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ENVIRONMENTAL CARCINOGENESIS WITH A FOCUS ON BREAST AND CERVICAL CANCER: INTEGRATIVE REVIEW

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Abstract: The present work presents an integrative review with recent research on environmental factors linked to breast and cervical cancer. We sought to highlight these two types of cancer due to their relevance in female mortality in the Brazilian and global context. Given this importance, regarding methodology, 1072 articles were found after searching with descriptors for an integrative review, screening 171 articles and subsequently 80 articles on environmental carcinogenesis with a focus on breast and cervical cancer. This is a quantitative study based on data from articles already existing in research databases, to synthesize knowledge from the a priori studies carried out. Data from the research design on environmental carcinogenesis was combined and there was a systematic analysis using exclusion criteria from databases such as SCIELO, PUBMED, VHL, articles were collected, and due to similarity, articles were combined with the results presented in summary form. The results are based on the oncology literature and several works complement each other. For breast cancer, the following factors stand out: physical activity, higher levels of estrogen, progesterone and androgens, female life cycle, diet and dairy products, consumption of light, moderate and chimarrão coffee, obesity and inflammation of WAT, alcohol and tobacco, maternal breastfeeding habit, pesticides and polluted areas. In parallel, regarding cervical cancer there are: HPV, smoking, multiple partners and oral contraceptives, vaginosis and changes in the microbiota.
Keywords: Breast cancer, cervical cancer, environmental carcinogen, cancer.

INTRODUCTION

Breast cancer, epidemiologically, in the world was responsible for 2.3 million cases in 2020, representing 24.5% of total female neoplasms. In the Brazilian context, for 2023, 73,610 new cases are estimated, at a rate of 41.89 cases per 100,000 patients. Deaths in Brazil, in 2020, were 11.84 deaths per 100,000, with the highest rates concentrated in the Southeast and South regions. In the country, for 2023, 17,010 cases of cervical cancer are projected, which symbolizes 13 25 cases per 100,000 women, being the third highest incidence of cancer in Brazilian women and the fourth highest mortality rate in the country (COUTO et al., 2017; COUTO et al., 2019; INCA, 2021; INCA, 2022).

Cancer is defined as a malignant tumor, the nomenclature comes from "crab", one that obstinately adheres to the desired location. Malignant neoplasms derive from mutations whose factors can be endogenous or exogenous and which, finding an environment favorable to carcinogenesis, cause the cancerous state. Exogenous agents are the focus of the project as they stimulate primordial neoplastic processes: activation of proto-oncogenes to oncogenes and silencing of tumor suppressor genes – which interfere with apoptosis and cell proliferation either through mutations in the DNA or through changes in the epigenetic pattern (ABBAS et al., 2008; GOMES, 2014).

Environmental factors are grouped into three groups: chemical agents (chemicals, hormonal changes), physical agents (ultraviolet radiation, X-rays and gamma rays) and biological agents (viruses, bacteria, helminths). The influence on cancers commonly varies in each of the three groups, and may overlap in neoplastic occurrence (MEDRADO, 2015; GONZÁLEZ MORENO et al., 2022).

The main biological agent of cervical cancer is the Human Papilloma Virus (HPV), since its presence in the female genital tract can cause malignant lesions in the uterine cervix. HPV DNA interconnects with cellular DNA, inactivating genes and promoting abnormal cell proliferation. Other neoplastic factors such as smoking, multiple partners, use of oral contraceptives, vaginosis and changes in the microbiota are potential causes of cervical cancer (MEDRADO, 2015; YURTÇU et al., 2022).

In parallel, in breast cancer, it is observed that higher levels of endogenous estrogen are associated with an increased risk of the disease, as well as lower levels of sex hormone binding globulin (SHBG). In addition to the factors mentioned above, obesity and lack of physical exercise can promote inflammation of breast white adipose tissue (WAT) that predisposes to breast cancer; diet and dairy products, alcohol and tobacco, maternal breastfeeding habits, contact with pesticides and polluted areas are influential elements for breast neoplasia (JIANG et al., 2021; SWAIN et al., 2021).

