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REVIEW

Menopause hormone treatment after cancer

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ABSTRACT

Regular improvement in survival of women after treatment for cancer has been reached in these last years. Menopause hormone therapy (MHT) remains the most efficient treatment to alleviate climacteric symptoms and improve quality of life in symptomatic women. The long-term effects of estrogen deficiency can be, at least partially, prevented by MHT. However, using MHT in an oncologic context can be associated with contraindications. Patients who have experienced breast cancer frequently face severe climacteric symptoms, but results from randomized trials are not in favor of using MHT in these women. Three randomized trials are available in women treated by MHT after ovarian cancer, and report better survival rates in the active group of treatment, suggesting that, at least in serous high-grade ovarian carcinoma, MHT could be allowed. No robust data are available for MHT after endometrial carcinoma. According to various guidelines, MHT could be possible in low grades with good prognosis. Progestogen, however, is not contraindicated and can help to alleviate climacteric symptoms. Squamous cell cervical carcinoma is not hormone-dependent and therefore patients can be treated with MHT without restrictions, whereas cervical adenocarcinoma is likely to be estrogen-dependent, despite lack of robust data, and thus only progesterone or progestin might be potentially used. It is possible that, in future, better molecular characterization of genomic profiles of various cancers may allow MHT to be used with some patients.

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Introduction

Management of menopause and of its consequences on health is particularly important in female cancer survivors. Primary ovarian insufficiency can be induced by treatment, whether surgical or medical (chemotherapy and/or radiotherapy). Survival rates are increasing for most cancers, raising the importance of long-term management of the various consequences of cancer treatment, including estrogen deprivation.

In this narrative review, we will address the question of menopause hormone therapy (MHT) in women after breast cancer (BC) and gynecological cancers. Contraindications occur for hormone-dependent cancer, but depending on the oncologic context, the age of the patient and the impact of gonadal failure, a tailored decision can be proposed for some patients.

Breast cancer survivors

BC is the leading cancer in women worldwide. There are several types of BCs characterized by their hormone receptor (HR) expression, amplification of the oncogene human epidermal growth factor receptor type 2 (HER2+) or the absence of any of them (triple negative [TN]). Most BCs contain estradiol receptors (ERs) and some also contain progesterone receptors (PRs). The molecular classification consists of the luminal A type, which is ER+ and PR+ and has a good prognosis (85% survival at 5 years), and the luminal B type, which is ER+ and can be HER2– or HER2+. Luminal B HER2– has a worse prognosis than luminal A. HER2+ and TN BCs have the worse prognosis. The prognosis may vary according to the age of the patients (worse in younger women) and the stage of the BC; the youngest patients having more TN and HER2+ BC than postmenopausal women.

The majority of BCs arising during MHT are of luminal A type and to a lesser extent luminal B type. MHT is not associated with an increase in TN or HER2+ types [1–5], nor with an increase in mortality from BC [6,7].

Breast cancer survivors (BCS) have more severe climacteric symptoms than women without BC, because of the use of hormonotherapy [8]. Treatments can also reinforce the occurrence of cardiovascular events, cardiovascular toxicity and neuropathy, osteoporosis [9], musculoskeletal [9] and cognitive disorders, such as aromatase inhibitors (AIs) [10] and some chemotherapies [11,12] (anthracyclins, anti-HER2, immune check-point inhibitors, etc.). Radiotherapy on the left breast can also contribute to cardiovascular toxicity. Although most BC cases occur in postmenopausal women, approximately 25% will occur before menopause. The

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chemotherapies used can be associated with a primary ovarian insufficiency according to age and the dose of cyclophosphamide, but this is not always the case and amenorrhea does not always persist after the end of therapies.

MHT has the best efficacy on climacteric symptoms, can also prevent osteoporosis and alleviate sleep disorders and vulvovaginal atrophy, and in most cases improves sexual disorders and, as a whole, quality of life in women deprived of estrogen. Most BCs are ER + and MHT is associated with ER + BCs. This strongly indicates that MHT is contraindicated in women with ER + BC. In addition, the efficacy of hormonotherapy by AI/tamoxifen also reinforces the position against estrogen administration to these patients.

Evidence on the risk of recurrence or second cancers in women treated by MHT

There have been five randomized trials (RTs) in BCS who received conventional MHT or tibolone.

