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Mortality from breast cancer and use of pesticides in the western mesoregion of Santa Catarina – Brazil

Mortalidade por câncer de mama e uso de agrotóxicos na mesorregião oeste de Santa Catarina – Brasil

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ABSTRACT

Chronic exposure to endocrine-disrupting pesticides may be related to breast cancer emergence in agricultural regions. This study aimed to investigate whether the consumption of pesticides is correlated with breast cancer mortality rates in the female population of western Santa Catarina. A retrospective ecological study was carried out. The number of deaths from breast cancer and agricultural production per planted area in the western mesoregion were obtained from public databases. The average of the standardized mortality coefficients was calculated in the periods: 2005 to 2009, 2010 to 2014, and 2015 to 2019. Raw data on pesticide consumption were grouped from 2000 to 2004, considering that the biological effects of chronic exposure occur late. Thus, previous exposure was considered in this study, in which consumption of pesticides occurred five, ten, and 15 years before death. For statistical analysis, thematic cartography and the Quantum GIS technique were used. The overlay method was applied to perform the spatial correlation. Considering 15 years of exposure, the sum of municipalities with an above-average rate of mortality from breast cancer occurred in 93 of the 118 municipalities in western Santa Catarina, which have an above-average history of pesticide consumption (R^2=0.69). In 79% of cases, mortality occurred at a frequency above the average in municipalities whose pesticide consumption also exceeded the regional average. A proportional correlation between breast cancer mortality rates and the use of endocrine-disrupting pesticides was found.

Keywords: agrochemicals; ecological studies; environmental exposure; breast neoplasms; agricultural production.

RESUMO

A exposição crônica aos agrotóxicos disruptores endócrinos pode relacionar-se ao surgimento de câncer de mama em regiões agrícolas. Objetivou-se investigar se o consumo de agrotóxicos possui correlação com as taxas de mortalidade por câncer de mama na população feminina do oeste catarinense. Realizou-se um estudo ecológico retrospectivo. De bancos de dados públicos obtiveram-se o número de óbitos por câncer de mama e a produção agrícola por área plantada da mesorregião oeste. A média dos coeficientes padronizados de mortalidade foi calculada nos períodos: 2005 a 2009, 2010 a 2014 e 2015 a 2019. Os dados brutos do consumo de agrotóxicos foram agrupados de 2000 a 2004, considerando-se que os efeitos biológicos de uma exposição crônica ocorrem tardiamente. Assim, considerou-se uma exposição pregressa, em que o consumo de agrotóxicos antecedeu os períodos de mortalidade em cinco, dez e 15 anos. Para a análise estatística, utilizaram-se a cartografia temática e a técnica *Quantum GIS*. Empregou-se o método de *overlay* para realizar a correlação espacial. Considerando-se 15 anos de exposição, a soma dos municípios com taxa acima da média de mortalidade por câncer de mama foi de 93 dos 118 dos municípios do oeste catarinense, que apresentam histórico acima da média para o consumo de agrotóxicos (R^2=0,69). Em 79% dos casos, a mortalidade ocorreu a uma frequência acima da média em municípios cujo consumo de agrotóxicos também ultrapassou a média regional. Foi possível correlacionar, proporcionalmente, as taxas de mortalidade por câncer de mama com o uso de agrotóxicos disruptores endócrinos.

Palavras-chave: agroquímicos; estudos ecológicos; exposição ambiental; neoplasias da mama; produção agrícola.

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Introduction

The State of Santa Catarina has important agricultural productivity and is among the ten largest consumers of pesticides in Brazil (Brasil, 2018; IBGE, 2019). It stands out for its grain production, granted in the 2021/2022 harvest, which exceeded 6.5 million tons (EPAGRI, 2022). In the western mesoregion of the state, grain production is also noteworthy, especially corn and soybean (IBGE, 2019), in which endocrine-disrupting pesticides are systematically used in the production chain of these transgenic crops (Dutra et al., 2020).

Chronic exposure to pesticides may be related to the emergence of breast cancer, especially in agricultural regions. In Santa Catarina, considering female deaths due to malignant neoplasms that occurred in 2020, 35.1% were related to breast neoplasms (DIVE, 2020). Breast cancer is the leading cause of cancer death among women and is a relevant public health problem worldwide (Sung et al., 2021). Similarly, in Brazil, the South and Southeast regions have higher mortality rates than other regions of the country, with approximately 15 and 16 deaths per 100,000 women, respectively (INCA, 2021).

The etiology of breast cancer is multifactorial. Aging, heredity, hormonal and reproductive history, lifestyle, as well as genetic and environmental factors are conditions that can trigger the disease (INCA, 2020). From this perspective, genetic and environmental influences can markedly interfere with the disease process. Genotoxic and carcinogenic environmental pollutants have been investigated, as they can induce mutations by DNA methylation, and therefore, these substances can be initiators or promoters in the oncogenesis process (IARC, 2016; Starek-Świechowicz et al., 2021; Sasikala et al., 2023).

Genotoxic carcinogens are synthetic chemicals that exert carcinogenicity through mutation induction, due to their DNA interaction properties (IARC, 2016). It is believed that there is no exposure limit or safe dose of these compounds. Thus, the presence of only one molecule within the organism is enough to cause interaction with DNA, causing some carcinogenic risk, which increases according to the level of exposure. Even at very low doses, these substances can cause cancer in humans (Nohmi, 2018).

In contrast, non-genotoxic carcinogens, which induce cancer through other mechanisms including hormonal effects, cytotoxicity, cell proliferation, or epigenetic changes, are considered to have a safe exposure threshold or dose. Its use in society is allowed when the level of exposure or intake does not exceed the limit (Nohmi, 2018).

Genotoxic carcinogens are generally not acceptable for use as food additives, pesticides, or pharmaceuticals, due to the carcinogenic risk even at very low doses (FAO/WHO, 2020). However, non-genotoxic compounds, classified as endocrine disruptors such as pesticides of the organophosphate, carbamate and pyrethroid classes are widely used. They have the property of acting at very low concentrations, and in cases of chronic intoxication may be related to the emergence of breast cancer (Casals-Casas and Desvergne, 2011; Miret et al., 2019; Calaf, 2023).

Breast tissue cells undergo hormone-regulated proliferation, and the development of some invasive carcinomas of the breast parenchyma may be influenced by hormonal stimuli (Poudel et al., 2019) and immunotoxicity (Dos Santos et al., 2023). Thus, chronic exposure to low concentrations of pesticides may not produce immediate effects on the health of a given population, but over time will contribute to an increase in the number of cancers (Grisolia, 2022).