According to demographic factors, breast cancer affects 100 times more women compared to men; the most affected group are women between 35 and 75 years old; After the age of 75 this tendency tends to reduce. Epidemiologically, around 10% of patients with a history of breast cancer in first-degree relatives are affected. The hereditary genetic change normally occurs in the BRCA1 or BRCA2 genes. The woman's pathological history is also a fundamental piece of information: previous invasive breast cancer, that is, cancer cells that appear in the breast duct but do not develop, increases the risk of a new cancer by 0.5 to 0.7%, in addition to benign breast diseases, such as proliferative breast lesions that can increase the risk of developing cancer by up to 6 times (BURANELLO et al., 2018; MARTINEZ-CANNON, et al., 2021).

Protective and preventive factors are fundamental and are guided by knowledge of the environmental factors linked to breast and cervical cancer: inhibition of smoking, alcohol consumption, as well as excessive coffee. On the contrary, physical activities, breastfeeding, weight loss, hormonal control and complementary exams are essential to prevent such cancers (HARFOUCHE et al., 2017; ZHU; TIAN; GAO, 2019; MUTEBI et al., 2020; VILLARREAL- GARZA et al., 2021; LI et al., 2021).

Based on the information presented, this work aimed to understand the impacts of environmental factors on cervical and breast carcinogenesis. Through the analyses, we sought to favor the oncology area through the knowledge acquired and encourage the strengthening of public policies, benefiting health and encouraging more research in the area covered.

METHOD

This is an integrative review of the reading carried out in virtual databases: Virtual Health Library (VHL), PUBMED, SCOPUS and MEDLINE. The inclusion criteria were articles published between 2018 and 2022, in English and Portuguese, being analyzed during the period from March to December 2022.

The search was carried out using the keywords in English and Portuguese: "breast cancer", "cervical cancer", "environmental carcinogenesis", "cancer and environment "(cancer and environment)" and "environmental factors cancer".

The selection of articles occurred in 3 stages. Initially, 1,072 articles were analyzed and those that presented repetition of the theme, inconclusive data, experimental trials, dissertations, theses and conference abstracts were excluded. In the end, 171 articles were selected. The 171 articles were analyzed in full

(or in summary) and 80 studies were found, due to the repetition of environmental factors that still existed for the two types of cancer analyzed, repetitions of information between articles, inconclusive or redundant analyses. From this final count, a new stage in the project began, which consisted of re-reading the data present in these articles and final structuring of the research.

Screening	Number of articles
First	1072
Second	171
Third	80
Total for analysis	80

Table 1: methodology used in the work

RESULT

In this study, several factors linked to breast cancer were found, ranging from dietary and behavioral habits, female hormonal cycle (climacteric, menopause, post-menopause), gestational habits and contact with pesticides and pollution (TIEZZI et al., 2019); (VARUZZA et al., 2019); (TEIXEIRA; ARAÚJO NETO, 2019); (BOURLON et al., 2021). Table 2 presents the risks linked to environmental factors for breast cancer.

PHYSICAL ACTIVITY, HIGHER LEVELS OF ESTROGENS, PROGESTERONE AND ANDROGENS

High and moderate physical activity influences hormonal levels and sex hormone binding globulin (SHBG). High hormonal levels of estrogen, progesterone and androgens favor cancer, therefore, by reducing these levels with physical activity, the risk of breast carcinogenesis is reduced. Conversely, physical activities increase SHBG, which at a high rate prevents malignant breast neoplasms. Therefore, intense and moderate physical exercise has been proven to reduce circulating hormones and, therefore,