Two independent RTs were started in 1997 in Sweden to evaluate the rate of recurrence: the Hormonal Replacement After BC – Is it Safe? (HABITS) trial and the Stockholm trial (Table 1). A joint data monitoring committee was constituted. Following an interim analysis, showing a significant increase in recurrences with hazard ratio 1.8 (1.03–3.1), both studies were prematurely stopped in 2003, but the follow-up continued [14,16–18]. The HABITS trial reported a significant risk of recurrences after 2.1 years of treatment whereas the Stockholm trial did not see any increase after a mean of 4.1 years. Differences in the characteristics of the patients included and in the composition of MHT may have contributed to these different results.

In the Stockholm trial, the treatment was scheduled for 5 years and the trial was interrupted at 4.1 years but the follow-up reached 10.8 years [18]. Among 11 women in whom a contralateral BC occurred using MHT, 10 used tamoxifen, which thus did not offer a prevention [13]. Four contralateral BCs occurred in women with MPA given every 3 months and eight in the sequential schedule [18].

In the HABITS trial, women with complete follow-up were 174 with MHT and 171 controls, with a median follow-up of 2.1 years [17].

The regimens were different between both trials as there was no continuous combined treatment in the Stockholm trial and norethisterone acetate was used in the HABITS trial.

Two other small RTs did not bring any additional information on the rate of recurrence in BCS using MHT. One concerned 77 women randomized estrogen-only treatment (ET) and did not see any increase in the risk [13]. Another trial looked at the feasibility of a RT in women after BC but the treatment was scheduled for 6 months [19].

A third important RT has been conducted with tibolone in BCS, the LIBERATE trial [20] (Table 1). A higher risk of recurrence was observed in users of AIs at baseline (the number was low) than in tamoxifen users: hazard ratio 2.42 (1.01–5.79; $p = 0.047$) versus hazard ratio 1.25 (0.98–1.59; $p = 0.076$) [20]. Tibolone is metabolized into a Δ4-isomer with androgenic and progestin properties and two estrogen derivatives with low affinities for ER [21]. Tamoxifen may antagonize the estrogen derivatives, but not the Δ4-isomer, and AIs cannot oppose the mild estrogenic activity of tibolone.

A meta-analysis of these RTs (including tibolone) found a risk of global recurrence (Table 1) [22].

Table 1. Risk of recurrence in survivors of BC with MHT (randomized trials).

		Breast cancer		
Study	*Design*	*Number of patients*	*Hazard ratio (95% CI)*	*Comments*
Stockholm [13]	RT MHT Women aged <55 years: E2 2 mg × 21 days + MPA 10 mg × 10 days, 7 days free Women >55 years: E2 2 mg × 84 days + MPA 14 days, 7 days free Hysterectomized women: E2 2 mg continuously	188/190 22% 50% 23%	Recurrence: 1.3 (0.9–1.9) In women who started MHT <2 years after BC any first event: hazard ratio = 1.7 (1.0–3.0)	60 events vs. 48 (MHT vs. control) 11 vs. 15 local recurrences 12 vs. 12 metastases 10 vs. 11 deaths from BC Node+: 16% 52% tamoxifen In 224 women who received MHT <2 years after BC, increase in contralateral BC hazard ratio = 4.8 (1–2.2)
HABITS [14]	RT E2 2 mg/day + norethisterone Sequential in women <2 years since BC Continuous in women >2 years Hysterectomized women: E2 2 mg continuously	219/215	Recurrence: 3.3 (1.5–7.4)	Node+: 26% 21% tamoxifen
LIBERATE [20]	RCT Tibolone	1556/1542	Recurrence: 1.40 (1.14–1.70)	Node+: 58% 71% ER+, 67% tamoxifen AIs: 6% then +22% Recurrence lower in node– Less recurrence in tamoxifen users
Meta-analysis [15]	Included the three RTs	2022/2023	Recurrence 1.46 (1.12–1.91)	Risk significant only for ER+

AI, aromatase inhibitor; BC, breast cancer; CI, confidence interval; E2, estradiol; ER, estradiol receptor; HABITS, Hormonal Replacement After BC – Is it Safe?; MHT, menopause hormonal treatment; MPA, medroxyprogesterone acetate; RCT, randomized control trial; RT, randomized trial.

