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Review Article

# Hormone Therapy and Breast Cancer: a literature review about the influence of hormonal treatment on neoplastic development

## *Terapia de reposição hormonal e câncer de mama: uma revisão de literatura acerca da influência do tratamento hormonal no desenvolvimento neoplásico*

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## ABSTRACT

Menopause is due to the gradual drop in ovarian hormonal secretion, and, during this period, many women have symptoms that compromise quality of life. Hormone therapy (HT) has emerged as an important tool to alleviate climacteric symptoms. However, suspicions were raised about the correlation between treatment and the increased risk of breast cancer (BC). The present study aims to evaluate the relationship between BC and HT, covering the implications of therapy for menopausal symptoms, the incidence of neoplasia and mortality. This is a narrative review of the literature, in which articles published between July 2010 and July 2020 were searched for in the LILACS, MEDLINE and SciELO databases. The main types of HT are estrogen alone and combined formula with progesterone. In the studies analyzed, combined therapy was related to a higher incidence of BC when compared to the estrogenic regimen. According to the literature, changes in mammographic density, induced by HT, can increase the risk for breast carcinoma. The articles reported that factors other than hormone therapy, such as lifestyle, can interfere with the incidence of BC and should be analyzed individually. Mortality from BC influenced by HT did not show a significant increase. Overall, HT was considered to be the most effective treatment for relieving climacteric symptoms. Although, long-term studies that analyze the risks and reliability of therapy should be encouraged in order to indicate the safest therapeutics and to avoid unnecessary interventions.

**Keywords:** Climacteric; Menopause; Breast Neoplasms; Estrogen Replacement Therapy; Hormone Replacement Therapy.

## RESUMO

A menopausa é decorrente da queda gradativa de secreção hormonal ovariana e, nesse período, muitas mulheres apresentam sintomas que comprometem a qualidade de vida. A terapia hormonal (TH) surgiu como importante ferramenta para amenizar a sintomatologia climatérica. No entanto, foram levantadas suspeitas sobre a correlação entre o tratamento e o aumento do risco do câncer de mama (CM). O presente trabalho objetiva avaliar a relação entre CM e TH, abrangendo as implicações da terapia nos sintomas da menopausa, na incidência da neoplasia e na mortalidade. Trata-se de uma revisão narrativa de literatura, em que foram buscados artigos publicados entre julho de 2010 e julho de 2020, nas bases de dados LILACS, MEDLINE e SciELO. Os principais tipos de TH são o estrogênio isolado e o combinado com progesterona. Nos estudos analisados, a terapia combinada foi relacionada à maior incidência de CM quando comparada ao regime estrogênico. De acordo com a literatura, modificações na densidade mamográfica, induzidas pela TH, podem elevar o risco para carcinoma mamário. Os artigos relataram que fatores além da terapia hormonal, como o estilo de vida, podem interferir na incidência de CM e devem ser analisados individualmente. A mortalidade por CM influenciada pela TH não demonstrou aumento significativo. No geral, a TH foi considerada o tratamento mais eficaz para aliviar sintomas climatéricos. Entretanto, estudos a longo prazo que analisem os riscos e a confiabilidade da terapia devem ser estimulados, a fim de indicar a terapêutica mais segura e evitar intervenções indevidas.

**Palavras-chave:** Climatério; Menopausa; Neoplasia da Mama; Terapia de Reposição de Estrogênios; Terapia de Reposição Hormonal.

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## Introduction

Menopause, a natural phenomenon of the female organism, is the physiological transition characterized by the loss of ovarian function and the cessation of menstrual periods.[1,2] Comprised within the climacteric, it is divided into pre-menopause, perimenopause and postmenopause and the Ministry of Health defines the age limit between 40 to 65 years of age for its occurrence. Annually, the number of women who undergo this modification is around 25 million. It is estimated that in 2030 the global population at menopause and postmenopause will reach 1.2 billion, with 47 million new cases per year.[1] Statistics show that 25% of women show substantial and debilitating symptoms during the climacteric, which disrupt the quality of life.[3]

