Objective: Thousands of women are treated each year for cancer; many of these are already in menopause, while other younger patients will go into early menopause due to surgery, or chemotherapy, or the need for radiotherapy to the pelvic region. In most cases the oncologist and the gynaecologist would advise these women against the use of HRT. The purpose of this paper is to review biological and clinical evidences in favour and against HRT use in the different tumours and to propose an algorithm that can help choosing the treatment for the single woman.

Methods: We performed a systematic literature review through April 2002 concerning: (1) biological basis of hormonal modulation of tumour growth; (2) epidemiological data on the impact of HRT on different cancers risk in healthy women; (3) safety of HRT use in cancer survivors; (4) alternatives to HRT.

Results: With the exception of meningioma, breast and endometrial cancer, there is no biological evidence that HRT may increase recurrence risk. In women with previous breast and endometrial cancer HRT is potentially hazardous on a biological basis, even if published data do not show any worsening of prognosis.

Conclusions: Even if a cautious approach to hormonal-dependent neoplasias is fully comprehensible and the available alternative treatment should be taken into greater consideration, the reticence to prescribe HRT in women previously treated for other non-hormone-related tumours has neither a biological nor a clinical basis. An algorithm based on present knowledge is proposed.

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Keywords: Menopause; Hormone replacement therapy; Cancer survivors

1. Introduction

Thousands of women are treated each year for cancer, many of these are already in menopause, while other younger patients, with normal ovarian function at diagnosis, will go into early menopause due to surgery, or chemotherapy, or the need for radiotherapy to the pelvic region.

Progress in the diagnostic and therapeutic fields has cured many women undergoing cancer treatment or provided longer survival periods after primary surgery. The symptoms and the long-term consequences of estrogen deprivation are thus a problem also for these patients, in terms of both the quality of life and for
preserving health from the effects of ageing and hormone deficiency.

However, in most cases, and independently from tumour type and disease stage, the oncologist and the gynaecologist would advise these women against the use of HRT.

Even if a cautious approach to hormonal-dependent neoplasias, such as breast and endometrial cancers, is fully comprehensible, the reticence in use of HRT for other tumours, uncorrelated to sex hormones, is apparently inexplicable. A clear example is in the case of hematopoietic tissues tumours that often appear in younger women and require massive chemotherapy; in these patients, damage from early oestrogen deficiency can be greater than that correlated to the original disease [1–3].

This subject is hotly debated, also because clinical and epidemiological results are scarce. In this paper, the available data on the correlations between sex hormones and induction and proliferation of different tumour types will be analysed in an attempt to draw conclusions as to whether or not HRT should be used in the different cases.

2. Endometrial cancer

Endometrial carcinoma is the oestrogen-dependent neoplasm par excellence and the association between unopposed oestrogens and increase of endometrial cancer in non-hysterectomized postmenopausal women has been recognised for over 30 years [4].

On the other hand, endometrial carcinoma has a good prognosis; overall 85% of women operated for this tumour are cured and could benefit from HRT.

Moreover, 25% of all women with endometrial cancer are premenopausal and 5% are under 40 years at primary surgery, leading to premature menopause.

The concern regarding HRT for women with endometrial carcinoma is that, even after uterus removal, estrogens may stimulate growth of occult foci of tumour cells.

The effect of HRT on the recurrence risk of endometrial cancer after primary surgery is unknown, although retrospective studies have pointed to an absence of adverse outcomes [5–7]. These studies mainly included stages I–II patients with negative lymphnodes. However, the lack of a control group, the retrospective type of analysis and the lengthy time between cancer surgery and HRT initiation, is a limiting factor. Recently, a matched control study was published on HRT evaluating 130 patients with endometrial cancer, considered to be at low risk and comparable for disease characteristics [8]. Of these, only 14% had stages II–III or G3 carcinoma and lymphnodes were positive in only one case. Hormone users have a statistically significant longer disease-free interval than non-oestrogen users ($P < 0.006$) at a mean follow-up of 83 months. In the group receiving HRT there were only 2 pelvic recurrences versus 11 recurrences (8 pelvic and 3 distant) in the non-treated group and the survival curve is clearly favourable in the treated patients ($P < 0.006$).

