The Association of Ovarian and Uterine Cancers With Postmenopausal Hormonal Treatments

MANUEL NEVES-E-CASTRO
Clinica de Feminologia Holistica, Lisbon, Portugal

Abstract: During hormone treatments for the relief of the symptoms of postmenopausal women a number of side effects may occur. Some may be due to the wrong choice of the steroids used for treatment or to the route of administration. However, the more important ones deserving much attention are the rare occurrences of malignancies of the uterus and ovaries. The risk for ovarian cancer, if it exists, is minimal and clinically irrelevant. Estrogen only treatments are used only in hysterectomized women. Continuous combined estrogen-progestin treatments have a very low risk of association with endometrial cancers compared with sequential regimens. Tibolone may be associated with a very small risk for endometrial cancers and thus must be properly monitored by transvaginal ultrasound. Breast cancer patients being treated with tamoxifen require careful attention to the endometrium to exclude a carcinoma. For the protection of the endometrium, a progestin-releasing intrauterine device is an attractive choice.Raloxifene used for a long time to prevent osteoporosis is safe for the endometrium. None of the above-mentioned side effects is enough to prevent a physician from using hormone treatment in postmenopausal women if there are no past or current contraindications.

Key Words: HRT, hormonal introgenesis, ovarian cancer, uterine cancer

Introduction
Although ovarian and uterine cancers are less frequent than breast cancer, they are certainly very serious conditions requiring good clinical and diagnostic skills for those women who start hormonal treatment (HT) for the relief of menopausal symptoms.

The occurrence of spotting and bleeding during HT is a worrying sign and warrants adequate diagnostic techniques that may detect malignancies. Unfortunately, the ovary is not as accessible for diagnosis as are the endometrium and the uterine cervix. Regular examinations in women receiving HT are mandatory and may result in an early diagnosis, thus permitting early treatment with a better prognosis. Clinical history and biannual examinations complemented by ultrasound by the vaginal route, cytology,
and endometrial biopsies are the essential tools at the disposal of the clinician.

The diagnosis of a malignancy during the course of HT can hardly be proof of a causal relationship. With millions of mitosis going on every day in all tissues, it would be difficult to assume that they are all normal. Some may be abnormal and induce in a cell the initial traits of malignancy. These cells may remain dormant for years and be prevented from further growth by the body’s defence mechanisms (eg, immune defences). At a given moment, either because the defences weaken or because additional growth stimuli emerge these dormant cells may start their disorganized growth that leads to the formation of a tumor. This could very well be the case for certain ovarian and endometrial cancers.

Whether estrogens and progestagens cause cancer mutations or stimulate the growth of dormant cancer cells is a question of academic interest. What is clinically important is the knowledge that such cancers may appear in the course of HT prescribed for the relief of the symptoms of postmenopausal women, and thus must be diagnosed and treated to prevent morbidity and mortality.

**Ovarian Cancer**

"The age standardized incidence of ovarian cancer, worldwide is 6.5/100,000 females. Epithelial ovarian cancer, which accounts for more than 90% of ovarian malignancies, is the gynecologic tumors with the worse prognosis in part because more than 70% of cases are diagnosed at an advanced stage of the disease.¹ Women who carry a BRCA1 mutation have approximately a 60% lifetime risk of developing ovarian cancer, and women who carry a BRCA2 mutation have approximately a 30% lifetime risk of developing this malignancy. Other studies² concluded that HT does not seem to adversely influence the risk of ovarian cancer in BRCA mutation carriers. The evidence concerning a positive relationship between HT use and ovarian cancer risk is less consistent than that for endometrial and breast cancer.² A relative risk (RR) of ovarian cancer for ever-use of HT is reported as 0.9 in hospital-based and 1.1 in population-based studies, with no consistent duration-risk relation. "A collaborative reanalysis of 4 European studies based on 1470 cases of ovarian cancer found a RR of 1.71 [95% confidence interval (CI): 1.30-2.25] for ever-use of HT, a weak positive association with duration of use and some indication that the excess risk for ovarian cancer declined with time since last use." No association has been described between use of HT and ovarian cancer risk in a cohort study conducted in Britain; similar results have been obtained in various areas in the United States. Furthermore, a retrospective British Study and a South Africa prospective, randomized trial did not detect an adverse influence of HT on the clinical outcome of patients previously treated for ovarian cancer. Thus, there are no data contraindicating HT use in epithelial cancer survivors.²