The hormonal transition in menopause causes a gradual decrease in the secretion of hormones, mainly estrogen and progesterone, culminating in the last menstruation.[1] This process can be asymptomatic or symptomatic, with menstrual irregularities, painful intercourse**,** decreased libido, urinary disfunction**,** dryness or vaginal atrophy, vasomotor symptoms, and hot flushes.[1,2,3] Sleep disorders**,** adynamia, and anxiety are also reported symptoms.[1,2]

Hormonal therapy (HT) is recommended for the improvement of climacteric symptoms resulting from the interruption of hormonal secretion, and can be performed in the form of estrogen alone or combined with progestogens.[2,3,4,5,6] In the 1960s, the prescription of estrogen-alone therapy was indicated without precise criteria needed for women that were in menopause. In the same period, there were the appearance of the first complications involving the endometrium, issues which were resolved, already in 1980, by the discovery of the protective effect of progesterone. The great optimism surrounding estrogen therapy persisted until 2002, as the risks documented were surpassed by the benefits, such as promising studies for prevention of coronary heart disease, bone loss and colon cancer.[6]

In 2002 and 2004, the publications of Women's Health Initiative (WHI) raised suspicions about the safety of HT, outlining a new perspective by demonstrating the risks of the use of combined therapy for the increase of the incidence of breast cancer (BC).[2,6,7] From these adverse results, it was initiated a search for alternative therapies and individualized criteria to hormonal prescriptions in menopause, such as: age of the patient, time of menopause, symptoms, doses, administration pathways and comorbidities.[1,6]

Therefore, menopause and the control of its symptoms are public health issues.[1,3] Thus, HT needs to be analyzed within the scope of subsequent risks for the development of hormone-dependent cancers. However, the dangers of the therapy should not be discussed apart from its benefits, since this direct association, without considering the individualized criteria, can negatively interfere in the decisions, in the beginning and in the continuation of the therapy. Lifestyle, characteristics of the reproductive period and environmental interferences must be considered in the clinical decision.[8]

The present work aims to evaluate the relationship between breast cancer and HT, covering the implications of therapy in the incidence of cancer, mortality, and the symptoms of menopause. In addition, it seeks to compare the types of therapy and the routes of administration, to analyze the effects of alternative therapies and to outline other factors that may influence the risk of developing this neoplasm.

## Methodology

This is a narrative review of the literature on the association between the use of hormone therapy and the increase in the incidence of breast neoplasm. The following criteria of eligibility were used: temporal delimitation of the publication between July, 2010 and July, 2020; publications in English, Portuguese, French or Spanish; analysis of the title, abstract and, subsequently, the reading of the full articles.

The descriptors used, accordingly with the Health Science Descriptors (HSD), were "hormonal therapy", "estrogen reposition therapy", "breast neoplasia", "climacteric" and "menopause". The combination of these by boolean operators occurred in the databases: Literatura Latino-Americana e do Caribe em Ciências da Saúde (LILACS), Medical Literature Analysis and Retrieval System Online (MEDLINE) e Scientific Electronic Library Online (SciELO).

## Results

After the application of the eligibility criteria, 22 articles were included, among which there are primary and secondary studies that fell within the scope of the research. Table 1 shows these studies, their objectives and outcomes.

## Discussion

### Types of therapy and routes of administration.

Hormone therapy (HT) is the most effective treatment for improving women's quality of life in the face of menopausal symptoms.[1] There are many types of HT and different ways to apply them. Estrogen alone, considered the most efficient medication to control hot flushes, is prescribed to hysterectomized women, while combined therapy is indicated to those with an intact uterus or with partial hysterectomy. Both, but mainly progestogen therapy, should be used to treat the symptoms of menopause with the lowest effective dosage for the shortest possible time, but low doses are not supported by good controlled and prospective studies.[2,6]

The main synthetic estrogens are administrated orally (OV), while the natural estrogens most used in menopause are conjugated estrogens (OV) and transdermic estradiol. Synthetic and natural estrogens, in general, are important in preserving bone mass and reducing symptoms of menopause, but natural estrogens are more indicated in HT**.**[6]

In non-hysterectomized women, estrogen alone formulations increase the risk of endometrial neoplasia, so progestogene must be added, which can be cyclical or continuous.[2] In cyclic combined therapy, estrogen is prescribed continuously and the progestogen for 10 to 12 days per month, with bleeding at the end of each progesterone cycle. In continuous combined therapy, both are used uninterruptedly and there is no bleeding.[6] The continuous regimen appears to be more effective than the cyclic in reducing the likelihood of endometrial cancer, but observational studies report a greater propensity to develop BC in the first. Studies that analyzed the general effects of combined therapy show a significant increase in

