Hormone Replacement Therapy in Menopause and Ovarian Cancer: new data

Paula Cortiñas Sardi*

Do we must content ourselves with these two relations of contiguity and succession as giving us an idea of causation? In any way. Can an object be contiguous and prior to another without being considered as its cause?


Until recently, there was not enough scientific evidence that established a clear relationship between the use of hormone replacement therapy (HRT) and ovarian cancer. The development of a neoplasia is a multifactorial process, and causation is difficult to establish for different biases and the difficult to isolate and control all the variables involved in the development of a disease as complex as cancer. For some time a causal relationship is presumed, but it was not strong enough to be accepted.

In February 2015, is published in The Lancet, a meta-analysis of 52 epidemiological studies (17 prospective and 35 retrospective) relating the use of HRT and the development of ovarian cancer. The Collaborative Group on Epidemiological Studies of Ovarian Cancer, since 1998, assesses the association between the use of different hormone formulations, with different times of current or past use, with minimum bias, and the development of ovarian cancer.

In this study information was obtained from 21,488 post-menopausal women with ovarian cancer. The results were stratified by type of study, age and body mass index, and adjusted for parity, hormonal contraceptive use, age of menopause and hysterectomy story. According to the analysis made in this elegant study, the risk of developing ovarian cancer was significantly higher in women who used HRT compared with those who never used it, with a RR: 1.20 (p < 0.0001) in prospective studies and a RR: 1.14 (p < 0.0001) for all studies combined. The risk related convincingly to use of TRH, being maximum in current HRT users with a RR: 1.41 and resulting higher even in current...
users with less than 5 years of use with a RR 1.43. Registered risk decreased with time of suspension of use, but remained present at least for 5 years after suspended therapy.

The risk was similar for the different drugs with estrogen and progestin combined and estrogen alone. The majority of diagnosed tumors were epithelial (98%). HRT users had a lower risk for developing clear cell tumors, within the subtypes of epithelial, with a difference without statistical significance (p 0.04). The age of onset of HRT had any effect on the risk of ovarian cancer. Based on the above results, the authors conclude that the use of HRT at least for 5 years, starting at age 50, results in an additional case of ovarian cancer for every 1,000 users and an additional death from cancer of ovary by every 1,700 users. Then, according to the data obtained in this study: is there a causal relationship between the use of HRT and ovarian cancer development?

It is necessary in order to analyze these results, to put them in context. According to GloboCan in 2012\(^2\), global ovarian cancer incidence was 6 x 100,000 women, with a mortality rate of 3.7 x 100,000 women; colorectal cancer presents an incidence of 14 x 100,000 women, with a mortality of 6.9 x 100,000 and endometrial cancer incidence of 14.3 x 100,000 with 1.8 x 100,000 mortality. In the WHI\(^3\) study, to mention one of the best known studies on HRT, it was found a decrease in the incidence of 37% of colorectal cancer and 17% of endometrial cancer in patients HRT users. Fractures of hip in America and Europe, range from 900 to 100 x 100,000, depending on the latitude and certain features of the population\(^4\). The same study WHI found a reduction of 35% in the incidence of hip fractures in patients receiving HRT. If, according to the study recently published in The Lancet, the use of HRT results in an additional case of cancer of ovary for every 1000 users, then, under that same approach, there would be 2 less colorectal cancer cases, 1 case less of endometrial cancer and close to 100 cases less of fractures of hip, i.e. while HRT use increases cases of ovarian cancer, decreases cases of colorectal and endometrial cancer, and fractures of the hip, that are most common diseases. On the other hand, from an epidemiological point of view, it is considered that a causal association is weak when the relative risk (RR) ranges between 1.2 and 1.5 and moderate to strong above 1.5\(^5\). As a result, it can be concluded that the relationship between HRT use and development of ovarian cancer is weak, so it is not possible to assert that the use of HRT results in ovarian cancer. However, this risk can not be dismissed.

Far from demonizing HRT, a careful analysis of the results of this meta-analysis is required to be able to prescribe it responsibly. Causal associations must have certain characteristics such as temporal association, specificity, consistency, biological plausibility, relation dose-response and reversibility between exposure to the agent and the development of the disease\(^5\). As mentioned, cancer is a multifactorial disease and avoiding the use of HRT is not going to prevent the development of ovarian or breast cancer because the degree of causality does not meet the requirements to be considered as such. It is important, on the basis of these new findings, to discriminate what patient really benefits of HRT and is not at risk for developing ovarian cancer and weighing the risk/benefit ratio prescribed therapy that suits her. Also it is important to note that these findings should not be extrapolated to the use of HRT in young women due to ovarian failure, condition in which puts at risk to the patient if not used, except for formal contraindication to the use of hormones.
The concept of HRT as a preventive measure should definitely be reevaluated. HRT is a therapy for the relief of symptoms that occurs during the immediate menopause in patients without risk of comorbidities that worsen with therapy and/or developing disease that its risk is increased by the use of the same. Should not be seen either as a preventive therapy for other diseases, nor as a carcinogenic. Must be a change in the perception on HRT use, overcoming the vision of "rejuvenating" treatment or "Fountain of eternal youth" to a therapy for symptom control, with precise indications aimed to improve the quality of life in patients without risk that require this treatment.

*Gynecologist, Instituto de Oncología Luis Razetti, Salud Chacao y Clínica Santa Sofía. Caracas, Venezuela.

2. www.globocan.iarc.fr