Although the Million Women Study (MWS) showed an increased risk of ovarian cancer with HT, the WHI did not report any significant association for ovarian cancer risk in HT-treated women. The MWS reported that women who use HT are at increased risk of both incident and fatal ovarian cancer.³ Although statistically significant, their results are clinically irrelevant as the attributable risk over 5 years is only 4/10,000 HT users, a figure that is extremely small, and which has not been confirmed by other large studies. The risk is much lower than that associated with obesity, lack of physical exercise, smoking, and nulliparity, all of which are preventable.⁴ The MWS has been severely criticized. The risk of ovarian cancer was no longer increased once women stopped using HT, an effect that
was pathologically and clinically incompatible with causation. The estimated numbers of additional cases of incident and fatal ovarian cancer that were attributed to HT use were spurious, and arbitrary. Data were extrapolated back to 1991, which was many years before the MWS, a design that had no scientific rationale.\textsuperscript{5}

The MWS concluded that women who stopped taking HT had a similar risk of ovarian cancer to never users, an astonishing disappearance of the excess risk after stopping therapy. Furthermore, if this association was causal, an increased incidence of ovarian cancer in Europe between 1975 and 2000, when HT use increased, would have been seen: this is not the case, and both the incidence and mortality of ovarian cancer have remained stable.\textsuperscript{6,7} Therefore, HT should continue to be prescribed for symptom relief and improvement of quality of life because the benefits far outweigh the very low potential risks.\textsuperscript{4}

**Uterine Cancer**

**CERVIX**

Although the major concern with uterine cancer is the endometrium, the cervix is not unaffected by HT as viral expression (human papillomavirus) may increase, thus subsequently increasing risk for cancer. Past users had a significantly higher risk using combination HT regimens with increasing duration [adjusted odds ratio (OR) = 1.8/y; 95\% CI = 1.1-1.3]. These findings suggest that a significant percentage of older women are infected with human papillomavirus and that this may put them at increased risk of cervical cancer with longer duration of HT use.\textsuperscript{5}

**MYOMETRIUM/ENDOMETRIUM**

Low-grade endometrial stromal sarcomas are hormonally sensitive. The annual incidence is very low, <0.2/100,000 women. These tumors have been reported to occur in women with exogenous or endogenous hyperestrogenism.\textsuperscript{9}

**ENDOMETRIUM**

The age-standardized incidence of endometrial cancer worldwide is 6.4/100,000 women. Endometrial cancer is the fifth most common cancer in women; its incidence to mortality ratio is much lower, 2:1 for African American women and 7:1 for white women.

There are the 2 major types of endometrial cancer: Type I or “endometrioid adenocarcinoma” represents about 80\% of all endometrial malignancies and occurs mostly in perimenopausal and early postmenopausal women. It is related to estrogen exposure and is frequently associated with endometrial hyperplasia. Type I cancers are associated with several risk factors such as unopposed exogenous estrogen exposure, obesity, etc. Type II, nonendometrioid endometrial cancers (usually serous or clear cell carcinoma) develop more often after the menopause. They are unrelated to estrogen stimulation or endometrial hyperplasia, occasionally arising in endometrial polyps or from precancerous lesions that develop in atrophic endometria. The endometrial adenocarcinoma which is correlated with estrogen (type I), and the nonestrogen associated (type II) have different malignancy potentials, with the first being characterized as a low-grade malignancy, and the latter being more aggressive.\textsuperscript{10}

