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REVIEW

Safety of hormone replacement therapy in gynaecological cancer survivors

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Therapy for endometrial, ovarian and cervical cancer in young women can cause sudden onset of intense menopausal symptoms, such as hot flushes, emotional disorders and sexual dysfunction. In order to overcome these unpleasant and sometimes severe symptoms, hormone replacement therapy (HRT) has proven to be very effective. However, its safety remains controversial. We reviewed English literature and examined whether administration of HRT in this specific population is related with more recurrences and worse prognosis. Current scientific data, comprising mainly retrospective studies, suggest that recurrence rates and survival are comparable between HRT users and non-users. However, large randomised trials are missing and definitive conclusions cannot be drawn. Gynaecological cancer survivors using HRT, although they seem to have little if any risk for recurrence, should be correctly informed about the lack of strong evidence.

Keywords: Cervical cancer, endometrial cancer, oestrogens, HRT, menopause, ovarian cancer

Introduction

Treatment of endometrial, ovarian and cervical cancer usually results in ovarian loss and intense menopausal symptoms like hot flushes, sexual dysfunction and depression. Hormone replacement therapy (HRT) is highly effective in alleviating these symptoms and improving quality of life (MacLennan et al. 2001), but its safety remains a matter of debate. Major concern about HRT use in endometrial, ovarian and cervical cancer survivors is the fear of recurrence. In order to discuss whether HRT can be safely administered in this specific population, we should first examine if oestrogens or progestins can initiate a carcinogenic process.

Epidemiological studies have shown that the longer a woman is exposed to oestrogen, either when an early menarche is involved or through HRT, the higher is the risk of developing oestrogen-depended cancers (Weiderpass et al. 1999; Rodriguez et al. 2001; Yager and Davidson 2006). The mechanisms of oestrogen carcinogenesis are highly complex and poorly defined. It is considered that they stimulate cell proliferation, through nuclear oestrogen receptor pathways, thus increasing the likelihood of genomic mutations left unrepaired. Furthermore, they may induce DNA damage through two different, 'non-genomic' pathways, involving newly diagnosed membrane oestrogen receptors and oestrogen metabolism products (Bolton and Thatcher 2001).

In addition, the National Toxicology Program of the National Institute of Environmental Health Sciences (NIEHS) declared that steroidal oestrogens, both of endogenous nature and as components of HRT formulations, are 'known to be human carcinogens', causing breast and endometrial cancers (US Department of Health and Human Services 2005).

Recently, results from the Nurses' Health Study, a large cohort study with 24 years of follow-up, were published. The study compared women with and without ovarian conservation at hysterectomy for benign disease and reported that when bilateral oophorectomy was performed, the risk of breast (hazard ratio (HR) 0.78; confidence interval (CI) 0.68–0.84); ovarian (HR 0.04; CI 0.01–0.09) and total cancer (HR 0.9; CI 0.84–0.96) was significantly reduced (Parker et al. 2009).

The above suggest that HRT may be positively associated to gynaecological cancer risk. But what about patients who have already suffered from and have been treated successfully for such a malignancy? Can HRT induce a recurrence when the uterus and the ovaries have been surgically excised? In order to give answers to these questions, we searched the English literature through PubMed for the last 30 years, using the terms 'hormone replacement therapy', 'menopause', 'endometrial, ovarian and cervical cancer', 'recurrence'. This review aims to provide evidence-based data on the use and safety of HRT in gynaecological cancer survivors.

Endometrial cancer

Endometrial cancer (EC) is the most common gynaecological malignancy worldwide. It is usually diagnosed at an early stage due to abnormal vaginal bleeding and exerts a favourable prognosis. At the time of diagnosis, approximately 85% of patients are in stage 1 and 2 and 5-year overall survival exceeds 85% (DiSaia and Creasman 2002). The median age of women at diagnosis is 57 years, however 20% of affected women are premenopausal and 5% are younger than 40 years (Gallup and Stock 1984). Consequently, a large number of women will suffer a sudden iatrogenic onset of postmenopausal morbidity as therapy consists of total abdominal hysterectomy and bilateral oophorectomy, usually accompanied by radiation therapy or chemotherapy.

Endometrioid type of EC is related to oestrogen exposure and is frequently associated with endometrial hyperplasia. Reproductive history of unopposed oestrogens, like polycystic ovarian syndrome, obesity and nuliparity are well known risk factors of EC. In addition, several large cohort studies have reported that women using HRT, compared with never users, had a higher risk of

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endometrial cancer (Beresford et al. 1997; Pike et al. 1997; Weiderpass et al. 1999; Hill et al. 2000). However, the role of oestrogens in provoking a recurrence after hysterectomy for EC is less clear and a matter of debate.