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Environmental factors breast cancer	Risk	Relation of articles
Physical activity	It decreases	(SWAIN et al., 2021; JIANG, et al., 2022; MOTOKI et al., 2021 ZAKARIA; SHAW, 2017; MACHADO, 2018; UCHIHARA, et al. 2018; VITELLI-STORELLI et al., 2020; MOTOKI et al., 2021; BORTOLOZO et al., 2021)
Higher levels of estrogens, progesterone and androgens	It increases	(ZAKARIA; SHAW, 2017; MACHADO, 2018; UCHIHARA, et al. 2018; LAMB et al. 2019; VITELLI-STORELLI et al., 2020; MOTOKI et al., 2021;
Lower levels of sex hormone binding globulin (SHBG)	It increases	BORTOLOZO et al., 2021;)
Light, moderate coffee consumption	It decreases	(CALIXTO et al., 2020; KIM et al., 2021)
Obesity	It increases	ZAKARIA; SHAW, 2017; KOPS et al., 2018; GODINHO, 2018; LAMB et al., 2019; GONZÁLEZ, et al.,2019; ZHU; TIAN; GAO, 2019; PARK et. al, 2021; FUKUI et al., 2021, CHENG et. al 2021; CASTRO et. al 2022)
WAT inflammation	It increases	(ZAKARIA; SHAW, 2017; KOPS et al., 2018; GODINHO, 2018; LAMB et al., 2019; PARK et. al 2021; FUKUI et al., 2021)
Diet	It varies	(MIGOWSKI, et al., 2018; DIERSSEN-SOTOS et al., 2020; ESCRICH et al., 2020; GARCÍA et al., 2020; WIGGS et al., 2021; LA TORRE et al., 2021; MÄNNISTÖ et al, 2021; CHO, et al., 2021; SHEIKHHOSSEIN, et al. 2021; BOTTERI et, al. 2021; FARVID et al. 2021)
Alcohol	It increases	(GRAM et al., 2021; BOTTERI et, al. 2021
Tobacco	It increases	(GRAM et al., 2021; BOTTERI et, al. 2021
Dairy products	It decreases	(DIERSSEN-SOTOS et al., 2020; ESCRICH et al., 2020; WIGGS et al., 2021; LA TORRE et al.,2021)
Breast-feeding	It decreases	(VILLARREAL-GARZA et al., 2017; RODRIGUES et al., 2021; SILVA, et al, 2022)
Pesticides	It increases	(SANTOS, 2018; CARDOSO et al.,2018; COUTO et al., 2020; MONTANA, 2020; KASS et al., 2020; GUIDA et al., 2021; RODRÍGUEZ et al., 2021; CASTRO et al., 2022).
Chimarrão	It decreases	(CALIXTO et al., 2020)
Pollution	It increases	(CALEFFI, et al.,2018; CALVO et al.,2018; O'CALLAGHAN-GORDO et al., 2018; GARCÍA-PÉREZ et al., 2018; MONTANHA et al.,2020; MARTÍNEZ-RAMÍREZ et al., 2021)
Female life cycle	It varies	(ZAKARIA; SHAW, 2017; HARFOUCHE et al., 2017; VILLARREAL-GARZA 2017; BURANELLO 2018; MACHADO, 2018; UCHIHARA, et al. 2018; COUTO et al. 2019; LAMB et al. 2019; PINTO et al., 2021; VITELLI- STORELLI et al., 2020; MOTOKI et al., 2021; BORTOLOZO et al., 2021; VILLARREAL-GARZA et al. 2022; MARTINEZ-GARZA et al., 2021; GONZÁLEZ et al., 2021)

Table 2: Analysis of the risks linked to environmental factors of breast cancer

prevent cancer (ZAKARIA; SHAW, 2017; MACHADO, 2018; UCHIHARA, et al. 2018; VITELLI-STORELLI et al., 2020; MOTOKI et al. al., 2021; BORTOLOZO et al., 2021).

FEMALE LIFE CYCLE

The main estrogens circulating in the body are estrone, estriol and estradiol, with estradiol being the most biologically active. The general increase in circulating hormones increases the risk of breast cancer, which occurs between 35 and 45 years of age during the female fertile period. Postmenopausal women convert androstenedione into estrone, which can be metabolized in the liver via cytochrome P450 enzymes. The 2-hydroxylation pathway of both estrone and estradiol demonstrated a protective effect against the development of breast neoplasia; Furthermore, in post-menopause, circulating hormones are in lower concentration, which means there is a reduction in cancer occurrence at the age of 75 (CARDOSO et al., 2018; PINTO et al., 2019; MACHADO, 2018; BREYER et al., 2018; VITELLI-STORELLI et al., 2020).

