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Environmental Factors and Breast Cancer Mortality

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This is to certify that the doctoral dissertation by

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Walden University
2023

Abstract

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by

Joel Collazo Rodriguez

MS, Barry University, 2014

MD, Higher Institute of Medical Sciences, Havana, Cuba, 1994

Dissertation Submitted in Partial Fulfillment

of the Requirements for the Degree of

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Public Health

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Abstract

Breast cancer is a public health problem in the United States that impacts diverse ethnic female groups in different ways regarding incidence and mortality. Much is known about the factors increasing the risk of developing breast cancer, but little is known about those that increase the chances of dying from it, other than access to health care, screening, and appropriate treatment. This study aimed to understand the association between exposure to Environmental Protection Agency-regulated air pollutants and breast cancer mortality, including how the interaction between these air contaminants impacts the outcome of interest, considering median income, education level, and percentage of White women. The ecosocial theory and probabilistic epigenesis guided the study. These theories explain the disease development concerning the historical exposure of individuals to their environment. An ecological study design was conducted, using secondary data from the Outdoor Air Quality Data, the U.S. Cancer Statistics Data Visualizations Tool, and the U.S. Census Bureau. The results of the regression analyses indicated that particulate matter$_{2.5}$, a type of inhalable particulate of less than 2.5µm; percent of adults with less than a high school diploma; and percentage of White women were statistically associated with age-adjusted breast cancer mortality. Implications for positive social change including a better understanding of the predictors of breast cancer will serve public health policymakers and government officials to make evidence-based decisions and enact rules and laws aimed at controlling air pollution.

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Dedication

This work is dedicated to all the women and their families who are battling breast cancer. Especially to a Spanish warrior who has been battling breast cancer since 2017, Hilda Siverio, who has fought for more research and access to treatment for women diagnosed with metastatic triple negative breast cancer in her country. Hilda has been an inspiration to many in the world, sharing love and smiles through her motto “Un poquito más” (A little more), referring to live each day a little more for her and her family.

Acknowledgments

I want to thank my family for their support and understanding during this long journey. To my friends and colleagues who have encouraged me all the time. To my professors at Walden for their dedication and professionalism.

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Chapter 1: Introduction to the Study

Introduction

This study on breast cancer focused on the association between air pollution and breast cancer mortality. This neoplasm is among the most frequent among females, with an incidence of 126.9 per 100,000 women per year, age-adjusted, and the second leading cause of death from cancer in females after lung cancer (19.9 per 100,000 women per year, age-adjusted; American Cancer Society [ACS], 2022). While this pattern has been recognized in recent years (Siegel et al., 2015, 2016, 2017), it is essential to remark the increased incidence among most ethnic and racial groups, except for non-Hispanic White women (DeSantis et al., 2017).

Much is known about breast cancer risk factors, including individual and environmental and modifiable and nonmodifiable risks that increase the odds of breast cancer development in a woman (Centers for Disease Control and Prevention [CDC], 2018). Several authors have determined the role of environmental factors on breast cancer incidence (Hwang et al., 2020; Lecomte et al., 2017; Siddique et al., 2016; Yaghiyan et al., 2017). However, little has been researched on how the environmental pollutants, specifically air pollutants, contribute to breast cancer mortality and how they interact, leading to a more substantial impact on mortality from this cancer. This research aimed to determine the contribution of exposure to air pollutants to breast cancer mortality, including an understanding of the interaction between them and the mentioned outcome.

The present chapter introduces the study, which includes a background about the research topic and the problem statement, followed by the problem statement and the research questions. The next section presents the theoretical framework and the nature of the study. To better understand this study, definitions and assumptions are provided. The chapter describes scopes and limitations, followed by the significance of the study, to finalize with a summary of the main points in this chapter.

Background

Several researchers have studied the association between environmental factors and breast cancer incidence (Hwang et al., 2020; Lecomte et al., 2017; Siddique et al., 2016; Yaghiyan et al., 2017). Some have researched environmental exposure and breast cancer mortality (Hwang et al., 2020). However, most studies do not include all the air pollutants regulated by the Environmental Protection Agency (EPA), or there are inconsistencies across different studies. For example, Hwang et al. (2020) and Zhang et al. (2019) found a statistically significant association between particulate matter 10 (PM_{10}) and breast cancer mortality, while Kim et al. (2018) did not find PM_{10} associated with breast cancer mortality but with other types of neoplasms. Cheng et al. (2020) found that air pollutants were positively associated with mortality due to breast cancer, cardiovascular disease, and all-cause mortality among the 3,089 cases from the Multiethnic Cohort Study. Furthermore, Turner et al. (2020) encountered an association between exposure to PM and all-cause mortality in women diagnosed with breast cancer.

Regarding other air pollutants, carbon monoxide (CO) seems not to be associated with breast cancer mortality (Huang et al., 2020; Liu et al., 2020), although there is a

statistically significant association between cervical cancer and indoor fuel combustion (Liu et al., 2020). Many metals are known to act as endocrine disruptors, lead included, including the risk of breast cancer (Gray et al., 2017; Hiatt & Green, 2018). However, no statistically significant association between lead exposure and breast cancer mortality has been found. According to Cantor et al. (1995) and McElroy et al. (2006; as cited in Hiatt & Green, 2018), most epidemiological studies with lead have been conducted in males. Nitrogen dioxide (NO_2) has been positively associated with breast cancer mortality as a multiple pollutant in combination with PM_{10} and $PM_{2.5}$ (Cheng et al., 2020). Still, Hwang et al. (2020) found that NO_2 was associated with breast cancer mortality as a single pollutant and part of a multipollutant with CO, sulfur dioxide (SO_2), and PM_{10}. Finally, SO_2 has been little studied as a single pollutant and not as extensively as others. Hwang et al. found a little statistically significant association between SO_2 exposure and breast cancer mortality. However, the increment in its concentration can increase the incidence of this neoplasm.

Breast carcinogenesis can be explained by air pollutants' carcinogenic and mutagenic effects (Kim et al., 2018; Turner et al., 2020). Moreover, early life exposure to environmental factors increases the risk of breast carcinogenesis, putting women at higher chances to develop this neoplasm later in life due to the suggested influence of such factors on young mammary tissue. This increases the potential of molecular changes and epigenetic changes that have been found associated with breast carcinogenesis and a resulting increased risk of mortality from breast cancer (Natarajan et al., 2020). It is critical to remark that the risk of mortality is associated with the epigenetic age, which is

the time an individual has been exposed to any factor, leading to epigenetic modification (Fransquet et al., 2019). In this sense, some researchers have found that minorities are more exposed to environmental factors (Vick & Burris, 2017), which can be considered the explanatory factors for higher breast cancer mortality among Black women than White women (DeSantis et al., 2017).

This study was needed because, as previously stated, most studies have not included all the pollutants listed by the EPA in its Outdoor Air Quality Data, which is relevant to the United States. Most of the research has focused on the association between air pollutants and breast cancer incidence, and a few did not address breast cancer mortality. Because some air pollutants have been studied as part of other pollutants, such as PM_{10} and $PM_{2.5}$, a comprehensive study that considered them was needed to understand their association with breast cancer alone and as part of multipollutants. Finally, the most relevant reason for conducting this study was that it included, as stated, all the pollutants regulated by the EPA in the United States.

Problem Statement

With an incidence of 126.9 per 100,000 women per year, age-adjusted, and a mortality of 19.9 per 100,000 women per year, age-adjusted (ACS, 2022), breast cancer remains one of the neoplasms that poses a concern to public health officials despite the widespread utilization of screening mammograms. Although there is no question that mammograms have had a substantial impact on decreasing mortality since their introduction, mortality is still a concern despite the introduction and improvement of screening methods (DeSantis et al., 2017). While access to early and effective treatment

depends on early diagnosis and the molecular subtype of breast cancer, some authors have suggested that the intensity and time of exposure play a significant role in determining the mortality risk (Natarajan et al., 2020).

Therefore, it was vital to study how exposure to EPA-regulated air pollutants affects breast cancer mortality. In this study, I sought to disclose the association between these air pollutants and breast cancer mortality, with the aim of enlightening public health policymakers and government officials at the local, state, and federal levels on the necessity to improve the environmental conditions on behalf of the public in general and particularly the female population. This study sets the foundation for further epidemiological and public health studies to find causal relationships between environmental exposure and breast cancer mortality. Also, studies that deepen in the genetic and epigenetic changes that result from these environmental exposures could prevent the development of breast cancer incidence and, consequently, mortality.

Opportunities for Social Change

This study serves to guide and recommends aggressive screening for breast cancer in counties where strong associations between exposure to EPA-regulated air pollutants and breast cancer mortality are found. Also, I specifically stress the necessity to strengthen the education of the population on exposure to EPA-regulated air pollutants, as well as to provide awareness to local, state, and federal health authorities in the regulation of industries that release those pollutants. Finally, the results of the study provide better guidance in relation to the health actions that should be taken in relation to

prediagnosis, diagnosis, and postdiagnosis of breast cancer in relation to the exposure to environmental pollutants.

Purpose of the Study

The purpose of this ecological study was to determine the association between air pollutants and breast cancer mortality. I also sought to disclose the interactions between air pollutants and how they impact mortality. The study's independent variables were the air pollutants regulated by the EPA and contained in the Outdoor Air Quality Data. These pollutants are CO, lead (Pb), NO_2, ozone (O_3), PM_{10}, $PM_{2.5}$, and SO_2. Also, median income, median education level, and percentage of White women were introduced as independent variables. The dependent variable was age-adjusted breast cancer mortality. The population selected was the female population of the United States by county.

Research Questions and Hypotheses

Research Question (RQ)1: Is there an association between specific percentiles of exposure of air pollutants (CO, Pb, NO_2, O_3, PM_{10}, $PM_{2.5}$, and SO_2) and age-adjusted breast cancer mortality, considering median income, median education level, and percentage of White women?

$H_0$1: There is no statistically significant association between any percentile of exposure of air pollutants (CO, Pb, NO_2, O_3, PM_{10}, $PM_{2.5}$, and SO_2) and age-adjusted breast cancer mortality, considering median income, median education level, and percentage of White women.

H_A1: There is a statistically significant association between specific percentiles of exposure of air pollutants (CO, Pb, NO_2, O_3, PM_{10}, $PM_{2.5}$, and SO_2) and age-adjusted breast cancer mortality, considering median income, median education level, and percentage of White women.

RQ2: Is there any association between the interaction of specific percentiles of exposure of air pollutants (CO, Pb, NO_2, O_3, PM_{10}, $PM_{2.5}$, and SO_2) and age-adjusted breast cancer mortality, considering median income, median education level, and percentage of White women?

H_02: There is no statistically significant association between the interaction of specific percentiles of exposure of air pollutants (CO, Pb, NO_2, O_3, PM_{10}, $PM_{2.5}$, and SO_2) and age-adjusted breast cancer mortality, considering median income, median education level, and percentage of White women.

H_A2: There is a statistically significant association between the interaction of specific percentiles of exposure of air pollutants (CO, Pb, NO_2, O_3, PM_{10}, $PM_{2.5}$, and SO_2) and age-adjusted breast cancer mortality, considering median income, median education level, and percentage of White women.

Theoretical Framework of the Study

The ecosocial theory supported this study. This theory seeks to explain, predict, and understand how diseases are distributed in the population, considering a multilevel

perspective (Krieger, 2011). This theory analyzes disease distribution from the biological, social, historical, and ecological aspects through an integrative approach. Such integration also helps comprehensively explain health inequities considering the interaction between genotype and environmental factors and social and psychological aspects of individual development in the community.

Probabilistic epigenesis has helped understand disease development from an evolutive perspective. This model emphasizes the bidirectional relationship between genes and the environment (Gottlieb, 2007). The bidirectional nature of this theoretical model was remarked by Lerner and Overton (2017). They introduced the concept of relational developmental systems, referring to the interaction between environment and genes in the disease process as a result of this interaction, providing epigenetic links and the nonmutational modifications of the genome that regulate gene expression as a process that results from the genetic-environmental interaction.

The theoretical framework of this study guided this research on the existing differences in breast cancer mortality in the United States related to environmental exposure. These two theories provided the foundation for understanding the association between air pollutants and breast cancer mortality because it is known that air pollutants play a role in breast cancer development (Evans et al., 2019; Hwang et al., 2020; Lecomte et al., 2017). The ecosocial and probabilistic epigenesis theories provided the theoretical framework to guide this study. They helped me understand breast cancer from its development to the outcome depending on the geographic area where individuals spend most of their lives, impacted by the environment.

Nature of the Study

The research was a quantitative retrospective cohort ecologic study. An ecologic study allows the study of groups of individuals (Chapter 6. Ecological studies, 2021) or geographically defined populations (Szklo & Nieto, 2014). In this study, the units of observation were the counties of the United States. Ecologic studies are helpful to evaluate relationships between risk factors and outcomes (Szklo & Nieto, 2014). This design was appropriate for this study because the intent was to determine whether exposure to air pollutants was associated with breast cancer mortality in the exposed population. I compared counties in terms of mortality in association with exposure to air contaminants.

The independent variable was the level of outdoor air pollutants CO, Pb, NO_2, O_3, PM_{10}, $PM_{2.5}$, and SO_2, obtained from the Outdoor Air Quality Data (EPA, 2021). The dependent variable was age-adjusted breast cancer mortality from the U.S. Cancer Statistics Data Visualizations Tool (U.S. Cancer Statistics Working Group, 2022). The association between the variables was assessed using simple linear regression and multiple linear regression analyses for the first RQ and multiple linear regression in the second RQ. Some authors have used this same study design and statistical analysis (see Hwang et al., 2020).

Definitions

Air pollutant: Any agent or their combination that is emitted into the ambient air or that enters it. Air pollutants can be classified as physical, chemical, or biological (Cornell Law School, n.d.).

Carbon monoxide (CO): A chemical compund made up of carbon and oxygen in gaseous state that can be fatal as it may cause severe hypoxia (Francisco et al., 2018). The most common outdoor sources of this gas are photochemical oxidation of methane emissions coming from wetlands and oxidation of biogenic volatile organic compounds from vegetation and garbage disposal areas (Dey & Dhal Chandra, 2019).

Environmental exposure: Any chemical and compound that an individual encounters during their life. Exogenous chemicals to which an individual can be exposed may arise from a myriad of sources, including air pollutants (Rappaport, 2018).

Human Epidermal Growth Receptor 2: This is a molecular subtype of breast cancer noted by the overexpression of this receptor and the absence of estrogen and progesterone receptors. Clinically, this type of breast cancer is among the most aggressive types of this cancer with a high mortality (Sareyeldin et al., 2019).

Lead (Pb): A natural occurring metal found in the Earth crust. It can be harmful to animals and humans and is a ubiquitous element (EPA, n.d.-d). The most common indoor source are house Pb-containing paints. Other significant sources are pipelines, ceramic, and plumbing materials (Turner et al., 2020), yet it can remain in the environment, resulting in damage to the health of humans (EPA, n.d.-c).

Nitrogen dioxide (NO_2): This compound is a highly reactive gas. The primary source of this gas in the air is fuel-burning from from in-road and off-road vehicles and power plants (EPA, n.d.-a). It contributes to the formation of PM and O_3.

Ozone (O_3): This gas is found in the upper layers of the atmosphere of the Earth and at ground level and is made of three atoms of oxygen (EPA, n.d.-b). While

stratospheric O_3 occurs naturally and is benefial for the human health, ground-level O_3 is associated with human health disroders and is an important component of smog (EPA, n.d.-b).

Particulate matter 2.5 ($PM_{2.5}$): This is another complex mixtura of fine inhalable PM less than 2.5 µm. It is present in the atmosphere and originates from combustion materials, organic compounds, and even some metals (EPA, 2020). Its health effects include oxidative damage to the DNA (Guo et al., 2020).

Particulate matter 10 (PM_{10}): A complex mixture of inhalable particles with a diameter of 1010µm and less, found in the air with significant geographic variations (EPA, 2020; White et al., 2019). The most important sources of this mixture are chemical reactions between pollutants like SO_2 and nitrogen oxides from automobiles, power plants, and some industries (EPA, 2020).

Sulfur dioxide (SO_2): A gas that belongs to a group of gases: $S0_2$. It is of significant concern for public health because of its elevated concentrations in the air. Its reaction with other compounds contributes to the formation of PM (EPA, 2020). The major source of SO_2 found in the atmosphere is power plants and burning of fossil fuels (EPA, 2019).

Assumptions

The first assumption in this study was that the data on air pollutants were accurately collected and entered correctly into Air Quality System database from which the data could be obtained (see EPA, 2021). The second assumption was that the data on age-adjusted mortality from the U.S. Cancer Statistics Data Visualization Tool followed

the ethical norms required for any research involving human data. Finally, I assumed that all the data collected from both datasets were accurate and reliable to conduct this study.

Scope and Delimitations

This study focused on determining the association between air pollutants and age-adjusted breast cancer mortality and, if possible, determining whether there was an interaction between air pollutants and how it affected the outcome variable. This study used data from all U.S. counties on age-adjusted mortality from female breast cancer from the U.S. Cancer Statistics Data Visualization Tool 2015-2019.

Limitations of the Study

This study presented several limitations. One was related to the use of secondary data collected for a different purpose than the one of this study. In this sense, there were missing values that needed to be adequately addressed to avoid misleading interpretations of the results (see Cheng & Phillips, 2014). The data did not specify a place of birth nor informed about the length of time the individuals had lived in the counties where they died from breast cancer.

As an ecological study, a significant limitation is a phenomenon known as ecological fallacy. Ecologic studies are helpful to assess the association between risk factors and outcomes at an aggregate level but are not necessarily accurate at the individual level (Szklo & Nieto, 2014). This means that this study's results should be considered to influence policymakers and not necessarily to educate individuals about exposure. Also, there is an inability to control for confounding and more complex

relationships between the risk factors, and breast cancer mortality can be masked in this type of study design (see Szklo & Nieto, 2014).

Significance of the Study

Breast cancer is the most frequent neoplasm among females and the second leading cause of death from cancer in the United States (ACS, 2022). It is a multifactorial neoplasm with well-recognized risk factors (CDC, 2018). However, there is growing evidence on the role of environmental factors in breast carcinogenesis (Hwang et al., 2020; Lecomte et al., 2017; Siddique et al., 2016; Yaghiyan et al., 2017). Breast cancer mortality has been controlled due to early diagnosis after the introduction and the growing use of mammograms as the screening method for breast cancer (DeSantis et al., 2017). However, some authors have found that environmental exposure is also a risk factor that influences mortality from breast cancer (Cheng et al., 2020; Huang et al., 2020; Hwang et al., 2020; Liu et al., 2020; Zhang et al., 2019). Understanding the relationship between exposure to air pollutants and age-adjusted breast cancer mortality can open new avenues for public health actions to influence the health and political leadership to establish strict regulations on industries to decrease environmental pollution and improve Americans' quality of life and health. This can also help reduce the existing inequalities in terms of breast cancer mortality that affect Black women more than other ethnic groups and the disparities in terms of air quality in general.