Several observational studies have shown no increase or even a decrease in the risk of recurrences with MHT in BCS, but selection bias of women with better prognosis is very likely. Some have been discussed in recent reviews [15,23].

Uncertainties

The question of possible MHT use in HR– BCs can be debated. Against it is the existence of a two-fold to six-fold increased risk of developing a contralateral BC in women who have already experienced a BC, whether ER + or ER– [24]. The metachronous BC can be of the same type or of a different type [24]. The hormone-dependency of a BC is a complex issue and even HR– BC can be controlled by paracrine mechanisms such as the Rank ligand (produced by PR + cells but acting on cells devoid of PR). ER and PR membranous receptors may play a role together with some other mechanisms, as discussed by van Barele et al. [25].

One theoretical possibility to decrease the risk of recurrence could be to combine an antiestrogen with an estrogen. There is only one RT in postmenopausal women without BC which showed a benefit of tamoxifen on luminal A BC: 1884 postmenopausal women on MHT were included, randomized between tamoxifen 5 mg/day or placebo for 5 years. The follow-up was 6.2 ± 1.9 years. During this period, 24 BCs were diagnosed on placebo and 19 on tamoxifen with relative risk 0.80 (0.44–1.46). Stratifying on luminal A type, the relative risk was 0.32 (0.12–0.86), and for a treatment below 5 years the relative risk was 0.35 (0.15–0.85) in ET-treated women. But compliance at the end of 5 years was only 55.6% on placebo and 52.6% on tamoxifen ($p = 0.19$). There was an increase in side-effects with tamoxifen: climacteric symptoms, and hysterectomy for benign disorders. Maybe in the future, topical administration of selective estrogen receptor modulators on the breast could be combined with administration of estrogens in BCS.

In conclusion

From all this evidence, there is no recommendation to use MHT in BCS and non-hormonal alternatives should always be preferred (level of evidence I, grade E[1]; Table 3). In rare cases, where the quality of life is severely impacted, as a last line of treatment, after an individual evaluation with the oncologist and full information of the patient, MHT can be discussed. This statement is reproduced by most of the scientific societies [8,26]. At odds with this, a group of Spanish experts classified MHT as indicated in women with HR– BC, and in women with HR + BC with more disadvantages than benefits (grade 3) but not contraindicated [27].

Vaginal administration of hormonal treatment

There are no RTs providing definite conclusions. Systemic diffusion of estrogens from topical administration is always possible but the plasmatic levels are dependent on the dose and remain very low when using low-dose compounds [8]. Several observational studies did not report any increased risk of recurrence [28–30]. The general consensus [8,31,32] is to recommend non-hormonal treatment as a first line and then, if necessary, allows topical estrogens in women using tamoxifen. In women using AIs, even a low amount of estrogens could have some deleterious effects, without knowing the threshold for these levels [33]. A recent observational study reported for the first time an increased risk associated with the use of topical estrogens and AIs [34]. So far there are no data for prasterone use and the risk of recurrence in BCS, where systemic levels of androgens and estrogens appear to be low [35]. There are same theoretical restrictions in women with AIs, since safety of androgens is not well predictable, in particular in TN BC.

Survivors of ovarian cancer

Ovarian cancer is much less frequent but is the most severe among gynecological cancers. Over a third (37%) occur in premenopausal women. Treatment, in most cases, is oophorectomy and chemotherapy. Progress in treatment is associated with an increasing survival rate, with a 45% 5-year survival rate. There are different types of epithelial ovarian cancer. The most frequent is the high-grade serous, then the high-grade endometrioid type. Other types of epithelial ovarian cancer are mucinous, clear cell and transitional cell tumors. Non-epithelial tumors are germ cell tumors and sex cord-stromal tumors.

Chronic fatigue, depression, cognitive complains and sleep disorders are pre-eminent in epithelial ovarian cancer survivors (EOCS) [36]. We conducted a study in 166 EOCS for at least 3 years after their treatment [37]. All of the patients had surgery, and 97% received platinum and taxane chemotherapy. Their mean age was 55.8 ± 11.5 years at the end of treatment (range 16–79 years) and 62 ± 11 years at the time of the survey. At the time of the survey, 52% had still vasomotor symptoms (72% in the case of surgical menopause and 41% for natural menopause), 62% complained of arthralgia, 65% had a decrease in libido, 63% complained of vaginal dryness and 45% were sexually active. All symptoms were more severe after surgical menopause. Despite the prevalence of vaginal dryness, only 17% of the women used vaginal ovules and 27% a lubricating gel. Among the 85 EOCS with vasomotor symptoms, 80 (94%) did not receive MHT after their cancer treatment whereas 76% had no contraindications for MHT according to a consensus statement [38].