DIET AND DAIRY PRODUCTS

In general, a balanced diet (whole foods, grains, seeds, legumes, berries, cruciferous vegetables) reduces the predisposition to breast cancer. Components of dairy products such as calcium, vitamin D, rumenic acid, butyric acid, fatty acids and whey protein reduce the incidence of breast neoplasia (DIERSSEN-SOTOS et al., 2020; ESCRICH et al., 2020; WIGGS et al., 2021; LA TORRE et al., 2021).

CONSUMPTION OF LIGHT, MODERATE AND CHIMARRÃO COFFEE

Coffee in moderate doses has the ability to express its elements as polyphenols that mediate anticancer effects. An example of polyphenols is chlorogenic acid, which represents 3% of coffee powder and reduces reactive oxygen species, leaving the physiological environment unfavorable for cancer: it prevents inflammation and angiogenesis through cascades involving NF-κB, EGFR and VEGF. Another innovative element is chimarrão, which has antioxidative properties, interfering with the inflammatory process and altering pathogenesis (CALIXTO et al., 2020; KIM et al., 2021).

OBESITY AND WAT INFLAMMATION

Adipose tissue secretes cytokines, estrogen hormone and adipokines. In obese women, the amount of this tissue is greater and, therefore, cytokine cascades will occur in greater concentration due to the greater production of cytokines, in addition to increasing the rate of circulating hormones. Another important factor is inflammation of breast white adipose tissue (WAT), this inflammation is more common in people with obesity, but may be present in those with a normal BMI. Defense cells (macrophages, neutrophils, CD4 T lymphocytes) are expressed in greater quantities in women with excess adipose tissue or WAT inflammation (ZAKARIA; SHAW, 2017; KOPS et al., 2018; GODINHO, 2018; LAMB et al., 2019; PARK et al., 2021;

ALCOHOL AND TOBACCO

Smoking cessation correlates with an improvement in the body's systemic effect, since carcinogenic substances present in cigarettes are absorbed by the body, therefore, it is related to a reduction in the onset of neoplastic processes. In the same sense, alcohol consumption increases the risk of breast cancer and this occurs, especially in postmenopause (GRAM et al., 2021).

MATERNAL BREASTFEEDING HABIT

Breastfeeding works by altering the activation status of the estrogen receptor (ER), meaning less estrogen is signaled to the breast cells. Some physiological mechanisms such as sudden involution of the breast and epigenetic reprogramming can, together, affect the pool of progenitor cells and favor cancer if breastfeeding is not encouraged (VILLARREAL-GARZA et al., 2017; RODRIGUES et al., 2021; SILVA, et al, 2022).

PESTICIDES AND POLLUTED AREAS

The number of cases of women with breast cancer who are exposed to pesticides has increased exponentially and studies have shown that contact with these chemical compounds alter defense mechanisms against tumors and the consequent onset of the disease. Contact often occurs during farming, handling compounds, spraying or even cleaning contaminated clothing. Some pesticides such as DDT, polychlorinated biphenyls (PCBs), dioxins, hexachlorocyclohexane (HCH) and hexachlorobenzene are considered organochlorine pesticides. The known

worldwide and banned in many countries, DDT, is considered a human carcinogen and tumor promoter. Both DDT and its metabolite DDE are fat-soluble, undergo a process of bioaccumulation at higher levels in body adipose tissue and have been associated with the emergence of liver cancer, respiratory tract cancer and lymphomas, presenting effects on the breast that are correlated to those resulting from exposure to estrogen. (O'CALLAGHAN-GORDO et al., 2018; GARCÍA-PÉREZ et al., 2018; MARTÍNEZ-RAMÍREZ et al., 2021). Regarding cervical cancer, the environmental factors represented in Table 3 were found.