Summary

This chapter provided background information on breast cancer incidence and mortality, the risk factors associated with breast cancer incidence, and information from

studies assessing the association between environmental exposure and breast cancer mortality. This chapter also presented the problem statement and the purpose of the study, the RQs that I sought to respond to and the corresponding hypotheses. I explained the theoretical framework that guided the research and how it connected with it, the nature of the study, and the rationale for its selection. The final sections of this chapter presented definitions of critical terms, the assumptions, scope and delimitations, limitations, and finally, the significance of this research. In the next chapter, I review peer-reviewed literature relevant to this study that includes articles published within the past 5 years.

Chapter 2: Literature Review

Introduction

Breast cancer is a public health problem in the United States. It is the most frequent type of cancer in females, with an incidence of 126.9 per 100,000 women per year, age-adjusted (ACS, 2022) and the second leading cause of death from cancer among females, with a mortality of 19.9 per 100,000 women per year, age-adjusted, after lung cancer (ACS, 2022). Siegel et al. (2015, 2016, 2017) have consistently recognized this pattern in the United States during recent years. According to DeSantis et al. (2017), breast cancer incidence has increased among all races/ethnicities from 2005 to 2014, except for non-Hispanic White women.

There are several well-known risk factors associated with breast cancer development. These risk factors are categorized as modifiable and nonmodifiable. Among the modifiable risk factors are sedentary life, overweight and obesity, hormonal replacement therapy, reproductive history (age of the pregnancy, breastfeeding, never getting to full-term pregnancy), and alcohol abuse (CDC, 2018). Nonmodifiable risk factors include aging, somatic genetic mutations, reproductive history (early menarche – before 12 years of age and late menopause – after 55 years), breast density, family and personal history of breast cancer, and previous radiotherapy (CDC, 2018). Several studies have also demonstrated the association between emerging environmental contaminants and breast cancer incidence (Hwang et al., 2020; Lecomte et al., 2017; Siddique et al., 2016; Yaghiyan et al., 2017).

The role of emerging environmental contaminants in breast cancer development mimicking estrogens or increasing estrogen levels has been recognized (Lecomte et al., 2017; Siddique et al., 2016). Hwang et al. (2020) conducted an ecological study of South Korea and found an association between air pollution and breast cancer incidence and mortality in all the country's 252 administrative districts. The researchers found women exposed to nitrogen oxides, PM, and polycyclic aromatic hydrocarbons were at a higher risk of developing this neoplasm. Yaghiyan et al. (2017) found exposure to $PM_{2.5}$ and O_3 was associated with breast density, a factor that increases the risk of breast carcinogenesis. Several environmental factors, especially emerging breast cancer risk factors, are well known to originate from specific industries (Evans et al., 2019; Hwang et al., 2020; Lecomte et al., 2017; Siddique et al., 2016; Turner et al., 2020). Paz et al. (2017) posited that environmental exposures lead to genetic instability associated with breast carcinogenesis.

On the other hand, mortality has decreased among all ethnicities by 39% from 1989 to 2015, possibly due to mammogram screening resulting in early detection (DeSantis et al., 2017). However, mortality due to breast cancer is still considered significantly high (ACS, 2022) despite the advances in the diagnosis and treatment approaches. Breast cancer mortality is associated with different factors, notably the stage at initial diagnosis, being essential for any type of cancer treatment (DeSantis et al., 2017). Some researchers have found associations between environmental factors and breast cancer mortality. However, there are gaps in the understanding of this association. For example, Hwang et al. (2020), who had determined a significant association between

air pollutants and breast cancer incidence, only found a statistically significant association between PM_{10} and breast cancer mortality. These researchers suggested the association between PM_{10} and breast cancer mortality interacts with social and demographic factors because there is no apparent relationship between the incidence and mortality in some of the regions studied.

There is additional evidence environmental exposure is associated with an increased risk of mortality from different causes. Kim et al. (2018) found that exposure to $PM_{2.5}$ contributes to mortality in various types of cancers, including bladder cancer, liver cancer, colorectal cancer, and kidney cancer; while exposure to PM_{10} tends to increase mortality from lung cancer, pancreas cancer, and laryngeal cancer. Similarly, Cheng et al. (2020) analyzed the all-cause, breast cancer, cardiovascular disease, and nonbreast cancer and noncardiovascular disease mortality in the Multiethnic Cohort Study in Los Angeles County in California. These scholars found a positive association between exposure to air pollutants and mortality due to breast cancer, cardiovascular disease, and all-cause mortality among the 3,089 cases from the Multiethnic Cohort Study.

Natarajan et al. (2020) suggested that exposure to environmental exposures during early life could lead to molecular changes, including epigenetic modifications related to breast carcinogenesis and, to some extent, the risk of mortality from breast cancer. These authors explained that prepubertal and pubertal exposure to environmental factors contribute to the pathogenesis of breast cancer due to the mammary gland tissue's vulnerability of alteration at these ages, which could be linked with the severity of the disease and consequently mortality, especially in underserved populations. According to

Turner et al. (2020), there is an association between exposure to PM and all-cause mortality in women diagnosed with breast cancer. While lung cancer incidence and mortality are strongly associated with environmental exposure, notably air pollution, other diseases and cancers are also related to environmental exposure due to the mutagenic and carcinogenic effects of the metabolic modification of air contaminants after being inhaled and gaining access to the tissues of other organ systems. Such effects result in increased inflammation and cellular oxidation and epigenetic changes leading to carcinogenesis (Turner et al., 2020).

Finally, there is evidence that environmental exposure is associated with incidence and mortality from different diseases, including several types of cancers. There is less consistent evidence about the association between air contaminants as environmental exposure and breast cancer mortality. This was a critical gap needing further study. It is well understood air contaminants are ubiquitous and pose a continuous threat to human health (Kim et al., 2018; Turner et al., 2020).

The purpose of this study was to investigate the associations between specific environmental exposures and breast cancer mortality, including potential interactions that may occur. It is known that environmental exposure at early age may lead to mutations and genetic instability (Paz et al., 2017) and epigenetic modifications (Natarajan et al., 2020), increasing the risk of breast cancer later in life. This understanding underpins the need to evaluate mortality risk to the exposure of environmental air contaminants. While many environmental exposures have been identified to play a significant role in breast carcinogenesis, their contribution to breast cancer mortality was not well understood.

This gap in knowledge is an essential aspect of tackling breast cancer effectively from a public health perspective and improving the overall preventive measures based on evidence.

Literature Search Approach

The current section is a presentation of the methods used for the literature search to examine the association between environmental exposure and breast cancer mortality. The search included quantitative studies, including one ecological study, meta-analyses, and one scientific report exploring environmental exposure and breast cancer incidence and mortality, as well as the biological foundation seeking to explain the effects of air contaminants and breast cancer incidence and mortality. For the search, keywords used to identify the literature included *breast cancer, incidence, mortality, risk factors, environmental factors, environmental exposure, air pollutant, air contaminant, epidemiology of breast cancer,* and *breast cancer epigenetics*. The searches were conducted through different databases: PubMed, the Walden Library database from ProQuest, and Google Scholar (saving Walden University in the library links). The database from which the environmental factors literature was obtained was from the EPA. Most articles included had been published no more than 5 years ago at the time of this writing. Those articles older than 5 years were included due to their relevance and quality of their contributions. This includes the theoretical framework.

Much of the literature addressed the risk factors, especially environmental exposures for breast cancer, their contribution to incidence, and mortality from breast cancer and other diseases. Most of articles presented an investigation of the association

between environmental exposure and breast cancer incidence, while some investigations evaluated the contribution of environmental factors and breast cancer mortality. The biological aspects of such associations were briefly explained or hypothesized by some of the authors included in the literature search, which requires further study. Very few studies addressed the public health aspect of environmental exposure and breast cancer mortality, with no article specifying the public health aspect of the association between environmental exposure and breast cancer mortality. My current study addressed the public health aspect of the association between environmental exposure and breast cancer mortality.

Conceptual Framework

The theoretical foundation of this study was Krieger's (2011) ecosocial theory. This theory helps explain, predict, and understand phenomena of the distribution of disease from a multilevel perspective, based on the integration and interaction of different factors, rejecting biomedical reductionism. The ecosocial theory has been used to develop an understanding of the distribution of diseases through the biological, social, historical, and ecological perspectives integrated to provide a plausible and comprehensive explanation of health inequities.

The probabilistic epigenesis theory provided a theoretical framework that helped to understand the processes of development and evolution. This theoretical model is orthogonal, with the unidirectional sense of genetic activity by emphasizing the bidirectional impact between environment and genes (Gottlieb, 2007). Lerner and Overton (2017) introduced the concept of relational developmental systems, which

considers the probabilistic epigenesis as a bidirectional process on the interaction between genes and the environment. Such a theoretical model explains the human behavioral development from both the genetic and environmental perspectives linked by epigenetics, the nonmutational modifications that regulate gene expression (Gottlieb, 2007; Lerner & Overton, 2017).

This theoretical approach guided the study of the existing differences in breast cancer mortality across the United States as related to environmental exposures. The attempt to identify an association between environmental factors and breast cancer mortality was well fitted to the theoretical framework selected because it is well known that air pollutants originating from industrial wastes and residues play a role in breast tissue carcinogenesis (Evans et al., 2019; Hwang et al., 2020; Lecomte et al., 2017). Human-made pollutants are linked to breast cancer, but naturally occurring gases may impact this process. According to Yaghiyan et al. (2017), high levels of O_3 seem to have a protective effect, leading to low breast density opposed to high breast density, a well-known risk factor for breast cancer. In summary, the ecosocial and probabilistic epigenesis theories guided the understanding of the role of environmental exposure on breast cancer development and, eventually, mortality, considering that the geographic location where people spend most of their lives would determine the level of exposure to environmental risks.

Literature Review Related to Key Variables

Breast Cancer Mortality

Breast cancer is a multifactorial neoplasm affecting the parenchyma of the mammary gland of both males and females. In terms of mortality, male cancer shows an estimated 19% higher adjusted overall mortality than female breast cancer (Wang et al., 2019). However, male breast cancer is rare compared to female breast cancer, accounting for approximately 1% of all cancers affecting males and 1% of male breast cancer around the world (Gucalp et al., 2019).

Female breast cancer is a burden to society and the health system. It is the most frequent cancer type among females (incidence of 126.9 per 100,000 women per year, age-adjusted; ACS, 2022). Despite a 39% decline in mortality from 1989 to 2015 (DeSantis et al., 2017), it is the second leading cause of mortality (19.9 per 100,000 women per year, age-adjusted) attributed to cancer in women after lung cancer (ACS, 2022). As previously noted, there is evidence that air pollution is associated with breast tumorigenesis. According to Sahay et al. (2019), toxicants in the environment increase the risk of developing breast cancer via epigenetic regulation. These authors conducted a meta-analysis and found traffic-related air pollution and exposure to NO_2 are significantly associated with breast carcinogenesis. Further, the authors asserted this association is mostly when exposure occurred early in life – puberty and the woman's first birth. Such findings are consistent with the theoretical framework for my study. The impact of environmental factors, precisely air quality, is a key contributor to oncogenic

gene expression, a key aspect in cancer development linking to where people live and their longevity of exposure.

In general, the risk of mortality has been linked to epigenetic age – the time of exposure leading to epigenetic modifications, particularly DNA methylation (Fransquet et al., 2019). These authors found some evidence that every 5-year increase in DNA methylation is associated with an 8% to 15% increased risk of dying.

Environmental exposure plays a key role and is recognized as a critical disruptor of epigenetic mechanisms, particularly DNA methylation, leading to increased risk of disease and mortality among minorities due to specific higher exposure (Vick & Burris, 2017). Such disparities include higher mortality from breast cancer among Black women (DeSantis et al., 2017; Siegel et al., 2015, 2016, 2017; Vick & Burris, 2017).

CO and Breast Cancer Mortality

CO is a gas that can be fatal in large quantities due to a great affinity with hemoglobin (about 200 times more compared to oxygen), which may lead to tissue hypoxia. This is commonly known as CO intoxication (Francisco et al., 2018). This gas is a silent killer because it does not provide a clear warning to its victims, leading to potential health damages, including, as mentioned, death (Dey & Dhal Chandra, 2019; Francisco et al., 2018). There are various sources of CO, among which are natural sources and anthropogenic sources (Dey & Dhal Chandra, 2019) and in-buildings (mostly associated with incomplete combustion). According to Francisco et al. (2018), potential sources of CO in buildings are unvented combustion appliances, gasoline engines, indoor operation of grills, and smoking.

Regarding outdoor CO concentrations, an important source is natural CO resulting from the photochemical oxidation of methane emissions coming from wetlands and oxidation of biogenic volatile organic compounds from vegetation and garbage disposal areas (Dey & Dhal Chandra, 2019). However, these authors argued that anthropogenic CO is the most important source of ambient concentrations of this gas (60%) due to human tasks and behavior. These sources include on-road and off-road vehicles and several industries (thermal and steel, coke ovens, hydrogen production, coal gasification, petroleum refining, among others.). The National Institute for Occupational Safety and Health (as cited in Dey & Dhal Chandra, 2019) recommended lowering the CO short term exposure limits to 35 ppm/hour or 9 ppm in 8 hours. Either limit must not be exceeded more than once per year, as recommended by the National Ambient Air Quality Standards (NAAQS), as required by the Clean Air Act amended in 1990 that measures the CO outdoor levels in the air throughout the United States (EPA, 2016). Some authors have associated CO exposure with lung, cardiovascular, and neurological disorders, either due to acute CO poisoning or lengthy exposure at lower and steady concentrations (Dey & Dhal Chandra, 2019; Francisco et al., 2018). It is pivotal to remark that these standards are revised periodically, and the standards presented are current at the time of this writing.

The association of breast cancer and CO gas exposure has been studied. Huang et al. (2020) conducted a nationwide population-based cohort study using the Taiwan National Health Insurance Research Database. The researchers compared the risk of developing breast cancer in 7,053 women diagnosed with CO poisoning between 2002

and 2009 with 42,318 women without CO poisoning. The authors followed the cohorts until the end of 2014 with free mammogram screening, as stated by the Taiwanese government's protocol. The authors concluded a significantly lower risk of developing breast cancer in the cohort of women diagnosed with CO poisoning than their counterparts (0.7% vs. 1.0%, $p < .001$). They suggested that these results are consistent with other studies that establish a connection between CO and cell death due to hypoxia. Additionally, they did not link CO exposure to the risk of breast cancer mortality. In a recent study, Liu et al. (2020) found an association between indoor fuel combustion and cervical cancer death with an adjusted hazard ratio (HR) of 1.75 (95% CI: 0.91-3.38) for wood utilization and 2.23 (95% CI: 1.09-4.59) for the combined use of coal and wood. However, these researchers did not find any statistical association between fuel combustion and breast cancer deaths.

Pb and Breast Cancer Mortality

Pb is a naturally occurring metal and it is found in the crust of Earth. Despite many beneficial uses, Pb can be toxic to animals, including humans (EPA, n.d.). Pb is typically recognized as both an outdoor and indoor pollutant. While outdoor sources include industrial emissions, Pb processing industry, and combustion of leaded fuels, the primary indoor sources are Pb painted houses (Turner et al., 2020). According to the EPA (n.d.-d), Pb is a ubiquitous element found in the soil, water, and inside homes. However, most of the exposure results from human activities including industry caused exposure. Although Pb use in home paints, pipes, ceramic, and plumbing materials, it can enter and

remain in the environment, affecting human health (EPA, n.d.-d). According to the EPA, mining and smelting sites can increase the environmental burden of Pb.

Pb concentrations in the air vary according to the region. Major sources of Pb in the air are ore and metal processing, and leaded aviation fuel, with the highest concentrations, found close to Pb smelters (EPA, n.d.c). Pb can be inhaled, and, especially children, can also swallow Pb dust from different sources such as soil, water, and dust. Since Pb does not decay or decompose, it can remain for years in soil (EPA, n.d.c). According to the EPA current standards in the NAAQS, the maximum Pb exposure cannot exceed 0.15µg/m3 of air. This standard for Pb is the same since 2008 (EPA, 2016).

The risk of breast cancer has been linked to exposure to endocrine disruptors. Many metals are known to have this effect, including Pb, thus increasing breast cancer risk (Gray et al., 2017; Hiatt & Green, 2018). Gray et al. (2017) expressed that, higher concentrations of various metals in cancerous breast biopsies of women, including Pb, were found compared to noncancerous biopsies. These scholars also posited these metals have estrogenic effects on cancerous breast cells cultured in vitro. However, various authors concluded the most critical metal associated with breast carcinogenesis is cadmium (Gray et al., 2017; Hwang et al., 2020; O'Brien et al., 2019), with some researchers finding little or non-significant or no association between Pb exposure and breast cancer incidence (Gray et al., 2017; O’Brien et al., 2019). Nevertheless, Cantor et al. (1995) and McElroy et al. (2006; as cited in Hiatt & Green, 2018) stated most

occupational studies involving Pb had been conducted in males. This observation led Hiatt and Green (2018) to remark there is little epidemiological evidence in females.

NO_2 and Breast Cancer Mortality

NO_2 is a gas that belongs to highly reactive gases known as nitrogen oxides (NO_X). NO_2 is used as an indicator of NO_X. Fuel-burning is the primary source of NO_2 in the air and forms from in-road and off-road vehicles and power plants (EPA, n.d.-a). According to this Federal Agency, most of the health effects of NO_X exposure, particularly NO_2, are associated with respiratory diseases when individuals are exposed for short periods at high concentrations. Prolonged exposures have been associated with asthma development and increased risk of respiratory infections (EPA, n.d.-a). It is vital to remark NO_X react with some other chemicals, contributing to form PM and O_3, and are associated with respiratory disorders (EPA, n.d.-a). The EPA's NAAQS established the primary standard (provide general public health safety) for NO_2 exposure up to 100 ppb per hour and for primary and secondary (secondary refers to public welfare protection) up to 53 ppb per one year (EPA, 2016).

There is evidence NO_2 is associated with the risk of developing breast cancer. Goldberg et al. (2017) conducted a population-based, case-control study on the street level concentrations of NO_2 and ultrafine particles in Montreal, Canada, and its association with breast cancer incidence in postmenopausal women. These scholars found the odds ratio per increase in the interquartile range (IQR = 3.75 ppb) was 1.08; 95% CI: 0.92–1.27. They concluded exposure to NO2 increases the risk of developing breast cancer in postmenopausal women. Turner et al. (2020) also concluded outdoor air

pollution is associated with breast cancer, although they recognized little evidence for this and a limited understanding of such association. In their report, these researchers exposed one analysis of 47,433 women under the Sister Study in the U.S., and determined an adverse association between NO_2 and incidence of breast cancer (HR per 5.8 ppb, 1.06; 95% CI, 1.02-1.11). In the Canadian National Breast Cancer Screening Study (as cited in Turner et al., 2020), adverse associations between NO_2 and breast cancer were found (HRs per 9.7 ppb, range 1.13-1.17). Lemarchand et al. (2019) found NO_2 exposure was associated with breast cancer incidence. Without including the Geographical Weighting Score (GWS), the OR was 1.30 (95%CI 1.13-1.51) per 10µg/m3 increase, but lower with the GWS the OR was lower: 1.12 (95%CI 0.97-1.29) (Lemarchand et al., 2019).

