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REVIEW ARTICLE

Systemic hormone therapy after breast and gynecological cancers: an Italian expert group consensus opinion

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ABSTRACT

The specific Italian Group of Study of the Menopause formulated a consensus opinion on the use of estrogen therapy (ET) or combined estro-progestin hormone therapy (HT) after breast and gynecological cancers. This consensus is based on the risk of recurrence of the specific cancer during ET/HT, the presence of steroid receptors in cancer cells, the use of adjuvant hormone therapies and data on the use of ET/HT after cancer. The following positions were reached. ET/HT can be used after vulvar cancers and melanoma, but with great caution after the rare adenocarcinomas. ET/HT can be used after cervical cancer, but ET should be used with caution after adenocarcinomas. ET/HT can be used after International Federation of Obstetrics and Gynecology (FIGO) stage I–II estrogen-dependent endometrial cancers, except in Black women, and can probably be used after estrogen-independent endometrial cancers. ET/HT cannot be administered or should be used with great caution after most uterine sarcomas. ET/HT can probably be used after ovarian neoplasms except for granulosa cell tumors, and with great caution after low-grade serous ovarian carcinoma and serous borderline ovarian tumors. ET/HT can be used with great caution in women after estrogen receptor (ER)/progesterone receptor (PR)-positive breast cancer and is probably allowed after ER/PR-negative breast cancer.

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Introduction

The consequences of surgery and antitumoral therapies can markedly impact quality of life of survivors of breast and gynecological cancers. Systemic estrogen therapy (ET) or combined hormone therapy (HT), when allowed, may be a possible tool to improve climacteric and genitourinary symptoms, to prevent postmenopausal osteoporosis and to decrease the risk of cognitive decline and cardiovascular diseases [1]. To clarify the possible use of ET/HT in cancer survivors, the Italian Society of Gynecology and Obstetrics (SIGO) endorsed the two national societies on menopause – the Italian Society for Menopause (SIM) and the Italian Society of Gynecology for the Third Age (SIGiTE) – to select a group of expert clinicians to produce an integrated consensus opinion on the possible use of ET/HT after breast and gynecological cancers.

Methods

The members of the group selected the relevant articles for any type of cancer. Articles were identified through a comprehensive search of medical databases, including Medline, PubMed, Scopus and the Cochrane Central Register of Controlled Trials. The search terms used were 'hormone therapy', 'hormone replacement therapy', 'menopausal hormone therapy', 'estrogen', 'progestin', 'cervical uterine cancer', 'ovarian cancer and neoplasms', 'endometrial cancer', 'uterine sarcomas', 'vulvar neoplasms and cancer', 'breast cancer', 'steroid receptors', 'estrogen receptors' (ERs), 'progesterone receptors' (PRs), 'adjuvant therapy', 'tamoxifen' and 'aromatase inhibitors'. The search was limited to full articles, published in English from 1987 onwards. Randomized controlled trials, cohort and case–control studies, systematic reviews and meta-analyses were considered. When

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necessary, cited older manuscripts were manually selected and analyzed. The conclusive opinion was based on a shared integrated analysis of the available evidence, and was condensed as follows: ET/HT allowed – the available data are sufficient to indicate that cancer recurrence or mortality is not increased by ET/HT; ET/HT probably allowed – there are insufficient data on cancer recurrence or mortality during ET/HT, but the few available reports or the integrated evaluation of evidence (no indication to adjuvant endocrine therapy, ET/HT not being a risk factor for that cancer, absence of ERs) do not indicate possible harm; ET/HT prescribed with great caution – there is no direct evidence that ET/HT can be detrimental, but integrated evaluation of evidence may indicate a possible harm; and ET/HT not allowed – there is direct evidence that ET/HT can increase recurrence or mortality. In some articles, HT was also performed with tibolone, a synthetic molecule degraded in molecules with estrogenic and progestin/androgenic properties [2]. When appropriate, we mention whether data with tibolone differ from those with HT.

Vulvar neoplasia

Vulvar neoplasms mostly include vulvar squamous cell carcinomas (80–90%), basal cell carcinoma, malignant melanoma, adenocarcinoma and rare neoplasms like sarcoma and lymphoma [3].

Squamous cell carcinoma can be human papilloma virus (HPV) or non-HPV related, the latter being predominantly associated with lichen sclerosus, squamous cell hyperplasia or differentiated intraepithelial neoplasia [4].

Basal cell carcinoma originates from the basal cells of the epidermis and hair follicles [5]. Rare adenocarcinomas are represented by invasive Paget's disease, originating from a pluripotent epidermal cell of the interfollicular epidermis or apocrine-sebaceous unit, and adenocarcinoma of the Bartholin's gland, of sweat glands, breast-like and apocrine [5]. Among skin neoplasia, malignant melanoma is the most aggressive [5].