**Table 1.** Representation of the articles included in the study.

| Database | Autorship | Design | Objective | Conclusion |
|---|---|---|---|---|
| Lilacs | Manica, Bellaver e Zancanaro[1] | Narrative review | Review information concerning the treatment of menopausal symptoms | The decision to adopt a therapy must be individual according to the analysis of cost/benefit |
| Medline | Hill, Crider e Hill[2] | Narrative review | Update on HT and menopause | Combined HT increases the risk of BC when used for more than 3-5 years |
| Medline | Rymer, Brian e Regan[3] | Editorial | Approach the study "Type and timing of menopausal hormone therapy and breast cancer risk: individual participant meta-analysis of the worldwide epidemiological evidence". | The increased risk of BC can persist for up to 15 years with the longest duration of combined HT use |
| Medline | Jones et al.[4] | Cohort study | Estimate the risk rates for BC at menopausal age. | O risco aumentado de CM pode persistir por até 15 anos com a maior duração do uso de TH combinada. |
| Medline | Lasserre e Fournier[5] | Consensus | Association between HT and the risk for breast, ovarian and endometrial cancer, according to treatment modalities | When necessary, the minimum effective dose and the shortest possible duration of HT is recommended, respecting the precautions for use and the contraindications |
| Lilacs | Pardini[6] | Narrative Review | Summary of the literature on the principles of HT | MD, influenced by combined and alone therapy, is a strong risk factor for BC |
| Medline | Byrne et al.[7] | Case-control study | Address the relationship between the change in MD after the beginning of combined HT | The change in MD after the combined HT was an intermediate substitute marker for the risk of BC |
| Medline | Antoine et al.[8] | Randomized-controlled essay | Analyze the changes in the incidence of BC related to the selling of HT in 11 European countries | Relationship with the incidence of BC evidenced only for tibolone |
| Medline | Stuenkel et al. [9] | Guideline | Create a guideline about the management and treatment of menopausal symptoms. | The increased risk of BC was more observed in combined HT and is associated with the duration of therapy |
| Medline | Marsden[10] | Consensus | Declaring the British Menopause Society consensus, exemplifying the risks and benefits of HT before and after the diagnosis of BC | In women with low chances of BC, the short-term benefits of HT exceed potential damage and the risk is equal or less than that of other factors |
| Medline | Shufelt et al.[11] | Prospective multicenter cohort study | Compare different doses of estrogen, formulations and routes of administration with the incidence of invasive BC. | The chances of BC do not differ significantly between low-dose and normal-dose CEE. No differences were observed between oral and transdermal estradiol |

| | | | | |
|---|---|---|---|---|
| Medline | Green et al.[12] | Cohort studies | Obtain prospective information about BC associated with the use of different types of HT | Users of combined HT have higher absolute risks of BC than users of estrogen alone or who do not use HT |
| Medline | Chlebowski et al.[13] | Long-term follow-up of randomized clinical trials | Report findings on the incidence of BC and its mortality over 20 years of follow-up with CEE + MPA and CEE in the post-menopause | CEE alone was associated with a lower incidence and mortality from BC, while CEE+ MPA was associated with a higher incidence of breast cancer with no significant difference in mortality |
| Medline | Beral et al.[14] | Correspondence | Compile worldwide evidence on HT and the incidence of invasive BC | The risk of BC was higher for combined HT and remained for more than a decade after interruption of treatment. |
| Medline | Salagame et al.[15] | Analysis of the database of CLEAR study | Investigate the relation between the use of HT and subtypes of receptors of tumor of BC | BC related to the use of HT are more likely to express ER and PR receptors and there is an increased risk of BC ER+ by HT |
| Medline | Collaborative Group on Hormonal Factors in Breast Cancer et al.[16] | Meta-analysis | Gather epidemiologic evidence about BC and HT types | 5 years of HT, starting at age 50, may increase the incidence of BC to 1/50 users of continuous combined HT, 1/70 users of cyclic HT and 1/200 users of estrogen alone |
| Medline | Liu, Chen e Hwang[17] | Longitudinal cohort study | To investigate if HT increased the risk of breast cancer in the Asian population | More than four years of current use of HT can increase the risk of breast cancer and the longer duration is related to higher risk |
| Lilacs | Albernaz et al.[18] | Editorial | Update doctors about the controversial relationship between HT and the risk of BC. | The incidence of BC, although variable and controversial, is higher for combined HT. |
| Medline | Yu et al. [19] | Systematic review and meta-analysis of observational studies | To evaluate relevant studies regarding the effect of HT on breast cancer survival. | The average effect of using HT is not detrimental to breast cancer survival based on the results of observational studies. |
| Medline | Azam et al.[20] | Cohort study | Assess whether MD mediates or modifies the association between HT and BC | Positive association between HT combined and BC, with 10% of mediation for MD |
| Scielo | Azevedo et al.[21] | Quantitative, descriptive and cross-sectional study | Analyze the knowledge of women between 35-69 years of age regarding the screening of BC | Knowledge about preventive exams and their importance is related to the regularity with which women perform them |