The endometrium is a target for estrogenic, progestagenic, and androgenic ligands. There are 2 types of estrogen receptors (ERs): \(\alpha\) and \(\beta\). The progesterone receptors are also present in 2 isoforms: A and B. The endometrium and the breast epithelium both contain the same receptors. However, they react differently to estrogens and progestagens. Endometrial carcinoma increases with estrogen therapy whereas estrogen-progestagen HTs reduce its risk. Conversely
combined HTs increase the risk of breast carcinoma whereas estrogens alone do not increase the risk of breast carcinoma. These clinical findings suggest that the biologic role of estrogens and progestagens in tumorigenesis are certainly different between the endometrium and breast, although both are considered estrogen-dependent tissues. The enzymes responsible for intratumoral estrogen metabolism and biosynthesis are markedly different between breast and endometrial carcinomas. Estrogens are interconverted by 2 enzymes, 17 hydroxysteroid dehydrogenase (17HSD) types 1 and 2. Type 1 converts estrone to estradiol and types 2 catalyzes the reverse reaction. 17HSD type 1 plays an important role in the regulation of high estradiol levels in breast carcinoma tissues, whereas 17HSD type 2 seems to be essential for the maintenance of estradiol concentrations in endometrial carcinoma. In addition, the biologic significance of progesterone receptor isoforms differs between endometrial and breast carcinomas. Therefore, some molecules used for HT may bind either to the ER α, like estradiol 17β, or to both α and β ERs, like tamoxifen, or to ERβ alone, like raloxifene. Other molecules, such as tibolone are prodrugs that are metabolized into estrogenic, progestagenic, and androgenic molecules that bind to the respective endometrial receptors. Thus, one has to consider separately each group of molecules used in HT as far as cancer risk is concerned.

Estrogens (alone) are well known to increase markedly the risk for endometrial cancer (RR = 2.3). The risk can persist even after many years of stopping estrogen administration. Continuous estrogen HT may safely be used if the endometrium is protected with a progestagen-releasing IUD although some reports do not confirm such protection.

Comparing women only using combined estrogen and progestin therapy for 3 or more years to those women only using unopposed estrogens for 3 or more years, it was found that the adjusted OR was 0.2 (95% CI: 0.1-0.6). Thus, this HT is to be used in women with an intact uterus as there is a benefit of adding progestagens to the regimen. Progestagens counteract the adverse effect of estrogens on the endometrium, the effect being greater the more days every month that they are added to estrogens, and the more obese the women.

However, one case has been reported of an endometrial carcinoma occurring while on continuous combined HT, which had been preceded by a sequential regimen. This patient was completely asymptomatic. A routine transvaginal ultrasound (TVU) showed an increased endometrial echo (10 mm), and a biopsy showed a well-differentiated grade II endometrial carcinoma with squamous differentiation. This is a rare event, but this possibility should not to be ignored.

Other studies, however, have suggested that even combined HT results in an increased risk of endometrial carcinoma. In a study of 30,379 postmenopausal women, endometrial carcinoma was significantly associated with estrogen plus progestin only use (RR: 2.5; 95% CI: 1.9-3.5) including both sequential (progestin < 15 d/cycle RR: 3.0; 95% CI: 2.0-4.6) and continuous (progestin at least 15 d/cycle RR: 2.3; 95% CI: 1.3-4.0) regimens. The RR increased by 0.38 (95% CI: 0.20-0.64) per year of estrogen plus progestin use, and RRs increased with increasing duration of use of both regimens. Thus, all estrogen progestin regimens may increase endometrial carcinoma risk. Combined HT is safer for the endometrium but long-term (> 6 y) sequential therapy may result in an increased risk (OR: 2.0; 95% CI: 1.2-3.5). This association seemed to occur only among women with body mass index
<25 kg/m² (OR: 2.6; 95% CI: 1.4-4.9). Obese women showed the greatest reduction in risk (OR: 0.24; 95% CI: 0.10-0.60) when using combined HT.20 Other studies have concluded that sequential HT is associated with a low risk of endometrial hyperplasia and atypical hyperplasia (1%) for regimens with more than 10 days of higher doses of progestogens, and that continuous combined HT is not associated with the development of hyperplasia or malignancy.21 A study using a transdermal route of continuous HT delivery showed no increased risk of endometrial hyperplasia or endometrial cancer over a 96-week period.22