The need for adding progestins to estrogens in these patients is unknown at present. Progesterone inhibits the stimulatory effects of oestrogen on normal and hyperplastic endometrium, but high dose progestin as adjuvant treatment after endometrial cancer surgery does not affect recurrence rate. A Gynaecologic Oncology Group (GOG) trial, who randomises between estrogen and placebo two groups of over 1000 patients with menopausal symptoms, treated for stage I and occult IIa endometrial carcinoma, is at present underway. On the other side, in retrospective studies and in the recent study by Suriano, approximately 50% of the patients treated had also received progestins in combination with oestrogen.

Currently, no conclusive data is available to support specific recommendations regarding use of HRT in endometrial cancer patients. The American College of Obstetricians and Gynaecologists highlighted last year the lack of clinical trails and the need to adequately inform patients, illustrating possible risk of recurrence, based on tumour characteristics, and the benefits in using HRT [9]. Furthermore, it would be mandatory to inform patients about alternative therapies other than estrogens, in particular for prevention of osteoporosis and cardiovascular disease.

3. Ovarian cancer

Most ovarian epithelial tumours appear in women over 55 years. However, even when the disease occurs in premenopausal age, the radical surgical treatment induces premature menopause. Independently
from age, disease prognosis is poor and less than 30% of patients with stages II–IV tumours survive over 5 years from diagnosis. Thus, even if long-term prevention of osteoporosis or cardiovascular disease may be hardly significant in these patients, it is of great importance to guarantee a good quality of life.

There is no conclusive evidence that HRT acts as an initiating or promoting factor in women who subsequently develop epithelial ovarian cancer. Epidemiological data on the association between HRT use in menopause and incidence or death from ovarian cancer are inconsistent, but it is unlikely that estrogens play a relevant role on this tumour. If we consider the two most recent meta-analyses on the subject, one shows no increase in RR of ovarian cancer in women taking HRT (RR = 1.1; 95% CI, 0.9–1.3) [10], while the other shows globally a fairly small, but significant, increase in risk (RR = 1.15; 95% CI, 1.05–1.27) [11]. Also the association with therapy duration is controversial: in a metaanalysis [11] the use of estrogens for over 10 years gives a RR of 1.27 (CI 95%, 1.00–1.61), while in the more recent one [10] there is no significant correlation with the duration of use.

Pregnancy and use of oral contraceptives reduce the risk of ovarian cancer, and in women with stage I disease treated with unilateral oophorectomy, the recurrence rate is not increased as compared to women treated with bilateral oophorectomy. Furthermore, there is no experimental data to support the hypothesis that oestrogens might stimulate quiescent epithelial ovarian cancer cells and there is no evidence of a clinical role of the hormonal receptors in epithelial ovarian cancers.

There are few studies on the use of HRT in patients with ovarian cancer [12–14]. These have reported no difference of survival in patients treated with estrogens compared to the control, while the improvement in the quality of life is evident. As far as we know today, there is nothing to show that HRT should not be used in women treated for epithelial ovarian carcinoma, independently from tumour stage.

4. Cancer of the cervix

There is evidence to suggest that sex hormones may influence cervical tumours. At puberty, growth and development of cervical tissue are promoted by sex hormones and normal and neoplastic tissue continue to express hormone receptors even after menopause and in advanced age. However, association between use of HRT and cervical carcinoma has never been proven. In fact, the few available epidemiological studies suggest a protective role of HRT on the risk of this tumour, even if it cannot be excluded that this may be due to a tighter medical control of women on HRT compared to non-treated women [15]. Ploch reported 120 women treated for stages I–II cervical cancer in which HRT showed no change either in survival or disease free survival at 5 years [16]. In the recent years, there has been an increase in the proportion of cervical adenocarcinoma (15% of all cervical cancers). According to some, this histotype is dependent on oestrogen stimulation in the same way as endometrial carcinoma. In a case-control study, the group of women on HRT showed an overall RR of 2.1 (95% CI, 0.95–4.6) for adenocarcinoma versus 0.85 (95% CI, 0.34–2.1) for squamous cell carcinoma [17]. The risk was higher in case of estrogens alone: RR for adenocarcinoma 2.7 (95% CI, 1.1–6.8) versus 0.86 (95% CI, 0.26–2.8) for squamous cell carcinoma. With combined treatment the RR for adenocarcinoma was 1.1 (95% CI, 0.26–5.0). According to these data, treatment approach should be the same as for endometrial adenocarcinoma.