Due to their molecular conformations, endocrine disruptors may present biochemical properties similar to those of endogenous hormones and, consequently, provoke additional hormonal stimuli in the female organism (Kass et al., 2020). In addition, they can interact with hormone receptors by acting through physiological mechanisms by which they replace hormones in the human body, or block their natural action. They can also increase or decrease the original levels of hormones, altering endocrine functions (Endocrine Society, 2014). Exposure to endocrine disruptors may impair the normal development of the mammary gland or increase the occurrence of lesions (Kass et al., 2020).

In this scenario, the high production of the agricultural sector and the intensive use of pesticides generate concern about occupational and environmental exposure and the occurrence of diseases such as cancer (INCA, 2021). Above all, the use of these substances negatively impacts the public health system, burdening it, due to poisoning and exposure-related diseases. Thus, areas with higher consumption of endocrine-disrupting pesticides are expected to present increased mortality rates from chronic diseases, including cancer (Dutra et al., 2020).

In view of the above, the objective of this study was to verify whether the consumption of pesticides is correlated with breast cancer mortality rates in the female population of western Santa Catarina.

Material and Methods

Study design

This is a retrospective quantitative, ecological study that used secondary, public databases that provide the number of deaths from breast cancer and agricultural production per planted area in the western mesoregion of the State of Santa Catarina, Brazil.

Data source and study protocol

For the collection of data on mortality from breast cancer, records of deaths due to malignant neoplasms of the breast were verified, which correspond to code C50 of the Tenth Revision of the International Classification of Diseases (ICD), made available by the Mortality Information System (MIS) of the Brazilian Public Unified Health System (SUS) Department of Informatics (DATASUS). The municipalities considered for the search were those of women's residences in the western mesoregion of Santa Catarina.

Data on deaths were grouped, for each municipality, by age groups: 20–39, 40–49, 50–59, 60–69, 70–79, and ≥80 years, including deaths that occurred between 2005 and 2019. Population projections were obtained from preliminary estimates prepared by the Ministry of Health (MH), Department of Health Surveillance (DHS). Data were organized in Microsoft Excel® (version 19) spreadsheets, where the annual mortality coefficients per 100,000 women were calculated. To obtain the standardized cancer rates, the direct method was used, considering the Brazilian population as the standard population, according to the 2010 Demographic Census, and the specific coefficients for each age group. Afterwards, the mean of the coefficients obtained for three five-year periods was calculated: 2005 to 2009, 2010 to 2014, and 2015 to 2019.

As for agricultural production, the annual sum of planted area of corn, soybean and wheat crops per hectare (ha) was calculated in the period between 2000 and 2004. Data on planted areas were obtained from the Brazilian Institute of Geography and Statistics (IBGE) Automatic Recovery System (IBGE, 2020). The classification of municipalities between rural and urban was organized using the rural-urban municipal typology of IBGE (IBGE, 2017a).

Due to the lack of public data on the consumption of pesticides in the state, an estimate of consumption was made, as described by Dutra and Ferreira (2017), with some adaptations. The recommended dose, applied per crop (L or kg/ha) for each pesticide, was multiplied by the planting area in hectares, as recommended in the pesticide package inserts. Due to the variation in the indicated doses, up to seven package inserts per pesticide active ingredient were consulted in order to obtain a mean amount applied per type of crop. The sum of pesticide consumption was calculated for a period of five years, between 2000 and 2004, considering that the biological effects of a period of chronic exposure occur late.

Data on the pesticides used in the selected crops were obtained by accessing the website of the Integrated Company for Agricultural Development of Santa Catarina (*Companhia Integrada de Desenvolvimento Agrícola de Santa Catarina* — CIDASC). All endocrine-disrupting pesticides, released for use in Santa Catarina, were consulted for corn, soybean and wheat crops, through the Santa Catarina Agricultural Defense Management System (SIGEN) (CIDASC, 2016). Pesticides classified according to what was proposed by Mnif et al. (2011) were considered endocrine disruptors.

Cartographic analysis

The spatial analysis of this article was based on the investigation of data on mortality from breast cancer and pesticide consumption in each municipality in the western region of Santa Catarina. In this study, neighborhood relationships were not explored, but rather, how the two variables have been related in each municipality. We sought to investigate the history of pesticide consumption and whether there is a correlation with the breast cancer mortality rate. The correlation criterion was the crossing of values above the mean, both for mortality rate and consumption of pesticides.

Thematic cartography was used with its data classification methods, in which spatial clustering trends were sought. The main technique used was the classification by ranges by the Quantum Geographic Information System (QGIS) cartometric method, known as quartile deviation. This method "divides the data series into four groups with an equal number of occurrences, each comprising 25% of the total values" (Ramos and Sanchez, 2000).

In particular, the fourth class for pesticide data was generated with the objective of isolating the cases of municipalities with very high magnitudes of pesticide consumption which established a considerable deviation in the distribution of data. Thus, raw data on pesticide consumption were grouped and classified according to ranges and classes for the period 2000–2004.

In 2020, the mortality rate from breast cancer in the female population was 11.84 deaths/100,000 women in Brazil, with 12.79 in the South Region and 12.71 in the State of Santa Catarina. According to data presented by the Ministry of Health (INCA, 2022), the mortality rates of the western mesoregion of Santa Catarina were classified into four ranges: "low" (0–5), "medium" (6–15), "high" (16–20), and "very high" (21–53.6). The following periods were considered for analysis: 2005 to 2009, 2010 to 2014, and 2015 to 2019.

The overlay method was used to search for the spatial correlation between the mortality rate and the history of pesticide consumption. The application of the overlay technique (topological overlay of geographic themes) in a vector environment requires the establishment of topological compatibility stages in the polygon-line interface (Sampaio and Brandalize, 2018). To this end, we sought to convert the polygons of the municipalities into centroids to the primitive point indicating the breast cancer mortality rates, and the data on pesticide consumption spatialized in the primitive area by the polygons of the municipalities was maintained. After the topological conversion stage of the data, the investigation was carried out by crossing the geo-objects. These topological expressions (point and area) reflect the same geographical reality of the municipality where the information comes from and, therefore, validate the correlation.

Results and Discussion

The following maps are spatial expressions of the crossing of breast cancer mortality rates in three distinct periods (2005–2009, 2010–2014, and 2015–2019) with pesticide consumption data for the period 2000–2004. The consumption of pesticides in the aforementioned period was the parameter of comparison to observe the evolution of mortality rate in the three periods.

Figure 1 shows the comparison of the data, considering a period of five years between pesticide consumption (2000–2004) and breast cancer mortality rates detected later (2005–2009). In this map, as well as in the other maps below, the visual effect of the overlay technique, that is, the overlap of different layers that represent the different spatial variables is observed.

