REVIEW ARTICLE
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Lifestyle and breast cancer: review article

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ABSTRACT

The aim of this study was to improve our knowledge about carcinogenesis and lifestyle, given their impact on the occurrence of breast cancer, emphasizing the importance of lifestyle changes as a preventive factor in the development of the disease. We conducted a bibliographic review with the analysis of 31 articles in English and Portuguese. As a result, the articles selected for study showed that factors such as diet, alcohol intake, smoking, obesity, physical activity, occupational exposure, hormonal factors (hormone therapy, contraceptives) and reproductive factors (menarche, menopause, nulliparity, pregnancy, breastfeeding) have a protective or risk effect on breast cancer. We conclude that eating healthy, with fruits, vegetables and greens, practicing moderate physical activity, avoiding alcoholic beverages and breastfeeding exclusively reduce the risk of developing breast cancer by 28%. Therefore, it is necessary to make the public aware of these modifiable risk factors.

KEYWORDS: breast cancer; lifestyle; carcinogenesis.

INTRODUCTION

Currently, breast cancer (BC) is the most prevalent cancer in the world, followed by lung and colorectal cancer, while BC mortality ranks fifth among cancer-related deaths, representing a major global public health problem. In Brazil, it is the most frequent neoplasm in all regions, with 66,280 new cases and an adjusted incidence rate of 43.74 cases/100,000 women in 2021[1].

The diagnosis of BC occurs mainly in women over 40 years old, and it is one of the most feared types of cancer for them, because of its high frequency and its psychological effects, such as changes in sexuality and body image, low self-esteem, fear of relapse, anxiety and depression.

Lifestyle, in turn, is the result of choices and priorities listed by each person. This can be the result of habits learned from the family culture, the environment or the place where one lives, but it can also be learned and modified at any time in life. Knowing the life habits that are modifiable risk factors for BC is the first step towards a healthier life, with a reduction in the possibility of the disease occurring. The physician's role is to motivate their patients regarding these choices and also to encourage discipline to maintain acquired good habits.

The causes of BC are multifactorial with interaction between genetic and environmental factors. According to data from the Brazilian National Cancer Institute (INCA), genetic factors account for 10% to 20% and other factors account for 80% to 90% of cases, including random cases (with no related cause). It is therefore understood that factors related to lifestyle (diet, physical activity, sleep, stress management) and also environmental factors (exposure to pesticides and other xenoestrogens, for example) play a significant role in the pathogenesis of BC. Considering the percentage related to non-genetic factors in BC, it is important to know these factors to try to minimize the risks. Nowadays, the population is increasingly exposed to environmental risk factors such as inadequate diet, sedentary lifestyle, excessive alcohol consumption, smoking, alteration of the circadian cycle and high levels of stress. Several studies claim that these are risk factors for BC, and it is necessary to know these factors to better guide the public.

In this study, a review of the literature on BC was carried out, with emphasis on carcinogenesis and lifestyle, including diet, alcohol intake, smoking, obesity, physical activity, occupational exposure, hormonal factors (hormone therapy, contraceptives), reproductive factors (menarche, menopause, nulliparity, pregnancy, breastfeeding). Our objective was to expand our knowledge of the subject and raise awareness about preventive care.

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METHODS

A bibliographic search was conducted in the indexed databases MEDLINE, Embase, JAMA and NEJM, with articles published between 2003 and 2022. The keywords used were "breast cancer", "lifestyle" and "carcinogenesis", and 31 articles in English and Portuguese were analyzed.

RESULTS

Mammary carcinogenesis

BC begins with a genetic mutation in a single cell in the ductal-tubular unit of the breast. This embryonic or somatic stem cell develops an altered cell clone that grows and proliferates according to the phenotypic characteristics it acquires from exposure to new damage to DNA: genome instability and loss of integrity of the repair mechanisms of these modifications[2-4].

