Breast Cancer and Hormonal Replacement Therapy: an update

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“You are between what I want to have and what I'm afraid to have”.
Marilyn Monroe

One of the most exciting topics in Gynecology is the controversial influence of supplementary female hormones or hormone replacement therapy (HRT) on the risk of breast cancer. Recalling that the cancer, and especially, of the breast is multifactorial and HRT is a grain of sand in it, we will discuss a series of works in favor and against the possible relationship of this therapy in its genesis.

One of the first publications in which the controversy was established was the review presented in the Lancet\(^1\) in 1997 where 51 epidemiological studies involving 52,700 patients with breast cancer and 108,411 women in the control group were evaluated. The conclusion was that the risk of developing breast cancer increased with HRT in relation to the time of use and disappeared after five years of discontinuing it. However, the relationship between alcohol and increase of the body mass index with risk of developing breast cancer, which were superior in relationship with HRT, were not highlighted.

In 2002 appears the influential Women’s Health Initiative (WHI)\(^2\) study, which evaluated the use of conjugated equine estrogens (CEE) combined with medroxyprogesterone acetate, found an increase in the incidence of invasive breast, 8 cases of cancer more per 10,000 women, with no increase in the incidence of cancer in situ. The average age of patients included was 63-year-old. However, most of the women in the study were overweight or obese, this fact may have affected regardless their risk of breast cancer, so it is difficult to extrapolate this finding in younger reliably and without overweight women.

In 2003 the controversial study of the Million Women Study\(^3\) (MWS), which concluded that the risk of death by breast cancer in the HRT users was higher without statistically significant difference.

In 2004 was published the WHI\(^4\), with the analysis of the arm of estrogen alone in patients with history of hysterectomy, and found a reduction in the risk of breast cancer (RR: 0.8).

Subsequently, the "Mission"\(^5\) French study was published, whose results showed that there was no significant evidence of increased risk of cancer of the breast in HRT users (RR: 0.64 users vs. non-users 0.70).
Even with all this accumulated evidence, are still questions unanswered and is still a controversial subject. In 2012 an study\(^6\) on the influence of the CEE is published in hysterectomized patients after suspend such therapy\(^6\), with an average follow-up of 5.9 years of use, it was found that the incidence of breast cancer with CEE, not increased regardless of the age of the patient, registering a decrease of risk, giving to the CEE a protective effect against breast cancer.

According to a study of Salagame\(^7\) it seems that there is an increase in the incidence of breast cancer with both formulations, estrogen alone or combined, if used for more than 5 years, for what it must be used the shortest possible time and reassessed every 6-12 months.

In 2013, Luo\(^8\) published the first work on the influence of HRT in \textit{in situ} ductal breast cancer, evaluating the two branches of the WHI, concluding that in combined therapy there is an increase in \textit{in situ} ductal carcinoma (RR: 1.23), but that there was no statistically significant difference with CEE alone.

In 2013, Shapiro and cols\(^9\), make a new analysis of 3 previous studies on the relationship of HRT and breast cancer (WHI, Reanalysis Collaborative, MWS) and point out that the evidence is very limited to either support or refute that HRT raise the risk of breast cancer.

Evaluation of the relationship between metabolites of estrogen and its relationship with breast cancer\(^10\) started in January 2014, reaffirming that high doses of circulating estradiol are related to an increase in the risk of breast cancer, while the hydroxylated derivatives of estrogen (estradiol or estrone) are related to a reduction in the risk, as well as the increase in the estrogen metabolite, 2-OHE1, is associated with a decrease in breast cancer estrogen receptor positive in postmenopausal women.

Similarly, in 2014 is published a study which concludes that the use of progesterone micronized or dydrogesterone has a lower risk of association with breast cancer than other progestins\(^11\).

According to the International Menopause Society (IMS)\(^12\), the incidence of breast cancer varies in different countries, therefore, the available data may not be applicable everywhere. The degree of association between HRT and breast cancer remains controversial. The possible increase in the risk of breast cancer associated with HRT is discreet (less than 0.1% per year, or an incidence of < 1.0 per 1000 women per year of use) and factors such as alcohol consumption, obesity and physical inactivity are associated with an increased risk for breast malignant neoplastic disease. Random data controlled from the WHI study showed no increased risk of HRT users during the 5 - 7 years from the initiation of treatment. The WHI study also showed that 7.1 years of treatment with CEE unopposed decreased the risk of diagnosis and mortality from breast cancer in hysterectomized women. For example, the United Kingdom with the MWS, a large observational study, expressed concern for the safety of HRT long term from the perspective of breast cancer. However, it has been described causal, as biases and Biological plausibility criteria, to assess the results of MWS. The analysis highlights several design flaws that potentially biased the results.

According to the consensus of IMS, a broad European observational study suggested that the dydrogesterone used in association with oral or percutaneous estradiol or micronized progesterone may be associated with a better profile of risk of breast cancer than synthetic progestins. A study of the record of Finland also reported no increased risk with dydrogesterone after five or more years of use in
comparison with synthetic progestins, which were associated with a small increase in the risk. However, there is no sufficient data from adequate clinical and statistical studies that evaluate reliably the possible differences in the incidence of breast cancer, using different types, doses and routes of administration of estrogens, progestins, micronized progesterone and the use of androgens.

On the recommendations of the IMS, there is also settle that mammographic density is an independent factor of risk of breast cancer and some preparations of HRT increase mammographic density, predominantly in women with high baseline density. Increase of mammographic density related to the combined estrogen-progestin treatment, may impede the diagnostic mammography interpretation. The possible largest risk of breast cancer seen with HRT may decrease partially, through the selection of women with one lower risk of base, knowing and evaluating basal mammographic density and providing education about preventive measures of lifestyle. The Tibolone does not seem to be associated with an adverse effect on mammographic density and could lead to a lower risk of breast cancer than conventional estrogen-progestin therapy.

On the other hand, the Global consensus 2013\textsuperscript{13} concluded that the risk of breast cancer in women older than 50 years associated with HRT is a complex issue since it is multifactorial. The increased risk of breast cancer is mostly associated with adding progestin to estrogen treatment and is related to the time of use. The risk of breast cancer attributable to HRT is low and decreases after stopping treatment. Importantly, current safety data strongly discourage the use of HRT in breast cancer survivors.

To date, there is insufficient evidence to conclude that HRT is directly related to mammary carcinogenesis, the responsible use of HRT which is only imposed in patients who require it and who present a low risk, without associated comorbidity profile and the shortest possible time.

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References:

4. Women’s Health Initiative Sterring Committee. Effects of conjugated equine estrogens in postmenopausal women with hysterectomy. JAMA 2004;291:1701
5. Espié M, Daures JP, Chevallier T, Mares P, Micheletti MC, de Reilhac P. Breast cancer incidence and hormone replacement therapy: Results from the MISSION study,