the chances of developing breast cancer, especially when it is administered since the beginning of menopause.[9]

In Brazil, the most widely used route is oral, due to its popularity, followed by transdermal, due to the possible reduction of adverse effects and safety.[1] Observational studies show that transdermal estrogen offers a lower risk of venous thromboembolism, besides the mitigated levels of estrone and its conjugates in the gastrointestinal mucosa and liver, when compared to oral administration.[1,2,6] In contrast, the OV allows a greater reduction in LDL. Vaginal administration of estradiol is the most indicated for isolated treatment of vaginal atrophy and other urogenital issues, while progesterone by the same route provides adequate local concentrations, endometrial protection and lower systemic levels of the compound. However, this hypothesis still lacks studies to prove.[1]

It is a consensus that the benefits of HT are best achieved when it starts between 50 and 59 years old or with less than 10 years of menopause, because it is in this age group that the advantages outweigh the risks, and women over 60 should not start treatment.[1] The patient's will should guide the choice of therapy, except when there are contraindications, such as history of BC or venous thromboembolism and severe liver disease.[2]

## Great studies

Observational studies, largely nonrandomized, have drawn different conclusions about the association between HT and BC. Despite this, clinical counseling and prescription habits followed a pattern influenced by the first results, released at the beginning of the 21st century, of the main studies on this relationship.[10]

The Women's Health Initiative Study (WHI) was a randomized, placebo-controlled American clinical study conducted with women from 50 to 79 years old, postmenopausal, recruited between 1993 and 1998.[8,11] The research compared women treated with the combination of conjugated equine estrogens (CEEs) and medroxyprogesterone acetate (MPA) with women who received placebo.[8] The mean study intervention was 5.6 years and detected an increase of 24% in the incidence of BC in combined HT. Furthermore, the use of estrogen combined with progesterone statistically interfered in the detection of breast cancer, which led to the diagnosis at a more advanced stage of the disease and increase mortality.[11]

During the intervention phase, there was no increase of breast neoplasia chances due to the estrogen alone.[9,11] The CEE did not increase the likelihood of breast cancer, but some analysis indicated an increase among women who started using transdermal estradiol at the beginning of menopause. In the combined therapy, the high risk of BC during the intervention phase persisted for 7 years after the end of treatment.[9]

The Million Women's Study (MWS), a prospective observational study, looked at women aged 50 to 64 years, between 1996 and 2001, and showed that combined therapy increased the risk of BC more than the use of estrogen alone and non-medicalization.[12] However, both therapies were statistically associated with a greater possibility of mortality from breast neoplasia.[13,14]

The E3N cohort was the main French study to evaluate the effect of HT on the chances of developing breast cancer in a long term. The research concluded that the use of combined therapy with micronized progesterone or didrogesterone for a short time does not increase the possibility of breast cancer. However, the combination with other types of progesterone increases these risks, even when they are used for a short period of time. Their use for a time more than 5 years may increase the likelihood of developing BC for more than 5 years after the end of treatment.[5]