There is expansion of mutant clones, during tumorigenesis, along with secretion of growth factors from cell contact. In a healthy state, cells have the ability to trigger the apoptotic chain when there is DNA damage that cannot be repaired, in such a way that in neoplastic genesis, an important step is the breakdown of this homeostatic mechanism, in which tumor cells obtain the capacity of apoptotic inhibition in situations where, physiologically, the ideal would be to initiate the process of programmed cell death[5].

Chronic inflammation is a process resulting from unwholesome habits — stress, medication use, sedentary lifestyle, poor diet. This process leads to an increase in oxidative stress, without adequate repair of cellular changes, and also to cell damage, in addition to changes in the intestinal microbiome. All of this together makes a perfect scenario for the onset of chronic diseases such as cardiovascular disease, diabetes, obesity and also cancer. In all these cases, there is an increase in the formation of mutated cells and a decrease in the body's repair capacity[6].

The presence of an inflammatory process, which would originally be beneficial for the tissue to repair it, may also facilitate tumor progression, as inflammation may result in the appearance of new blood vessels, which can nourish the neoplastic cells, and the release of growth factors, which can promote proliferative cell growth. Finally, there are "immortal" mutant cells, with the capacity to proliferate, being able to invade the lamina propria, lymphatic tissues and bloodstream.

Epigenetics

Epigenetics is an emerging area of research that studies the alteration of gene expression, either by silencing or activating genes, without changing the structure of DNA.

The set of genes that make up DNA is called the genome. The modifications that regulate the activity (expression) of these genes constitute the epigenome. The activation or silencing of some genes determines, in turn, the final product of that cell. These gene modifications can be passed on to "daughter cells" in the process of cell division, and they can also be passed from generation to generation (the child inherits these maternal and paternal DNA modifications).

Lifestyle plays an important role in epigenetics, since it is directly related to this gene activation/silence process. Diet, physical activity, sleep and stress can modify gene expression and thus protect neoplasms or stimulate their appearance[7,8].

Lifestyle

Diet

Studies show that different food components can impact cellular health through different processes that relate to the onset of BC.

A diet high in refined carbohydrates and trans fats has been linked to inflammatory diseases, while healthy eating patterns are associated with lower levels of inflammation[9].

Oxidative stress is a state of imbalance between antioxidants and oxidative factors, leading to the formation of free radicals. Under oxidative conditions, pro-oxidants are dominant over antioxidants, potentially leading to direct damage to lipids, proteins or DNA. Both inflammation and oxidative stress play an important role in increasing the risk of cancer[9-12].

Regarding the use of artificial sweeteners (used in many foods and beverages), a recent cohort study of 102,865 participants in France investigated the associations between consumption of artificial sweeteners and cancer risk. Among them, the most consumed are aspartame, acesulfame-K and sucralose. This study showed that the first two (aspartame and acesulfame-K) have a high association with BC (n=979 cases, HR=1.22 [95%CI 1.01 to 1.48], p=0.036, for aspartame). Great care must be taken when consuming industrialized and ultra-processed products. The consumption of these types of sweeteners should be discouraged for all people[13].

Physical activity

IA patient's level of physical activity appears to be another significant factor in the pathogenesis of BC, as it affects several regulatory systems in the body, including inflammatory mediators, sex hormones, metabolic hormones, adipokines and gut microbiota. Physical activity is responsible for regulating other mechanisms that also appear to be important in carcinogenesis such as telomere elongation, DNA hypomethylation, immune function and reduction of oxidative stress[14,15].

Women with high estrogen and androgen levels are at greater risk of developing BC. A meta-analysis investigated the impact of physical activity on sex steroids, showing that this practice decreases the risk of developing BC, since it decreases the level of sex hormones and reduces obesity, reducing the peripheral conversion of androgens into estrogens by aromatase, an enzyme

present in the subcutaneous tissue. As to the effects of physical activity on BC, it is observed that the beneficial effect is more evident in the postmenopausal period[16].