ET/HT and risk of neoplasia

ERα staining is completely lost in vulvar squamous cell carcinomas, while ERβ shifts from nuclear to mainly cytoplasmic staining, with a currently unknown functional role [6]. Prevalence of this carcinoma is not influenced by ET/HT use [7].

The extra-mammary Paget's disease is rich in androgen receptors (ARs) and has a low expression of ERs and PRs [8]. For this reason, anti-androgens were proposed as an adjuvant therapy. Except for apocrine cancer, adenocarcinomas, particularly Bartholin's gland adenocarcinoma, express ERs and PRs [8,9]. The quality of life of affected individuals can be improved by adjuvant therapy with anti-estrogens [9]. Malignant melanoma and basal cell carcinoma are not hormone-related, and their prevalence is not associated with the use of ET/HT [10].

ET/HT in women with previous vulvar neoplasia

Due to the rarity of the disease, there are no data on the use of ET/HT after vulvar neoplasia. HT users had a prolonged survival in an observational prospective study performed on 206 women with cutaneous malignant melanoma [11] (Table 1).

Conclusive opinion

There is no reason to contraindicate ET/HT after squamous cell and basal cell carcinoma. ET/HT is allowed after localized malignant melanoma. There is no direct evidence, but ET/HT should be used with great caution after adenocarcinomas rich in ERs, particularly Bartholin's gland adenocarcinoma

Cervical uterine cancer

Squamous cell carcinoma and adenocarcinoma are the most frequent cancers; uncommon types are adenoma-squamous carcinoma and neuroendocrine cervical cancers. Squamous cell and adenocarcinomas find their pathogenesis in the infection and persistence of oncogenic types of HPV [12]. Hormonal contraceptives are among the risk factors for HPV infection and persistence [13]. ERs are expressed by metaplastic cells and cells of the squamous epithelium and endocervical glandular [14].

ET/HT and risk of cervical cancer

In the HPV-infected cervix, estradiol induces DNA instability via ER-independent mechanisms [15].

A case–control study reported that the risk of cervical cancer was reduced in 645 HT users versus non-users regardless of time of use (hazard ratio [HR] 0.5, 95% confidence interval [CI] 0.3–0.8) [16]. In a cohort study with 308,036 women, ever use of an unspecified HT for >1 year was associated with a reduction of cervical cancer (HR 0.3, 95% CI 0.1–0.7) [17]. In another cohort study performed with 22,579 women with a 13-year follow-up, the use of HT (any type) was associated with a decreased cancer-related mortality (HR 0.3, 95% CI 0.2–0.6) [18]. In a case–control study with 124 women with adenocarcinoma and 139 women with squamous cell carcinoma, ever use of HT was not associated with an increased risk of overall cervical cancer, but with a time-related increase of adenocarcinoma (HR 2.7, 95% CI 1.1–6.8) [19]. In a large cohort study with 243,857 postmenopausal women with a 5-year follow-up, estradiol administered by different routes and in association with various progestins decreased the risk of squamous cell carcinoma (HR 0.41, 95% CI 0.28–0.58). The risk of adenocarcinoma increased but only when ET was associated every 3 months with a progestin (HR 1.31, 95% CI 1.01–1.67). This risk further increased after 5 years of exposure (HR 1.83, 95% CI 1.24–2.59) [20]. In the Woman's Health Initiative (WHI), a placebo-controlled clinical trial performed with 15,733 women, the use of continuous combined conjugated estrogens (CEE) plus medroxyprogesterone acetate (MPA) ($n = 8070$)

Table 1. Clinical evidence on the use of ET/HT after breast or gynecological cancers.