Concerning NO_2 and breast cancer mortality, Cheng et al. (2020) found NO_2 (per 20 ppb) and NO_X (50 ppb) – together with $PM_{2.5}$ (per 10µg/m3) and PM10 (per 10µg/m3) – were associated with increased risk of all-cause mortality (HR range: 1.25-1.72; $p < 0.004$). They analyzed 3,089 cases of breast cancer, among which there were 1,125 all-cause deceases, 474 from breast cancer. Hwang et al. (2020) found an association between NO_2 as a single pollutant (per 10 ppb) and breast cancer mortality (OR: 1.02; 95% CI: 0.983–1.05) and as part of multi-pollutant with CO, SO_2, and PM_{10} (OR: 1.03; 95% CI: 0.985–1.06).

It is critical to remark that Plusquin et al. (as cited in Sahay et al., 2019) found an association between NO_2 exposure and lower DNA methylation in CpG islands of breast tumor suppressor genes (EPHB2), which overexpresses in breast cancer, playing a

significant role in breast carcinogenesis. Also, prenatal exposure to NO_2 has been found to increase breast cancer risk later in life due to lower DNA methylation and activation of the gene LonP1, key in breast cancer development (Gruzieva et al., 2017). These associations with breast cancer risk may be conducive to hypothesizing there is an epigenetic explanation for the associations found between NO_2 exposure and breast cancer mortality and consistent with the theoretical framework.

O_3 and Breast Cancer Mortality

O_3 is a gas made up of three atoms of oxygen and is found in the upper atmospheric layers of the Earth's atmosphere and ground level. Stratospheric O_3 occurs naturally and has beneficial effects as it shields living things from ultraviolet rays. On the other hand, ground-level O_3 has significant harmful effects on human health and is a significant smog component. The formation of ground-level O_3 results from the chemical reactions between NO_X and volatile organic compounds coming from industrial boileries, cars, power plants, or refineries in the presence of sunlight (EPA, n.d.-b).

Most of the health effects of O_3 exposure are associated with respiratory conditions, especially in individuals with pre-existing lung conditions, and low intake of antioxidants such as vitamins E and C and certain nutrients (EPA, n.d.-b). Air pollution has been recognized as a critical environmental factor in developing many respiratory and cardiovascular diseases, including lung cancer (Turner et al., 2020). These authors stated that other cancers had also been correlated to air pollution. According to these scholars, bladder cancer and breast cancer seem to be related to air pollution, mainly PM, to which O_3 contributes. However, there is limited epidemiological evidence regarding bladder and

breast cancer. The role of O_3 as an air pollutant is significant in places where smog is present (EPA, n.d.-b), especially photochemical smog (Turner et al., 2020).

The harmful effects of O_3 on human health result from its oxidizing characteristics, leading to the production of free radicals harming cells (Havas, 2019). However, this author stated in their report that O_3 could be used as an adjuvant treatment for breast cancer in small concentrations. In their ecological study of South Korea, Hwang et al. (2020) found collinearity between NO_2 and O_3 with a correlation coefficient (*r*) of -0.862. They decided to exclude O_3 concentrations from the multivariate model because they found a lesser correlation between O_3 (*r*: 0.659) than of NO_2 (*r*: 0.774) with breast cancer incidence. Regarding breast cancer mortality, concentrations of both pollutants were found poorly associated with mortality rates from breast cancer (< 0.2) (Hwang et al., 2020). A study conducted by Turner et al. (2017) showed similar weak associations between O_3 exposure and breast cancer mortality.

PM_{10} and Breast Cancer Mortality

PM_{10} consists of a complex mixture of inhalable particles with a diameter of usually 10µm and less, found in the air with significant geographic variations (EPA, 2020; White et al., 2019). PM_{10} originates from different sources such as construction sites, fires, or smokestacks. However, most atmospheric particles in PM_{10} result from chemical reactions between pollutants similar to SO_2 and nitrogen oxides emitted by automobiles, power plants, and diverse industries (EPA, 2020). White et al. (2019) argued that PM, in general, is associated with breast density, a recognized risk factor for breast cancer. Further, these authors specified the geographical differences in the levels

of the PM might, in part, explain the differences in the incidence of breast cancer between different geographic regions.

According to the EPA standards (2016), the maximum level of exposure to PM_{10} to avoid health problems is 150µg/m3/per day. This level must not be exceeded more than once per year in three years on average for both primary and secondary standards.

It is vital to remark that environmental exposure during early life is a recognized way of being exposed to carcinogens act on the epigenome. This includes inhaled carcinogens found as air pollutants (Natarajan et al., 2020; Sahay et al., 2019). PM_{10} contributes to air pollution (EPA, 2020; Hwang et al., 2020; White et al., 2019). Not only is PM_{10} associated with breast cancer incidence (Andersen et al., 2017; Hwang et al., 2020; Sahay et al., 2019). Some authors have found an association between PM_{10} exposure and breast cancer mortality as well. For example, Hwang et al. (2020), in their ecological study in South Korea, found that exposure to PM_{10} was positively associated with breast cancer mortality (PM_{10} per 10µg/m3 OR = 1.05; 95% CI = 1.01-1.09). Zhang et al. (2019) conducted a meta-analysis where they analyzed the hazard ratio (HR) and 95% CI, concluding that there is an increased risk of dying from breast cancer upon exposure to PM_{10} (PM_{10} per 10µg/m3 HR = 1.11, 95% CI = 1.05-1.21, p = 0.021). However, Kim et al. (2018) found a heterogeneous association between PM_{10} and breast cancer mortality (RR = 1.06, 95% CI = 0.93-1.21, I2 = 64.6%) in their meta-analysis. Similar results were reported by Guo et al. (2020): exposure to PM_{10} per 10µg/m3 resulted in a RR = 1.07, 95% CI = 0.93, 1.20, I2 = 56.4%, p = 0.130. Different mechanisms appear to be associated with exposure to PM_{10} and risk of cancer in general.

Kim et al. (2018) explained two mechanisms involved: chronic inflammation caused by the inhalation of particulate air pollutants that lead to the release of proinflammatory cytokines. The second mechanism relates to DNA damage caused by oxidative stress by the action of reactive oxygen species generated as a response to PM exposure (Kim et al., 2018).

$PM_{2.5}$ and Breast Cancer Mortality

Fine $PM_{2.5}$ is a type of inhalable PM of less than 2.5μm found in the air consisting of combustion materials, organic compounds, and even some metals (EPA, 2020). The effects of $PM_{2.5}$ in humans are oxidative damage to DNA and the increase of several oxidation markers in the organism. These effects, in turn, make the cells respond by releasing inflammatory chemicals, activation of transcription factors, among other chemical signaling systems causing to dysregulate the cellular metabolism leading to apoptosis or molecular damage (Guo et al., 2020). Hwang et al. (2020) argued that there are two main physiological mechanisms involved in the association between air pollutants and breast cancer incidence: DNA mutations and increased breast density, a well-known risk factor for breast cancer (White et al., 2019). According to Kim et al. (2018), the levels of $PM_{2.5}$ have increased about 11.2% since 1990 globally, becoming the "fifth most common cause of death" worldwide by 2015. Air pollution has been recognized as a carcinogenic agent by the International Agency for Research on Cancer (Guo et al., 2020; Kim et al., 2018; Sahay et al., 2019).

According to the EPA standards (2016), the acceptable maximum levels of exposure to $PM_{2.5}$ primary standard is a mean of 12.0μg per year averaged in three years.

For the secondary standard, the number is set at 15.0µg under the same criteria. Although PM, in general, poses health risks, $PM_{2.5}$ is more dangerous to humans' health, causing a variety of diseases, including cancers (stomach, breast), dermatomyositis, and cardiac failure, among others (Guo et al., 2020). Several researchers have recognized that $PM_{2.5}$ is associated with an increased risk of breast carcinogenesis (Andersen et al., 2017; Ayuso-Álvarez et al., 2020; Huang et al., 2020; Yaghiyan et al., 2017). As previously explained, the mechanisms by which breast cells transform into cancerous cells result from inflammatory responses and molecular damage, and this process depends on different factors. One of the most relevant factors is early life exposure, causing critical epigenetic modifications in tumor suppressor genes including BRCA 1 and BRCA 2. Mutations in these genes can result in carcinogenesis (Natarajan et al., 2020).

With regards to mortality, $PM_{2.5}$ has been studied by various researchers resulting in various conclusions. Hwang et al. (2020) found a weak positive association between air pollution and breast cancer mortality, except for PM_{10}, as previously explained. Moreover, they found a positive but weak association between breast cancer incidence and mortality in South Korea (Pearson's $r = 0.150$, $p = 0.0173$). Cheng et al. (2020) found an association between $PM_{2.5}$ and all-cause and cardiovascular disease deaths in breast cancer patients. They studied the association between outdoor air pollution and breast cancer mortality in 3,089 cases of breast cancer from the Multiethnic Cohort in Los Angeles, California. There was a total of 1,125 deaths, of which 474 died from breast cancer, 272 from cardiovascular diseases, and 379 from other causes in an average of 8 years of follow up. $PM_{2.5}$ per 10µg/m3 was associated with a risk of all-cause deaths

(Hazard Ratio [HR] = 1.25-1.72; p<0.004) and a risk of cardiovascular mortality (HR = 1.62-3.93; p's<0.0005). These scholars did not find a statistically significant association between $PM_{2.5}$ and breast cancer mortality.

Contrastingly, Guo et al. (2020) concluded that $PM_{2.5}$ is significantly associated with breast cancer mortality ($PM_{2.5}$ per 10µg/m3 RR = 1.09; 95% CI = 1.02-1.16, PQ-test = 0.158). Kim et al. (2018) conducted a meta-analysis of 30 cohort studies, 29 prospective, concluding $PM_{2.5}$ per 10µg/m3 was also associated with overall cancer mortality (RR = 1.17; 95% CI = 1.11–1.24). For breast cancer, however, Kim et al. (2018) found a large amount of heterogenicity in the results of the studies analyzed in their meta-analysis regarding $PM_{2.5}$ exposure and breast cancer mortality (RR = 1.60; 95% CI = 0.94-2.72; I^2 = 83.4%). In the meta-analysis performed by Zhang et al. (2019), which included 14 articles, the authors determined that $PM_{2.5}$ per 10µg/m3 increased the risk of breast cancer mortality (HR = 1.17; 95% CI = 1.05–1.30, p = 0.004). Interestingly, these authors suggested that $PM_{2.5}$ does not seem to be associated with breast cancer morbidity.

SO_2 and Breast Cancer Mortality

SO_2 belongs to the group of sulfur oxides (SO_X). It is the most significant concern for human health and its environment due to its high atmospheric concentration. This gas reacts with other compounds leading to the formation of small particles, contributing to PM. The maximum acceptable levels of SO_2 are 75ppb for primary standards, in one hour daily, averaged in three years. For the secondary standard, the maximum acceptable levels are 0.5ppb in three hours and must not be exceeded more than once a year (EPA,

2020). The primary source of atmospheric SO_2 is power plants burn fossil fuels. Minor SO_2 emissions come from metal extraction from ore, volcanoes, vehicles, and heavy machinery relying on burning fuels with a high content of sulfur, such as locomotives and ships—the direct effects on human health impact the respiratory system by inhalation (EPA, 2019).

SO_2, as part of PM, has been studied concerning breast cancer, although not as extensive as other air pollutants. However, few researchers have studied SO_2 alone in association with breast cancer. Hwang et al. (2020) found that an increment of 1ppb of SO_2 – as a single pollutant – increased the risk of breast cancer (odds ratio [OR] = 1.04; 95% CI = 1.02-1.05). As a multipollutant with CO, NO_2, and PM_{10}, the OR was 1.04; 95% CI = 1.02–1.06. The association of SO_2 and breast cancer mortality was of little statistical significance (OR = 1.02; 95% CI = 0.991–1.04) and as a multipollutant with CO, NO_2, and PM_{10} (1.01; 95% CI = 0.989–1.03; Hwang et al., 2020). As previously stated, no other results were obtained studying the association between SO_2 and breast cancer incidence and mortality. Most of the studies cited include SO_2 as part of PM without specifying its role in breast cancer incidence and mortality.

Educational Level and Breast Cancer Mortality

Level of education at the individual and population level has been identified to be associated with health outcomes, including cancer and breast cancer. According to Mootz et al. (2020), a healthier lifestyle is associated with better health outcomes. Such association is correlated with a higer educational level since it allows people to have a better income, leading to benefits at the social and psychological level, and more

importantly, access to good health care (Mootz et al., 2020). These autohors conducted a meta-analysis where they conlcuded that people with lower levels of education have poorer breast cancer prognosis. In a study that included 5547 women diagnosed with invasive breast cancer from the Pathways and Life After Cancer Epidemiology cohorts, the Aoki et al. (2021) found that low neighborhood-level of socioeconomic status (a composite score based on income, poverty, education, occupation, employment, rent, and house value), was significantly associated with luminal B type of breast cancer (OR_{Q1vQ4}, 1.31; 95% CI 1.11-1.54, $p = .05$) and with triple-negative breast cancer subtypes (OR_{Q1vQ4}, 1.32; 95% CI, 1.02-1.71; $p = .037$). Also, a significant association between individual education and human epidermal growth factor receptor 2 enriched (HER2-e) subtype of breast cancer (OR for high school degree or less vs. postgraduate, 1.68; 95% CI, 1.03-2.75; $p = .030$) (Aoki, et al., 2021). Although these authors did not make direct reference to mortality, these subtypes of breast cancer are characterized by their invasiveness and higher risk of poor outcomes. It is important to remark that there are no many recent studies that address education leval as a risk factor or predictor of breast cancer mortality. A study by Moore et al. (2018) indirectly suggested that low income level and breast cancer mortality seem to be associated. The study aimed at identifying racial/ethnic variation in breast cancer mortality at the county level in the continental US. The researchers found that the regions with the highest breast cancer mortality rates were the southern states, where the residents were more likely to have lower educational level and lower income. The majority of counties with non-Hispanic Black (NH-Black) women residents (98.3, $p < .001$) are in Southern states. The majority of counties with Hispanic

women residents were located in the Southwest of the US with 61.45% in the South and 33.73% in the West (Moore et al., 2018).

Income and Breast Cancer Mortality

Income is an important component of socioeconomic status. The results of a study performed by Bellanger et al. (2018) in 177 countries with different income level indicated that breast cancer mortality was higher (60%) among women living in higher-income countries (37.5%) and upper middle income countries (23.1%). However, for women aged less than 50 years was higher in women from lower middle-income countries (12.3%). The study conducted by Moore et al. (2018) also included income (income is a component of the socioeconomic status). The results described in the section above apply to this section; the autors observed disparities in breast cancer mortality in terms of geography and ethnic/racial groups. They found that NH-Black and Hispanic breast cancer deaths were more concentrated in southern counties - with lower socioeconomic status. There seems to be some discrepancies between the two studies cited. It is possible that differences in the methodology or in the countries' populations characteristics and health systems have implications in the results. In their review, Prakash, et al. (2020) related lower socioeconoic status with higher incidence of triple-negative breast cancer and diagnosis of breast cancer, in general, with a diagnosis in more advanced stages and at younger ages ($p < .05$), which are factors implicated in higer mortality among this ethnic group.

Percentage of White Women and Breast Cancer Mortality

Racial disparities related to breast cancer incidence and mortality have been reported by many researchers. DeSantis et al., (2017) argued that despite an overall decrease in breast cancer mortality by 39% from 1989 to 2015, non-Hispanic Black women have higher mortality rates (29.5 per 100,000) compared to White women (20.38 per 100,000). Contrastingly, the incidence is higher among White women (128.7 per 100,000) than their Black counterparts (125.5 per 100,000). These differences may be, in part, explained by higher incidence of more invasive subtypes of breast cancers in Black women compared to White women due to different types of exposures (DeSantis et al., 2017). According to Scott et al. (2019), Black women have a higher odds to be diagnosed more frequently with triple-negative breast cancer (OR, 2.27; 95% CI, 2.23-2.31) compared to their White counterparts (OR, 1.22; 95% CI, 1.19-1.25). These authors concluded that Black women carry a higher burden of being diagnosed with more this invasive subtype of breast cancer, which could also explain the higher mortality in this ethnic group. These findings are consistent with other researchers such as Prakash, et al. (2020), who also link this high incidence of invasive breast cancer in Black women to other factors that affect Black women disproportionately like obesity and lower socioeconomic status.

Summary and Conclusions

This chapter began with an explanation of breast cancer as a public health problem in the United States, considering both incidence and mortality. The description of well-known risk factors for breast cancer – both modifiable and nonmodifiable was

provided, followed by an explanation of emerging environmental factors and their association with breast cancer. The goal of this study resided in determining how specific environmental factors impact breast cancer mortality and to bring clarity to the relationship between some of these factors and breast cancer mortality as there are inconsistencies in the literature. Another important aspect this study addressed is determining the interaction between these environmental factors and breast cancer mortality, which has not been addressed in the literature (at the time of this writing) since not all the air contaminants have been studied in a single study. Even more, environmental pollutants have not been individually studied as they are part of bigger groups of air contaminants, as PM. This chapter unveiled the necessity to deepen the study of environmental factors that are known to be associated with breast cancer incidence, breast cancer mortality, and how these may interact. I also sought to open the avenues to adjoining research to focus on the epigenetic mechanisms that may play a role in breast cancer prognosis. Discovery of epigenetic mechanisms maybe of significant interest to linking between the genome and the environment. Chapter 3 will be a presentation and detailed explanation of the research design, the methodology and rationale, the RQs, and the analysis plan for the data.

Chapter 3: Research Method

Introduction

Breast cancer is a public health problem in the United States, with an incidence of 126.9 per 100,000 women per year, age-adjusted, and is the second leading cause of death from cancer among females after lung cancer, with a mortality rate of 19.9 per 100.000 women per year, age-adjusted (ACS, 2022). Although the pattern in incidence and mortality has been maintained for the recent years (Siegel et al., 2015, 2016, 2017), an increased incidence from 2005 to 2014 among all races and ethnicities, except for non-Hispanic White women, has been noted (DeSantis et al., 2017). It is a complex and multifactorial cancer with many well-established risk factors, classified as modifiable and nonmodifiable. However, new research has supported the association between exposure to environmental contaminants and breast cancer incidence (Hwang et al., 2020; Lecomte et al., 2017; Siddique et al., 2016; Yaghiyan et al., 2017). Environmental contaminants are considered endocrine disruptors, mimicking and increasing the organism's estrogen levels (Lecomte et al., 2017; Siddique et al., 2016; Yaghiyan et al., 2017).

