Journal of Advances in Medicine and Medical Research

Volume 35, Issue 24, Page 254-259, 2023; Article no.JAMMR.110117
ISSN: 2456-8899
(Past name: British Journal of Medicine and Medical Research, Past ISSN: 2231-0614, NLM ID: 101570965)

Estrogenic Disruption by Pesticides Exposure Associated with Breast Cancer: A Systematic Review Focusing on Epigenetic Mechanisms

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JAMMR/2023/v35i245344

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/110117

Systematic Review Article

Received: 16/10/2023
Accepted: 21/12/2023
Published: 30/12/2023

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ABSTRACT

Breast cancer (BC) has been highlighted worldwide in view of its high prevalence. There are several risk factors that can be associated with the occurrence of BC, such as reproductive aspects, genetic mutations and family history. In this sense, lifestyle and environmental conditions may also be relevant - factors that are related to environmental contamination by pesticides, which in Brazil stands out, given the high consumption rates, therefore, exposure of the population. Since some types of BC associate themselves to the positive regulation of ERs, being sensitive to certain pesticides, it is valid to assume the existence, thus, an epigenetic association between cases. Thus, through a systematic review of the literature of studies reporting pesticides that alter estrogenic expression and activity and esstablish a risk for BC, focusing on epigenetic mechanisms. Descriptors were used and inclusion and exclusion criteria were established, so that 195 articles were found, and 3 were selected by the criteria. It is evident the existence of a relationship between estrogenic regulation and activity according to mechanisms that interfere in the expression of associated control genes, and the set of these factors is determinant for the increased risk of developing BC. However, the epigenetic genetic mechanisms described, associated with BC, are not standardized, and further research in the area is necessary in order to delineate more clearly the epigenetic aspects that permeate the disease.

Keywords: Pesticides; estrogen; breast cancer; epigenetic.

1. INTRODUCTION

According to the World Health Organization (WHO), by 2020 “there were 2.3 million women diagnosed with breast cancer (BC) worldwide, making it the most prevalent cancer in the world. BC occurs in all countries in women of any age after puberty, but with increasing rates in adulthood”.

Several risk factors are related to BC, including reproductive aspects, genetic mutations, and family history, for example. In addition, lifestyle and environmental and/or occupational conditions may be important in this context. The International Agency for Research on Cancer (IARC) has evaluated the carcinogenicity of numerous substances that can possibly cause BC, however, there is still insufficient evidence data, so research in this field is encouraged [1,2].

Environmental contamination by pesticides is a global concern, especially in Brazil, one of the largest consumers of pesticides [3,4]. The uncontrolled use of pesticides can cause large-scale contamination and spread to various sources that will be consumed by the population, an example of this is the presence of pesticide residues classified as persistent organic pollutants in drinking water [5].

Consequences of this long-term exposure have an impact on human health, especially in cases of cancer [3,4]. According to Ledda et al. [6], pesticide exposure may contribute to the risk of BC, especially in young women and those who had early menarche. This can be explained by the fact that some types of BC are associated with positivity for estrogen receptors (ERs) and the estrogenic activity presented by certain pesticides, such as organochlorines.

Several sources of excess estrogen have been related to the development of BC and knowing that cancer is not only a genetic disease but also an epigenetic one, that epigenetic mechanisms regulate different aspects of cancer biology and that endocrine disruptions of estrogen levels may be caused by modifications of the epigenome, it is understood that there is a relation between pesticides that disrupt this environment and the risk of developing BC [7,8]. In this context, the emerging field of epigenetics may be a promising way to establish the pathophysiological basis of this relation.

Thus, the aim of this study was to conduct a systematic literature review of studies reporting pesticides altering estrogenic expression and activity, and establishing a risk to BC, with a focus on epigenetic mechanisms.

2. METHODS

2.1 Protocol

Review protocol the systematic review followed the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) protocol, 2020.

2.2 Literature Search

Science Direct and *PubMed* was used to perform the search (February 24th, 2023). The descriptors applied were “epigenetic”, "breast cancer", “estrogen” and “pesticide”. Then, some filters were selected: English language, type of document (article), no year restriction. The studies were pre-selected by reading their titles and abstracts and separated for further analysis and extraction of data.

2.3 Inclusion and Exclusion Criteria

Inclusion criteria: studies with complete data and statistical results that observed epigenetic effects caused by exposure to different pesticides and resulted in estrogenic disruption, increasing the risk of developing BC.

Exclusion criteria: review studies, meta-analyses, commentaries, studies that contained incomplete data and/or data outside the context of the study purpose.

2.4 Biases

The possible biases were analyzed according to the limitations of each study, such as sample size, statistics of the results and the parameters involved.

3. RESULTS

In total, this search found 195 published works, of which 3 were selected according to the eligibility criteria, as detailed in Fig. 1. Three evaluators carried out the selection process of studies for review and those underwent a screening in two phases: initially, the studies were sorted by titles and abstracts and, if they were considered potentially relevant, these were moved to a later stage in which the full articles were selected for data extraction (presented in Table 1).