Author	Study	Patients	Age (years)	Hormones	Duration	Follow-up	Outcome	OR/HR/% (95% CI)
Vulvar cancer								
No specific study								
Malignant melanoma								
MacKie (2004) [11]	Prospective	83 ET or HT/123 no HT	45–55	21 unspecified ET/62 unspecified HT	1–19 years	20 years	Survival	HR 0.173 (0.048–0.621)
Any cervical cancer								
Ploch (1987) [29]	RCT	40 HT/40 no HT	32–35	E2 + E3 + NETA trisequential dienestrol + chlormadinone	2–5 years	5 years	Recurrence survival	20% HT/32% controls 5% HT/65% controls
Cervical adenocarcinoma								
Lee (2018) [27]	Retrospective	32 HT/38 no HT		Tibolone	–	5 years	Risk of progression risk of death	HR 1.71 (0.46–6.37) HR 1.59 (0.06–45.66)
Richardson (2021) [28]	Retrospective	20 HT/13 no HT/25 with ovaries	43/40/24	Unspecified	–	6 years	Disease-free survival Progression-free survival	95%/73%/95% 90%/68%/81%
Endometrial cancer								
Maxwell (2008) [44]	Retrospective	110 Black HT/1049 White HT	50–70	Unspecified ET	3 years	3 years	Disease-free survival in Black women Disease-free survival in White women	HR 7.58 (1.96–29.31) HR 1.24 (0.17–8.80)
Londero (2021) [48]	Meta-analysis	1867 HT/6077 no HT	54.4/57.4	ET/HT mainly CEE	3.5 years pooled	5 years	Recurrence Disease-free survival	OR 1.17 (0.54–2.55) HR 0.81 (0.31–2.12)
Sarcoma								
No specific study								
Epithelial ovarian carcinoma								
Li (2015) [81]	Meta-analysis	419 HT/1029 no HT	CEE or E2 E2+Progesterone E2+Tibolone		28 months	4 years	Overall survival Recurrence	HR 0.69 (0.61–0.71) 0.83 (0.64–1.07)
Achimaș-Cadariu (2023) [83]	Meta-analysis	912 HT/2666	20–61	Different ET/HT	2 months–10 years	1–19 years	Overall survival	HR 066 (0.57–0.76
		266 HT/347 no HT	20–61	Different ET/HT				
							Progression-free survival	HR 0.73 (0.57–0.95)
Low-grade serous carcinoma/BOTs/ dysgeminoma/ Sertoli or Leyding cell tumors/adult granulosa cell tumors								
No specific study								
Breast cancer								
Zang (2021)	Umbrella	3174 HT	Various	Various	Various	Various	Cancer survival	HR 0.72 (0.59–0.88)
Meta-analysis		24,753 no HT 12,969 HT/39,593 no HT	Various	Various	Various	Various	Overall survival	HR 0.82 (0.75–0.89)
Poggio (2022)	Meta-analysis	2049 HT/2175 no HT	38–81	CEE E2 + NETA E2 or E2 + MPA Tibolone	2–10 years	2.1–10.8 years	Recurrence	HR 1.46 (1.12–1.91)

BOT, borderline ovarian tumor; CEE, conjugated equine estrogens; CI, confidence interval; E2, estradiol; E3, estriol; ET, estrogen-only therapy; HR, hazard ratio; HT, combined estrogen–progestin therapy; MPA, medroxyprogesterone acetate; NETA, norethisterone acetate; OR, odds ratio; RCT, randomized controlled trial.

increased the risk of cytologic abnormalities (HR 1.4, 95% CI 1.2–1.6) after 6 years of follow-up [21]. The same observation was not replicated in the Heart Estrogen/progestin Replacement Study (HERS), a placebo-controlled clinical trial performed with 2561 postmenopausal women treated for years with continuous combined CEE + MPA (HR for cervical abnormalities 1.36, 95% CI 0.93–1.99) [22]. There was no evidence of an increased risk of cervical cancer associated with CEE + MPA utilization (HR 1.44, 95% CI 0.47–4.42) in the very limited number of cases of the WHI trial ($n = 13$) [23].

ET/HT in women with previous cervical cancer

Cervical cancer tends to lose ERs and PRs in the epithelium but not in the stroma [14,24], and the presence of ERs and PRs is associated with a better prognosis [25,26].

In one retrospective study with a 5-year follow-up, progression-free survival and death from stage 1 adenocarcinomas were not increased in 38 users of tibolone versus 32 non-users [27]; and in another retrospective study, unspecified HT (25 treated vs. 13 untreated and 25 women with conserved ovaries) was not detrimental for the 6-year progression-free survival of International Federation of Obstetrics and Gynecology (FIGO) stage I–II adenocarcinomas [28]. In one randomized controlled study of HT versus no HT performed in 80 FIGO stage I–II cervical cancer survivors, HT (estradiol and norethisterone or dienestrol and chlormadinone) did not affect the 5-year disease-free survival and cancer-specific survival [29] (Table 1).

Conclusive opinion

ET/HT is allowed after FIGO stage I–II squamous cell carcinoma. Limited evidence indicates that HT may be allowed with caution after stage I–II adenocarcinoma. In this case, the use of combined HT rather than ET appears more appropriate, as in a normal population ET increases the risk of adenocarcinoma

Endometrial cancer

Endometrial cancer can be estrogen-dependent or estrogen-independent. Therapy of endometrial cancer is surgical, combined, if needed, with chemo-radiotherapy [30]. Ovaries can be preserved in women younger than 45 years of age and with FIGO stage I cancer, at low or intermediate risk. In all the other cases, the ovaries are removed at the time of hysterectomy.

ET/HT and risk of cancer

ERs and PRs are present in normal endometrial cells and in estrogen-dependent endometrial cancer [31].