5. Vulvar cancer

Carcinoma of the vulva is an infrequent tumour, typical of advanced age; its aetiology is not yet fully known. Normal and neoplastic vulva tissue have oestrogen, progesterone and androgen receptors, albeit in lesser quantities than in other hormonal dependent tissues and recent studies indicate that neoplastic transformation of vulva cells by HPV can be mediated by progesterone.

Epidemiological studies have not shown any association between patient’s reproductive history or taking estrogen in menopause and in situ or invasive vulva carcinoma. In a case-control study, the RR of developing vulva carcinoma in women who had taken estrogen was 1.2 (95% CI, 0.7–2.1) for in situ and 1.2 (95% CI, 0.6–2.3) for invasive cancers; data is not
sufficient on the effect of combining progesterone and estrogens [18]. Similar results were reported in a recent Swedish study, considering together carcinoma of vulva and vagina, with RR of 1.2 for women on HRT (95% CI, 0.7–1.8) [19].

It is thus believed that there is no contraindication to the use of HRT in women treated for vulva or vaginal neoplasm [20].

6. Breast cancer

Breast carcinoma is considered to be an absolute contraindication for estrogen therapy as it can activate or accelerate occult micrometastasis or favour secondary tumour growth. It has recently been suggested to review this dogma, at least in selected groups of patients, who are disease free after surgery, at low risk of recurrence and complain severe menopausal symptoms that cannot be held under control by other therapies. A US survey showed how 27% of post-menopausal women with a history of breast tumour consider that they need HRT, although the majority (78%), think that this might be harmful regarding disease prognosis [21].

In favour of estrogen use in these cases is the reassuring data of the so-called “natural experiments”, such as breast carcinoma diagnosed during pregnancy or during the use of oral contraceptives or HRT, that do not appear to have a worse prognosis than comparable tumours occurring in women not taking estrogen. Some circumstances go against HRT use: (1) oophorectomy efficiently reduces the risk of recurrence and death in premenopausal women with receptor positive breast carcinoma [22]; (2) the observation that late menopause increases the risk; (3) the increase of breast cancer risk associated with HRT use over long periods of time [23].

The available clinical studies on HRT in women with previous breast tumour do not allow deductions about the safety of its use [24–32]. None of the studies has demonstrated an increase in recurrence or death for breast cancer associated to HRT use after primary surgery. However, the number of cases and observation time are not sufficient.

A consensus conference was held at the end of 1997 in Charlottesville on the subject that defined guidelines to follow both regarding clinical approach and in drawing-up study protocols [33]. Given the lack of controlled trials to exclude a possible detrimental effect of estrogen on the disease prognosis, a cautious line of action was taken. Before proposing HRT, alternative treatment should be used, both for menopause symptoms and for preventing osteoporosis and cardiovascular disease. HRT should be used only in those women who do not respond to other treatments or if they make specific request of HRT, for short treatment periods, at low estrogen dosage and preferably within controlled clinical trials.

There are no criteria regarding selection of women to propose HRT treatment to. It would then appear sensible to treat preferably: (1) patients at low risk of recurrence according to biological characteristics of the tumour (small diameter, low grade, negative lymph nodes); (2) patients with negative receptor cancers, for which it is considered that an eventual proliferative effect of the sexual hormones is very unlikely. Moreover, tamoxifen treatment is considered to give fairly good protection against estrogen stimulation of the breast. In fact, tamoxifen is an efficient anti-tumour drug also in premenopausal patients showing high endogenous estradiol levels and should retain its anti-proliferative effect on breast tissue also in menopausal women treated with low-dose estrogen regimens.

