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Review

Hormone replacement therapy and women with premature menopause – A cancer survivorship issue

Judy King [a,*], *Catherine Harper Wynne* [b], *Laura Assersohn* [c], *Alison Jones* [a]

[a] *Oncology Department, Royal Free Hampstead NHS Trust, Pond Street, London NW3 2PF, United Kingdom*
[b] *Oncology Department, Maidstone and Tunbridge Wells NHS Trust, Hermitage Lane, Maidstone, Kent ME16 9QQ, United Kingdom*
[c] *Oncology Department, St. George's Healthcare NHS Trust, Blackshaw Road, London SW17 0QT, United Kingdom*

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ABSTRACT

The importance of addressing survivorship issues has been emphasised in recent years. As cancer therapies improve there is a growing population of cancer survivors, which includes many women with premature menopause. Women who are premenopausal at the time of their cancer diagnosis may have specific survivorship issues to be addressed, including infertility, early menopause and sexual dysfunction. These factors can continue have a significant impact on the quality of life of these patients at long term follow up.

Data for this Review were identified by searches of MEDLINE, PubMed, and references from relevant articles using the search terms 'HRT', 'women/female cancer/tumour', 'menopause' and 'survivorship'. Abstracts and reports from meetings were excluded. Only papers published in English between 1980 and 2010 were included.

The aims of this review are to:

- Address the hormonal factors which impact on cancer survivorship for premenopausal women
- Review the debate for the role of hormone replacement therapy (HRT) in cancer survivors
- Provide information for physicians and patients regarding the management of hormonally driven survivorship issues (for different tumour types), based on current evidence

The recommendations for practice are that HRT may be offered for the alleviation of vasomotor symptoms in cancer survivors who undergo premature menopause up to the age of natural menopause (51 years in the UK). HRT (including vaginal oestrogen preparations) is contraindicated in survivors of oestrogen receptor positive breast cancer and low grade endometrial leiomyosarcoma, where non-HRT alternatives should be considered to alleviate symptoms.

1. Introduction

The United Kingdom has been one of the first European countries to focus on cancer survivorship. The National Cancer Survivorship Initiative Vision (UK),[1] has emphasised the need to provide a personalised assessment and care plan for a growing population of cancer survivors, which includes many women with premature menopause. Between 1977 and 2006,

* *Corresponding author:* Tel.: +44 7939 516 414; fax: +44 207 034 8883.
E-mail address: judyking@doctors.org.uk (J. King).
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incidence rates for cancer in the UK increased by 32% in women, with a fall of 19% in mortality rates from cancer over the same period Approximately 30,000 cases of cancer are diagnosed annually in women aged 25–49 years, with breast cancer, malignant melanoma, bowel and cervical cancer being the most common diagnoses in women in this age group.[2] 18000 women who are diagnosed with cancer before the age of 55 years, the majority having had breast cancer, survive more than 5 years beyond diagnosis. (Table 1: cancer incidence and survival in women <55 years).

Survivors may be at risk of the sequelae of their cancer treatment both during and beyond their 5-year follow up. Survivorship issues are medically and psychologically varied (Box 1: survivorship issues). They include the risk of cardiac problems or secondary cancers,[3,4] weight gain,[5] cognitive impairment,[6] fatigue, psychological distress and depression.[7] Premenopausal women diagnosed with cancer may have additional survivorship issues to face, since they are at risk of amenorrhoea, infertility, early menopause, sexual dysfunction, osteopaenia and associated problems including osteoporotic fractures.[8] The impact on the quality of life of these patients is significant, with survivors of breast cancer rating premature menopause, sexual dysfunction and infertility highest of the problems experienced since diagnosis.[9]

Box 1 Survivorship issues.

30% of patients reported 5 moderate or severe unmet needs at the end of treatment. Key survivorship issues identified by the National Cancer Survivorship Initiative[1]

- *Psychosocial*: anxiety, depression, isolation, negative impact on identity or self image
- *Physical*: 31% of patients had 1 or more physical concerns, e.g.: fatigue, shortness of breath, pain/reduced movement secondary to surgery/radiotherapy scars, gynaecomastia, neuropathy, lymphoedema, urinary or gastrointestinal symptoms, increased risk of medical problems including heart disease (secondary to chemotherapy/radiotherapy) and secondary cancers
- *Sexuality*: loss of libido, impotence, infertility, dyspareunia
- *Work*: lack of advice from medical staff regarding return to work, difficulties secondary to a lack of awareness in employers or colleagues, e.g.: only 1 in 5 employers know that cancer is covered by the Disability Discrimination Act
- *Financial*: 91% of cancer patients' households suffer a loss of income or increased costs as a direct result of cancer
- *Information*: lack of verbal and written information on the issues above, as well as potential for lifestyle benefit through diet, exercise, financial assistance, and who to contact for advice or support. 75% of patients did not know who to contact outside office hours, nor if they had a care plan.