The type of progestogen used may also be important testosterone-derived progestins (eg, norethisterone acetate), such as those included in regimens commonly used in Europe, may be more potent than progesterone-derived progestins (eg, medroxyprogesterone acetate) which dominate the US market.23 This could explain why some European studies show a protective effect of combined HTs as opposed to other US studies. “Bio identical” HTs may also be associated with endometrial cancer risk.24

Although combined HTs are safer for the endometrium it must be kept in mind that they may be associated with an increase in the risk of breast cancer.25 Estrogen plus progestins might either promote existing lesions or induce new lesions if continued estrogen exposure is genotoxic or if supraphysiologic estrogen levels increase risk regardless of progestin levels.18

In terms of the diagnosis of endometrial cancer, a cut off of 5-mm thickness of the endometrium with TVU seems adequate to exclude endometrial pathology in patients on sequential or continuous HT, provided TVU is performed during the period immediately after progestin withdrawal, whereas an endometrial thickness up to 4 mm can be also regarded as completely normal finding in patients on continuous combined HT.18

Polyps: They may occur during HT but the relationship remains unclear. HT has no demonstrable effect on the estrogen and progesterone receptor expression in polyps. However, HT does not seem to inhibit apoptosis and cell proliferation in endometrial polyps, which may affect polyp growth.26 Conversely, others report that HT may cause endometrial polyp involution by decreasing proliferation and stimulating apoptosis.27

Tibolone
Tibolone is a steroidal prodrug. Treatments of symptomatic menopausal women with 1.25 or 2.5 mg/d in a total of 3240 women for up to 2 years did not induce endometrial hyperplasia or carcinoma.28 However, a recent study29 reported that women exposed to tibolone for at least 3 years have a RR of endometrial cancer of 2.03 compared with untreated women. The risk was 3-fold higher in women with normal weight, but was unchanged in obese women. This study has been questioned by many on the basis of validity of its methodology.30 It is unusual that the risk of endometrial cancer would persist for many years after cessation of therapy, which does not happen with breast cancer. It is possible that tibolone has been prescribed selectively to women experiencing bleeding problems who also are at greater risk of endometrial cancer.

An earlier report of 4 cases of endometrial cancer in patients using tibolone had indicated that the adenocarcinoma developed from an atrophic endometrium, which is different from the more common transition through hyperplasia that occurs with unopposed estrogens. Nevertheless, although the RR suggests a 79% increased risk of endometrial cancer, when this is converted into absolute figures the excess endometrial cancer risk in 1000 women over a 5 years period is only 3
cases. A biologic explanation for the increase in endometrial cancer risk during tibolone treatment could be that the 2.5 mg is more estrogenic with regard to the endometrium than previously anticipated.

The development of endometrial cancer during treatment with tibolone could also be explained by the relatively weak progestogenic activity of the Δ4-isomers of tibolone, which might be insufficient to inhibit the proliferative effect of 7α-methylthiophinestradiol in all patients. After oral administration tibolone is rapidly aromatized in the liver resulting in the formation of that estrogenic molecule that has a potency which reaches that of ethinylestradiol. However, the endometrial thickness with tibolone closely mimics the naturally atrophic postmenopausal state. A few other cases have been reported but it remains uncertain whether tibolone is an etiologic agent or co-factor in the development of endometrial hyperplasia or carcinoma.

A possible explanation for these findings in the MWS might be that in the United Kingdom general practitioners seem to prescribe tibolone preferentially to women with increased risks of breast and endometrial cancer as compared with others.