Air pollution has been associated with breast carcinogenesis. Exposure to nitrogen oxides, PM, and polycyclic aromatic hydrocarbons leads to an increased risk of breast cancer (Hwang et al., 2020). Breast density, a recognized risk factor for breast cancer, has been associated with exposure to $PM_{2.5}$ and O_3 (Yaghiyan et al., 2017). Different types of industries give origin to many of these environmental contaminants (Evans et al., 2019; Hwang et al., 2020; Lecomte et al., 2017; Siddique et al., 2016; Turner et al., 2020). Also,

environmental contaminants may lead to genetic instability, critical to cancer development (Paz et al., 2017).

The introduction of mammogram screening and its gradual expanded use since 1989 has been associated with a 39% decreased mortality from breast cancer among all ethnicities (DeSantis et al., 2017). Nonetheless, according to the ACS (2022), it is still significant despite the advances in both diagnosis and treatment approaches. Mortality has been associated with several factors, one of them being the stage at initial diagnosis, which is critical to implementing adequate treatment for any cancer (DeSantis et al., 2017). There is evidence on the association between environmental exposure and cancer mortality (Cheng et al., 2020; Hwang et al., 2020; Kim et al., 2018; Turner et al., 2020). Nonetheless, there still are gaps in understanding such association. While Hwang et al. (2020) found a significant association between air pollutants and breast cancer incidence, these authors concluded that only PM_{10} and breast cancer mortality were significantly associated and suggested that such association interacted with social and demographic factors due to an apparent lack of relationship between incidence and mortality in some specific regions they studied. The association between environmental factors and breast cancer mortality is complex. Cheng et al. (2020), studying the 3,089 participants in the Multiethnic Cohort Study in Los Angeles, California, found that there is an association between air pollutants and all-cause, breast cancer, nonbreast cancer, cardiovascular, and noncardiovascular deaths. Turner et al. (2020) determined a positive association between PM_{10} exposure and all-cause mortality in women diagnosed with breast cancer.

Environmental exposure contributes to the occurrence of molecular changes and epigenetic modifications observed in breast cancer tissue samples. These changes seem to be more severe in individuals exposed to it since early life, increasing the risk of this neoplasm and, potentially, the risk of dying. A possible explanation for this temporal association is the breast tissue's vulnerability during prepubertal and pubertal ages (Natarajan et al., 2020). The ubiquitous nature of environmental pollutants and their evident threat to human health (Kim et al., 2018; Turner et al., 2020), plus the lack of consistency in the research about the association between air pollution and breast cancer mortality, makes it crucial to study this association further.

Research Design and Rationale

As stated, there are modifiable and nonmodifiable risk factors for breast cancer survival. Moreover, mortality has been associated with the stage at diagnosis and some critical environmental factors. For this study, the independent variables were exposure to specific air pollutants: CO, Pb, NO_2, O_3, PM_{10}, $PM_{2.5}$, and SO_2. The dependent variable was age-adjusted breast cancer mortality. A secondary data analysis was conducted to understand the association between exposure to outdoor air pollution and breast cancer mortality and the interaction between the air contaminants, and how these environmental factors impact the 10-year survival of women diagnosed with breast cancer.

I performed a retrospective cohort ecologic study design to analyze the association between environmental factors, specifically air contaminants and breast cancer mortality in the United States, considering median income, median education level, and percentage of White women. The study design selected was appropriate for this

study because it allowed me to study the association between exposures and outcomes in groups of individuals (see Chapter 6. Ecological studies, 2021), such as geographical defined populations (see Szklo & Nieto, 2014). In this study, the unit of observation were the counties of the United States. The use of an ecological design permitted geographical comparison between counties in terms of breast cancer mortality in association with exposure to the air pollutants. It was retrospective because it included the deaths and exposures from 2015 to 2019. Other studies have used this approach to determine the association between exposure to environmental factors and breast cancer incidence and mortality (Hwang et al., 2020). As previously stated, the independent variables were exposure to air pollutants (CO, Pb, NO_2, O_3, PM_{10}, $PM_{2.5}$, and SO_2), the dependent or outcome variable was age-adjusted breast cancer mortality, and the covariates were median income, median education level, and percentage of White women.

The theoretical foundation of this study was the ecosocial theory, which helps explain, predict, and understand how the environment contributes to the development and distribution of disease in the population from an integrative approach and avoiding biological reductionism (see Krieger, 2011). I also used the probabilistic epigenesis theory, which explains the gene-environment interaction. Not only does this theory help in the understanding of evolution but also in gaining insight in the process of disease development based on the interaction between the individual genetic information and the environment emphasizing the bidirectional sense of this interplay (Gottlieb, 2007). I found this theoretical framework to be of guidance for this study as my goal was to understand the impact of environmental factors on breast cancer mortality and survival.

This chapter presents the research design and methodology and the rationale for using a quantitative retrospective cohort ecological study based on analysis of secondary data. With regards to the methodology, I discuss the procedures for data collection, how the datasets were accessed, and the statistical analyses used. I also explain the threats to validity, ethical concerns and procedures, and the operationalization of the variables.

Methodology

Population

The population under study was the female population of any race/ethnicity of the United States by counties and state that died from breast cancer. For every 100,000 women, 20 died from breast cancer between 2015 and 2019, and the total deaths from breast cancer were N = 209,755 (U.S. Cancer Statistics Working Group., 2022). This number was the size of the population for this research.

Data Sources

The independent variables (exposure to specific air pollutants described above) were obtained from the Outdoor Air Quality Data, EPA, for 2015 through 2019 (EPA, 2021). These data are publicly available for download from the EPA website and were extracted by pollutant, state, and county. The dependent variable (age-adjusted breast cancer mortality) was obtained from the U.S. Cancer Statistics from the CDC, years 2015 to 2019 (see U.S. Cancer Statistics Working Group, 2022), which is also publicly available. According to this site, the mortality data come from the CDC and National Center for Health Statistics, covering 100% of the U.S. population, with rates and counts

being suppressed if there were fewer than 16 deaths reported by cancer type, race/ethnicity, state, and age.

Data on education levels: percent of adults with less than a high school diploma, percent of adults with a high school diploma only, percent of adults completing some college or associate degree, and percent of adults with a bachelor's degree or higher were obtained from the United States Department of Agriculture (USDA) Economic Research Service (USDA, 2021). The percentage of White women by County was obtained from the County Population by Characteristics: 2010 – 2020 (U.S. Census Bureau, 2021-a). Finally, I obtained the data on median income from the U.S. Census Bureau provided by the Small Area Income and Poverty Estimate program (SAIPE; U.S. Census Bureau, 2021-b). These datasets are also publicly available.

Sampling and Sampling Procedures

This study included all females reported to have died from breast cancer between 2015 and 2019 in the United States (209,755) per county and state within the U.S. Cancer Statistics from the CDC, years 2015 to 2019. I excluded any county death data with "considered missing data" due to fewer than 16 deaths reported.

Statistical Power

I employed G*Power 3.1.9.7 to calculate the minimum sample size required using the parameters: a Power of 0.80, a significant level (α) of 0.05, and effect size (f^2) of 0.15 (medium) for multiple linear regression. For RQ1, the multiple linear regression tests, the required minimum sample size was $N = 85$. For RQ2, the multiple linear regression tests

with a maximum number of predictors $n = 7$, the required minimum sample size needed was $N = 103$.

Recruitment and Data Collection

The Outdoor Air Quality Data is a public database from the EPA that provides daily data on air quality regarding the concentration of the following air pollutants: CO, Pb, NO_2, O_3, PM_{10}, $PM_{2.5}$, and SO_2. The tool queries air quality summary statistics daily for the contaminants, and the data can be obtained at the city, county, or state level (EPA, 2021). I downloaded the data from the site by air pollutant and by state/county. The U.S. Cancer Statistics: Data Visualizations from the CDC provides data on the incidence and mortality of different cancers (U.S. Cancer Statistics Working Group, 2022). I downloaded the age-adjusted breast cancer mortality by state, which contains their respective counties. Because both datasets are public, I did not need to request authorization to gain access to any of them. The data on the education levels were obtained from the USDA Economic Research Service (USDA, 2021). Data on median income was extracted from the U.S. Census Bureau provided by the SAIPE (U.S. Census Bureau, 2021-b). Finally, the data on percentage of White women were downloaed from the County Population by Characteristics: 2010 – 2020 (U.S. Census Bureau, 2021-a).

Operationalization of the Variables

This study has seven independent variables: exposure to CO, exposure to Pb, exposure to NO_2, exposure to O_3, exposure to PM_{10}, exposure to $PM_{2.5}$, and exposure to SO_2. Each air pollutant was operationalized to an ordinal variable, with ordinal levels being 10% of the EPA recorded measures for each air pollutant, and according to the

levels recommended by the EPA (see Table 1). Three covariates were included: median income, median education level, and percentage of White women. The dependent variable is age-adjusted breast cancer mortality.

Table 1

Ordinal Levels of EPA Air Pollutants

Pollutant	Percentiles (10%)								
	10%	20%	30%	40%	50%	60%	70%	80%	90%
CO	0.1808	0.2423	0.2940	0.3339	0.3636	0.4041	0.4410	0.4876	0.5354
Pb	0.0014	0.0019	0.0027	0.0037	0.0049	0.0073	0.0114	0.0207	0.0332
NO2	4.3099	7.0972	9.3665	11.8656	14.7144	17.1902	19.4801	22.5209	25.8201
O3	0.0357	0.0370	0.0381	0.03.90	0.0400	0.0411	0.0423	0.0436	0.0455
PM10	10.6663	12.2993	13.9706	15.0634	16.3648	17.4275	19.1033	20.7791	24.2643
PM2.5	4.4336	5.6833	6.4639	6.9937	7.4661	7.9225	8.3238	8.7908	9.5028
SO2	0.4632	0.7330	0.9996	1.3177	1.6973	2.1323	2.7963	3.9020	6.2775

Note. CO = carbon monoxide; Pb = lead; NO_2 = nitrogen dioxide; O_3 = ozone; PM_{10} = particulate matter 10; $PM_{2.5}$ = particulate matter 2.5; SO_2 = sulfur dioxide.

Data Analysis Plan

The purpose of this study was to determine whether exposure to specific air pollutants is associated with breast cancer mortality, whether there is an interaction between the specific air pollutants and the association between such interactions and breast cancer mortality.

RQs and Hypotheses

RQ1: Is there an association between specific percentiles of exposure of air pollutants (CO, Pb, NO_2, O_3, PM_{10}, $PM_{2.5}$, and SO_2) and age-adjusted breast cancer mortality, considering median income, median education level, and percentage of White women?

$H_0$1: There is no statistically significant association between any percentile of exposure of air pollutants (CO, Pb, NO_2, O_3, PM_{10}, $PM_{2.5}$, and SO_2) and age-adjusted breast cancer mortality, considering median income, median education level, and percentage of White women.

H_A1: There is a statistically significant association between specific percentiles of exposure of air pollutants (CO, Pb, NO_2, O_3, PM_{10}, $PM_{2.5}$, and SO_2) and age-adjusted breast cancer mortality, considering median income, median education level, and percentage of White women.

RQ2: Is there any association between the interaction of specific percentiles of exposure of air pollutants (CO, Pb, NO_2, O_3, PM_{10}, $PM_{2.5}$, and SO_2) and age-adjusted breast cancer mortality, considering median income, median education level, and percentage of White women?

$H_0$2: There is no statistically significant association between the interaction of specific percentiles of exposure of air pollutants (CO, Pb, NO_2, O_3, PM_{10}, $PM_{2.5}$, and SO_2) and age-adjusted breast cancer mortality, considering median income, median education level, and percentage of White women.

H_A2: There is a statistically significant association between the interaction of specific percentiles of exposure of air pollutants (CO, Pb, NO_2, O_3, PM_{10}, $PM_{2.5}$, and SO_2) and age-adjusted breast cancer

mortality, considering median income, median education level, and percentage of White women.

Statistical Analysis

To answer the first RQ, I conducted seven simple linear regression tests to determine whether exposure to specific percentiles of exposure of air pollutants (CO, Pb, NO_2, O_3, PM10, $PM_{2.5}$, and SO_2) were associated with age-adjusted breast cancer mortality. Then, seven multiple linear regressions were conducted when considering the median educational level, median income, and percentage of White women in the analyses. The second RQ was answered using multiple linear regression to determine the potential interactions between specific air pollutants. After the multiple linear regression was conducted, only $PM_{2.5}$ was a statistically significant predictor of age-adjusted breast cancer mortality, and no further analyses were conducted.

Validity

The data on age-adjusted mortality were obtained from the U.S. Cancer Statistics Data Visualizations Tool (U.S. Cancer Statistics Working Group, 2022). Only two studies have declared that the data from this source could lead to internal validity problems if used in health disparities research due to inaccuracies in the classification in race/ethnicity and immigration status (Arias et al., 2008; Clegg et al., 2007). According to the U.S. Cancer Statistics Working Group (2022), these problems have been addressed by linking the data provided in the Demographics and State/County tabs with the Indian Health Service. Because this research did not address racial, ethnic, or immigration status, these issues are not of concern to the validity of this study. The data from the U.S.

Cancer Statistics Visualization Tools came from the National Center for Health Statistics (NCHS) and the National Vital Statistics System (NVSS; U.S. Cancer Statistics Working Group, 2022).

The data on air quality were obtained from the Outdoor Air Quality Data, which are collected at outdoor monitors nationwide (see EPA, 2021). One can download recent and historical data collected by monitors located in specific locations, allowing one to obtain data based on specific monitors, all monitors, cities, counties, or states (EPA, 2021). Therefore, these measurements are precise and reliable for their use in this study.

Ethical Considerations

This study used data that did not include any personal identifier from the U.S. Cancer Statistics Visualization Tools, which offers mortality data obtained from the NCHS and the NVSS. The data from the EPA did not include information on human subjects. Neither the CDC nor the EPA required any permission to gain access to the data. I proceeded with data download and used after I obtained approval by Walden University's Institutional Review Board, approval number 02-28-22-0519841.

Summary

This chapter presented a discussion on the methodological aspects of this study. The introduction included background information about breast cancer, including risk factors, incidence, mortality, screening, and air pollutants. The Research Design and Rationale section presented the study's independent and dependent variables: exposure to air pollutants and age-adjusted breast cancer mortality, respectively. I explained that to assess the association between the independent and dependent variables, I analyzed

secondary data. Next, I explained that the study design was a quantitative retrospective cohort ecologic study and why it had been selected to perform the research. This section ended with a brief explanation of the theoretical framework and how it helped guide the study. The methodology section described the population studied, followed by the data sources: U.S. Cancer Statistics Visualization Tool and the Outdoor Air Quality Data. Afterward, I explained the sampling and sampling procedures, the statistical power, how I collected the data, followed by the operationalization of the variables. The data analysis plan included the RQs and the corresponding hypotheses, and the statistical analysis conducted to respond to the RQs, followed by an explanation of the validity of the study.

Chapter 4: Results

Introduction

This ecological study aimed to determine whether there is an association between exposure to environmental factors (air pollutants) and breast cancer mortality, considering the educational level, median household income, and the percentage of White women per U.S. County. I also sought to find whether any interaction between pollutants posed a risk of dying from this neoplasm. The population selected for the study was the U.S. female population who died from breast cancer by U.S. County between 2015 and 2019.

I formulated two RQs: (a) Is there an association between specific percentiles of exposure to air pollutants (CO, Pb, NO_2, O_3, PM_{10}, $PM_{2.5}$, and SO_2) and age-adjusted breast cancer mortality, considering median income, education level (percent of adults with less than a high school diploma, percent of adults with a high school diploma only, percent of adults completing some college or associate degree, and percent of adults with a bachelor's degree or higher), and percentage of White women, and (b) Is there an association between specific percentiles of exposure to air pollutants (CO, Pb, NO_2, O_3, PM_{10}, $PM_{2.5}$, and SO_2) and age-adjusted breast cancer mortality, considering median income, education level (percent of adults with less than a high school diploma, percent of adults with a high school diploma only, percent of adults completing some college or associate's degree, and percent of adults with a bachelor's degree or higher), and percentage of White women? The purpose of RQ1 was to determine whether exposure to air pollutants was associated with dying from breast cancer, considering the median

income, educational level (less than high school, associate degree or some college, and bachelor's degree or higher), and the percentage of White women in the population. The second question sought to determine the association between specific percentiles of air pollutants and breast cancer mortality, considering the same covariates.

This chapter describes the data collection methods followed by a descriptive statistic of the sample. Next, I evaluate the assumptions of multilinear regression, followed by the results of the statistical analyses conducted to respond to the RQs.

Deviation From the Plan

During the time spent in data cleaning and preparation for this study, I made some changes concerning the initial plan of this study. First, I did not find any dataset including the covariate median education level by county. Four variables replaced this covariate: percent of adults with less than a high school diploma, percent of adults with a high school diploma only, percent of adults completing some college or associate degree, and percent of adults with a bachelor's degree or higher. The data were obtained from the USDA Economic Research Service, citing the U.S. Census Bureau as the source (USDA, 2021). The variables were provided in percentages for the period between 2015 to 2019. All other variables in the data set were excluded because they were not of interest to this study. The RQs reflected this modification by replacing median education level with education level (percent of adults with less than a high school diploma, percent of adults with a high school diploma only, percent of adults completing some college or associate degree, and percent of adults with a bachelor's degree or higher) for clarity.

During the cleaning and organization of the data, the U.S. Cancer Statistics Visualization Tool issued data for 2015 to 2019 (U.S. Cancer Statistics Working Group., 2022). I decided to download these new data to conduct the analysis with the most recent available data. Due to this update, the total population was 209,755 (women who died from breast cancer) between 2015 to 2019 instead of 208,686 between 2014 to 2018.

Data Collection

For this study, I used five data sets. I obtained age-adjusted breast cancer mortality (the dependent variable) from the U.S. Cancer Statistics Visualization Tool, which provides mortality data from the NCHS and the NVSS (see U.S. Cancer Statistics Working Group, 2022). This dataset only provided information on the counties from states within the continental United States, including Washington, DC. I filtered the data to obtain specific data on female breast cancer mortality by state (including the respective counties) across the United States from 2015 through 2019. Finally, any county death data with less than 16 deaths reported were excluded because there are no data reported by the U.S. Cancer Statistics Visualization Tool. The data on EPA-regulated air pollutants (the independent variable) were obtained from the Outdoor Air Quality Data (EPA, 2021) by selecting the pollutant, then the year, and finally the geographic area (state and county). I followed this procedure for each of the seven pollutants that are monitored by the EPA (CO, Pb, NO_2, O_3, PM_{10}, $PM_{2.5}$, and SO_2). I calculated the statistical means of each pollutant per year for each county, obtaining each pollutant's statistical mean per county between 2015 and 2019. The final step was the operationalization of this variable in ordinal levels, 10% of the EPA recorded measures

for each EPA-regulated air pollutant, according to the levels recommended by the regulatory agency.