This article focuses on hormonal issues in women who were premenopausal at the time of their cancer diagnosis. Aims of this review:

- Address the hormonal factors which impact on cancer survivorship for premenopausal women.
- Review the debate for the role of hormone replacement therapy (HRT) in cancer survivors.
- Provide information for physicians and patients regarding the management of hormonally driven survivorship issues (for different tumour types), based on current evidence.

1.1. *Search strategy and selection criteria*

Data for this Review were identified by searches of MEDLINE, PubMed, and references from relevant articles using the search terms 'HRT', 'women/female cancer/tumour', 'menopause' and 'survivorship'. Abstracts and reports from meetings were excluded. Only papers published in English between 1980 and 2010 were included.

2. Hormonal survivorship issues in women and effect on quality of life

Menopause is defined as the cessation of menstruation. Premature menopause may be defined as a menopause occurring more than 2 standard deviations below the mean average for the population (51 years in the UK), although the age of 40 years is commonly used as a cut off.[10] Some treatments for cancer may result in premature menopause. These include:

- *Surgery and radiotherapy* to the pelvis e.g.: for gynaecological cancers
- *Chemotherapy* reduces ovarian reserve, and its effect on an individual patient relates to the type of chemotherapy used, the cumulative dose and the patient's age, with an increased risk of menopause and infertility in women over 35 years.[11–14]
- *Anti-oestrogen therapy*: premenopausal women with oestrogen receptor positive (ER+) breast cancer also receive anti-oestrogen therapy, the effects of which may mimic the menopause and may also contribute to ovarian dysfunction.[13,15]

In contrast to a natural menopause, early menopause due to cancer treatment has an abrupt onset of symptoms which are often more severe, and include sleep disturbance (86%), hot flashes (85%), myalgia/arthralgia (72%), sexual problems (60%), vaginal dryness (55%) and urinary problems (55%).[12,16,17] Young women who experience an abrupt onset of menopausal symptoms are at highest risk of sexual dysfunction.[18,19] Premature menopause is also associated with an age related increased risk of osteopenia, osteoporosis and osteoporotic fractures with a greater risk seen when menopause occurs at a younger age.[20,21] All of these risks are accelerated by the use of aromatase inhibitors for adjuvant therapy, which are also associated with joint pain (47%) and stiffness (44%).[22] Patients may continue to experience menopausal symptoms even if menses resume. Furthermore, amenorrhoea secondary to chemotherapy and endocrine therapy may be transient – although when ovarian function resumes there may be reduced ovarian reserve

Table 1 – UK Cancer incidence in females (2006) CRUK statistics.

	Incidence	% all female cancers	No. women diagnosed aged <55 years (pre-menopausal)	Age standardised 5 year survival (from 2001–2006)/%	Premenopausal survivors (women diagnosed <55 years × 5 year survival)
Breast	45,505	31	13,655	81	11,061
Colorectal	17,084	12	1700	51	867
Lung	16,646	11	1253	6	752
Uterus	7045	5	1048	76	797
Ovary	6596	5	1594	34	542
Malignant melanoma	5607	4	2474	90	2227
Non-hodgkins lymphoma	4911	3	849	52	442
Pancreas	3929	3	281	2	56
Leukaemia	3008	2	689	36	248
Kidney	2961	2	434	43	187
Cervix	2873	2	1852	64	1185
Other	31,231	21			
Total	1,46,378	100			18,362

– so these women experience an iatrogenic menopause, as well as a second (premature or natural) menopause at a later date.[23,24]

Cancer survivors often report unmet needs at the end of treatment.[25] Standard oncology follow up focuses primarily on surveillance for cancer recurrence, rather than premature menopause symptoms which may continue to have a negative impact on quality of life at long term follow up.[18,26,27] Vasomotor and urogenital menopausal symptoms are theoretically amenable to treatment with HRT (see benefits of HRT below), but there remains some debate amongst clinicians with regard to the safety of HRT use in cancer survivors. The majority of the evidence on HRT is in healthy women, rather than cancer survivors specifically, in whom data are limited. This article will first review the HRT debate of safety and efficacy in healthy women and then examine these data in relation to cancer survivors according to tumour type.