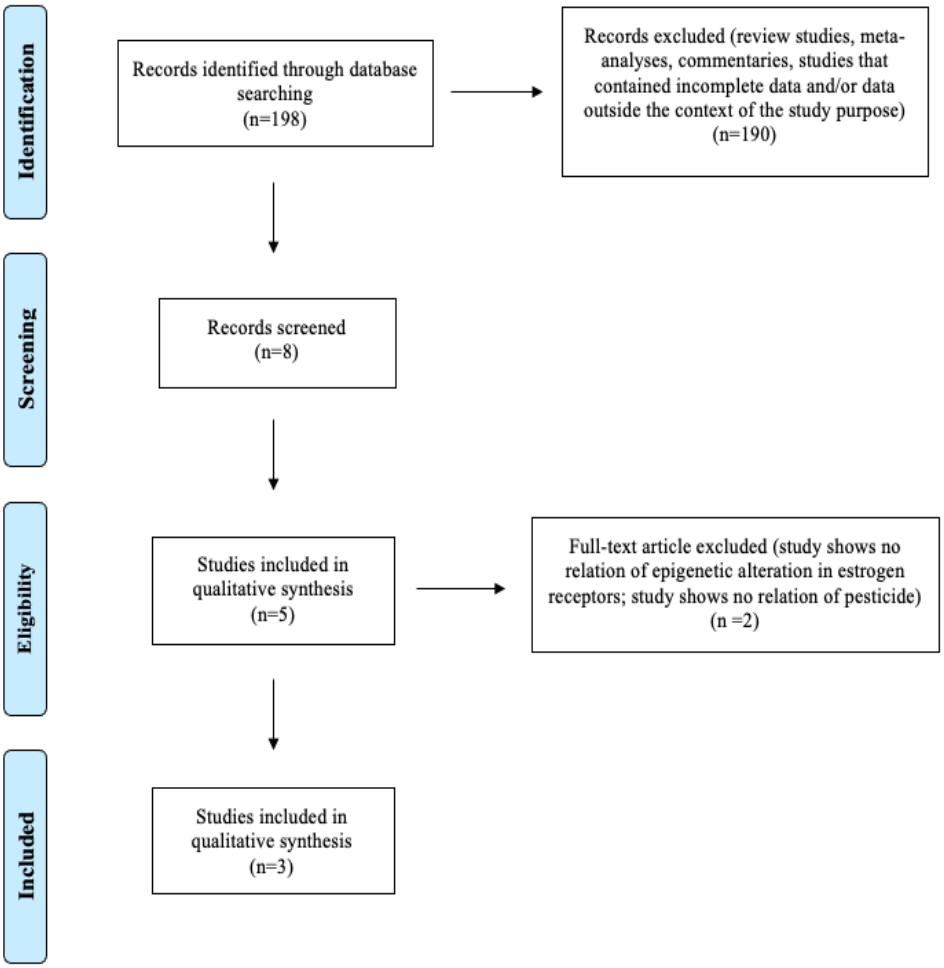

Fig. 1. Flowchart of the selection of studies adapted from PRISMA.

Table 1. Data extracted from the selected studies

Authors	Aims	Results
Lorenz et al. (2019)	Analysis of perinatal exposure to a glyphosate-based herbicide (GBH) on the expression of the ERα uterine gene in an animal model	▪ GBH positively regulates the expression of total ERα mRNA, increasing the expression of the transcript variant of ERα-O
Ghosh et al. [9]	Analysis of the potential of α-Endosulfan in the modulation of multiple epigenetic enzymes in MCF-7 cells	▪ α-Endosulfan significantly promotes the viability of MCF-7 cells ▪ Positively regulates the expression of DNMTs (DNA methyltransferases) ▪ Initially affects the global methylation status of DNA (subsequently recovered) ▪ Increases total intracellular activity of HDAC (histone deacetylase) ▪ Modulates expression and activity of arginine and lysine methylation enzymes (arginine methyltransferase 5 - PRMT5 and Enhancer of Zeste homologous 2 - EZH2) ▪ Increases the expression of histones H3 and H4, trimethylation of H3K27 (product of EZH2) and dimethylation and H4R3 (product of PRMT5) ▪ Increases the expression of five unidentified proteins whose arginine residues are dimethylated symmetrically (by increasing the level of PRMT5) ▪ Induces overexpression of the baseline level of the ERα receptor
Zou, Matsumura (2003)	Analysis of the impact of long-term in vitro exposure to ®-HCH (®-hexaclorociclohexano) in the transformation and metastatic potentials of MCF-7 cells	▪ ®-HCH increases the trend of transformation and invasion capacity ▪ Induces biochemical changes related to transformation in MCF-7 cells, such as a decline in ERα and P44/42 MAP kinase levels and a significant increase in the expression of c-ErbB2 and MMP-9 (matrix metallopeptidase 9) levels

4. DISCUSSION AND CONCLUSION

This review is based on estrogen disruption by pesticide exposure associated with BC, focusing on epigenetic mechanisms. According to Hervouet et al. [10], estrogen signaling is mediated by ERα and ERβ in hormone receptor positive BC, and during the last decade, epigenetic pathways have been related to tumorigenesis, such as modifications in gene expression regulation and chromosomal instability. In this study, the results of 3 studies are presented that showed that pesticide exposure affects estrogen regulation and activity, possibly constituting a risk for BC development.