Following the publication of the aforementioned findings, there was a reduction in the use of combined therapy in some countries covered by the studies. Taking into account the particularities of each location, such as the hormonal therapy prescription strategies adopted, this decrease was associated with a lower incidence of invasive breast carcinoma. However, even though these events were and still are highly correlated, the time between their occurrences, and the extent of the reduction in the use of HT and the numbers of BC are variable due to several characteristics, such as confounding factors and study methodology.[7,8]

## Hormone therapy and Breast Cancer

Estrogen receptors (ER) and progesterone receptors (PR) are biomarkers of breast cancer development. The breast neoplasia associated with these receptors differs in etiology, epidemiology, progression, prognosis and response to treatment.[15] In Western countries, 75% of the incidence and mortality from BC in postmenopausal women come from estrogen-receptor-positive (ER+).[16] Thus, hormonal preparations, such as estrogen hormone therapy (HT) alone or combined, exerts intracellular signaling for the neoplastic effects mediated by receptors.[15,17] Thereby, HT in menopause is associated with BC by the mechanism of higher expression of ER and PR.[15]

Studies that analyzed the propensity of BC during HT, for estrogenic receptors, indicated a higher risk of ER+ neoplasia. In the evaluations that were considered ER and PR, a positive increase was shown for estrogenic and progestagenic receptors (ER+/PR+). According to these findings, from the disclosure of the WHI results, there was a decrease in the use of HT in the population of several countries, which was concomitant to a lower incidence of breast carcinomas positive to the estrogenic receptor.[15] Knowledge of this pathophysiology made possible the treatment based on antiestrogens for BC, which act in blocking the production of estrogen, blocking the ovarian function and in the selective modulation of estrogen receptors.[11,16] Previously, it was prescribed a high dose of synthetic estrogen, which is a contradictory resource, since they can potentiate BC.[11]

During the climacteric, the therapies recommended with unopposed estrogen – conjugated equine estrogens (CEEs), estradiol or estriol – appear to reveal a minimal or no risk on the diagnosis of BC, when used for up to 5 years. After prolonged medicalization, for more than 10 years, the risk may be increased.[10,13] In hysterectomized women who used estrogen alone, lower rates of breast neoplasia were found compared to placebo.[13] In addition, among women who developed BC, the relationship between placebo and alone therapy found a lower mortality rate for those who underwent drug treatment.[11]

However, it is not possible to say that estrogen alone is completely safe or that it has a protective effect. This application lacks more research, since it was not found in most observational studies. Therefore, the evidences shows a possibility, which may be linked only to groups of women who are overweight or who started treatment several years after the end of menopause.[5] Regarding the routes of administration, the Million Women's Study and the E3N compared the alone estrogenic therapy orally and transdermal routes, revealing an insignificant increased neoplastic risk for both. However, there are findings that address a reduction for transdermal therapy, when analyzed against the conventional dose of CEE, especially when performed in the first 10 years of menopause. The presentation of these results is still inconclusive, requiring greater scientific investment.[11]

The WHI revealed an increased risk of breast cancer for the combined HT arm, but not for alone therapy.[11] In women with an intact uterus, the analysis of CEE and

medroxyprogesterone acetate (MPA) administrated orally was consistent and also revealed an inclination towards an increase in neoplastic chances when used for more than 5 years, however they are low absolute risks and with no incidence on mortality.[13,18]

The maintenance of the risk pos-intervention and exposition to the medication, CEE and MPA, seems to continue for more than a decade after discontinuation, possibly because of the anti-inflammatory effects of MPA in neutralizing estrogen-induced apoptosis of stem cells in the mammary epithelium.[13] For E3N, this only occurs in treatments lasting more than 5 years and, therefore, the risk may persist for another 5 years after discontinuation. However, there are disagreements regarding the long-term regimen, in which research also addresses the risk reduction after the interruption. Currently, micronized progesterone and its isomer, didrogesterone, are the focus of observance, as they do not seem to significantly increase the neoplastic tendency in short-term use, when compared to other combined regimens.[5]

Mortality because of BC due to HT, in randomized controlled studies, did not show considerable rates of increase. However, the proposition that hormonal therapy does not hinder survival in BC cannot be generalized, one must analyze the individualities of the case.[19]

