of Women with Breast Cancer C	Total	Number of Breast Cancer Cases per 100,000 Women D
0 km $\leq$ X $\leq$ 2 km A	35,917	219	36,136	606
2 km $<$ X $\leq$ 4 km A	75,639	290	75,929	382
4 km $<$ X $\leq$ 6 km A	87,647	210	87,857	239
6 km $<$ X $\leq$ 8 km A	56,118	143	56,261	254

Table Abbreviations: (A) X represents radial distance; (B) Demographic data from INEGI Census 2010, women registered from ages $\geq$ 18 years old; (C) Archive data from public hospitals (HGE, CEO) and private hospitals (CIMA, Clínica del Noroeste, Hospital San José) in Hermosillo; (D) The number of breast cancer cases per 100,000 persons was calculated as follows: $100,000 \times [x = \text{number of women with breast cancer} / \text{total}]$; GPP1, Gas Power Plant 1.

The effect of the two GPPs is analysed in this section. The GPP2 has no population within a radial distance of X $\leq$ 2 km. However, the GPP2 reports inhabitants within a radial distance of 2 km $<$ X $\leq$ 4 km. To evaluate population at-risk for both GPP, the total of inhabitants within X $\leq$ 4 km for both GPP1 and GPP2 were considered as exposed. Therefore, two populations were considered

for this second analysis. The subpopulation GPP-exposed were that of residents within a radial distance of X $\leq$ 4 km. The GPP-non-exposed were those inhabitants within a radial distance of X $>$ 4 km. The analysis indicated an OR = 1.55 (1.36, 1.77) (p -value $<$ 0.0001); (Figure 5).

Figure 5: Comparison of the female population living in neighbourhoods within $\leq$ 4 km to a GPP to those living in neighbourhoods $>$ 4 km to a GPP. OR = 1.55 (1.36, 1.77) (p -value $<$ 0.0001).

Residential exposure to residual water sites (RWS) and breast cancer risk: The aim of this section is to assess the RWS as a possible risk factor by comparing the subpopulation residentially exposed to RWS with the RWS-nonexposed in Hermosillo city.

According to INEGI Census 2010, there are three RWS in Hermosillo. Two of them are located southwest (zone 12 N, 497,593.732 m E/ 3,215,073.566 m N; and 501,156.242 m E/ 3,215,639.044 m N), while the third RWS at the west end of the

city (zone 12 N, 492,334.789 m E/ 3,216,487.260 m N). Risk assessment to RWS exposure was evaluated by radial distance to an RWS (in km) of interest. Neighbourhoods within 3 km to an RWS were considered as RWS-exposed, while those locations beyond 3 km were classified as RWS-nonexposed. Women living in RWS-exposed neighbourhoods had an OR = 1.45 (1.26, 1.66) (p -value < 0.0001) for breast cancer risk in comparison to those residing in RWS-nonexposed locations (Figure 6).

Figure 6: Comparison of the female population living in neighbourhoods within 3 km of an RWS to those residing in locations beyond 3 km from an RWS. OR = 1.45 (1.26, 1.66) (p -value < 0.0001).

Accumulative residential exposure to potentially hazardous sites (PHS) and breast cancer risk in Hermosillo: It is expected that, if a population is exposed to more than one risk factor, then the number of cases, the ORs or the β of the logistic regression model, increases. Those risk factors could be highly industrialized (≥ 7 industries), GPP-exposed (≤ 4 km), and RWS-exposed (≤ 3 km) neighbourhoods. There are eight possible combinations of risk factors. Those include the case where a risk factor is not present to the case where three risk factors are present. All possible comparisons, their OR and their logistic regression model are obtained and depicted in Table 2.

Females residentially exposed to one or more PHS had a higher risk than their non-exposed counterparts (all p -values < 0.0001). There are two types of evidence: their ORs are increasing as the number of risk factor increases or the β are increasing in the logistic regression model as the number of risk factor increases (monotonic property).