These guidelines may be revised in the light of recent studies that have shown improvement in prognosis in patients taking HRT after surgery. O’Meara, on 174 HRT treated women, compared each with four controls comparable for disease stage, observed a reduction in recurrence rate (RR, 0.50; 95% CI, 0.3–0.8) and death (RR, 0.48; 95% CI, 0.29–0.78) in the group taking HRT, independently from HRT regimen (estrogens alone, estrogens + progestins or vaginal estrogens) [34]. Di Saia observed a reduction in deaths of 78% (95% CI, 0.11–0.71) in HRT treated patients; in this study, however, the average length of use was only 22 months and HRT was started on average after 47 months from the primary diagnosis [35]. In a recent analysis of 11 trials, four of which with control group, for a total of 214 breast cancer survivors who began HRT after a mean interval of 52 months from primary surgery, the annual recurrence rate was 4.2% in the estrogen group and 5.4% in the non-treated group; the difference was not statistically significant [36].
7. Estrogen alternatives for menopause

Despite these reassuring results, we are still far from having scientific evidence to state that HRT is completely harmless in patients previously treated for breast cancer. The main problem afflicting women undergoing surgery for breast cancer are vasomotor symptoms. To relieve hot flushes, substances have been used that often give similar results to placebo, that in itself provides a response in around 20–30% of women. Other, more efficient, results have been obtained in placebo-controlled studies with progestins, in particular low-dose megestrol acetate [37,38], and with the use of Selective Serotonin Re-uptake Inhibitors, such as venlafaxine [39] and fluoxetine [40], that guarantee a good control over hot flushes and have only marginal side-effects, with no effect on tumour proliferation. For prevention of osteoporosis and cardiovascular diseases, there is a consensus on the use of other drugs of proven effectiveness, such as difosphonates [41], raloxifen [42], statins [43], associated to adopting a correct lifestyle [44]. Finally, there is interest in the use of tibolone, a synthetic steroid with estrogen, progestin and androgen activity, efficient in controlling vasomotor symptoms [45] and osteoporosis [46]. Preliminary data suggest an antiproliferative effect on breast tissue [47] and a European study with this drug for women operated for breast carcinoma is now under approval.

8. Non-gynaecologic cancers

When it comes to non gynaecologic tumours, the scientific literature is even poorer as to the specific issue of HRT use in women apparently cured of the disease. All we can conclude is derived from plausible biological data or on the ability of steroid hormones to stimulate or inhibit the disease and from the present knowledge about possible associations between the use of other drugs of proven effectiveness, such as difosphonates [41], raloxifen [42], statins [43], associated to adopting a correct lifestyle [44]. Finally, there is interest in the use of tibolone, a synthetic steroid with estrogen, progestin and androgen activity, efficient in controlling vasomotor symptoms [45] and osteoporosis [46]. Preliminary data suggest an antiproliferative effect on breast tissue [47] and a European study with this drug for women operated for breast carcinoma is now under approval.

9. Thyroid cancer

The greater incidence of thyroid cancer in women than in men, particularly marked during the reproductive years, has suggested that female sex steroids may have a role in the development of this malignancy [48]. However, other clinical observations do not seem to confirm this hypothesis. For instance, the prognosis of differentiated thyroid cancer is the same in pregnant and non-pregnant women of the same age [49,50]. There is no evidence of increased incidence of thyroid cancer in women taking oral contraceptives (OC) [48,51,52]. The study by Rossing et al. [48] showed that OC use significantly reduces malignancy risk (OR, 0.6%; 95% CI, 0.4–0.9) in women younger than 45 years of age. Conversely, the pooled analysis of 13 case-control studies showed that the risk was increased for current OC users (OR, 1.5; 95% CI, 1.0–2.1), but decreased with time after stopping (OR = 1.1 for more than 10 years since last use) [53]. This moderate excess risk in current users could be partly due to a more accurate surveillance for thyroid diseases in these women.

In the literature no increased risk of thyroid cancer in HRT users has been shown [51,53,54]. Persson et al. [54], in a study on cancer incidence and mortality in a cohort of 22,597 Swedish women prescribed with HRT, reported that after 13 years follow-up, the relative risk (RR) of thyroid cancer was 0.9 (95% CI, 0.6–1.4). Similarly, the pooled analysis of eight case-control studies, including a total of 1305 cases and 2300 controls, revealed an OR of 0.8 (95% CI, 0.6–1.1) for HRT users [53].