In summary, based on the results under construction, the use of estrogen alone for more than 5 years may be favorable to the increase in the diagnostics of breast carcinomas, but to a lesser extent than combined therapy. The possible neoplastic effect after discontinuation of therapy is also assumed, but with discrepancies between the temporality of its persistence and the causalities that cause it.[3]

## Alternative drug therapies

Although hormonal therapy (HT) is the most efficient treatment for reducing climacteric symptoms, it is necessary to evaluate its implications. Stuenkel (2015) suggests the use of alternative therapies for women with a high or intermediate propensity to develop BC in order to alleviate the consequences of the menopause. Among these alternative therapies are tibolone and raloxifene.[9]

Tibolone is a synthetic steroid that has estrogenic, progestogenic, and androgenic effects and is capable of decreasing the circulating levels of sex hormone-binding globulin (SHBG).[1,6,9] It is approved in Brazil to treat symptoms of menopause at a dose of 1.25 - 2.5mg in the Libiam® formulation, indicated for women with no history of cancer and it should not be prescribed together with conventional forms of HT.[1,9,18] It has efficiency equal to or less than conventional therapy and is recommended to relieve vasomotor symptoms, prevent bone loss and improve urogenital atrophy, mood, sleep and libido.[1] The prescription is made continuously, which generates endometrial atrophy and amenorrhea.[6]

In general, observational studies relate tibolone to an increased risk of breast cancer, while a randomized, placebo-controlled study points to a reduction in women over 60 to the daily dose of 1.25mg.[18] The LIFT study, when evaluating the treatment of osteoporosis with low dose of tibolone for elderly women, observed a lower chance of occurrence of BC among the users of the drug, compared to placebo. On the other hand, in the MWS and the LIBERATE, the risk and recurrence of BC were higher among tibolone usuaries.[8]

Raloxifene is a selective estrogen receptor modulator (SERM) that acts as an antagonist of the receptors of estrogen in the breast tissue, uterus, vaginal epithelium and brain centers related to hot flushers. Because of the action on the breast, it is important in the prevention of BC.[1,6] However, according to Pardini (2014), despite reducing the numbers of breast cancer and improving bone density, raloxifene increases the occurrence of stroke and thromboembolism, in addition to worsening vasomotor symptoms.[6]

## Mammography Density

The mammographic density (MD), radiologically, refers to the fraction of epithelial or stromal tissue displayed in light color on mammography, while the adipose tissue, radiotransparent, appears in the dark color. Alterations in the mammographic pattern may indicate changes in the percentage of stromal, epithelial and fatty tissues. Because it is considered a risk factor for breast cancer, the MD is used as a biomarker in preventive monitoring of the sickness.[20]

According to the literature, women who had more than 75% of the breasts dense had more chances of developing breast carcinoma, it in comparison to those with mostly fat or low-density breast constitutions. In the majority of women who used HT, a 16% increase in the possibility of having mixed / dense DM was pointed out.[20] Thereby, responses in the breast tissue, mediated by hormones, may result in an increased risk for BC.[7]

Evidence on which HT regimen most affects the percent mammographic density (PMD) is not yet consistent, what exists is the agreement that changes in MD may vary according to the regimen used.[6,20] The administration of estrogen alone was not related to any of the modifications to the PMD. However, the combined regimen provoked a greater epithelial cell growth compared to estrogen alone or not using hormone therapy. Epithelial hyperplasia – unusual proliferation and accumulation of cells that encompass the ducts or lobes of the breasts – may be responsible for the increase in the MD and the consequent increase of breast neoplastic risk.[20]

In short, the use of HT influenced about 10% in the likelihood of breast cancer mediated by alterations in breast density, and for each increase of 1% in the MD the neoplastic chances were raised by 3.4%. It is reasonable to consider that combined therapy acts as a risk factor for the increase in mammography density, which may interfere with the incidence of breast carcinomas, an analysis that should be interpreted with caution.[7,20] Besides that, the monitoring and evaluation of mammography density should be done during hormone treatment.[7]

## Lifestyle and its influence

Despite the focus on the relationship between BC and HT, there are other factors that increase the incidence of carcinoma, such as the lifestyle adopted by women. Body mass and alcohol consumption exert neoplastic factors that can be compared to postmenopausal HT.[10,21] In this context, overweight and obesity represent risks six times greater than combined HT, according to the National Institute for Health and Care Excellence (NICE).[3]