A mathematical model to predict the probability of PHS-exposure by age is depicted as follows:

$$\text{logit}[\pi(x)] = \log\left(\frac{\pi(x)}{1-\pi(x)}\right) = \alpha + \beta x = -5.039 + 0.064x$$

Where x = Age

Where β represents the change in the log odds associated with a unit of increase in x . The odds are multiplied by $e\beta$ for each unit of increase in x . In this case, $e0.064=1.066$, which means an increase

of 6.6% for the probability of living in a neighbourhood where the three risk factors are present.

The process to verify the monotonic property is the following: first, one of the factors must be chosen and the β of the corresponding logistic regression model is registered; second, one factor is added to the model and the β of the corresponding logistic regression model is registered. Note that this β is greater than the previous one. Third, add the remaining factor to the model and the β of the corresponding logistic regression model is registered. That process must be followed until all the variables are included in the model. If for a chosen factor, the β is always greater than the β of the previous model, the effect of the factor is monotone. If this property is satisfied for all the factors, it is said that the model is in monotone for all the factors. It is expected that, if a population is exposed to more than one risk factor, then the β increases. Note that the monotonic property is satisfied for this breast cancer data set. Note that an increased behaviour is obtained also for the variable OR, that behaviour is expected if the risk is increased.

Age Distribution of Breast Cancer Population and PHS-Exposure

Breast cancer development relates to an advanced age. For this reason, it expected to observe a different density of breast cancer cases in the older population (≥ 60 years old). In order to establish a comparison of the PHS-exposed and non-exposed groups to three environmental risk factors (highly industrialized neighbourhoods,

GPP, and RWS-exposed), two subpopulations were compared in terms of the age distribution. Subpopulation 1 depicted the age distribution of breast cancer cases residually exposed to all three PHS, whereas subpopulation 2 represented that of breast cancer cases non-exposed to PHS (Figure 7).

Age distribution by PHS exposure (three risk factors) indicates an older population for PHS-exposed in comparison to that of

PHS-nonexposed (Figure 7). The median age for the distribution of the PHS non-exposed cases is lesser than the median age for the distribution of the PHS-exposed cases. Additionally, the 75 percentiles of the distribution of PHS non-exposed are lesser than the median of the distribution of PHS exposed. Previous statement means that if you are a case, you have a greater probability to live in a neighbourhood in which one or more risk factors are present.

Table 2: Comparison of the female population residing in neighbourhoods exposed to one, two, and three PHS with that of nonexposed-PHS locations.

Comparison of Female Population Living in PHS-Exposed Locations vs Nonexposed-PHS Neighbourhoods A	Odds Ratio for Breast Cancer Risk	Logistic Regression Model
High-industrialized neighbourhoods vs nonexposed-PHS locations	1.69 (1.41, 2.02)	$\text{logit}[\pi(x)] = \log\left(\frac{\pi(x)}{1-\pi(x)}\right) = \alpha + \beta x = -3.85 + 0.038x$
GPP-exposed neighbourhoods vs nonexposed-PHS locations	1.55 (1.36, 1.77)	$\text{logit}[\pi(x)] = -1.26 + 0.0302x$
RWS-exposed neighbourhoods vs nonexposed-PHS locations	1.45 (1.26, 1.66)	$\text{logit}[\pi(x)] = -1.94 + 0.023x$
GPP and RWS-exposed neighbourhoods vs nonexposed-PHS locations	1.68 (1.44, 1.96)	$\text{logit}[\pi(x)] = -4.28 + 0.059x$
High-industrialized, RWS-exposed neighbourhoods vs nonexposed-PHS locations	2.03 (1.61, 2.55)	$\text{logit}[\pi(x)] = -5.14 + 0.057x$
High-industrialized, GPP-exposed neighbourhoods vs nonexposed-PHS locations	2.10 (1.71, 2.58)	$\text{logit}[\pi(x)] = -2.12 + 0.035x$
High-industrialized, RWS-exposed & GPP-exposed neighbourhoods vs nonexposed-PHS locations	2.29 (1.80, 2.91)	$\text{logit}[\pi(x)] = -5.03 + 0.0642x$

Table Abbreviations: (A) Female population by neighbourhood was ≥ 18 years old. Those included non-breast cancer cases as reported by INEGI Census 2010, and breast cancer cases as reported by local hospitals (HGE, CEO, CIMA, Hospital San José, Clínica del Noroeste) at Hermosillo city from the period January 1st, 2013 to September 20th, 2019. PHS, Potential Hazardous Sites. GPP, Gas Power Plant. RWS, residual water site.

