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EPIDEMIOLOGY AND RISK FACTORS FOR BREAST CANCER: A LITERATURE REVIEW

LITERATURE REVIEW

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ABSTRACT

A brief context: Breast cancer is the malignant neoplasm that most affects and kills women worldwide. The incidence and mortality rates of this important form of cancer grow year after year in a linear fashion. Despite numerous advances in science and technology in basic and clinical research, breast cancer remains an important global public health problem. Guiding question: Currently, we understand that breast cancer is a multifactorial disease, therefore, greater recognition of risk factors is important for its prevention. General objective: The main objective of this narrative review article was to discuss the factors that influence and contribute to the initiation, maintenance and progression of breast cancer. Methodology: In this work, we identified scientific articles through the “PubMed” database. The search terms “breast cancer” were used in combination with specific terms covering the different epidemiological patterns and factors that favor or prevent this malignancy, as appropriate. Main results: The following text describes epidemiological data at the global and national level (Brazil) and the main modifiable (physical inactivity, alcohol consumption, smoking, number of pregnancies, diet and long-term pharmacological interventions) and non-modifiable risk factors (age, sex, ethnicity, exposure to endogenous steroid hormones, benign proliferative lesions in the mammary gland, and genetic predisposition) to breast cancer. Conclusion: This work consists of a brief review of the epidemiology and risk factors for breast cancer, serving as a quick consultation tool for the multidisciplinary health team and for all women, especially those at higher risk of developing this disease, since many risk factors are preventable.

Keywords: Breast cancer, Risk factors, Epidemiology, Malignant neoplasm, Breast disease.

INTRODUCTION

Cancer has become a leading cause of morbidity and mortality worldwide in recent decades, largely as a result of demographic, economic and epidemiological changes (BRAY *et al.*, 2012; HARBECK *et al*., 2019). Despite the many efforts of the World Health Organization (WHO) and the International Agency for Research on Cancer (IARC) in the implementation of technical guidelines to develop and execute cancer prevention and control activities in the context of public policy approaches, it is estimated that worldwide annually, there are 19.6 million new cases and 10.2 million deaths from cancer (FERLAY *et al*., 2021; PRAGER *et al*., 2018). According to GLOBOCAN (Global Cancer Incidence, Mortality and Prevalence), the most commonly diagnosed solid tumors globally in the general population (i.e., men and women) were breast (2.26 million), lung (2.21) and prostate (14.1) and the most lethal tumors were lung (1.79 million), liver (830.000) and stomach (769.000) (FERLAY *et al*., 2021).

In the current context, it is observed that cancer is overtaking cardiovascular diseases as one of the main causes of death, due to the increasing number of new cases of the disease worldwide, thus putting an enormous pressure on the health systems of countries of all socioeconomic levels, especially in countries with low Human Development Index (HDI) (CAO *et al*., 2017; PRAGER *et al*., 2018). Additionally, in the USA alone, the financial burden of cancer care has increased substantially over the past two decades, jumping from $57 billion in 2001 to approximately $170 billion in 2020 according to the National Cancer Institute (NCI) (ALTICE *et al*., 2017; MARIOTTO *et al*., 2011).

In this work, we briefly describe the epidemiology and the main risk factors for breast cancer, based on our guiding question. Furthermore, the general objective of this narrative review article was to discuss the factors that influence and

contribute to the initiation, maintenance and progression of breast cancer, due to its clinical relevance as the malignant neoplasm with the highest incidence and mortality in women worldwide. world. For this, the methodology used in this study was to identify scientific articles through the “PubMed” database with greater relevance in clinical practice.

ARTICLE SEARCH AND SELECTION STRATEGY

This work is a narrative review of the literature (non-systematic), in which scientific articles referring to epidemiological aspects and the main risk factors of breast cancer were selected. For this, scientific articles were identified through the “PubMed” database written only in English. Relevant articles were also identified by searching the authors' files and reviewing other articles and their respective bibliographies.

The search terms “breast cancer” were used in combination with specific terms covering the different epidemiological patterns and factors that favor or prevent this malignancy, as appropriate. Scientific articles were selected primarily on the basis of their clinical applicability, using the following types of study: Systematic reviews, meta-analyses, comprehensive reviews and original studies, published in the last 6 years (60.34% of selected articles). However, we did not exclude older, commonly referenced and highly regarded publications in this area of knowledge (39.66% of selected articles). All references cited in this article have been revised. The final list of references was generated based on originality and relevance to the relevant scope of this review.