Pizot et al. conducted a meta-analysis of 38 prospective studies with 116,304 cases of BC, comparing the light or high level of physical activity, and they found that the risk reductions were not influenced by the type of physical activity, fat or menopausal status[17]. Risk reductions increased with increasing amount of exercise. Results indicate that a physically inactive woman (less than 150 minutes per week of vigorous physical activity) would increase her lifetime risk for BC by 9%[18].

An article published in JAMA in 2022 analyzed a population of adults and tried to establish the relationship between the level of physical activity practiced by them and the risk of death, with about 100 thousand participants. A reduction in mortality was observed for all participants who engaged in physical activities compared to sedentary individuals, mainly activities practiced with rackets and running were the ones that had the greatest impact. Even low-intensity physical activities were associated with reduced mortality in older patients studied (71 years old) in this study, showing that physical activity can be an ally in reducing the risk of cancer mortality[19].

Studies on physical activity and BC are also important because they address an important and sometimes neglected risk factor, sarcopenia. Sarcopenia is muscle wasting, associated with loss of function, which occurs progressively with aging. Some authors associate the loss of muscle mass with a worsening of the clinical outcome during and after cancer treatment, in BC as well. Care with nutritional support and encouragement of resistive exercise are essential in all stages of treatment to prevent or minimize this muscle loss[20].

Body mass index

Obesity is an isolated risk factor for several cancers; it is related to altered hormone levels, insulin and elevated adipokines, factors related to breast carcinogenesis.

There are several criteria for defining obesity, but body mass index (BMI) is a practical and accessible measurement. An individual is considered obese if BMI is above 30. Between 28–30 is classified as overweight, and below 25 is considered normal. Waist circumference measurement is also a useful and easy measurement. Values are normal up to 88 cm for women. Measurements above this value are associated with obesity and higher cardiovascular, cancer and mortality risk.

Both in cases of obesity and overweight, there is an increase in adipose tissue and, consequently, an increase in aromatase activity. Ultimately, the peripheral conversion of androgens to estrogens increases circulating levels of this hormone as well. Elevated estrogen levels are associated with BC by increasing bioavailable estrogen and, consequently, stimulating angiogenesis and cell proliferation. Obesity is related to a higher prevalence of insulin resistance, in which there is an increase in serum insulin and also in insulin-related growth factor (IGF-1). These two factors, as well as estrogen, stimulate cell proliferation and also angiogenesis. Finally, obesity alters the production of adipokines and inflammatory cytokines (adiponectins, IL-6, TNFα, leptin). This alteration, in addition to inducing cell proliferation, also acts on cell survival mechanisms, which stimulates the growth of tumor clones[21]. BC risk is related to BMI but depends on menopausal status.

Postmenopausal woman

In a meta-analysis by Keum et al., a total of 50 studies were included. For every 5-kg increase in adult weight gain, the relative risk was 1.11 (95%CI 1.08 to 1.13) for postmenopausal BC among users of hormone replacement therapy (HRT)[22].

Associations between adult BMI and postmenopausal BC have been observed in several studies, particularly for estrogen receptor-positive tumors. Waist circumference and body weight gain in adulthood were also associated with postmenopausal BC risk.

Premenopausal woman

The 2018 Continuous Update Project Expert Report (CUP) identified 37 dose-response meta-analyses of premenopausal BC (n=13,371 cases) and showed a statistically significant 7% decrease in risk per 5 kg/m^2 in all incidence and mortality studies.

In the Iowa Women's Health Study, which evaluated 34,000 women, weight loss of at least 5% before or after menopause reduced the risk of cancer by 25% to 40% compared with women who continued to gain weight. On the other hand, Eliassen et al. reported a 50% risk reduction in women with a 10% weight loss compared to women with stable weight in the Nurse's Health Study of 37,000 women[23].

Alcohol and smoking

Epidemiological studies have shown an association of alcohol and smoking with cancer. Specifically for BC, research has shown that alcohol use is a risk factor for developing this disease[24].