This consensus was established by a group of 35 French experts of ovarian cancer [38]. Observational studies in EOCS who used MHT after their cancer, with the exception of one, reported a better survival in women with MHT than without. But a bias of healthy patient selection is likely in these studies. There are now three RTs [39–41] on EOCS and MHT use. All three reported no harm from MHT (Table 2).

A meta-analysis [42] has pooled the first two RTs and four cohort studies (Table 2). The risk for death was decreased (Table 2).

From this evidence and additional data which are outside the scope of this review, the conclusions are that MHT can be used in high-grade serous tumors and probably high-grade endometrioid tumors but is contraindicated in low-grade serous and

Table 2. Risk of recurrence, deaths and overall survival in epithelial ovarian cancer survivors.

Study	Design	Number of patients	Recurrences/OS	Comments
Guidozzi and Daponte [39]	RT Women aged <59 years CEE vs. no treatment Follow-up 48 months	130	Recurrences: 32 vs. 41 OS: 44 months vs. 34 months	In active group vs. control: Serous 39 vs. 46 Mucinous 16 vs. 11 Endometrioid 2 vs. 7 Clear cell 2 vs. 2
Li et al. [40]	RT CT Follow-up 31.4 months	90	No difference in OS	Serous 47 Mucinous 28
Eeles et al. [41]	RT Median follow-up 19.1 years 43 women used ET 19 used CT	150	Recurrence: hazard ratio = 0.67 (0.47–0.97) OS: hazard ratio = 0.63 (0.44–0.90)	In active group vs. control: Serous: 29 vs. 30 Endometrioid:11 vs. 4 Mucinous: 8 vs. 14 Clear cells: 9 vs. 7
Li et al. [42]	Meta-analysis of first two RTs and four cohort studies	419 used MHT and 1029 non-users	Deaths: hazard ratio = 0.68 (0.54–0.86) Cohort studies: hazard ratio = 0.63 (0.49–0.81) 2 RTs: hazard ratio = 1.03 (0.58–1.83)	

CEE, conjugated equine estrogens; CI, confidence interval; CT, combined treatment; ET, estrogen-only treatment; OS, overall survival; RT, randomized trial.

Table 3. Summary of indications and contraindications for MHT.

Cancer	Contraindication	Relative contraindication	Possible
Breast	ER + and ER−		Vaginal estrogens in women with tamoxifen With AIs? Possible risk
Ovarian	Low-grade serous and endometrioid Borderline with implants, invasion Granulosa cell tumors Cell cord tumors	High-grade endometrioid? Lack of data	High-grade serous Mucinous Borderline of good prognosis (lack of data) Progesterone progestins in granulosa tumors
Endometrial	High stages Avoid vaginal estrogens	Low grade and low stages at distance from the treatment Lack of data	Progesterone/progestins
Cervical	Adenocarcinoma HPV? Others?? Lack of data	*In situ* adenocarcinoma	Squamous cell carcinoma

AI, aromatase inhibitor; ER, estradiol receptor.

endometrioid tumors as well as sex-cord and granulosa cell tumors (level of evidence II and grade A for high-grade serous and grade E for low-grade, level of evidence IV and V for sex-cord and granulosa cell tumors). In this last type, high-dose progestins are used as adjuvant treatment so that progesterone/progestin are not contraindicated (level of evidence V). MHT can be prescribed in women with a history of mucinous tumors (not hormone-dependent), clear cell or serous borderline tumors without histological high-risk criterion (level of evidence III; Table 3). There is only one observational study available on borderline tumors and more information is necessary. In women previously treated for a high-risk serous borderline tumor (micropapillary pattern, stromal microinvasion, peritoneal implants), individual risk/benefit evaluation is recommended before prescribing MHT. The choice of MHT type (ET or combined treatment) should take into account the context (history of hysterectomy, familial BC risk, tolerance of the treatment).

The recommendations existing on this question are relatively concordant, excluding low-grade serous cancer and granulosa cell tumors from the indication of MHT and calling for more data on the other types. However, in younger women in particular, MHT can be used after individualization of the treatment benefits [26,32,43].