Meta-analysis of randomized studies shows that the risk of endometrial hyperplasia develops after 1 year of low-dose ET. The risk is magnified by the dose and length of ET use, with the odds ratio (OR) increasing from 1.1 to 13.1 [32]. Hyperplasia does not increase when ET is sequentially or continuously associated with a progestin (mainly MPA), norgestimate (NGM) or nerethisterone (NETA) [32]. A meta-analysis of observational and clinical trials indicates that hyperplasia does not increase with ET sequentially (12 days/month) or continuously associated with either oral (200 mg/day) or vaginal (100 mg/day) progesterone [33].

In a large observational study, the Million Women Study, the risk of endometrial cancer was increased by ET (relative risk [RR] 1.45, 95% CI 1.02–2.06), not modified by sequential HT (RR 1.05, 95% CI 0.91–1.22) and reduced by continuous combined HT (RR 0.71, 95% CI 0.56–0.91) [34]. The risk also increased in women treated with tibolone alone (RR 1.79, 95% CI 1.43–2.25) [34]. All of these differences were evident in normal weight women (body mass index < 25 kg/m^2) but disappeared in obese women (body mass index > 30 kg/m^2). In the WHI study, the HR of endometrial cancer was reduced (RR 0.72, 95% CI 0.56–0.94) after approximately 5.2 years of continuous combined HT [35]. A meta-analysis of 30 observational studies indicated that the risk of endometrial cancer is increased by ET (RR 2.3, 95% CI 2.1–2.5) with a RR of 9.3 (95% CI 7.4–12.3) after 10 years of exposure [36]. The risk is not increased by the use of continuous combined or sequential HT [36]. A meta-analysis reported that the sequential HT performed with micronized progesterone also does not increase the risk of endometrial cancer [33], despite two cohort studies [37,38] included in the analysis showing a double risk of cancer after 5 years of sequential HT with progesterone [38]. A recent meta-analysis of 15 observational studies, including 25,827 HT users and 56,537 non-users (controls), indicates that continuous combined HT reduces the risk of endometrial cancer (OR 0.71, 95% CI 0.59–0.86) [39].

ET/HT in women with previous endometrial carcinoma

ERs and PRs are present in estrogen-dependent endometrial cancer [31,40], and ARs in estrogen-independent endometrial cancer [41]. The decreased expression of ERs and PRs is associated with a worse cancer prognosis [31,42,43]. In a retrospective study including 110 Black and 1049 White patients with stage I and II endometrial cancer, ET increased the risk of tumor recurrence in Black but not in White women (RR 11.2, 95% CI 2.86–43.59) [44] (Table 1), to indicate racial disparities in the molecular subtypes of endometrial cancer [45]. In the few ($n = 10$) reported cases of steroid receptor-negative endometrial cancer, the use of HT was not associated with a worse prognosis [46].

A Cochrane meta-analysis concluded that, despite limited evidence, HT is probably not contraindicated in women with FIGO stage I–II endometrial cancer [47]. A more recent meta-analysis including one clinical trial and eight observational studies, totaling 1867 ET/HT users and 6077 non-users, shows that ET/HT does not increase the risk of cancer (OR 1.17, 95% CI 0.54–2.55) both in HT (HR 0.81, 95% CI 0.31, 2.12) and ET (HR 1.21, 95% CI 0.11–13.15) users [48] (Table 1).

Conclusive opinion

ET or HT (not tibolone, which was not tested) is allowed after FIGO stage I–II endometrial cancer. There are no data on women with an advanced stage of endometrial cancer. In Black women, ET is not allowed for a higher risk of recurrence, and HT was not tested. ET/HT is probably allowed after ER-negative endometrial carcinoma. The data are too limited to reach a strong conclusion, but a negative impact cannot be anticipated.

Uterine sarcoma

Uterine leiomyosarcoma, endometrial stromal sarcoma and undifferentiated uterine sarcoma are the most frequent sarcomas [49,50]. The high-grade endometrial stromal sarcoma is highly aggressive, while low-grade endometrial stromal sarcoma has a 5-year survival rate of 80–100% [51]. ERs and PRs are absent in high-grade endometrial stromal sarcoma, but are present in low-grade endometrial stromal sarcoma and some uterine leiomyosarcoma [52,53]. Their presence or overexpression in early stages is associated with a prolonged disease-free and overall survival [52,54]. In premenopausal women affected by low-grade endometrial stromal sarcoma, ovary removal [55] and adjuvant HT with high-dose progestins, aromatase inhibitors and gonadotropin releasing hormone analogues (GnRH-a) [56–58] decreases recurrence of stage II–IV neoplasia [59]. There are no convincing data on the role of adjuvant HT after high-grade endometrial stromal sarcoma [60].