Several studies suggest that there is an increased risk for BC with the use of alcohol, and there is no safe amount for consumption. A meta-analysis of observational studies reported that postmenopausal women who drank alcohol had a 22% greater relative risk of BC (95%CI 9% to 37%) than those who did not consume alcohol. The analysis estimated that every additional 10 g of ethanol consumed per day (approximately one drink) was associated with a 10% (95%CI 5% to 15%) increased relative risk of BC[25-27].

In a multicenter, case-control study, with n=1578, it was concluded that the greater the cumulative consumption of alcohol throughout life, the greater the risk of BC, especially in postmenopausal women. Exposure to these modifiable risk factors should be reduced if necessary.

Sleep

Sleep is an important moment of anyone's day, in which several cellular mechanisms are activated or inhibited, regulating gene expression and DNA itself. These mechanisms, in turn, are stimulated, or not, by hormones secreted from triggers aligned with the circadian cycle.

The circadian cycle is, as the name implies, the cycle of a day (from the Latin "*circa diem*") and is regulated by light intensity. Our body perceives light and its absence through photoreceptors in the retina. From this perception, several hormones are secreted in sequence.

An article published in 2016 reviews the mechanisms related to breast biology and the consequences caused by changing the circadian cycle. The authors describe alterations in the circadian cycle resulting from aging, genetic alterations and also work issues (night workers or workers who work rotating shifts). In addition to these issues, the modern world has several situations that contribute to changes in the circadian cycle — greater exposure to screens and home office work, in addition to the so-called social jet lag (when people distort the circadian cycle every weekend for social commitments). Regardless of the cause of the alteration of this sleep rhythm, its consequences are perceived by alteration of the cell cycle and inhibition of apoptosis, as well as metabolic alterations and melatonin secretion.

Occupational exposure

According to a study published in 1981, *The causes of cancer: quantitative estimates of avoidable risks of cancer in the United States today*, occupational exposures account for 4% of cancers.

In Brazil, the publication by INCA on guidelines for the surveillance of work-related cancer presents a list of specific agents for each type of cancer. The agents found with regard to BC were pesticides, benzene, low frequency electromagnetic fields, magnetic fields, volatile organic compounds, hormones and dioxins. And the related occupations were: hairdresser, radio and telephone operator, nurse and nursing assistant, flight attendant and night worker[28].

Literature reviews confirm the risk of night work, especially for health professionals, on the basis of the work process of nurses[29] and flight attendants[30]. The explanation mechanism has been called *light-at-night* (LAN), which associates exposure to artificial light with reduced melatonin secretion, which regulates the secretion of ovarian hormones, including estradiol.

The mechanisms associated with the increase in BC in night workers are related to a decrease in cell apoptosis, changes in cell cycle regulation mechanisms, changes in metabolism inducing proliferation, changes in melatonin levels, favoring tumor growth and also altering epithelial-mesenchymal transition and favoring metastasis processes.

Metals such as iron, nickel, chromium, zinc, cadmium, mercury and lead have been found in higher concentrations in BC biopsies than in breast biopsies in women without cancer. These metals function as endocrine disruptors[31].

These data alert us to prioritize prevention measures, such as removing the carcinogenic substance, avoiding exposure to these agents and eliminating their use.

Hormonal factors

Menarche

Early menarche alone is related to a higher incidence of BC, and the earlier this event, the greater the risk. This is likely due to having menses longer, with a longer period of estrogen exposure. In addition, early menopause is associated with other risk factors for BC, such as parity, earlier age at first birth, height and BMI, as well as increased adiposity throughout life. The opposite findings hold for women who had a later menarche. When confounding factors are accounted for, high BMI lowers the risk difference between patients diagnosed with postmenopausal BC. Early menopause seems to play a more important role as a risk factor for patients with lobular BC compared to patients with ductal BC[32]. Later menarche is associated with reduced risk of triple-negative BC and likely reduces the risk of luminal A BC[33]. Early menarche has a greater impact on the risk of developing postmenopausal BC than does late menopause[32]. This relationship is also found in patients carrying the BRCA1 mutation but not in patients with the BRCA2 mutation (Pan, 2013).