Only few retrospective case–control studies have assessed the use of HRT in EC survivors suffering from intense postmenopausal symptoms, but none has been able to show an increased risk of recurrence (Creasman et al. 1986; Lee et al. 1990; Chapman et al. 1996; Suriano et al. 2001).

The first study (Lee et al. 1990) compared 44 women on HRT vs 99 non-users after therapy for EC, and found eight recurrences in the non-users group. However, HRT was prescribed only in low risk EC patients (stage 1A, 1B grade 1 or 2) while 37% of non-users had high risk disease (stage 1C grade 3). When only low risk patients were compared, no difference in recurrences was noted.

The same selection bias was encountered in the next study (Chapman et al. 1996) a few years later. They evaluated 62 early stage EC patients on HRT vs 61 non-users. No difference in recurrence rate or overall survival was noted. They suggested that the HRT group had a greater disease-free interval. However, significant differences existed between the two groups. HRT users were younger, more likely to have used HRT before treatment and had an earlier stage disease.

The first well matched case–control retrospective study came from Suriano et al. (2001). They examined 75 EC cases stage 1–3 on HRT vs 75 non-users. They also concluded that the HRT group had a significantly greater disease-free interval as well as lower recurrence risk (1% vs 14%).

The first prospective trial on this topic was published a few years later (Ayhan et al. 2006). They compared 50 patients with early EC starting HRT 4–8 weeks after surgery to a well matched group of 61 non-users. During a mean follow-up of 49.1 months, there was no recurrence in the HRT group, while only one non-user died of the disease. Because of the low number of patients and narrow follow-up, survival analysis was not performed, although it became obvious that HRT did not increase recurrence rate, nor had any protective effect.

Finally, a Gynecologic Oncology Group study was designed in order to give the definitive answer whether oestrogen replacement therapy (ERT) can be given safely in EC survivors (Barakat et al. 2006). Unfortunately, after publication of the Women's Health Initiative Randomized Trial (WHI) results (Chlebowski et al. 2003), the trial had to close prematurely, because enrolment decreased significantly and the accrual goal could not be reached. It was a randomised double-blind study of ERT vs placebo in women with early stage EC. A total of 1,236 treated EC patients presenting with vasomotor symptoms, vaginal atrophy and increased risk for osteoporosis or cardiovascular disease, were randomly assigned to receive ERT or placebo within 20 weeks of surgery. After a median follow-up of 35.7 months, no statistically significant differences were noted in terms of recurrences (2.3% vs 1.9%) or EC deaths (0.8% vs 0.6%) for ERT and placebo, respectively. However, two main limitations were recorded. First, fewer patients in the ERT group were compliant with therapy (41.1%) than in the placebo group (50.1%). In addition, after 2 years of follow-up, 45.6% of ERT patients had discontinued treatment compared with only 9.7% of patients in the placebo group, who begun to take open label oestrogens. Second, the majority of patients enrolled had a low-risk profile, resulting in an insufficient number of recurrences and suboptimal power for the clinical trial.

Considering the above data, no study has so far reported a detrimental effect of HRT in early stage EC survivors. However, advanced stage disease has never been assessed and HRT should not be an option when considering such patients. Residual malignant cells, after a suboptimal surgical effort for advanced disease, could be restimulated by HRT and provoke a recurrence.

Other histological types of endometrial cancer

Serous papillary and clear cell carcinomas are both aggressive variants of EC with poor prognosis, even when diagnosed at an early stage. They account for approximately 8% of all EC and occur mainly in postmenopausal women. They lack oestrogen and progesterone receptors and thus are not considered to be stimulated when HRT is used after surgical treatment.

Uterine sarcomas are a heterogeneous group of EC including carcinosarcomas, leiomyosarcomas, adenosarcomas and endometrial stromal sarcomas. Only the latter type is considered oestrogen dependent, as it expresses oestrogen and progesterone receptors and HRT should be avoided. However, no study has addressed the use of HRT after treatment of all the above histological subtypes of EC and thus, a safe suggestion cannot be raised.

Ovarian cancer

Epithelial ovarian cancer (EOC) is the leading cause of death among gynaecological malignancies, accounting for 14,000 deaths per year in the USA. At the time of diagnosis, more than 75% of women have advanced stage disease and their 5-year survival is very poor; not exceeding 25% (Berek 2002). For this reason, relief of vasomotor symptoms and improvement of quality of life after surgical treatment of EOC seems more important than fear of recurrence.