10. Melanoma

There is conflicting data about hormonal and reproductive factors and risk of melanoma in women. Immuno-cytochemical and immuno-histochemical assays hardly ever detected ER in melanoma tissues [55–57]. Miller et al. [57] found ER only in 2 (2.9%) of 69 cases of melanomas, and staining in these lesions was very poor. In vitro studies have failed to detect a stimulating effect of estrogens on proliferation or invasiveness of melanoma cell lines in vitro [58–60]. Pregnancy before, during, or after the diagnosis of early-stage melanoma does not affect the clinical outcome of patients [61]. OC use does not increase the risk of melanoma [61–65]. The meta-analysis of 18 case-control studies, including 3796 cases of cutaneous melanoma and 9442 controls, found no evidence for an etiological role of OC
in the development of this malignancy: the overall RR for pill users was 0.95 (95% CI 0.87–1.04) [62]. Melanoma is not responsive to progestins, antiandrogens or aromatase inhibitors [66–68]. Moreover, tamoxifen has a modest activity, with response rates lower than 10% [69]. A randomised study by Cocconi et al. [70] on metastatic melanoma revealed that the addition of tamoxifen to dacarbazine significantly improved the overall response rate and median survival of female patients. However, subsequent randomised trials failed to detect a significant benefit for the addition of tamoxifen to single-agent dacarbazine [71] or platinum-based regimens [69,72,73].

Several authors [54,61,63,74–76] have reported that HRT use does not increase the risk of melanoma. For instance, in the study by Persson et al. [54], women taking HRT showed a RR of melanoma of 0.9 (95% CI, 0.7–1.1) and the RR of death for this malignancy was 0.5 (95% CI, 0.2–1.0).

11. Meningioma

The high proportion of meningiomas in females, their accelerated growth during the luteal phase of the menstrual cycle and during pregnancy, and the association between meningioma and breast cancer have suggested that sex steroid hormones may be involved in the growth of these tumours [77,78]. There are several inconsistencies in the literature about the mitogenic effect of steroids on meningiomas both in vitro and in vivo models [78–80].

Human meningioma tissues are mostly ER negative and PgR positive in ligand-binding and enzyme immuno-assays [81–85]. Hsu et al. [82] detected PgR and ER in 83% and 8.6%, respectively, of 70 meningiomas, and Hilbig and Barbosa-Coutinho [83] reported that all the 116 cases of meningiomas were ER negative, whereas PgR was found in 58.3% of typical and in 48.2% of atypical meningiomas. The lack of PgR is often associated with high tumour grade, increased mitotic activity and brain invasion, and represents an unfavourable prognostic factor for these tumours.

It is still unknown how PgR expression is regulated in meningiomas, since ERs are virtually absent. Several splice variants of ER mRNA have been identified in human meningioma tissues, including variants lacking exons 4, 5, and 7, but they are not involved in PgR expression [81,84]. Other ER-inducible proteins are either not expressed at all [pS2] or expressed at a very low level (cathepsin-D) in meningioma when compared to their expression in breast cancer [86]. No data is currently available about the risk of meningioma in HRT users.

12. Hematologic malignancies

Adult acute myeloid leukaemia (AML) and lymphomas are the most frequent haematological malignancies in the reproductive years. ERs have been detected in leukaemia cells as well as in myeloma cells [87–89]. ER methylation is a frequent molecular alteration in adult AML, and appears to be a favourable prognostic factor for overall survival [87]. Micromolar concentrations of 17-beta estradiol and testosterone induce a significant inhibition of proliferation of the human monoblastic leukaemia cell line U937, which is mainly due to a cell cycle arrest in the G2/M phase [90].

Pregnancy seems to exert a protective effect against the development of Hodgkin’s lymphoma [91], and does not induce reactivation or worsening of the disease in women previously treated for this malignancy [92]. In a hospital-based case-control study conducted in Northern Italy, Tavani et al. [91] found that the OR for Hodgkin’s lymphoma was 0.6 for women with three or more pregnancies compared to nulligravidae, and 0.5 for women with one or more abortions compared to women reporting no abortions. It is worth noting that compared to nulliparous women, the OR of Hodgkin’s lymphoma was 0.3 for women with first birth when aged less than 20 years.