Menopause

Later menopause is also a known risk factor for BC due to longer exposure to estrogen. It is known that the risk of BC shows great variability in the climacteric period, given the hormonal influence: there is a greater risk in premenopausal women than in postmenopausal women, with an intermediate risk in perimenopausal women. Adiposity attenuates the difference between groups: premenopausal women with BMI <25 have a higher risk of BC than patients with BMI ≥25, with the opposite observed in postmenopausal women. This happens because postmenopausal women with greater adiposity have higher levels of circulating estrogens due to the peripheral conversion of androgens into estrone. Estrogen receptor-positive tumors increase in incidence with age in pre- and postmenopausal women, but there is a reduction in estrogen receptor-positive tumors after menopause, with the same occurring for lobular tumors. When analyzing postmenopausal women, the later the age at which menopause occurred, the greater the risk was for developing BC, with no difference between induced menopause (oophorectomy or hormonal blockade) and natural menopause, this relationship being more important in estrogen receptor-positive tumors and lobular tumors. The differences found were attenuated by the BMI of the patients, in which a high BMI provided a greater risk of neoplasia in the postmenopausal period, and the opposite occurring in the premenopausal period[32].

Use of hormonal therapy

HRT consists in estrogen supplementation, with or without progestogens, in postmenopausal patients with symptoms of hypoestrogenism. It is known that endogenous or exogenous estrogen exposure confers an increased risk of developing BC. However, when it comes to HRT, estrogen replacement combined with medroxyprogesterone acetate has an increased risk of BC. The WHI study showed that, in patients with a previous hysterectomy, estrogen alone implied a reduction in the risk of developing BC. Recent observational studies point to an increased risk with therapy alone, as opposed to the WHI trial[34]. The risk seems to be related to the duration of therapy, with women who received estrogen + progesterone for less than three years did not seem to have a significantly increased risk[34]. The most closely related subtypes are estrogen receptor-positive and lobular BC[32]. After stopping HRT, the risk of developing BC drops every year. The tumors most related to the use of HRT are luminal A, and some studies point to a relationship with luminal B tumor[33].

Contraceptives

Women exposed to combined oral contraceptives (OCs) for up to 10 years have a small increase in the risk of developing BC after discontinuing the OCs. Furthermore, BC related to OC use has a lower risk of metastasis than BC in patients who have never used OCs. Duration of use appears to increase the risk of developing BC. Patients who discontinued use more than 10 years ago do not appear to be at increased risk[35,36].

The effect of OCs on the development of BC is related to duration, dose, pattern of use, type of OCs and age at first use. Two main theories are proposed to explain the increased risk of developing BC in this population: the first would be due to the use of estrogen in OCs, which is related to the development of BC; and the second is related to the fact that contraception reduces the number of pregnancies per woman, and, as a consequence, these women spend long periods of their life exposed to estrogen, since, during pregnancy, the levels of this hormone are reduced. However, patients who engage in physical activity while using OCs have reduced estrogen levels and, as a consequence, lower risk of developing BC[37]. Exposure to OCs is related to the development of triple-negative tumors, and some studies have shown a reduction in the risk of luminal A BC[33].

Breastfeeding

Breastfeeding acts as a protective factor in BC both by local breast factors (breastfeeding supports the differentiation of breast cells after pregnancy, and differentiated cells are less likely to become cancerous; the processes involved during its interruption such as apoptosis may decrease the risk of cancer by removing cells with early DNA damage from breast tissue)[38] and by reducing estrogen levels and other associated factors. During breastfeeding, prolactin exerts an inhibitory effect on the hypothalamic-pituitary-ovarian axis, which decreases circulating levels of progesterone and estrogen, thereby reducing the risk of developing hormone-dependent BC. Therefore, patients who do not breastfeed are at increased risk of developing BC because of the absence of this mechanism[37]. Women who exclusively breastfeed have a relative risk of developing BC that is 28% lower than in women who have had children and have not breastfed. In addition, without considering the breastfeeding regimen, duration longer than one year increases this protective factor[39]. The duration of breastfeeding appears to reduce the risk of luminal A, luminal B and triple-negative cancers[33]. Exclusive breastfeeding has a more important hormonal effect, since it demands more energy for milk production, greater mobilization of fat and glucose stores by the breast, decreasing insulin levels. Furthermore, exclusive breastfeeding leads to longer periods of postpartum amenorrhea by reducing estrogen exposure. Finally, women who exclusively breastfeed generally do so for longer periods, further reducing their risk of developing BC[39].