EPIDEMIOLOGY OF BREAST CANCER

In the female population, breast cancer is the most common malignancy in the world (154 out of 185 countries), with the exception of West Africa, where cervical cancer is the most prevalent. In 2018, an estimated 2.1 million women were

diagnosed with breast cancer, with a new case diagnosed approximately every 18 seconds. In addition, breast cancer also has the highest cancer mortality rate in women worldwide (103 out of 185 countries), with an estimated 626.600 deaths from the disease, with the main exceptions being Northern Europe, North America North and Sub-Saharan Africa, where the leading cause of death is cervical and/or lung cancer (BRAY *et al*., 2018; FERLAY *et al*., 2019; TORRE *et al*., 2017).

While breast cancer deaths have declined in high HDI countries since the 1990s, death rates in other historically low- and middle-income countries have increased, largely due to barriers to access to diagnosis and treatment and the economic burden (BELLANGER *et al*., 2018). Although described by the Egyptians more than 3.500 years ago, breast cancer remains an important public health dilemma, especially due to urbanization, economic development, changes in cultural and lifestyle patterns, ineffective prevention and awareness campaigns, significant deficits. of trained human resources and disparities in access to high-quality cancer care (AKRAM *et al*., 2017; HARBECK *et al*., 2019; LUKONG, 2017).

In Brazil, according to the latest publication for the triennium 2020-2022 produced by the Division of Surveillance and Situation Analysis of the Prevention and Surveillance Coordination of the National Cancer Institute (INCA), an estimated 66.280 new cases of breast cancer per year, with an estimated risk of 61.61 cases per 100.000 women. Disregarding non-melanoma skin cancers, this type of malignancy is the second most common in the general population and the one with the highest incidence among Brazilian women, accounting for approximately 29.7% of all cancer cases in this population, more than the average worldwide is estimated at about 24.2%. In addition, breast cancer is the deadliest malignancy among Brazilian women, accounting for an estimated 18.068 annual deaths, representing 16.4% of cancer-related causes of death (SCHILITHZ *et al*., 2019).

BREAST CANCER RISK FACTORS

Breast cancer, not unlike many other tumor types, has a complex and multifactorial etiology in its history. Furthermore, these tumors exhibit impressive intertumoral heterogeneity, such as epidemiologic and clinical stage levels, and intratumoral heterogeneity, occurring at morphologic, genomic, transcriptomic, and proteomic levels, ultimately culminating in distinct clinical courses and major challenges in diagnosis, prognosis. and treatment of different individuals (AKRAM *et al*., 2017; SKIBINSKI; KUPERWASSER, 2015; TUASHA; PETROS, 2020; TURASHVILI; BROGI, 2017).

Basically, the risk factors for breast cancer are divided into intrinsic factors known as non-modifiable, such as age, sex, race, exposure to endogenous steroid hormones, benign proliferative breast lesions and genetic susceptibility, and those known as modifiable external factors. or potentially modifiable, which are conditioned by lifestyle (inactivity, alcohol consumption, smoking, and number of pregnancies), diet, and long-term pharmacological interventions, such as the use of oral hormonal contraceptives or hormone replacement therapy (KAMIŃSKA *et al*., 2015; RIVENBARK; O'CONNOR; COLEMAN, 2013). The identification of modifiable or potentially modifiable risk factors can facilitate the development of attractive preventive strategies at the primary health care level, implemented by researchers and multidisciplinary professionals, to reduce the incidence of breast cancer (GUERRERO *et al*., 2017; KOLAK *et al*., 2017).

Genetic predisposition: Family history is an important and well-established risk factor for inherited genetic predispositions in the development of breast cancer, accounting for up to 10% of all newly diagnosed cases (HOWELL *et al*., 2014; SHIOVITZ; KORDE, 2015). These individuals with susceptibility to the development of breast cancer inherit mutations with an autosomal dominant pattern in tumor suppressor genes or proto-oncogenes, conferring an increased

risk of breast cancer at an early age, bilateral breast cancer and male breast cancer (KLEIBL; KRISTENSEN, 2016; MELVIN *et al*., 2016).