2.1. *The HRT debate*

The most comprehensive evidence regarding the risks and benefits of HRT in the general population comes from the Women's Health Initiative (WHI) Hormone Program in the USA and the Million Women Study in the UK. The WHI program aimed to determine the cardiovascular benefits and cancer risks associated with the use of HRT. It comprised 2 trials, which randomised women with an intact uterus to oestrogen (625mcg daily) plus progestin (medroxyprogesterone acetate 2.5 mg daily) ($n = 8506$) or placebo ($n = 8102$) (WHI E/P), or randomised women who had undergone hysterectomy to estrogen alone ($n = 5310$) versus placebo ($n = 5429$) (WHI E alone).[28,29] The Million Women Study was a cohort study which enrolled 1.3 million women in the UK and evaluated health outcomes in women who were or were not using HRT. The results of these studies in healthy women (Tables 2a,b) have not resolved the uncertainties surrounding the risks and benefits of HRT, and indeed the prevalence of HRT use has declined since their publication, e.g.: in the United States there was a 38% decrease in HRT use by the end of 2002.[30,31]

2.2. *Benefits of HRT in healthy women*

The main indication for HRT is for relief of menopausal symptoms. The current recommendations for prescribers are shown in Box 2.[32] Although HRT is reported to improve a range of symptoms, randomised placebo controlled trials have only demonstrated that HRT is effective for the relief of vasomotor and urogenital menopausal symptoms.[33,34] The other main benefit is that HRT has also been shown to reduce bone loss, and randomised data from the WHI study showed a significant reduction in incidence of fractures

Box 2 Current recommendations for prescribers regarding HRT use in healthy women.

For the treatment of menopausal symptoms that adversely affect quality of life the balance of risks and benefits of HRT is generally favourable. However, *the lowest effective dose should be used for the shortest possible duration*; each decision to start HRT should be made on an individual basis with a fully informed woman; and treatment should be re-evaluated at least annually in light of new knowledge and any changes in a woman's risk factors.

- HRT should not be the first choice of therapy for the prevention of osteoporosis.
- For younger women who have experienced a premature menopause (due to ovarian failure, surgery or other causes) HRT may be used to treat their menopausal symptoms and to prevent osteoporosis until the age of 50 years. After this age, therapy for preventing osteoporosis should be reviewed and HRT considered a second-line choice.

Table 2a – Risks and benefits of HRT in healthy women: summary of the findings of the WHI E/P and E alone randomised controlled trials (Hazard ratio (HR) or relative risk (RR) and 95% confidence interval (CI) shown in brackets).

Benefit	No difference vs placebo	Adverse effects
E/P HRT (in women with an intact uterus)		
↓Risk of colorectal cancer (HR 0.63; CI 0.43–0.92)	Endometrial cancer (HR 0.83; 0.47–1.47)	↑Risk of breast cancer (HR 1.26; 1.0–1.59)
↓Risk of fracture (*hip*: HR 0.66; CI 0.45–0.98, *spine*: HR 0.66; CI 0.44–0.98)	Total cancers (HR 1.03; CI 0.9–1.17)	↑Risk of heart disease (HR 1.29; CI 1.02–1.63)
		↑Risk of CVA (HR 1.41; CI 1.07–1.85)
		↑Risk of PE (HR 2.13, CI 1.39–3.25)
		↑Risk of urinary incontinence (RR 1.87; CI 1.61–2.18)
		↑Risk of dementia (HR 2.05; CI 1.21–3.48)
E alone HRT (in women without a uterus)		
>↓Risk of breast cancer (non-significant) (HR 0.77; 0.59–1.01)	CHD (HR 0.91; CI 0.75–1.12)	↑Risk of CVA (HR 1.39; CI 1.10–1.77)
↓ fracture (*hip*: HR 0.61; CI 0.41–0.91, *spine*: HR 0.62; CI 0.42–0.93)	PE (HR 1.34; CI 0.87–2.06)	↑DVT (HR 1.47; CI 1.04–2.08)
	Colorectal cancer (HR1.08; CI 0.75–1.55)	↑Urinary incontinence (RR 2.15; CI, 1.77–2.62)
	All cancers (HR 0.93; CI 0.81–1.07)	

Table 2b – Cancer risk with HRT: summary of the findings from the WHI and Million Women Studies (figures indicate the hazard ratio for the WHI and the relative risk for the Million Women Study. 95% confidence interval shown in brackets).