Two large cohort studies have concluded that ever users of ERT have a significantly greater risk of EOC. Rodriguez et al. (2001) analysing 211,581 postmenopausal women in the USA treated for more than 10 years with oestrogen alone, reported that oestrogen use was associated with increased risk of EOC mortality (HR 1.23 CI 1.06–1.43). In addition, Lacey et al. (2002) showed a strong positive relationship between duration of ERT and risk of EOC. In detail, when ERT was used for 10–19 years, HR was 1.8, while for over 20 years use, HR rose to 3.2. Meta-analysis of published results on the relative risk of EOC in current users of HRT compared with never users showed an increased risk in favour of the former (HR 1.28; CI 1.2–1.36) (Garg et al. 1998). However, others concluded that an association between HRT and EOC risk does not exist (Coughlin et al. 2000). Adding progestins to oestrogen preparation seems to reduce the risk of EOC but the matter is still debated. A few studies have concluded that adding progestins leads to a significant better outcome (Lacey et al. 2002), while others favour the opposite (Beral et al. 2007; Mørch et al. 2009).

Despite all the conflicting previous data, HRT use after surgery for EOC has proven to be safe in various retrospective and two prospective studies (Eeles et al. 1991; Guidozzi and Daponte 1999; Ursic-Vrscaj et al. 2001; Mascarenhas et al. 2006).

The first study (Eeles et al. 1991) compared 78 EOC survivors under HRT use, with 295 controls. They found that overall survival and disease-free survival were comparable between the two groups and suggested that HRT use does not have a detrimental effect on prognosis. In a small single centre retrospective study (Ursic-Vrscaj et al. 2001), 24 EOC survivors on HRT use were compared with 48 non-users. Recurrence rate was 21% and 31%, respectively showing that HRT use is not correlated with worse outcome.

The only randomised controlled trial on this topic was published in 1999 (Guidozzi and Daponte 1999). A total of 130 EOC patients were randomly assigned to receive ERT or not 6–8 weeks after surgery. A total of 32 recurrences (54%) occurred in the ERT group and 41 in the non-ERT group (62%). Both disease-free interval and overall survival were similar among two groups.

Finally, a large prospective cohort study was reported by Mascarenas et al. (2006). Overall survival among 649 EOC patients was correlated to HRT before and after treatment. They showed that women using HRT after treatment for EOC had a lower risk of dying (HR 0.57; CI 0.42–0.78) compared with non-users. These better survival results were correlated only to serous tumours (HR 0.65; CI 0.44–0.96) but neither to the duration of use nor the type of HRT used. The same study addressed also the issue of HRT use after treatment for borderline ovarian tumours (BOT), but no significant differences in survival were noted between users and non-users.

The lifetime risk of developing ovarian cancer when BRCA 1 and 2 gene mutations are expressed is reported to range between 11–56% (Antoniou et al. 2003; King et al. 2003). Thus, a lot of women affected decide to undergo a risk-reducing bilateral oophorectomy (RRBO) after they have completed childbearing. These women are usually < 40 and experience severe menopausal symptoms. HRT use after RRBO does not seem to have any adverse effect in these patients (Kotsopoulos et al. 2006).

As in endometrial cancer, existing data suggest that HRT use after treatment for EOC is safe and does not increase the risk of recurrence. However, large randomised trials are missing.

Other histological types of ovarian cancer

Germ cell and sex-cord ovarian malignancies account for approximately 8% of all OC cases. HRT use after treatment for these histological subtypes is very important, as most cases of dysgerminoma (commonest germ cell tumor) and ovarian granulosa tumor (commonest sex-cord stromal tumor) appear in young females (Zalel et al. 1996). In the majority of cases, stage I disease is surgically diagnosed and therapy usually consists of unilateral salpingo-oophorectomy with preservation of the contralateral ovary. However, adjuvant chemotherapy, which may be necessary, can irreversibly suppress ovarian function and lead to intense menopausal symptoms (Tangir et al. 2003). Unfortunately, there are no trials evaluating the use of HRT in these patients. It is, however, believed that HRT can be used safely for germ cell tumours, but not for granulosa tumours, as they are considered to be hormone dependent carcinomas.

Cervical cancer

Cervical carcinoma is the second most common gynaecological malignancy in the USA. Mean age at diagnosis is 48 years and it is estimated that approximately 70% of all cervical cancers are diagnosed in women younger than 54 years of age (Horner et al. 2009). These women, depending on stage, age and histology of the disease, are more likely to undergo radical hysterectomy without preservation of the ovaries or chemoradiation therapy, both leading to sudden onset of menopause.

Squamous cell carcinomas (SCC) account for approximately 80%, adenocarcinomas for 15% and adenosquamous lesions for 5% of cervical cancers. HRT has never been linked with the development of squamous cell carcinomas. However, a study by Lacey et al. (2000) reported a significant risk of adenocarcinoma of the cervix in women under oestrogen therapy (OR 2.7). Furthermore, epidemiological data have shown that prolonged use of oral contraceptive pills may be related with an increased risk for cervical adenocarcinoma (Smith et al. 2003).