ET/HT and uterine sarcoma risk

In a Finnish national study, 243,857 postmenopausal women having used an estradiol-based sequential or continuous HT (oral/transdermal) for at least 6 months did not show an increased risk of sarcomas in the first 5 years of use, but the standardized incidence ratio of sarcomas (events in users / event in background population) increased to 2.0 (95% 1.4–2.9) after 5–10 years and to 3.0 (95% CI 1.3–5.9) after 10 years of HT use [61].

ET/HT in women with previous uterine sarcomas

A review of observational studies reported that in some patients affected by low-grade endometrial stromal sarcoma, the elimination of HT or tamoxifen, stabilizes the disease [57]. Likely, these data cannot be extended to sarcomas with no ERs and PRs, such as high-grade endometrial stromal sarcoma or some uterine leiomyosarcoma.

Conclusive opinion

ET/HT is not allowed after low-grade endometrial stromal sarcoma and ER-positive uterine leiomyosarcoma. No data are available on ER-negative uterine leiomyosarcoma, high-grade endometrial stromal sarcoma and undifferentiated uterine sarcoma. After these tumors, ET/HT could be administered with great caution, and probably for a period of time <5 years.

Ovarian neoplasia

Ovarian neoplasia represents 2.5% of all female malignancies and is responsible for 5% of all female cancer deaths [55].

More than 90% of ovarian malignancies are epithelial carcinomas, which include high-grade (70%) and low-grade (<5%) serous carcinoma, endometrioid (10%), clear cells (10%), mucinous carcinoma (3%) [62] and their respective borderline ovarian tumors (BOTs) [63]. Borderline or malignant Brenner tumors, carcinosarcoma and mixed carcinoma are rarer forms of epithelial carcinoma [64]. Non-epithelial ovarian tumors are germinal cell tumors (3% of all ovarian malignancies; dysgerminoma, yolk sac tumor, embryonal carcinoma, non-gestational chorion carcinoma, mixed cell tumor, ovarian carcinoid and rarer forms) and sex cord stromal tumors (2%; variate tumors among which juvenile and adult granulosa cell tumor, Sertoli cell tumor and Leydig cell tumor) [64]. ERs and PRs are mainly expressed in endometroid, low-grade and high-grade serous carcinoma, and little expressed in mucinous and clear cell carcinoma [65–67]. They are overexpressed in adult granulosa cell tumor [68], and absent in germinal cell tumors. The balance between ERα (pro-mitotic) and ERβ (anti-mitotic) is critically important [67,69], as well as the contemporaneous expression of PRs, whose stimulus exerts anti-mitotic and pro-apoptotic effects. In high-grade serous carcinoma, the expression of PRs is associated with a favorable prognosis and a longer disease-free survival [70]. Forty percent of high-grade serous carcinoma benefits from adjuvant HT with tamoxifen or aromatase inhibitors [67]. Adjuvant therapy with GnRH-a did not significantly increase disease-free survival in nine cases of optimally debulked low-grade serous carcinomas versus 15 controls (76.4 months vs. 22.9 months) [71], and was ineffective in incompletely debulked cases [71]. In another study, adjuvant therapy (anti-estrogens or aromatase inhibitors) prolonged disease-free survival in 70 women with stage II–IV low-grade serous carcinoma versus 133 controls (81 months vs. 30 months), but did not affect disease-specific mortality [72]. Data on adjuvant therapy after endometroid carcinoma are scanty [67], while there are data for a good response rate of granulosa cell tumors (46–48%) [67,68]. A meta-analysis on adjuvant endocrine therapy indicated a clinical benefit (complete response, partial response, stable disease or no progression) in 41% of women surviving epithelial ovarian cancers, of which 46% were ER/PR-positive and 36% had an unknown receptor status. Interestingly, the clinical benefits were similar with aromatase inhibitors, tamoxifen, tamoxifen plus a progestin or ethynyl-estradiol (an estrogen) plus a progestin [73]. Thus, the co-administration of progesterone with an exogenous estrogen appeared to induce the same benefit as the administration of anti-estrogens or aromatase inhibitors.

ET/HT and the risk of ovarian neoplasia

In a meta-analysis of 52 epidemiological studies, the use of ET or HT was associated with a similar increase of ovarian cancer risk (RR 1.37, 95% CI 1.29–1.46), mainly of serous and endometrioid cancer [74]. Women on combined HT may have previously used ET. A subsequent pooled analysis of five population-based case–control studies, including 1509 cases and 2295 postmenopausal controls, did not show an increased risk of ovarian cancer in users of continuous combined HT (OR 0.85, 95% CI 0.72–1.0). Subgroup analysis indicated a decreased risk of mucinous ovarian cancer (OR 0.40, 95% CI 0.18–0.91) [75]. In another meta-analysis, with no distinction between ET, HT and HT regimens, the risk of ovarian cancer

was increased by therapy (RR 1.16, 95% CI 1.06–1.26) [76]. In the randomized placebo-controlled WHI, prevalence of ovarian cancer evaluated after 5.6 and 13 years of follow-up was not increased by continuous combined HT (CEE and MPA) [77].