The covariates were the median educational level, median income, and percentage of White women. The data on the levels of education were obtained from the data set "Educational attainment for adults aged 25 and older for the U.S., States, and counties, 1970-2019." I obtained this set from the U.S. Census Bureau, 1970, 1980, 1990, 2000 Censuses of Population, and the 2015-19 American Community Survey 5-year average county-level estimates (see USDA, 2021). This dataset contains raw numbers and percentages of educational attainment of the U.S. population by county/year from 1970 until 2000 and between 2015 and 2019. I used the 5 years of data for this study, presented in four levels: percent of adults with less than a high school diploma, percent of adults with a high school diploma only, percent of adults completing some college or associate degree, and percent of adults with a bachelor's degree or higher.

The median income data were obtained from the U.S. Census Bureau provided by the Small Area Income and Poverty Estimate program (SAIPE; U.S. Census Bureau, 2021-b). I downloaded the data for each year from 2015 to 2019 and per county. Next, I kept the data on median household income, excluding all other data that were not of interest to this study (poverty estimate and poverty percentage by age range and all ages). Then, I calculated the means of the median household incomes for the 2015 to 2019 period.

The percentage of White women per county and year was obtained from the County Population by Characteristics: 2010 – 2020 (U.S. Census Bureau, 2021-a). From

this data set, I used the total female population of the county and the White female population to calculate the percentage of White women for each county per year (from 2015 to 2019). Then, I calculated the mean of the percentage of White females for the period between 2015 to 2019. Finally, all the data were merged using the Federal Information Processing Standards codes as the common identifier for state/county into a unique dataset.

Results

Descriptive Statistics

I used SPSS (version 28) to conduct the descriptive statistics for the variables air pollutants (CO, Pb, NO_2, O_3, PM_{10}, $PM_{2.5}$, and SO_2), median income, percent of adults with less than a high school diploma, percent of adults completing some college or associate degree, percent of adults with a bachelor's degree, percentage of White women, and age-adjusted breast cancer mortality.

The statistical means were calculated using SPSS (version 28). The statistical means of each independent variable were CO percentiles (N = 190): 5.49, NO_2 percentiles (N = 282): 5.50, O_3 percentiles (N = 757): 5.49, Pb percentiles (N = 138): 5.49, PM_{10} percentiles (N = 390): 5.50, $PM_{2.5}$ percentiles (N = 828): 5.50, and SO_2 percentiles (N = 370): 5.50. The statistical mean of the dependent variable, age-adjusted breast cancer mortality (N = 1,754) was 21.2. The statistical means of the covariates were median income (N = 3,141): 51,544, percent of adults with less than a high school diploma (N = 3,142): 13.05, percent of adults with high school diploma only (N = 3,142): 34.15, percent of adults completing some college or associate degree (N = 3,142): 30.81,

percent of adults with a bachelor's degree (N = 3,142): 22.0, and percentage of White women (N = 3,142): 84.8.

Statistical Assumptions

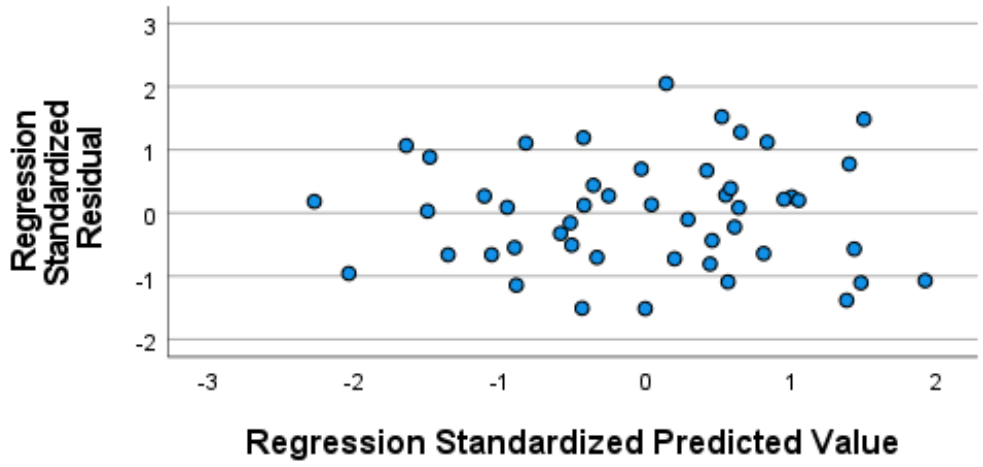
The assumptions of multiple linear regression that must be met to perform this statistical test are the linear relationship between the independent variables and the dependent variable, multivariate normality, no or little multicollinearity, no autocorrelation, and homoscedasticity (see Green & Salkind, 2014, 2017).

Linearity

The independent and dependent variables' linearity was tested together using a residuals plot (see Figure 1). The plot shows the residuals forming a horizontal band, indicating a likely linear relationship between the independent variables (percentiles of air pollutants CO, Pb, NO_2, O_3, PM_{10}, $PM_{2.5}$, and SO_2) and age-adjusted breast cancer mortality.

Figure 1

Multiple Linear Regression Assumption of Linearity Residuals Plot



Multivariate Normality

Multivariate linear regression assumes that the residuals follow a normal distribution. The results of the normal P-P plot (see Figure 2) and the histogram (see Figure 3) show that this assumption was met.

Figure 2

Normality P-P plot of Standardized Residuals

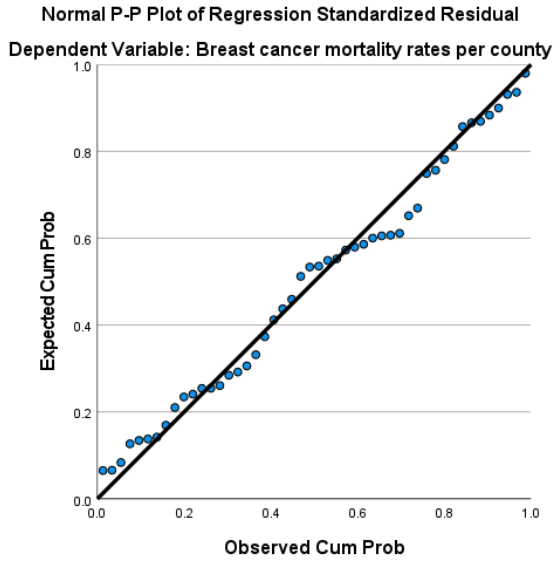
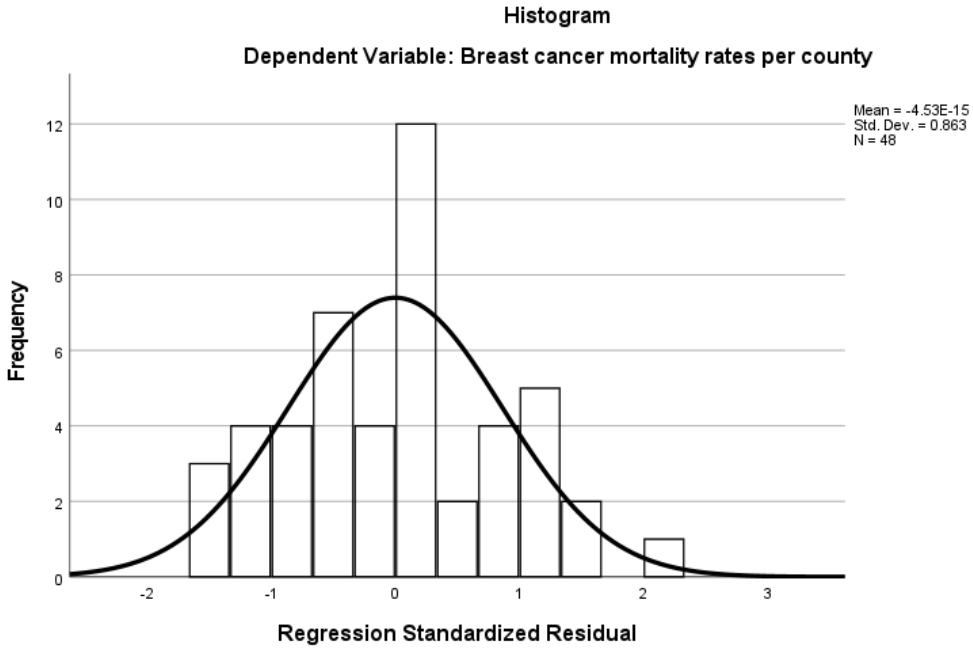


Figure 3

Normality Histogram of Standardized Residuals



No or Little Multicollinearity

This assumption requires that all the independent variables are independent of each other. The results of the collinearity statistics demonstrate that this assumption was met because tolerance is above 0.01 and VIF is below 10 for all the independent variables (see Table 2).

Table 2

Multicollinearity Statistics

	Collinearity statistics	
Independent variables	Tolerance	VIF
CO percentiles	0.555	1.802
NO_2 percentiles	0.562	1.779
O_3 percentiles	0.688	1.454
Pb percentiles	0.466	2.145
PM_{10} percentiles	0.446	2.241
$PM_{2.5}$ percentiles	0.632	1.582
SO_2 percentiles	0.700	1.428

No Autocorrection

This assumption implies that the values of the residuals are independent. The Durbin-Watson value of 2.002 (close to 2) indicates that this assumption was met.

Homoscedasticity

Homoscedasticity refers to the homogeneity of the variance; this means that the variance of the residuals is constant. This assumption was met as indicated by the residuals plot in Figure 1.

Inferential Statistics

RQ1

To approach RQ1 Is there is any association between specific percentiles of exposure of air pollutants (CO, Pb, NO_2, O_3, PM_{10}, $PM_{2.5}$, and SO_2) and age-adjusted breast cancer mortality, seven simple linear regression analyses were conducted to evaluate the prediction of age-adjusted breast cancer mortality from specific percentiles of exposure of air pollutants (CO, Pb, NO_2, O_3, PM_{10}, $PM_{2.5}$, and SO_2). The results of each simple linear regression analysis revealed specific percentiles of exposure of air pollutants (CO, Pb, NO_2, and PM_{10},) not to be statistically significant predictors to the models ($p > .05$). However, the results of the simple linear regression analysis revealed a statistically significant association between specific percentiles of exposure of air pollutant O_3 ($n = 638$). The regression coefficient, $B = 0.118$, 95% C.I. (0.027, 0.210) $p = .011$ associated with specific percentiles of exposure of air pollutant O_3 suggests that with each additional 10 percentile increase of exposure of air pollutant O_3, the age-adjusted breast cancer mortality increases by approximately 0.118 per 100,000 persons. The R^2 value of 0.010 associated with this regression model suggests that the specific percentiles of exposure of air pollutant O_3 account for approximately 1% of the variation in age-adjusted breast cancer mortality, which means that almost 99% of the variation in age-adjusted breast cancer mortality cannot be explained by specific percentiles of exposure of air pollutant O_3 alone. The confidence interval associated with the regression analysis in the model does not contain 0, which means the null hypothesis, there is no association

between specific percentiles of exposure of air pollutant O_3 and age-adjusted breast cancer mortality can be rejected.

The results of the simple linear regression analysis revealed a statistically significant association between specific percentiles of exposure of air pollutant SO_2 (n = 316). The regression coefficient B = 0.187, 95% C.I. (0.065, 0.310) p = .003 associated with specific percentiles of exposure of air pollutant SO_2 suggests that with each additional 10 percentile increase of exposure of air pollutant SO_2, the age-adjusted breast cancer mortality increases by approximately 0.187 per 100,000 persons. The R^2 value of 0.028 associated with this regression model suggests that the specific percentiles of exposure of air pollutant SO_2 accounts for almost 3% of the variation in age-adjusted breast cancer mortality, which means that approximately 97% of the variation in age-adjusted breast cancer mortality cannot be explained by specific percentiles of exposure of air pollutant SO_2 alone. The confidence interval associated with the regression analysis in the model does not contain 0, which means the null hypothesis, there is no association between specific percentiles of exposure of air pollutant SO_2 and age-adjusted breast cancer mortality can be rejected.

The results of the simple linear regression analysis revealed a statistically significant association between specific percentiles of exposure of air pollutant $PM_{2.5}$ (n = 672). The regression coefficient B = 0.233, 95% C.I. (0.137, 0.330) $p < .001$ associated with specific percentiles of exposure of air pollutant $PM_{2.5}$ suggests that with each additional 10 percentile increase of exposure of air pollutant $PM_{2.5}$, the age-adjusted breast cancer mortality increases by approximately 0.233 per 100,000 persons. The R^2

value of 0.033 associated with this regression model suggests that the specific percentiles of exposure of air pollutant $PM_{2.5}$ accounts for more than 3% of the variation in age-adjusted breast cancer mortality, which means that almost 97% of the variation in age-adjusted breast cancer mortality cannot be explained by specific percentiles of exposure of air pollutant $PM_{2.5}$ alone. The confidence interval associated with the regression analysis in the model does not contain 0, which means the null hypothesis, there is no association between specific percentiles of exposure of air pollutant $PM_{2.5}$ and age-adjusted breast cancer mortality can be rejected.

Table 3

Simple Linear Regression for Specific Percentiles of Exposure of Air Pollutants and Age-Adjusted Breast Cancer Mortality

			95% CI	
Specific percentiles of exposure of air pollutant	*B*	Sig	Lower	Upper
CO	0.009	.908	-0.141	0.158
Pb	-0.017	.711	-0.239	0.205
NO_2	0.019	.801	-0.132	0.171
O_3	0.118	.011	0.027	0.21
PM_{10}	-0.036	.592	-0.167	0.096
$PM_{2.5}$	0.233	.001	0.137	0.33
SO_2	0.187	.003	0.065	0.31

Note. CO = carbon monoxide; Pb = lead; NO_2 = nitrogen dioxide; O_3 = ozone; PM_{10} = particulate matter 10; PM $_{2.5}$ = particulate matter 2.5; SO_2 = sulfur dioxide.

To approach Is there any association between specific percentiles of exposure of air pollutants (CO, Pb, NO_2, O_3, PM_{10}, $PM_{2.5}$, and SO_2) and age-adjusted breast cancer mortality, considering median income, percent of adults with less than a high school diploma, percent of adults with a high school diploma only, percent of adults completing

some college or associate degree, percent of adults with a bachelor's degree, and percentage of White women?, seven multiple linear regression analyses were conducted to evaluate the prediction of age-adjusted breast cancer mortality from specific percentiles of exposure of air pollutants (CO, Pb, NO_2, O_3, PM10, $PM_{2.5}$, and SO_2) considering median income, percent of adults with less than a high school diploma, percent of adults with high school only, percent of adults completing some college or associate degree, percent of adults with a bachelor's degree, and percentage of White women.

The results of the multiple linear regression for specific percentiles of exposure of CO (n = 177) considering median income, percent of adults with less than a high school diploma, percent of adults with high school only, percent of adults completing some college or associate degree, percent of adults with a bachelor's degree, and percentage of White women, revealed specific percentiles of exposure of CO, percent of adults with a high school diploma only, percent of adults completing some college or associate degree, and median income not to be statistically significant predictors to the model ($p > .05$). However, the results revealed a statistically significant association between percentage of adults with less than a high school diploma and percentage of White women with age-adjusted breast cancer mortality.

Controlling for percentage of adults with less than high school diploma and specific percentiles of CO, the regression coefficient B = -0.68, 95% C.I. (-0.089, -0.048) $p < .001$ associated with percentage of White women suggest that with each additional percentage of White women, the age-adjusted breast cancer mortality decreases by

approximately 0.68 per 100,000 persons. The confidence interval associated with the regression analysis in the model does not contain 0, which means the null hypothesis, there is no association between percentage of White women and age-adjusted breast cancer mortality, can be rejected.

Controlling for percentage of White women and specific percentiles of exposure of CO, the regression coefficient B = -0.118, 95% C.I. (-0.185, -0.050) $p < .001$ associated with percent of adults with less than a high school diploma suggests that with each additional percent of adults with less than a high school diploma, the age-adjusted breast cancer mortality decreases by approximately 0.118 per 100,000 persons. The confidence interval associated with the regression analysis in the model does not contain 0, which means the null hypothesis, there is no association between percent of adults with less than a high school diploma and age-adjusted breast cancer mortality, can be rejected.

The R^2 value 0.421 associated with this regression model suggests that the percentage of adults with less than high school and the percentage of White women accounts for more than 42% of the variation in age-adjusted breast cancer mortality, which means that approximately 58% of the variation in age-adjusted breast cancer mortality cannot be explained by specific percentiles of exposure of CO, percentage of adults with less than high school, and Percentage of White women.

Table 4

Multiple Linear Regression for Specific Percentiles of Exposure of Carbone Monoxide (CO) Considering the Covariates

			95% CI	
Variables in the model for CO	*B*	Sig	Lower	Upper
Specific percentiles of exposure of air pollutant CO	0.114	.890	-0.017	0.246
Median income	- 8.507 E-5	< .001	0.000	0.000
Percent of adults with less than a high school diploma	-0.118	< .001	-0.185	-0.050
Percent of adults with high school only	0.051	.121	-0.013	0.115
Percent of adults completing some college or associate degree	0.050	.182	-0.023	0.123
Percentage of White women	-0.680	< .001	-0.089	-0.048

The results of the multiple linear regression for specific percentiles of exposure of Pb (n = 130) considering median income, percent of adults with less than a high school diploma, percent of adults with high school only, percent of adults completing some college or associate degree, percent of adults with a bachelor's degree, and percentage of White women revealed that specific percentiles of exposure of Pb, percent of adults with less than a high school diploma, percent of adults completing some college or associate degree, and median income not to be statistically significant predictors to the model (p > .05). However, the results revealed a statistically significant association between percent of adults with high school diploma only and percentage of White women with age-adjusted breast cancer mortality.

Controlling for percentage of White women and specific percentiles of exposure of Pb, the regression coefficient B = 0.141, 95% C.I. (0.042, 0.240) p = .006 associated with percent of adults with high school only suggest that with each additional percentage of adults with high school only, the age-adjusted breast cancer mortality increases by

approximately 0.141 per 100,000 persons. The confidence interval associated with the regression analysis in the model does not contain 0, which means the null hypothesis, there is no association between percent of adults with high school only and age-adjusted breast cancer mortality, can be rejected.

Controlling for percent of adults with high school only and specific percentiles of exposure of Pb, the regression coefficient B = -0.087, 95% C.I. (-0.121, -0.053) $p < .001$ associated with percentage of White women suggest that with each additional percentage of White women, the age-adjusted breast cancer mortality decreases by approximately 0.087 per 100,000 persons. The confidence interval associated with the regression analysis in the model does not contain 0, which means the null hypothesis, there is no association between percentage of White women and age-adjusted breast cancer mortality, can be rejected.