Non-Hodgkin’s lymphomas are less frequent in women than in men, but conflicting data exist about the relationship between reproductive factors and risk of these malignancies [93]. For example, Olsson et al. [94] found that late age at first full-term pregnancy was associated with increased risk, whereas Adami et al. [95] did not observe such relationship. In the study by Tavani et al. [91] the ORs of non-Hodgkin’s lymphomas in relation to number of pregnancies, abortions, births and age at first birth were close to one. A population-based case-control study, including 177 women with high- or intermediate-grade
B cell non-Hodgkin’s lymphomas and 177 control age-matched females, showed that the use of OC and lactation suppressants containing high levels of estrogens was associated with a significantly lowered incidence of these malignancies (OR, 0.47; 95% CI, 0.26–0.86, and, respectively, OR, 0.50; 95% CI, 0.29–0.85) [96]. Postmenopausal women who had used HRT had somewhat lower risk than those who had not used HRT (OR, 0.64; 95% CI, 0.32–1.29).

Therefore, exogenous estrogens seem to have a protective effect on the risk of these malignancies. In vitro studies have shown that marrow stroma cells from women receiving HRT secrete lower amounts of interleukin-6 that acts as a paracrine growth factor for intermediate- or high-grade non-Hodgkin’s lymphomas [97,98]. Complete response rates, disease-free survival rates and overall survival rates are significantly higher for diffuse large-cell lymphomas patients with normal interleukin-6 levels when compared to those of patients with high interleukin-6 levels [97]. Estrogens influence differentiation, proliferation and survival of early B cell precursors in mouse models [99]. Transdermal estradiol inhibits mixed lymphocyte reactions and delayed hypersensitivity skin tests in postmenopausal women [100]. Therefore, a history of oestrogen exposure appears to be associated with a decreased risk of non-Hodgkin’s lymphomas, which could be due to alterations in cytokine expression, B cell modulation, and immune reactivity.

13. Colon cancer

Colon cancer incidence and mortality trends are lower in females than in males, and a number of experimental and clinical observations seems to suggest a protective effect of estrogens on this malignancy [101–103]. Estrogens inhibit the synthesis of bile acids [104]. The growth of colon cancer cell lines in vitro is affected by estrogens and is dependent on ER expression [102]. Recent data have revealed that ER-beta is the predominant ER-subtype in human colon and that the activation of ER-beta mediated processes in the superficial colon epithelium may have an antineoplastic effect, whereas decreased levels of ER-beta mRNA are associated with colon tumorigenesis in females [103]. Methylation-associated inactivation of the ER gene in ageing colon mucosa could be one of the earlier events in this process [105]. Estrogens are also involved in the modulation of Vitamin-D receptor (VDR) expression in colon mucosa [106]. Vitamin-D metabolites and analogues are potent antineoplastic and prodifferentiative agents in several cell types, including colon-derived cells. In an experimental model, estrogens exert a protective effect against the chemically induced murine colon carcinogenesis, which is associated with reduced methylation of VDR gene and with up-regulation of VDR gene transcription and protein expression.

According to the majority of studies, HRT reduces colon cancer risk and mortality [54,107–112]. This protective effect significantly decreases after stopping treatment [109]. A meta-analysis of studies specifically addressed to the relationship of HRT with colon cancer showed that recent use of HRT (either at time of assessment or within the previous year) was associated with a RR of 0.67 (95% CI, 0.59–0.77) of developing this malignancy [112]. Protection was limited to recent users, since the risk of colon cancer with ever HRT users was 0.92 (95% CI, 0.79–1.08). As for the studies on the risk of fatal colon cancer, the summary RR for death from this malignancy in HRT users was 0.72 (95% CI, 0.64–0.81).

Recently, Slattery et al. [113] reported that in women estrogen exposure reduces the risk of microsatellite instability-positive colon cancer, whereas the lack of estrogen in older women increases the risk. In these women, HRT may again reduce the risk of unstable tumours.

14. Other solid tumours

14.1. Liver cancer

There is evidence that combined oral contraceptive use increases the risk of hepatocellular carcinoma in developed countries in which the rates for this cancer are extremely low and hepatitis B virus is not endemic. On the contrary, epidemiologic studies have shown an inverse association between ever use of HRT and liver cancer [115,116,54,117]. In a cohort Swedish study the risk estimates for liver and biliary tract cancers were reduced by about 40% in HRT users [116]. In animal models estradiol suppresses
hepatic carcinogenesis; hepatic ERs mediate estradiol action in the liver. Chronic hepatitis C appears to progress more rapidly in men than in women. E2 is a potent endogenous antioxidant and suppresses hepatic fibrosis via ERs interaction [118]. HCV-related cirrhotic patients who developed hepatocellular carcinoma were more likely to have low hepatic levels of ERs, age greater than 49 years and male sex [119].