**Tamoxifen**

The reported RR for endometrial cancer associated with tamoxifen use ranges from 0.6 to 15.2 (Table 1). A recent meta-analysis including 4914 women found a RR of 4.1 (95% CI: 1.9-8.9) whereas others report a RR of 7.5 (CI: 1.7-32.7).

Endometrial surveillance in women who use tamoxifen is mandatory. An endometrial thickness greater than 8 mm on ultrasonography has a 100% positive predictive value for endometrial disease.

Sonohysterography and hysteroscopy are useful in identifying endometrial polyps, which occur frequently, in both premenopausal and postmenopausal patients receiving tamoxifen, as a common cause of abnormal bleeding.

Cervical cytology is useful provided there is no cervical stenosis that prevents the vaginal egress of uterine bleeding. A Papanicolaou smear-based diagnosis of atypical glandular cells of undetermined significance or the finding of benign endometrial cells on the Papanicolaou smear in postmenopausal women warrants endometrial sampling. Some have suggested that annual endometrial biopsy is also recommended for women with familial cancer syndromes, such as hereditary nonpolyposis colon cancer.

**Polyps**

Tamoxifen has a significant effect on hormone receptor expression and markers of apoptosis in endometrial polyps. Studies with markers of all proliferation/apoptosis (Ki 67 and Bcl-2) in endometrial polyps in women exposed or unexposed to tamoxifen support the hypothesis that tamoxifen promotes polyp growth by inhibiting apoptosis, a mechanism that does not seem to be ER medicated.

Endometrial polyps are the most common endometrial pathology described in association with postmenopausal tamoxifen exposure with an incidence of up to 10.7% of malignancy. A high rate of malignancy was reported in these polyps. Long-term tamoxifen users are more likely to succumb to endometrial cancer and endometrial sarcoma than nonusers. The endometrium may be protected with a levonorgestrel-mediated IUD.

Although a dose of 20 mg of tamoxifen taken daily for 5 years has been shown to decrease the incidence of contralateral breast cancer in 40% of breast cancer women and increase the disease-free survival, especially in postmenopausal women, the prolonged administration of tamoxifen is associated with an increased risk of endometrial cancer, sometimes many years after its discontinuation.
Table 1. Risk of Endometrial Cancer, by Histologic Type, in Relation to Duration of Tamoxifen Treatment

<table>
<thead>
<tr>
<th>Duration of Tamoxifen Treatment</th>
<th>Endometrioid Adenocarcinoma and Viscous Carcinomas</th>
<th>Clear cell and Papillary Serous Carcinomas</th>
<th>Mullerian and Mesodermal Mixed Tumors and Sarcomas</th>
</tr>
</thead>
<tbody>
<tr>
<td>No mention of tamoxifen</td>
<td>136.1.0 (baseline)</td>
<td>3.1.0 (baseline)</td>
<td>4.1.0 (baseline)</td>
</tr>
<tr>
<td>Tamoxifen treatment Duration**</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>&gt; b = 2 y</td>
<td>132.1.2 (0.94.7)</td>
<td>2.7 (0.4-19.9)</td>
<td>12.6.1 (1.6-23.6)</td>
</tr>
<tr>
<td>2-4 y</td>
<td>164.1.8 (1.3-2.4)</td>
<td>2.9 (0.4-23.3)</td>
<td>15.7.1 (1.9-26.4)</td>
</tr>
<tr>
<td>5-7 y</td>
<td>116.2.2 (1.5-3.2)</td>
<td>4.9 (1.0-34.2)</td>
<td>27.20.2 (5.7-71.9)</td>
</tr>
<tr>
<td>8-9 y</td>
<td>54.4.6 (2.7-7.7)</td>
<td>1.9 (0.0-27.2)</td>
<td>7.18.0 (4.0-82.4)</td>
</tr>
<tr>
<td>≥ 10 y</td>
<td>40.6.8 (3.3-13.9)</td>
<td>12.7 (0.0-49.5)</td>
<td>5.33.0 (5.7-192.5)</td>
</tr>
<tr>
<td>Used, duration unknown</td>
<td>32.2.2 (1.3-3.7)</td>
<td>2.4 (0.0-32.7)</td>
<td>8.18.4 (4.5-75.6)</td>
</tr>
<tr>
<td>Trend: OR/yr†</td>
<td>1.17 (1.12-1.21)</td>
<td>1.13 (0.96-1.33)</td>
<td>1.31 (1.19-1.44)</td>
</tr>
</tbody>
</table>