The R^2 value 0.296 associated with this regression model suggests that the percent of adults with less than a high school diploma and the percentage of White women accounts for almost 30% of the variation in Age-adjusted breast cancer mortality, which means that approximately 70% of the variation in Age-adjusted breast cancer mortality cannot be explained by percentage of adults with less than high school only and percentage of White women.

Table 5

Multiple Linear Regression for Specific Percentiles of Exposure of Lead (Pb) Considering the Covariates

			95% CI	
Variables in the model for Pb	*B*	Sig	Lower	Upper
Specific percentiles of exposure of air pollutant Pb	-0.038	.711	-0.240	0.164
Median income	-6.029 E-5	.017	0.000	0.000
Percent of adults with less than a high school diploma	-0.052	.386	-0.171	0.067
Percent of adults with high school only	0.141	.006	0.042	0.240
Percent of adults completing some college or associate degree	0.031	.649	-0.103	0.165
Percentage of White women	-0.087	< .001	-0.121	0.053

The results of the multiple linear regression for specific percentiles of exposure of NO_2 (n = 241) considering median income, percent of adults with less than a high school diploma, percent of adults with high school only, percent of adults completing some college or associate degree, percent of adults with a bachelor's degree or higher, and percentage of White women revealed specific percentiles of exposure of NO_2, percent of adults with less than a high school diploma, and median income not to be statistically significant predictors to the model ($p > .05$). However, the results revealed a statistically significant association between percent of adults with high school only, percent of adults completing some college or associate degree, and percentage of White women with age-adjusted breast cancer mortality.

Controlling for specific percentiles of exposure of NO_2, percent of adults with high school only, and percent of adults with some college or associate degree, the regression coefficient B = -0.067, 95% C.I. (-0.090, -0.04) $p < .001$ associated with percentage of White women suggest that with each additional percent of White women,

the age-adjusted breast cancer mortality decreases by approximately 0.067 per 100,000 persons. The confidence interval associated with the regression analysis in the model does not contain 0, which means the null hypothesis, there is no association between percentage of White women and age-adjusted breast cancer mortality, can be rejected.

Controlling for specific percentiles of exposure of NO_2, percent of adults with high school only, and percentage of White women, the regression coefficient $B = 0.084$, 95% C.I. (0.007, 0.161) $p = .033$ associated with percent of adults with some college or associate degree suggest that with each additional percent of adults with some college or associate degree, the age-adjusted breast cancer mortality increases by approximately 0.084 per 100,000 persons. The confidence interval associated with the regression analysis in the model does not contain 0, which means the null hypothesis, there is no association between percent of adults with some college or associate degree and age-adjusted breast cancer mortality, can be rejected.

Controlling for specific percentiles of exposure of NO_2, percent of adults with some college or associate degree and percentage of White women, the regression coefficient $B = 0.126$, 95% C.I. (0.062, 0.190) $p < .001$ associated with percent of adults with high school only suggest that with each additional percent of adults with high school only, the age-adjusted breast cancer mortality increases by approximately 0.126 per 100,000 persons. The confidence interval associated with the regression analysis in the model does not contain 0, which means the null hypothesis, there is no association between percent of adults with high school only and age-adjusted breast cancer mortality, can be rejected.

The R^2 value 0.337 associated with this regression model suggests that the percent of adults with less than a high school diploma, percent of adults with some college or associate degree, and percentage of White women accounts for almost 40% of the variation in age-adjusted breast cancer mortality, which means that approximately 60% of the variation in age-adjusted breast cancer mortality cannot be explained by percentage of adults with less than a high school diploma, percentage of adults with some college or associate degree, and percentage of White women.

Table 6

Multiple Linear Regression for Specific Percentiles of Exposure of Nitrogen Dioxide (NO_2) Considering the Covariates

			95% CI	
Variables in the model for NO_2	*B*	Sig	Lower	Upper
Specific percentiles of exposure of air pollutant NO_2	0.110	.140	-0.036	0.256
Median income	-5.773 E-5	< .001	0.000	0.000
Percent of adults with less than a high school diploma	-0.036	.305	-0.106	0.033
Percent of adults with high school only	0.126	< .001	0.062	0.190
Percent of adults completing some college or associate degree	0.084	.033	0.007	0.161
Percentage of White women	-0.067	< .001	-0.090	-0.045

The results of the multiple linear regression for specific percentiles of exposure of PM_{10} (n = 315) considering median income, percent of adults with less than a high school diploma, percent of adults with high school only, percent of adults completing some college or associate degree, percent of adults with a bachelor's degree, and percentage of White women revealed specific percentiles of exposure of PM_{10}, percent of adults with less than a high school diploma, percent of adults completing some college or associate degree, and median income not to be statistically significant predictors to the model (p > .05). However, the results revealed a statistically significant association between percent

of adults with high school only and percentage of White women with age-adjusted breast cancer mortality.

Controlling for specific percentiles of exposure of PM_{10} and percent of adults with high school only, the regression coefficient B = -0.053, 95% C.I. (-0.076, -0.029) p < .001 associated with percentage of White women suggest that with each additional percentage of White women, the age-adjusted breast cancer mortality decreases by approximately 0.053 per 100,000 persons. The confidence interval associated with the regression analysis in the model does not contain 0, which means the null hypothesis, there is no association between percentage of White women and age-adjusted breast cancer mortality, can be rejected.

Controlling for specific percentiles of exposure of PM_{10} and percentage of White women, the regression coefficient B = 0.133, 95% C.I. (0.067, 0.200) p < .001 associated with percent of adults with high school only suggest that with each additional percent of adults with high school only, the age-adjusted breast cancer mortality increases by approximately 0.133 per 100,000 persons. The confidence interval associated with the regression analysis in the model does not contain 0, which means the null hypothesis, there is no association between percent of adults with high school only and age-adjusted breast cancer mortality, can be rejected.

Table 7

Multiple Linear Regression for Specific Percentiles of Exposure of Particulate Matter 10 (PM_{10}) Considering the Covariates

			95% CI	
Variables in the model for PM_{10}	*B*	Sig	Lower	Upper
Specific percentiles of exposure of air pollutant PM_{10}	0.071	.297	-0.063	0.204
Median income	-5.081 E-5	.004	0.000	0.000
Percent of adults with less than a high school diploma	-0.067	.069	-0.140	0.005
Percent of adults with high school only	0.133	< .001	0.067	0.200
Percent of adults completing some college or associate degree	-0.013	.738	-0.088	0.062
Percentage of White women	-0.053	< .001	-0.076	-0.029

The R^2 value 0.182 associated with this regression model suggests that percent of adults with high school only and percentage of White women account for more than 18% of the variation in age-adjusted breast cancer mortality, which means that approximately 82% of the variation in age-adjusted breast cancer mortality cannot be explained by percent of adults with high school only and percentage of White women.

The results of the multiple linear regression for specific percentiles of exposure of SO_2 (n = 316) considering median income, percent of adults with less than a high school diploma, percent of adults with high school only, percent of adults completing some college or associate degree, percent of adults with a bachelor's degree, and percentage of White women revealed specific percentiles of exposure of SO_2, percent of adults completing some college or associate degree, and median income not to be statistically significant predictors to the model ($p > .05$). However, the results reveal a statistically

significant association between percent of adults with high school only and percentage of White women with age-adjusted breast cancer mortality.

Controlling for specific percentiles of exposure of SO_2 and percent of adults with high school only, the regression coefficient B = -0.069, 95% C.I. (-0.093, -0.046) p < .001 associated with percentage of White women suggest that with each additional percentage of White women, the age-adjusted breast cancer mortality decreases by approximately 0.069 per 100,000 persons. The confidence interval associated with the regression analysis in the model does not contain 0, which means the null hypothesis, there is no association between percentage of White women and age-adjusted breast cancer mortality, can be rejected.

Controlling for specific percentiles of exposure of SO_2 and percentage of White women, the regression coefficient B = 0.129, 95% C.I. (0.065, 0.193) p < .001 associated with percent of adults with high school only suggest that with each additional percent of adults with high school only, the age-adjusted breast cancer mortality increases by approximately 0.129 per 100,000 persons. The confidence interval associated with the regression analysis in the model does not contain 0, which means the null hypothesis, there is no association between percent of adults with high school only and age-adjusted breast cancer mortality, can be rejected.

The R^2 value 0.173 associated with this regression model suggests that percent of adults with high school only and percentage of White women accounts for more than 17% of the variation in age-adjusted breast cancer mortality, which means that

approximately 83% of the variation in age-adjusted breast cancer mortality cannot be explained by percent of adults with high school only and percentage of White women.

Table 8

Multiple Linear Regression for Specific Percentiles of Exposure of Sulfur Dioxide (SO_2) Considering the Covariates

			95% CI	
Variables in the model for SO_2	*B*	Sig	Lower	Upper
Specific percentiles of exposure of air pollutant SO_2	0.063	.320	-0.061	0.188
Median income	-2.762 E-5	.096	0.000	0.000
Percent of adults with less than a high school diploma	-0.060	.182	-0.148	0.028
Percent of adults with high school only	0.129	< .001	0.065	0.193
Percent of adults completing some college or associate degree	0.058	.171	-0.025	0.140
Percentage of White women	-0.069	< .001	-0.093	-0.046

The results of the multiple linear regression analysis for specific percentiles of exposure of $PM_{2.5}$ (n = 672) considering median income, percent of adults with less than a high school diploma, percent of adults with high school only, percent of adults completing some college or associate degree, percent of adults with a bachelor's degree or higher, and percentage of White women, revealed that percent of adults completing some college or associate degree and median income not to be statistically significant predictors to the model (p > .05). However, the results revealed a statistically significant association between specific percentiles of exposure of $PM_{2.5}$, percent of adults with less than a high school diploma only, percent of adults with a bachelor's degree or higher, and percentage of White women with age-adjusted breast cancer mortality.

Controlling for percent of adults with less than a high school diploma, percent of adults with a bachelor's degree or higher, and percentage of White women, the regression coefficient $B = 0.173$, 95% C.I. (0.079, 0.268) $p < .001$ associated with specific percentiles of exposure of air pollutant $PM_{2.5}$ suggests that with each additional 10 percentile increase of specific percentiles of exposure of $PM_{2.5}$, the age-adjusted breast cancer mortality increases by approximately 0.173 per 100,000 persons. The confidence interval associated with the regression analysis in the model does not contain 0, which means the null hypothesis, there is no association between specific percentiles of exposure of air pollutant $PM_{2.5}$ and age-adjusted breast cancer mortality, can be rejected.

Controlling for specific percentiles of exposure of $PM_{2.5}$, percent of adults with a bachelor's degree or higher, and percentage of White women, the regression coefficient $B = - 0.100$, 95% C.I. (- 0.168, - 0.031) $p = .005$ associated with percent of adults with less than a high school diploma suggests that with each additional percent increase of percent of adults with less than a high school diploma, the age-adjusted breast cancer mortality decreases by approximately 0.100 per 100,000 persons. The confidence interval associated with the regression analysis in the model does not contain 0, which means the null hypothesis, there is no association between percent of adults with less than a high school diploma and age-adjusted breast cancer mortality, can be rejected.

Controlling for percent of adults with less a than high school diploma, specific percentiles of exposure of $PM_{2.5}$, and percentage of White women, the regression coefficient $B = - 0.078$, 95% C.I. (- 0.122, - 0.034) $p < .001$ associated with percent of adults with a bachelor's degree or higher suggests that with each additional percent

increase of percent of adults with a bachelor's degree or higher, the age-adjusted breast cancer mortality decreases by approximately 0.078 per 100,000 persons. The confidence interval associated with the regression analysis in the model does not contain 0, which means the null hypothesis, there is no association between percent of adults with a bachelor's degree or higher and age-adjusted breast cancer mortality, can be rejected.

Controlling for percent of adults with less a than high school diploma, specific percentiles of exposure of $PM_{2.5}$, and percent of adults with a bachelor's degree or higher, the regression coefficient B = - 0.047, 95% C.I. (- 0.064, - 0.030) $p < .001$ associated with percentage of White women suggests that with each additional percent increase of percentage of White women, the age-adjusted breast cancer mortality decreases by approximately 0.047 per 100,000 persons. The confidence interval associated with the regression analysis in the model does not contain 0, which means the null hypothesis, there is no association between percentage of White women and age-adjusted breast cancer mortality, can be rejected.

The R^2 value of 0.172 associated with this regression model suggests that the specific percentiles of exposure of air pollutant $PM_{2.5}$, percent of adults with less a than high school diploma, percent of adults with a bachelor's degree or higher, and percentage of White women accounts for more than 17% of the variation in age-adjusted breast cancer mortality, which means that approximately 83% of the variation in age-adjusted breast cancer mortality cannot be explained by specific percentiles of exposure of air pollutant $PM_{2.5}$, percent of adults with less a than high school diploma, percent of adults with a bachelor's degree or higher, and percentage of White women.

Table 9

Multiple Linear Regression for Specific Percentiles of Exposure of Particulate Matter 2.5 ($PM_{2.5}$) Considering the Covariates

			95% CI	
Variables in the model for $PM_{2.5}$	*B*	Sig	Lower	Upper
Specific percentiles of exposure of air pollutant $PM_{2.5}$	0.173	< .001	0.079	0.268
Median income	-5.332 E-5	< .001	0.000	0.000
Percent of adults with less than a high school diploma	-0.100	.005	-0.168	-0.031
Percent of adults completing some college or associate degree	-0.047	.150	-0.111	0.017
Percent of adults with a bachelor's degree	-0.078	< .001	-0.122	-0.034
Percentage of White women	-0.047	< .001	-0.064	-0.030

The results of the multiple linear regression analysis for specific percentiles of exposure of O_3 (n = 638) considering median income, percent of adults with less than a high school diploma, percent of adults with high school only, percent of adults completing some college or associate degree, percent of adults with a bachelor's degree, and percentage of White women, revealed percent of adults with less than high school diploma, percent of adults completing some college or associate degree, and median income not to be statistically significant predictors to the model (p > .05). However, the results revealed a statistically significant association between specific percentiles of exposure of O_3, percent of adults with a high school diploma only and, percentage of White women with age-adjusted breast cancer mortality.

Controlling for percent of adults with a high school diploma only and percentage of White women, the regression coefficient B = 0.175, 95% C.I. (0.090, 0.260) p < .001 associated with specific percentiles of exposure of air pollutant O_3 suggests that with each additional 10 percentile increase of exposure of air pollutant O_3, the age-adjusted

breast cancer mortality increases by approximately 0.175 per 100,000 persons. The confidence interval associated with the regression analysis in the model does not contain 0, which means the null hypothesis, there is no association between specific percentiles of exposure of air pollutant O_3 and age-adjusted breast cancer mortality, can be rejected.

Controlling for specific percentiles of exposure of air pollutant O_3 and percentage of White women, the regression coefficient $B = 0.154$, 95% C.I. (0.111, 0.197) $p < .001$ associated with percent of adults with a high school diploma only suggests that with each additional percent increase of percent of adults with a high school diploma only, the age-adjusted breast cancer mortality increases by approximately 0.154 per 100,000 persons. The confidence interval associated with the regression analysis in the model does not contain 0, which means the null hypothesis, there is no association between percent of adults with a high school diploma only and age-adjusted breast cancer mortality, can be rejected.

Controlling for specific percentiles of exposure of air pollutant O_3 and percent of adults with a high school diploma only, the regression coefficient $B = - 0.081$, 95% C.I. (- 0.099, - 0.063) $p < .001$ associated with percentage of White women suggests that with each additional percent increase of percentage of White women, the age-adjusted breast cancer mortality decreases by approximately 0.154 per 100,000 persons. The confidence interval associated with the regression analysis in the model does not contain 0, which means the null hypothesis, there is no association between percentage of White women and age-adjusted breast cancer mortality, can be rejected.

The R^2 value of 0.205 associated with this regression model suggests that the specific percentiles of exposure of air pollutant O_3, percent of adults with a high school diploma only and percentage of White women accounts for more than 20% of the variation in age-adjusted breast cancer mortality, which means that approximately 80% of the variation in age-adjusted breast cancer mortality cannot be explained by specific percentiles of exposure of air pollutant O_3, percent of adults with a high school diploma only and percentage of White women alone.

Table 10

Multiple Linear Regression for Specific Percentiles of Exposure of Ozone (O_3) Considering the Covariates

			95% CI	
Variables in the model for O_3	*B*	Sig	Lower	Upper
Specific percentiles of exposure of air pollutant O_3	0.175	< .001	0.090	0.260
Median income	-1.958 E-5	.087	0.000	0.000
Percent of adults with less than a high school diploma	-0.037	.210	-0.096	0.021
Percent of adults with high school only	0.154	< .001	0.111	0.197
Percent of adults completing some college or associate degree	0.026	.378	-0.031	0.083
Percentage of White women	-0.081	< .001	-0.099	-0.063

RQ2

To approach Is there any association between the interaction of specific percentiles of exposure of air pollutants (CO, Pb, NO_2, O_3, PM_{10}, $PM_{2.5}$, and SO_2) and age-adjusted breast cancer mortality?, a multiple linear regression analysis was conducted to evaluate the prediction of age-adjusted breast cancer mortality from specific percentiles of exposure of air pollutants (CO, Pb, NO_2, O_3, PM_{10}, $PM_{2.5}$, and SO_2). The results of the multiple linear regression analysis revealed specific percentiles of exposure

of air pollutants (CO, Pb, NO_2, O_3, PM_{10}, and SO_2) not to be statistically significant predictors to the model ($p > .05$). However, the results of the multiple linear regression analysis revealed a statistically significant association between specific percentiles of exposure of air pollutant $PM_{2.5}$. The regression coefficient $B = 0.580$, 95% C.I. (0.191, 0.969) $p = .004$ associated with specific percentiles of exposure of air pollutant $PM_{2.5}$ suggests that with each additional 10 percentile increase of exposure of air pollutant $PM_{2.5}$, the age-adjusted breast cancer mortality increases by approximately 0.580 per 100,000 persons. The R^2 value of 0.291 associated with this regression model suggests that the specific percentiles of exposure of air pollutant $PM_{2.5}$ accounts for more than 29% of the variation in Age-adjusted breast cancer mortality, which means that approximately 70% of the variation in age-adjusted breast cancer mortality cannot be explained by specific percentiles of exposure of air pollutant $PM_{2.5}$ alone. A sensitivity analysis using G*power 3.1.9.7 software $n = 48$, alpha error prob = 0.05, power = 0.80, predictors = 7 calculated Effect size $f^2 = 0.354$ a large effect. The confidence interval associated with the regression analysis does not contain 0, which means the null hypothesis, there is no association between number of specific percentiles of exposure of air pollutant $PM_{2.5}$ and age-adjusted breast cancer mortality, can be rejected.