14.2. Bladder cancer

The role of estrogens in human bladder cancer still remains to be defined. In recent studies ERs were detected in 12–18% of patients with superficial transitional cell carcinoma; an association between the ER staining intensity and higher tumour grade was observed, but survival was not affected by ER expression [120,121]. A recent systematic analysis from a network of case control studies conducted in Italy between 1983 and 1999 including 106 patients with urinary bladder cancer found an excess risk for use of HRT (OR = 2.0) and the development of this cancer [115]. No clinical trials are available on HRT use after treatment for bladder cancer.

14.3. Renal cancer

Human renal cell carcinoma is considered refractory to hormone therapy also if ER may be observed in these tissues. A population based case-control study of risk factors for kidney cancer conducted in Denmark shows a significant increase in risk for obese women, but no association with number of pregnancies, age at menopause or use of estrogens containing medication [122]. A recent study evaluating the influence of pregnancy did not find any correlation between reproductive variables and the size or the stage of renal cancer [123]. All the epidemiological studies failed to show any association between use of HRT and increased incidence of renal cancer [115,116,124,125].

14.4. Gastric cancer

The role of hormonal receptors in stomach adenocarcinoma has been controversial. In a recent study the positive rate of ERs was 46% in female patients with gastric cancer. The ERs were more likely to be expressed in diffused and in poorly differentiated gastric carcinoma with regional lymph nodes metastases [126]. The survival rate after surgery is significantly lower in the ER positive cases (15% compared to 62% in ER negative cases) and also significantly lower in PgR positive tumours [127]. In another study all gastric adenocarcinoma specimens, including the signet ring cell type, demonstrated clear ER beta nuclear staining [128]. Despite these biological data, a reduced gastric cancer risk was observed in women with later menopause (OR = 0.6; P < 0.005) [129] and the few studies that have evaluated the relationship between HRT use in postmenopausal women and gastric cancer incidence failed to demonstrate any significant association [115,129]. In the absence of data from clinical trials in gastric cancer survivors caution should be used when prescribing HRT to patients with hormone receptors positive tumours.

14.5. Lung cancer

Lung cancer is now the leading cause of death from neoplasia in US men and women and was responsible for one quarter of all cancer deaths among US women last year, killing approximately 67,000 women. Epidemiologic evidence suggests that women are more susceptible to tobacco-induced carcinogenesis than men and more recently there has been increasing biologic and genetic data to support this male-female difference in susceptibility. There are conflicting results regarding immunohistochemical detection of the ERs and PgRs expression in non-small cell lung cancer. In a study on 32 samples of lung carcinoma tissues obtained by lobectomy or pneumonectomy, none of the specimens expressed PgR and a weak ER expression was detected only in 1 women with adenocarcinoma [130]. In cultured human non-small cell lung cancer cells, Western blot analysis of ERalpha suggested that the main protein expressed in these cells is a variant; also protein for ERbeta was found to be a mixture of full length as well as alternatively spiced variants [131]. In another study on primary pulmonary adenocarcinomas nuclear ERs were seen only with the use of monoclonal antibodies to 6F11 clone in 56–80% of the examined specimens; no ERs were seen using the 1D5 clone and there was no PgR detectable [132]. The clinical significance and ramifications of ERs in pulmonary adenocarcinoma remain unknown.
Some old epidemiological data suggested that sex hormones may influence lung cancer risk. In the Swedish cohort study there was a non significantly increased risk (RR, 1.3; 95% CI, 0.9–1.7) that need cautious interpretation because of its low magnitude, the absence of a duration response and the slightly higher prevalence of smokers in the cohort than in the background population [116]. More recent data do not support this unfavourable effect of estrogens.

In a case control study conducted in four US centres during 1976–2001 the OR for lung cancer among ERT users was 1.0 (95% CI, 0.8–1.4); risk did not increase with the duration of use [133]. A reduced risk of death from lung cancer (RR, 0.22; 95% CI, 0.04–1.15) was reported among long term ERT users (at least 5 years of use) compared to non users [134]. According to these data the use of HRT in lung cancer survivors seems not contraindicated.