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May increase the proliferation of a subset of cells, thereby increasing the likelihood of mutations. Alternatively, it may promote the growth of cells that have already sustained mutations. The carcinogenic effect of tamoxifen may be due to genotoxic DNA damage. It may also promote an occult endometrial cancer. 48

The apoptosis/proliferation ratio in benign endometria from tamoxifen users is lower than in controls, indicating that the tamoxifen-induced higher proliferation is not compensated for by increased apoptosis. An imbalance between proliferation and apoptosis, and possibility suppression of the antitumor immune responsible by FasL overexpression in tamoxifen-exposed endometrium might play a role in the development of endometrial cancer.49

Endometrial proliferation and mitotically active leiomyoma of the uterus also may be related to tamoxifen therapy. 50

Ralofoxifene

As ralofoxifene is a benzothiophene frequently used for the prevention of osteoporosis and also for the prevention of breast cancer, its endometrial safety is reviewed here. It is not a steroid hormone but it binds preferentially to the ERβ thus being theoretically devoid of endometrial proliferative effects.

However, in estrogen-depleted mice ralofoxifene has partial agonistic effects on the uterus 51 although this was not confirmed by other studies. 52 In women no significant differences were found either in the pulsatility indices (reflecting uterine blood flow) or in endometrial thickness during 6 months of treatment. 53

Nevertheless, ralofoxifene has been associated with a very low incidence of spotting/bleeding compared with tibolone 54 a situation that is very rare in postmenopausal women under ralofoxifene treatment. 55 In 25 healthy postmenopausal women on 60 mg/d of ralofoxifene during 6 months of therapy there was no significant change in endometrial thickness or uterine artery blood flow, 56,57 and it seems to act as an endometrial antagonist. 58 The only exception is a case where there was an association between ralofoxifene and the development of a malignant mixed mesodermal tumor, a rare variant of uterine cancer, in a 64-year-old woman with a bicornuate uterus. 59
Summary
Although the association of genital tumors with hormonal treatments is real (Table 2), it should not prevent the well-informed clinician from using HT for the relief of symptoms in postmenopausal women, provided there are no contraindications. Any side effect occurring during treatment must be investigated in detail to determine if it is related and, therefore, a contraindication for continuing HT.

Although women on HT may feel well with no detectable side effects it is mandatory for them to have a cytologic and ultrasound (transvaginal) screening on a yearly basis.

Breast cancer patients under treatment with tamoxifen, who have an intact uterus, must be followed more carefully, perhaps every 6 months. These women may benefit with a progestagen-releasing intrauterine device that will protect the endometrium. 60,61

Conclusions
Depriving a woman of the benefits of a sound postmenopausal hormone therapy because of the fear of rare side effects does not seem to be satisfactory medicine.

<table>
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<th>Hormonal Treatments</th>
<th>Endometrial Cancer</th>
<th>Ovarian Cancer</th>
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<tbody>
<tr>
<td>Estrogens alone</td>
<td>+ + +</td>
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<tr>
<td>Estrogens alone + P-IUD</td>
<td>–</td>
<td>?</td>
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<tr>
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<tr>
<td>Sequential</td>
<td>+</td>
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P-IUD indicates levonorgestrel-releasing intrauterine device.

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References


56. Christodoulakos GE, Botis DS, Lambrianoudakis IV, et al. A 5-year study on the