Table 11

Multiple Linear Regression for Specific Percentiles of Exposure of Air Pollutants (Model 1)

			95% CI	
Specific percentiles of exposure of air pollutant	*B*	Sig	Lower	Upper
CO	-0.337	.139	-0.789	0.114
Pb	-0.201	.353	-0.635	0.232
NO_2	0.229	.406	-0.323	0.782
O_3	0.082	.600	-0.233	0.398
PM_{10}	-0.063	.761	-0.481	0.354
$PM_{2.5}$	0.580	.004	0.191	0.969
SO_2	0.131	.503	-0.261	0.523

Note. CO = carbon monoxide; Pb = lead; NO_2 = nitrogen dioxide; O_3 = ozone; PM_{10} = particulate matter 10; $PM_{2.5}$ = particulate matter 2.5; SO_2 = sulfur dioxide.

To approach Is there any association between the interaction of specific percentiles of exposure of air pollutants (CO, Pb, NO2, O3, PM10, PM2.5, and SO2) and age-adjusted breast cancer mortality, considering median income, percent of adults with less than a high school diploma, percent of adults completing some college or associate degree, percent of adults with a bachelor's degree, and percentage of White women?, a multiple linear regression analysis was conducted to evaluate the prediction of age-adjusted breast cancer mortality from specific percentiles of exposure of air pollutants (CO, Pb, NO_2, O_3, PM_{10}, $PM_{2.5}$, and SO_2) considering median income, percent of adults with less than a high school diploma, percent of adults completing some college or associate degree, percent of adults with a bachelor's degree, and percentage of White women. The results of the multiple linear regression analysis revealed specific percentiles of exposure of air pollutants (CO, Pb, NO_2, O_3, PM_{10}, and SO_2) and median income,

percent of adults completing some college or associate degree, and percent of adults with a bachelor's degree or higher not to be statistically significant predictors to the model ($p > .05$). However, the results of the multiple linear regression analysis revealed a statistically significant association between specific percentiles of exposure of air pollutant $PM_{2.5}$, percent of adults with less than a high school diploma and percentage of White women.

Controlling for percent of adults with less than a high school diploma, and percentage of White women, the regression coefficient $B = 0.479$, 95% C.I. (0.123, 0.835) $p = .010$ associated with specific percentiles of exposure of air pollutant $PM_{2.5}$ suggests that with each 10 percentile increase of exposure of air pollutant $PM_{2.5}$, the age-adjusted breast cancer mortality increases by approximately 0.479 per 100,000 persons. The confidence interval associated with the regression analysis in the model does not contain 0, which means the null hypothesis, there is no association between specific percentiles of exposure of air pollutant $PM_{2.5}$ and age-adjusted breast cancer mortality, can be rejected.

Controlling for specific percentiles of exposure of air pollutant $PM_{2.5}$ and percentage of White women, the regression coefficient $B = -0.414$, 95% C.I. (-0.673, -0.154) $p = .003$ associated with percent of adults with less than a high school diploma suggests that with each additional percent increase in percent of adults with less than a high school diploma, the age-adjusted breast cancer mortality decreases by approximately 0.414 per 100,000 persons. The confidence interval associated with the regression analysis in the model does not contain 0, which means the null hypothesis, there is no

association between percent of adults with less than a high school diploma and age-adjusted breast cancer mortality, can be rejected.

Controlling for specific percentiles of exposure of air pollutant $PM_{2.5}$ and percent of adults with less than a high school diploma, the regression coefficient B = -0.068, 95% C.I. (-0.110, -0.027) p = .002 associated with percentage of White women suggests that with each additional percent increase in percentage of White women, the age-adjusted breast cancer mortality decreases by approximately 0.068 per 100,000 persons. The confidence interval associated with the regression analysis in the model does not contain 0, which means the null hypothesis, there is no association between percent of White women and age-adjusted breast cancer mortality, can be rejected.

The R^2 value of 0.632 associated with this regression model suggests that the specific percentiles of exposure of air pollutant $PM_{2.5}$, percent of adults with less than a high school diploma and percentage of White women accounts for more than 63% of the variation in age-adjusted breast cancer mortality, which means that approximately 37% of the variation in age-adjusted breast cancer mortality cannot be explained by specific percentiles of exposure of air pollutant $PM_{2.5}$, percent of adults with less than a high school diploma and percentage of White women alone. A sensitivity analysis using power 3.1.9.7 software n = 48, alpha error prob = 0.05, power = 0.80, predictors = 7 calculated Effect size f^2 = 0.475 a large effect. The confidence interval associated with the regression analysis does not contain 0, which means the null hypothesis, there is no association between specific percentiles of exposure of air pollutant ($PM_{2.5}$), percent of

adults with less than a high school diploma and percentage of White women and age-adjusted breast cancer mortality, can be rejected.

Table 12

Multiple Linear Regression for Specific Percentiles of Exposure of Air Pollutants (Model 2)

			95% CI	
Variables	*B*	Sig	Lower	Upper
CO	-0.127	.511	-0.517	0.262
Pb	-0.101	.585	-0.475	0.272
NO2	0.243	.355	-0.284	0.770
O3	0.193	.201	-0.108	0.495
PM10	0.094	.630	-0.298	0.485
PM2.5	0.479	.010	0.123	0.835
SO2	-0.103	.557	-0.456	0.249
Median income	-4.092 E-5	.257	0.000	0.000
Percent of adults with less than a high school diploma	-0.414	.003	-0.673	-0.154
Percent of adults completing some college or associate degree	-0.980	.532	-0.407	0.211
Percent of adults with a bachelor's degree	-0.126	.180	-0.312	0.061
Percentage of White women	-0.068	.002	-0.110	-0.027

Note. CO = carbon monoxide; Pb = lead; NO_2 = nitrogen dioxide; O_3 = ozone; PM_{10} = particulate matter 10; $PM_{2.5}$ = particulate matter 2.5; SO_2 = sulfur dioxide.

Summary

In this chapter, I describe the results obtained from the study. First, I evaluated the association between specific percentile of exposure of air pollutant (CO, Pb, NO_2, O_3, PM_{10}, $PM_{2.5}$, and SO_2) and age-adjusted breast cancer mortality by conducting seven simple linear regressions. The results indicated a statistically significant association between specific percentiles of exposure of O_3, SO_2, and $PM_{2.5}$. Following, seven multiple linear regressions were conducted including median income, percent of adults

with less than a high school diploma, percent of adults with a high school diploma only, percent of adults completing some college or associate degree, percent of adults with a bachelor's degree, and percentage of White women. These analyses indicated a statistically significant association between specific percentiles of exposure of air pollutant $PM_{2.5}$ and O_3. The covariates with statistically significant associations with age-adjusted breast cancer mortality showed slight variation between the multiple linear regressions performed for each EPA-regulated air pollutant.

Then, I evaluated the association between the interaction of specific percentiles of exposure of air pollutants (CO, Pb, NO_2, O_3, PM_{10}, $PM_{2.5}$, and SO_2) and age-adjusted breast cancer mortality, considering median income, percent of adults with less than a high school diploma, percent of adults completing some college or associate degree, percent of adults with a bachelor's degree, and percentage of White women. The results of the multiple linear regression for specific percentiles of exposure of air pollutants (CO, Pb, NO_2, O_3, PM_{10}, $PM_{2.5}$, and SO_2) and age-adjusted breast cancer mortality, revealed a statistically significant association between specific percentiles of exposure of $PM_{2.5}$ and age-adjusted breast cancer mortality. The results of multiple linear regression for specific percentiles of exposure of air pollutants (CO, Pb, NO_2, O_3, PM_{10}, $PM_{2.5}$, and SO_2) and age-adjusted breast cancer mortality, considering median income, percent of adults with less than a high school diploma, percent of adults completing some college or associate degree, percent of adults with a bachelor's degree, and percentage of White women, revealed a statistically significant association between specific percentiles of exposure of

air pollutant $PM_{2.5}$, percent of adults with less than a high school diploma, and percentage of White women.

The next chapter will provide the interpretation of the findings of the study. I will discuss the limitations of the study and provide recommendations for future research on this topic. Finally, I will mention the implications of this study for social change and provide the conclusions of the research.

Chapter 5: Discussion, Conclusions, and Recommendations

Introduction

Despite research and advances in diagnosis and treatment, breast cancer continues to have significant morbidity and mortality, thus being considered a public health problem. Not only is breast cancer one of the most frequent cancers among women, with an incidence of 19.9 per 100,000 women per year, age-adjusted (ACS, 2022), but also there are disparities among Black and White American women. For example, although the incidence is higher among White women (White women: 128.7 per 100,000 versus Black women: 125.5 per 100,000), the mortality is higher among their Black counterparts (Black women: 29.5 per 100,000 versus White women: 20.38 per 100,000; DeSantis et al., 2017). In this sense, relevant social determinants have been targeted to explain these disparities. Environmental exposure, specifically to air pollutants, affects breast cancer incidence. Many studies have focused on environmental exposure and breast cancer incidence (Andersen et al., 2017; Ayuso-Álvarez et al., 2020; Goldberg et al., 2017; Gruzieva et al., 2017; Guo et al., 2020; Hwang et al., 2020; Natarajan et al., 2020; Paz et al., 2017; Sahay et al., 2019; Turner et al., 2020; Yaghiyan et al., 2017). However, mortality, reduced since the 1990s after the introduction of screening mammograms (DeSantis et al., 2017), is still a concern, and little has been studied about the role of exposure to air contaminants and breast cancer mortality (Cheng et al., 2020; Guo et al., 2020; Hwang et al., 2020; Kim et al., 2018; Zhang et al., 2019).

In the United States, the EPA is the agency that regulates and monitors environmental exposure. The purpose of this quantitative, ecological retrospective cohort

study was to assess the impact of exposure to EPA-regulated air pollutants (CO, Pb, NO_2, O_3, PM_{10}, and SO_2) on breast cancer mortality, considering median income, percent of adults with less than a high school diploma, percent of adults completing some college or associate degree, percent of adults with a bachelor's degree or higher, and percentage of White women. The study of these pollutants was relevant because it evaluated the role of the air contaminants monitored by the EPA in the United States.

Summary of Key Findings

The simple regression analyses conducted for each specific percentile of exposure of CO, Pb, NO_2, O_3, PM_{10}, and SO_2 revealed that only specific percentiles of exposure of $PM_{2.5}$ [B = 0.233, 95% C.I. (0.137, 0.330) $p < .001$], O_3 [B = 0.118, 95% C.I. (0.027, 0.210) $p = .011$], and SO_2 [B = 0.187, 95% C.I. (0.065, 0.310) $p = .003$] were statistically significant predictors of age-adjusted breast cancer mortality without considering median income, percent of adults with less than a high school diploma, percent of adults with a high school diploma only, percent of adults completing some college or associate degree, percent of adults with a bachelor's degree or higher, and percentage of White women.

When including median income, percent of adults with less than a high school diploma, percent of adults with a high school diploma only, percent of adults completing some college or associate degree, percent of adults with a bachelor's degree or higher, and percentage of White women in the models, the multiple regression analysis for specific percentiles of $PM_{2.5}$ indicated that this pollutant [B = 0.173, 95% C.I. (0.079, 0.268) $p < .001$], percent of adults with less than a high school diploma [B = - 0.100, 95% C.I. (- 0.168, - 0.031) $p = .005$], percent of adults with a bachelor's degree or higher [B =

- 0.078, 95% C.I. (- 0.122, - 0.034) $p < .001$], and percentage of White women [B = - 0.047, 95% C.I. (- 0.064, - 0.030) $p < .001$] were statistically significant predictors of age-adjusted breast cancer mortality. Finally, the multiple regression analysis of specific percentiles of exposure of O_3 indicated that this pollutant [B = 0.175, 95% C.I. (0.090, 0.260) $p < .001$] and percent of adults with a high school diploma only [B = 0.154, 95% C.I. (0.111, 0.197) $p < .001$], and percentage of White women [B = - 0.081, 95% C.I. (- 0.099, - 0.063) $p < .001$] were statistically significant predictors of age-adjusted breast cancer mortality.

The multilinear regression analysis performed with all the specific percentiles of exposure of CO, Pb, NO_2, O_3, PM_{10}, and SO_2 without considering median income, percent of adults with less than a high school diploma, percent of adults with a high school diploma only, percent of adults completing some college or associate degree, percent of adults with a bachelor's degree or higher, and percentage of White women (Model 1) indicated that only specific percentiles of exposure of $PM_{2.5}$ [B = 0.580, 95% C.I. (0.191, 0.969) $p = .004$] was a statistically significant predictor of age-adjusted breast cancer mortality alone. Model 2 additionally included median income, percent of adults with less than a high school diploma, percent of adults with a high school diploma only, percent of adults completing some college or associate degree, percent of adults with a bachelor's degree or higher, and percentage of White women. The results indicated that specific percentiles of exposure of $PM_{2.5}$ [B = 0.479, 95% C.I. (0.123, 0.835) $p = .010$], percent of adults with less than a high school diploma [B = -0.414, 95% C.I. (-0.673, -

0.154) p = .003], and percentage of White women [B = -0.068, 95% C.I. (-0.110, -0.027) p = .002] were statistically significant predictors of age-adjusted breast cancer mortality.

Interpretations of the Findings

RQ1

Seven simple linear regressions (one per specific percentile of exposure of CO, Pb, NO_2, O_3, PM_{10}, $PM_{2.5}$, and SO_2, excluding the covariates median income, percent of adults with less than a high school diploma, percent of adults with a high school diploma only, percent of adults completing some college or associate degree, percent of adults with a bachelor's degree, and percentage of White women), and seven multiple linear regressions (including the covariates) were performed to approach the first RQ: Is there any association between specific percentiles of exposure of air pollutants (CO, Pb, NO_2, O_3, PM_{10}, $PM_{2.5}$, and SO_2) and age-adjusted breast cancer mortality, considering median income, percent of adults with less than a high school diploma, percent of adults with a high school diploma only, percent of adults completing some college or associate degree, percent of adults with a bachelor's degree, and percentage of White women?

The results of each simple linear regression revealed that the specific percentiles of CO, Pb, NO_2, and PM_{10}, were not statistically significant predictors of age-adjusted breast cancer mortality (p > .05).

Specific Percentiles of Exposure of CO

The results for CO are consistent with other studies (see Huang et al., 2020; Liu et al., 2020). Most studies on CO have primarily associated exposure to this contaminant with other health problems, such as pulmonary, cardiovascular, and neurological

disorders (Dey & Dhal Chandra, 2019; Francisco et al., 2018). In the model, including the covariates, specific percentiles of exposure of CO was not a statistically significant predictor of age-adjusted breast cancer mortality. However, the percentage of adults with less than a high school diploma [*B* = -0.118, 95% C.I. (-0.185, -0.050) *p* < .001] and percentage of White women [*B* = -0.68, 95% C.I. (-0.089, -0.048) *p* < .001] were statistically significant predictors of age-adjusted breast cancer mortality. The increase in the percent of adults with less than a high school diploma resulted in a negative association with age-adjusted breast cancer mortality [*B* = -0.118]. This result is inconsistent with the meta-analysis conducted by Mootz et al. (2020), who concluded that people with lower educational levels have a poorer prognosis. However, in this study, the variable did not specify the gender of the subjects, which could help clarify this discrepancy. In one of the studies consulted, the authors found a strong association between lower social economic status (SES) with highly invasive and metastatic subtypes of breast cancer (Luminal B type of breast cancer [ORQ1vQ4, 1.31; 95% CI 1.11-1.54, *p = .05*], triple-negative breast cancer subtypes [ORQ1vQ4, 1.32; 95% CI, 1.02-1.71; *p* = .037], and HER2-e (OR for high school degree or less vs. postgraduate, 1.68; 95% CI, 1.03-2.75; *p* = .030; Aoki et al., 2021). These authors considered SES as a composite score of income, poverty, education, occupation, employment, rent, and house value, which can explain the differences in the results. The authors did not make direct reference to mortality in their study. The percentage of White women is also negatively associated with age-adjusted breast cancer mortality [*B* = -0.68]. This result is consistent with the results from the studies conducted by DeSantis et al. (2017), Prakash et al.

(2020), and Scott et al. (2019). The study conducted by Scott et al. concluded that Black women have higher odds of being diagnosed with triple-negative breast cancer (OR, 2.27; 95% CI, 2.23-2.31) compared to their White counterparts (OR, 1.22; 95% CI, 1.19-1.25). The authors remarked that these subtypes increase the risk of dying from breast cancer. Similar results were reported by Prakash et al. (2020).

Specific Percentiles of Exposure of Pb

The results of the studies consulted did not correlate exposure to Pb to breast cancer mortality, which is consistent with the results that I obtained. Various authors concluded that cadmium is the metal that mainly contributed to breast carcinogenesis (Gray et al., 2017; Hwang et al., 2020; O'Brien et al., 2019). No study concluded that Pb is a predictor of breast cancer mortality. However, Cantor et al. (1995) and McElroy et al. (2006; as cited in Hiatt & Green, 2018) argued that Pb had been mainly studied in males, which was not the case in my study that focused only on females. However, in the multiple linear regression for this pollutant, the results revealed that percent of adults with high school diploma only [$B = 0.141$, 95% C.I. (0.042, 0.240) $p = .006$] and percentage of White women [$B = -0.087$, 95% C.I. (-0.121, -0.053) $p < .001$] are associated with age-adjusted breast cancer mortality. These results are consistent with the results from the studies that were discussed above.

Specific Percentiles of Exposure of NO_2

NO_2 was linked to breast cancer incidence (Goldberg et al., 2017; Gruzieva et al., 2017; Lemarchand et al., 2019). Concerning mortality, the only researchers who reported an association between NO_2 as a single pollutant and breast cancer mortality were Hwang

et al. (2020). However, these authors and Cheng et al. (2020) referred to this gas as part of multipollutants. Hwang et al. found a weak association between NO_2 and breast cancer mortality (although stronger compared with O_3). It is vital to note that South Korea has a low breast cancer mortality (6.1 per 100,000, age-adjusted), a universal health care system, a high relative 5-year survival for breast cancer, and a strict follow-up system cases by place of residence. Finally, the authors recognized that air pollution in South Korea is relatively more severe than in the United States (Hwang et al., 2020), and the composition and concentration of pollutants may differ. There are also differences in the covariates included. These factors may help explain the inconsistencies between the results of the two studies.

When including the covariates, specific percentiles of exposure of NO_2 was still not found to be a statistically significant predictor of age-adjusted breast cancer mortality ($p > .05$). However, the results revealed a statistically significant association between percent of adults with high school only [$B = 0.126$, 95% C.I. (0.062, 0.190) $p < .001$], percent of adults completing some college or associate degree [$B = 0.084$, 95% C.I. (0.007, 0.161) $p = .033$], and age-adjusted breast cancer mortality, consistent with the findings of Aoki et al. (2021) and Mootz et al. (2020). Also, the percentage of White women [$B = -0.067$, 95% C.I. (-0.090, -0.04) $p < .001$] was a statistically significant predictor of age-adjusted breast cancer mortality. This is consistent with the studies conducted by DeSantis et al. (2017), Prakash et al. (2020), and Scott et al. (2019), as previously discussed.