Thirteen municipalities were identified as having very high pesticide consumption range, namely: Abelardo Luz, Campo Erê, Concórdia, Cunha Porã, Chapecó, Faxinal dos Guedes, Guaraciaba, Palma Sola, Palmitos, Quilombo, São Domingos, São José do Cedro, and Xanxerê. Also, 24 municipalities with very high breast cancer mortality rates were found, including: Abelardo Luz, Água Doce, Caibi, Descanso, Erval Velho, Formosa do Sul, Jaborá, Lajeado Grande, Luzerna, Paial, Presidente Castello Branco, Salto Veloso, São Miguel da Boa Vista, São Bernardino, São João do Oeste, São Lourenço do Oeste, Saudades, and Romelândia.

Figure 2 shows the comparison of pesticide consumption data between 2000 and 2004 and mortality rates from breast cancer, detected after ten years, in the period between 2010 and 2014.

Twenty-seven municipalities were identified with very high breast cancer mortality rates, namely: Abelardo Luz, Águas Frias, Bandeirante, Bom Jesus, Coronel Freitas, Cunhataí, Entre Rios, Formosa do Sul, Guatambú, Irani, Irati, Matos Costa, Modelo, Ouro, Passos Maia, Pinhalzinho, Pinheiro Preto, São Carlos, São Domingos, São Miguel da Boa Vista, São João do Oeste, Serra Alta, Tigrinhos, Tunápolis, Vargeão, Vargem Bonita, and Videira.

Next, Figure 3 shows the comparison of pesticide consumption data (2000 and 2004) and breast cancer mortality rates considering a subsequent period of 15 years (2015 and 2019).

Twenty-nine municipalities with very high breast cancer mortality rates were identified: Água Doce, Anchieta, Belmonte, Concórdia, Cordilheira Alta, Coronel Freitas, Dionísio Cerqueira, Faxinal dos Guedes, Formosa do Sul, Guaraciaba, Guatambú, Iporã do Oeste, Irani, Joaçaba, Luzerna, Macieira, Nova Itaberaba, Peritiba, Pinheiro Preto, Presidente Castello Branco, Quilombo, Rio das Antas, Salto Veloso, São Domingos, São João do Oeste, Tigrinhos, União do Oeste, Vargeão, and Xavantina.

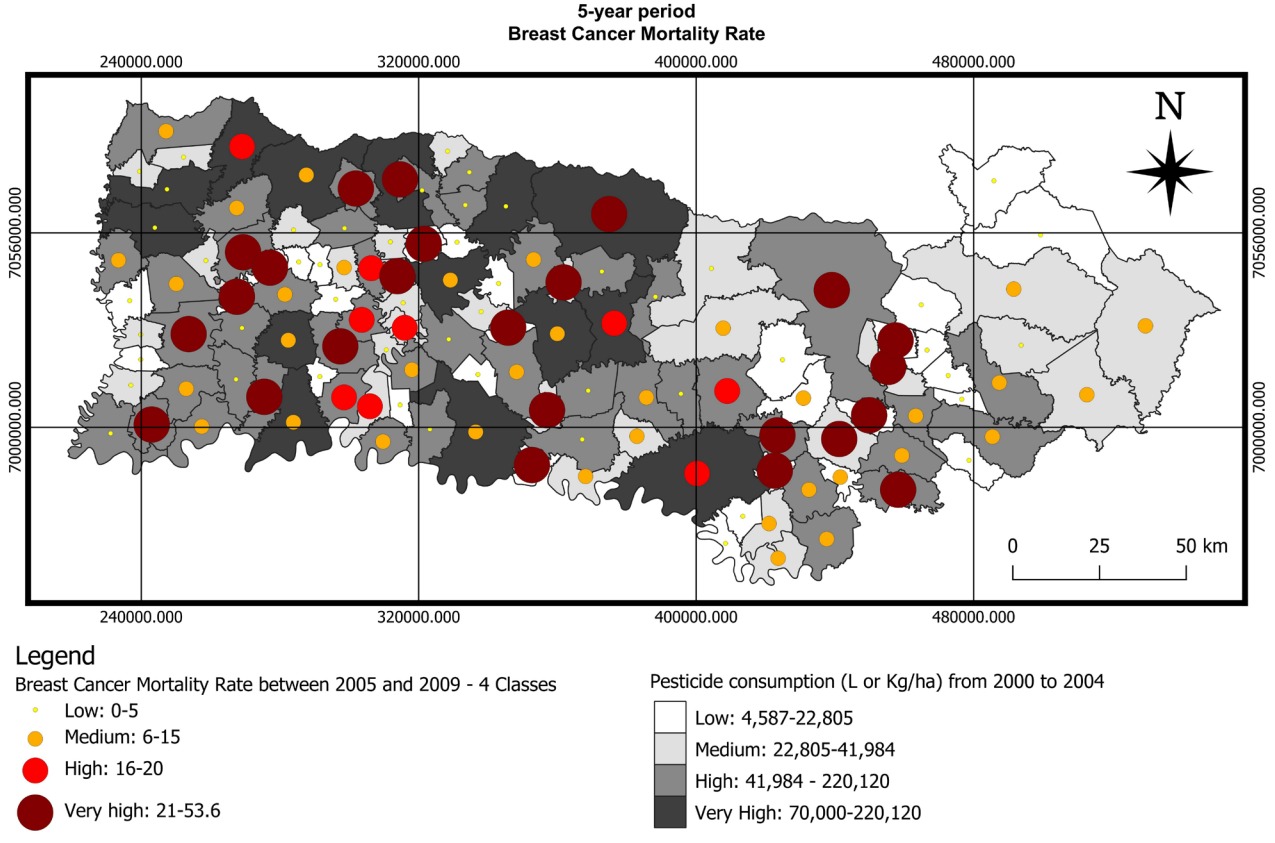


Figure 1 – Spatial distribution of breast cancer mortality rates (2005–2009) according to pesticide consumption (2000–2004) in corn, soybean and wheat crops in the western mesoregion of Santa Catarina, Brazil.