The westernization caused changes in the lifestyle of women, while the younger generation, in relation with the older women, have specific particularities, such as: intake of fatty foods, higher obesity rate, early menarche, delay

to the parturition age, increase of nulliparity, and shorter breastfeeding time for children. A study carried out with a population of women in Taiwan reported that although the use of HT had a decrease after the publication of WHI, the incidence of breast cancer continued to increase and, therefore, the investigation of endocrine and environmental factors was necessary. The study exposed that the risk of breast cancer in Taiwan was higher in young women, with a peak in the age of perimenopause, but it is still not known what is responsible for this difference, the influence of the generation or the effects of HT.[17]

Although the results are not conclusive, it is evident that many factors can influence the propensity for BC.[10] The greater weight attributed to HT, with an approach unrelated to its benefits, causes an unharmonious discussion and little information about other conditions are exposed in the clinical orientation.[3,10] Therefore, it is not prudent to analyze the risk factors in restricted ways, nor even to generalize which women would benefit or have damage with the use of HT. It is advised that counseling must be individualized and that non-modifiable risk factors and lifestyle must be added in the discussion.[10]

### Limitations

Although there is a considerable range of research on the relationship between HT and the incidence of breast carcinoma, the bibliographic material pointed out some limitations that hindered the consolidation of the subject. In this logic, the duration of the studies was pointed out as a possible restriction.[8] In order to make conclusive statements, it would be necessary long-term studies long enough to evaluate HT in actual users or that made a long-term use of the therapy, and the increase of carcinoma risk.[16]

Another factor is that the incidence of breast cancer depends on the quality of notification from the health system and, because of that, it can suffer variations.[8] The epidemiological rates for BC are analyzed by the tracking system. In countries that do not have this screening, researchers face difficulties in data collection that aims to analyze the incidence of neoplasia influenced by HT.[16] Small samples and unavailability of data also fit the limitations, as they reverberate in the interpretation of the results and in the insufficiency of information that composes the patient's history.[11,19,20]

## Conclusion

The substantial prevalence of symptoms generated by menopause is responsible for framing the period in the areas of public health. The most efficient treatment for the improvement of symptoms, hormone therapy, has controversial results on its carcinogenic potential. The influence of HT on breast neoplasia evaluated by mammography density and the mechanism of expression of estrogenic and progestogenic receptors, revealed that the combined therapy, in long-term use, may be favorable to the increase in the diagnosis of breast carcinomas. This association occurred to a lesser extent for estrogen alone. However, is important to note that the impact of HT on the diagnosis of BC is discussed in isolation from the therapeutical benefits, with the exception of the lack of mention that the risk is in line with the duration of therapy. Besides that, endocrine, environmental factors and contraindications should also be considered in the clinical decision. Thus, informing and analyzing together with the patient and with individualized conduct, the disadvantages and the benefits that HT will bring to women is extremely necessary to indicate the safest propaedeutics and avoid the prescription of undue interventions. After all, the presence of limitations in research reveals the importance of screening measures in the incidence of BC and the need of studies that evaluate the effectiveness, risks, reliability and long-term effect of hormone therapy.

### Copyright Agreement & Authors' Contribution



## References

1. Manica J, Bellaver EH, Zancanaro V. Efeitos das terapias na menopausa: uma revisão narrativa da literatura. J Heal Biol Sci. 2018;7(1):82.

2. Hill A, Crider M, Hill S. Hormone therapy and other treatments for symptoms of menopause: Discovery Service for Endeavour College of Natural Health Library. Am Fam Physician [Internet]. 2016;94(11):884–9. Available from: https://www.aafp.org/afp/2016/1201/p884.html

3. Rymer J, Brian K, Regan L. HRT and breast cancer risk. BMJ [Internet]. 2019;367(October):10–1. Available from: http://dx.doi.org/doi:10.1136/bmj.l5928

4. Jones ME, Schoemaker MJ, Wright L, Mcfadden E, Griffin J, Thomas D, et al. Menopausal hormone therapy and breast cancer: What is the true size of the increased risk? Br J Cancer. 2016;115(5):607–15.