In the study of Lorenz et al (2019) it was found that rats exposed to glyphosate-based herbicide (GBH) demonstrated higher levels of mRNA of the ERα-O variant than those of the control group, in the pre-implantation period, so that the results obtained are suggestive that specific activation of the promoter ERα-O in rats exposed to GBH may be related to the induction of ERα expression. In this sense, epigenetic mechanisms were investigated in order to elucidate which mechanisms would be associated with this induction of such that, since the DNA methylation status of the ERα-promoting regions and the corresponding ERα expression levels, when altered in addition to the normal changes that occur throughout development, may alter the expression of ERα pathologically. Therefore, the study demonstrated a decreased methylation state at the BstUI-site1 in the promoter ERα-O that correlates to higher levels of mRNA of ERα in rats exposed to GBH, suggesting that changes in the DNA methylation

level of the promoter region of ERα is an epigenetic mechanism sensitive to environmental factors, especially in early life. In addition, the authors also identified a hypomethylated site in the group exposed to GBH, a potential binding site for transcription factors E2F-1 and E47, which may also participate in the positive regulation of transcription of ERα in rats exposed to GBH. Also, findings related to histone changes with post-translational modifications in the GBH-induced ERα-O promoter could explain the increased expression of the ERα gene.

Furthermore, Ghosh et al. [9] investigated "the potential of α-Endosulfan in modulating multiple epigenetic enzymes in MCF-7 cells (breast cancer cell line), it was shown that α-Endosulfan at 1 and 10μM concentration significantly promoted the viability of MCF-7 cells, the expression of DNA methyltransferases was positively regulated, while the overall DNA methylation status was initially affected but later recovered. The total intracellular HDAC (histone deacetylase) activity was significantly increased (positive regulation of HDAC1), the expression and activity of arginine and lysine methylation enzymes, arginine protein methyltransferase 5 and Enhancer of Zeste homolog 2 were also modulated, in addition, increased expression of histones H3 and H4, trimethylated H3K27, the symmetric dimethylation of H4R3 and overexpression of the basal level of ERα were observed".

In addition to the other effects observed, the two studies indicate that the different types of pesticides studied can interfere with the regulation of estrogen expression, reflecting on its activity, but in different aspects. In the review by Rossetti et al. [11], in relation to GBHs only, it was concluded that abnormal mammary gland growth after exposure to GBHs may occur, in part, due to aberrant DNA methylation and differences in the methylation pattern of histones. Furthermore, these changes may occur even after exposure has ceased, indicating that these effects may manifest themselves over the long term.

In contrast, Mesnage et al. [12] reports that GBHs activate ERα in breast cancer cells, but only at high concentrations, suggesting exposure would not result in ER activation at typical exposure levels. However, the study did not discuss epigenetic mechanisms and the clinical relevance justifies further investigation due also to the sum of different environmental estrogenic sources.

Finally, in the study by Zou and Matsumura (2003) "the impact of long-term *in vitro* exposure to β-HCH on cell transformation and metastatic potentials of MCF-7 cells was analyzed. Continuous exposure of MCF-7 cells to β-HCH at 100 nM and 1 μM or to 17β-estradiol at 1 nM for up to 13 months not only increased their transformation tendencies, but also promoted their invasion capacity. β-HCH induced transformation-related changes in MCF-7 cells, such as a decline in ERα and p44/42 MAP kinase levels and a significant increase in the expression of c-ErbB2 and MMP-9 levels. In contrast, long-term treatment with 17β-estradiol resulted in negative regulation of ERα and p44/42 MAP kinase and positive regulation of MMP-9 only, but no changes in c-ErbB2. Such results indicate that these changes may be related to the phenotypic expression of transformed cells in BC and support the hypothesis that exposure to β-HCH is epigenetically related to progression of BC cells to an advanced stage of malignancy".

The limitations of this review are related to the few studies available in the literature that aimed to establish a relation between these changes and epigenetic mechanisms, making clear the importance of conducting studies in this context with a design focused on the investigation of epigenetic changes involved in this process [13].

PERSPECTIVES

Few publications have described the epigenetic mechanisms involved in this context, however, the results of the studies analyzed and presented in this review demonstrate that there is a relationship between estrogenic regulation and activity according to mechanisms that interfere with the expression of associated control genes, and the set of these factors is crucial to the increased risk of developing BC. Thus, it is necessary that studies be carried out in a more directed way, so that it is possible to clarify and better characterize the epigenetic mechanistic associated with BC. Still, it is clear the need for further research in the area, in order to more clearly delineate the epigenetic aspects, since all studies included in this review approached the same theme from a different perspective.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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