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Case Study
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Prophylactic Hysterectomy after Tamoxifen Therapy in BRCA Mutation Carriers. Should It Be Systematically Recommended?

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Case Study

Risk Reducing Salpingo-Oophorectomy (RRSO) by age 40 years and bilateral Risk-Reducing Mastectomy (RRM) are recommended to carriers of germline BRCA1/2 mutations for the prevention of ovarian and breast cancer [1,2].

Concerning the gynecological risk reducing surgery in these patients, the role of hysterectomy at the time of RRSO is an open question. There are different reasons that could support the beneficial role of hysterectomy in BRCA mutations carriers. One argument is that these women may have an increased risk of endometrial cancer.

A large study of over 11,000 women with a germline BRCA1 mutation reported a slightly increased relative risk of Endometrial Cancer (EC) of 2.65 (95% CI = 1.69-4.16, P<0.001) [3]. Other studies have reported a higher prevalence of serous EC in BRCA carriers [4,5], but these data were not confirmed in all the published series [6-8].

A recent meta-analysis published in 2021 [9], reported a low prevalence of EC and serous EC in BRCA1/2 carriers (0.59% and 0.16% respectively), with a risk of serous EC of 0.2% and 0.08% among BRCA1 and BRCA2 mutation carriers, respectively.

Considering these latest data, the risk of endometrial cancer and of its worst prognosis forms in BRCA carriers is low. However, another important argument in favor of hysterectomy at the time of RRSO is that BRCA mutation carriers who take tamoxifen may have an increased risk of uterine cancer compared to population rates. This argument is very relevant in our opinion and there is some valid evidence to support this position in the scientific literature.

Tamoxifen is a known risk factor for endometrial cancer with a consensus relative risk of 2.4 but it's not associated with an increased risk of endometrial cancer mortality [10]; furthermore the histologic types of endometrial cancer are more aggressive in women who received tamoxifen than in women who did not, and it seems that mixed mesodermal tumors or carcinosarcomas are over-represented among tamoxifen users [11-13].

The role of tamoxifen in increasing the risk of endometrial cancer in BRCA mutation carriers is reported in a study of Beiner published on Gynecologic Oncology in 2007 [14]. Beiner et al. presented the results of a prospective study examining the incidence of endometrial cancer in a multicenter cohort of 857 BRCA mutation carriers. In this study during a follow-up period of 3.3 years, 6 women with BRCA mutation were diagnosed with endometrial cancer, compared to 1.13 cancers expected for age and country (Standardized Incidence Ratio [SIR]=5.3, p=0.0011). Four of the cancers were diagnosed in women treated with tamoxifen. Among the 226 patients who used tamoxifen the relative risk for endometrial cancer was 11.6 (p=0.0004), but the risk among women who had never been exposed to tamoxifen was not significantly elevated (SIR=2.7, p=0.17). Among women who took tamoxifen for a minimum of 2 years, the SIR was 21.6 (p<0.0001). Despite the sample size being small and the confidence intervals being wide, the authors concluded that the main contributor to the increased risk of endometrial cancer among BRCA carriers is tamoxifen treatment for a previous breast cancer and that the risk and benefits of prophylactic hysterectomy should be discussed with women with a BRCA mutation considering tamoxifen therapy [14].

A larger study published in 2013 by Segev [15], of 4456 women with a BRCA1 or a BRCA2 mutation reported that the risk of endometrial cancer is higher in BRCA1 mutation carriers than

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in the general population. Concerning the use of tamoxifen, they demonstrated a SIR of 4.14 (95% CI: 1.92 to 7.87) for women who received tamoxifen and of 1.67 (95% CI: 0.81 to 3.07) for women who did not receive tamoxifen. The ten-year cumulative risk of endometrial cancer in women who were treated with tamoxifen was 2.0%. They concluded that this excessive risk in BRCA carriers is largely attributable to a history of tamoxifen use, but the ten-year absolute risk is low, and they emphasize the need to discuss prophylactic hysterectomy among these women.