Figure 7: Comparison of the age distribution of breast cancer patients residually exposed to three PHS (highly industrialized neighbourhoods, GPP, and RWS-exposed) versus their non-exposed counterparts.

DISCUSSION

This observational retrospective study evaluated the associations between environmental risk factors and breast cancer risk. Main findings show monotony between the number of risk factors (highly industrialized neighbourhoods, GPP-exposed, and RWS-exposed) and the number of breast cancer cases (OR, b) in

Hermosillo city. The results indicate breast cancer risk is higher for females living in neighbourhoods with HAPs' sources.

Spatial Heterogeneity of Breast Cancer Period Prevalence in Hermosillo Municipality

Hermosillo municipality presents statistically significant

spatial heterogeneity for breast cancer prevalence during the period 2013 to 2019: Spatial cluster analysis indicated six hot spots in Hermosillo city, the capital of Sonora state. All the high-high clusters identified at the capital are in proximity to potentially hazardous sites (PHS). Other rural communities in Hermosillo municipality showed no evidence of hot spots.

Other environmental studies provided evidence of geographic heterogeneity, in the present case, about breast cancer heterogeneity. Soto-Perez-de-Celis indicated higher mortality rates in the Southwest (APC 2.7%, $p < 0.05$) and Center-North regions (APC 1.7%, $p < 0.05$) of Mexico in the period 2001 to 2011 Soto-Perez-de-Celis et al. [5].

Likewise, Castrezana-Campos reported 120 municipalities with the highest morbidity and mortality rates for breast cancer, where environmental pollutants Castrezana-Campos [6] are studied as non-genetic factors for this disease. Hermosillo was one of the 120 municipalities reported by Castrezana-Campos [6].

The present research provides evidence of regional variations of breast cancer prevalence in Hermosillo municipality during a specific period of time (January 1st, 2013 to September 20th, 2019) therefore contributing to a better understanding of the possible associations between breast cancer and HAPs. To the best of our knowledge, there are no prior reports on the geographical distribution of breast cancer prevalence by neighbourhood in Hermosillo municipality.

Higher breast cancer risk is present in PHS-exposed neighbourhoods: In order to explore potential associations, the OR was calculated between residential exposure to PHS and non-breast cancer residents per unit (neighbourhood). Only women equal or older than 18, as registered by INEGI Census 2010, were considered in this study. This approach included all the neighbourhoods across Hermosillo and was not restricted to those locations previously identified as H-H spatial clusters.

Results for this study give evidence that breast cancer risk is higher for women residing in neighbourhoods where sources of hazardous air pollutants (HAPs) are present. The evidence is exhibited in terms of OR, in the number of cases, and different subpopulation distributions. The OR for women residing in highly industrialized (≥ 7 industries) neighbourhoods and low-industrialized (≤ 6 industries) neighbourhoods is 1.69 (p -value < 0.0001). For GPP-exposed, the number of breast cancer cases per 100,000 persons increased by residential proximity to a GPP1 ($n=606$ for $X \leq 2$ km, $n=382$ for 2 km $< X \leq 4$ km, $n=239$ for 4 km $< X \leq 6$ km, and $n=254$ for 6 km $< X \leq 8$ km, where X is the radial distance, all p -values < 0.0001), and may indicate a higher prevalence of this disease with a closer exposure to HAPs' produced by GPP1. For GPP = (set of women possibly affected by GPP1 and GPP2) where women residing in GPP-exposed locations (≤ 4 km) were at higher risk (OR = 1.55, p -value < 0.0001) than those living in GPP-nonexposed neighbourhoods (> 4 km).