15. Conclusions

Iatrogenic menopause worsens the quality of life of apparently healthy women after treatment for malignancies in fertile years and may have long-term consequences on incidence of cardiovascular diseases and osteoporotic fractures. The safety of HRT in these patients has not been extensively studied and evidence-based conclusions can not be drawn from available data. Criteria for HRT use can be mainly based on laboratory data (ER and PgR expression, effects of sex steroids on the proliferation of neoplastic cells in vitro) and on the epidemiological data, when available, on the influence of HRT use on the risk of development of the specific tumour.

HRT causes a 30% reduction in colon cancer risk, and there is consensus on prescribing this therapy to colon cancer survivors [114]. No firm conclusions can be drawn, based on epidemiological data, about the safety of HRT in patients previously treated for other non-gynaecological malignancies assessed in this review. However, based on the biological considerations, we think that HRT can be safely prescribed to patients with previous thyroid, liver, lung and renal cancer, melanoma, leukaemia and lymphoma, whereas it should not be administered, at least its progestin component, to women treated for meningioma, a tumour often showing high PgR levels. Due to the ambiguous significance of hormone receptors in gastric cancer the use of HRT should be discussed in depth with the patient. The sporadic evidence of a possible association between HRT use and excess risk of bladder cancer needs to be confirmed.

It is still a controversial issue whether patients with a history of gynaecologic malignancies can be safely prescribed HRT. Squamous cell cancers of the cervix, vulva and vagina are unlikely to be influenced by HRT. Although the endocervical epithelium does contain estrogen and progesterone receptors, a correlation between steroid hormones and cervix cancer has never been shown. No evidence exists to show that HRT negatively influences survival after treatment for ovarian cancer.

Fears and uncertainties regard hormone-dependent, endometrium and breast, tumours. Surgery for endometrial cancer guarantees complete removal of the neoplasm when it is confined to the uterus and the few clinical studies carried out have not shown any worsening of prognosis in patients who received estrogen after surgery. However, as available data does not yet allow drawing absolute conclusions as to the safety of HRT use, it is necessary to inform patients about the potential risks and alternative therapies.

The problem is even more complex in women with previous breast carcinoma. The possibility that estrogen can stimulate or anticipate proliferation of micrometastatic foci is all but a theory, above all in the case of receptor positive tumours. Moreover, late recurrence is possible, even in patients presenting with first stage disease. Despite these doubts, the available data on selected groups of patients are all favourable and point to the possibility of treating good risk women and women with hormone receptor negative tumours without any increase of the risk of recurrence or death.

Randomised clinical trials are needed to obtain definite results, but this will take a very long time and a large number of subjects. In the meantime, it is necessary to provide relief to patients who complain of menopause symptoms, both by offering them the several alternatives of proven effectiveness to HRT already available, and by giving them no-biased informations on the present state of knowledge on the effects of HRT use in women with previous breast cancer and on the possibility of prescribing HRT to selected, well informed patients.
Menopause after cancer

Non hormone-sensitive tumours
- Thyroid
- Ovary
- Melanoma
- Hematologic malignancies
- Colon
- Liver
- Leiomyosarcoma
- Kidney
- Lung

Symptoms
- Osteoporosis
- Cardiovascular risk

Hormone-sensitive tumours
- Breast
- Endometrium

Symptoms
- Osteoporosis
- Cardiovascular risk

1st choice:
- Tamoxifen
- Raloxifen

Alternative treatment
- SSRIs
- megestrol
- HRT

ERT or ERT?
- Tamoxifen
- Raloxifen
- Diphosphonates
- Statins
- Lifestyle modification

HRT caution
- Meningioma
- Progesterin contraindicated
- Cervix
- No HRT endometrial adenoc.
- Endometrial stroma sarcoma

HRT contraindicated

Fig. 1. Summary of current evidence and tentative suggestions for management of menopausal problems in patients with previous cancer. ERT: estrogen replacement therapy. HRT: estrogen + progesterin replacement therapy. SSRIs: selective serotonin reuptake inhibitors. CV risk: cardiovascular risk.

An algorithm summarising the above mentioned model is provided to help in everyday’s clinical practice (Fig. 1).

Article precis
Treatment of menopausal symptoms and related diseases need different approaches in survivors of hormone-dependent and hormone-independent tumours. Proposal of an algorithm.

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References