HPV

In the structural axis of the review there is cervical cancer, intensely articulated in the environment due to its triggering factor being derived from the persistent infection of the HPV virus in the cervix. HPV is small, around 55nm, contains double DNA with region L (distal) that encodes capsular elements, region E (proximal) - the latter is fundamental for the environmental carcinogenesis of this virus by controlling the transcription of the genetic code inside the cell infected and another LCR control region (NAKAGAWA; et al., 2010).

In lesions of the cervix and those related to cervical cancer, the HPV genome is linked to chromosomes 13 and 15. As a result, there is deregulation of elements in the E region of HPV, mainly those that interact with tumor suppressor genes such as p53 and Rb proteins. The evasion of tumor suppressors is an efficient neoplastic mechanism: because the evacuation of factors such as the RB gene - which encodes the Rb protein responsible for cellular genetic silencing and the TP53 suppressor gene - which favors cellular apoptosis in case of stress - causes cellular chaos and replication intense, favoring cervical cancer (NAKAGAWA; et al., 2010; BARCELOS et al., 2017; MARTÍNEZ-RAMÍREZ et al., 2018; LOPES; RIBEIRO,

2019; ROZARIO et al., 2019; VALE et al., 2019; REICHHELD et al., 2020; 2021; FISCHER et al., 2022;

SMOKING

It is not known for certain how tobacco influences cervical cancer, but it is well known that nicotine causes depression of Langerhans cells, which may be related to immunosuppression. Exposure, age of onset, period and frequency of cigarette consumption appear to influence the incidence of cervical cancer. What influences on a large scale is epithelial exposure to nicotine and its metabolic derivatives (BARCELOS et al., 2017; LOPES; RIBEIRO, 2019; VALE et al., 2019; PEREIRA et al., 2020; RIBEIRO et al., 2021).

MULTIPLE PARTNERS AND ORAL CONTRACEPTIVES

Studies show an increase in HPV infection in women who have unprotected sex with multiple partners. As it is a virus that is frequently transmitted sexually, it affects women who use oral contraceptives and who only aim to prevent pregnancy. The viral production cycle follows a sequence: adsorption, penetration, transcription, translation, DNA replication and maturation. Oral contraceptives that are mandatory steroid hormones (estrogen and progesterone) are related to increased transcription of HPV types. These hormones, in particular progesterone, inhibit the transcriptional transactivation of genes measured by p53 (tumor suppressor), making it difficult to interrupt the cell cycle with damage and apoptosis (BARCELOS et al., 2017; CADET et al., 2017; SZALACHA, et al., 2017 MARTÍNEZ-RAMÍREZ et al., 2018; RIBEIRO et al., 2021;

Environmental factors of cervical cancer	Risk	Relation of articles
HPV virus	It increases	(BARCELOS et al., 2017; MARTÍNEZ-RAMÍREZ et al., 2018; LOPES; RIBEIRO, 2019; ROZARIO et al., 2019; VALE et al., 2019; REICHHELD et al., 2020; CLARO; at al., 2021; BIAZIN, 2021; RIBEIRO et al., 2021; CASTANON et al., 2021; ELFSTRÖM et al., 2021; VAN KEER et al., 2021; FISCHER et al., 2022; MIYAJI et al., 2022)
Smoking	It increases	(BARCELOS et al., 2017; LOPES; RIBEIRO, 2019; VALE et al., 2019; PEREIRA et al., 2020; RIBEIRO et al., 2021)
Use of oral contraceptives	It increases	(CADET et al., 2017; SZALACHA et al, 2017); REICHHELD et al., 2020);
Multiple partners	It increases	(BARCELOS et al., 2017; MARTÍNEZ-RAMÍREZ et al., 2018; LOPES; RIBEIRO, 2019; PEREIRA et al., 2020; RIBEIRO et al., 2021; ARAFAH et al., 2021)
Vaginosis and changes in the microbiota	It increases	(BARCELOS et al., 2017; MARTÍNEZ-RAMÍREZ et al., 2018; ROMERO-MORELOS et al., 2019; LOPES; RIBEIRO, 2019; VALE et al., 2019; CASTANON et al., 2021; CHATZISTAMATIOU et al., 2021); (MIYAJI et al., 2022)