As regards BOTs, observational studies indicate that the risk of serous or mucinous BOT is either not increased in HT users (unspecified regimen) [78] or increased after any type of HT used for a period ≥4 years [79]. In a nationwide study from Denmark with 885 cases and 13,122 age-matched cases, unspecified HT use was associated with an increased risk of serous BOTs (OR 1.32, 95% CI 1.02–1.72) [80].

ET/HT in women with a previous ovarian neoplasia

A review of two randomized and six cohort studies, including 419 HT users and 1029 HT non-users, indicated that at follow-up of 48 months, the administration for a median time of 28 months of CEE or estradiol alone, estradiol plus progesterone or estradiol plus tibolone had a favorable impact on overall survival after epithelial ovarian cancer (HR 0.69, 95% CI 0.61–0.79), independently of FIGO stage and cancer differentiation [81] (Table 1). Cancer recurrence was not affected by ET/HT use. A meta-analysis included one study with a considerable number of BOTs ($n = 150$) [82]. A subsequent systematic review with meta-analysis included two randomized clinical studies and nine cohort studies totaling 4191 cases of stage I–IV epithelial ovarian cancers [83]. Overall (HR 0.6, 95% CI 0.57–0.76) and progression-free (HR 0.73, 95% CI 0.57–0.95) survival was improved by ET/HT. Different molecules were used (estradiol, CEE, estrogen plus tibolone, progesterone and MPA). The effect of ET/HT was not influenced by the type of study (clinical randomized or cohort), by the stage of the disease (from stage I to stage IV), by cancer differentiation, by resectability (optimal or suboptimal) and by the age of the patients (from <29 to 50–59 years of age) (Table 1). No study has specifically evaluated the effect of HT after low-grade serous carcinoma. Fertility sparing is an accepted management of BOTs [84]. There are no data indicating a contraindication to HT after mucinous BOT [85]. There is also no specific evidence on HT after serous BOT. BOT recurrence or transformation in low-grade serous ovarian carcinoma is favored by peritoneal dissemination and pejorative criteria (micropapillary, microinvasion) [85]. There is no evidence that this process is favored by ET/HT, even if other consensus opinions indicate that in these cases HT may increase BOT recurrence and transformation [85]. There are no specific data on other BOTs, on dysgeminoma or on Sertoli or Leyding cell tumor. There are also no data on ET/HT after adult granulosa cell type tumors, but they have a high rate of clinical response to adjuvant HT [68].

Conclusive opinion

After epithelial ovarian cancers, HT is more indicated that ET, as in healthy individuals ET increases the risk of these cancers and most of the evidence after cancers were obtained with HT. HT is allowed after high-grade serous ovarian carcinoma, endometroid carcinoma, mucinous ovarian cancer and, probably, clear cell carcinoma. These cancers express ERs and PRs, but their recurrence is not increased by HT.

HT should be prescribed with great caution after low-grade serous ovarian carcinoma. There are no specific data indicating that HT increases tumor recurrence, but its disease-free survival (not mortality) is increased by adjuvant HT.

HT is allowed after mucinous BOTs, and probably allowed after endometroid, clear cell and Brenner's BOTs.

HT can be prescribed with great caution after serous BOTs. There are no specific data in cancer survivors, but in healthy individuals HT increases the risk of serous BOTs.

ET/HT is allowed after non-epithelial ovarian cancers with the exclusion of granulosa cell tumor.

Breast cancer

Breast cancer is the most common tumor in women, with subtypes characterized by the expression of ERs and PRs, of human epidermal growth factor receptor 2 (HER2+) or of none of them (basal-like or triple-negative tumors) [86]. Adjuvant HT is indicated after ER/PR-positive [87,88], but not negative tumors [89].

ET/HT and breast cancer risk

Exogenous hormones are considered among the risk factors for breast cancer [86]. In a meta-analysis of 58 observational studies were included 108,647 women who developed breast cancer. After 1–4 years the risk of breast cancer was slightly higher with HT than with ET (OR 1.60, 95% CI 1.52–1.69 vs. OR 1.17, 95% CI 1.10–1.26) and tended to increase with the length of ET/HT use, disappearing almost 10 years after ET/HT discontinuation [90].