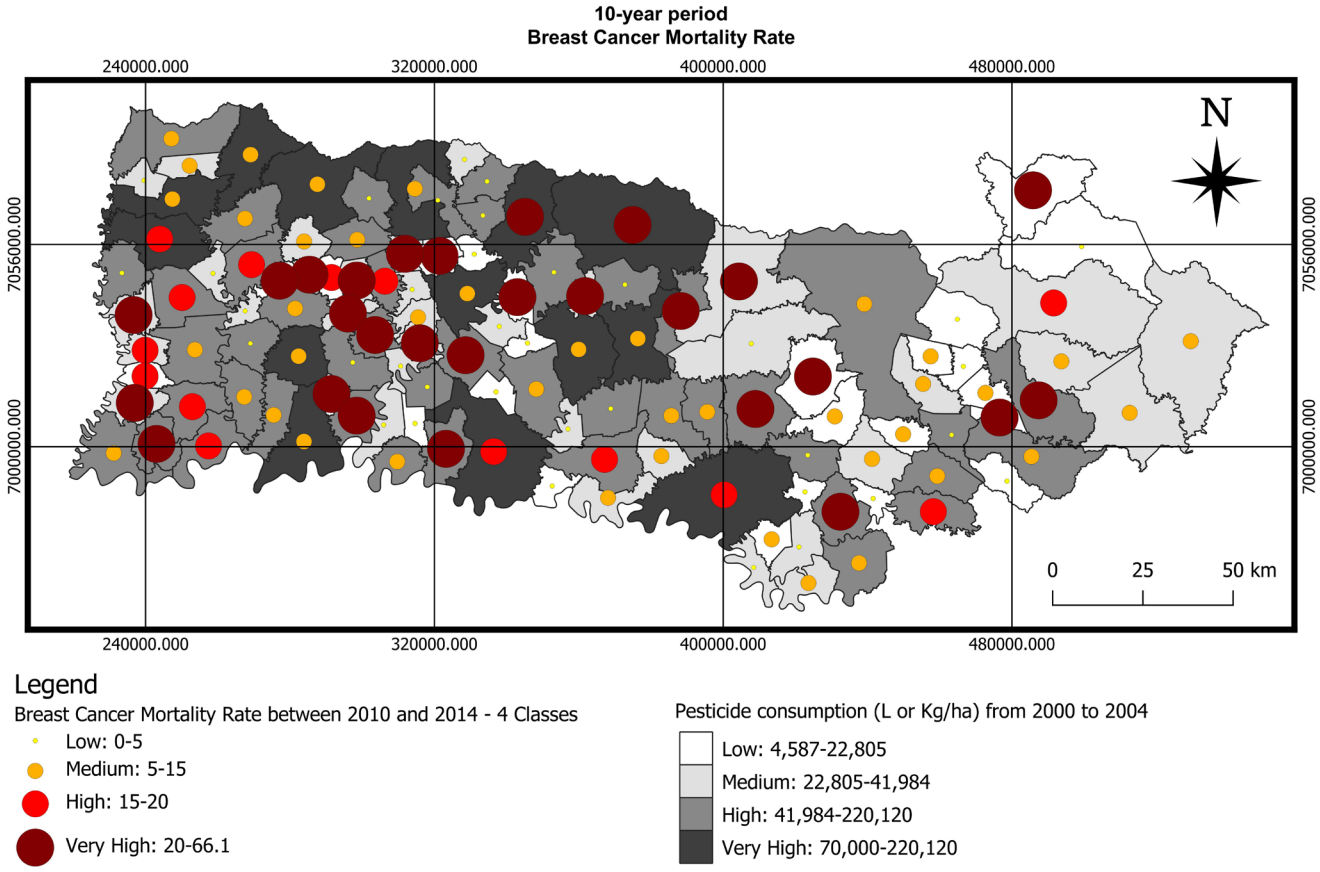


Figure 2 – Spatial distribution of breast cancer mortality rates (2010–2014) according to pesticide consumption (2000–2004) in corn, soybean and wheat crops in the western mesoregion of Santa Catarina, Brazil.

In comparison, the three maps showed an increase in the frequency in the very high range for breast cancer mortality within five (2005–2009), ten (2010–2014), and 15 years (2015–2019), respectively in the proportion of 24, 27 and 29 municipalities in the western mesoregion of Santa Catarina.

Through the analysis of the maps, it is important to highlight that this increase in frequency does not occur *pari passu* in each municipality with the increase in the frequency of pesticide consumption. This does not mean that there is no correlation, as geographical and temporal factors contribute to complicating the correlation

First, it is evident that the consumption of pesticides and the emergence of mortality cases are separated in time by an order of five to 15 years. The mobility of the population can contribute to the fact that exposure in a given municipality is only detected in another municipality, often far from the place of contamination.

Second, the place where the pesticide was potentially used within a municipality is not the same as where the population's residence is concentrated, except for those residing in the vicinity of agricultural areas. People focus on urban perimeters, while pesticides are applied elsewhere. It is possible through cartography to link the mortality rate to urban perimeters. On the other hand, it is not possible to establish the exact location where the pesticides were applied or consumed, so spatial proximity, a strategic geographical factor for the spatial relationship, cannot be satisfactorily established.

Since the data do not occur diachronically, it was decided to use the centroids of the polygons of the municipalities. For these reasons, the methodology sought the existing crossings between the various consumption ranges and the mortality rate in order to search for the frequencies of correlations above and below the mean between the variables. These crossings were only possible through mapping.

In this study, most of the municipalities whose mortality rates from detected breast cancer were high are those classified as adjacent rural, according to the IBGE, and that have a low degree of urbanization (IBGE, 2017a). Similarly, Parrón et al. (2014) found in Spain that the prevalence and risk rates of several cancers were significantly higher in districts with higher pesticide use than those with lower pesticide use.