Cancer type	WHI		Million Women Study		
	E/P	E alone	E/P	E alone	Tibolone
Breast	↑ risk 1.26 (1.0–1.59)	↔ 0.77 (0.59–1.01)	↑ risk 2.0 (1.88–2.12)	↑ risk 1.3 (1.21–1.4)	↑ risk 1.45 (1.25–1.68)
Endometrial	↔ 0.83 (0.47–1.47)	n/a	↔ 1·05 (0·91–1·22)	↑ risk 1·45 (1·02–2·06)	↑ risk 1·79 (1·43–2·25)
Ovarian	n/a	n/a	↑ risk: 1.2 (1.09–1.32) No difference between different HRT preparations		
Colorectal	↓ risk 0.63 (0.43–0.92)	↔ 1.08 (0.75–1.55)	n/a	n/a	n/a

compared with placebo (HR 0.76, 95% CI 0.69–0.85, combined fracture risk).[29] However, HRT is not a first line treatment for osteoporosis, and bisphosphonates are as effective as HRT in preventing fractures.[35]

2.3. *Non-cancer risks of HRT in healthy women*

HRT was previously thought to be cardioprotective, but the original WHI results disproved this and both the WHI E/P and WHI E alone studies were terminated early when researchers reported that the risks of HRT outweighed the benefits (Table 2a).

E/P HRT preparations were associated with an increased risk of:

- breast cancer (HR 1.26; 95%CI: 1.00–1.59)
- coronary heart disease (CHD) (HR1.29; 95% CI: 1.02–1.63)
- stroke (HR 1.41; 95%CI: 1.07–1.85)
- DVT and PE (HR 2.07; 95% CI: 1.49–2.87 and HR 2.13; 95% CI: 1.39–3.25, respectively)
- urinary incontinence[28,36]
- an increased risk of dementia in E/P users was also demonstrated by the WHI Memory Study (HR 2.05 95% CI 1.21–3.48)[37]

Absolute excess risks attributable to E/P HRT: 7 more CHD events, 8 more strokes, 8 more PEs, 8 more invasive breast cancers and 23 more cases of dementia per 10,000 women per year, while absolute risk reductions per 10,000 person-years were 6 fewer colorectal cancers and 5 fewer hip fractures.[28,37]

E alone HRT was associated with increased risk of:

- stroke (HR 1.39; CI 1.10–1.77)
- DVT (HR 1.47; CI 1.04–2.08)
- urinary incontinence (RR 2.15; CI, 1.77–2.62)[29,36]

For the outcomes significantly affected by E alone HRT, there was an absolute excess risk of 12 additional strokes per 10,000 person-years and an absolute risk reduction of 6 fewer hip fractures per 10,000 person-years.[29]

2.4. *Cancer risk associated with HRT (Table 2b)*

In the WHI E/P study, the risk of endometrial cancer, ovarian cancer and cervical cancer was no different to that in the placebo group. The risk of colorectal cancer was decreased compared to placebo (HR 0.56; 95%CI 0.38–0.81), and the risk of breast cancer was increased (HR 1.26; 95%CI: 1.00–1.59). However, the risk overall remains small, at 8 new invasive breast cancers per 10,000 women treated with HRT each year. Although the risk increases with duration of use, it returned to that of the placebo group within two years of stopping HRT.[38] The question of whether the 'gap time' between onset of menopause and starting HRT has an effect on breast cancer risk is also unresolved, with observational studies yielding discordant results and the interpretation of data under debate.[39–41]

With E alone HRT (in women who had previously undergone hysterectomy), the risk of colorectal cancer was the same as the placebo group (HR 1.08, 95%CI 0.75–1.55), there were no reported cases of ovarian or cervical cancer and the risk of breast cancer was reduced, albeit not a statistically significant difference (HR 0.77, 95% CI 0.59–1.01, $p = 0.06$).[29] This may be due to the high proportion of obese women in the WHI study (45% had a body mass index >30 kg/m^2), since HRT has been shown to exert a reduced cancer risk in obese women.[42,43]

Taken together, the WHI studies suggest that E alone has advantages over combination E/P HRT for treating healthy postmenopausal women as it does not cause an increase in coronary heart disease or breast cancer and is just as beneficial as E/P in decreasing fracture rates.[28,29] However, E only supplements should not be used in women with an intact uterus due to the increased risk of endometrial cancer.