Ploch (1987) studied the use of HRT in cervical cancer survivors. All patients enrolled were younger than 45 years of age and had early stage disease treated with surgery or radiotherapy. After treatment, they administered HRT in 80 patients, while the remaining 40 were used as controls. Overall, no significant difference in recurrence rate or survival was noted between the groups.

Table I summarises all studies performed on HRT use in endometrial, ovarian and cervical cancer survivors, recurrences that were observed and type of HRT used.

Discussion

Surgically induced menopausal symptoms tend to be more severe than those resulting from natural menopause. Hot flashes, emotional distress and vaginal atrophy are the main causes of suffering in young women undergoing treatment for a gynaecological malignancy. Quality of life deteriorates and the need for alleviating these symptoms is essential.

Existing data suggest that use of HRT in this setting is safe as recurrence rate and survival is comparable with non-users. However, definitive conclusions cannot be drawn, as the majority of the studies are retrospective and have included only a small number of patients. In addition, HRT types used and route of administration were also different among studies, rendering the comparison between them even more difficult.

Safety of HRT in endometrioid endometrial cancer survivors seems to be the most debatable. Published data suggest that after treatment for early stage disease, HRT use has no detrimental effect in terms of recurrence and overall survival. This could be

Table I. Studies on HRT use vs controls in gynaecological cancer survivors.

Author	Population (HRT vs controls)	Tumour stage	Recurrences (HRT vs controls)	Type of HRT used
Endometrial cancer				
Creasman et al. 1986	47/174	Stage I	1 vs 26	Oral and vaginal oestrogens
Lee et al. 1990	44/99	Stage I	0 vs 8	Oral conjugated oestrogens
Chapman et al. 1996	62/62	Stage I–II	2 vs 8	Oral/vaginal oestrogens ± progesterone
Suriano et al. 2001	75/75	Stage I–III	2 vs 11	Oral conjugated oestrogens ± progesterone
Ayhan et al. 2006	50/52	Stage I–II	0 vs 1	Oral conjugated equine oestrogens ± progesterone
Barakat et al. 2006	618/618	Stage I–II	14 vs 12	Oral oestrogens
Ovarian cancer				
Eeles et al. 1991	78/295	Stage I–IV	NS	Oral oestrogens ± progesterone/progesterone/testosterone
Ursic-Vrscaj et al. 2001	24/48	Stage I–III	5 vs 15	Oral/intramuscular oestrogens ± progesterone
Guidozzi and Daponte 1999	59/66	Stage I–IV	32 vs 41	Oral conjugated oestrogens
Mascarenhas et al. 2006	649 EOC 150 BOT	Stage I–IV	NS	Oral conjugated oestrogens ± progesterone
Cervical cancer				
Ploch 1987	80/40		16 vs 13	Trisequens/dinestrol + chlormadinon

HRT, hormone replacement therapy; EOC, epithelial ovarian cancer; BOT, borderline ovarian cancer; NS, not specified.

explained due to radical removal of the disease accomplished with total abdominal hysterectomy. In contrast, insufficient management of advanced disease may result in residual cancer cells. As these are oestrogen-dependent, HRT could restimulate them and provoke recurrent disease.

Existing data also show that HRT can be safely administered after treatment of epithelial ovarian cancer, squamous cervical carcinoma and aggressive variants of endometrial cancer. These neoplasms are not considered oestrogen-dependent and HRT use has never been associated with worse prognosis.

Considering all the above, HRT use in gynaecological cancer survivors seems to have little, if any risk for recurrence in the majority of cases. However, after the WHI results, the era of HRT seems to be less attractive than before. Indeed, physicians in Germany were asked if they were willing to prescribe ERT in symptomatic women with previous endometrial cancer. The vast majority (88%) responded that they would prefer to use other non-hormonal regimens and 75% believed that HRT is contraindicated in high-grade disease (Hancke et al. 2010). In recent years, a great increase in studies evaluating other regimens that may reduce vasomotor symptoms has been observed. Antidepressants, gabapentin and clonidine are the three most studied and appear to provide the best relief reducing vasomotor symptoms by 50–67% and also being well-tolerated by patients (Pinkerton et al. 2009).

Young patients treated for a gynaecological malignancy usually suffer from intense menopausal symptoms. HRT has proven to be very effective in alleviating these symptoms and improving quality of life. However, clinicians hesitate to use it, fearing recurrence. Existing data suggest that HRT could be used safely for most endometrial and ovarian cancer survivors, but patients should be carefully informed, as large randomised controlled trials are missing.

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