Meta-analyses of randomized placebo-controlled studies were published in the same manuscript, as a supplement [90]. The risk of breast cancers was decreased by ET (HR 0.77, 95% CI 0.64–0.93) in six trials totaling 519 cases [90], and increased by HT (HR 1.26, 95% CI 1.10–1.45) in five trials totaling 5864 cases [90]. In the WHI, the risk with HT was not evident in naïve women [91], in women with a family history of breast cancer and when the crude HRs are adjusted for confounding (HR 1.20, 95% CI 0.94–1.53) [92]. The risk pertained also to ER/PR-negative breast cancers [91], probably as the consequence of paracrine stimulatory signals produced by ER/PR-positive breast cells [93]. A systematic review indicates that the risk of breast cancer is increased after 5 years of HT with progesterone (RR 1.33, 95% CI 1.15–1.48) [94]. The intrauterine levonorgestrel system (LNG-IUS) can be associated with ET [95] to protect the endometrium, and its use alone or as HT is associated with an increased risk of breast cancer (OR 1.16, 95% CI 1.06–1.28) [96]. Recent observational evidence indicates that the breast cancer risk is not increased by ET (CEE) plus bazedoxifene, a selective ER modulator molecule (RR 0.79, 95% CI 0.58–1.05) [97].

ET/HT in women with previous breast cancer

Three randomized, placebo-controlled trials were performed to evaluate the risk of breast cancer recurrence during HT

[98–100], and they were prematurely stopped due to an increased recurrence rate. A Swedish study, initiated in 1997, randomized 188 cancer survivors to HT and 190 to no HT [98]. Breast cancer recurrence was not increased after 4 and 10.8 years of follow-up (HR 1.3, 95% CI 0.9–1.9) [98]. The study was prematurely stopped in 2003 because of a joint analysis with another Swedish study [99], that randomized 442 cancer survivors to HT or no HT, and after 2.1 years documented an increased cancer recurrence in HT users (22% vs. 8%) (HR 2.4, 95% CI 1.3–4.2) [99]. In the Livial Intervention following Breast cancer: Efficacy, Recurrence, And Tolerability Endpoints (LIBERATE) clinical trial, breast cancer survivors were randomized to placebo ($n=1542$) or HT with tibolone ($n=1556$). At a median follow-up period of 3.1 years, the risk of breast cancer recurrence was increased by HT (HR 1.44, 95% CI 1.16–1.79) [100]. In all studies, the increased risk was observed only for ER and PR-positive breast cancers [99,100]. A recent meta-analysis confirms a higher risk of recurrence (RR 1.46, 95% CI 1.12–1.91) during ET/HT (CEE, estradiol, estradiol and NETA or MPA, tibolone), limited to ER/PR-positive breast cancers [101]. An umbrella review indicates that administration of ET/HT pre and post breast cancer is associated with a higher risk of cancer but with better cancer-specific (RR 0.72, 95% CI 0.59–0.88) and overall (RR 0.82, 95% CI 0.75–0.89) survival [76]. No data are available for the use of CEE and bazedoxifene after breast cancer.

Conclusive opinion

Data in healthy women indicate that the risk of breast cancer is higher with HT than ET, but this does not emerge in breast cancer survivors. ET/HT increases breast cancer recurrence but decreases cancer-specific and overall survival. ET/HT can probably be used with great caution after breast cancer. ET/HT is probably allowed after ER/PR-negative breast cancers. HT represents a risk factor for these cancers, but the limited data in cancer survivors do not show an increased recurrence rate with ET/HT.

Discussion

The present analysis was focused on the effect that systemic ET/HT can exert in survivors from breast and gynecological malignancies. Different to previous positions regarding this issue, we placed considerable effort to evaluate the differences among different types of tumors, also of the same specific organ and to differentiate between the use of ET and HT. In addition, when the data on ET/HT were scanty, we used a combination of indirect evidence to reach a sufficiently reliable indication. For example, the post-cancer need for an adjuvant hormonal therapy was considered one of the parameters possibly contraindicating ET/HT use. Yet after epithelial ovarian cancers [65], adjuvant HT was performed also with the administration of a potent estrogen (ethynyl-estradiol) combined with a progestin [65], and this led us to conclude that HT is not contraindicated after epithelial ovarian cancer.