The WHI results were echoed in part by the observational Million Women Study (MWS) involving 1084,000 women aged 50–64 years, which found that users of HRT at recruitment were more likely than never users to develop breast cancer (adjusted relative risk RR 1.66; 95% CI: 1.58–1.75) and die from it (RR 1.22; 95% CI: 1.00–1.48).[43] However, this study found that incidence of breast cancer was significantly increased for current users of both E only (RR 1.30; 95% CI: 1.21–1.40) and E/P combinations (RR 2.00; 95% CI: 1.88–2.12), and that the risk increased with duration of HRT. Tibolone was also associated with an increased risk of breast cancer (RR 1.45, 95% CI 1.25–1.68). The MWS authors estimated that 10 years' use of HRT resulted in 50 (95% CI 30–70) additional breast cancers per 10,000 users of E alone and 190 (95% CI 150–230) additional cancers per 10,000 users of E/P combinations. The MWS also found an increased risk of ovarian cancer in current users of HRT, who were significantly more likely to develop and die from ovarian cancer than never users relative risk 1.2 (95% CI 1.09–1.32; $p = 0.0002$) for incident disease and 1.23 (95% CI 1.09–1.38; $p = 0.0006$) for death, estimating 4 extra ovarian cancers in roughly 10,000 users, with 3 extra ovarian cancer deaths in roughly 10,000 users.[44]

The similarities and differences between the results of the WHI and Million Women Studies are summarised in Table 2. However, both studies had significant limitations. The MWS data are not randomised and therefore subject to responder bias and recall, and data on HRT use were only collected at the start of the study (i.e: any change to, or discontinuation of, HRT use was not documented). The WHI data, while randomised, cannot be extrapolated to other doses or preparations of HRT. In particular, the applicability of this data to European premenopausal cancer survivors is debatable, since a high proportion of the women in the US WHI study were obese and had an average age of 63 years. Participants in both studies were often well past menopause: in the MWS women were aged 50–64 years at recruitment (average 56 years), and in the WHI were aged 50–79 years (average 63 years). The limitations of these studies have been described in more detail elsewhere.[45,46]

3. HRT in cancer survivors

In women with ovarian failure and a previous history of cancer there remains uncertainty regarding the use of HRT, depending on the tumour type and expression of steroid hormone receptors. HRT is considered by some to be contraindicated in patients with breast or endometrial cancer due to the risk of stimulating occult metastases, despite the fact that HRT produces a lower serum level of estradiol than that produced by a functioning ovary. The situation is further complicated by a lack of randomised data, as well as a lack of uniformity regarding the role of ER in the tumorigenesis of different ER expressing cancers.

3.1. *Role of the oestrogen receptor (ER) in cancer*

Oestrogens influence many physiological processes by binding to the ER in the nucleus (*classical* mechanism) or the plasma membrance, or to other oestrogen binding proteins. ER exists in 2 main forms: ERα and ERβ, which are encoded separately and have distinct expression patterns in both normal and healthy tissue.[47] ERα is found in endometrium, breast cancer cells, ovarian stroma cells and in the hypothalamus, whereas ERβ expression has been documented in kidney, brain, bone, heart, lungs, intestinal mucosa, prostate and endothelial cells.[48] Although the ER is implicated in breast and endometrial cancer, this is not the case in other cancers, where ER expression does not correlate with endocrine responsiveness. Binding to ER in different circumstances/locations results in different downstream activity, as demonstrated by the selective oestrogen receptor modulators (SERM) tamoxifen and raloxifene. Tamoxifen is an ER agonist in bone and uterus, but an antagonist in breast tissue. Raloxifene exhibits similar properties, but demonstrates comparatively higher agonist activity in bone and less in the uterus.[49]

3.2. *Breast cancer survivors*

Approximately 75% of breast cancers express the ER or progesterone receptor (PR).[50] However, breast cancers in women