Germinated Mutations: The most common germline mutations occur in the BRCA1 and BRCA2 tumor suppressor genes, which play a key role in maintaining genomic instability, due to their roles in identifying and repairing DNA damage and regulating cell proliferation (KOTSOPOULOS, 2018; ROY; CHUN; POWELL, 2012). However, due to the large structure of both genes, in addition to the complexity of their numerous functions, the penetrance of these genes will depend on the type of mutation, genetic variants and exogenous factors, and therefore is not a direct indicator of disease (MEHRGOU; AKOUCHEKIAN, 2016). In a recent prospective analysis using a cohort of approximately 4.000 women carrying deleterious BRCA1 and BRCA2 germline mutations, an average cumulative risk of breast cancer at age 80 years of 72% and 69%, respectively, was reported (KUCHENBAECKER *et al*., 2017). Other genes have been identified associated with an increased risk for familial breast cancer, these include high penetrance genes such as TP53, PTEN, CDH1, STK11, RAD51C and RAD51D (LARSEN *et al*., 2014). The rest of the cases are distributed among moderate or low penetrance genes, such as CHEK2, BRIP1, ATM, and PALB2 (LARSEN *et al*., 2014; SHIOVITZ; KORDE, 2015). In Brazil, Li-Fraumeni syndrome, which is an autosomal dominant genetic disorder, inherited by a mutation in TP53 with substitution of an arginine for a histidine at codon 337 (R337H), predisposing patients to a wide variety of early-onset tumors, among them breast cancer, has been attracting the attention of many geneticists and oncologists, due to its high prevalence, mainly in the south and southeast regions, being present in 0.3% of these local populations (ANDRADE *et al*., 2016, 2017).

Somatic Mutations: However, the vast majority of breast tumors occur sporadically due to mutations and genomic instability, epigenetic phenomena, acquisition of mechanisms of resistance to programmed cell death, increased cell proliferation and alterations in the processes of differentiation and motility in

somatic cells constituting the tissue of the breast mammary gland (FENG *et al*., 2018; HANAHAN, 2022).

Sex: Breast cancer is primarily (but not exclusively) a disease of women (HOWELL *et al*., 2014). Male breast cancer cases are rare, accounting for less than 1% of all newly diagnosed events (OTTINI *et al*., 2010). Despite this sporadic occurrence, some analyzes of epidemiological data suggest that the frequency of cases has increased in the last 3 decades (CHEN *et al*., 2020).

Age and ethnicity: The incidence of breast cancer is commonly seen in menopausal women (BAN; GODELLAS, 2014). In contrast, younger women (<40 years) were less affected (ANGAHAR, 2017; BAN; GODELLAS, 2014). In 2016, it was reported that approximately 71% of breast cancer-related deaths in the United States occurred in women over the age of 40, suggesting that aging inevitably increases the risk of breast cancer (SIEGEL; MILLER; JEMAL, 2017). In general, Caucasian women are more likely to develop breast cancer than African American women, while Asian and Hispanic women have a lower risk for this malignancy (DESANTIS *et al*., 2017; SUN *et al*., 2017).

Hormonal exposure: Due to early menarche and late menopause, the longer the breast is exposed to endogenous steroid hormones will directly affect the higher risk of breast cancer (ANGAHAR, 2017). Women in whom menarche occurred before age 12 years, the cumulative risk is 6% for breast cancer for each year before the age of puberty (DAY *et al*., 2017). Likewise, for every year of complete menstrual cycle, especially after age 55, the risk of breast cancer increases by 6% (DAY *et al*., 2015). However, women who underwent prophylactic bilateral oophorectomy (induced menopause) at age 40 had a 50% lower risk of breast cancer compared to women who entered menopause naturally (ANJUM *et al*., 2017; BAN; GODELLAS, 2014).

Reproductive factors: Reproductive factors such as age at first pregnancy, breastfeeding, nulliparity and use of oral hormonal contraceptives can affect breast cancer risk (HOWELL *et al*., 2014; KOLAK *et al*., 2017). Women who had their first full-term pregnancy before age 20 had a 40% lower risk of breast cancer compared to women who conceived after age 35 (KAMIŃSKA *et al*., 2015; RUSSO; RUSSO, 2011). Proposed explanations include, altered sensitivity of the mammary gland to subsequent hormonal exposure; reduced number of stem cells, thus eliminating targets for malignant transformation; and changes in gene expression patterns, resulting in decreased mammary cell proliferation and increased differentiation (HARBECK *et al*., 2019). Among nulliparous women, epidemiological studies have shown a fourfold increased risk of breast cancer during menopause compared with women who conceived at term at a young age (RUSSO; RUSSO, 2011). Prolonged lactation confers a protective effect against the development of cancer, and it is estimated that for each year of breastfeeding, a risk reduction of approximately 4% (BERAL *et al*., 2002; GIUDICI *et al*., 2017).