Cancer expression of ERs and PRs was also considered among the other parameters possibly contraindicating the use of ET/HT. Vulvar squamous cell carcinomas express ERs but they are cytoplasmatic ERβ, with an unclear functional role, and we concluded on the basis of the other indirect evidence that ET/HT can be used after vulvar squamous cell carcinomas [4]. Also, estrogen-dependent endometrial cancer expresses ERs but endometrial cancer recurrence is not increased by ET/HT, except in Black women [42], and we concluded that ET/HT is not contraindicated after endometrial cancer. Similarly in the ovary, high-grade serous ovarian cancer, endometrioid ovarian cancer, mucinous ovarian cancer or clear cell ovarian cancer express ERs but the response of the tumor depends on the levels of ER expression, on the type of ERs expressed (ERα or ERβ) and on the co-presence of PRs. The recurrence of these cancers is not increased by HT [61,63] and we concluded that HT can be used after these cancers. For some authors, low-grade serous ovarian cancer represents a contraindication to HT, because of the high expression of ERs and some positive results obtained with the use of adjuvant therapy. HT seems to be as effective as anti-estrogens or aromatase inhibitors in reducing overall epithelial ovarian cancer recurrence [65] and we did not find any evidence of an increased recurrence of low-grade serous ovarian cancer during HT, or that either hormonal contraceptives or

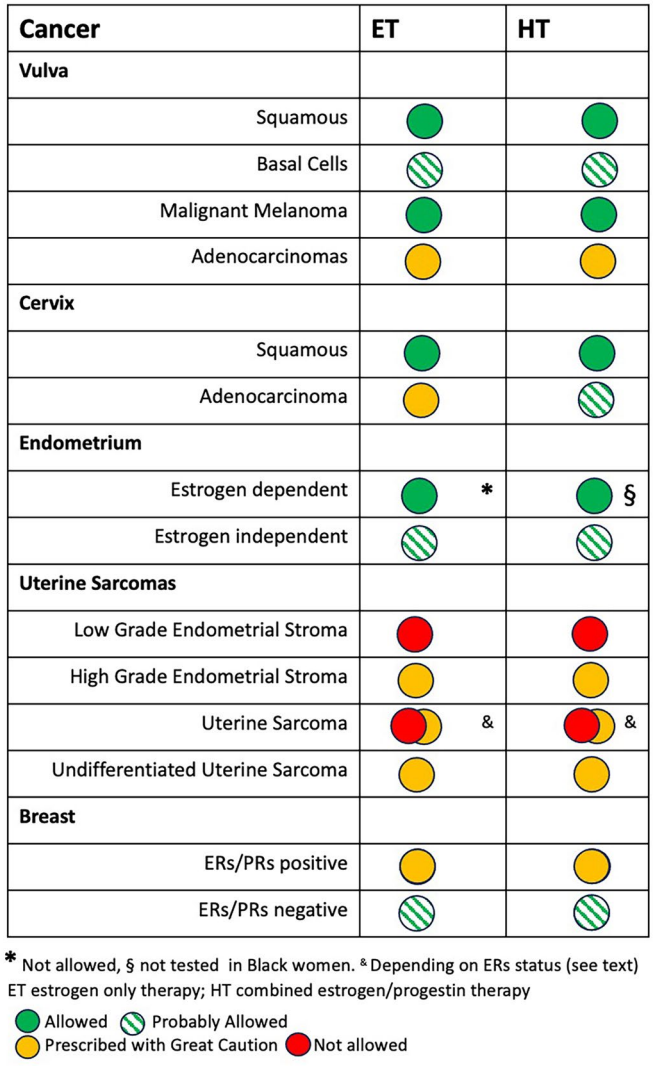

Figure 1. Schematic representation of the possibility to prescribe estrogen-only therapy (ET) or combined hormone therapy (HT) after different types of gynecological cancers of the vulva, cervix, endometrium, uterus and breast.

Cancer	ET	HT
Ovary		
Low Grade Serous		
High Grade Serous		
Endometrioid		
Mucinous		
Clear Cells		
Borderline Serous		
Borderline Serous Pejorative criteria		
Borderline Mucinous		
Borderline Endometrioid		
Borderline Clear Cells		
Borderline Brenner		
Dysgerminoma		
Granulosa Cells		
Sertoli or Leyding cells		

ET estrogen only therapy; HT combined estrogen/progestin therapy

Allowed Probably Allowed
Prescribed with Great Caution Not Allowed

Figure 2. Schematic representation of the possibility to prescribe estrogen-only therapy (ET) or combined hormone therapy (HT) after ovarian cancers.

HT represent risk factors for low-grade serous ovarian cancer. Accordingly, we left the option that ET/HT can be used with great caution after this tumor. ET/HT could be a potential risk factor for ER/PR-negative breast cancers [87], because the risk of these tumors is increased by HT [87]. Yet recurrence is presumably not increased by ET/HT [93–95].

Overall, we used a combination of information to reach a consensus on the effect of ET/HT use after different types of breast and gynecological cancers. There are several limitations to our analysis due to the lack of specific data on different types of cancer, and on different ET/HT molecules, regimens and routes of administration. Yet the analysis details and balances the available evidence of the literature as much as possible, and may be useful in counseling, in indicating practical guidelines and in stimulating clinical studies aimed to implement the scanty evidence available for many types of cancers.

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