A prospective study published in 2017 that included 1,083 women demonstrated a not increased overall risk for uterine cancer after RRSO without hysterectomy [16]; however the risk for serous/serous-like EC (e.g., serous, undifferentiated, carcinosarcoma) was increased in BRCA1 carriers (4 cases observed among BRCA1 carriers versus 0.18 expected [O:E ratio, 22.2; 95% CI, 6.1–56.9; P<0.001]) [16]. In this study the role of tamoxifen was also studied: Three serous/serous-like carcinomas in 273 tamoxifen-exposed women (0.12 expected; O:E ratio, 24.4; 95% CI, 5.0–71.3; P<0.001) and two serous/serous-like carcinomas in 655 women without prior tamoxifen use (0.18 expected; O:E ratio, 11.3; 95% CI, 1.4–40.8; P=0.01) were identified [16]. It seems that these values, although with wide and overlapping confidence intervals, tend to demonstrate a higher incidence of endometrial carcinoma cases in BRCA carriers who have taken tamoxifen than in the general population and compared to BRCA carriers who have not taken tamoxifen. The authors also stated that tamoxifen exposure cannot explain the loss of the wild-type BRCA1 allele seen in 2 of the 3 available serous/serous-like tumors in their series but it may act as a risk modifier in the presence of decreased BRCA1 protein expression, as reported by Wen et al. [17]; in this case tamoxifen exposure may account for some of the serous-like carcinoma risk seen in their series report [16].

Indeed, the most important question of which the answer may definitively clarify the role of prophylactic hysterectomy in these women is whether tamoxifen can increase the risk of high-risk endometrial cancer in BRCA patients to a greater extent than it does in the general population and, if it exists, a molecular mechanism underlying this process.

The data published in the recent meta-analysis of Matanes [9], to investigate the justifiability of prophylactic hysterectomy at the time of RRSO [9], that reported a low prevalence of EC and serous EC in BRCA1/2 carriers (0.59% and 0.16% respectively) could not be adjusted for Tamoxifen use and history of breast cancer as the authors stated; for this reason these cannot apply to all BRCA carriers.

Matanes et al. [9] concluded that, considering the slightly increased risk of EC in BRCA mutation carriers, mainly BRCA1, the proposal of hysterectomy should be tailored individually based on the following factors:

i) Plans for Hormone Replacement Treatment (HRT) without increasing the risk of endometrial and breast cancers (avoiding the use of progesterone);

ii) Medical history including breast cancer and other risk factors for EC such as Tamoxifen treatment;

iii) Surgical risk factors;

iv) Quality of life following hysterectomy.

Concerning surgical risk factors, hysterectomy may carry some degree of morbidity [18,19], however hysterectomy to RRSO in BRCA1 mutation carriers adds 4.9 months of overall survival and is cost effective compared with RRSO alone [20].

It is true that the prevalence of endometrial serous EC reported in BRCA1/2 carriers at this moment is low [9]; however these are the more aggressive endometrial neoplasms presenting a very poor prognosis [21]. Although some hypotheses about better oncological outcomes of BRCA carriers with advanced-stage endometrial cancer compared to non-carriers at the same stage have been presented, there is very little evidence [22].

Furthermore, if we consider that many patients discover the mutation when breast cancer is diagnosed and undergo adjuvant therapy with tamoxifen, the prevalence of EC could be higher.

There is currently no evidence to demonstrate whether the slightly increased risk of EC in these patients is predominantly related to mutation status, tamoxifen therapy or a combination of the two conditions.

In conclusion, considering the literature data available at this time and our clinical experience, we suggest that for BRCA mutation carriers with a history of tamoxifen therapy, hysterectomy at the time of RRSO for the prophylaxis of high-risk endometrial cancer may be a valid proposal; however, the surgical risk factors of the patient must be considered.

More evidence is certainly needed to investigate the role of tamoxifen use in increasing the risk of endometrial cancer in BRCA carriers compared with women who have not BRCA mutations; we encourage the scientific community in further prospective studies on the subject to clarify this role and eventually support the hysterectomy in BRCA carriers with history of tamoxifen as a clinical practice.

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