Exposure to exogenous hormones: The relationship between the use of oral hormonal contraceptives (estrogen and progesterone) and the risk of breast cancer has not been fully elucidated. Overall, some epidemiological studies suggest that women who use these exogenous hormone-containing oral contraceptives have an approximately 20% higher risk of breast cancer compared to women who do not use this contraceptive method (BAN; GODELLAS, 2014; HUNTER *et al*., 2010; MØRCH *et al*., 2017). Hormone replacement therapy has been used to alleviate menopausal symptoms and prevent osteoporosis, however, it increases the risk of breast cancer, and the incidence of this increase will be directly dependent on the hormonal composition, duration and time of cessation of treatment (BAN; GODELLAS, 2014; NAROD, 2011).

Body weight: Overweight and obesity, especially in postmenopausal women, are considered significant risk factors for breast cancer, since the postmenopausal ovaries stop producing estrogen, most of which is a product of adipose tissue

activity, thus increasing the serum levels of this steroid hormone and at the same time increasing the risk for this neoplasm (BUDNY *et al*., 2019; FENG *et al*., 2018). In addition, overweight and obesity have been associated with a worse prognosis in breast cancer, with a higher risk of recurrence, resistance to treatment, and increased formation of metastases (BOUSQUENAUD *et al*., 2018).

Physical activity and food: On the other hand, regular physical activity 3 to 5 times a week, especially in menopausal women, has been shown to reduce the risk of breast cancer by about 25%, mainly due to improved general health, weight control, strengthening the immune system and energy balance (AKRAM *et al*., 2017; WOLIN; TUCHMAN, 2011). The consumption of high-fat products, especially red meat and dairy, as well as ultra-processed products, can be a trigger for the neoplastic transformation of breast cells (ANGAHAR, 2017; ANJUM *et al*., 2017). On the other hand, eating foods rich in antioxidants or rich in vitamin D can reduce the risk of developing this disease (BAUER *et al*., 2013; KOLAK *et al*., 2017).

Alcoholism and smoking: Numerous epidemiological studies suggest that regular alcohol consumption may slightly increase the risk of breast cancer, and that this increased risk is directly related to the amount and frequency of alcohol consumption (BAGNARDI *et al*., 2013; SUN *et al*., 2017). As for smoking, many epidemiological studies have claimed little or no association with increased risk of breast cancer (HOWELL *et al.*, 2014; KAWAI *et al*., 2014).

Ionizing radiation: High exposure to ionizing radiation is not only a recognized cause of breast cancer, but also of many other types of tumors (BAN; GODELLAS, 2014). Younger women are at greater risk than women exposed after age 40, possibly due to incomplete differentiation of breast tissue. Risk increases linearly with dose and duration of exposure (HOWELL *et al*., 2014).

Nonproliferative lesions of the mammary gland: Certain non-proliferative lesions in the mammary gland may impact a small risk for breast cancer, these

lesions include, for example, fibrosis, adenosis and squamous metaplasia (HARTMANN *et al*., 2005). However, benign proliferative lesions in the breast ducts or lobules (hyperplasia with atypia) confer a four- to five-fold increased risk of breast cancer (MEISNER; HOUMAN FEKRAZAD; ROYCE, 2008; SUN *et al*., 2017).

CONCLUSION

As detailed in this review article, breast cancer is characterized by being a complex and multifactorial disease. As stated above, this study answers our question guided by an attempt to reinforce the importance of pertinent and relevant information for women, especially those at higher risk for breast cancer, about the main risk factors for the disease, since many are preventable, in addition to the epidemiological profile of this important malignant neoplasm. Currently, many studies are focused on providing effective and safe tools for prevention, clinical screening, differential diagnosis and personalized treatment. However, more epidemiological studies, both in vitro and in vivo, are needed for a deeper understanding of the effect of exposure to different risk factors on women's health.

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