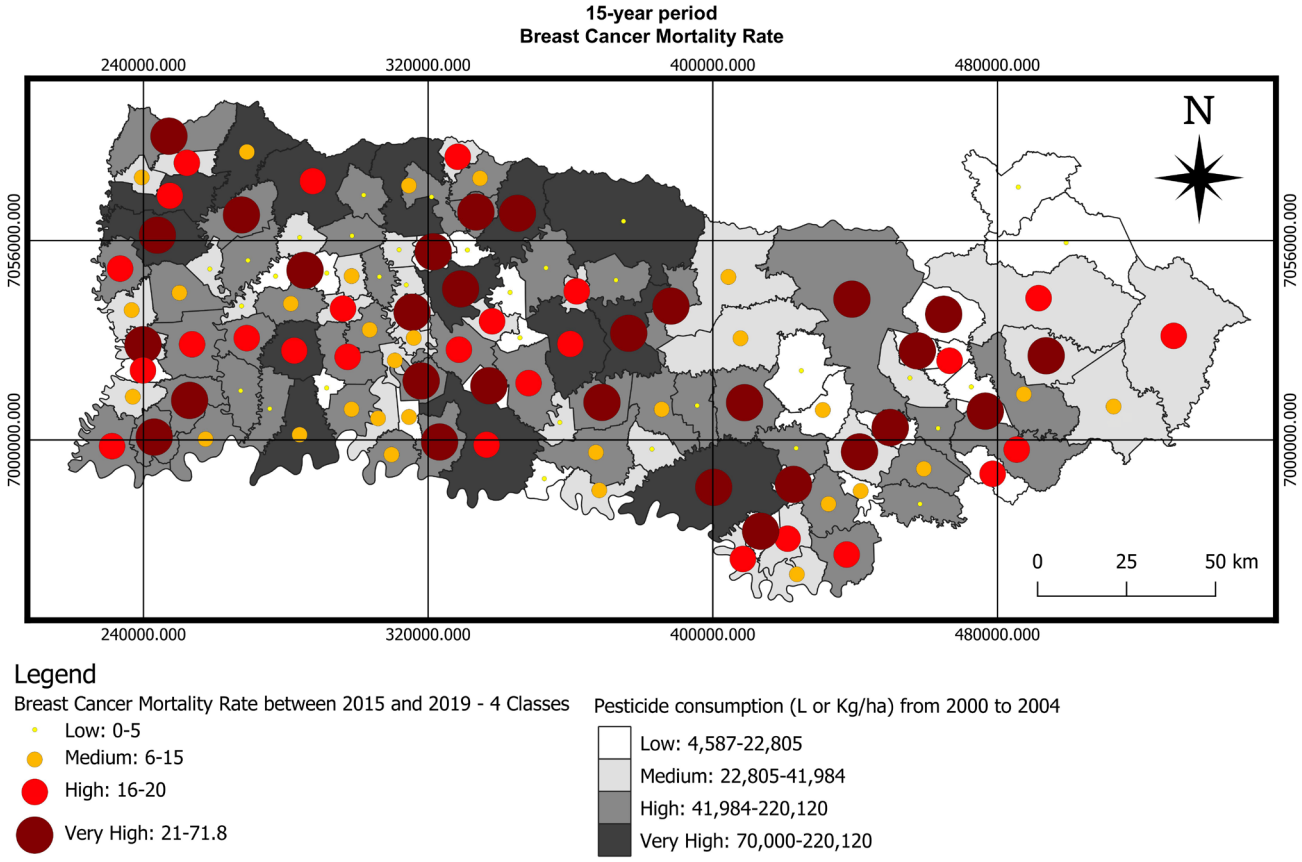


Figure 3 – Spatial distribution of breast cancer mortality rates (2015–2019) according to pesticide consumption (2000–2004) in corn, soybean and wheat crops in the western mesoregion of Santa Catarina, Brazil.

They also found that the population living in areas with high pesticide use had an increased risk of all types of cancer. Thus, they concluded that environmental exposure may be a risk factor for different types of cancer in the general population.

Therefore, it is relevant to monitor the health of the population of adjacent rural municipalities, whose activities related to agriculture can make women more vulnerable to environmental exposure. Agricultural regions have impact on cities, that is, even urban citizens who have no contact with the countryside are also at risk and suffer the consequences of what occurs there (Parrón et al., 2014). Though in low exposure to pesticides by the population, there is still a risk, and chronic exposure is not foreseen by Brazilian legislation (Grisolia, 2022).

According to data from the Directorate of Epidemiological Surveillance of Santa Catarina, deaths from malignant neoplasms in women were largely related to breast neoplasms (35.1%) (DIVE, 2020). Several factors are related to the increased incidence and mortality from breast cancer: aging (Barros et al., 2020), genetic constitution, poor eating habits, lifestyle linked to alcohol consumption and smoking, physical inactivity, and economic and environmental factors (INCA, 2019).

Considering that hereditary predisposition is related to 5–10% of breast cancer cases (Adami et al., 2008), it is understood that most cancers are diagnosed with non-hereditary causes. Thus, factors related to women's environmental exposure are significant causes, as they can influence the occurrence of mutations in genes involved in carcinogenic processes throughout life (Starek-Świechowicz et al., 2021).

Although research using cancer incidence better reflects the risk of the disease, there are no reliable data available in public open-access databases for research. Thus, we chose to use mortality that was reported in the DATASUS. According to the main findings of this study, which show the correlation of mortality rates from breast cancer above mean with the use of pesticides also above mean over time, it is considered that special attention should be paid to environmental factors that may be related to the disease.

In this sense, the excessive use of pesticides is a relevant public health problem, bringing negative impacts to populations, especially

those most exposed in regions of monoculture cultivation and intense agricultural production (Miranda Filho et al., 2014; Dutra et al., 2020, Pardo et al., 2020). The western mesoregion of Santa Catarina is nationally known for the important presence of agribusiness, whose base consists of family farming, which represents 84.1% of the agricultural establishments in the region (IBGE, 2017b).

The west of Santa Catarina is responsible for most of the state's agricultural production, reaching 40.5%, taking into account temporary and permanent crops. It concentrates more than thirty types of crops, which confers the productive diversity and economic importance of the region (Dentz and Espíndola, 2019). In addition to livestock, the agricultural crops that should be highlighted, considering the representativeness of production between temporary and permanent crops, are corn and soybean (EPAGRI, 2020).

In these genetically modified crops, the pesticides classified as the most commonly used endocrine disruptors include 2,4 dichlorophenoxyacetic acid (2,4-D), acephate, captan, carbendazim, chlorothalonil, chlorpyrifos, pyrethroids such as cypermethrin and deltamethrin, epoxiconazole, cyproconazole, diuron, flutriafol, glyphosate, methomyl, and tebuconazole (CIDASC, 2016). These compounds are mainly formulations of herbicides, insecticides, and fungicides used in crops. Glyphosate is a herbicide with the capacity to cause endocrine disruption of great commercialization in tons of active ingredients in Brazil and in the world (Samsel and Seneff, 2013; IBAMA, 2021; Codex Alimentarius, 2023).

In the scatter plots of the following figures, the numbering corresponds to the patterns: 1-low, 2-medium, 3-high and 4-very high. In the balloons, there is a distribution of the number of municipalities in the western mesoregion of Santa Catarina, 118 in all, by types of intersections. The warm colors indicate the number of municipalities in which the intersections of the classes are equivalent: "low consumption of pesticides x low mortality rate", "medium consumption x medium rate", "high consumption x high rate", and "very high consumption" x "very high rate". The colors in dark blue represent the number of municipalities where the above-mean crossing occurs, both for breast cancer mortality rates and pesticide consumption history.

In Figure 4, it is possible to verify the intersections of the ranges of the mortality rate by the ranges of pesticide consumption. The colors in the table correspond to the colors adopted in the graphical expression of the maps. For the 15-year period, it was identified that the sum of the municipalities with the mortality rate for breast cancer above the mean occurs in 93 of the 118 municipalities in western Santa Catarina, which have a history above the mean for the consumption of pesticides (R^2=0.69). That is, in 79% of cases, mortality from breast cancer occurred at an above-mean frequency in municipalities whose pesticide consumption also exceeded the regional mean.