<45 years are often characterised by lower levels of ER expression, higher tumour grade and a worse prognosis.[51] For women with ER positive breast cancer, the mainstay of adjuvant endocrine treatment in premenopausal women is ER blockade with tamoxifen or tamoxifen plus ovarian function suppression, and in postmenopausal women either ER blockade or oestrogen production blockade by aromatase inhibitors (AI).[52] The use of HRT in these women would seem counter-intuitive, as a greater degree of oestrogen blockade/depletion is associated with a reduction in ER positive breast cancer recurrence: with SERM, the greatest reduction in recurrence is seen in women with the highest pre-treatment levels of estradiol[53] and randomised trials have shown that 3rd generation AI (which demonstrated higher levels of aromatase inhibition), were associated with improved clinical outcomes.[54,55]

There are only two randomised trials which looked at HRT use in breast cancer survivors, with the rest of the data coming from observational studies. A meta-analysis of 8 observational studies ($n = 3710$, mean age range 47–64.7 years) showed no increased risk of breast cancer recurrence in women taking HRT, with a mean follow up of 57.1 months: RR 0.64 (95% CI 0.65–0.82).[56] However, these studies had design limitations making them open to bias, e.g.: women taking HRT in these studies were more likely to have had node negative disease than controls. Two randomised trials comparing menopausal HRT with no therapy in patients with early stage breast cancer were set up in Sweden in 1997: Hormonal Replacement Therapy after Breast cancer – Is it safe? (HABITS) and the Stockholm study.[57,58] These trials yielded discordant results: HABITS demonstrated a relative hazard (RH) of HRT use of 3.3 (95% CI: 1.5–7.4), whereas the Stockholm study showed a RH of 0.82 (0.35–1.9); there was statistically significant heterogeneity between the studies ($p = 0.02$). The design of both studies was similar, the main differences between the studies were that the proportion of node positive patients was higher in the HABITS trial than the Stockholm study (26% and 16%, respectively), the proportion of patients receiving adjuvant tamoxifen was lower in the HABITS study (21% and 52%, respectively) and the Stockholm protocol aimed to reduce the amount of progestogen women received, with 73% of women assigned to either oestrogen alone or oestrogen plus progestogen for 14 days at 3 month intervals[58] (Table 3). However, the relative hazard of HRT use for the two studies combined was 1.8 (95% CI; 1.03–3.1), following which both trials were discontinued. Subsequently, the advice is that HRT use after ER positive breast cancer is not recommended as first line treatment[59], and the HABITS data at 4 years extended follow up confirmed an increased risk of cancer recurrence in HRT users (HR 2.4, 95% CI 1.3–4.2).[57] More recently, a randomised controlled trial of tibolone versus placebo in 3098 breast cancer survivors also showed an increased risk of cancer recurrence in the tibolone arm (hazard ratio 1.4, 95% CI 1.14–1.7).[60] Even vaginal oestrogen tablets raise serum estradiol levels in women on AIs and may be contraindicated.[61]

However, for women whose menopausal symptoms do not respond to alternative agents, and which are having significant adverse effects on their quality of life, a trial of HRT should be discussed. Although the Stockholm data suggest that HRT regimes which minimise progestogen dose may be safe, this remains debatable and patients should be made aware of the potential risks. HRT is not generally thought to be contraindicated in women with ER negative breast cancer; an unplanned subset analysis of the HABITS trial data showed no increase in ER negative breast cancer on HRT (relative hazard 1.9, 95% CI 0.4–9.6) and the increase in ER negative breast cancers seen in women on HRT in the WHI E/P study did not reach statistical significance.[29,57] In metastatic disease, where quality of life and symptom control is paramount, individual patients may feel that the symptomatic benefit of HRT is worth the risk of exacerbating their disease.

3.2.1. *Recommendations for practice in breast cancer survivors*

Hormone receptor +ve: HRT not recommended as first line treatment. Consider alternatives to HRT (see Box 3). If significant quality of life impact – patient choice with risk/benefit discussion.

Hormone receptor –ve: HRT may be offered as per recommendations (see Box 2).

Table 3 – Comparison of the Stockholm and HABITS trials of HRT in survivors of early stage breast cancer.

Study	Median follow up/years	Treatment	N	Age/years	ER+ve/%[a]	Node positive disease/%	Recurrence (n)
HABITS N = 345	2.1	HRT: directed by local practice	174	Mean 55.5	86	25.9	26
		Nil	171	Mean 55.5	73	21.4	7
Stockholm N = 378	4.1	HRT: <55 years: cyclical 2 mg estradiol d1–21 plus d15–21 10 mg medroxyprogesterone acetate, d22–28 no treatment 55 years and older: 'spacing out' estradiol plus medroxyprogesterone acetate Previous hysterectomy: estradiol alone	188	Median 56.9	65	16	11
		Nil	190	Median 57.5	56	20	13

[a] where status known.