Specific Percentiles of Exposure of PM_{10}

Specific percentiles of exposure of PM_{10} was not a statistically significant predictor of age-adjusted breast cancer mortality ($p > .05$). These results are not consistent with the findings of Hwang et al. (2020) and Zhang et al. (2019). Kim et al. (2018) also reported an association between exposure to PM_{10} and breast cancer mortality, but they concluded that the association was heterogeneous (RR = 1.06, 95% CI = 0.93-1.21, *I2* = 64.6%). The studies by Zhang et al. and Kim et al. were meta-analyses, which differed from the design of this study, while Hwang et al. conducted an ecological study in South Korea. The differences in the results between the study by Hwang et al. and this study could be explained by the differences between South Korea and the United States, as well as some methodological differences, which were previously exposed.

No changes were observed for specific percentiles of exposure of PM_{10} in the multiple linear regression (where the covariates were included). However, I found a statistically significant association between percent of adults with high school only [B = 0.133, 95% C.I. (0.067, 0.200) $p < .001$] and the percentage of White women [B = -0.053, 95% C.I. (-0.076, -0.029) $p < .001$] with age-adjusted breast cancer mortality. These results are consistent with other studies, as previously discussed.

Specific Percentiles of Exposure of O_3

The results of this simple linear regression revealed a statistically significant association between specific percentiles of O_3 [B = 0.118, 95% C.I. (0.027, 0.210) p = .011] and age-adjusted breast cancer mortality. Some studies found a poor positive correlation between O_3 and breast cancer mortality (Hwang et al., 2020; Turner et al.,

2017), which is consistent with the results of this study. In this study, O_3 alone cannot explain 99% of the variation in the age-adjusted breast cancer mortality (R^2: 0.010), consistent with a weak predictive value of exposure to O_3 levels in the variation of the outcome variable. Hwang et al. (2020) found collinearity between O_3 and NO_2 (correlation coefficient *r*: -0.862) and a weaker association between O_3 and breast cancer mortality (*r*: 0.659) compared to NO_2 (*r*: 0.774). Other studies found a similar weak association between O_3 and breast cancer mortality (Turner et al., 2017).

The multiple linear regression also revealed a statistically significant association between specific percentiles of O_3 [*B* = 0.175, 95% C.I. (0.090, 0.260) $p < .001$], percent of adults with a high school diploma only [*B* = 0.154, 95% C.I. (0.111, 0.197) $p < .001$], and percentage of White women [*B* = - 0.081, 95% C.I. (- 0.099, - 0.063) $p < .001$] with age-adjusted breast cancer mortality. These results are consistent with those found in the literature consulted and discussed above.

Specific Percentiles of Exposure of SO_2

The simple linear regression analysis for specific percentiles of exposure of SO_2 [*B* = 0.187, 95% C.I. (0.065, 0.310) $p = .003$] revealed that SO_2 was associated with age-adjusted breast cancer mortality. This result is consistent with the findings of Hwang et al. (2020). However, these researchers concluded that this gas had a little statistically significant association with breast cancer mortality, also as a single pollutant (OR = 1.02; 95% CI = 0.991–1.04). In the same study, Hwang et al. included this gas as a part of PM without marking its role in breast cancer mortality. This weak association seems to be consistent with the relatively poor role in the variation of specific percentiles of exposure

to SO_2 alone as a predictor of age-adjusted breast cancer mortality in this study (R^2: 0.028).

In the multiple linear regression, the specific percentiles of exposure of SO_2 is no longer associated with Age-adjusted breast cancer mortality ($p > .05$). However, percentage of White women [B = -0.069, 95% C.I. (-0.093, -0.046) $p < .001$] and percent of adults with high school only [B = 0.129, 95% C.I. (0.065, 0.193) $p < .001$] were statistically significantly associated with age-adjusted breast cancer mortality. The results are again consistent with those found by other authors and previously discussed.

Specific Percentiles of Exposure of $PM_{2.5}$

The results of the simple linear regression for specific percentiles of exposure of $PM_{2.5}$ [B = 0.233, 95% C.I. (0.137, 0.330) $p < .001$], indicated a statistically significant association with age-adjusted breast cancer mortality. These results are generally consistent with all the research consulted. Cheng et al. (2020) found that $PM_{2.5}$ was associated with all-cause deaths (HR = 1.25-1.72; $p < .004$) and risk of cardiovascular mortality (HR = 1.62-3.93; p's < .0005) deaths in breast cancer patients. However, they declared that the association with breast cancer mortality was not statistically significant, which is the only study with results that are inconsistent with the results I obtained. Hwang et al. (2020) found a positive, although weak, association between $PM_{2.5}$ and breast cancer incidence and mortality (Pearson's r = 0.150, p = .0173). However, other researchers did find a stronger correlation between $PM_{2.5}$ and breast cancer mortality. Guo et al. (2020) found a statistically significant association with breast cancer mortality ($PM_{2.5}$ per 10µg/m3 RR = 1.09; 95% CI = 1.02-1.16, PQ-test = 0.158). Although Kim et

al. (2018) found a large heterogenicity in the association between $PM_{2.5}$ and breast cancer mortality, they concluded that this pollutant is associated with breast cancer mortality (RR = 1.60; 95% CI = 0.94-2.72; $I2$ = 83.4%). Finally, Zhang et al. (2019) also found a statistically significant association between $PM_{2.5}$ and breast cancer mortality (HR = 1.17; 95% CI = 1.05–1.30, p = .004).

The multiple linear regression model revealed that specific percentiles of exposure of $PM_{2.5}$ [B = 0.173, 95% C.I. (0.079, 0.268) p < .001], percent of adults with less than a high school diploma [B = - 0.100, 95% C.I. (- 0.168, - 0.031) p = .005], percent of adults with a bachelor's degree or higher [B = - 0.078, 95% C.I. (- 0.122, - 0.034) p < .001], and percentage of White women [B = - 0.047, 95% C.I. (- 0.064, - 0.030) p < .001] were statistically significant predictors of changes of age-adjusted breast cancer mortality when respectively controlling for the other variables in the model. These results are consistent with the studies consulted, except for percentage of adults with less than a high school diploma, as discussed in specific percentiles of exposure of CO. As previously discussed, $PM_{2.5}$ was found to be associated with breast cancer mortality by different researchers (Guo et al., 2020; Hwang et al., 2020; Kim et al., 2018; Zhang et al., 2019). The results found for percentage of White women and percent of adults with a bachelor's degree or higher were consistent with the studies consulted and previously discussed.

RQ2

To approach the second RQ, Is there any association between the interaction of specific percentiles of exposure of air pollutants (CO, Pb, NO_2, O_3, PM_{10}, $PM_{2.5}$, and

SO_2) and age-adjusted breast cancer mortality, considering median income, percent of adults with less than a high school diploma, percent of adults completing some college or associate degree, percent of adults with a bachelor's degree, and percentage of White women?, a multiple linear regression with two models was performed. The first model included specific percentiles of exposure of air pollutants (CO, Pb, NO_2, O_3, PM_{10}, $PM_{2.5}$, and SO_2) and age-adjusted breast cancer mortality. In the second model median income, percent of adults with less than a high school diploma, percent of adults completing some college or associate degree, percent of adults with a bachelor's degree, and percentage of White women were added.

Model 1

In this model, specific percentiles of exposure of $PM_{2.5}$ was the only statistically significant predictor of age-adjusted breast cancer mortality [B = 0.580, 95% C.I. (0.191, 0.969) p = .004].

Model 2

In the second model, the results revealed that specific percentiles of $PM_{2.5}$ [B = 0.479, 95% C.I. (0.123, 0.835) p = .010], percent of adults with less than a high school diploma [B = -0.414, 95% C.I. (-0.673, -0.154) p = .003], and percentage of White women [B = -0.068, 95% C.I. (-0.110, -0.027) p = .002] were statistically significant predictors of age-adjusted breast cancer mortality when respectively controlling for the other variables in the model.

The results revealed that, according to the reported levels of air pollutants monitored by the EPA, and considering the covariates, only specific percentiles of

exposure of $PM_{2.5}$ were statistically significant predictors of age-adjusted breast cancer mortality. This association is consistent with the findings of other researchers (Cheng et al., 2020; Guo et al., 2020; Hwang et al., 2020; Kim et al., 2018; Zhang et al. l., 2019), as previously discussed. The results of percentage of White women are also consistent with those observed in other studies, as previously discussed. However, percentage of adults with less than a high school diploma is inconsistent with the literature consulted, revealing a statistically significant negative association with age-adjusted breast cancer mortality. This discrepancy was discussed previously also.

$PM_{2.5}$ is a significant and ubiquitous air pollutant that consists of combustion materials, organic compounds, and some metals (EPA, 2020) that lead to oxidative damage to the DNA, increasing the oxidation markers in the body. As a result, the cellular metabolism is disrupted, causing apoptosis or molecular damage (Guo et al., 2020). Furthermore, several chemical components of $PM_{2.5}$ are associated with producing reactive oxygen species and releasing inflammatory cytokines (Xu et al., 2020). According to the EPA (2020, 2022), $PM_{2.5}$ can get into the lungs and from here to the bloodstream quickly because of the small size of its components. This makes $PM_{2.5}$ pose a greater risk to general health than other air contaminants (EPA, 2022). There is evidence that components of PM (including $PM_{2.5}$) act as endocrine disruptors with significant implications in breast carcinogenesis. For example, Darbre (2018) argued that increased traffic-related air pollution might be associated with an increased incidence of endocrine-sensitive breast cancer.

With air pollution being identified as a significant single environmental risk to human health (Guo et al., 2020; Kim et al., 2018; Prada et al., 2021; Sahay et al., 2019), the global increase in the levels of $PM_{2.5}$ (Kim et al., 2018) and it being a significant contributor to air pollution (EPA, 2022), the results of this study are vital to the prevention efforts of breast cancer. Additionally, other factors were found to be significant predictors of age-adjusted breast cancer mortality. The percentage of White women revealed a statistically significant association with age-adjusted breast cancer mortality. This observation confirms the findings of other authors in the United States, such as DeSantis et al. (2017), which corroborate the existing health disparities regarding incidence and mortality between White and Black women in the United States. Unfortunately, Black women tend to be more frequently diagnosed with more aggressive breast cancer subtypes, increasing their risk of dying compared to White women (Prakash et al., 2020; Scott et al., 2019).

Interpretation of the Findings in the Context of the Theorerical Frameworks

This study used the ecosocial theory of Krieger (2011) as one of the theoretical frameworks. This theory rejects biomedical reductionism by explaining disease distribution from a multilevel perspective, emphasizing the integration and interaction of different factors, such as biological, social, historical, and ecological perspectives. In this sense, the ecosocial theory also contributes to explaining health inequities. This study assessed the EPA-regulated pollutants considering sociodemographic factors such as income, educational level, and race/ethnicity. The results obtained reflect the impact that exposure to air contaminants has on breast cancer mortality and indicate that in

populations with a higher percentage of White women, the risk of dying from breast cancer tends to be lower.

The probabilistic epigenesis theory was also used in this study. This theory focuses on the role of the bidirectional interaction between genes and the environment. The results of the simple linear regressions for O_3, SO_2, and $PM_{2.5}$ without considering the covariates revealed the association between them and breast cancer mortality. When including the covariates, the multiple linear regressions per pollutant were consistent for O_3 and $PM_{2.5}$. The results of the multiple linear regression revealed a statistically significant association between $PM_{2.5}$, the percentage of White women, and the percent of adults with less than a high school diploma with breast cancer mortality.

The findings of this study suggest that exposure to air pollutants disproportionately affects women depending on their sociodemographic condition. In all the regression analyses conducted, $PM_{2.5}$ was revealed to be a statistically significant predictor of breast cancer mortality, increasing the risk of dying from breast cancer when exposed to it. Many of the studies consulted emphasized the history of exposure as a critical factor in breast carcinogenesis. On the other hand, a higher percentage of White women in the population was consistently observed to have a negative association with breast cancer mortality. While this study did not focus on ethnicity, the results suggest that the higher the percentage of White women, the lower the mortality. Finally, educational level, in general, was found to be associated with breast cancer mortality in many of the regression analyses conducted in this study.

Both ecosocial theory and the probabilistic epigenesis emphasize the interaction between genes and the environment, rejecting the biological reductionism in disease occurrence and distribution. It is vital to remark that $PM_{2.5}$ was consistently found to be a statistically significant predictor of breast cancer mortality. The influence of this pollutant was also found to increase the risk of breast cancer mortality when other pollutants and the covariates were added to the regression models. Such findings are essential to understand that the mortality from breast cancer is multifactorial as breast carcinogenesis, and in alignment with the theoretical framework used in this study, targeting environmental exposure is pivotal to decrease the risk of mortality when women are diagnosed with breast cancer, considering other factors as well.

Limitations of the Study

The first limitation of this study was the use of secondary data from different sources since no dataset provided all the data necessary for this study. The age-adjusted breast cancer mortality was obtained from the U.S. Cancer Statistics Visualization Tool for the period between 2015 and 2019 by US County, not allowing to obtain the data by US County per year. This forced me to obtain data for that period instead of per year. The data on air pollutants were obtained from the Outdoor Air Quality Data by the EPA. Regarding educational level, I used data from the USDA Economic Research Service, citing the U.S. Census Bureau, to replace the variable median educational level with for variables because I did not find any data on median educational level. Data on income was obtained from the SAIPE program from the U.S. Census Bureau (2021-b). Finally,

the data on White women was obtained from County Population by Characteristics provided by the U.S. Census Bureau (2021-a).

Another limitation of this study is the ecologic fallacy, which allows making associations at the population level but not at the individual level. This is important because although the study provides an understanding of the role of environmental exposure, in this case at the county level easing the work at different levels of policymaking, it cannot be used to make inferences at the individual level. Finally, US territories were not included. Thus, attention must be paid when trying to generalize these results.

Recommendations

This study excluded U.S. territories because there was no data available for breast cancer mortality or the data on EPA-regulated air pollutants was inconsistent for some pollutants and territories. In part, future studies should include them to improve the generalizability of the results found in this study. Other variables should be included. For example, future studies exploring the accessibility to health care as a covariate are of practical significance to assess the impact of this factor on breast cancer mortality when assessing exposure to air contamination. In this sense, including the utilization of breast cancer screening could improve the understanding of early diagnosis in exposed women who have genetic factors and are exposed to air pollutants.

At the policy level, the findings of this study will serve to inform policymakers and politicians at the local, State, and Federal levels of government. It is not enough to monitor the concentrations of air pollutants, particularly $PM_{2.5}$. Government officials can

use the results of this study to enact regulations and laws aimed at achieving a stricter control on air pollution through regulation of industry emissions and work to find ways to reduce the $PM_{2.5}$ pollution from motor vehicles by gradually introduce more fuel efficient and environmentally friendly vehicles. Less cars on the streets should be encouraged through promoting collective and ecological means of transportation accessible to all the population.

Likewise, it is recommended that the political actors and health authorities emphasize both primary and secondary prevention of breast cancer. Emphasis must be made on secondary prevention and make it accessible to all women by creating nationwide programs that ensure that all women have access to breast cancer screening in coordination with the State and local governments and health authorities. Regarding primary prevention, more education on environmental exposure is needed. Also, political and health authorities need to adjust the educational effort on environmental exposure to the demographic characteristics of the population taking into consideration their SES, educational level, and accessibility to health care.

All women diagnosed with breast cancer must be able to benefit from personalized medicine according to the stage and subtype of cancer. Based on the findings of this study, it is recommended that clinicians are aware of the influence that $PM_{2.5}$ has on breast cancer mortality. Not only will this help the treating physicians understand the role of environmental factors on the risk of mortality for their patients but provide them with comprehensive information and education on their treatment and the prognosis, allowing the patients and their families to make more informed decisions on

the treatment. A final recommendation for women is to prevent exposure to environmental pollutants and to exert their rights to know the level of pollution in their places of residence through their government officials. Also, to demand action through these governmental officials to take effective action to reduce air pollution. Women diagnosed with breast cancer must avoid further exposure to environmental pollution and take an active role in the decision-making process related to their treatment.

Implications for Social Change

Breast cancer is one of the most frequent life-threatening diseases among women. Given the health disparities observed in incidence and mortality between White and Black American women, this study has implications for social change. First, the results consistently indicated that exposure to $PM_{2.5}$ increases the risk of dying from breast cancer. Regulating $PM_{2.5}$ emission and maintaining levels below the maximum recommended by the EPA is essential since with each 10 percentile increase of exposure to $PM_{2.5}$, the mortality rate from breast cancer mortality increases. This suggests that, in the United States, this pollutant requires stricter control and identification of the sources across the country. As the country's environmental regulatory agency, the EPA should have all the resources necessary for this. Particular attention should be paid to regions where these air contaminant levels are higher or over the maximum permitted level. Public health officials can use the results of this study to influence the health and political leaders at the local, State, and Federal levels to pass legislation aimed at monitoring and controlling the levels of air contaminants through industry regulation and other sources of air contaminants, particularly $PM_{2.5}$.

This study confirms that White women tend to die less from breast cancer than other ethnic female groups. Such findings were consistently found in this study, together with the association between $PM_{2.5}$ and breast cancer mortality. This suggests an exposure disparity, which the governmental authorities must address at the local, State, and Federal levels to equally improve the air quality nationwide. Based on the results of this study, health authorities, public health officials, and elected government officials at different levels can target the necessities of the different communities to reduce or eliminate the existing health disparities regarding breast cancer mortality. Also, community leaders can better advocate for their communities to improve the quality of life and health of the people living in underserved areas.

Women diagnosed with breast cancer must understand the factors that increase the risk of mortality, including air pollution. Being aware of the degree of air pollution where they live will allow them and their family to make educated decisions on their treatment, based on the stage of breast cancer at diagnosis and the prognosis of their case. As previously mentioned, women and the entire population, must take an active role in the decisions made by their elective representative at all levels of government and the health authorities to control and reduce environmental pollution. A more empowered population will be conducive to a healthier population.

Conclusions

In this research, I studied the contribution of EPA-regulated air pollutants to breast cancer mortality. I included other factors such as educational level, income, and race/ethnicity. The findings of this study reveal that exposure to air pollution increases

the risk of dying from breast cancer. $PM_{2.5}$ was a statistically significant predictor of breast cancer mortality alone, combined with other air pollutants and sociodemographic factors. Other pollutants associated with breast cancer were O_3 (alone and combined with other sociodemographic factors) and SO_2 (alone). The study also showed that White women have less risk of dying from breast cancer than Black women in the United States. Therefore, it is required that public health officials work to influence other health authorities and politicians at different levels of government to improve air quality across the country by identifying, monitoring, and controlling air pollution. Emphasis must be made on reducing health inequalities to reduce or eliminate the high breast cancer mortality among Black women and the mortality from breast cancer in general in the United States.

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