Topical estrogens are not contraindicated, except in women treated with AIs (level of evidence V).

Survivors of endometrial cancer

Endometrial cancer occurs predominantly after menopause but 25% occurs in premenopausal women and 2.5–14.4% in patients aged <40 years. In most cases, treatment will consist of hysterectomy and bilateral oophorectomy.

There are two types of endometrial cancer. Type 1, well differentiated and hormone-dependent, with a good prognosis, represents 85% of cases, and type 2 is more aggressive and less hormone-dependent. The major risk factors are unopposed estrogens and obesity. The important role of estrogens in the pathophysiology suggests that ET in survivors of endometrial cancer (ECS) could be associated with a higher number of recurrences. Observational studies reported less risk of recurrence in women treated by MHT. Most of them indicated MHT at a distance from the endometrial cancer treatment and in well-differentiated cases with low stages. There is only one RT [44], a double-blind, phase III non-inferiority trial of ET for 3 years. The trial was initiated in 1997 and closed prematurely due to the Women's Health Initiative (WHI) trial publication in 2002. A total of 1236 patients were randomized instead of 2108. In the ET group, only 41.1% of patients were compliant for the entire treatment period and only 50.1% of patients in the placebo group. Fifty-nine percent of the patients were grade 1 and

30% were grade 2. Fourteen patients (2.3%) experienced disease recurrence in the ET group and 12 patients (1.9%) in the placebo group. The rate of free recurrence survival was 94.7% for the entire group and the relative risk of recurrence/death in the ET group compared with the placebo group was 1.27 (0.9–1.7). The limits are the premature interruption of the trial and the low rate of compliance which impeded the conclusions. Data from this RT were also used to look at recurrence in Black women. Five of 56 Black patients in the ET group compared with 8 of 521 white patients experienced a recurrence [45].

A Cochrane analysis concluded that 'There was no data to say whether MHT had an effect on overall survival after hysterectomy for EC' [46,p.2].

A meta-analysis looked at the risk of recurrence after MHT in ECS [47]. It included the RT and seven observational studies, comprising 1801 ECS treated with MHT and 6015 controls. The global hazard ratio was 0.90 (0.28–2.87). The mean age of ECS with MHT was 54.39 years (48.3–60.4 years), significantly younger than controls by 3.3 years. The mean follow-up time was 63.55 months.

One of the factors for recurrence is the delay of MHT after diagnosis since most of the endometrial cancer recurrences occur within the first 24 months of follow-up; however, the treatment delay was different in the different studies, and in most of the studies the characteristics of the patients were different between the cases and controls (age, grades), leading to bias. There were some suggestions that a combined treatment could be safer than an ET.

Concerning vaginal estrogen treatment, it is not recommended as a first-line treatment because of the risk of recurrence from the vagina.

Progesterone or progestin can be used in the context of ECS to alleviate vasomotor symptoms and for sleep disorders (progesterone; Table 3).

Recommendations from the European Menopause and Andropause Society (EMAS) and the International Gynecologic Cancer Society are that 'the limited data suggest that women with low-grade, early stage endometrial cancer may consider systemic or topical estrogens' [32,p.429]. Also, the Society of Gynecologic Oncology with the North American Menopause Society (NAMS) considered MHT to be 'possible in stages I and II' [43] (level of evidence III).

Our opinion is that evidence is still lacking to use ET in ECS. After a delay of 3 years, in women with impacted quality of life, with low grades/stages, MHT may be discussed with an individual appraisal of the context and with the woman and the oncologist.

Cervical cancer

Cervical cancer (CC) is the fourth most common cancer in women worldwide. It is the third most frequent cancer in women younger than 45 years in 146 of 185 countries [48], directly related to low-income context and absence of screening, and HPV vaccine will bring improvement. In high-income countries, CC is detected mostly around the age of 40 years, whereas in lower-income countries the incidence increases up to age 55–69 years [48].

The most frequent type is squamous cervical cancer (SCC), representing 85% of CC; adenocarcinoma (AK) constitutes the rest of CC. SCC has a 74% survival rate at 5 years but varies with the stage at diagnosis, age and ethnicity [49]. In local stages, 5-year survival can be 96%, whereas distant ones have a worse prognosis around 45% [49].