Metastatic disease: HRT may exacerbate disease. Patient choice – consider quality of life issues.

3.2.1.1. *HRT options*. *Vaginal oestrogen* – has been shown to increase serum oestrogen levels in women on AIs and should be considered as per other forms of HRT because of the risk of systemic absorption.

Tibolone – in women < 60years the risk profile of tibolone is similar to that of combined HRT. The Million Women Study showed an increased risk of breast cancer in tibolone users (RR 1.5) which was similar to that of oestrogen alone HRT (RR 1.3), and lower than that of E/P combined HRT (RR 2.0).

Box 3 Alternatives to HRT for the management of menopause related survivorship issues.

Sexual dysfunction

- vaginal lubricants (Replens, KY jelly)
- Topical oestrogen (except in breast cancer survivors on aromatase inhibitors)
- Pelvic floor muscle training
- Education
- Psychological intervention: counselling, cognitive behavioural therapy, relaxation techniques, couples therapy

Vasomotor symptoms

- Pharmacological agents
  SSRI (except breast cancer survivors on tamoxifen)
  Venlafaxine
  Gabapentin
- Alternative therapies
- Psychological intervention: stress management, counselling, relaxation techniques

E alone (in women without a uterus) – suggestion of reduced risk of breast cancer recurrence in WHI study, but this may be because 45% of women in this study were obese (BMI >30 kg/m^2).

E/P – likely to carry highest risk of breast cancer recurrence; suggestion from Stockholm study that spacing of progesterone may be beneficial.

3.3. *Endometrial cancer survivors*

It is well established that unopposed oestrogen can cause endometrial adenocarcinoma,[62] while the addition of progesterone to oestrogen preparations reduces this risk.[63] A prospective cohort study of 23,244 patients showing a relative risk of developing cancer after 3 years of unopposed estradiol compounds of 2.7 (95% CI 1.4–5.1), and a relative risk of 2.2 (95% CI 1.2–4.4) after 3 years of conjugated oestrogen.[64] 15% of endometrial cancers in the UK are diagnosed in women under 55 years. Survivors – who have undergone a hysterectomy – would generally be offered oestrogen alone HRT, given the reduced risk profile compared to E/P HRT. The question therefore arises as to whether occult metastases from endometrial cancer would be stimulated by oestrogen alone HRT. Although small retrospective studies suggest that HRT does not affect recurrence risk in early stage endometrial cancer survivors, there is no randomised data available.[55–58] A Gynaecologic Oncology Group (GOG) trial randomised women with Stage 1/2 endometrial carcinoma after hysterectomy to 3 years of Premarin (conjugated oestrogen) 0.625 mg or placebo, but failed to recruit when the WHI-E study was published and closed early. A preliminary report of 1236 women at a median follow up of 35.7 months, demonstrated a recurrence rate in the HRT group of 2.3% vs 1.6% in the placebo group, with deaths due to endometrial cancer of 0.8% and 0.6%, respectively.[65] The RR of recurrence/death in the HRT group compared with the placebo group was 1.27 (80% CI, 0.916 to 1.77). In summary, there is currently no evidence that HRT is contraindicated in endometrial adenocarcinoma. Of note, however, it has been suggested that low grade endometrial stromal sarcomas may be sensitive to oestrogen: in a retrospective series of 22 patients, recurrence rates were 80% (4/5) and 35% (6/17) for patients who did and did not receive oestrogen, respectively.[66] A recent review of HRT in survivors of gynaecological cancers also concluded that HRT is only contraindicated in low grade endometrial sarcoma survivors.[67]

3.4. *Ovarian cancer survivors*

24% of ovarian cancers occur in premenopausal women and 5 year survival overall is 34%. Thus the prevalence of survivors with early menopause is low (Table 1), and there is no randomised data on HRT use in ovarian cancer survivors. Randomised data in healthy women from both the WHI E alone and WHI E/P studies did not demonstrate an increased risk of ovarian cancer in HRT users, in contrast to the Million Women Study, which showed an increased risk of developing and dying from ovarian cancer in current HRT users, although the absolute risk was low (Table 2).[28,29] There is some suggestion that HRT should be avoided in granulosa cell tumours, although this is not an absolute contraindication.[67] Sex cord stromal tumours and germ cell tumours are more likely to affect young women, and to be treated by oophorectomy. ER is not implicated in the tumorigenesis of these cancers, and HRT use in these women is not contraindicated.