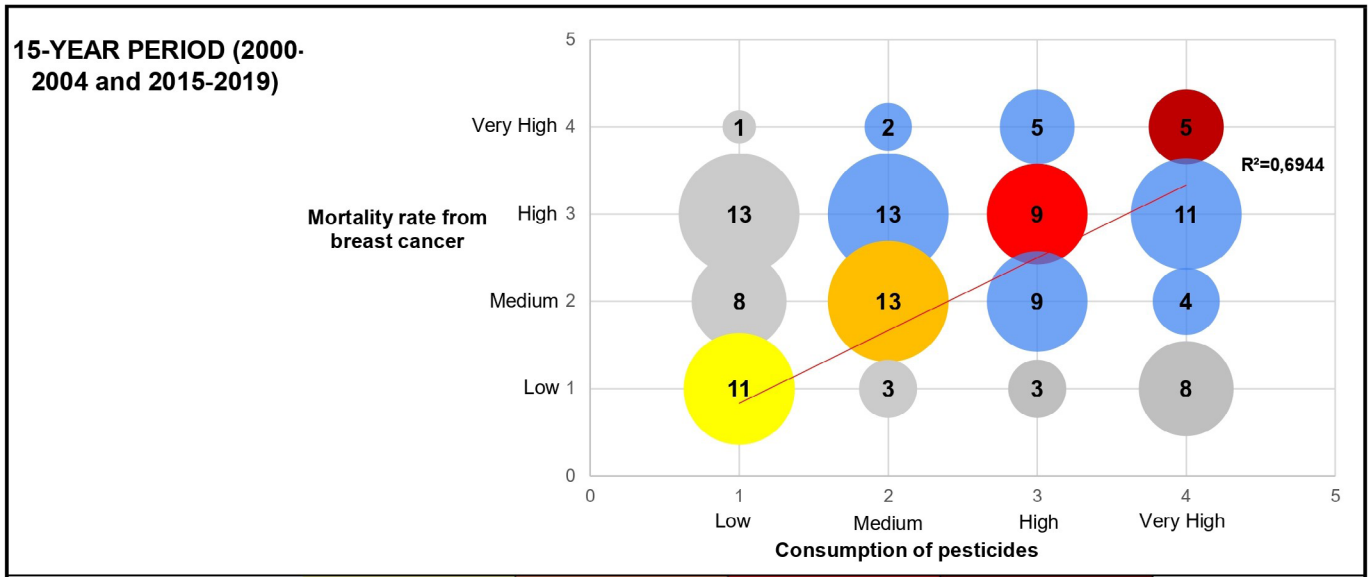
According to Figures 5 and 6, from one period to the next, some municipalities changed their classes in terms of mortality rates and pesticide consumption. Despite these small variations, the same percentage of 79% or 93 municipalities was detected, respectively, for the ten-year (2010–2014) and five-year (2005–2009) periods, in which the above-mean rates of breast cancer mortality remained in the historical above-mean rates of pesticide consumption (R^2=0.69).

Through the scatter plots, it is possible to notice the small variations mentioned, and some of these we can highlight by the analysis of crossings in similar ranges. In this sense, we sought to cross the "low-low", "low-medium", "low-high", and "low-quite-high" ranges. Compared to Figures 4, 5, and 6, we can observe that there is an increase in the frequency of municipalities where the intersections are equivalent.

For the very high x very high crossing, we have the evolution in the frequency of municipalities that went from one, in the period of five years, to two, in the period of ten years, jumping to five in the period of 15 years. The same is true for the high x high crossing. The frequency of municipalities goes from four in the period of five years to seven in ten years, and then to nine municipalities in the period of 15 years. We can also observe the same evolution for the medium x medium crossing. The frequency of municipalities increases from nine in the five-year period, to 11 in the ten-year period and then to nine municipalities in the 15-year period. When we observe in a more generic way the distribution of data, it is noted that most frequencies occur in values above the mean of pesticide consumption, being related to values above the mean in the mortality rate.

From the results presented in the maps, it is possible to observe the significant number of municipalities in the western mesoregion that presented high mortality rates from breast cancer, which exceeded the rates calculated for the State of Santa Catarina (12.71), for the South region (12.79), and Brazil (11.84/100,000 women). In fact, the South region is affected by the disease, which is reflected in mortality rates. The State of Santa Catarina, in 2020, was the third Brazilian state with the highest mortality due to malignant breast neoplasm, remaining behind only Rio de Janeiro (15.08) and Rio Grande do Sul (13.76/100,000 women) (INCA, 2022).

Corroborating this, Pignati et al. (2017) found that health indicators such as acute intoxication, incidence of fetal malformation, and mortality due to juvenile cancer showed a positive correlation with pesticide consumption in a region of intense agricultural production. It is considered that the pesticides used in food production crops do not remain restricted to the environment where they were applied (Carneiro et al., 2015). Toxic molecules may also be present in water for human and animal consumption. Panis et al. (2022) analyzed the extent of contamination of drinking water with 11 likely or potentially carcinogenic pesticides in 127 grain-producing municipalities in the State of Paraná. The study showed water contamination significantly correlated with the sum of estimated cancer cases for all 11 pesticides detected in each city. Pesticide residues also persist in food. The Pesticide Residue Analysis Program (PARA) analyzed 4,616 samples of 14 foods of plant origin representative of the diet of the Brazilian population; the study showed that 51% of the samples were contaminated with pesticide residues at some level (ANVISA, 2019).



2000 - 2004	Breast Cancer LOW rate (0-5 cases)		Breast Cancer MEDIUM rate (6-15 cases)		Breast Cancer HIGH rate (16-20 cases)		Breast Cancer VERY HIGH rate (21 cases or more)		Sum of municipalities with cancer rates due to pesticide consumption	
2000-2004	2015-2019		2015-2019		2015-2019		2015-2019		2015-2019	
Classes of Pesticide Consumption	Number of Mun.	%	Number of Mun.	%	Number of Mun.	%	Number of Mun.	%	Number of Mun.	%
Low - 4587 - 20603	11	33%	3	10%	3	12%	8	28%	25	21%
Medium - 20603 - 27634	8	24%	12	40%	9	35%	5	17%	34	29%
High - 27634 - 70000	13	39%	13	43%	9	35%	11	38%	46	39%
Very High - 70000 - 220120	1	3%	2	7%	5	19%	5	17%	13	11%
Total municipalities	**33**	**100%**	**30**	**100%**	**26**	**100%**	**29**	**100%**	**118**	**100%**
Municipalities where the cancer rate is related to above-average agro consumption	22	67%	27	90%	23	88%	21	72%	93	79%
Municipalities where the cancer rate is related to below-average agro consumption	11	33%	3	10%	3	12%	8	28%	25	21%

