Menopause hormone therapy in women with BRCA1 mutation

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I have a little clear patch that contains bio-identical estrogen. A progesterone IUD was inserted in my uterus. It will help me maintain a hormonal balance, but more important it will help prevent uterine cancer. I chose to keep my uterus because cancer in that location is not part of my family history. Regardless of the hormone replacements I'm taking, I am now in menopause. I will not be able to have any more children, and I expect some physical changes. But I feel at ease with whatever will come, not because I am strong but because this is a part of life. It is nothing to be feared…

Diary of a Surgery.

Angelina Jolie, New York Times 2015.

Women with BRCA1 mutations have an increased risk of developing breast and ovarian cancer (about 60% and 45%, respectively) when compared to the general population. For this reason, bilateral adnexectomy is recommended around the age of 35, once the parity is completed, as a measure to reduce the risk of ovarian cancer by 80% and of breast cancer by approximately 48%. Due to the hypoestrogenism that follows this measure, knowing the short and long term risks associated with premature ovarian failure, the use of menopausal hormone therapy (MHT) in these women has been considered at least until around 50 years of age, average onset of menopause. Due to the fact that it is a very specific and small population, the risk of developing breast cancer related to the use of these therapies in women with BRCA1 mutations has not been conclusively studied to date.

To evaluate the risk of breast cancer with MHT in women undergoing risk-reduction adnexectomy for a BRCA1 mutation, Kotsopoulos et al., performed a prospective study, published in *JAMA Oncology* in April 2018[1]. They included 872 women with this mutation from 80 centers in 17

countries. Questionnaires were conducted every 2 years and the group that was prescribed MHT after adnexectomy (377 patients) were compared with those that did not receive exogenous hormones (495 patients).

In this series, women who received MHT were younger than patients who did not receive hormones and underwent adnexectomy also at a younger age. During the follow-up of 7.6 years, 92 cases of invasive breast cancer were diagnosed, with an annual risk of 1.4%. The proportion of cases of breast cancer was similar in the group that received MHT and in the group with no treatment (10.3% vs. 10.7%, p: 0.86). Taking these results into account, women using MHT have a HR: 0.97 to develop breast cancer.

The types of MHT used in this series were the following: 69% took estrogen-only, 18% estrogen and progesterone, and 21% used other formulations. When analyzing the cases according to the type of MHT, those who used estrogen-only had a significantly lower risk of developing breast cancer when compared to the group of patients who used estrogen in combination with progesterone (12% vs 22%, p: 0.04). This effect was more noticeable in those who underwent adnexectomy before age 45 (9% vs. 24%, p: 0.009). The risks of developing breast cancer, grouped according to the type of MHT are: estrogen-only HR: 0.73, estrogen with progestogens HR: 1.31 and for other formulations HR: 1.29. The risk is even lower in patients with adnexectomy at a younger age who use only estrogens as MHT with a HR: 0.45 and a HR: 1.64 for estrogen and progestins combined. In the case of patients who underwent an adnexectomy after 45 years, the HR with estrogen-only use was 1.18 and 0.96 in patients with combined MHT.

Regarding the risk of breast cancer for each year of use of MHT, it is evident that there is a statistically significant decrease of 8% of the risk for each year of use of MHT containing estrogen-only and a non-significant increase of 8% for each year of use with MHT also containing a progestogen in its composition. In women undergoing oophorectomy before age 45, the risk reduction per year of estrogen use was 18%, however, a 14% increase in risk with the use of MHT combined with progestogens. In patients with oophorectomy after 45 years, there was no risk association for breast cancer with the use of MHT in any of the formulations.

The results of the present study are similar to those obtained in the WHI study, which showed a decrease breast cancer risk with the use of estrogen-only therapy and an increased risk with the use of combined MHT with estrogen and progestins. However, it is clear from the results of the study by Kotsopoulos et al, that in addition, MHT in younger patients with estrogen-only has a favorable effect when compared with older women.

Why does the association with progesterone in MHT increase the risk of breast cancer? The RANKL/RANK system through progestagenic stimulation, induces the proliferation of mammary epithelial cells during pregnancy to prepare the gland for lactation. The effect of progesterone on the increased risk of breast cancer in women with BRCA1 mutations, seems to be associated with activation by the progesterone receptor of the RANK signaling pathway. Progesterone induces the RANK ligand (RANKL) that binds to RANK and stimulates the production of NF-kB, which increases the transcription of cyclin D1, inducing mammary carcinogenesis through this pathway[2].

As can be seen from these results, there is no contraindication for MHT use in young people with BRCA1 mutation with respect to the increased risk of breast cancer, as recommended in 2016 by

the *North American Menopause Society (NAMS)*[3]; however, the recommendation in risk reduction surgery in these patients is to perform a bilateral adnexectomy with hysterectomy to avoid the use of MHT combined with progestogen as endometrial protection. Another option could be the use of the levonorgestrel-releasing intrauterine system, although its risk with respect to breast cancer has not been evaluated in the context of women with BRCA1 mutations, the use because of its exclusive local level progestagenic effect seems to be a safe alternative. The combination of conjugated equine estrogens with bazedoxifene has not been evaluated either, which has an endometrial protective effect due to its antiestrogenic effect, because bazedoxifene is a selective estrogen receptor modulator that behaves as an antiestrogen at the uterine level.

Oophorectomy in young women is associated with an increased risk for developing cardiovascular disease, cognitive disorders, increased incidence of osteoporosis, and poor quality of life of these patients. The use of MHT, preferably with estrogen-only, is advisable and safe in these patients to avoid the consequences derived from hypoestrogenism, since there is no greater risk of developing breast cancer due to therapy, with a positive impact on the health of women carriers of the mutation. It is necessary to alert the patients, always fearful of developing breast cancer, of the advantages of the use of MHT if they are subjected to an risk-reduction adnexectomy: the evidence suggests a clear benefit of the therapy with an acceptable safety profile.

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