3.5. *Survivors of other malignancies*

HRT has not been shown to be a risk factor in the development of other non-endocrine dependent malignancies, nor is there randomised trial data to suggest that HRT use is detrimental in these survivors. In malignancies where a high proportion of survivors are rendered menopausal by cancer therapy (e.g. lymphoma, leukaemias, and cervical cancer), it is standard practice to offer HRT up to the age of 51, alongside osteoporosis prevention advice and monitoring.[67,68]

3.5.1. *Recommendations for practice in non-breast cancer survivors*

HRT is not contraindicated in survivors of endometrial, ovarian and other non-breast cancers.

HRT for premature ovarian failure should be reviewed at the age of 50 years. After this age, the lowest dose should be

used for the shortest possible duration, in line with the RCOG guidelines for use of HRT.[53]

3.6. *Alternatives to HRT for the management of menopausal symptoms (Box 3)*

The management of menopausal symptoms requires a multidisciplinary approach as there is interplay between psychological factors and the perceived severity of physical symptoms. Distress, depression and lack of emotional closeness to their partner are correlated with higher rates of hot flashes and sexual dysfunction.[69–71] Relaxation training, cognitive behavioural therapy, counselling and couples therapy may therefore be useful adjuncts to medication. Women may benefit from brief counselling combined with information on vaginal lubricants or pelvic floor muscle training.[72] Topical oestrogen is an effective alternative to oral HRT for vaginal atrophy[73], although this may interfere with aromatase inhibition in breast cancer survivors.[61] For vasomotor symptoms, the only agents shown to be more effective than placebo in randomised trials are venlafaxine, gabapentin and selective serotonin reuptake inhibitors (SSRI).[74] However, some SSRI (e.g. paroxetine, fluoxetine) are strong inhibitors of the CYP2D6 P450 enzyme which metabolises tamoxifen, leading to reduced plasma concentrations of its active metabolite, endoxifen.[75–77] This may be associated with poorer clinical outcomes.[75,78] There is no evidence that complementary therapies – including soy isoflavone, phytooestrogens, black cohosh and acupuncture – are more effective than placebo. Since the placebo effect is very strong (20–30%), women should not be discouraged from using such remedies, with the exception of soy proteins which can increase the proliferation of breast cells.[74,79–81]

4. Conclusion

Few European countries other than the UK and Sweden have cancer survivorship initiatives, although Italy has also developed a research programme around cancer survivorship.[82] Data from the European cancer registry-based study of cancer patients' survival and care (EUROCARE) have repeatedly shown that the survival of European cancer patients varies markedly by country, region, age and sex, after adjustment for case mix. For example, the relative excess risk of death is 28% higher in Eastern Europe than central Europe.[83] However, the European Commission has included cancer patient survival in the priority list of health indicators,[84] and as survival from cancer improves, so survivorship will become an increasingly important topic for European oncologists to address.

A growing number of women across Europe are living with and beyond a diagnosis of cancer, with specific survivorship issues to be addressed.[1] In its recent report, the US Institute of Medicine (IOM) noted that many cancer survivors become lost in the transition from cancer patient to cancer survivor.[85] Key recommendations from the UK National Cancer Survivorship Initiative emphasise a shift from a one size fits all approach 'towards holistic assessment, information provision and personalised care planning. . .based on assessment of individual risks, needs and preferences'.[1] Clinicians need an awareness and understanding of the issues that female cancer survivors face, the potential impact this may have on their quality of life, the range of treatment options available and the local referral pathways. The unresolved HRT debate in healthy women and a lack of randomised data in cancer survivors have added to the uncertainty regarding the safety of HRT. However, at present, the available data do not demonstrate an increased risk of cancer recurrence in HRT users, with the exception of ER+ breast cancer and low grade endometrial lyomyosarcoma. With an increasing number of previously pre-menopausal cancer survivors affected by these issues, further randomised studies may become feasible. In the meantime, decisions must be made on a case by case basis according to the needs of the individual patient.

5. Additional educational resources

British Menopause Society (www.the-bms.org).

North America Menopause Society (www.menopause.org).

Australian Menopause Society (www.menopause.org.au.).

European Menopause and Andropause Society (www.emasonline.org).

International Menopause Society (www.imsociety.org).

Conflict of interest statement

None declared.

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