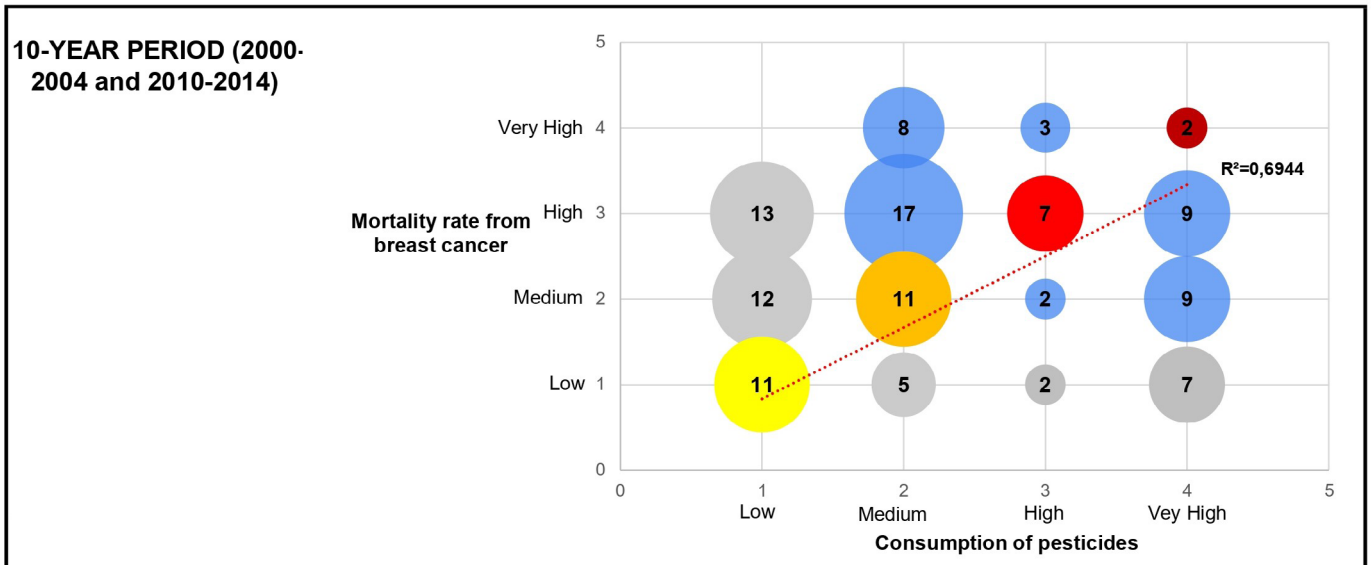
Figure 4 – Frequency of municipalities in the crossing of the ranges of breast cancer mortality rates (2015–2019) with the ranges of pesticide consumption (2000–2004) in the western mesoregion of Santa Catarina, Brazil.

In the case of breast tissue cells, proliferation regulated by systemic hormones must be considered, and the development of some breast carcinomas is influenced by estrogens (Gompel, 2019). Endocrine-disrupting pesticides can cause additional hormonal stimuli in the female body, increasing the occurrence of breast lesions (Kass et al., 2020), inducing DNA mutations and, consequently, the carcinogenesis process (IARC, 2017; Miret et al., 2019).

Another mechanism associated with changes in genes related to the control of cell death is linked to epigenetic modifications. Among these changes, we can mention DNA methylation, which generates damage to genes, causing changes in gene expression patterns (Barroso et al., 2020).

The term epigenetics is defined as molecular factors and processes around deoxyribonucleic acid (DNA) that regulate genome activity, independent of DNA sequence, and are mitotically stable (Ben Maamar et al., 2021). Epigenetic modifications include DNA methylation, histone post-translational modifications, and differential expression of non-coding ribonucleic acids (RNAs). Epigenetic processes can lead to silencing/activation of gene expression, genomic imprinting, and development of pathologies such as cancer (Nelson et al., 2008; Carvalho et al., 2018; Hemmatzadeh et al., 2020).

In addition, epigenetic changes can be maintained over time and, therefore, transmitted to offspring in the second, third, and fourth generation (Anway et al., 2005). The importance of epigenetics in linking the impacts of environmental factors to changes in gene expression has gained increasing acceptance in recent years (Bukowska et al., 2022). It is becoming clearer that epigenetic changes play a crucial role in health and disease, including cancer (Moggs et al., 2004; Chappell et al., 2016; Ors Kumoglu et al., 2022).



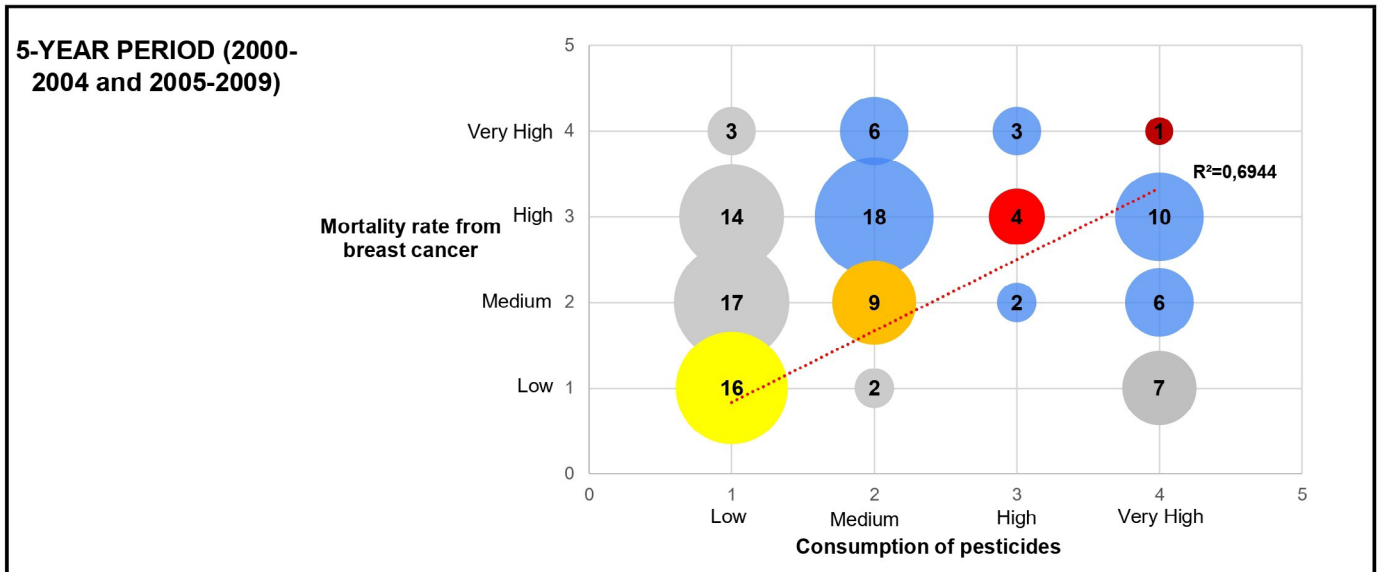
2000 - 2004	Breast Cancer LOW rate (0-5 cases)		Breast Cancer MEDIUM rate (6-15 cases)		Breast Cancer HIGH rate (16-20 cases)		Breast Cancer VERY HIGH rate (21 cases or more)		Sum of municipalities with cancer rates due to pesticide consumption	
2000-2004	2010-2014		2010-2014		2010-2014		2010-2014		2010-2014	
Classes of Pesticide Consumption	Number of Mun.	%	Number of Mun.	%	Number of Mun.	%	Number of Mun.	%	Number of Mun.	%
Low - 4587 - 20603	11	31%	5	12%	2	14%	7	26%	25	21%
Medium - 20603 - 27634	12	33%	11	27%	2	14%	9	33%	34	29%
High - 27634 - 70000	13	36%	17	41%	7	50%	9	33%	46	39%
Very High - 70000 - 220120	0	0%	8	20%	3	21%	2	7%	13	11%
Total municipalities	36	100%	41	100%	14	100%	27	100%	118	100%
Municipalities where the cancer rate is related to above-average agro consumption	25	69%	36	88%	12	86%	20	74%	93	79%
Municipalities where the cancer rate is related to below-average agro consumption	11	31%	5	12%	2	14%	7	26%	25	21%

Figure 5 – Frequency of municipalities in the crossing of the ranges of breast cancer mortality rates (2010–2014) with the ranges of pesticide consumption (2000–2004) in the western mesoregion of Santa Catarina, Brazil.