5. Lasserre A, Fournier A. Traitements hormonaux de la ménopause et risques de cancers. Gynecol Obstet Fertil. 2016;44(7–8):424–7.

6. Pardini D. Terapia de reposição hormonal na menopausa Hormone replacement therapy in menopause. Arq Bras Endocrinol Metab. 2014;58(2):10.

7. Byrne C, Ursin G, Martin CF, Peck JD, Cole EB, Zeng D, et al. Mammographic Density Change With Estrogen and Progestin Therapy and Breast Cancer Risk. J Natl Cancer Inst. 2017;109(9):1–7.

8. Antoine C, Ameye L, Paesmans M, De Azambuja E, Rozenberg S. Menopausal hormone therapy use in relation to breast cancer incidence in 11 European countries. Maturitas [Internet]. 2016;84:81–8. Available from: http://dx.doi.org/10.1016/j.maturitas.2015.11.010

9. Stuenkel CA, Davis SR, Gompel A, Lumsden MA, Murad MH, Pinkerton JA V., et al. Treatment of symptoms of the menopause: An endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2015;100(11):3975–4011.

10. Marsden J. British Menopause Society consensus statement: The risks and benefits of HRT before and after a breast cancer diagnosis. Post Reprod Heal. 2019;25(1):33–7.

11. Shufelt C, Bairey Merz CN, Pettinger MB, Choi L, Chlebowski R, Crandall CJ, et al. Estrogen-alone therapy and invasive breast cancer incidence by dose, formulation, and route of delivery: findings from the WHI observational study. Menopause. 2018;25(9):985–91.

12. Green J, Reeves GK, Floud S, Barnes I, Cairns BJ, Gathani T, et al. Cohort Profile: The Million Women Study. Int J Epidemiol. 2019;48(1):28-29E.

13. Chlebowski RT, Anderson GL, Aragaki AK, Manson JE, Stefanick ML, Pan K, et al. Association of Menopausal Hormone Therapy with Breast Cancer Incidence and Mortality during Long-term Follow-up of the Women's Health Initiative Randomized Clinical Trials. JAMA - J Am Med Assoc. 2020;324(4):369–80.

14. Beral V, Peto R, Pirie K, Reeves G. Menopausal hormone therapy and 20-year breast cancer mortality. Lancet [Internet]. 2019;394(10204):1139. Available from: http://dx.doi.org/10.1016/S0140-6736(19)32033-1

15. Salagame U, Banks E, O'Connell DL, Egger S, Canfell K. Menopausal hormone therapy use and breast cancer risk by receptor subtypes: Results from the New South Wales cancer lifestyle and evaluation of risk (CLEAR) study. PLoS One. 2018;13(11):1–14.

16. Group C, Cancer B. Type and timing of menopausal hormone therapy and breast cancer risk: individual participant meta-analysis of the worldwide epidemiological evidence. Lancet [Internet]. 2019;394(10204):1159–68. Available from: http://dx.doi.org/10.1016/S0140-6736(19)31709-X

17. Liu JY, Chen TJ, Hwang SJ. The risk of breast cancer in women using menopausal hormone replacement therapy in Taiwan. Int J Environ Res Public Health. 2016;13(5).

18. Albernaz MA, Wender MCO. Consenso sobre terapia hormonal e câncer de mama. Femina [Internet]. 2013;41(2):55–80. Available from: http://files.bvs.br/upload/S/0100-7254/2013/v41n2/a3791.pdf

19. Yu X, Zhou S, Wang J, Zhang Q, Hou J, Zhu L, et al. Hormone replacement therapy and breast cancer survival: a systematic review and meta-analysis of observational studies. Breast Cancer. 2017;24(5):643–57.

20. Azam S, Lange T, Huynh S, Aro AR, von Euler-Chelpin M, Vejborg I, et al. Hormone replacement therapy, mammographic density, and breast cancer risk: a cohort study. Cancer Causes Control [Internet]. 2018;29(6):495–505. Available from: http://dx.doi.org/10.1007/s10552-018-1033-0

21. Azevedo A, Ramos AL, Gonçalves ACV, Souza CF de, Batista GS, Silva RBV, et al. O conhecimento de mulheres acerca do rastreamento do câncer de mama e suas implicações. Rev Med. 2019;98(3):187–93.