Other studies evaluated the exposure to HAPs and breast cancer risk, where women residing in urban areas presented a higher risk for breast malignancies Garcia et al. [8]; Liu et al. [9]. Hormone-positive breast cancers were related to long-term exposure to air pollutants such as acrylamide, benzidine, carbon tetrachloride, ethylidene dichloride, and vinyl chloride Garcia et al. [8], while hormone-negative breast cancers were related to cadmium exposure Liu et al. [9]. However, the link between HAPs and breast cancer burden is not consistent through the literature. Hart et al.

[12] reported no evidence of an increased risk for exposure to HAPs.

In Mexico, only one study aimed for HAPs and breast cancer risk assessment Castrezana-Campos [6], where 120 municipalities were correlated with high NO_x and SO₂ emissions as reported by the Commission for Environmental Cooperation (CCA) in 2010. Our work contributes to the unmet need for breast cancer risk assessment to HAPs' exposure in a community considered at-risk, given its high-industrialized activities.

The link between exposure to contaminated water sources (CWS) and breast cancer risk is also a matter of debate. Investigations suggest chemicals ingested in water, like tetrachloroethylene (PCE) and organic solvents, accumulate in the breast and increase the risk for cancer development Labreche et al. [17]. Few studies reported a moderate increase in cancer burden given PCE-exposure Aschengrau et al. [18]; Gallagher et al. [19]. Others report no associations between CWS-exposure and breast cancer risk Brody et al. [20].

In Mexico, only one study aimed at evaluating chemical exposure in water sources with breast cancer risk. Where the high incidences of mortality and morbidity in 120 municipalities were associated with chemicals in water sources. In the present work, women were at higher risk for breast cancer when living in RWS-exposed (≤ 3 km) neighbourhood in comparison to those residing in an RWS-nonexposed location, with an OR = 1.45 (p -value < 0.0001).

It is expected that if a population is exposed to more than one risk factor, then the number of cases, or the ORs, or the β of the logistic regression model, increase. Those risk factors could be highly industrialized neighbourhoods (≥ 7 industries), GPP-exposed (≤ 4 km), and RWS-exposed (≤ 3 km) neighbourhoods. Women residentially exposed to one or more PHS had a higher risk than their non-exposed counterparts (all p -values < 0.0001). There are three types of evidence: their ORs, the β of the logistic regression model and the number of cases, which increase as the number of risk factor increases. That monotonic property is evidence of increasing risk as the number of risk factors present increases. To the best of our knowledge, this work is the first in Hermosillo, Sonora to propose a model of cumulative residential exposure to hazards in a community considered at-risk for breast cancer. Larger samples are required to confirm our findings.

Strengths and Limitations

The most important strength of this research is that results provided evidence that breast cancer risk is higher for women residing in neighbourhoods where sources of hazardous air pollutants (HAPs) are present. A confirmation of this fact is the monotonic relation between the number of risk factors present and the increase of the β coefficient in the logistic regression model. An additional strength is that the sample includes only cases with a verifiable ID address with at least 10 years of same residence. This was an advantage in assessing residential exposure to PHS.

This study has several limitations related to the lack of information available on water supply, indoor air quality, and air pollutants other than those produced by anthropogenic sources across Hermosillo municipality. Future work may include this information.

CONCLUSION

Our hypothesis is that there are possible associations between breast cancer and risk factors such as highly industrialized

neighbourhoods, GPP and RWS in Hermosillo Sonora, Mexico. Evidence of those possible associations are expressed in terms of OR, a number of cancer cases and the coefficient β from the logistic regression model. This finding is meaningful because it could be useful for developing current environmental and public health policies. Additionally, hospital administrations could allocate resources in order to satisfy the possible demands of health services implicated in breast cancer treatments. More studies may focus on breast cancer prevention policies by reducing exposure to environmental hazards in high-risk populations.

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AVAILABILITY OF DATA

The data that support the findings of this study are available on request from the corresponding author, [DVG]. The data are not publicly available due to relevant data protection laws in Mexico for the protection and privacy of human subjects participating in this research.

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