Aside from endocrine disruption, genotoxicity, and epigenetic changes, other mechanisms may be involved in the etiology of cancer such as metabolic activation, genomic instability, oxidative stress, chronic inflammation, immunosuppression, and alteration of cell proliferation (Smith et al., 2016). It is essential to note that the use of several types of pesticides can simultaneously activate more than one of these mechanisms, which increases the risk of oncogenesis (Sarpa and Friedrich, 2022).

One of the most widely used herbicides in corn and soybean crops is glyphosate, which can induce the proliferation of estrogen-dependent human mammary cells (MCF-7) in vitro (Mesnage et al., 2017) besides deregulating the cell cycle and causing changes in metabolism (Stur et al., 2019). In animal studies, postnatal exposure to glyphosate-based herbicides caused an increase in the percentage of hyperplastic ducts in the breasts. In addition, there was an increase in the expression of estrogen and progesterone receptors in hyperplastic lesions, which suggests the occurrence of changes in the female mammary gland in the long term (Zanardi et al., 2020).

Recent findings show that the mechanism of action of glyphosate may include epigenetic modifications (Rossetti et al., 2020). These are reversible mechanisms linked to tissue-specific silencing of gene expression, genomic imprinting, and tumor growth. The herbicide glyphosate produces changes in global DNA methylation, specific gene methylation, histone modification, and differential expression of non-coding RNAs in human and rodent cells (Rossetti et al., 2020). The International Agency for Research on Cancer (IARC) stated that glyphosate and its products are likely human carcinogens, classifying these substances in Group 2A (IARC, 2017).



2000 - 2004	Breast Cancer LOW rate (0-5 cases)		Breast Cancer MEDIUM rate (6-15 cases)		Breast Cancer HIGH rate (16-20 cases)		Breast Cancer VERY HIGH rate (21 cases or more)		Sum of municipalities with cancer rates due to pesticide consumption	
2000-2004	2005-2009		2005-2009		2005-2009		2005-2009		2005-2009	
Classes of Pesticide Consumption	Number of Mun.	%	Number of Mun.	%	Number of Mun.	%	Number of Mun.	%	Number of Mun.	%
Low - 4587 - 20603	16	32%	2	6%	0	0%	7	29%	25	21%
Medium - 20603 - 27634	17	34%	9	26%	2	22%	6	25%	34	29%
High - 27634 - 70000	14	28%	18	51%	4	44%	10	42%	46	39%
Very High - 70000 - 220120	3	6%	6	17%	3	33%	1	4%	13	11%
Total municipalities	**50**	**100%**	**35**	**100%**	**9**	**100%**	**24**	**100%**	**118**	**100%**
Municipalities where the cancer rate is related to above-average agro consumption	**34**	**68%**	**33**	**94%**	**9**	**100%**	**17**	**71%**	**93**	**79%**
Municipalities where the cancer rate is related to below-average agro consumption	**16**	**32%**	**2**	**6%**	**0**	**0%**	**7**	**29%**	**25**	**21%**

Figure 6 – Frequency of municipalities in the crossing of the ranges of breast cancer mortality rates (2005–2009) with the ranges of pesticide consumption (2000–2004) in the western mesoregion of Santa Catarina, Brazil.

The pesticide 2,4-D can confer an androgenic effect by acting in combination with testosterone (Kim et al., 2005) as well as atrazine. The herbicide atrazine inhibits androgen hormones, inducing the activity of the aromatase enzyme and increasing estrogen production, among other effects (Thibaut and Porte, 2004).

In humans, we seek to establish a causal relationship between the levels of pesticides in the body and the incidence of breast cancer. However, the detection of levels of circulating pesticides in the period known as the exposure window, or even the presence of biomarkers, are difficult to perform (Campos, 2018). A first difficulty is the fact that exposure does not usually occur to only one type of pesticide, since different pesticides with different active principles can be applied in the same period. If you consider exposure to only one pesticide, the collection of the biological sample must be carried out within a period in which the pesticide has not undergone major degradation or elimination, so that the diagnosis is not negative by mistake. In this case, the short half-life of these compounds, such as carbamates and organophosphates, hinders the analysis processes (Peres and Moreira, 2003).

However, epidemiological studies have demonstrated the association between exposure to pesticides and an increase in the incidence of cancer (Mostafalou and Abdollahi, 2017). The amount of pesticides, such as organochlorines, detected in the body may be related to distinct subtypes of breast cancer, differing according to the clinical characteristics of the primary carcinoma, stage, and hormonal status (Ellsworth et al., 2018). The use of various organophosphate insecticides has also been associated with an elevated risk of breast cancer (Engel et al., 2017).

When considering the time of exposure, positive associations between the use of pesticides and breast cancer can be found (Souza et al., 2011; Cohn et al., 2019). Exposure to pesticides in regions of intense agricultural productivity are also pointed out as a potential risk factor for the occurrence of cancers (Campos, 2018), which can be corroborated by this investigation, which portrays the correlation between breast cancer mortality rates and the consumption of endocrine-disrupting pesticides in a mesoregion with intense agricultural activity.

Although this study was built with information collected from reliable public databases, it is important to mention some limitations. Besides the possibility of underreporting, the calculated pesticide consumption estimate cannot be extrapolated as a measure of individual exposure, although it was the means of developing the study, since so far, Santa Catarina does not have a database that gathers all the necessary information. In addition, the results demonstrated do not infer causality, a limitation inherent to observational and ecological studies.

Conclusion

Although a direct relationship between municipalities with high pesticide consumption and those with high mortality rates from breast cancer was not presented, in this study, it was found that in 79% of municipalities in the western mesoregion of Santa Catarina, breast cancer deaths occurred at an above-mean frequency, and in municipalities whose use of endocrine-disrupting pesticides also exceeded the regional mean. The results were repeated in the periods of five, ten and 15 years. It was demonstrated, therefore, that there is a proportional correlation between breast cancer mortality rates and pesticide use in corn, soybean and wheat crops in the studied period.

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Authors' contributions

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