All of the data show that SCC is not hormone-dependent and thus there is no limitation to treat women who experience a symptomatic menopause, whether by systemic MHT or topical estrogens (Table 3). The only available study did not report any impact of MHT on overall survival and recurrence [50].

Concerning AK, the issue is complex. AK is now classified as HPV-associated or not HPV-associated [51]. Among the two classes, different histological types are associated with different prognosis [52]. They are considered as potentially hormone-dependent, but due to the rarity of their different types, no recent data according to the new classification are available. A few studies with relative low power of evidence have suggested that MHT, especially ET, could be contraindicated. A case–control study of 124 women with AK and 139 women with SCC reported an increase in the risk of AK with ET, odds ratio 2.7 (1.1–6.8), but based on 10 cases [53]. A retrospective study using tibolone included 70 patients with AK; 38 received tibolone and 32 did not. The hazard ratio was 1.71 (0.46–6.37; $p = 0.43$). Thus, this was rather reassuring, with an equivalent overall survival and recurrence. But the prognosis factors were worse in the control group (more parameters and lymph-vascular space invasion), impeding clear conclusions.

By analogy with EC, progesterone and progestin can probably be used (level of evidence V).

In the case of AK of good prognosis, if the quality of life of the woman is severely impacted, at distance from the treatment, a discussion with the oncologist and the patient could help to indicate MHT in some cases.

Topical estrogens should be avoided due to the risk of local recurrence.

Gynecological sarcoma

Uterine sarcomas (US) are rare tumors and usually severe diseases. They can consist of uterine leiomyosarcoma, low-grade endometrial stromal sarcoma, high-grade endometrial stromal sarcoma, adenosarcomas and high-grade undifferentiated sarcoma [54]. US can contain HR. Anti-hormonal treatment and high-dose progestin can be efficient in low-grade US (stage II–IV) [55], suggesting that progestin can be used in symptomatic women. Ovarian preservation in young women with low-grade endometrial stromal sarcoma is associated with worse outcome, suggesting to avoid hormone use [56].

A study from Finish registers looked at the incidence of US in women users of MHT. They recorded 45 (59%) leiomyosarcoma, 24 (32%) stromal sarcoma and seven (9%) others. The observed rate/expected rate of US increased by two-fold

in MHT use for 5–10 years and three-fold at 10 years of use, compared to those using MHT for under 5 years [57].

Depending on HR positivity [32,43], use of MHT is contraindicated in case of HR+, according to most recommendations (level of evidence V).

A discussion between the oncologist and the woman is, in these rare tumors without sufficient evidence, recommended before indicating MHT.

Other cancers or neoplasia

Some cancers are known as a contraindication to MHT. This is the case for meningioma and severe melanoma (level of evidence III).

Some cancers can express ER ± PR, such as lung cancer, gastric cancer and bladder cancer. Lung cancer is very heterogeneous; MHT users have a lower incidence of lung cancer but could have a higher mortality, according to a few studies [58–60]. No data are available on MHT in lung cancer survivors. Bladder cancer has a lower incidence but a more severe outcome in women than in men [61]. Studies showed either less or more cancer in women using MHT. It is thus again impossible to reach a conclusion. Gastric and esophageal cancer were found to be less frequent in an observational study in women using MHT [62]. Gastric cancer expressing ER has a worse prognosis than ER–. But no data are available with MHT in gastric cancer survivors.

There is no contraindication to use MHT in lymphoma, low-risk melanoma, liver cancer, colorectal cancers, pancreatic cancer, kidney cancers, thyroid cancer and prolactinoma.

Conclusions

Women who experienced gynecological cancers and BC have an increasing overall survival with the progress in treatments. Their climacteric symptoms, the psychological consequences of their diagnosis and the consequences of the treatments for cancer can impact their quality of life even more than menopause in women without cancer. The risk of recurrence and death is a complicating factor for the potential use of MHT in those women. Knowledge is progressing, but there are still insufficient data on most types of cancer to indicate MHT use without hesitation. Modern tools will very likely help in the future to better decipher in which cases MHT use is appropriate according to the characteristics of the tumors. Meanwhile, in most of the cases, a cost–benefit evaluation with the oncologist including the voice of the woman is the best that we can offer.

Note

1. Level of evidence and grades for recommendations according to the European Society for Medical Oncology.

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