Table 3: Analysis of the risks linked to environmental factors of cervical cancer

VAGINOSIS AND CHANGES IN THE MICROBIOTA

The microbiota and its imbalance are decisive for the vaginal microenvironment, some bacteria such as: *Atopobium vaginae* and *Gardnerella vaginalis,* promoters of vaginal bacterial infection, are favorable to persistent lesions on the cervix (BARCELOS et al., 2017; MARTÍNEZ-RAMÍREZ et al., 2018; ROMERO-MORELOS et al., 2019; LOPES; RIBEIRO, 2019; VALE et al., 2019; CASTANON et al., 2021; CHATZISTAMATIOU et al., 2021; MIYAJI et al., 2022).

DISCUSSION

The results found allowed us to understand how much environmental factors impact the process of carcinogenesis, promoting or hindering it. In particular, breast cancer has environmental factors that increase the risk of the disease, such as: obesity and WAT inflammation, lack of physical activity, female reproductive hormonal cycle, alcohol consumption, smoking, diet and exposure to pesticides and polluted environments. Breastfeeding, for example, acts inversely by reducing neoplastic predisposition by correlating with estrogen receptors; other environmental factors such as a balanced diet, moderate coffee, physical activity and post-menopause, together, reduce the chances of breast carcinogenesis (DINIZ et al., 2017; ZAKARIA; SHAW, 2017; GARCÍA-PÉREZ et al., 2018; ESCRICH et al., 2020).

The factors correlate with each other when analyzing the rate of free hormones estrone, estriol and estradiol that predisposes to breast cancer, but can be reduced with physical activity, reducing the rate of obesity in society and reducing WAT inflammation; In parallel, the physiological cycle in which the woman finds herself is fundamental: in the reproductive phase (25-35 years) hormonal levels are higher, which normally influences the increase in circulating hormones, however, the opposite occurs at 75 years of age. in female postmenopause that reduces hormones.

The habit of breastfeeding is also related to hormonal levels: breastfeeding reduces the activity of estrogen receptors (ER), influencing the androgen uptake of breast cells. Other behavioral factors are important in preventing breast cancer, such as a balanced diet, consumption of antioxidants such as coffee and chimarrão and non-exposure to polluted environments and pesticides.

In the same sense, cervical cancer is related to habits: unprotected sexual activity that can transmit the HPV virus, responsible for generating neoplastic lesions, smoking and

prolonged exposure to contraceptive pills (ZAKARIA; SHAW, 2017; VRINTEN et al., 2019; BIAZIN, 2021; RIBEIRO et al., 2021;

FINAL CONSIDERATIONS

Thus, notoriously, a reason for doubts and secular concerns, cancer has multiple causes such as external (environmental) and internal (genetic inheritance). This way, the risk factors acquired throughout life through exposure to physical, chemical and biological agents are environmental ones, the focus of the work in question. These external agents interfere with the structure of the cell's genome by promoting mutations in normal genes, stimulating proto-oncogenes to become oncogenes, silencing tumor suppressor genes, and can also alter the pattern of gene expression through epigenetics.

In particular, breast cancer has environmental factors such as: obesity and WAT inflammation, physical inactivity, alcohol consumption, smoking, female hormonal cycle, breastfeeding habits of pregnant women, diet and exposure to pesticides and polluted environments. In the same sense, cervical cancer is related to unprotected sexual activity that proliferates HPV, smoking and prolonged exposure to contraceptive pills.

Therefore, according to the data analyzed during the research, we can understand the concept of breast and cervical cancer in its magnitude and that several factors contribute to the emergence of neoplastic disease, not just genetic inheritance. Studies show that the number of positive diagnoses for cervical carcinogenesis and breast cancer could be reduced by including actions such as healthy eating, physical exercise, encouraging breastfeeding, reducing alcohol and tobacco in women's routine, in addition to reducing the prolonged action of pills contraceptives - the latter still controversial and conflicting between studies (PAPPA, et al., 2021; MIYAJI et al., 2022).

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