Reproductive characteristics

Nulliparity is an important risk factor in the development of BC and may carry up to a 30% risk of developing BC. This relationship is directly linked to the fact that these women do not breastfeed and, therefore, have a long exposure to estrogen. Multiparity seems to reduce the risk of luminal A BC, but a few studies relate multiparity to triple-negative BC[33].

Parity does not influence the risk of developing BC in patients with a BRCA1 or BRCA2 mutation. Later age at first birth is associated with a lower risk of BC in BRCA1 mutation carriers, but does not influence BRCA2 carriers[40].

Age at first delivery is related to the risk of developing luminal AC A; the younger the age, the lower the risk[33]. However, it does not seem to interfere with the risk of developing BC in patients with BRCA1 and BRCA2 mutations[40].

The differences found between patients with BRCA1 and BRCA2 mutations suggest different hormonal responses in BC subtypes. This can be reinforced by the fact that only 10%–24% of BRCA1 mutation-related BCs are estrogen receptor negative, in contrast to 65%–79% of BRCA2[40].

It is plausible to presume that hormone exposure is related to the risk of developing estrogen receptor-positive BC[40].

DISCUSSION

The relationship between the incidence of BC and lifestyle has been increasingly discussed by professionals who treat this disease. The modifiable risk factors that increase the incidence of BC should be known by every physician who deals with women's health, and guidance about these factors should be given at every consultation. Women at high risk for developing BC should

be especially advised about lifestyle changes that can modulate genetic expression inherited from their ancestors.

This article brings information about lifestyle points that should be discussed with women, offering the doctor data that may be useful at the time of this conversation. It is up to the doctor to know each of these factors and know how to provide guidance in relation to carcinogenesis, diet, alcohol and tobacco use, physical activity, sleep and also the use of hormonal therapies in various stages of life. Combating obesity is a key point in this scenario of reducing modifiable risk factors, since this is an important risk factor not only for the outcome of BC but for other chronic diseases that impact women's morbidity and mortality.

CONCLUSIONS

Understanding the carcinogenesis of BC and knowledge of its modifiable and non-modifiable risk factors are of utmost importance for the monitoring and counseling of patients in the prevention of BC.

Today, the main modifiable risk factors for BC are alcohol consumption (10 g/day), both premenopausal and postmenopausal, and obesity, especially in postmenopausal women. The use of contraceptives (period of 10 years) shows a small increase in risk, as does the use of hormone replacement therapy with estrogen and progesterone. There is a need to weigh risks and benefits for the use of these therapies individually.

Reproductive factors such as breastfeeding, adoption of healthy habits with the consumption of a varied diet with fruits and vegetables, practice of physical activity and maintenance of a low BMI minimize the risk of BC in premenopause and postmenopause. Furthermore, these changes may lower risk in populations at increased risk, such as patients with early menarche and late menopause.

AUTHORS' CONTRIBUTION

KPCL: Conceptualization, Data curation, Investigation, Methodology, Project administration, Resources, Software, Writing – original draft, Writing – review & editing. VFWM: Data curation, Investigation, Methodology, Project administration, resources, Software, Writing – original draft. TPM: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Software, Supervision, Validation, Writing – original draft, Writing – review & editing. RCSF: Formal analysis, Validation, Visualization, Writing – original draft. FMOC: Conceptualization, Data curation, Methodology, Software. MFSVG: Conceptualization, Data curation, Methodology, Software. JTA: Conceptualization, Formal analysis, Project administration, Supervision, Validation.

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